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2021 World Conference on Lung Cancer

SEPTEMBER 8-14, 2021 | WORLDWIDE VIRTUAL EVENT

ABSTRACTS

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Plenary Sessions

PL01 OPENING PLENARY: ACCESS AND DISPARITIES (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
WEDNESDAY, SEPTEMBER 08, 2021 - 07:00-08:00

PL01.02 Disparities in Lung Cancer Care Across the Population

R. Osarogiagbon
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Health disparities: 'differences in the incidence, prevalence, mortality, and burden of disease, and other adverse health conditions that exist among specific population groups….' (NIH, 2014).1 Lung cancer, the oncologic scourge of our age, with 2.2 million cases and 1.8 million deaths estimated worldwide in 2020, is the leading cause of cancer death among men in 93 countries, and women in 25 countries. Global aggregate 5 year survival is only 10% to 20% in most countries.2 In the United States (US), aggregate lung cancer incidence rates have been sequentially decreasing, in men since the mid-1980s and in women since the mid-2000s, at a rate of -2.2%/year. From 2014 to 2018, US lung cancer mortality rates declined by 5% per year for men and 4% per year for women.3 However, these aggregate statistics belie the reality of great geographic difference in evolution of lung cancer incidence and mortality statistics in the US, which is evident at the state and, even more so, at the county levels (geographic disparity).4 A simple, functional definition of 'disparity' is 'avoidable difference.' Such avoidable differences emerge or worsen with discovery and innovation; their patterns are predictable and similar; their causes are multi-level- including patient, provider, healthcare organizational and social policy levels. Clustering of these multi-level drivers leads to geographic disparities. From the perspective of corrective intervention, there is an inverse relationship between the number of intervention targets (individual> provider> organizational> social policy) and the impact of corrective intervention (social policy> organizational> provider> individual). Unfortunately, most disparities research tends to focus on the individual level, the least efficient target for corrective intervention, with the unpleasant side-efffect of stigmatizing the victims of disparate healthcare delivery. Disparities exist across the spectrum of lung cancer care: prevention (tobacco control, environmental pollution), screening, diagnosis, staging, biomarker testing, treatment selection, quality of treatment, survivorship care, and outcomes. Once anything is proven to be effective in healthcare, a predictable pattern of disparities emerges. Illustrating this principle of predictable emergence and exacerbation with discovery and innovation, early detection (low-dose screening CT adoption),5 personalized therapy (biomarker testing and targeted therapy),6 and use of immune checkpoint inhibitor therapy,7 all innovations in lung cancer care within the past decade, have already demonstrated the predictable emergence of new disparities, which threaten to worsen pre-existing population-specific gaps in lung cancer care delivery and outcomes. For example, in the United States, where insurance payment for low-dose CT screening for lung cancer has been the law since 2015, there has emerged a striking mis-match between the per-capita incidence and mortality of lung cancer and the density of low dose CT lung cancer screening facilities, potentially exacerbating the pre-existing geographic disparity in lung cancer mortality between Southern/Midwestern and Northeastern/West Coastal populations.5 In the plenary session lecture, we apply the multi-level framework for describing disparities from the intervention perspective to highlight emergent disparities in lung cancer care across the spectrum from prevention to treatment of advanced disease. We will emphasize the need for a comprehensive, proactive approach to discovery and implementation as a means of preventing, eliminating or, at the very least, minimizing predictable disparities in lung cancer care and outcomes. We give examples of innovative programmatic approaches designed to tackle the problem of inequitable lung cancer care delivery that especially target the organizational and provider-levels, for example the concurrent institution-level deployment of early lung cancer detection programs that combine low dose CT screening and algorithmic management of incidentally-detected lung nodules. Finally, we emphasize the fundamental socio-political origin of healthcare disparities, and advocate for social policy interventions, where the greatest leverage exists.

Keywords: Health equity, Quality improvement, lung cancer

PL02 PLENARY 2: PRESIDENTIAL SYMPOSIUM (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
THURSDAY, SEPTEMBER 09, 2021 - 06:30-08:00

PL02.01 Durvalumab ± Tremelimumab + Chemotherapy as First-line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study

M. Johnson[1], B.C. Cho[2], A. Luft[3], J. Alatorre-Alexander[4], S.L. Geater[5], K. Laktionov[6], A. Vasiliev[7], D. Trukhin[8], S. Kim[9], G. Ursol[10], M. Hussein[11], F. Lim[12], C. Yang[13], L. Araujo[14], H. Saito[15], N. Reinmuth[16], X. Shi[17], L. Poole[18], S. Peters[19], E. Garon[20], T. Mok[21]

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This abstract is under embargo until September 9 at 09:00 Mountain Time.

PL02 PLENARY 2: PRESIDENTIAL SYMPOSIUM (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
THURSDAY, SEPTEMBER 09, 2021 - 06:30-08:00

PL02.03 Lurbinectedin/Doxorubicin versus CAV or Topotecan in Relapsed SCLC Patients: Phase III Randomized ATLANTIS Trial

L. Paz-Ares[1], T. Ciuleanu[2], A. Navarro[3], A. Fulop[4], S. Cousin[5], L. Bonanno[6], E. Smit[7], A. Chiappori[8], M..E. Olmedo[9], I. Horvath[10], C. Grohé[11], J.A. Lopez-Vilariño[12], R. Nuñez[12], A. Nieto[12], M. Cullell[12], N. Vasco[12], C. Kahatt[12], A. Zeaiter[12], E. Carcereny[13], J. Roubec[14], K. Syrigos[15], G. Lo[16], I. Barneto[17]

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PL02 PLENARY 2: PRESIDENTIAL SYMPOSIUM (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
THURSDAY, SEPTEMBER 09, 2021 - 06:30-08:00

PL02.05 IMpower010: Characterization of Stage IB-IIIA NSCLC Patients by Type and Extent of Therapy Prior to Adjuvant Atezolizumab

N. Altorki[1], E. Felip[2], C. Zhou[3], E. Vallieres[4], V. Moiseyenko[5], A. Smolin[6], A. Rittmeyer[7], R. Vereshchako[8], M. Perol[9], W. Schutte[10], J. Fang[11], M. Tao[12], E. Teixeira[13], Y. Kim[14], B. Gitlitz[15], E. Bennett[15], V. Mcnally[15], F. Wu[15], Y. Deng[15], H. Wakelee[16]

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PL02 PLENARY 2: PRESIDENTIAL SYMPOSIUM (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
THURSDAY, SEPTEMBER 09, 2021 - 06:30-08:00

PL02.07 Global Variability in Lung Cancer Deaths Attributable to Air Pollution

C. Berg, J. Schiller
Consultant, Bethesda/MD/US

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PL02 PLENARY 2: PRESIDENTIAL SYMPOSIUM (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
THURSDAY, SEPTEMBER 09, 2021 - 06:30-08:00

PL02.09 International Association for the Study of Lung Cancer (IASLC) Study of the Impacts of COVID-19 on International Lung Cancer Clinical Trials

M. Smeltzer[1], P.A. Bunn, Jr.[2], R. Clark[3], R. Arndt[3], C. Pruett[3], U. Roy[4], F. Hirsch[5], T. Mitsudomi[6], H. Wakelee[7], G. Scagliotti[8]

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This abstract is under embargo until September 9 at 09:00 Mountain Time.

PL03 PLENARY 3: PLENARY 3: SCREENING: THE GLOBAL LANDSCAPE, PROGRESS, AND FUTURE DIRECTIONS (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
SUNDAY, SEPTEMBER 12, 2021 - 16:15-17:15

PL03.02 Lung Cancer Screening in Latin America: Current Status and Challenges

R. Santos[1], J. Franceschini[2]
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Cancer is becoming increasingly important in Latin America (LATAM), as the population is aging. Among the five main types of solid tumors, lung cancer (LC) stands out as one of the tumors with the highest incidence and lethality, being responsible for a high mortality rate worldwide. LC has a global five-year survival rate of approximately 15%, directly related to stage at the time of diagnosis. The survival rate is higher in cases where the disease is diagnosed in the early stages, when it is still localized. However, only a small percentage of cases (<16%) are diagnosed without regional spread or distant metastases. Most LC cases occur in individuals with a history of smoking and this risk decreases at any age from smoking cessation. Only in Brazil, LATAM's largest country, tobacco-related illnesses represent expenditures in the order of more than 11 billion US dollars annually, with related direct deaths in the order of 160 thousand people, LC encompassing almost 20% of those. The approach of the smoking population, carried out in a systematic way including screening, tobacco cessation and organization of lines of care may be successful, bringing cost savings to the health system and reducing mortality due to several tobacco related diseases. Low dose computed tomography (LDCT) screening has been approved worldwide as a reasonable option to reduce LC mortality; however, access to LDCT is variable among LATAM countries. Taking trips for exams, especially for the growing elderly population, can represent a challenge or even an impediment for cancer prevention. Many patients only go for exams after the onset of symptoms, when LC is usually on advanced staging. On the other hand, regions that have low economic development rates or social and political conflicts have challenges in infectious diseases and others conditions related to sanitation, nutrition and housing conditions, with early cancer diagnosis not being considered a medical priority yet. There is certainly no substitute for primary prevention; however, there are hundreds of thousands of current smokers users in LATAM, as well as millions of former smokers who remain at increased risk of lung cancer, for whom secondary prevention through early detection is of great value. Moreover, nowadays the offer of LDCT screening in most countries of LATAM is made in a decentralized and uncomprehensive manner; with the majority of the centers being in developed regions. Patients with radiological findings of a pulmonary nodule or abnormalities in the chest are often referred to different specialists and may not be followed up properly. The outcome is generally unknown for institutions or physicians who obtained the first report of the finding. The quality of LC care is directly related to the toxicity and cost of the therapeutic modality employed. Chemotherapy for many years was the main pillar of treatment in the advanced phase, despite its little therapeutic effectiveness. Surgery is the treatment of choice at an early stage, with increasingly better results with the use of minimally invasive techniques. Immunotherapy and targeted therapy drugs are becoming the best choice in more advanced stages of the disease; however, the related cost is an impediment to its use on a large scale, especially for low or middle-income countries. Currently, the most cost-effective way to offer a cure for lung cancer, individually or possibly in a population way, is to obtain an early diagnosis and proceed with surgical treatment quickly and safely. There are > 20 countries in LATAM. Brazil was the first country in LATAM to publish data on LDCT screening. The First Brazilian Lung Cancer Screening Trial (BRELT1) was established as the first program for lung cancer screening in Brazil, following the National Lung Screening Trial (NLST) and International Lung Cancer Action Program (I-ELCAP) results and guidelines. Initial results from BRELT1 indicated 39.4% of 790 participants had positive CT scans (nodules greater than 4mm), significantly higher from results of the NLST, and a non–small-cell lung cancer prevalence of 1.3%, similar to that of NLST and other studies. These results support the role of LDCT screening in countries with a high incidence of granulomatous inflammation. In this study, most patients (80%) were diagnosed with early-stage IA or IB non–small-cell lung cancer. Data presented at the 2020 World Conference on Lung Cancer (WCLC20) of the International Association for the Study of Lung Cancer (IASLC) from the second national effort in LDCT screening in Brazil (BRELT2), with 3,819 patients from six Brazilian institutions, demonstrate that the prevalence of lung cancer in the high-risk population is close to 2% with indexes of 6% of suspected cases (Lung Rads 4) and biopsies performed in 3% of included participants: numbers that are compatible with the international literature. The supply of thoracic surgery in LATAM is certainly limited to the largest urban centers. The increased number of thoracic surgeons over the last two decades has allowed the allocation of these professionals in smaller cities; however, disparity in access to LC care

occurs for 2 main reasons: lack of technology for early diagnosis and lack of resources to perform highly complex procedures. LDCT programs should also intervene at the first reason, connecting patients to urban centers where the complexity of care is greater and more accessible to the population. LDCT programs may perfom collaborative multidisciplinary work to conduct coordinated care for best practice on LC management. Therefore, the main goals for LATAM efforts on LDCT screening must include: 1) to perform LDCT screening in high-risk population; 2) to expand access to LDCT in undeveloped regions of LATAM; 3) to increase the number of lung cancer cases detected at earlier stages, 4) to connect LC patients to regional specialized cancer centers. As part of this process, LATAM's health professionals must deliver clear information based on current evidence about who is a candidate for LDCT screening, exposing risks and benefits in an appropriate language for the public, implementing a comprehensive LC care as recommended by international standards. N Engl J Med. 2011 Aug 4;365(5):395-409. doi: 10.1056/NEJMoa1102873. J Glob Oncol. 2018 Sep;4:1-10. doi: 10.1200/JGO.17.00040. Ann Thorac Surg. 2016 Feb;101(2):481-6; discussion 487-8. doi: 10.1016/j.athoracsur.2015.07.013. https://www.iaslc.org/iaslc-news/ilcn/lung-cancer-brazilian-health-system-screening-drug-approvals-barriers-care-and

Keywords: early diagnosis, LDCT screening, Latin America

PL04 PLENARY 4: STIGMA AS RISK FACTOR: WHY YOU SHOULD CARE (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
TUESDAY, SEPTEMBER 14, 2021 - 16:15-17:15

PL04.04 Psychological Distress and Stigma for People with Lung Cancer: Time to Act

S. Chambers[1], J. Dunn[2], B. Scott[3], D. Ball[41]

Australian Catholic University, Banyo/QLD/AU, 2University of Southern Queensland, Springfield/QLD/AU, 3Chris O'Brien Lifehouse, Sydney/AU, 4Peter Maccallum Cancer Centre, Melbourne/AU

The heightened psychological distress associated with lung cancer is well acknowledged with prevalence rates of up to 62% for clinically significant distress reported. [1] Major depression prevalence rates are significantly higher for lung cancer patients compared to people with other primary cancers and most do not receive potentially effective treatments for this depression.[2] This lack of care not only compromises quality of life and well-being, but may also negatively impact survival, treatment adherence, and the ability to comply with supportive care recommendations, such as smoking cessation and adequate nutrition and physical activity.[3] Related to this, health-related and iatrogenic stigma is well described as part of the patient experience of lung cancer. Stigma about a lung cancer diagnosis and the associated feelings of shame and guilt are associated with increased psychological distress and likely impede help seeking, again potentially blocking uptake of supportive care.[4] Oncology treatment guidelines therefore play a potentially important role in legitimising psychological care as a clinical priority, and within this understanding and addressing the issue of stigma. Parallel to this, is the need to have patient or consumer involvement in such guidelines as a method of ensuring those issues important to patients, such as psychosocial care and stigma, are considered. Indeed it is arguable that consumer involvement should be at the heart of supportive care guidelines to ensure that health care interventions are salient to the group they seek to serve. Historically it is consumers, cancer patients and survivors, who have placed supportive care needs on the table and asked that this be addressed in oncology care. De Ruysscher et al have highlighted the need for supportive care for people with Stage III non-small-cell lung cancer (NSCLC) who are undergoing concurrent chemotherapy and radiotherapy (CCRT). [5] The morbidities associated with CCRT are well described and considerable. It is however problematic that this review, guided by the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Society of Medical Oncology (ESMO), did not include a recommendation for psychological care, screening for distress or referral to evidence-based intervention is not included, nor is the importance of stigma addressed. In addition, in this expert panel review consumer input is absent.[6] There are models and approaches for developing care frameworks and guidelines in other cancer types that are likely suitable for consideration in the context of lung cancer. In the area of prostate cancer survivorship, a unique alliance of 47 leading clinical, nursing and allied health groups and agencies and consumer groups in Australia and New Zealand came together in a policy Delphi activity to produce a Cancer Survivorship Essentials Framework that includes six domains: Health Promotion and Advocacy; Shared Management; Vigilance; Personal Agency; Care Coordination and Evidence-based Survivorship Interventions.[7] Within this framework the perspective of the patient is prioritised, with personal empowerment, information provision and shared decision making, effective care coordination, and symptom management mandated. This framework and methodology could be adapted or incorporated to the benefit of those affected by lung cancer, and those who care deeply about this patient cohort and in so doing broaden the perspective to include the importance psychological care and of stigma. We propose three elements for action on psychological care for people with lung cancer and action on stigma. First, recognition and inclusion of the consumer voice in all deliberations. Second, including psychological health and wellbeing as a vital sign for people with lung cancer, not an optional extra, and being transparent about the influence of stigma.[8] Third, building on and applying the evidence-base we already have towards this problem and moving to implementation. It is time to act. **References** 1. Graves KD, Arnold SM, Love CL, Kirsh KL, Moore PG, Passik SD. Distress screening in a multidisciplinary lung cancer clinic: prevalence and predictors of clinically significant distress. Lung Cancer. 2007;55(2):215-24. 2. Walker J, Hansen CH, Martin P, Symeonides S, Ramessur R, Murray G, et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. The Lancet Psychiatry. 2014;1(5):343-50. 3. Kissane DW. Unrecognised and untreated depression in cancer care. Lancet Psychiatry. 2014;1(5):320-1. 4. Chambers SK, Dunn J, Occhipinti S, Hughes S, Baade P, Sinclair S, et al. A systematic review of the

impact of stigma and nihilism on lung cancer outcomes. BMC Cancer. 2012;12(1):184. 5. De Ruysscher D, Faivre-Finn C, Nackaerts K, Jordan K, Arends J, Douillard JY, et al. Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer. Ann Oncol. 2020;31(1):41-9. 6. Armstrong MJ, Bloom JA. Patient involvement in guidelines is poor five years after institute of medicine standards: review of guideline methodologies. Research involvement and engagement. 2017;3:19-. 7. Dunn J, Green A, Ralph N, Newton R, Kneebone A, Frydenberg M, et al. Prostate Cancer Survivorship Essentials Framework: Guidelines for Practitioners. BJUI. 2020; https://doi.org/10.1111/bju.15159. 8. Holland J, Watson M, Dunn J. The IPOS new International Standard of Quality Cancer Care: integrating the psychosocial domain into routine care. Psychooncology. 2011;20(7):677-80.

Keywords: distress stigma survivorship

PL05 PLENARY 5: CLOSING PLENARY: IMMUNOTHERAPY AND BEYOND: FUTURE DIRECTIONS (JAPANESE, MANDARIN, SPANISH TRANSLATION AVAILABLE)
TUESDAY, SEPTEMBER 14, 2021 - 21:15-22:15

PL05.01 CAR T-Cell Therapy for Thoracic Cancers

P. Adusumilli

Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York/NY/US

Immunity against solid tumors is restricted by factors including limited tumor infiltration of T cells, antigen heterogeneity and suppressive tumor microenvironment. Adoptive cell therapy aims to overcome these limitations by administering cancer-antigen specific, genetically engineered T cells. Three main approaches are being tested in clinical trials. Adoptive transfer of tumor harvested and expanded lymphocytes combined with immune checkpoint inhibitory (ICI) agents is currently in clinical trials in thoracic cancers. TCR (T-cell receptor) T-cell therapy is the second strategy wherein patient-derived T lymphocytes are genetically modified to incorporate an antigen-targeting TCR, most of the targeted antigens are intracellular. Chimeric antigen receptor (CAR) T cells, the third approach to adoptive cell therapy uses patient's own T cells that are transduced with genetically engineered synthetic receptors to target a cancer cell surface antigen. In addition, neoantigen-directed T-cell therapies are currently in clinical trials for thoracic cancers. CAR T cells are redirected to the tumor and are HLA-independent for their antigen activation and cancer cell lysis. The remarkable clinical response rates achieved by adoptive transfer of T cells that target CD19 in patients with leukemia and lymphoma have led to a growing number of clinical trials exploring CAR T-cell therapy for solid tumors. Our laboratory has developed, optimized and translated mesothelin, a cancer-cell surface antigen targeted CAR T-cell therapy. We have treated 41 thoracic cancer patients (mesothelioma, metastatic breast and lung cancers) to date with remarkable safety and evidence of anti-tumor efficacy. In this trial, patients were administered mesothelin-targeted CAR T cells intrapleural. We have previously published the immunological advantages of regional delivery of CAR T cells – early antigen activation, proliferation, augmented CD4-dependant immunity as well as systemic immunity. In a second clinical trial, patients with triple-negative breast cancer received systemically infused mesothelin-targeted CAR T cells. We further developed strategies to overcome the barriers to successfully translating CAR T-cell therapy for solid tumors. One such strategy already in clinic for patients with pleural mesothelioma is combination immunotherapy with CAR T cells and CPB agents. Checkpoint blockade therapy can elicit durable clinical responses by reactivating an exhausted immune response. However, response rates remain limited, likely secondary to a lack of a tumor-reactive immune infiltrate. CAR T cells may provide the necessary tumor-targeting immune infiltrate and a highly specific antitumor immune response. This can be further amplified by the addition of ICI agents, which serve to counteract the immune inhibitory environment undermining optimal CAR T-cell efficacy. Our phase I/II trial results will be discussed. Combination immunotherapies with cell therapy and ICI agents are in multiple clinical trials. Our recent approach incorporates T-cell intrinsic ICI strategy by a PD1 dominant negative receptor that is incorporated within the CAR, thereby the functional persistence of the T-cell is ensured. These trials are ongoing in patients with thoracic cancers.

Keywords: CAR T-cell therapy, Adoptive Cell Therapy, Mesothelin, Mesothelioma, Checkpoint Blockade agents

Education Sessions

ES01 PROACTIVE TOBACCO AND CANCER CONTROL
FRIDAY, SEPTEMBER 10, 2021 - 07:30-08:05

ES01.03 Integration of Cessation Services in Low Dose CT Screening

E. Stone
St Vincent'S Clinic, Sydney/ACT/AU

Lung cancer screening with low dose computed tomography (LDCT) of the chest has picked up momentum over the last decade. The publication of results from the National Lung Screening Trial (NLST) in 2011 confirmed the mortality benefit of this intervention in high-risk tobacco smokers. Nearly a decade later, this was supported by the results of the NELSON study. Subsequent analyses have showed that in these high-risk candidates, the impact of smoking cessation could be profound. In people who already have a diagnosis of lung cancer, smoking cessation can improve outcomes. This includes prolonged survival across all stages of cancer as well as a reduction in the development of second primary lesions. Data from the NLST have shown that in those candidates who stopped smoking, the risk of dying from lung cancer fell. This reduction matched the benefit of CT screening by seven years of abstinence. The mortality benefit of LDCT screening was nearly doubled in candidates who achieved fifteen years of smoking abstinence. Despite the high impact of smoking cessation, the best way to achieve this in LDCT screening candidates has not yet been established. Many studies are now investigating this, in countries that have formally instituted lung cancer screening such as the United States and in those where national screening programs remain under consideration. In the United States, eight studies form the SCALE Collaboration (Smoking Cessation within the Context of Lung Cancer Screening) across a range of sites and institutions. Strategies include digital advice, comparisons of behavioural interventions and various nicotine replacement regimens among several thousand screening candidates. In the United Kingdom, the Yorkshire Enhanced Stop Smoking (YESS) study will test the impact of personalized interventions in screening candidates, including the use of incidental CT findings and matched CT imagery. Data from previous lung cancer screening studies support the addition of specific smoking cessation intervention in eligible candidates, including the Danish Lung Cancer Screening Trial and the UK Lung Cancer Screening Trial as well as the NLST and the NELSON. Screening candidates often have high rates of motivation to quit, higher quit rates than the background smoking population and respond to CT abnormalities with greater smoking abstinence. Smoking cessation as part of LDCT screening contributes significantly to cost-effectiveness of screening programs. In general, LDCT screening guidelines strongly support smoking cessation as part of screening programs but refrain from making specific recommendations on detailed cessation interventions. As jurisdictions around the world move to introduce formal lung cancer screening, the impact of rigorous, specific smoking cessation interventions will grow. Implementation research programs that help LDCT screening candidates quit smoking represent a major opportunity to enhance screening success.

ES02 MULTIDISCIPLINARY COLLABORATION IN THE TREATMENT OF OLIGOMETASTATIC DISEASE
FRIDAY, SEPTEMBER 10, 2021 - 08:15-08:50

ES02.04 Systemic Therapy Influenced Trials in Oligometastatic Disease

P. Mitchell
Medical Oncology, Olivia Newton-John Cancer Centre, Heidelberg/ACT/AU

A working definition of Oligometastatic Disease (OMD) in Non-Small Cell Lung Cancer (NSCLC) is no more than 5 metastases involving 3 organs 1. This definition of OMD is largely for the purposes of offering local ablative therapy (LAT) - which includes surgery, or more frequently radiotherapy and, in particular Stereotactic Ablative Body Radiotherapy (SABR). However, OMD is a heterogenous state – which encompasses many clinical scenarios: at diagnosis of NSCLC with synchronous metastases; at recurrence after effective therapy; at progression after systemic therapy; and persistent site (s) of disease on therapy. Cures in the setting of lung surgery and resection of a solitary brain and sometimes adrenal metastasis are well recognised, including in a synchronous setting although the longer the time to recurrence the greater the cure rate. However, the intent of aggressive management of OMD is to delay progression or NSCLC death. There may be other benefits including delaying onset of symptoms, and LAT of large metastases may delay the emergence of resistance clones. Generally, the data for combining systemic therapy and LAT in NSCLC come from the pre-immunotherapy era. The SABR-COMET trial recruited 99 solid tumour patients (18 NSCLC), with 1-5 metastases, and randomised them to standard care or standard care plus SABR to all metastases. At median follow-up of 51 months (mths), progression free survival (PFS) was increased, and most importantly overall survival (OS) was increased with estimated 42.3% of SABR-treated patients alive at 5 years versus 17.7% (p=0.006) receiving standard care alone 2. Iyegar et al have reported on their trial of NSCLC patients stable for 3 mths and continuing on systemic maintenance therapy (mostly chemotherapy) with up to 6 tumour sites, randomised to receive SABR or no SABR. The trial recruited 29 patients and accrual was ceased early due to a positive result. PFS favoured the SABR plus systemic therapy arm at median 9.7 mths versus 3.5 mths with chemotherapy alone (HR 0.304; 95% CI 0.113-0.815) 3. A similarly designed study including 49 NSCLC patients on maintenance chemotherapy (or EGFR or ALK tki, as appropriate) with up to 3 metastases, again closed to accrual early due to a positive result. Patients could receive LAT with surgery or radiotherapy. PFS for LAT-treated patients was 14.2 mths vs 4.4 mths (p=0.02) and OS 41.2 mths vs 17 mths (p=0.017) 4. The recent SINDAS trial recruited 133 patients receiving first line first generation EGFR tki with up to 5 metastatic sites. Patients were randomised to SABR or no SABR. PFS favoured the SABR-treated arm (HR 0.62, p< 0.001) as did OS 25.5 mths vs 17.4 mths, HR 0.69, p<0.001. It remains to be determined if similar results will be achieved for patients receiving Osimertinib or the new generations of EGFR therapies. Similarly, the role of LAT in metastatic ALK-translocated NSCLC with newer-generation tkis is unclear. Almost all stage III – IV NSCLC patients now receive immunotherapy as first line treatment, mostly combined with chemotherapy. As oncologists gained experience with checkpoint inhibitors, radiotherapy, often given as SABR, has become standard practice to control metastases which escape immune control. However, for patients with high tumour PD-L1 score and treated with checkpoint inhibitors, it remains to be determined whether the already substantial proportion surviving 5 years can be augmented by LAT. There has recently been a focus on the role of radiotherapy in enhancing tumour control with checkpoint inhibitors via the abscopal effect – which is a recognised but infrequent out of field response in metastases distant from the radiotherapy-treated tumour. In the PEMBR-RT phase II trial 76 patients were randomised to receive ongoing pembrolizumab or pembrolizumab preceded by SBRT to a single tumour deposit. Outcomes favoured the SABR-treated patients with response rate at 12 weeks 36% vs 18% (p=0.07), median PFS 6.6 mths vs 1.9 mths, and OS 15.9 mths vs 7.6 mths. The primary endpoint was not met but there were clear trends 6. In a similar phase II trial patients randomised to radiotherapy could be treated with SABR or conventional radiotherapy, and in addition patients randomised to pembrolizumab alone could receive radiotherapy after the second 3-weekly pembrolizumab dose if the was progression 7. A combined analysis of these two trials indicated improved PFS, out of field (abscopal) response and OS in the experimental arm 8. The benefit of adding SABR to pembrolizumab were predominantly seen with tumours PD-L1 < 1%. Important questions remain: these two trials were conducted with pembrolizumab alone whereas most patients now receive chemo-immunotherapy, and this is certainly the case with PD-L1 low tumours. In addition, the ideal dose and fractionation of radiotherapy to elicit an abscopal effect in the context of immunotherapy is unclear. Nevertheless, these encouraging results warrant a phase III study. 1 Dingemans A-M, et al. Definition of synchronous oligometastatic non-small cell lung cancer. J Thorac

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Keywords: Oligometastatic Disease, Systemic Therapy, non-small cell lung cancer

ES04 ANTIBODY–DRUG CONJUGATES: CURRENT STATUS AND FUTURE PERSPECTIVES
FRIDAY, SEPTEMBER 10, 2021 - 09:00-09:35

ES04.02 Antibody Drug Conjugates about Non-small Cell Lung Cancer

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ADC are being developed for a number of types of cancer, including advanced NSCLC. ADC drugs target oncogenic driver gene mutations such as HER2, or highly expressed molecules in NSCLC such as HER3, TROP2, c-MET and CEACAM, to achieve high therapeutic efficacy by utilizing their drug deliverability. A number of ADCs are currently under development in clinical studies. Among them, ADC based on Deruxtecan (DXd) as a payload has been the most widely developed in NSCLC. T-DXd, an ADC designed based on HER2-targeted trastzumab and deruxtecan, has shown promising results in early phase clinical trials in NSCLC with HER2 mutation and expression. In HER2-expressing NSCLC, the efficacy of T-DM1, which was already a standard treatment for HER2-positive breast cancer, has been investigated but did not show favorable clinical efficacy (1, 2). In contrast, T-DXd showed noteworthy efficacy, especially in HER2 mutated NSCLC with overall response rate (ORR) of 61.9% and median progression-free survival (PFS) of 14.0 months (3). Additionally, in HER2 expressing NSCLC, ORR and median PFS was 24.5% and 5.4 months, respectively, suggesting the encouraged activity of T-DXd, although it was only short-follow up small phase 2 trial result (4). The issue is Interstitial lung disease (ILD) found in 11.5% of lung cancers, which is similar to breast and gastric cancers that have already been approved Another ADC target ERBB family is HER3-DXd, being developed mainly for EGFR mutation-positive NSCLC, based on several data that HER3 is one of the resistance mechanisms for EGFR-TKIs (5). In phase I trial, ORR and median median PFS was 39% and 8.2 months for EGFR-TKI and platinum-based chemotherapy (PBC) treated NSCLC with EGFR mutations (6). Although the potential biomarkers of efficacy are not yet identified, a phase II trial is currently underway in this population based on the promising efficacy, and the combination with EGFR-TKI is also being investigated in other phase I trial. Trop2 is a transmembrane calcium signal transducer. It is overexpressed in many epithelial cancers, and stimulates cancer-cell growth (7). In triple-negative breast cancer, Trop2-ADC, Sacituzumab govitecan, demonstrated definite efficacy comparing with standard chemotherapy in phase 3 trial. Datopotamab-DXd (Dato-DXd), other Trop2-ADC, showed promising efficacy and feasibility in phase I trial for advanced NSCLC, despite of relatively high frequency of ILD (14/175, 8%, including 3 G5) (8). Now, phase 3 confirmatory trial for PBC- and ICIs-treated advanced NSCLC without oncogenic driver mutation is ongoing. In addition, a phase II trial for driver mutation-positive NSCLC that has become resistant to the corresponding molecular targeted therapy is underway. CEACAM5, also know as CEA, is detected in adenocarcinoma NSCLC(9) and CEACAM5-DM4 (SAR408701) is CEACAM5 targeted ADC, which preliminary efficacy and safety of phase I trial has been reported (10). ORR and duration of response was 20.3% and 5.6 months in high CEACAM5 expressing NSCLC defined as >50% at >2+ intensity by IHC. Whereas GI and hematological toxicity was moderate, noteworthy corneal AE (38.0% including 10.9% G3) and peripheral neuropathy (27.2% including 1% G3) were observed. Phase 3 trial comparing with docetaxel for CEACAM5 expressing patients (IHC, >2+) is ongoing. c-Met is widely expressed on different types of cancers, with expression observed in 35%–72% of NSCLC and also resistance to EGFR-TKIs due to MET amplification has been reported (11). Telisotuzumab-vedotin (Teliso-V) is an anti–c-Met ADC of the telisotuzumab conjugated to the MMAE. Recently, phase 2 trial results revealed that ORR for c-MET high expressing EGFR-wt NSCLC was 54% (12). From those promising results, phase 3 trial comparing with docetaxel for c-MET expressing patients is ongoing. In summary, different types of ADCs are under development for NSCLC. It is needed to consider the use of each type of ADC for each target. Additionally, combination treatment strategies of ADCs would be considered in the future.

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Keywords: ADC, NSCLC, EGFR

ES09 PATHOLOGY ASSESSMENT AND BIOMARKER TESTING: IMPLICATIONS OF AND FOR ADJUVANT AND NEOADJUVANT THERAPY
FRIDAY, SEPTEMBER 10, 2021 - 10:30-11:05

ES09.03 The Role of Biomarkers for Immunotherapy in the Adjuvant and Neoadjuvant Setting

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For patients with NSCLC and absence of oncogenic addiction immune checkpoint inhibitors targeting PD1/PD-L1 change the therapeutic field. These treatments became standard of care in metastatic setting and are rapidly emerging in adjuvant and neoadjuvant setting. While more than 50% of patients with operable NSCLC will experience recurrence after surgery, neoadjuvant or adjuvant chemotherapy provides only a modest improvement in overall survival and could be highly toxic. Recent clinical trials underline the high rate of major pathological response in neoadjuvant setting and increase progression free survival in adjuvant setting. While such data will rapidly be practice changing immune checkpoint inhibitors are not effective in all patients and like in metastatic setting biomarkers remains unmet need. Various biomarkers are currently testing going from simple clinical biomarkers, to complex genomic and transcriptomic tests. Most biomarkers seem to behave similarly in adjuvant/neoadjuvant setting and in metastatic setting. Clinical patient's characteristics are important to predict efficacy of adjuvant or neoadjuvant treatment. In IMPOWER 10 trial, testing adjuvant treatment with atezolizumab, oncogenic addiction with EGFR mutation or ALK translocation are associated with absence of efficacy of atezolizumab (1). Tumor with EGFR and ALK genomic alteration tumor are frequently poorly infiltrated in CD8 T cells and present poor level of mutations which render them resistant to immune checkpoint inhibitors. PD-L1 is also an important biomarker of efficacy in early NSCLC. In Checkmate 816 trial (2) which tests neoadjuvant chemotherapy versus nivolumab plus chemotherapy underlines that PD-L1 >1% is associated with higher rate of pathological complete response but nivolumab enhance efficacy of chemotherapy in either PD-L1 positive or negative tumors. In contrast in IMPOWER 10 trial (1), atezolizumab improves progression free survival only in patients with PD-L1 positive tumors. Efficacy proportionally increase with PD-L1 expression. Interestingly, similar observation was previously performed in PACIFIC trial (3). Importantly, a post-hoc analysis underlines that durvalumab give survival benefit only in PD-L1 positive patients raising question on this utility in this subset of patients. Smaller studies testing anti PD-1 alone or in association with anti CTLA-4 in neoadjuvant setting observed major responses irrespective of PD-L1 status (4,5). So, PD-L1 expression is an imperfect surrogate marker of hot tumors richly invaded by anti tumoral CD8 T cells. Such data underline the difficulty to use PD-L1 to avoid immune checkpoint inhibitors usage. In addition, PD-L1 assessment in neoadjuvant setting only relies on a tumor biopsy which is an imperfect surrogate marker of PD-L1 expression in the whole tumor. Tumor mutational burden (TMB) represents the total number of mutation found in coding region of cancer cell genome. High number of mutation is correlated with high capacity of cancer cells to present neoantigens, and cancers cells which present high level of neoantigen are more easily recognized by T cells. In CHECKMATE 816 (2) high TMB is associated with better response to neoadjuvant immunotherapy (pathological complete response of 22.44% for TMB low and 30.8% for TMB high). Similarly, in a small study using nivolumab and ipilimumab in neoadjvuvant setting, there was a significant correlation between the pathological response and the pretreatment TMB (5). Additional works are awaiting to determine if HLA status or intratumoral heterogeneity are also important to predict response to adjuvant or neoadjuvant immunotherapy like in metastatic setting. In addition to such classical biomarkers some emerging biomarkers are described in small cohort of neoadjuvant immunotherapy. Gut microbiome could influence response to checkpoint inhibitors by different mechanisms like modulation of tumor microenvironement or bacterial mimicry. In NEOSTAR trial (4), higher abundance of Akkermansia in baseline samples of gut microbiote is associated with better response to nivolumab + ipilimumab and is positively correlated with intratumoral immune response. Similarly, Akkermansia was also associated with favorable clinical outcomes in patients with melanoma, NSCLC and renal cell carcinoma receiving immunotherapy in metastatic setting thus confirming the important role of gut microbiota and akkermansia in the response to immunotherapy. References: 1. Wakelee HA et al., ASCO® 2021, Abs #8500 2. Forde PM et al. – AACR® 2021 - CT003 3. Antonia SJ et al. N Engl J Med 2017; 377:1919-1929 4. Cascone T et al. Nat Med 2021 ; 27 :504–514 5. Forde PM et al. N Engl J Med 2018

Keywords: biomarkers, Neoadjuvant, checkpoint inhibitors

ES11 SMALL CELL LUNG CANCER: RECENT PRECLINICAL ADVANCES AND EMERGING APPROACHES TO THERAPY
FRIDAY, SEPTEMBER 10, 2021 - 11:15-11:50

ES11.02 Advances in Thoracic Radiation in SCLC

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Concurrent chemotherapy and thoracic radiotherapy (TRT) have been standard treatment for limited stage (LS) small-cell lung cancer (SCLC) since the 1990's, but the optimal dose and schedule of TRT is debated. The Intergroup 0096 trial published in 1999 established twice-daily (BID) TRT of 45 Gy in 30 fractions as the best documented schedule.[1] However, BID TRT caused more esophageal toxicity than once daily (QD) TRT, and it has been argued that the biologically effective dose (BED) in the control arm (45 Gy in 25 fractions) was inferior, and population based studies show that BID TRT is poorly implemented.[2,3] Results from single arm studies suggest that high dose QD TRT might be an alternative to 45 Gy BID, and such schedules are widely used. However, the first randomized trial comparing high dose QD with BID TRT failed to show that 66 Gy in 33 fractions was superior to 45 Gy BID, and numerically, survival was better in the 45 Gy BID arm.[4] At this year's ASCO Annual meeting (2021), the first survival data from the long awaited CALGB 20610/RTOG 0538 trial were presented. Patients were randomized to 45 Gy BID, 70 Gy in 35 fractions (QD) or 61.2 Gy in 34 fractions (QD in 16 days followed by BID in 9 days). After a preplanned interim toxicity analysis, the 61.2 Gy arm was dropped in March 2012. The trial was designed to show superiority of the higher TRT-dose. Survival data in the 45 Gy BID and 70 Gy QD arms were similar, and the trial was per definition negative, but 70 Gy QD appears to be an alternative to 45 Gy BID. Notably, there was no difference in radiotoxicity between treatment arms.[5] A systematic review concluded that a shorter time from start of chemotherapy until end of TRT is associated with improved survival.[6] Consequently, it seems reasonable that high dose TRT might improve survival if it is accelerated, i.e. the treatment period is reduced, and two trials published this year have investigated such TRT schedules. A Chinese study randomized patients to receive moderately hypofractionated TRT of 65 Gy in 26 fractions or 45 Gy BID and showed that the hypofractionated schedule prolonged PFS (median PFS 17.2 vs. 13.4 months; p=0.031). There was, however, no statistically significant survival benefit (median OS 39.3 vs. 33.6 months; p=0.14), though the survival data are not yet mature.[7] A Nordic trial employed a different strategy. In this trial, patients were randomized to receive standard BID TRT of 45 Gy in 30 fractions or high-dose TRT of 60 Gy in 40 fractions. There was a large improvement for the primary endpoint, 2-year survival (74% vs. 48%; p=0.0005), and in median overall survival (37.2 vs. 22.6 months; p=0.012), though the difference in median PFS was not statistically significant (18.6 vs. 10.9 months; p=0.13). Final survival data will be presented in 2023.[8] There are differences in patient selection, definitions of limited stage disease, target volume definitions and radiotherapy techniques between these trials (and the Intergroup 0096), and they are not necessarily directly comparable. However, it appears that with improvement in assessing extent of disease, using modern radiotherapy techniques and omitting elective nodal irradiation, there is now far less radiotoxicity from 45 Gy BID than observed in the Intergroup 0096. Furthermore, the high dose TRT schedules mentioned here are not more toxic than 45 Gy BID. It has been commented that a non-inferiority trial is needed to establish high-dose QD TRT as an alternative to 45 Gy BID, but one might question whether this is a priority. Not many randomized LS SCLC trials have been completed the last 20 years (e.g. the CALGB/RTOG trial took 11 years to complete), and it seems more appropriate to further investigate the accelerated schedules which seem to hold a larger potential for improved survival. However, it might be a good idea to await final survival data from the Chinese and Nordic trials. Another factor to consider before designing the next TRT trial is the potential role of immune checkpoint inhibitors (ICIs) in the treatment of LS SCLC. Two trials have shown a survival improvement of adding atezolizumab or durvalumab to chemotherapy in extensive stage SCLC,[9,10] and several ongoing trials are investigating whether concurrent or consolidation ICI therapy improves survival also in LS SCLC. 1. Turrisi et al: Twice-daily compared with once-daily thoracic radiotherapy in LS SCLC treated concurrently with cisplatin and etoposide. N Engl J Med 340:265-71, 1999
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ES11.03 Emerging Strategies in ES-SCLC in the Frontline

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Small cell lung cancer (SCLC) is a particularly aggressive and deadly form of lung cancer characterized by a predilection for rapid growth, early metastasis and acquired therapeutic resistance. The standard chemotherapy regimen for SCLC, consisting of a platinum agent (cisplatin or carboplatin) combined with etoposide, was defined several decades ago. There has been little progress in the 1L treatment of ES-SCLC for 30 years, the outcomes remain poor, with a median OS of ~10 months. Addition of immunotherapy targeting the PD-L1 pathway to platinum-based chemotherapy has improved OS in the first-line setting. IMpower133 evaluated the atezolizumab plus carboplatin and etoposide and CASPIAN evaluated durvalumab with or without tremelimumab (anti CTLA 4), plus EP in 1L ES SCLC. The two trails make the critical milestone in the ES-SCLC first line setting. Although PD-L1 antibody combine with chemotherapy has improved median survival from 10.3 to 13 months, only 12.6% of patients remain progression-free at 1 year. There are still unmet needs in ES-SCLC treatment. So, where do we go from here now? Only in a small minority (~10%) patient can benefit from long term durable benefit. What are the Biomarkers of the patient? Are there any other biomarkers can we use in future? In the light of the exploratory analysis of IMpower133 and CASPAIN, there are no relationships between the biomarkers PD-L1 and bTMB to the treatment response. So, it is necessary to find new more useful biomarkers. Besides biomarkers, we can also learn more from the molecular subtypes of small cell lung cancer. Rudin at al used transcription regulators to distinguish four types of SCLC in both cell lines and human tumors. On the basis of the 81 primary tumours, it appears that the proportion of SCLC-A is greatest (0.70 95% CI [0.60, 0.79]), followed by SCLC-N (0.11 95% CI [0.06, 0.20]), SCLC-Y (0.02 95% CI [0.01, 0.09]) and SCLC-P (0.16 95% CI [0.10, 0.26]). At the 2021 ASCO meeting, Sonam Puri, et al represented the largest real-world dataset of human SCLC tumors profiled by whole transcriptomic sequencing. The differential expression of immune genes and predictive biomarkers across SCLC subtypes may inform therapeutic vulnerabilities for rational and personalized treatment approaches in SCLC. What we can do from the laboratory to the clinic in the future? Maybe we can try more novel agents and combinations, such as AURKA inhibition, Bcl-2 inhibitor, Delta-like (DLL3) inhibitor, PARPi and anti-TIGIT in SCLC.

Keywords: ES- SCLC, biomarker SCLC - subtypes

ES12 A PRECISION APPROACH TO STAGE III NON-SMALL CELL LUNG CANCER*
TUESDAY, SEPTEMBER 14, 2021 - 17:30-18:05

ES12.01 Defining Operability

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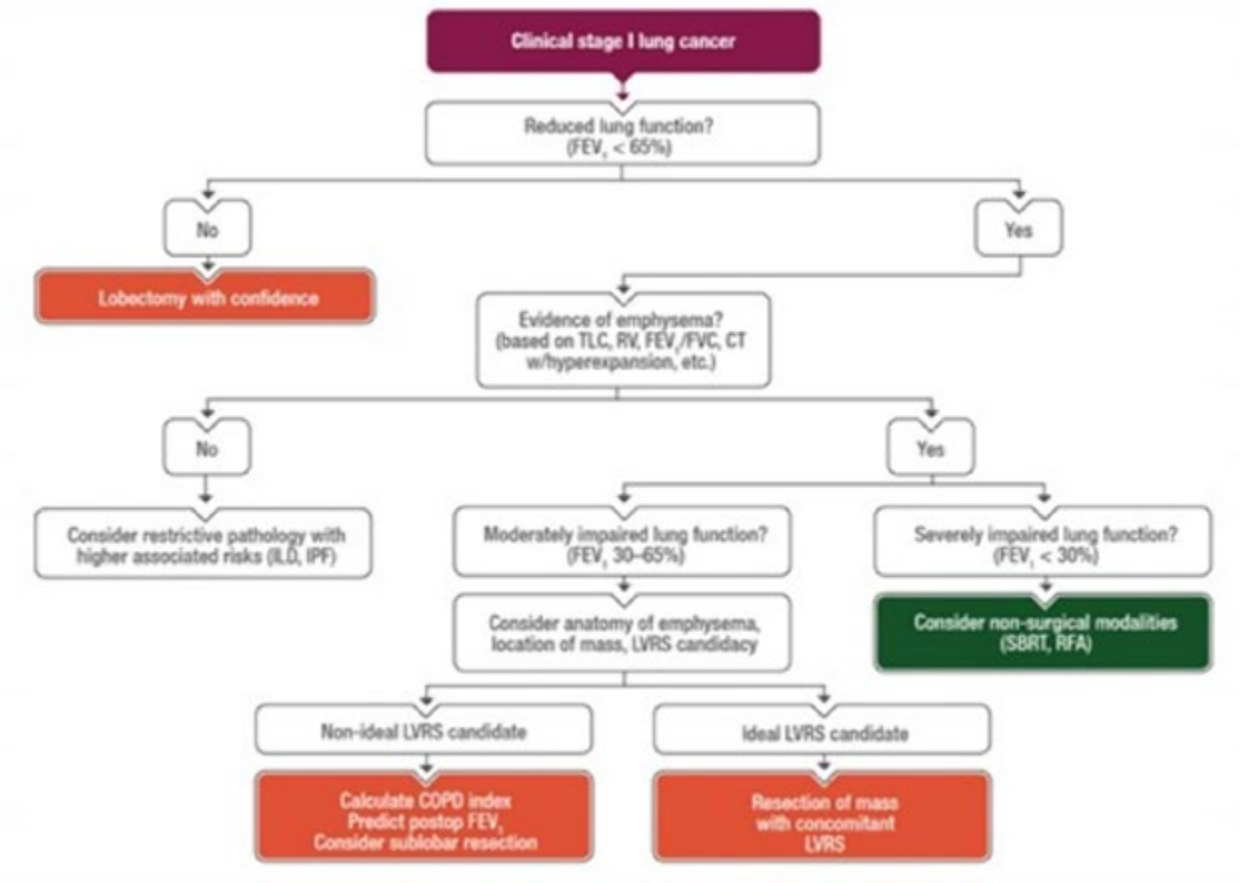
Stage III, so called loco-regionally or locally advanced» NSCLC comprises about one third of NSCLC patients and is very heterogeneous with varying outcome. Because of the heterogeneity (IIIA 36 %, IIIB 26% and IIIC 13% 5-years survival rate) a schematic management approach is very difficult, which is reflected in complex algorithms of existing guidelines. The current optimal staging and treatment decision for this patient group - usually a combination of local therapy (surgery or radiotherapy) and systemic therapy - requires multidisciplinary expert team effort.
The definition of functional, technical, and oncological operability is depending on many factors and is not standardized to date. For adequate decision-making, several points need to be taken into consideration:
Thorough preop-staging needs to be performed with caveat to differences between clinical and pathological staging. Recent analysis of Navani et al[1]. used individual participant data from randomized controlled trials (RCTs) and assessed agreement between clinical TNM (cTNM) stage at randomization and pathologic TNM (pTNM) stage. The results are based on 698 patients and demonstrated suboptimal agreement between clinical and pathologic staging. Discrepancies between clinical and pathologic T and N staging could have led to different treatment decisions in 10% and 38% of cases, respectively. Agreement between clinical N stage and pathologic N stage showed accordance between cN2 and pN2 is 67% (104/155) and if clinical staging overestimates the extent of nodal disease (114 patients [15%] in this meta-analysis), then this may mean patients are potentially denied from surgery. Eventually, further molecular and immunological staging of the tumors may help to move forwards to more personalized precision medicine.
Functional assessment is equally important for the indication for tumor resection. Current guidelines include algorithms[2]; however, patients with limited lung function and emphysema should be assessed for a potential lung volume reduction effect where resection can even lead to improvement of lung function[3-5]. Extremely important is also the patient's individual expectation for postoperative quality of life and fitness, and should be taken into account during decision-making (figure 1).

Figure 1: Algorithm illustrating the approach to patients with reduced lung function and stage I lung cancer[6]



The most critical point of operability assessment is how to define resectability. Across guidelines, only limited agreement exists (table 1) and in here, solely the fact that bulky N2 (only NCCN guidelines give a clear recommendation what “bulky” means > 3cm) should be excluded from surgery is in alignment between the different existing recommendations, besides clear resection margins. With regard to the number or zones of lymph node involvement, the variety ranges from “single”, to “discrete”, to “low volume” which are not further refined. Table 1: Summary of UK, European and American guidelines on the management of potentially resectable N2 NSCLC

Guideline	Definition of 'resectable'	Recommendations	Notes
BTS and SCTS 2010[7]	Non-fixed lymph nodes Non-bulky lymph nodes Single-zone N2 disease Reasonable chance of: Complete resection Clear pathological margins	Consider surgery as part of multimodality treatment in non-fixed, nonbulky, single-zone N2 NSCLC Further research into the role of surgery in non-fixed, non-bulky, multi-zone N2 NSCLC	Significant weight placed on IASLC staging database outcomes despite lack of comparator group and lack of clinical N2 Guidelines consider evidence for adjuvant chemotherapy more robust than pre-operative chemotherapy
ACCP 2013[8]	Discrete lymph nodes Easily measurable and defined lymph nodes Free from major structures, such as the great vessels and trachea	Definitive CRT or induction therapy (chemotherapy or CRT) followed by surgery Surgery followed by adjuvant chemotherapy not ecommended	Does not support the concept that surgery can only be justified in patients with minimal N2 disease Pre-operative chemotherapy better than surgery alone in all NSCLC (small studies) and therefore surgery plus adjuvant chemotherapy is not recommended
ESMO 2015[9]	Minimal, non-bulky N2 disease Single-station N2 disease	Definitive CRT, induction chemotherapy followed by surgery or induction CRT followed by surgery	Paramount importance of an experienced and high-volume multi-disciplinary team (MDT) and treatment centres able to minimise risk and complications from multi-modality treatment highlighted
NCCN 2018[10]	Low-volume lymph nodes Non-invasive lymph nodes Pathologically proven Measuring <3 cm	Definitive CRT or induction chemotherapy followed by surgery or induction CRT followed by surgery Maintenance durvalumab following cCRT	Benefit from pre-operative chemotherapy is similar to that of post-operative chemotherapy and either approach is justified
NICE 2019[11]	None provided	Consider CRT followed by surgery	CRT followed by surgery improves PFS and might improve survival compared with CRT alone

(created by Evison[12] using guidance from indicated Guidelines) ACCP American College of Chest Physicians, BTS British Thoracic Society, CRT chemoradiotherapy, cCRT concurrent chemoradiotherapy, ESMO European Society of Medical Oncology, IASLC International Association for the Study of Lung Cancer, NICE National Institute for Health and Care Excellence, NCCN National Comprehensive Cancer Network, NSCLC non-small cell lung cancer, PFS progression-free survival, SCTS The Society for Cardiothoracic Surgery in Great Britain and Ireland. A special condition of patients with stage III tumors represents bulky, centrally necrotic tumors difficult to control by radiotherapy and multiple nodules in one lobe deserves extra attention in favor of surgery. In any case, multidisciplinary tumor boards and clinics for treatment allocation are relevant, including here a thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology in NSCLC surgery for the assessment of functional, technical, and oncological operability.

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ES12 A PRECISION APPROACH TO STAGE III NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 14, 2021 - 17:30-18:05

ES12.04 Survivorship in Stage III Non-small Cell Lung Cancer: A Precision Approach

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Lung cancer remains the leading cause of cancer related death world-wide (1). 5-year survival in case of non-small cell lung cancer (NSCLC) range from 18 – 21%. A person can be defined as lung cancer survivor if he or she has diagnosed with lung cancer, undergoing treatment, had cancer free interval after cancer diagnosis or treatment. Lung cancer survivor's quality of life was reportedly affected in term of physical and emotional function and experience of certain symptoms such as dyspnea, fatigue, coughing and insomnia after the completion of treatment (2, 3). Many of the lung cancer patients are doing well in view of better therapeutic options but there are many challenges with the surviving patients. Survivorship challenges have been well addressed in long surviving cancer patients but it needs much more attention in Lung cancer survivors. In lung cancer, about 90% of patients undergoing chemotherapy and 57% of surgically resected patients experience fatigue (4).Observational studies have shown an inverse relationship between physical activity and fatigue, although physical activity does not appear to reduce recurrence rates it has been linked to longer average survival and better quality of life (5). A review suggested that a combination oncologists and kinesiologists may allow for the best development of exercise programs that take into account patients current fitness and psychological status to aim for improvement of physical fitness, quality of life, reduce treatment side effects and increase patient motivation to adapt to and maintain an active lifestyle (1). This is a phenomena linked to the interpersonal process of surviving harm while others do not (6). A study showed that the majority of patients in their study reported experiencing survivor guilt following diagnosis and treatment for lung cancer. Feelings of survivor guilt should be assessed to gain an understanding of the psychosocial challenges faced by lung cancer survivors, with available therapies to reduce the potential impact including; Self compassion interventions, Acceptance and Commitment Therapy and other "third wave" cognitive behavioural therapies (7). Long term smoking cessation can be a significant issue for survivors who go through a significant amount of both physical and emotional distress, in one study nearly 40% of smokers relapsed during postoperative periods (8, 9). One of the key factors associated independently with smoking, which could be addressed, is that lower emotional support (8). Smoking cessation is an integral part of cancer care but it is often ignored and not included in the continuum of lung cancer care. There are evidences that smoking cessation helps in maintaining a better quality of life by optimising the treatment responses. Patient education resources regarding common side effects based on current best practice with structured and culturally appropriate content (10). Patient education is an important concern in LMICs as patients are not well versed with the basic details of lung cancer management. There is a strong need to initiate lung cancer awareness program at community level. It should be noted that every lung cancer survivor needs specific approach to tackle emotional and physical challenges. Family members, close friends, caregivers, support groups and cancer care team including have an important responsibility to provide support especially emotional support to the survivor. References 1. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? The oncologist. 2020;25(3):e555-e69. 2. Hechtner M, Eichler M, Wehler B, Buhl R, Sebastian M, Stratmann J, et al. 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Keywords: Survivorship, Non-small Cell Lung Cancer, Precision Approach

ES13 ETHICS, COSTS, AND REGULATION OF LUNG CANCER
TUESDAY, SEPTEMBER 14, 2021 - 17:30-18:05

ES13.04 What Evidence Level is Enough for Approval and Reimbursement of Novel Cancer Drugs? Lessons from Lung Cancer

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In an ideal world, we would have prospective phase 3 randomized trial data with an ideal endpoint to demonstrate which interventions warrant regulatory approval and reimbursement – but we do not live in an ideal world and must strive to balance timely access to effective therapies for cancer with safety and avoidance of wasteful, often very costly treatments at risk of being favored based on preliminary data and surrogate endpoints. As the recent controversial approval of aducanumab should plainly illustrate, FDA approval should not be presumed as a de facto imprimatur of clinical utility, particularly when the FDA makes no pretense of considering cost or value of a therapy relative and often accepts obviated comparator arms. Instead, it is important to step back to clarify our true north for cancer therapies, which should be to have patients live longer and/or better. Accordingly, we should judge new interventions to the extent that they can improve overall survival (OS) and/or patient quality of life (QoL). One limitation of OS is that it may require extended follow-up to demonstrate an improvement, which provides the rationale for favoring a surrogate endpoint like disease-free survival (DFS) or progression-free survival (PFS) to provide earlier feedback that can potentially help us identify beneficial therapies destined to confer improvement in OS later. Additional variables may help modulate our confidence that it will accurately predict OS. For example, a greater magnitude of DFS difference is obviously more predictive of OS benefit than a DFS improvement that is only narrowly statistically significant, as in the ADAURA trial of adjuvant osimertinib vs. placebo in EGFR mutation-positive advanced non-small cell lung cancer (NSCLC).1 In addition, patients with more advanced stage disease typically have a higher probability of relapse/progression as well as a shorter and more direct link between the surrogate endpoint and OS. We can also have greater confidence that a surrogate endpoint is predictive of future OS benefit when an endpoint like DFS is not being measured when a patient is not on ongoing, active disease-suppressing but not necessarily curative therapy at the time (also as in the ADAURA trial1). When DFS or PFS is pursued, OS may be attenuated or even eliminated by subsequent therapies. While it is important to monitor cross-over and compare access to the investigational therapy over time to assess the true impact on OS, it is equally critical to distinguish between timing of therapy and overall access; if patients may achieve the same OS with subsequent treatment, we cannot ascribe a premium to earlier administration. In cases of adjuvant therapy, this means that proactive treatment merely overtreats the fraction of patients never destined to relapse if patients can achieve comparable OS with treatment only of the patients who ultimately demonstrate relapse of disease. However, it is worth remembering that QoL is also a relevant endpoint and that complications like earlier development of brain metastases may diminish functional capacity and QoL even if OS is not significantly improved. A question that remains controversial is whether cost of a therapy should be part of the equation of whether to favor a therapy with success predicated on a surrogate endpoint. Importantly, the high cost of many anti-cancer therapies limits access to these therapies in many health care systems around the world even when highly clinically meaningful benefits are observed with definitive endpoints. Moreover, the costs for these cancer therapies are most commonly shared by broader society, and especially when these treatments extend over a prolonged interval, the costs of these therapies translate to either escalated health care premiums for people who may not be able to accept them without sacrifice or difficult decisions about what other arguably worthy budgetary items, whether within or outside of the healthcare system, are going to be withheld to accommodate the costs of a new intervention. Because of this, a declaration that “my patient would want this” must be recognized as omitting critical stakeholders who are not represented in the exam room but are called upon to cover the costs; accordingly, we should aspire to justifying our interventions by a higher level of discrimination. As we turn our focus to more narrowly defined subgroups that are sometimes small populations of molecular oncology, we find ourselves asking clinical questions for which prospective randomized phase III trials may never be feasible. While we should seek the highest level of evidence possible, some of these interventions, such as with highly effective targeted therapies for rare, molecularly enriched patient groups, may confer such remarkable efficacy benefits in phase 1 (often greatly expanded) and 2 trials that we can reasonably consider a phase 3 trial infeasible or arguably unethical compared to a self-evidently inferior prior standard of care. Similarly, we may encounter trials

such as J-ALEX2 that are completed in specific countries and/or racial groups, leaving us to question whether it is appropriate to extrapolate these findings to a broader patient population around the world. Overall, with targeted therapies delivered to enriched patient populations, we have tended to see high concordance of efficacy and, somewhat more variably, toxicity profiles across distinct racial compositions. While these questions remain open, many would consider it appropriate to defer larger randomized trials that may be practically infeasible for narrow populations and are arguably unethical when the pre-test probability of a result highly favoring the new therapy is extremely high. Finally, we are left with a spectrum of trial results of varying strength, which typically correspond with varying degrees of availability in a given health care system. We must expect that these results will be associated with a range of probability of reimbursement, with the most definitive results being universally covered, while acknowledging that that proposed interventions with more tenuous associations with ideal endpoints will remain more subject to judgment and available resources. **References:** Wu, N Engl J Med 2020
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ES13 ETHICS, COSTS, AND REGULATION OF LUNG CANCER
TUESDAY, SEPTEMBER 14, 2021 - 17:30-18:05

ES13.05 The Ethics of International Research

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The key ethical principle for all International Research is that there is an equal partnership between high resource and low resource settings who are collaborating on research. The World Medical Association Declaration of Helsinki(DoH)[1] and the Council for International Organizations of Medical Sciences(CIOMS) International Ethical Guidelines for Health-related Research involving Humans[2], provide the ethical frameworks for International Research. Four key guidelines need to be highlighted when a high resource setting conducts research in a low resource setting. First, the proposed research must meet a need in the low resource setting[2]. Second, the low resource setting must be involved in the design of the research from the beginning. In order to make this collaboration effective, there may need to be training and capacity building in the low resource setting[2,3]. The next two requirements have been contentious[4]. In a randomized trial, the control arm should be a proven effective intervention unless very specific criteria are fulfilled[1,2]. There should also be fair benefits to all participants after the trial, usually including receiving the tested intervention if effective[1,2]. These two guidelines resulted in the US FDA no longer requiring that protocols be conducted in accordance with DoH because it now required social justice[4]. However, DoH and CIOMS do not require that a research sponsor achieves social justice for the entire country, but rather that the sponsor must treat participants in the research as partners, who deserve benefits from the research.

When conducting International Research, choosing the correct setting is crucial. Ethically, research cannot be conducted in a setting unless it has the potential to meet a local need. Empower Lung-1 was not conducted in the United States and certain western European countries because of the wide availability of anti-PD1 agents in those countries. An investigator could not in good conscience offer a trial that randomized participants to chemotherapy when PD-1 inhibitors were the standard of care. The trial report stated: “this study could not be run in certain countries (including the USA and many western European countries) owing to the availability of alternative anti-PD-1 therapy”[5]. Empower Lung-1 could be ethically conducted in settings without anti-PD-1 therapy, as long as the hosts supported the trial design and the control arm was an effective intervention, which brings us to the first contentious guideline. Using a placebo in a control arm of a randomized trial in a low resource setting was identified as a major concern in the late 1990s[6]. Even if the control arm is not a placebo, the debate still rages about whose standard of care treatment, the high resource’s or low resource’s, should be used in the control arm. Guideline 4 of CIOMS simply states “the control group of a trial must receive an established effective intervention.” Last, there must be fair benefits for all participants in the trial[7]. Fair benefits usually include receiving the tested intervention if proven effective, but the host setting can negotiate other benefits that will help the participants, such as added health facilities, equipment and trained healthcare workers. Taking a quick look at some International Immunotherapy trials for Lung Cancer, we see that those that were conducted mostly in high resource settings like the US and Europe were able to offer immunotherapy either as a crossover treatment during the trial or as a post-trial treatment, whereas Keynote 042, that stated it was mostly done in low resource settings[8], could only provide post-trial immunotherapy to 20% of those in the arm receiving chemotherapy(Table 1). Also, Keynote 042 did not claim to follow DoH. Given the difficulty of providing immunotherapy for lung cancer in low resource settings, there is a strong obligation to help improve healthcare infrastructure in that area and other fair benefits must be offered to trial participants. Keynote 042 may have done that. To summarize, high resource settings must negotiate fairly, which may require capacity building, so that fair benefits are offered first to all trial participants and second to the host setting.

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Table 1: Examples of recent immunotherapy trials and select benefits offered

Trial	**Accrual %**			**Guidelines followed**	**Crossover?**	**Subsequent immunotherapy for chemo arm**
	Europe/North America	Latin America	East Asia			
Empower Lung -1[5] (2021)	77%	-	-	DoH, GCP*	74% on chemo crossed over to immunotherapy	-
IMPOWER110[9] (2020)	74.6	-	-	DoH, GCP	No	30.4% >1 therapy:49.4%
Checkmate[10] 227[10] (2020)	67.4%	-	-	DoH	No	42.4%
Keynote 042[8] (2019)	23%	20%	30%	GCP	No	20%

*GCP: Good Clinical Practice guidelines

ES13 ETHICS, COSTS, AND REGULATION OF LUNG CANCER
TUESDAY, SEPTEMBER 14, 2021 - 17:30-18:05

ES13.06 Tobacco Moment: The Intersection of Tobacco Use, Health Disparities, and Inequities in Lung Cancer, Treatment, and Survival

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The risks linked to lung cancer mortality and cigarette smoking vary by race, socioeconomic status, and gender. Lung cancer mortality is 10 percent higher for Black men than White men but 31 percent higher for White women than Black women (1). Moreover, Black men have lower or equivalent mortality risks compared to those of white men at the two lowest socioeconomic status levels, but higher lung cancer mortality rates at higher levels of education. The lower socioeconomic class smokers are also more often intensely addicted to nicotine and therefore require more support in smoking cessation (2). This is also another difficult barrier as these citizens are less likely to seek out and receive adequate medical support (3). There is a higher incidence of lung cancer across the lower socioeconomic population due to their increased use of cigarettes. The impact of the socioeconomic class divide also shows differences in cancer survival rates, with lower survival rates amongst lower socioeconomic groups (4). Potentially this may be due to patients failing to seek out early medical attention before the prognosis of their cancer worsens, or perhaps the primary healthcare service in deprived areas is less effective. Therefore, lower socioeconomic patients are likely to present late or as a medical emergency. Socially and economically deprived patients who live in these circumstances have shown to be less likely to receive any form of treatment, whether that be chemotherapy, radiotherapy or surgery. Other mediating factors could include exposure to distinctive environmental conditions linked to residential segregation, genetic differences, resilience factors, nativity/migration, and cultural practices and beliefs (5). From the literature that is currently available it is clear to see that there is a disparity between socioeconomic classes and the use of tobacco. Despite there being an overall reduction in the number of smokers, the proportion of lower-class citizens remains the majority. The common habits of tobacco smoking include prolonged exposure and increased frequency of exposure. Both of which increase the risk of developing lung cancer, which is reflected with the higher incidence of lung cancer amongst this population. These patients are particularly difficult to treat as many present late and also mis presumptions are made by medical staff due to their class. Education inequalities are important factors for tobacco use and lung cancer management. More educated patients with early stage lung cancer reported better survival in many studies. A study on lung cancer from Sweden showed that early stage cancer with high education level had better survival whereas stage III cancer observed lower survival in high educated patients (6). Out of 3 studies conducted in England on socio-economic and educational inequalities in overall survival from lung cancer, 1 study observed higher overall survival in higher educated early stage disease (7). Similarly, role of educational inequalities in overall survival were explained by differences in stage of lung cancer at diagnosis, delivery of first-line treatment, co-morbidity and lower cancer survival in study from Denmark (8). Lung cancer patients living in deprived areas reported worst overall survival in view of difference in receipt of prescribed treatment as reported in two studies (9). An American study also observed overall survival disadvantage with higher concentration of deprivation and lower levels of education (10). §Income-based disparity is growing larger for the use of genetic tests, targeted therapy and Immunotherapy for lung cancer treatment and affecting the outcomes in lower socioeconomic group patients. More work is required to better educate the lower socioeconomic class to not undertake and to stop smoking as optimal strategy for preventing lung cancer is tobacco control. References: 1. American Cancer Society. 2011. “Cancer Facts & Figures for African Americans 2011- 2012” [accessed on March 7, 2012]. Available at: http://www.cancer.org/acs/ groups/content/@epidemiologysurveilance/documents/ document/acspc-027765.pdf. 2. Siahpush M, McNeill A, Borland R, Fong GT. Socioeconomic variations in nicotine dependence, self-efficacy, and intention to quit across four countries: findings from the International Tobacco Control (ITC) Four Country Survey. Tob Control 2006 Jun; 15 Suppl.3:iii71–75. 3. Arpey, N., Gaglioti, A. and Rosenbaum, M., 2017. How Socioeconomic Status Affects Patient Perceptions of Health Care: A Qualitative Study. Journal of Primary Care & Community Health, 8(3), pp.169-175. 4. Finke, I., Behrens, G., Weisser, L., Brenner, H. and Jansen, L., 2018. Socioeconomic Differences and Lung Cancer Survival—Systematic Review and Meta-Analysis. Frontiers in Oncology, 8. 5. Williams, D. R., S. A. Mohammed, J. Leavell, and C. Collins. 2010. “Race, Socioeconomic Status, and Health: Complexities, Ongoing Challenges, and Research Opportunities.” Annals of

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Keywords: Tobacco use, Health disparities, Inequalities, Lung Cancer treatment, and survival

ES14 LIQUID BIOPSY AND OTHER NON-INVASIVE DIAGNOSTIC MODALITIES
TUESDAY, SEPTEMBER 14, 2021 - 18:15-18:50

ES14.03 Liquid Biopsy and Early NSCLC Detection

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Liquid biopsy is an extremely powerful tool in cancer patients with several potential applications that range from early cancer detection/cancer interception to real-time monitoring during anticancer therapies and tumor genotyping in advanced disease. Over the last few years great attention has been focused on early cancer detection, using different methodological approaches and liquid biopsy sources, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), metabolomics, and micro-RNAs. The use of ctDNA is one of the most extensively studied strategy. Collectively, two broad strategies can be defined: tumor-informed and tumor-uninformed approaches. The former is based on the previous notion of the tumor genotype through a whole exome sequencing of the tumor tissue and the subsequent targeted mutation identification on plasma cell-free DNA. The latter is aimed to identify tumor-specific alterations without knowing the mutational profile of the tumor though a mutation discovery. One of the limitations of the use of ctDNA for early lung cancer detection is the very low variant allele frequency (VAF) of tumor-derived mutations in small tumors that might be under the detection limits of currently available technologies for cell-free DNA analysis. Different approaches have been used to date to analyze cell-free DNA and discriminate tumor-derived mutations from non-tumoral mutations. Recently, great interest has emerged on the analysis of tumor-specific methylation patterns that might be used as “fingerprints” of the tumor for early cancer detection. This approach has been recently showed to be a promising strategy in the Circulating Cell-free Genome Atlas (CCGA) study, as part of the development program of a multicancer detection test. This test is now commercially available in the US. Others have evaluated the role of cfDNA fragmentation profiles for cancer detection. Interestingly, lung cancer patients exhibit unique cfDNA fragmentation profiles and a specific prediction model, named DELFI, have been developed in order to predict the risk of cancer in asymptomatic subjects. However, ctDNA is not the only potentially exploitable source for early cancer detection and other components of the large liquid family are currently under active investigations, such metabolomics, extracellular vesicles (i.e. exosomes), and microRNAs. Integrated approaches coupled with conventional screening programs, such as low-dose computed tomography (LDCT), will likely reach sufficient sensitivity and specificity to change our current practice, adding lung cancer to the list of potentially early identifiable diseases.

ES15 THE IMPACT OF IMPLICIT BIASES IN ONCOLOGY CARE
TUESDAY, SEPTEMBER 14, 2021 - 18:15-18:50

ES15.06 Global Perspectives on Implicit Bias in Oncology Care: Canada

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A cure for lung cancer may remain elusive until biases in healthcare are resolved. Accessibility, comprehensiveness, and quality of care are key cornerstones that a healthcare system must address in order to be equitable for all its citizens; unfortunately, this is not always the case in Canada. Many Canadian lung cancer patients face numerous biases in care, ranging from systemic issues, social determinants of health, clinical trials design. In Canada, lung cancer has become a postal code disease. For example, targeted therapy drug coverage varies widely across each province, such as crizotinib for ROS1 positive NSCLC received marketing authorization in August 2017. However in September 2020, it was only publicly reimbursed in four provinces (Lung Cancer Canada, 2020). Unfortunately, this equity in access is common across Canada where access to one treatment or test may be accessible in one province, but completely inaccessible in another. Stigma on lung cancer patients, structural racism on minorities and indigenous populations, and discrimination all feed the biases in the healthcare system, leading to delays in testing and treatment. Geographical concerns arise for those in remote areas, particularly Indigenous communities, as traveling long distances for care has financial and emotional implications. However, the biggest factor influencing equity is the association between lung cancer risk and socioeconomic status, where incidence rates of those in the lowest income quintile are 2.1 times higher than those in the highest quintile (Mitra, Shaw, Tjepkema, & Peters, 2015). Education is also a major factor, where lung cancer incidence is 2.8 times higher for those with less than a secondary school diploma compared to those with a university degree, and this plays a role in health literacy and their ability to understand medical terminology, utilize available educational resources, and advocate for potential treatment physicians may not be aware of (Mitra, Shaw, Tjepkema, & Peters, 2015). Clinical trials also impose implicit biases on accessibility, as trials are typically done in large city centers where higher incidence rates are found, and thus, greater opportunity to fill placements. Disadvantaged populations such as ethnic minorities, low-income individuals, those In jobs with limited flexibility, and rural residents are often underrepresented in such trials, and thus, they do not consider the patient's perspective, leading to research that is inequitable. Significant systemic changes are needed to ensure underserved and underrepresented populations are able to access care for cancer prevention, treatment, and diagnosis. Within publicly funded healthcare systems, treatment costs are real concerns. However traditional assessments of value ignore costs such as time off work, travel to treatment. The value gained in non-traditional outcomes such as patient independence, mental wellness, and cultural preservation are real but difficult to capture. To preserve and further the medical gains in treatment advances, new assessments of value need to be developed, treatments planned with rollout and outreach in mind and clinical trials reflective of the real population they were designed to serve. Without these, a cure for lung cancer may be developed but remain unreachable for patients. **References** Lung Cancer Canada. (2020). (rep.). The Faces of Lung Cancer Report. Retrieved from https://www.lungcancercanada.ca/LungCancerCanada/media/Documents/LCC2020_FOLCR_ENGLISH.pdf Mitra, D., Shaw, A., Tjepkema, M., & Peters, P. (2015). Social Determinants of Lung Cancer Incidence in Canada: A 13-year prospective study. Health Reports, 26(6), 12–20. Retrieved from https://www150.statcan.gc.ca/n1/pub/82-003-x/2015006/article/14195-eng.htm

ES17 TNM STAGING AND DRUG-RELATED PNEUMONITIS
TUESDAY, SEPTEMBER 14, 2021 - 19:00-19:35

ES17.01 Current Anatomic Staging: Perspective of TNM Classification

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The current “stage” of the disease has been clearly defined as the anatomic extent of the disease in the TNM staging system for lung cancer. In the UICC/AJCC rules, this is uniform for tumors of all sites. This is also based on the observations that the extent of the disease is directly associated with the total tumor burden, which is increased as the cancer proceeds. Therefore, it is quite reasonable to classify the stage as localized (limited, advanced) or regional (extensive, limited) or distant. Here, it is important for us to realize that the stage is determined exclusively anatomically. That is, we use three parameters such as T (primary tumor), N (nodal metastasis), and M (distant metastasis), and the stage is determined according to the combination of T, N, and M. It has been widely recognized that the stage is precisely predicting the survival in many reports. However, as of now, several factors outside TNM are being used to determine the stage in cancers of some organs. Examples are age for thyroid cancer, histologic grade in soft part sarcoma and prostate cancer, tumor location in esophageal cancer. But we must realize that these are the exceptions. On the other hand, owing to the rapid progress in molecular biology for cancer, the new markers are being found and demonstrated to be related to the prognosis. The future staging may need to be changed from anatomic to functional, multifactorial, comprehensive to predict the survival more precisely in an individual basis.

ES17 TNM STAGING AND DRUG-RELATED PNEUMONITIS
TUESDAY, SEPTEMBER 14, 2021 - 19:00-19:35

ES17.03 Imaging of Pneumonitis

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Pneumonitis is one of the major adverse events from systemic anti-cancer therapy and provides clinical challenges in oncology practice. Imaging plays a key role in detection, diagnosis, and monitoring of pneumonitis in cancer patients. This lecture will discuss 1) diagnosis and monitoring of pneumonitis using CT patterns on imaging, 2) spectrum of CT patterns of pneumonitis focusing on immune-checkpoint inhibitors (ICI) and epidermal growth factor receptor (EGFR) inhibitors, and 3) emerging challenges and pitfalls in the era of COVID-19 pandemic. When approaching pneumonitis on imaging, it is very important to note that pneumonitis represents lung's response to injury. The lung's response patterns to injury has several histologic manifestations with corresponding CT patterns, which are originally described in idiopathic interstitial pneumonias and are also noted in the setting of pneumonitis secondary to cancer therapy. The assessment of extent and distribution of the lung abnormalities on CT is very important to recognize the distinct CT patterns. The spectrum of CT patterns is noted in pneumonitis from cancer therapies, and are associated with clinical severity of pneumonitis. Recognition of CT patterns helps to diagnosis, monitor, and prognosticate pneumonitis in cancer patients. In terms of pneumonitis from individual agents, the lecture will focus on pneumonitis from ICI and EGFR inhibitors, which are two representative agents used in lung cancer that can cause pneumonitis. ICI pneumonitis is relatively rare, but clinically serious and potentially life-threatening toxicity from ICI therapy, and is a leading cause of anti-PD-1/PD-L1-related deaths. The incidence of ICI pneumonitis is higher in lung cancer than in other cancers, indicating that pneumonitis is a particularly important issue in patients with lung cancer. The representative CT patterns of ICI pneumonitis include AIP/ARDS pattern, COP pattern, NSIP pattern, and HP pattern. Among these patterns, COP pattern is most common, noted in about two thirds of the patients. AIP/ARDS patten has the most severe clinical presentation and requires immediate clinical attention. The details of each of these CT patterns will be described with case presentations to demonstrate the characteristic features with clinical correlation. Pneumonitis is also a recognized class-effect for EGFR inhibitors. A higher incidence rate in Japanese population is noted, with a high mortality rate in the cohort studies from Japan, which is confirmed by the recent meta-analysis of 153 EGFR inhibitor trials in non-small cell lung cancer. The spectrum of CT patterns is also noted in EGFR inhibitor pneumonitis, and correlates with clinical severity and outcome. As the emerging issues with the advances of cancer therapies and the recent COVID pandemic, pneumonitis from combination ICI and radiotherapy is discussed, featuring the imaging manifestations from both ICI pneumonitis and radiation pneumonitis. Finally, the overlapping imaging features of ICI pneumonitis and COVID-19 pneumonia are presented, to demonstrate a unique challenge in the era of COVID-19 pandemic. The lecture concludes emphasizing the importance of multidisciplinary approach to further understand these emerging challenges to optimize diagnosis and management of pneumonitis in cancer patients. Abbreviations: AIP = Acute Interstitial Pneumonia; ARDS = Acute Respiratory Distress Syndrome; COP = Cryptogenic Organizing Pneumonia; HP = Hypersensitivity Pneumonitis; NSIP = Non-Specific Interstitial Pneumonia References: Nishino M, Sholl LM, Hatabu H, Ramaiya NH, Hodi FS. Anti-PD-1 Related Pneumonitis during Cancer Immunotherapy. N Engl J Med. 2015 Jul 16;373(3):288-290. 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Keywords: pneumonitis, computed tomography, Immune-checkpoint inhibitor

ES18.03 The Lung Microbiome and Lung Cancer Progression

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Cigarette smoke contains multiple carcinogens and has been identified as the major cause of lung cancer. However, the incidence of lung cancer among smokers is 15% and the prevalence of lung cancer among non-smokers is rising. Other environmental factors are likely playing a significant role in cancer pathogenesis. Both inflammation and effector lymphocyte dysfunction have been identified as important in this process. Immune checkpoint molecules, such as programmed death 1 (PD-1), mediates the responses of T cells to neoantigens and are now the target of first line therapy for advanced non-small cell lung cancer (NSCLC). The gut microbiome is associated affects patients' response to PD-1 blockade by unclear mechanisms. Interestingly, although different taxonomic signatures have been described across different studies, these investigations have paved the way for ongoing clinical trials targeting gut microbes through therapies such as fecal microbiota transplantation.1-3 The microbiota present in lung mucosa has not been studied as extensively despite being in topographical continuity with the external environment, having a large surface area and being the site of disease in lung cancer. Th17 inflammation seems to be playing a significant role in lung carcinogenesis, with extensive human data showing that local and systemic markers related to Th17 pathways are associated with NSCLC prognosis. Germ free or antibiotic treated preclinical models of lung cancer have provided proof of concept for the potential role that the microbiome can have in this disease.4 Importantly, our group has shown that lower airway dysbiosis can regulate the lower airway Th17 tone.5,6 This lower airway dysbiosis is characterized by enrichment with oral commensals, probably from microaspiration.5,7. We identified a distinct lung microbiota that we named pneumotypeSPT characterized by enrichment with supraglottic predominant taxa such as Prevotella and Veillonella.5 Notably pneumotypeSPT can be found in the lower airways of ~40% of healthy individuals, possibly due to microaspiration, and is associated with increased inflammatory cells with a Th17 phenotype.5,8 Thus, similar to the gut, specific lung microbiomes are associated with Th17 immunity.5 We then evaluated the lower airway microbiota among subjects with newly diagnosed lung cancer as compared with non-malignant lung nodules and disease controls. Using lower airway brushes from a group of subjects undergoing bronchoscopy for diagnosis of lung nodules and healthy controls, we demonstrated that the lower airway microbiota of patients with lung cancer is enriched with several oral commensals such as Streptococcus and Veillnella. Importantly, these same oral commensals were associated with upregulation of several host transcriptomic pathways found to be associated with lung carcinogenesis.9 Several of these pathways, such as ERK/MAPK and PI3K/AKT,9 can lead to chronic inflammation, altered Treg/Th17 balance, augmented Th17 differentiation, and induction of PD-L1 expression. We then extended these observations by profiling the lower airway microbiota of patients with local and advanced NSCLC (TNM stages <IIIB or ^{3}IIIB, respectively).10 In these subjects, patients with advanced stage disease had higher prevalence of pneumotypeSPT than patients with local stage disease. We also observed that mortality was increased among those patients where the lower airway microbiota was enriched with oral commensals. Parallel analyses of the lower airway host transcriptome showed that lower airway dysbiosis was distinctly associated with upregulation of several inflammatory pathway in NSCLC, including PI3K/AKT and IL-6. We then explored the effects of lower airway dysbiosis on the lower airway immune environment using an induced dysbiosis mouse model. To this end, we induced lower airway dysbiosis by biweekly intratracheal challenge with Veillonella parvula of B67BL/J6 female mice that developed lung cancer after intratracheal instillation of an adenocarcinoma cell line derived from tumors of KrasG12Dp53fl/fl mice. Exposure of wild type mice to Veillonella leads to increases in Th17 cells and PD-1+cells in the lung compartment but did not affect their survival or weight gain. Among lung cancer bearing mice that were challenged with Veillonella, there was an increase in Th17 cells compared to the lung cancer mice that received PBS. In addition, lung cancer mice challenged with Veillonella also had an increased amount of PD-1+ cells in the lung (both CD4+ and CD8+). Importantly, lung cancer mice challenged with Veillonella had decreased survival with increased tumor burden. These data suggest that lower airway dysbiosis induced an increase in pro-tumorigenic inflammatory state that contributes to inferior prognosis in lung cancer. We then showed that blocking IL-17 reduced tumor burden. Together, these data are supportive of the role that lower airway dysbiosis have in the

promotion a pro-inflammatory state that can contribute to lung cancer pathogenesis. Further investigations are warranted to evaluate directly targeting lower airway dysbiosis or anti-inflammatory approaches personalized based on the microbial pattern present in the lower airways.

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Keywords: lung cancer, microbiome

ES18 TUMOR BIOLOGY AND SYSTEMS BIOLOGY- BASIC AND TRANSLATIONAL SCIENCE
TUESDAY, SEPTEMBER 14, 2021 - 19:45-20:20

ES18.05 Response to Therapy Utilizing AI in CT Scan Image Analysis

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Checkpoint blockade immunotherapy demonstrates durable and long-term survival benefit in 20-50% patients with advanced stage non-small-cell lung cancer (NSCLC). Patient-level response to immunotherapy response is complex and includes various phenotypes including rapid disease progression, hyperprogression (HPD), and acquired resistance. Because of the complexity and heterogeneity of response to immunotherapy, there is an urgency to identify highly predictive biomarkers that can predict treatment response and potentially stratify patients into distinct risk groups of survival and progression. Although tumor expression of programmed cell death ligand-1 (PD-L1) measured by immunohistochemistry (IHC) is a standard-of-care biomarker, clinical trials and real-word data have demonstrated that statistically significant survival benefit for patients irrespective of tumor PD-L1 expression. Additionally, tumor mutational burden (TMB) has also shown to be a predictor of immunotherapy response, but tumor specimens have to be sufficient in both quantity and quality in order to assess TMB (and PD-L1) and laboratory methods to calculate tumor biomarkers can be timely and expensive. As such, complimentary biomarkers that are predictive, non-invasive, and measured in a timely fashion using standard-of-care modalities would have direct translational implications. This presentation will demonstrate the utility of AI in CT image analysis to: **1)** develop radiomic-clinical predictors of immunotherapy-induced hyperprogression, **2)** train and validate parsimonious models associated with survival outcomes among patients treated with immunotherapy, and **3)** develop and validate a non-invasive treatment decision support system for NSCLC.

ES20 CAVEATS, CHALLENGES, AND CONTROVERSIES IN IMMUNOTHERAPY OF LUNG CANCER: PHASE II AND PHASE III TRIALS
TUESDAY, SEPTEMBER 14, 2021 - 20:30-21:05

ES20.02 Charting a New Path: Defining Better Endpoints in Immune Therapy Trials in Lung Cancer

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The use of immune checkpoint inhibitor therapy has transformed the face of lung cancer management. Trials of such agents for metastatic and locally advanced disease have used the traditional endpoint of overall survival (OS) by time-to-event analysis. However, obtaining this endpoint in a randomized trial takes some time and other endpoints are being considered, particularly for the radical or operable setting. To consider the most appropriate endpoint to use for immunotherapy, we must consider the aims of our treatment of lung cancer. For radically treatable disease through surgery is the aim always to improve the cure rate, or is another aim such as delaying recurrence (e.g., disease-free survival) just as clinically meaningful, if it doesn't correlate with OS? We must also consider the magnitude of the effect size we wish to observe, particularly when using a surrogate endpoint of OS. Here, hazard ratios of 0.85 may not be clinically meaningful anymore, and we need to consider if we are prepared to accept uncertainty in effect by using a surrogate (earlier) endpoint for more rapid regulatory approval. If using a surrogate endpoint, will this give enough information to be able to pass HTA reimbursement value thresholds? We have clear guidance from the regulatory agencies on endpoints to be used for clinical trials. EMA give different definitions of endpoints for phase 1 and 2 trials from confirmatory phase 3 trials, giving a different stance for trials of cytotoxics to those non-cytotoxic based[1]. They recognize that immunomodulatory treatments may work most effectively where tumour bulk is low, and may take time to generate an defect, indeed with effect occurring post progression, and for phase 3 trials, progression-free survival remains acceptable. In the curative setting, EMA is clear that if event-free survival (EFS) is being used then this is justified under certain conditions and they give clear direction on using surrogates for the (neo)adjuvant setting[1]. The FDA also gives clear guidance on endpoints, with OS as the gold standard, but may allow other endpoints, recognizing that non-small cell lung cancer (NSCLC) is a heterogeneous disease, and the effects of different subsets should be explored[2]. When immunotherapy is being considered as the investigational medical product, endpoints such as progression-free survival (PFS), objective response rate (ORR) and even OS can have several benefits and risks. Measuring the benefit from immunotherapy can be difficult due to different patterns of benefit, and altered kinetics of benefit from cytotoxic therapy, alongside the heterogenous nature of NSCLC. Several surrogate endpoints e.g., ORR, duration of response, relapse-free survival, major pathological response or complete pathological response can be considered, but each give several benefits, but are prone to biases that need accounting for. The latter pathology-based endpoints have unclear definitions and the IASLC have proposed a structure for their definition[3]. When considering such surrogate endpoints, we should consider if such surrogates really to result in earlier approval or whether OS-based randomized trials are the main strategy-giving the example of extensive-stage small cell lung cancer[4]. Finally, if considering disease-free survival (DFS), multiple considerations need to be given. There are multiple emerging endpoints such as minimal residual disease in myeloma and the field of surrogate endpoints continues to evolve[5]. REFERENCES 1. EMA. Guideline on the clinical evaluation of anticancer medicinal products. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf 2. FDA. Clinical Trial Endpoints for the Approval of Non- Small Cell Lung Cancer Drugs and Biologics. Published 2015. https://www.fda.gov/media/116860/download 3. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. Journal of Thoracic Oncology. 2020;15(5):709-740. doi:10.1016/j.jtho.2020.01.005 4. Gill J, Cetnar JP, Prasad V. A Timeline of Immune Checkpoint Inhibitor Approvals in Small Cell Lung Cancer. Trends in Cancer. 2020;6(9):736-738. doi:10.1016/j.trecan.2020.05.014 5. EMA. Guideline on the use of minimal residual disease as a clinical endpoint in multiple myeloma studies. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf

Keywords: endpoint, immunotherapy, Clinical trials

Oral Abstract Sessions

OA01 THE IMPACT OF COVID-19 ON PATIENTS WITH LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

OA01.01 Analysis of Lung Cancer Patients Receiving SARS-CoV-2 Vaccines Revealed a Minority Subset With Poor Antibody Responses Relative to Controls

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Introduction: Patients with lung cancer (LC) were reported to have a high case fatality rate (30-40%) from SARS-CoV-2 infection, raising the question of whether LC patients mount a weaker antibody response to natural infection and/or vaccination, compared to healthy controls (HCs). We previously analyzed antibody responses to SARS-CoV-2 mRNA vaccination in several hundred healthy individuals, stratified by previous SARS-CoV-2 infection status. Using a validated enzyme-linked immunosorbent assay (ELISA) to the full-length spike protein (PMC8183627, PMC7235504), we found strong responses to infection and a robust neutralizing antibody response to vaccination. We compare these results to data from individuals diagnosed with LC undergoing different types of cancer treatment. **Methods:** This is an ongoing, prospective, control-matched longitudinal cohort study of 750 LC patients in all stages with or without previous SARS-CoV-2 infection and/or vaccination, comparing SARS-CoV-2 antibody titers at baseline (time of enrollment) and at 3-, 6-, 12- and 24-month intervals. We examine the quality, magnitude, and duration of the SARS-CoV-2 antibody titers against the full-length spike protein compared to the matched (age, tobacco history, sex and ethnicity) HC cohort. Types of Analysis and Data Reporting: ELISAs are performed in a CLIA-certified laboratory using an FDA-approved antibody assay along with other well-established, research-grade assays. We hypothesized that LC patients have a weaker antibody response to SARS-Cov-2 infection and/or vaccination due to cancer or its treatment compared to matched HCs. The non-parametric Kruskal–Wallis test was used to test this hypothesis. If confirmed, a tailored vaccination program would be necessary to ensure immune protection in patient with LC. **Results:** 111 LC patients have been enrolled to date; with 78 receiving at least one vaccination and 33 unvaccinated. Median age is 69, with 58% female. 39 patients were fully vaccinated (defined as 14+ days after second vaccination). Partially vaccinated (after 1st vaccine dose) LC patients had a lower median antibody level than partially vaccinated HCs (p=0.01). Fully vaccinated LC patients had substantial antibody titers but a lower median antibody level than fully vaccinated HCs (p=0.01) with a subset not raising large antibody titers. Especially important were the 30% of partially vaccinated LC patients who did not develop neutralizing antibodies. To date, there were no significant differences in median antibody levels in LC patients by gender, smoking status, age (< or > 65 years old), or treatment (with or without chemotherapy, immune checkpoint inhibitors, or targeted therapy). **Conclusion:** While most (~70%+) of LC patients mounted a good antibody response to vaccination, a subgroup had significantly lower anti-spike antibody/neutralizing levels compared to controls. Further studies are required to evaluate the role of further boost vaccinations in this patient population with a particular focus on patients not producing neutralizing antibodies to further understand the lack of response. We will continue to analyze the effect of systemic anti-cancer therapies as more data becomes available.

Keywords: covid-19, SARS-CoV-2, lung cancer

OA01.02 Impact of COVID-19 Outbreak on Lung Cancer Diagnosis and Continuum of Care: Data From an Italian Multicenter Study

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Introduction: Since March 2020 the coronavirus disease 2019 (COVID-19) has permanently shaped the global health care scenery. With Italy being one of the most heavily affected countries, medical oncologists had to elaborate a prompt response in order to ensure high-quality standards for diagnostic-therapeutic pathways in cancer care. Considering the clinical spectrum and potential overlap with COVID-19 disease, lung cancer (LC) patients represent a highly vulnerable population. Aim of this multicenter Italian study is to assess whether the COVID-19 outbreak has impacted on access to cancer diagnosis, staging and treatment for LC patients after March 2020 compared to pre-pandemic time. **Methods:** Medical records of all consecutive newly diagnosed LC pts referred to 24 Italian Oncology Departments between March and December 2020 were reviewed. Access rate (number of pts/days) and temporal intervals between date of symptoms onset, radiological diagnosis, cytohistological diagnosis, treatment start, and first radiological revaluation were computed and compared with those of the same period in 2019. Differences between the two years were analyzed using Fisher's exact test or chi-square test for categorical variables and unpaired Student t test, or the Mann-Whitney U test for continuous variables. **Results:** A slight reduction in newly diagnosed LC cases was seen when compared with 2019 (1381 vs 1443, access rate ratio = 0.95, p = 0.86). However, newly diagnosed LC patients in 2020 were more likely to have advanced disease (75% vs 69%, p < 0.01). Other clinical and tumor characteristics were similar regardless of the year, with the only exception of the number of current smokers, which was higher in 2020 (38% vs 34%, p = 0.02). Looking at pts management, no differences emerged in terms of interval between symptoms onset and radiological diagnosis (median 26 vs 25 days, p = 0.52), symptoms onset and cytohistological diagnosis (47 vs 45 days, p = 0.36), symptoms onset and treatment start (median 76 vs 77 days, p = 0.93), treatment start and first radiological revaluation (71 vs 71 days, p= 0.36). The interval between cytohistological diagnosis and treatment start was even shorter in 2020 (30 vs 33 days, p < 0.01). **Conclusion:** Despite COVID-19 had unprecedentedly changed the face of cancer care, our study provides a thorough insight on the effectiveness of the measures adopted by Italian Oncology Departments to optimally address quality of care issues and lung cancer patient's likelihood of receiving timely diagnosis and treatment. As COVID-19 shows no sign of abating, our results may prove even more valuable to guide further steps in the ongoing pandemic. Future investigations will offer a more exhaustive picture on the efforts made to contain the coronavirus tidal wave also in other cancer settings.

Keywords: covid-19, continuum of care, lung cancer

OA01 THE IMPACT OF COVID-19 ON PATIENTS WITH LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

OA01.03 Immune Checkpoint Inhibitor Dose Adaptation During the COVID-19 Pandemic in Non-Small Cell Lung Cancer– a Single-Center Experience

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Introduction: The COVID-19 pandemic forced all oncologists worldwide to reduce patient contacts to decrease risk of exposure to the virus, and to reallocate resources to provide necessary COVID-19 care. We realized such a reduction of site-visits in our center by adapting the dosing schedules of nivolumab and pembrolizumab monotherapy and consolidation therapy or adjuvant durvalumab for patients with stage III and IV non-small cell lung cancer (NSCLC). Here we report the toxicity of the adapted dose versus the standard dose schedule in a real-world NSCLC population. **Methods:** We retrospectively analyzed data of all patients with NSCLC, age ≥18 years, who were treated with dose-adapted ICI consolidation therapy (stage III disease) or adapted dose ICI mono- or consolidation therapy (stage IV disease) between March 1 2020 and January 31 2021 in our center. Dose adaptation was defined as followed: Pembrolizumab mono- or consolidation therapy was administered every 6 weeks at a dose of 400 mg (1), nivolumab every 4 weeks at a dose of 480 mg (2), and durvalumab every 4 weeks at a dose of 1500 mg (3). Toxicity of the adapted dose group was compared to consecutive patients who had received standard dose ICI between January 1 2019 and February 28 2020 in our center. **Results:** A total of 108 patients received dose-adapted ICI treatment. Baseline characteristics, including ECOG performance score, NSCLC subtype and PD-L1 expression, of the adapted dose group were similar to the standard group of 83 patients, except for a larger number of patients treated with durvalumab in the adapted dose group. A total of 229 adverse events were reported in the adapted dose group, versus 114 in the standard dose group. Low grade skin toxicity, fatigue, endocrinopathies and gastrointestinal toxicities were the most frequently registered adverse events with an occurrence of 33.7%, 26.5%, 20.5% and 24.1% in the standard dose group, and 70.4%, 46.3%, 37% and 23.1% in the adapted dose group. In both groups a similar number of high grade events was reported, 19/114 in the standard dose group and 18/229 in the dose adapted group. Ultimately, 7 patients (6.4%) of the dose adapted group were reduced to standard dose because of toxicity, and in 3 (2.7%) patients ICI treatment was discontinued. In the standard dose group a total of 10 patients (12%) were discontinued from treatment due to toxicity. Short-term treatment interruption occurred in 11 (13.2%) patients receiving standard dose and in 15 (13.9%) patients who received the adapted dose. **Conclusion:** In the adapted dose group low grade adverse events were observed more frequently compared to the standard dose group. During dose escalation, however, there was no increase in toxicity leading to dose reduction and/or discontinuation of treatment compared to the standard dose group. Based on this data, ICI dose adaptation seems a save strategy to decrease the number of visits to the oncology unit during the COVID-19 pandemic. Limitations of this analysis include its retrospective character and potential reporting bias, especially of low-grade adverse events in the adjusted dose group.

Keywords: covid-19, immune checkpoint inhibitor, NSCLC

OA02 CONTEMPORARY APPROACHES TO SUPPORTIVE CARE
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

OA02.01 Assessment of Patient-Reported Outcomes in Lung cancer Patients Treated with Thoracic Radiation

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Introduction: Patient reported outcomes is limited in Chinese lung cancer patients with radiation therapy (RT) to thorax. The purpose of this study is to investigate Patient Reported Outcome Measures (PROM) at baseline and end for RT in lung cancer patients receiving RT to thorax. **Methods:** This is a prospective study of quality of life. Lung cancer patients ≥ 18 years old requiring RT to thorax were eligible. [Office1] The PROM was assessed by self-administrated questionnaire PROMIS-29 Profile v2.1 and was completed prior to and at end of RT. Raw scores directly got from the PROMIS questionnaire were translated to T-scores according to the recommendation by the PROMIS INSTRUMENTS. A T-score of 50 is the average for general population and a higher PROMIS T-score represents more of the concept being measured. [Office1]Can be shortened as Patients received external brain radiation was eligible. **Results:** Between July 2019 and December 2020, a total of 22 patients enrolled and had completed PROMIS questionnaire at both baseline and end of RT. The median age was 64 (range 34-82), nineteen were men. There was 18 and 4 non-small cell lung cancer and small cell lung cancer, respectively. Ten (45.5%) had concurrent chemotherapy and 12 (54.5%) had RT alone. Ten (45.5%) received radical RT, eleven (50%) received consolidative or palliative RT and one (4.5%) received adjuvant RT. The median dose was 50Gy (range 20-60Gy). [Office1] For the seven domain teams, physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities and pain interference, the number of patients with each T-score greater than 50 was 11 (50.0%), 3 (13.6%), 3 (13.6%), 2 (9.1%), 6 (27.3%), 19 (86.4%) and 5 (22.7%) at baseline and 10 (45.5%), 3 (13.6%), 1 (4.5%), 4 (18.2%), 7 (31.8%), 17 (77.3%) and 7 (31.8%) at end of RT, respectively. None of the 7 domain teams' T-scores changed significantly at end of RT (Paired t-test). Pain intensity evaluated by NRS increased significantly (mean 0.77 vs 1.95, P=0.012, paired t-test). [Office1]You can remove this as needed for space saving **Conclusion:** This preliminary study demonstrated that despite the increased pain, thoracic RT did not significantly affect the quality-of-life in lung cancer patients.

Keywords: thoracic radiation therapy, patient-reported outcomes, lung cancer

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OA02.02 Development of Machine Learning Model to Estimate Overall Survival in Patients with Advanced NSCLC and ECOG-PS > 1

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Introduction: An accurate prognosis of patients (pts) with metastatic non-small cell lung cancer (mNSCLC) is crucial for treatment planning, early palliative care, quality of life improvement, and better resource allocation. Thus, our goal is to find a model to predict the 90-day survival rate of mNSCLC pts with ECOG-PS > 1. **Methods:** We collected 106 pts diagnosed with histologically proven, treatment-naive, mNSCLC (TNM 8th ed.) in a prospective, single-center, cohort study (Nov/17 – Jan/21). The 55 studied baseline features comprised the following information: demography, histology, metastatic sites, presence of EGFR activating mutations; nutritional status and body composition; medical history, smoking status, PS (ECOG and Karnofsky scales); symptoms and Edmonton Symptom Assessment System (ESAS); strong opioid use and oxygen supplementation; global quality of life score (EORTC QLQ C30), palliative scores (PPS and PaP), and laboratory values. We randomly split patients 100 times into different versions of training (n = 60), test (n = 26), and validation (n = 20) groups. We used the synthetic minority oversampling technique to balance the training groups artificially to improve the models' accuracy. We selected five sets of features associated with overall survival ≤ 90 days by analyzing each version of training and test groups through five feature selection models: Random Forest (RF), Extreme Gradient Boosting (XGB), Analysis of Variance (ANOVA) F-Score, Recursive Feature Elimination with Cross-Validation fitted with a Support Vector Machine (RFECV), and L1-penalized Cox regression. For classification, we used all 100 training and test groups to fit five machine learning models: RF, K-next-neighbors (KNN), XGB, linear regressor (LR), and a Voting Classifier (Ensemble) fed by the other models' predictions. We assessed the performance of the feature selection method and classification model combinations by the mean C-statistic of the prediction of the 100 validation groups. We considered a p-value threshold of 0.05 as statistically significant. **Results:** Of 106 pts, the median (interquartile range [IQR]) age was 66 y.o. (59-71), 45% were male, 65% were Caucasian, and 84% smokers (41 p-y [20-60]). We detected EGFR activating mutations in seven pts (7%). Median overall survival was 64 d (29-180), and 60 pts (56%) lived at least 90 d. We used the following features: PaP score, Karnofsky performance scale, oxygen supplementation, strong opioid need, symptoms (constipation, dry mouth, and mMRC scale), physical functioning, BMI, 6-month weight loss, hematocrit, neutrophil and leukocyte count, visceral, and subcutaneous adipose tissue content. All combinations of feature selection and classification showed statistically significant results (p-values ranged from 0.0025 to 0.0425), with mean C-statistic ranging from 0.6991 to 0.8097. The best-performing combination was the XGB feature selection and Ensemble classification (C-statistic 0.80965, p-value 0.0025). **Conclusion:** Machine learning-assisted survival assessment shows potential benefits in prognostic evaluation of mNSCLC. The pragmatic approach to feature selection identified poorer patient performance status, higher tumor-associated inflammation markers, and cachexia as negative prognostic indicators. Model adjustments with larger data sets and external validation are necessary to improve our model's accuracy before its use in the clinical setting.

Keywords: Artificial Intelligence, Palliative care, Decision Support Techniques

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OA02.03 Medical Assistance in Dying (MAiD) in Patients With Lung Cancer

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Introduction: On June 17th 2016, legislation was introduced in Canada allowing people with a "grievous and irremediable" medical condition access to an assisted death. Cancer accounts for 60-65% of MAiD deaths. Lung cancer, as the most common cause of cancer death (26% of all cancer deaths), is expected to make up a large proportion of MAiD cases. Prior studies suggest most patients are engaged with palliative care services leading up to MAiD, however involvement of oncology specialists and use of systemic and radiation therapy is unknown. The field of lung cancer has advanced significantly in recent years, with emphasis on immunotherapy and targeted therapy, making treatment both more effective and more tolerable. Oncologists are in a key position to provide patients with adequate information on their treatment options during the process of making an informed decision about MAiD. We performed a review of all patients with lung cancer who underwent MAiD at our centre to identify the demographic and treatment factors in this population and identify any gaps in our current system of care delivery. **Methods:** A review was completed of all patients with cancer referred to the Ottawa Hospital MAiD program from April 1 2019 – November 30 2020. This program provides the majority of MAiD services in the Champlain Local Health Integration Network, covering a population of 1.3 million people. Cases were filtered to identify those with lung cancer as the condition leading to MAiD request. Baseline demographics, diagnostic information, and treatment details were collected by retrospective review. **Results:** During the study period, 172 patients with cancer underwent MAiD. Of these, 29 (17%) had lung cancer, comprising our final study population. Median time from diagnosis to death was 20.4 weeks (range 3 – 421 weeks). Median age at diagnosis was 72, 59% female/41% male. Most patients had non-small cell lung cancer [adenocarcinoma 18(62%) / squamous cell carcinoma 4(14%) / NSCLC not otherwise specified 2(7%)], with only 1 case of small cell carcinoma. Four patients had a clinical diagnosis of lung cancer without a confirmatory biopsy. Twenty-five (86%) patients were evaluated by a medical oncologist. 12(41%) received at least 1 line of systemic therapy, and 19(66%) received radiotherapy. In 8 patients with NSCLC and PDL1>=50%, 4 (50%) received immunotherapy. Reasons for not receiving immunotherapy included poor performance status, patient decision, and lack of medical oncology consultation. Among patients with adenocarcinoma, 4 had an oncogenic driver mutation, and all received targeted therapy at some point in their disease course. Sixteen (55%) patients had a documented discussion with their oncologist regarding the transition to best supportive care prior to MAiD. **Conclusion:** Patients with lung cancer make up a smaller proportion of cancer-associated MAiD cases compared to population lung cancer death rates. An especially low rate of SCLC was seen. Most patients were assessed by an oncology specialist, though less than half received systemic therapy. Given the growing number of efficacious and well-tolerated treatment options in lung cancer, consultation with an oncologist may be reasonable to consider for all patients with lung cancer who request MAiD.

Keywords: lung cancer, medical assistance in dying, end of life care

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OA02.04 Phase II Trial of Antiemetic Oral Granisetron Plus Dexamethasone for Nausea and Vomiting Caused by Crizotinib in ALK or ROS1 Fusion-Positive NSCLC

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Introduction: Crizotinib is an ATP-competitive small-molecule inhibitor of the receptor tyrosine kinases ALK, ROS1, and C-Met, that show marked antitumor activity for ALK/ROS 1 fusion or MET exon 14 skipping mutation-positive NSCLC. However, crizotinib is associated with a high incidence of certain adverse effects, such as grade-1 or greater nausea (52%–58%) and vomiting (39%–44%) with median time to first onset of 2 d that frequently leads to treatment interruption. Further, crizotinib caused nausea and vomiting in 73% and 65% of the Japanese population, respectively. The optimal prophylactic regimen for crizotinib has not been established. We conducted this phase II trial to evaluate the efficacy and safety of a double combination antiemetic therapy with oral granisetron plus dexamethasone for nausea and vomiting caused by crizotinib in patients with ALK or ROS1 fusion-positive NSCLC. **Methods:** Patients with ALK or ROS1 fusion-positive NSCLC who were scheduled to recieve crizotinib were enrolled. Patients received oral granisetron at a dose of 2 mg (day 1–5) plus oral dexamethasone at a dose of 8 mg (day 1) with crizotinib treatment. The events of nausea, vomiting, and using rescue treatment were recorded in each phase [acute (first 24 h), delayed (24–120 h), overall (0–120 h), and long term (day 1–day 14)]. The primary end point was the complete response (CR; no emetic events and no rescue medication) rate in the overall phase. The secondary endpoints were CR in long term phase, complete control (CC) in each phase, total control (TC) in each phase, and safety. A CR rate of 65% would indicate potential usefulness, while a rate of 40% would be the lower limit of interest, with one sided $\alpha = 0.05$ and $\beta = 0.20$. **Results:** From September 2015 and March 2020, 25 patients were enrolled from 7 institutions. Patients characteristics were as follows: median age (range): 66 (41–88) y; women, n = 15 (60%); ROS1 fusion, n = 4 (16%), and history of motion sickness, n = 2 (8.0%). The CR rate in overall phase was 80.0% (90%CI, 62.5–91.8); the lower limit of 90% confidence interval exceeded the predefined threshold. Further, the CR rate in long term phase was 60% (95%CI, 38.7–78.9), suggesting that short-term oral administration of granisetron plus dexamethasone achieved long-lasting control of nausea and vomiting caused by crizotinib. The CC rate and TC rate in overall phase were 80.0% (95%CI, 59.3–93.2) and 76.0% (95%CI, 54.9–90.6), respectively. The most common adverse event (AE) of any grade was constipation (76.0%) followed by visual disorder (28.0%) and insomnia (24.0%). No grade-4 AEs and treatment-related deaths were observed. **Conclusion:** The double combination of oral granisetron plus dexamethasone is the valid prophylactic regimen for nausea and vomiting caused by crizotinib in patients with ALK or ROS1-positive NSCLC. Clinical trial information: jRCTs031180378.

Keywords: crizotinib, chemotherapy induced nausea and vomiting, supportive care

OA03 NOVEL APPROACHES TO CESSATION IN CANCER CARE
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OA03.01 Implementation of an Opt-Out Smoking Cessation Service for Oncology Patients

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Introduction: Cigarettes smoking is an important factor affecting lung cancer prognosis. This presentation describes implementation and enrollment in a opt out smoking cessation service for patients receiving care at oncology clinics affiliated with the Hollings Cancer (HCC) at the Medical University of South Carolina over a 6-month period between January and June 2020. **Methods:** Electronic health records of patients attending one of 30 different HCC clinics were scanned daily to identify patients who currently smoke cigarettes. Current smokers not already enrolled in the smoking cessation service in the prior 6-months were referred to tobacco treatment specialist TSS who attempted to call patients at home and offer them smoking cessation support. The service offered patients an opportunity to receive a series of free tele-counseling calls and access to a two-week starter kit of nicotine replacement therapy (NRT). Patients requiring additional stop-smoking medications were referred to the HCC pharmacist. A random sample of patients eligible for the service were identified to receive a brief 10-minute phone follow-up survey 6-9 later. The follow-up survey asked patients general questions about their overall satisfaction with care at HCC and information about their tobacco use behaviors (smoking status, quit attempts and methods used to try to stop smoking) over the previous 6-9 months. Participant in the follow-up survey received a $10 gift card to compensation for their time doing the phone survey **Results:** Between January and June of 2020, 31,420 adult outpatients were seen in HCC clinics of whom 2904 (9%) were identified as current cigarette smokers; 1248 (43%) of whom were eligible for the smoking cessation service. About 17% of patients seen in HCC have a diagnosed cancer. Many of the patients seen in these clinics were receiving cancer screening; all current smokers were eligible for the stop smoking service. Of those eligible for the service 680 (54%) were reached by TTS, of whom 57% (n=389) enrolled in the tele-counseling program, 211 (31%) opted out, and 80 (12%) reported that they had already stopped smoking and did not need the service. Follow-up surveys were attempted on 382 patients, of whom 221 (58%) completed the survey. Of those who completed the survey, most had made a quit attempt in the prior 6-9 months period, 69 (31%) reported not smoking, 95 (43%) reported having used a stop-smoking medication in the past 6-9 months. Those who enrolled in the tele-counseling service were more likely to have made a quit attempt (Prevalence Ratio =1.2; 95% CI=1.04-1.38), and report using stop-smoking medications (Prevalence Ratio =1.2; 95% CI=1.04-1.38) compared to those who opted-out of the service or never were reached for enrollment. **Conclusion:** Patient acceptance of an opt-out tele-counseling smoking cessation service was good and was associated with more quit attempts and greater likelihood of using stop smoking medications during quit attempts.

Keywords: Smoking Cessation, Telehealth, clinical care

OA03 NOVEL APPROACHES TO CESSATION IN CANCER CARE
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OA03.02 Tobacco Cessation Among Patients Undergoing Lung Cancer Screening: Success with Repetition

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Introduction: Lung cancer screening provides an opportunity for clinicians to captialize on a "teachable moment" for patients who continue to smoke. Limited data remain on the impact of lung cancer screening (LCS) on tobacco cessation. It is widely known that there is a relationship between intensity of counseling as well as frequency of counseling sesssion and tobacco cessation rates. However no data exists to describe the impact of repetative counseling over time in the lung cancer screening trajectory of current smokers. This study aims to identify tobacco cessation and cut back rates among a cohort of patients, who were current smokers at the inital visit, undergoing LCS over the course of at least three years. Evaluation of timing of quit in patient who adhere to lung cancer screening will be described. **Methods:** Data were collected between 2013 and 2018 among 254 patients undergoing lung cancer screening who identified themselves as "current smokers". Tobacco cessation rates were defined as self-reported abstinece for at least 6 consecutive months after the beginning of cessation and was idetified as Quit Rates (QR). Cut back rates (CBR) were defined as self-reported reduction in smoking frequency in those continuing to smoke by at least one cigarette daily for at least 6 consecutive months. Positive change rates (PCR) were the combination of quit rates and cut back rates in the patient population described. QR, CBR and PCR were evaluated at annual LCS intervals. QR, CBR and PCR were calcuated for each year of screening. Additional data was collected through 2020 for smoking status in cohort with additional 50% of patients who were identified as in CB group moving to quit groups. **Results:** Patients ranged in age 50 - 77 with 52% male/48% female. Average pack years: 50.7. The QR within the first 2 years of screening were 29.5%(n=75), CBR were 9.44%(n=24) and PCR were 38.98%(n=99). Although PCR were 38.98%, 90% of patients expressed willingness to decrease frequency of smoking at visit one. When addiitonal analysis was conducted through 2020, 90% of patients in the Quit group remained tobacco free and 50% in the Cut Back group had progressed to quit. **Conclusion:** Certified lung cancer screening programs are required to provide tobacco cessation(1). The details of what should be included however are vague. Current data on tobacco cessation rates among patients undergoing LCS has been reported to be 10-13%(2). This retrospective review reports higher cessation rates, potentially attributed to extensive cessation counseling at the time of CT results. This tobacco cessation study considered CBR and PCR as vital data in this patient population. Additional analysis of this patient group idenitifed that patients in the CBR group progressed to quit groups in 50% of the cases indicating that CBR and PCR are suggestive of future quit success. We propose that CBR and PCR be strongly considered in future reviews given the well described relationship between frequency of smoking and disease burden. The study is limited by self-reported cessation and lack of randomization. Further research is warranted.

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OA03.03 Patient Factors Associated With Engagement of an Academic Institution Tobacco Cessation Referral Program

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Introduction: Tobacco cessation is a critical but challenging intervention for cancer patients. We sought to identify patient specific factors associated with engagement with tobacco cessation efforts during cancer treatment within a National Cancer Institute (NCI) designated comprehensive cancer center **Methods:** Our tobacco cessation program was established in July 2019 and consisted of entirely remote cessation services provided by a certified tobacco cessation specialist including counseling, assessment of pharmacotherapy suitability, quit-line referrals, and SMS texting services. Baseline patient demographic data was captured for all patients, including age, gender, race, marital status, insurance provider, education level, religious affiliation, mental health diagnosis, and the median income of their documented ZIP code. Univariate logistic regression was performed, and factors that were significant for patient participation at an alpha of 0.2 were used. A multivariate logistic regression was performed adjusting for gender, race, marital status, and age. Alternatively, the backward elimination approach was utilized to select variables associated with referral acceptance. **Results:** From 7/2019 – 2/2021, 169 patients were referred for tobacco cessation services by their oncology care teams. Eighty-two agreed to participate in the program (48.5%). Of 169 patients, 92 were male (54.4%) and 77 were female (45.6%). The median age was 61 years old. The majority were Caucasian (54.4%), followed by African American (39.1%), and other races (6.5%). The majority (40.2%) were married, 32.6% were single, 14.2% were divorced, 8.3% were widowed, and 4.7% had unknown marital status. The majority had a religious affiliation (42%), 50 did not identify as being religious (29.6%), and 48 had unknown religious affiliation (28.4%). The majority of patients had private insurance (56.2%), followed by Medicare (25.4%), Medicaid (13.7%), or were uninsured (4.1%) or had unknown insurance (0.6%). Most patients (70.4%) lived an area with a median annual income of $40,000- $75,000, followed by over $75,000 (20.1%), less than $40,000 (8.3%), and 2 patients lived an area of unknown annual income (1.2%). There were 18 patients (22%) out of the 82 patients engaging with cessation services that had documentation of complete tobacco cessation, with 61.1% of patients who quit actively using pharmacotherapy. On multivariate logistic regression, Caucasian race as compared to other races was found to be statistically associated with referral acceptance (OR=0.45, p=0.026). Using backward elimination approach, married patients were more likely (OR= 1.36) and single patients were less likely (OR= 0.42) compared to widowed patients to accept a referral (p=0.038). **Conclusion:** Active engagement with tobacco cessation programs during cancer treatment remains challenging, with only 48% of referred patients actively engaging with cessation services. Married and non-Caucasian patients were more likely to use tobacco cessation services. Further interventions are needed to engage cancer patients around tobacco cessation, including unmarried and Caucasian populations.

Keywords: tobacco, cessation, interventions

OA04.01 Preconditioning with Move for Surgery Shortens Hospital Stay after Lung Cancer Surgery

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Introduction: Preconditioning before surgery can lower complication rates post-surgery, and hence shorten the length of stay (LOS) in hospital. However, there are significant barriers to the adoption of preconditioning in the lung cancer population, which is characteristically older, suffers multiple comorbidities, and is averse to exercise. In an effort to overcome these barriers, we designed Move For Surgery (MFS), a home-based, 3-4 week preoperative preconditioning program intervention for thoracic surgery patients which involves aerobic exercise using wearable technology and deep breathing exercises, and compared it to the usual preoperative standard of care (Control) through a prospective randomized controlled trial. **Methods:** Patients undergoing resection for early-stage NSCLC were preoperatively enrolled and randomized to either MFS or Control in a 1:1 allocation ratio. Those in MFS were provided with a wearable activity tracker and a booklet describing various aerobic and deep breathing exercises, and nutritional and smoking cessation tips and underwent the intervention, whereas those in the Control underwent usual preoperative care. The daily step count, sleep cycle, and calories burned were synced and tracked remotely. Daily step goals were set by increasing the participants' baseline step count by 10% each week until the day of surgery. Participants were encouraged and motivated to reach their daily step goal by daily automatic reminders through the wearable activity tracker. Participants completed the EQ-5D-5L health-related quality of life instrument at baseline and day of surgery. Data is presented as mean ± SD and median (range). Continuous variables were compared using Student's t-test, and categorical variables were compared using Chi-square test, with a level of significance $p<0.05$. **Results:** Of the 117 patients screened, 87.18% (102/117) were eligible and 93.14% (95/102) completed the trial. The median age was 68 (45-87) and 57.89% (55/95) were women. The mean predicted FEV1 and DLCO were 88.92% ± 17.05% and 77.11% ± 17.62%, respectively. There were significantly more women in MFS than Control ($p=0.04$), otherwise there were no other statistically significant differences between the groups' baseline demographics. LOS in hospital after surgery for MFS and Control were 2.67 ± 1.61 and 4.44 ± 3.48 days ($p=0.002$), respectively. Significant improvement was seen in the overall health component of the EQ-5D-5L health-related quality of life instrument from before MFS (69.38 ± 17.11) to after (79.60 ± 11.63; $p<0.001$). **Conclusion:** MFS significantly shortened LOS in hospital post-surgery when compared to usual preoperative care and resulted in improved patient-reported quality of life.

Keywords: Preconditioning, thoracic surgery, Randomized Controlled Trial

OA04.02 Diaphragm and Phrenic Nerve Preservation During Lung-Sparing Surgery for Malignant Pleural Mesothelioma: The Impact on Patient Outcomes

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Introduction: Lung-sparing surgery for malignant pleural mesothelioma (MPM) is associated with a difficult and prolonged recovery due to the extensive nature of the procedure. For a select group of patients, prolonged survival rates have been reported. A clear understanding of which patients will benefit from lung-sparing surgery is currently unknown. Despite having favorable tumor histologies, limited tumor burden and being deemed physically fit for surgery, some patients will still experience increased morbidity and/or mortality. These unfavorable outcomes will either delay or prevent a patient from receiving adjuvant treatments which ultimately negatively impacts their overall survival. By gaining a better understanding of the impact lung-sparing surgery has on a patient's functional capabilities and health-related quality of life, surgical teams will be better able to identify appropriate surgical candidates, prepare them for surgery, support them through their recovery and ultimately improve their survival, quality of life and lived experience. (Updated Abstract - previously presented as a Poster Presentation @ iMig2021) **Methods:** A retrospective review of 54 patients with MPM from 2015-2020 was performed. Physical functional performance in this cohort was measured using the Eastern Cooperative Oncology Performance Status Scale (ECOG). Post-operative patient outcomes were measured by tumor volume, chest tube days, ventilator days, hospital length of stay, percent of diaphragm preserved and phrenic nerve preservation. **Results:** Statistical analysis identified that preoperative ECOG status was a significant predictor of patient outcomes. Prolonged hospital length of stay (> 14 days) and more days on the ventilator (> 59 days) were seen for those with ECOG = 1 vs. those with ECOG = 0, p-values are 0.02 and 0.03, respectively. The higher percentage of diaphragm preservation showed a trend toward to shorter hospital length of stay ($p = 0.10$), days on the ventilator ($p = 0.08$) and the number of chest tube days ($p = 0.09$). Neither tumor size nor phrenic nerve preservation impacted patient outcomes. **Conclusion:** Analysis of the data generated from this study will serve as the foundation for continued research aimed at improving patient selection, decreasing symptom burden, improving functional capabilities and optimizing both health-related quality of life and patient experience. Knowing who will benefit from surgery and who will not benefit from surgery is a critical and currently unanswered question that multidisciplinary thoracic oncology teams ask every day. Our hope is that the results of this research will one day help teams to answer this question using scientific evidence to guide and support their decisions and recommendations.

Keywords: mesothelioma, surgery, functional measures

OA04.03 Feasibility of Prospective Dietetic Assessment and Intervention of Patients Receiving Chemo-Radiotherapy for Lung Cancer

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Introduction: Chemo-radiotherapy for lung cancer can be a morbid treatment, often in an older and co-morbid population. Our patients are not routinely seen by a dietitian. **Methods:** As a pilot project, all patients receiving either sequential or concurrent chemo-radiotherapy for lung cancer between May and November 2020, were identified by the lead lung radiographer and bookings team and referred to a specialist oncology dietitian. These patients were offered up to 3 routine fortnightly assessments on treatment. We recorded their symptoms (based on a standardised tool, PG-SGA) and weight during treatment. **Results:** 15 patients were referred to the dietitian: 7 male, 8 female. All patients accepted dietetic review. The median age was 64 years old; mean age 63 years old (range 50-79). The mean average number of cycles of chemotherapy was 3.4. Concurrent chemo-radiotherapy was given to 11 patients, with the remaining 4 having sequential treatment. Of all patients, 1 had small cell lung cancer, 1 had a mixed adenocarcinoma and small cell. The remaining 13 were non-small cell lung cancers, and of these 6 were adenocarcinomas and 6 were squamous cell carcinomas and 1 mixed histology. All patients were reviewed at least twice whilst on treatment. The most complete data was for the review in weeks 3/4 of radiotherapy. All 15 patients had scores for this time point. Mean number of symptoms was 5.5 (range 3-9). The commonest symptoms were fatigue (100%), loss of appetite (67%), pain (67%) and dysphagia (60%). For 12 patients receiving 6 weeks of radiotherapy median symptom number increased from 5 in 1st 2 weeks, to 5.5 in weeks 2nd 2 weeks, to 6.5 in final 2 weeks. All patients in this group lost weight. Median weight loss during treatment was 6.6% (range 1.8-15.9%). All patients received food fortification advice throughout their treatment and advice on symptom management. The symptom management advice for 12 of the 15 patients either reinforced advice, or, made adjustments to the timing of medications prescribed by medical or nursing staff. The other 3 patients did not have an existing prescription, and so recommendations were made of medications to manage symptoms, e.g. oxcetacaine, anti-emetics and laxatives. Oral nutritional supplements (ONS) were recommended if patients were not meeting their estimated nutritional requirements from dietary assessment. Seven patients received ONS prescription in addition to the food fortification advice. One patient declined an ONS prescription. **Conclusion:** 1. Routine dietetic review during radical chemo-radiotherapy is feasible and occurred successfully during the COVID-19 pandemic. It led to some simple, but vital changes in practice such as weekly weighing of patients on treatment 2. Patients undergoing chemo-radiotherapy have a high symptom burden. 3. All patients receiving 6 weeks of radiotherapy lost weight during treatment. 4. We received positive feedback from patients.

Keywords: Dietitian, radiotherapy, Dietician

OA05 PALLIATIVE CARE SERVICE MODELS
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OA05.01 Impact of an Embedded Palliative Care Clinic on Healthcare Utilization for Patients With an Advanced Thoracic Malignancy

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Introduction: While early palliative care is beneficial for patients with advanced cancer, the best method of palliative care delivery is unknown. We investigated healthcare utilization before and after embedding a palliative care clinic within a thoracic medical oncology clinic. **Methods:** This is a retrospective cross-sectional cohort study comparing healthcare outcomes in the "pre-cohort," 12 months prior to an embedded palliative care clinic and the "post-cohort," a 12-month period beginning 5 months after the embedded clinic start date of 9/1/2018. Patients were included if they had a new or established diagnosis of advanced thoracic cancer, received treatment at an academic medical center, had not been seen in the clinic in the previous year, and had at least 2 separate thoracic oncology clinic visits. During the pre-cohort time period, access to palliative care was available at a stand-alone palliative care clinic (2 miles away). Outcomes evaluated included rates of emergency department (ED) visits, hospital admissions, 30-day readmissions, and intensive care unit (ICU) admissions. Estimates were calculated in rates per-person-years and Poisson regression models with robust standard errors and time as an offset were used for statistical analyses. **Results:** The pre-cohort included 454 patients and the post-cohort included 468 patients. Among all patients, 52% were male and 48% were female with a median age of 65 years (range 23-92). Treatment received included chemotherapy (34%), radiation therapy (23%), immunotherapy (20%), and surgery (4%). The post-cohort had a 15% reduction in ED visits compared to the pre-cohort, controlling for age, race, marital status, sex, metro size, cancer type, and comorbidities (Adjusted relative risk: 0.85, 95% CI: 0.69, 1.03,Table
1).

Table 1: Healthcare utilization by cohort

		Number of events	Total person-years of exposure	Events per-person-year (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI) [1]
ICU admissions	Pre	65	171.6	0.38 (0.29, 0.48)	Reference	Reference
	Post	60	171.8	0.35 (0.27, 0.45)	0.92 (0.63, 1.36)	0.84 (0.56, 1.26)
ED visits	Pre	411	171.6	2.39 (2.17, 2.63)	Reference	Reference
	Post	370	171.8	2.16 (1.94, 2.39)	0.90 (0.74, 1.10)	0.85 (0.69, 1.03)
Hospital admissions	Pre	597	171.6	3.47 (3.20, 3.76)	Reference	Reference
	Post	584	171.8	3.40 (3.13, 3.69)	0.98 (0.84, 1.14)	0.95 (0.82, 1.11)
30-day readmission[2]	Pre	105	17.0	5.40 (4.42, 6.54)	Reference	Reference
	Post	98	19.4	5.77 (4.68, 7.03)	1.07 (0.79, 1.44)	0.92 (0.79, 1.09)

[1] Adjusted for age, race, marital status, sex, metro size, comorbidities, and cancer type.

[2] Individuals had at most 30-days of risk of a hospital readmission after each hospital admission.

* All p-values > 0.05.

Conclusion: Embedding palliative care clinics within medical oncology clinics may decrease healthcare utilization, particularly ED visits, for patients with advanced thoracic malignancies.

Keywords: palliative, embedded

OA05.02 Acceptability of Automatic Referrals to Supportive and Palliative Care, by Patients Living with Advanced Lung Cancer: A Co-Design Process

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Introduction: People living with advanced lung cancer often experience high symptom burden and emotional distress. Over a decade ago, a randomized controlled trial demonstrated that patients with metastatic non-small cell lung cancer who received early palliative care (PC) lived longer and had significantly improved quality of life and mood. Nevertheless, timely access to supportive and PC services remains a challenge. Barriers to accessing PC services include stigma around PC, and inconsistences in clinician referrals due to competing tasks and varied education, experience, interest, and understanding of palliative care. A proposed solution is to trigger an automatic referral process to PC by pre-determined clinical criteria, without the need for a formal clinician referral. However, patient acceptability of automatic referrals is unknown. To study whether an automatic process is acceptable, our group- Palliative Care Early and Systematic (PaCES), sought to co-design with patients and providers the operational processes and communication pieces for automatic PC referral for patients newly diagnosed with stage IV lung cancer. **Methods:** In Step 1 of this work, nine semi-structured one on one phone interviews were conducted with advanced lung cancer patients on their perspectives on the acceptability of phone contact by a specialist PC provider triggered by an automatic referral process. Interviews were thematically analysed using Sekhon's Theoretical Framework of Acceptability as a guiding framework for analysis. Step 2: Patient advisors, healthcare providers (oncologists, nurses from oncology and PC, clinical social worker, psychologist), and researchers were invited to join a co-design working group to develop and provide input on the operational and communication processes needed for the automatic referral process. Using the findings from step 1, the group developed the automatic referral process and met biweekly (virtually) over the course of 5 months. **Results:** From patient interviews, the concept of an automatic referral process and being phoned directly by a PC provider offering a consult was perceived to be acceptable and beneficial for patients with advanced lung cancer. Patients emphasized the need for timely support, access to peer and community resources. Patients also identified important components necessary for the automatic referral process such as the naming of the service, timing of the referral, and information needed from the phone call. Using these findings, the co-design working group identified the eligibility criteria for identifying newly diagnosed stage IV lung cancer patients using the cancer centre electronic health record, co-developed a telephone script for specialist PC providers, a patient handout about supportive care, and handout on supportive care resources. Additionally, interview and survey guides for evaluating the implemented automatic process were refined. **Conclusion:** A co-design process ensures stakeholders are involved in program development and implementation from the very beginning, to make outputs relevant and acceptable for stage IV lung cancer patients. The next phase of this work will use Sekhon's Theoretical Framework of Acceptability through mixed-methods to evaluate the acceptability of an automatic referral process from the perspective of the patients called and healthcare providers.

Keywords: stakeholder engagement, automatic referral, supportive care

OA05 PALLIATIVE CARE SERVICE MODELS
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

OA05.03 Onco-Pall Clinic: An Embedded Care Model for Thoracic Malignancy

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Introduction: Patients with advanced thoracic malignancies benefit from outpatient palliative care through symptom management, advance care planning, and goal-concordant care. Embedding a palliative provider within an oncology clinic may improve patient access to palliative resources. **Methods:** This is a single-center retrospective analysis of care access for patients with an advanced thoracic malignancy referred to an embedded thoracic onco-palliative clinic model. The total number of patients referred to outpatient palliative care were counted from September 2017-August 2019. Time intervals for pre- and post-intervention cohorts were defined as one year prior to and up to one year after opening of the embedded thoracic onco-palliative clinic, respectively. Time points collected in this study included date of initial medical oncology appointment, first ambulatory palliative referral order, and first outpatient palliative appointment. Patients were excluded from the study if time from first medical oncology appointment to outpatient palliative referral spanned the pre- and post-intervention time intervals or if the palliative referral was ordered after the post-intervention period. Calculated statistics include the completion rate of palliative referral, lag time to palliative clinic appointment, and the timing of palliative referral relative to first medical oncology appointment. Fisher's exact test was used for categorical variables and Wilcoxon rank-sum test was used for continuous variables. **Results:** Within the first year after opening, ambulatory palliative referrals increased by 137% (180 vs 76, respectively). For the pre-post comparison, 73 patients were included in the pre-intervention cohort and 97 patients were in the post-intervention cohort per inclusion criteria. After opening, more patients completed outpatient palliative referral (80.4% vs 69.9%) while median lag time from palliative referral order to palliative clinic appointment remained the same (15 days). Early palliative care referrals, defined as within 30 days of first medical oncology appointment, were higher in the post-intervention cohort (68.0% vs 47.9%).

Table 1: Ambulatory palliative referrals by cohort

	Pre-Intervention (n = 73)	Post-intervention (n = 97)	P-value
Palliative referral completion, % (n)	69.9 (51)	80.4 (78)	0.15
Lag time to palliative appointment in days, median (IQR)	15 (17)	15(20)	0.26
Palliative referral ordered within 30 days of establishing with medical oncology, % (n)	47.9 (35)	68.0 (66)	0.01
Palliative referral ordered same day as first medical oncology appointment, % (n)	31.5 (23)	38.1 (37)	0.42

Conclusion: An embedded onco-palliative clinic is an acceptable care model that can increase early referrals and improve patient access to outpatient palliative care concurrent with standard oncology care.

Keywords: palliative, thoracic, embedded

OA06 PROGNOSIS AND STAGING
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

OA06.01 Validation of the 8th Ed TNM: Invasive Size for Pathologic T Descriptor in Stage I-IIA Resected Nonmucinous Adenocarcinomas

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Introduction: After excluding a lepidic component, primary lung non-mucinous adenocarcinomas will fall into the same pathologic stages (p-stages) as pure invasive tumors with the same invasive size according to recommendations by the Eighth edition of the TNM staging system. The favorable survival for part lepidic tumors has raised the question whether they should be staged differently from purely invasive tumors lacking a lepidic component. We sought to investigate whether the presence or proportion of the lepidic component is associated with patient outcomes within the same p-stage according to invasive size. **Methods:** 1704 patients who underwent tumor resection for primary lung nonmucinous adenocarcinoma (p-Stages I-IIA) were analyzed. We compared disease-free survival (DFS), cumulative incidence of recurrence (CIR), and lung cancer–specific cumulative incidence of death (LC-CID) between patients whose tumors contained a lepidic component versus those without a lepidic component within each pathologic sub-stage. Multivariable Cox regression analysis (MVA) was used to quantify the relationship between the lepidic component and known high-risk clinicopathologic features. **Results:** We examined the association between different percentages of lepidic component and survival by DFS, CIR, and LC-CID. Stratification by 0%, ≤25%, ≤50%, and >50% showed the most pronounced difference in outcomes between patients with ≤25% and >25% lepidic component. However, after sub-stratification by pathologic stage according to invasive size, these differences were no longer observed, with isolated exceptions (DFS in p-Stage IA2, CIR in p-Stage IA1 and IA2, and LC-CID in p-Stage IA1). MVA for DFS, CIR and LC-CID revealed that lepidic component >25% in early stages was no longer statistically significant once adjusting for other high-risk factors (lymphovascular invasion, spread through air spaces). **Conclusion:** These data are supportive of the current TNM recommendation to use invasive size for the size T descriptor rather than proposing a different approach for early stage lung nonmucinous adenocarcinomas with a lepidic component. Although the presence of a lepidic component correlated with favorable prognosis in early stage nonmucinous lung adenocarcinomas, after adjustment for prognostically significant clinical and pathologic factors, the presence of a lepidic component was not an independent prognostic factor. Therefore, the current pathological T classification based on invasive size is adequate for predicting outcomes, without additional classification by lepidic component.

Keywords: Lepidic adenocarcinoma; staging; invasive size

OA06 PROGNOSIS AND STAGING
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

OA06.02 High-Grade Patterns Cause the Upstaging of Lung Adenocarcinomas From T1 to T2a: A Multicentric Analysis

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Introduction: In 2012, the IASLC/ERS/AJCC classification of lung adenocarcinoma identified different histological patterns, which own peculiar and well defined prognostic behaviors. More in details, the presence of micropapillary and solid adenocarcinoma patterns leads to worse survival and a significant higher tendency to recur. Moreover, to date, adjuvant therapy is usually offered in the majority of stage II patients and in high-risk stage IB patients. This study aims to assess the impact of pT descriptor combined with the presence of a high-grade component on long-term outcomes in early-stage lung adenocarcinomas. **Methods:** We retrospectively collected data of consecutive resected pT1-T3N0 lung adenocarcinoma from nine European centres. All patients with complete information regarding pathological stage and pathological description of different patterns were included. All patients were staged according to the eight edition of TNM. Patients must have undergone a radical resection of the tumor and lymphadenectomy. Open, Video Assisted (VATS) or Robotic Assisted (RATS) techniques were used according to surgeons' preferences. **Results:** Among 607 patients, the majority were male (54.5%) and receive a lobectomy (78.8%). At least one high-grade pattern was seen in 230 cases (37.9%), of which 169 solid and 75 micropapillary. We stratified patients by their T component and the presence of high-grade patterns: based on this stratification, T1a-b-c non-high-grade had a significant better survival compared to T1a-b-c high-grade (59.5 vs 56.2 months, p=0.020). Conversely, T1a-b-c high-grade and T2a non-high-grade had similar OS (56.2 versus 58.7 months, p=0.277). At multivariate analysis age and the T component stratified by high-grade patterns confirmed to be significant prognostic factors (p=0.002; HR 1.046 95% CI 1.017-1.075 and p=0.034; HR 1.089 95% CI 1.007-1.178 respectively). Regarding DFS, T1a-b-c with no high-grade component had a significant better DFS compared to T1a-b-c with high-grade pattern (p=0.034), while the latter's DFS was not significantly different to the T2a patients with no high-grade pattern (p=0.839). Univariate and multivariate analysis confirmed age and pathological T component as significant prognostic factors (p=0.020, HR 1.025 95% CI 1.004-1.047 and p<0.001; HR 1.123, 95% CI 1.059-1.192 respectively). We performed a propensity score matched analysis using as matching variables: gender, age, surgical approach (minimally invasive versus open) and pT factor. A total of 460 patients were included in the final analysis (230 for matched pairs). The analysis of this subgroup of patients confirmed the results found in the general cohort. T1 patients with no high-grade pattern had a significant better OS and DFS compared to those with a T1 with high grade pattern (p=0.024 and p=0.019 respectively), while no difference was seen when compared OS and DFS of T1 patients with high-grade component and T2a patients without high-grade component (p=0.661and p=0.890 respectively). Univariable and multivariable analysis confirmed the prognostic value of pT according to the high-grade component. **Conclusion:** Results of our study suggest that T1a-b-c lung adenocarcinoma presenting a high-grade pattern should be upgraded to T2a. The integration of these histological features in the TNM could better stratify patients according to their risk of recurrence. Concurrently, high grade T1a-b-c patients should be considered for adjuvant therapy since their higher prognostic risk.

Keywords: TNM staging, adenocarcinoma subtypes, Lung adenocarcinoma

OA06 PROGNOSIS AND STAGING
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

OA06.03 PL1/2 Status is Associated With Worse Survival in T2 Non-Small Cell Lung Carcinoma: Is There A Need for a New Subgroup in the T Classification?

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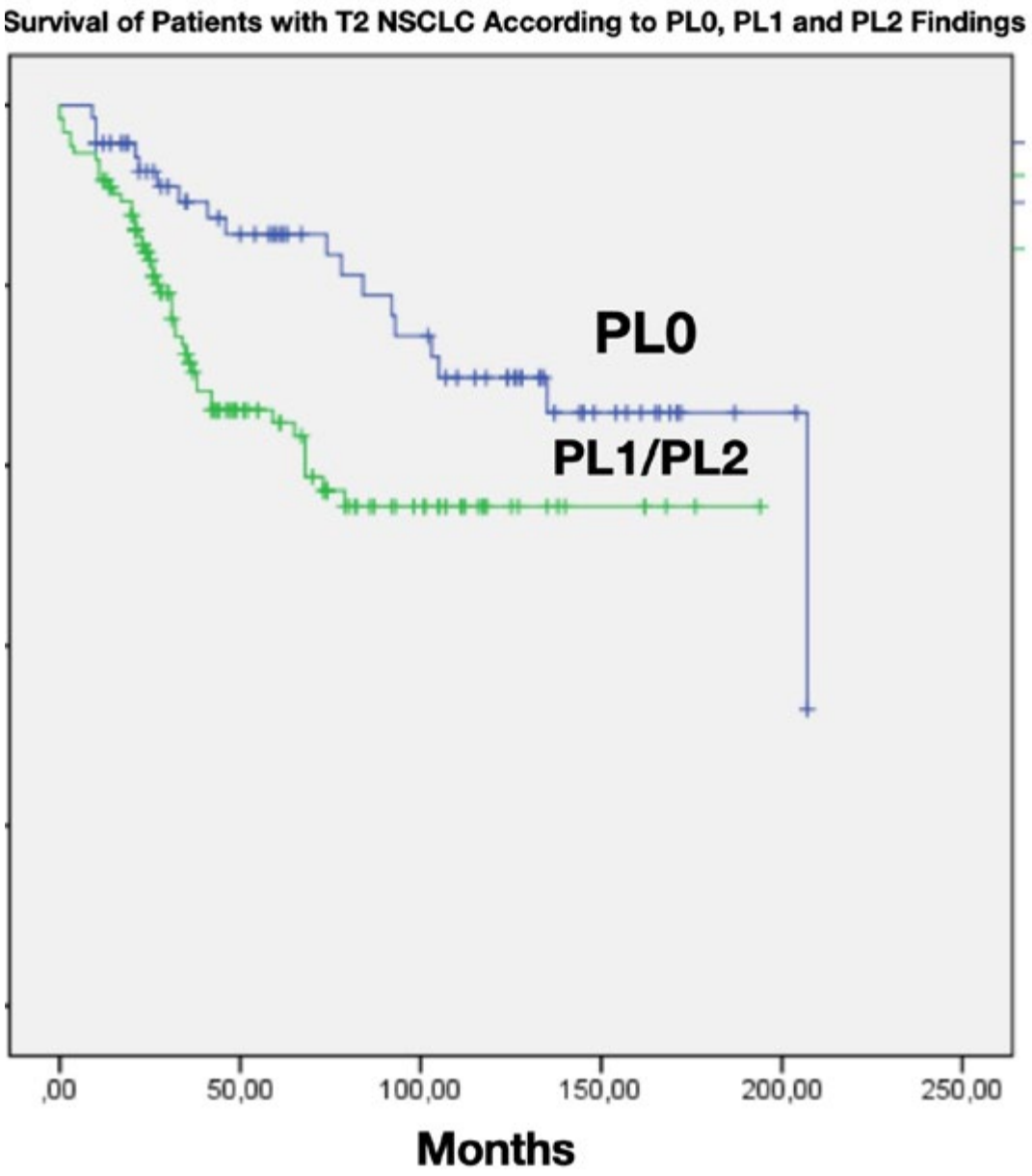
Introduction: In the current staging system visceral pleural invasion is well positioned as a T2 descriptor and confers a worse prognosis.Also, when the tumor diameter is between 3 and 5 cm it is staged as T2. Among T2 category, PL1 was defined as tumor invades beyond the elastic layer of the visceral pleura, whereas in PL2, tumor invades to the visceral pleura surface.Although those two subcategories represent same T2 grouping we aimed to analyze whether tumors with PL1 and PL2 involvement deserve another subgroup classification? **Methods:** Between 2003 and 2019, among 804 patients underwent resectional surgery for non-small cell lung cancer(NSCLC) and 203(25.2%) of the patients were considered to have T2 tumor. Among those PL1-2 reported in 132 patients (65.0%)(Group 1) and no pleural invasion(i.e.PL0) was disclosed in 71 patients(35.0) (Group 2). Patients were followed up at a mean of 38 months(1 to 164 months). Survival of patients were analyzed using Kaplan-Meier analysis, log-rank test and multivariate analysis was accomplished using Cox-analysis. **Results:** The patients with PL1/PL2 T2 tumor had a mean of 122 months (95% Confidence Interval: 106 to 138 months) of survival time whereas it was 159 months (95% CI: 140 to 179 months) in those with PL0 T2 tumor (p=0,016)(Figure). N factor, and presence of PL1/PL2 were found to be independently associated with survival(p=0.04 and 0.03 respectively).



Conclusion: PL1/PL2 involvement seems to be independently associated with worse survival and represents a different subgroup in patients with T2 NSCLC. It seems plausible to suggest that PL1-2 status could be considered as a new subgroup in T2 such as T2c.

Keywords: Staging, t factor, PL1/PL2

OA06 PROGNOSIS AND STAGING
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

OA06.04 Constructing a Global Molecular Database for Thoracic Malignancies: The IASLC Molecular Subcommittee Lung Cancer Dataset

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This abstract is under embargo until September 10 at 09:00 Mountain Time.

OA07 WHAT'S ON THE HORIZON FOR SCLC?
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

OA07.01 Signatures of Plasticity and Immunosuppression in a Single-Cell Atlas of Human Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy that includes subtypes defined by differential expression of ASCL1, NEUROD1, and POU2F3 (SCLC-A, -N, and -P, respectively), which are associated with distinct therapeutic vulnerabilities. The emerging consensus on SCLC subtypes has led to new questions, such as whether subtypes are associated with different disease stages, metastatic potential, or immune microenvironments; whether there is plasticity between subtypes; and whether novel SCLC phenotypes exist. Single cell RNA sequencing (scRNA-seq) offers a unique opportunity to address these questions by dissecting intratumoral transcriptional heterogeneity and the surrounding tumor microenvironment (TME). However, efforts to apply this technology to human SCLC tumors have been limited, as these tumors are infrequently resected. **Methods:** We have optimized protocols to process both surgical resections and biopsies to construct the first single-cell atlas of SCLC patient tumors (N=21), with comparative lung adenocarcinoma (LUAD) and normal lung data. We leverage computational methods including diffusion maps and non-negative matrix factorization to perform a deep annotation of SCLC phenotypes and the surrounding immune TME. We perform validation experiments using flow cytometry, Vectra, and immunohistochemistry in independent SCLC cohorts, as well as genetic manipulation in preclinical SCLC models. **Results:** Our data comprising the transcriptomes of 54,423 cells reveals substantial transcriptional heterogeneity in SCLC both within and across tumors and confirms a pro-metastatic gene program in SCLC-N subtype characterized by epithelial-mesenchymal transformation and axonogenesis. Beyond known subtypes, we discover a PLCG2-high tumor cell population with stem-like, pro-metastatic features that recurs across subtypes and predicts significantly worse overall survival. Manipulation of PLCG2 expression in cells confirms correlation with key metastatic markers. Treatment and subtype are associated with substantial phenotypic changes in the SCLC immune microenvironment, with greater T-cell dysfunction in SCLC-N than SCLC-A. Moreover, the recurrent, PLCG2-high subclone is associated with exhausted CD8+ T-cells and a pro-fibrotic, immunosuppressive monocyte/macrophage population, suggesting possible tumor-immune coordination to promote metastasis. **Conclusion:** This atlas of SCLC illustrates how canonical subtypes and a novel PLCG2-high recurrent tumor subclone enlist diverse gene programs to create tumor heterogeneity and facilitate metastasis in a profoundly immunosuppressed TME. Our dataset provides further insight into tumor and immune biology in SCLC at single-cell resolution, with potential implications for design of novel targeted therapies and immunotherapeutic approaches.

Keywords: Small cell lung cancer, Single cell sequencing, Transcriptional heterogeneity

OA07.02 TAZ Regulates SCLC Phenotypic Transition and Metastasis

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Introduction: Small cell lung cancer (SCLC) remains as the most lethal form of lung cancer with very poor prognosis. High metastatic capability and strong plasticity is the hallmark of SCLC. However, the exact cell subpopulation responsible for SCLC metastasis and critical regulators in contribution to SCLC plasticity still remain largely unclear. Growing evidence has revealed the importance of epigenetic reprograming during cancer malignant progression. Mammalian SWI/SNF complex BAF is an adenosine triphosphate (ATP)-dependent multi-component machinery, essential for remodeling chromatin architecture. Smarca4 (Brg1), the core ATPase component of BAF complex is preferentially required for the progression of SCLC with MAX (Myc-associated factor) inactivation. Also, it still remains elusive about the exact function of Brg1 and SWI/SNF complex in SCLC metastasis. **Methods:** Using the well-established $Rb1^{L/L}$/$Trp53^{L/L}$ (RP) mouse model, we here identify the $NCAM^{hi}CD44^{lo/-}$ subpopulation derived from RP model as SCLC metastasizing cells (SMC). Moreover, we find that the SMC is progressively transitioned from the $NCAM^{lo}CD44^{hi}$ cells (Non-SCLC metastasizing cells, Non-SMC) during malignant progression of SCLC. Through combined analysis of ATAC-seq and RNA-seq data of SMC vs. non-SMC, we observe a dramatic alteration in chromatin accessibility between these two subpopulations, and TAZ, the core transcription cofactor of the Hippo pathway, is epigenetically silenced by the SWI/SNF complex during SCLC malignant progression. Knockout of Brg1 in RP mouse promotes TAZ expression and abrogates the phenotype transition from Non-SMC to SMC and almost completely blocks SCLC metastasis. Allograft assay further confirms TAZ as the critical molecular switch during the phenotypic transition and SCLC metastasis. **Results:** In this study, we identify the $NCAM^{hi}CD44^{lo/-}$ subpopulation derived from RP model as SMC subpopulation, which is progressively transitioned from the Non-SMC during SCLC malignant progression. Through combined analysis of ATAC-seq and RNA-seq data, we observe a dramatic alteration in chromatin accessibility between these two subpopulations, which points to the alteration of SWI/SNF complex activation. We further find that genetic disruption of the SWI/SNF chromatin-remodeling complex through Brg1 knockout abrogates the phenotype transition from Non-SMC to SMC and blocks SCLC metastasis. Mechanistically, we find that TAZ, the core transcription cofactor of the Hippo pathway, is epigenetically silenced by the SWI/SNF complex. Down-regulation of TAZ promotes the transition from Non-SMC to SMC and facilitates SCLC metastasis. Conversely, ectopic TAZ expression or TAZ activation by digitoxin treatment reversibly promotes the transition from SMC to Non-SMC and thus alleviates SCLC metastasis. Importantly, the treatment of digitoxin, a clinically used drug for heart failure treatment, promotes TAZ activation and inhibits SCLC phenotypic transition and metastasis. Through the immunostaining analyses of 101 Chinese SCLC specimens, we further find that low TAZ expression significantly correlates with SMC features and poor patient prognosis. **Conclusion:** Collectively, these data uncover an important subpopulation in contribution to SCLC metastasis and highlights TAZ as the critical molecular switch in this process. Moreover, TAZ activation by digitoxin treatment provides an effective avenue to control SCLC phenotypic transition and metastasis, providing a potential therapeutic avenue for the metastatic SCLC management in clinic.

Keywords: SWI/SNF complex, TAZ, Small cell lung cancer

OA07.03 A Phase II Study of Frontline Rucaparib + Nivolumab in Platinum Sensitive ES SCLC: Interim Analysis

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Introduction: Immune checkpoint inhibitors (ICI) are part of standard of care frontline management of extensive stage small cell lung cancer (ES SCLC). However overall survival benefit by addition of ICI to frontline treatment of ES SCLC is modest and further improvement in treatment strategies are needed. We hypothesize that addition of poly (ADP-ribose) polymerase inhibition in platinum sensitive ES SCLC patients could improve antitumor efficacy of ICI. **Methods:** A single-arm, phase II trial (NCT03958045) enrolled patients with platinum sensitive ES SCLC who received Nivolumab 480 mg IV every 4 weeks, and Rucaparib, 600 mg PO twice a day. The primary outcome is median progression free survival. Secondary endpoint includes objective responses assessment and toxicity profile per CTCAE 5.0. Biomarker studies included pretreatment and during-treatment immune assay and circulating tumor DNA TP53 mutation status. **Results:** A total of 16 patients out of a planned total enrollment of 36 have been treated by April 7th, 2021. Median age was 62.5 years and all received at least 4 cycles of platinum doublet with at least a partial response (PR) by RECIST1.1at enrollment. Clinical benefit was observed in nine patients (56%; partial response 2 ,stable disease 7, progressive disease 7 per RECIST1.1). The median progression free survival (mPFS) is 2.8 months from time of enrollment on frontline maintenance (post platinum doublet). The Median mPFS is 7.4 months from time of diagnosis for our study cohort. Patients who did not progress at the time of analysis are still on active study treatment (n=5). The patient with longest active treatment is approaching 16 months of therapy. We expect to complete accrual and present updated efficacy and toxicity data at September meeting. **Conclusion:** In this interim analysis, 56% patients received clinical benefit. Of note, historical mPFS on frontline therapy with or without immune-checkpoint inhibitors ranges from 4-6 months. At this interim analysis, mPFS is 7.4 month from time of diagnosis. Selecting patients based on Platinum sensitivity is a promising approach for subsequent PARP inhibition/immune checkpoint maintenance in ES SCLC.

Keywords: PARP, Immunecheckpoint Inhibitor, SCLC

OA08 MOVING BEYOND NEW DRUGS: WHAT ELSE MATTERS?
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OA08.01 Trends in Within-Class Changes in US Prices of Drugs used for Metastatic Non-Small Cell Lung Cancer from 2015 to 2020

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Introduction: Several new therapeutics for treating metastatic NSCLC have come to market in the United States. While such increased competition might be expected to lower drug prices, policies promoting competition among brand-name drugs within the same class have not been associated with lower list prices.Here we report patterns in price changes for multiple brand-name medications within the same drug class for treating metastatic NSCLC. **Methods:** We conducted a cross-sectional study of average wholesale prices (AWPs) [for oral agents] and Wholesale Acquisition Prices (WAC) [for intravenous agents] in the US from August 13, 2015, to August 13, 2020, obtained from the Micromedex Red Book and Medi-Span database. We assessed the price in August of each year given most price changes stabilize during the time. AWP is the nationally recognized suggested wholesale price based on data obtained from manufacturers, distributors, and other suppliers. WAC is an estimate of the manufacturer's list price for a drug to wholesalers or direct purchasers but does not include discounts or rebates. We used AWP for oral agents since pharmacy benefit managers (PBMs) utilize this for reimbursing outpatient prescriptions. For intravenous medications, we selected the WAC as it is commonly used for hospital or clinic based administered medications. Multiple brand-name medications on the market contemporaneously in the following classes were assessed: immune checkpoint inhibitors (ICI), Epidermal Growth Factor Receptor (EGFR) inhibitors, and Anaplastic Lymphoma Kinase (ALK) inhibitors. Our primary outcome was the correlation in AWP/WAC unit prices among the multiple brand-name medications within each class available over time (measured using Pearson correlation coefficient). We additionally calculated compound annual growth rates (CAGRs) for brand-name medication costs within each class. CAGR denotes the mean annual growth rate of a drug over a specified period of time longer than one year. **Results:** The study included 4 ICIs (pembrolizumab, nivolumab, atezolizumab and durvalumab) , 5 EGFR inhibitors (Geftinib, Afatinib, Erlotinib, Osimertinib, and Dacomitinib), 5 ALK inhibitors (Crizotinib, Ceritinib, Alectinib, Brigatinib and Lorlatinib), and 2 BRAF (Dabrafenib, Vemurafenib) and 1 MEK inhibitor (Trametinib). The median (range) Pearson correlation coefficient values for drugs within each class were 0.964 (0.951-0.994) for ICIs, 0.898 (0.665-0.950) for EGFR inhibitors, 0.999 (0.982-0.999) for ALK inhibitors, 0.999 for BRAF/MEK inhibitors. A coefficient could not be calculated for therapies with 2 or fewer data points (dacomitinib, ceritinib, brigatinib, lorlatinib) or if prices did not change (vemurafenib). The median (range) CAGRs in costs over this 5-year period were: 1.81% (1.29%-2.13%) for ICIs, 2.56% (2.38%-5.26%) for EGFR inhibitors, 2.46% (1.75%-4.66%) for ALK/ROS inhibitors, and 3.06% (0%-3.06%) for BRAF/MEK inhibitors. Notably, decline in price occurred only in one instance for erlotinib between 2019 to 2020, correlating with introduction of generic competition to the market. **Conclusion:** Over the period studied, change in prices within drug classes correlated closely, with little price competition between manufacturers. The median change in drug costs for these lung cancer medications over this period outpaced that of other prescription drugs and the average inflation rate. There is an urgent need for reform in drug pricing for lung cancer therapeutic agents.

Keywords: non-small cell lung cancer, Economics, Drug Prices

OA08.02 First Line Treatment Patterns in Advanced NSCLC Patients With Compromised Performance Status or Comorbidities

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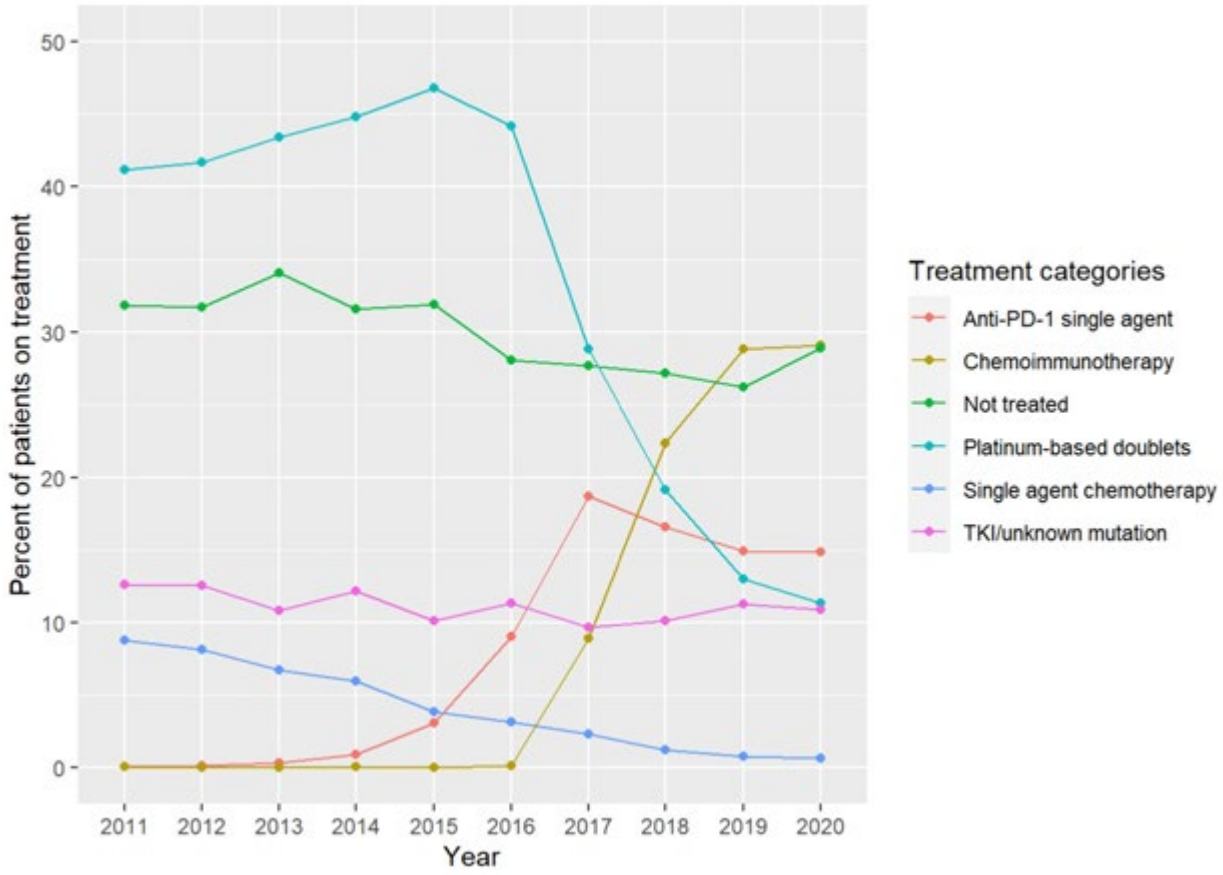
Introduction: Non-small cell lung cancer (NSCLC) is a disease of the elderly and most cases are related to tobacco. Therefore, concomitant organ dysfunction (dfxn), which increases the risk of toxicity with cancer directed therapy, is prevalent. Patterns of care studies have shown that the elderly, those with organ dfxn or compromised performance status (PS) are frequently not treated, despite prospective studies demonstrating survival benefit with active treatment (tx). We hypothesized that the advent of new, more active therapies has resulted in practice changes in these populations. This abstract was published online for ASCO Annual Meeting 2021. **Methods:** We conducted a retrospective, observational cohort study using the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database to compare first line tx patterns from 2011 to 2020 in patients (pts) with advanced NSCLC meeting at least 1 of the following criteria: age >70 years, organ dfxn (serum creatinine > 1.5 times the upper limit of normal [ULN] and/or total bilirubin > 2 times ULN), ECOG PS > 2 or documented HIV. Pts were excluded if there was a >90-day post-diagnosis gap in EHR data. Tx patterns were categorized as having received standard, non-standard or no frontline tx. Tx groups included PD-1/PD-L1 inhibitor single agent, chemoimmunotherapy, platinum-based (Plat) doublet +/- VEGF inhibitors (VEGFi), single agent chemotherapy (chemo) and tyrosine kinase inhibitors (TKIs). Descriptive statistics were used to analyze tx patterns, and the relationship between txs and variables of interest were tested using Chi-squared tests or t-tests. **Results:** Of the 58,145 pts with advanced NSCLC in the database, 33,701 met at least 1 criterion for inclusion. There was a small but significant increase in the number of pts treated with standard therapy from 2011 to 2020 ($p<0.001$). There was rapid uptake of PD-1/PD-L1 inhibitors as well as chemoimmunotherapy upon FDA approvals in 2016 and 2018, respectively. This correlated with a rapid decrease in the use of Plat-doublet chemo +/- VEGFi as well as a decrease in the number of pts receiving single agent chemo or not treated at all

(Figure).



Conclusion: Real world data from 2011 to 2020 demonstrates an increase in the use of standard therapies as well as the rapid incorporation of immunotherapy into first line tx in advanced NSCLC pts who are elderly, have a poor PS, or organ dfxn. However, a substantial proportion of pts (28.9%) still do not receive any documented tx, within the Flatiron Health network.

Keywords: non-small cell lung cancer, Real-world data, Geriatric Oncology

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OA08.03 The 5-year Survival Rate of Postoperative Non-small Cell Lung Cancer Patients with Two Different Follow-up Patterns

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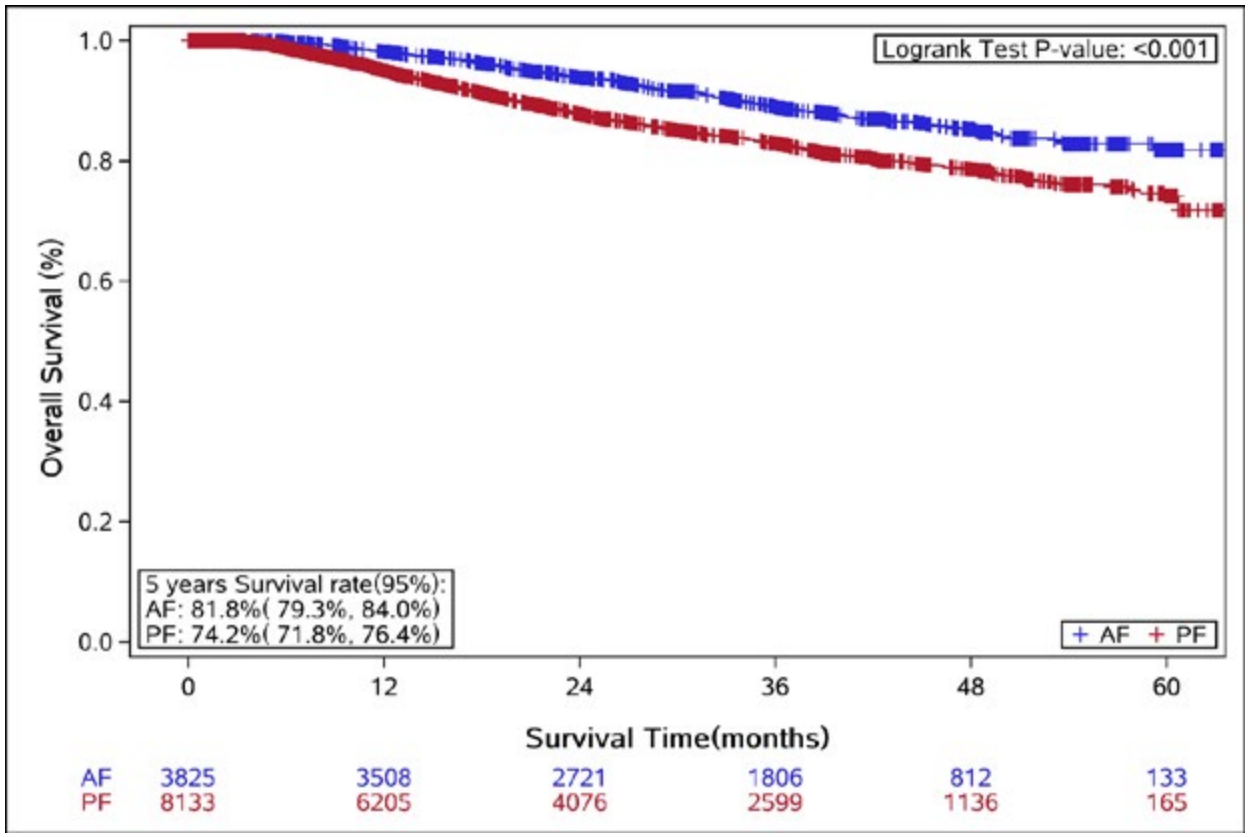
Introduction: Recent studies suggest that different follow-up patterns may influence the survival of cancer patients. This study aimed to compare the 5-year survival rates between the two post-operation follow-up patterns of the patients with stage I-IIIA non-small cell lung cancer (NSCLC). **Methods:** This is a China multicenter, retrospective, observational study. Clinical stage I-IIIA NSCLC (adjusted by AJCC 8th edition) patients who underwent surgical resection and received follow-up within 6 months after initial diagnosis through LinkDoc telephone follow-up system were included from July 2014 to July 2020. Patients who died within 3 months after the surgery were excluded. All enrolled patients are grouped into proactive follow-up (AF) group or passive follow-up (PF) group according to patients' behavior during follow-up. In the AF group, patients proactively reached out for medical advice at least once aside from routine follow-up. In the PF group, patients underwent routine follow-up (every 3 months for the first 2 years and every 6 months for the following years). The Kaplan-Meier and Cox proportional hazards regression model were used. **Results:** A total of 11,958 stage I-IIIA NSCLC patients were included from 9 hospitals with a wide geographical representation. No significant difference for the demographic and clinical characteristics were found between the AF group (N=3825) and the PF group (N=8133). In both groups, most patients were male, non-squamous histological type, stage I and the Eastern Cooperative Oncology Group Performance Status (ECOG-PS)≤2. In the AF group and PF group, median call duration were 3.77 and 3.58 minutes; the 5-year survival rate were 81.8% and 74.2% (Figure.1), respectively. Compared with the PF group, the AF group had better 5-year survival rate [hazard ratio (HR)=0.60, 95% confidence interval (CI), 0.53-0.67, P<0.001]. Further, in subgroups of clinical stages, the AF group all presented significantly better 5-year survival rate than the PF group (stage I subgroup, HR=0.59, 95%CI, 0.46-0.75, P <0.001; stage II subgroup, HR=0.64, 95%CI, 0.51-0.79, P <0.001; stage IIIA subgroup, HR=0.54, 95%CI, 0.46-0.64, P <0.001). Multivariate analysis showed that follow-up pattern, age, gender and operation mode were independent prognostic factors of stage I-IIIA NSCLC, and the results were consistent in all subgroups stratified by clinical stages.

Figure.1 Kaplan-Meier curve of overall survival between two follow-up patterns



Conclusion: This real-world study indicated that proactive follow-up through telephone follow-up system leads to better overall survival for resected stage I-IIIA NSCLC patients.

Keywords: 5-year survival rate, non-small cell lung cancer, follow-up pattern

OA08 MOVING BEYOND NEW DRUGS: WHAT ELSE MATTERS?
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OA08.04 Validation of Scalable, Automated Data Extraction in an Advanced Lung Cancer Patient Population

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Introduction: Manual extraction from electronic health records (EHRs) is currently the standard approach for accessing real-world healthcare data but can be time consuming and challenging to maintain over time. Automated data extraction using natural language processing (NLP) is emerging as a viable method of data extraction from structured and unstructured fields of EHRs. While speed of NLP-based data extraction is established, some question the validity of the extracted data. This study compares the accuracy of, and concordance between, manual and NLP-extracted data from EHRs of patients with advanced lung cancer (aLC). **Methods:** EHRs of 1209 patients with aLC were screened using the AI engine, DARWEN™, to identify a subset of 333 patients diagnosed and treated with systemic therapy at Princess Margaret Cancer Centre in Toronto between January 2015 and December 2017. Full feature models were run on all 333 patients to extract data from EHRs, from which 100 patients were randomly selected for manual data extraction by two trained abstractors to validate against NLP-extracted data. An expert adjudicator reviewed inconsistencies between manual and NLP-extracted results and was referenced as the gold standard when calculating accuracy and concordance. **Results:** NLP-extracted data from EHRs proved to be accurate and concordant with manual extraction methods (Table 1). Features with lower syntactic and semantic variation such as patient demographics (i.e., age and sex), characteristics (i.e., histologic subtype and comorbid conditions), and treatment details were reported with high accuracy and concordance. These tend to be the cases where manual reviewers would agree. Conversely, features with richer syntactic and semantic variation requiring deeper clinical interpretation had slightly lower accuracy by NLP extraction and, typically, manual review. By nature of the varying ways that biomarker testing and reporting is documented, extracting this data can be challenging. While NLP detection of biomarker testing was highly accurate and concordant, detection of results was more variable. NLP out-performed manual extraction in identifying metastatic sites with the exception of lung and lymph node metastases, which was due to analogous terms used in radiology reports that were not applied to variable definitions used to train DARWEN™.

Table 1. Accuracy and concordance between manual and NLP data extraction.

	Accuracy (%)		Concordance (%)
	NLP	Manual	
Date of birth	100	99	99
Sex	100	100	100
Date of Stage IV diagnosis (+/- 30 days)	94.0	83.0	77.0
ECOG PS at Stage IV diagnosis	93.0	78.0	71.0
Smoking status	88.0	94.0	82.0
Histologic subtype	98.0	98.0	96.0
First line treatment type	95.0-99.0	96.0-100	92.0-99.0
Treatment type (Any line)	94.0-99.0	84.0-98.0	83.0-96.0
Biomarker Testing Performed	98.0-99.0	97.0-100	96.0-98.0
Biomarker Status (Positive or Negative)	86.2-100	94.7-100	86.2-100
Metastatic Sites of Disease	66.0-99.0	71.0-100	58.0-99.0
Immunosuppressive medications	80.0-100	86.0-100	76.0-100
Comorbidities	96.0-100	96.0-100	93.0-100

Conclusion: The use of NLP technology in oncology provides opportunity for real-world evidence studies at a larger scale than ever before. NLP was not only faster than manual extraction but, for many features, was also more accurate than a traditional manual approach, demonstrating the advances of modern NLP techniques as a scalable alternative to manual extraction.

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OA09.01 First-line Nivolumab + Ipilimumab + Chemo in Patients With Advanced NSCLC and Brain Metastases: Results From CheckMate 9LA

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Introduction: Patients with advanced non-small cell lung cancer (NSCLC) and brain metastases have high unmet needs and could benefit from checkpoint inhibitors. In the randomized phase 3 CheckMate 9LA trial (NCT03215706), first-line nivolumab (NIVO) + ipilimumab (IPI) combined with chemotherapy (chemo) significantly improved overall survival (OS; primary endpoint) versus chemo alone in patients with advanced NSCLC. Clinical benefit was observed regardless of programmed death ligand 1 expression or histology. Here we report a post hoc analysis of efficacy and safety outcomes in patients with and without baseline (BL) brain metastases. **Methods:** Eligible patients were adults with stage IV/recurrent NSCLC, ECOG performance status ≤1, and no known sensitizing EGFR/ALK alterations. Patients with adequately treated brain metastases who were asymptomatic for ≥2 weeks prior to first treatment were eligible; corticosteroids were permitted if the dose was stable or decreasing at ≤10 mg daily prednisone (or equivalent) for ≥2 weeks prior to first study treatment. Patients were randomized 1:1 to NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + chemo (2 cycles) or chemo alone (4 cycles); treatment was until disease progression, unacceptable toxicity, or 2 years for immunotherapy. Brain MRI/CT was performed in all patients at BL, and in patients with history/symptoms of brain metastases during treatment, at 2 follow-up visits, and every 3 months thereafter until disease progression. Radiographic assessment of intracranial tumor response was performed per modified RECIST (adapted for brain metastases) by blinded independent central review. **Types of Analysis and Data Reporting:** Baseline and disease characteristics; efficacy and safety outcomes including OS, progression-free survival, and response; and treatment-related adverse events for patients with and without baseline brain metastases in CheckMate 9LA are reported. **Results:** Of 719 randomized patients, 101 (14%) had BL brain metastases. BL characteristics were generally similar between patients with and without BL brain metastases and between treatment arms, except for a slightly greater proportion of patients who had never smoked (NIVO + IPI + chemo arm) and patients with liver metastases (chemo arm) in the BL brain metastases subgroup. Survival and systemic efficacy outcomes were improved with NIVO + IPI + chemo versus chemo in patients with and without brain metastases (Table). Intracranial efficacy data will be reported in the presentation. In patients with BL brain metastases, any-grade neurological treatment-related adverse events occurred in 22% and 10% of the NIVO + IPI + chemo and chemo arms, respectively; most were grade 1/2.

Table. Efficacy by BL brain metastases in CheckMate 9LA				
	Patients with BL brain metastases		Patients without BL brain metastases	
	NIVO + IPI + chemo n = 51	Chemo n = 50	NIVO + IPI + chemo n = 310	Chemo n = 308
OS, median (95% CI), months	19.3 (12.3–23.9)	6.8 (4.7–9.7)	15.6 (13.8–19.4)	12.1 (10.2–13.7)
HR vs chemo (95% CI)	0.43 (0.27–0.67)	––	0.79 (0.65–0.95)	––
1-year rate, % (95% CI)	67 (52.0–77.8)	26 (14.9–38.6)	62 (56.6–67.4)	50 (44.6–55.8)
2-year rate, % (95% CI)	35 (22.6–48.2)	12 (4.9–22.6)	39 (33.3–44.1)	29 (23.9–34.0)
Systemic PFS,[a] median (95% CI), months	10.6 (6.7–12.6)	4.1 (2.8–5.4)	5.8 (5.2–7.3)	5.4 (4.5–5.6)
HR vs chemo (95% CI)	0.40 (0.25–0.64)	––	0.74 (0.62–0.89)	––
1-year rate, % (95% CI)	36 (22.4–50.2)	8 (2.2–19.5)	33 (27.2–38.0)	21 (15.8–25.8)
2-year rate, % (95% CI)	19 (9.1–32.3)	6 (1.0–15.9)	20 (15.5–24.9)	8 (5.3–12.6)
Systemic ORR,[a] n (%)	22 (43)	12 (24)	115 (37)	79 (26)
95% CI	29.3–57.8	13.1–38.2	31.7–42.7	20.9–30.9
Systemic DOR,[a] median (95% CI), months	15.5 (5.6–NR)	4.4 (2.8–7.1)	13.0 (8.6–20.2)	5.7 (4.4–8.0)
1-year rate, % (95% CI)	51 (28–70)	21 (3–49)	52 (42–60)	25 (16–35)
2-year rate, % (95% CI)	38 (17–59)	0	34 (24–44)	11 (5–19)
[a]Per blinded independent central review. CI, confidence interval; DOR, duration of response; HR, hazard ratio; NR, not reached; ORR, objective response rate; PFS, progression-free survival.				

Conclusion: In patients with advanced NSCLC and BL brain metastases NIVO + IPI + chemo provided durable survival benefit versus chemo, consistent with benefits observed in all randomized patients from CheckMate 9LA. No new safety signals were identified.

Keywords: brain metastases, Immune checkpoint inhibitors, Phase II and III Clinical Trials

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OA09.02 Atezo-Brain: Single Arm Phase II Study of Atezolizumab Plus Chemotherapy in Stage IV NSCLC With Untreated Brain Metastases

E. Nadal[1], B. Massuti[2], G. Huidobro[3], R. Lopez Castro[4], A. Estival[5], J. Mosquera[6], I. Sullivan[7], E. Felip[8], A. Blasco[9], M. Guirado[10], M. Simó[1], E. Pereira[11], V. Navarro[1], J. Bruna[1]

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This abstract is under embargo until September 10 at 09:00 Mountain Time.

OA09.03 Pembrolizumab in Combination With Platinum-Based Chemotherapy in Recurrent EGFR/ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Efficacy of single-agent immune checkpoint inhibitors is limited in patients with EGFR/ALK-altered NSCLC. We conducted a phase II study to assess the efficacy of pembrolizumab in combination with carboplatin and pemetrexed in these patients. **Methods:** Patients with recurrent EGFR-mutated or ALK-rearranged NSCLC, previously treated with targeted therapy, were eligible. Patients were treated with carboplatin AUC5, pemetrexed 500 mg/m^2 and pembrolizumab 200 mg I.V. every 3 weeks. After 4 cycles patients were maintained on pemetrexed and pembrolizumab for up to 2 years. Disease was assessed every 2 cycles for the first 6 cycles, then per investigator discretion. The primary end-point was RECIST 1.1 defined response rate. Secondary endpoints included PFS and OS. Tumor PD-L1 expression was assessed locally. Blood for circulating tumor cells (CTCs) was collected prior to the 1st and 3rd cycles. The plan was to enroll 28 evaluable patients in each of two separate cohorts of EGFR-mutated and ALK-rearranged NSCLC. Slow enrollment led to early termination of the trial. **Results:** Of the 33 patients enrolled, 26 had EGFR-mutated NSCLC (13 del19, 9 L858R), 64% were female and median age was 67 years. The median number of prior treatments was 1 (range 1-3). 22 of 26 EGFR+ NSCLC patients had received prior osimertinib. Median number of cycles was 6 (2-24 cycles), with 4 patients, all EGFR+, still on therapy. Response rates (95%CI) were 42% (23%, 63%) and 29% (4%, 71%) among EGFR+ and ALK+ patients, respectively. Median duration of response was 6.1 months in all patients and in EGFR+ patients. Other efficacy results are provided below. Tumor PD-L1 expression was available for 30 patients and was ≥ 1% in 17. There was no difference in survival between patients with tumor PD-L1 <1% vs. ≥ 1%. The median CTC count at baseline in 15 EGFR+ patients in whom samples were available was 4/ml (0-23). Median overall survival among EGFR+ patients with decreased vs. increased CTC count during treatment was not reached vs. 18.5 months, respectively (p=0.52 for OS). The most common adverse events were fatigue, nausea, cytopenias, cough and dyspnea. The most common ≥ grade 3 toxicities were neutropenia, thrombocytopenia, thromboembolism, and AST/ALT elevation. One patient developed pneumonitis.

	EFGR+ (n=26)	**ALK+ (n=7)**	**All (n=33)**
Median PFS (months. 95%CI)	8.3 (7.2, 16.5)	2.9 (1.1, NE)	7.3 (5.3, 14.1)
12-month PFS (95% CI)	29% (14%, 59%)	14% (2%, 88%)	26% (13%, 50%)
Median OS (months, 95% CI)	22.2 (20.6, NE)	2.9 (1.1, NE)	20.6 (10.1, NE)
12-month OS (95% CI)	76% (59%, 97%)	14% (2%, 88%)	61% (44%, 83%)

Conclusion: Pembrolizumab in combination with chemotherapy demonstrated a response rate of 42% and median survival of 22 months among patients with recurrent EGFR-mutated NSCLC. These results warrant further study of this combination in this patient population.

Keywords: EGFR, Pembrolizumab, Chemotherapy

OA10 IMPROVING CARE FOR PEOPLE WITH LUNG CANCER: BIOMARKER TESTING ACCESS, PSYCHOSOCIAL DISTRESS, CARE NAVIGATION, AND COVID-19 VACCINATION
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA10.01 Perceptions of Biomarker Testing for Underserved Patients With Lung Cancer: A Mixed-Methods Survey of Us-Based Oncology Clinicians

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This abstract is under embargo until September 10 at 09:00 Mountain Time.

OA10.02 Psychosocial Distress in Patients with Driver-Mutant Lung Cancer

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Introduction: Project PRIORITY, a collaborative research study between The EGFR Resisters and the LUNGevity Foundation, found that 29% of United States respondents had clinical depression. While tyrosine kinase inhibitors (TKI) prolong lives, the impact of an oncogene driven lung cancer diagnosis on emotional well-being is not well studied nor are resource utilization and potential contributing factors to psychosocial distress. A version of this abstract has been published at ASCO 2021. **Methods:** Our primary objective was to study cancer related distress in patients (pts) with newly diagnosed oncogene driver lung cancer. The secondary objective was to correlate distress with neutrophil to lymphocyte ratio (NLR) and body mass index loss (BMI) as a surrogate for cancer cachexia/precachexia to gauge the relationship to psychosocial distress. We retrospectively reviewed pts treated with TKI between 1/1/2008 and 2/1/2021. Sample size was based on estimates of depression in this population. A diagnosis of depression or anxiety was defined by documentation in the visit problem list, and active symptoms were based on progress note documentation. Depression and anxiety were recorded at 6 time points from diagnosis to progression on TKI, and their associations with treatment toxicities, progression free survival (PFS) and overall survival (OS) were assessed. Associations with serial BMI and NLR were assessed using longitudinal statistical models. The association between psychosocial distress and vulnerable populations was assessed using the Center for Disease Control Social Vulnerability Index (CDC SVI) at all Illinois zip codes. **Results:** We studied 78 pts: 71.8% female, 62.8% Caucasian, 15.4% African American, 15.6% Hispanic/LatinX, and 11.5% Asian. 94.9% had an EGFR mutation and 5.1% had an ALK mutation. Prevalence of depression at diagnosis and progression was 11.5% and 25%, with anxiety prevalence 28.2% and 40.6%, respectively. Of these pts, 22.2% had active depression symptoms and 54.5% had active anxiety symptoms at diagnosis, although symptoms were not addressed in 33.3% and 22.7%, respectively. At progression, 68.8% had active depression symptoms and 46.2% had active anxiety symptoms, but symptoms were not addressed in 6.3% and 26.9%, respectively. At diagnosis and progression, 24.4% and 35.9%, respectively, were on treatment for anxiety and/or depression. Social work and psychology evaluated 12.8% and 10.3% of all pts at diagnosis and 10.9% and 17.2% at progression. NLR >3.5 and >5 were not associated with depression or anxiety. A more rapid longitudinal decrease in BMI was associated with depression. Grade ≥3 toxicities were not associated with depression or anxiety. Shorter PFS and OS were associated with higher rates of depression but not anxiety. Higher SVI was associated with depression at progression (OR=1.03, p=0.04). **Conclusion:** In this retrospective study of an ethnically diverse patient group at an academic medical center, we found a prevalence of depression and anxiety consistent with the Project PRIORITY findings. We saw an association between depression and more rapid weight loss but did not see correlation with NLR. We also saw an association between social vulnerability and depression at progression. Prospective evaluation with accurate documentation is needed to better address these questions in future studies.

Keywords: Depression, Anxiety, Driver

OA10 IMPROVING CARE FOR PEOPLE WITH LUNG CANCER: BIOMARKER TESTING ACCESS, PSYCHOSOCIAL DISTRESS, CARE NAVIGATION, AND COVID-19 VACCINATION
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA10.03 How LungMATCH, A Personalized Treatment Navigation and Clinical Trial Matching Service, Affects the Treatment Journey

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Introduction: GO2 Foundation for Lung Cancer developed the LungMATCH program in response to the unmet need of truly personalized, free, and unlimited treatment navigation and clinical trial matching. The program gives patients and caregivers access to information pertaining to their specific type of lung cancer ranging from biomarker test interpretation and acquisition to interpretation of the medical science pertaining to their next line of treatment and nation-wide clinical trial searches and matching in addition to free educational materials in the forms of one pagers, brochures, and a quarterly educational newsletter. The program seeks to determine if empowering patients and caregivers with these resources affects the treatment journey. **Methods:** Data was collected as patient reported biomarker testing, history of all treatments received, and clinical trial participation through phone or email contact from 2018-2020. Data was interpreted and transformed using mean values to account for longitudinal consistency. Repeat patients or caregiver contacts were treated as separate and individual data points. Clinical trial accrual rates were measured only taking into account patients or caregivers who identified clinical trials as a potential treatment option. **Results:** As the years progressed, patients and caregivers reported increased usage of precision medicine as measured by targeted and immuno- therapy usage and biomarker testing rates (Table). Additionally, clinical trial accrual rates remained higher than the national average and increased each year (Table. Increased participation since program launch, despite the impact of the COVID-19 pandemic, suggests a positive impact of the service on a patient's treatment journey.

	2018 (n=267 total)	**2019 (n=415 total)**	**2020 (n=357 total)**
Percent of Patients Matched to a Clinical Trial	11.5 (n=26)	13.6 (n=22)	14.3 (n=7)
Percent of Patients Who Received Biomarker Testing and Know the Results	46	64	67
Percent of Patients Who Received Biomarker Testing and Don't Know the Results	3	5	6
Percent of Patients Who Ever Received Chemotherapy	58	63	57
Percent of Patients Who Ever Received Immunotherapy	34	41	40
Percent of Patients Who Ever Received Targeted Therapy	13	38	45

Conclusion: LungMATCH has been able to show that empowering patients with personalized information about their lung cancer correlates withhigh rates of biomarker testing, personalized medicine, and clinical trial accrual. It is important to highlight the success of LungMATCH in maintaining higher than national average clinical trial accrual rates and the identified best practices on how to increase accrual year over year. Preliminary data about reason for contact combined with the high percentage of patients who know the result of their biomarker testing, suggest LungMATCH could have a direct positive impact on patient education and empowerment in regards to their testing. Future directions of LungMATCH include analysis of quality of care as measured by NCCN guidelines and the identification of correlative practices that may point to NCCN guideline care.

Keywords: Clinical trials, precision medicine, Patient advocacy

OA10.04 COVID-19 Vaccine Acceptance and Communications Effectiveness Amongst Canadian Lung Cancer Patients.

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Introduction: COVID-19 vaccines have been developed at a rapid and historic pace. In December 2020, Health Canada provided authorization to the first COVID-19 vaccines in Canada. However, these have not been fully studied in certain populations, including cancer patients. In addition, due to limited vaccine supplies, provinces and territories each developed and implemented a phased prioritized approach to the vaccine rollout. Lung Cancer Canada developed a survey to access patients' thoughts and feelings around COVID-19 vaccine acceptance, understanding and communications. **Methods:** OBJECTIVE - A quantitative patient survey was conducted by Lung Cancer Canada to assess Canadian lung cancer patient's acceptance of the COVID-19 vaccine and determine their viewpoint around communication on the rollout process. METHODOLOGY - An iterative approach was used in the study design. A focus group made up of lung cancer patients was convened to explore their thoughts around the topic. Their thoughts and words were used to develop a patient-centred quantitative survey. The survey was fielded digitally and promoted using direct email and social media platforms. The results were discussed and analyzed by the focus group. **Results:** The survey was fielded between February 11th and 16th 2021. 124 Canadian lung cancer patients responded to the survey. 92% of lung cancer patients indicated they would receive the vaccine immediately if given. However, when asked about their understanding of whether or not lung cancer patients were part of those identified as a priority population, only 37% believed that they would receive the vaccine as part of a priority population. 38% were unsure and 24% of patients believed that they would receive it with the general population. In terms of communication, the survey respondents indicated a high level of dissatisfaction across various stakeholder groups in regards to how they are addressing the needs of cancer patients in the COVID-19 vaccine rollout, with elected officials 81%, federal government 77%, provincial government 74%, professional medical associations 58%, provincial cancer agencies 55% and national cancer agencies 52%. They also indicated they received information concerning the vaccine from various sources including the federal government 40%, provincial government 50%, healthcare providers 21%, traditional media 60% and social media 40%. The numbers signify the important role these sources play in the provision of information. **Conclusion:** The results indicate vaccine acceptance is actually quite high among lung cancer patients in Canada, but there are critical gaps in communication. Due to the unprecedented nature of the pandemic, it is understandable that information changes and updates happen quickly. The results of the survey underscore the need for collaborative and synergistic communications between all levels of government and cancer care teams to provide patients with consistent and correct information on the vaccine rollout. It is also important to note the changing information consumption environment. Although traditional media is still an important source of information, patients are also getting their information regarding the vaccine on social media. It is important for both government and cancer care providers to recognize and utilize "where patients are at" communication vehicles beyond traditional media in order to both reach and address patient concerns.

Keywords: COVID-19 vaccine, Lung Cancer Patients, Vaccine acceptance and communication

OA11 EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA11.01 Neoadjuvant Pembrolizumab for Early Stage Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant immune checkpoint inhibitor treatment is a promising approach for resectable cancer. The optimal treatment regimen has yet to be determined. This study was initially reported at the ESMO annual meeting 2018 and at the ASCO 2019 annual meeting. We currently report the final analysis for safety, the primary endpoint of the study, and updated efficacy results. **Methods:** We have conducted a phase I, investigator-initiated single-center study, to examine the safety of neoadjuvant pembrolizumab for stage I-II (TNM v7) resectable NSCLC, to identify the recommended phase II dose/schedule (RP2D/S) and to evaluate efficacy by remaining viable cells (10% or less defined as a major pathologic response, MPR). The study cohorts differed in number of pembrolizumab doses, and in treatment initiation-to-surgery intervals. Exploratory analyses were done to evaluate factors possibly correlated with MPR. **Results:** 26 patients initiated treatment on the study. Median age: 69 (range 51-79) years, 54% men, smoking status: 62%/31%/8% current/past/never. ECOG PS: 1/0 in 85%/15%. Histology: adenocarcinoma/squamous/adeno-squamous/NSCLC in 50%/42%/4%/4%. No DLT and no grade 5 TRAE occurred. Two patients (8%, 95% C.I 0-18%) had grade 3-4 TRAE; one patient had both grade 3 myositis and myocarditis (causing surgery deferral) and one patient had both grade 3 encephalitis and hepatitis (following surgery, 124 and 171 days respectively from pembrolizumab initiation). Median change in tumor diameter radiologically was -5% (range, -43% to 70%). By RECIST, one patient (4%; 95% C.I. 0-11%) had PR, 21 patients (81%; 95% C.I. 66-96%) had SD, two patients (8%; 95% C.I. 0-18%) had PD and two patients were non-evaluable. One patient refused surgery after treatment and one patient had a non-treatment-related myocardial infarct leading to surgery deferral. Pathologically, 7 patients (27%, 95% C.I 10-44%) achieved a MPR, 3 (12%, 95% C.I 1-24%) achieved pCR. Patients with MPR had longer treatment-surgery interval (Table). At a median follow up of 23 months (95% CI 13-32), 2 patients of the 26 treated patients (8%, 95% C.I 0-18) died, one of them with no evidence of disease. One of the 23 operated patients (4%, 95% C.I. 0-13%) had disease recurrence

Comparison of patients that underwent surgery (n=23) with and without MPR

Parameter	MPR achieved	No MPR	P value
N	7	16	
Age - median (min-max) years	71 (66-73)	64 (51-79)	0.138
Male - n (%)	6 (86%)	6 (38%)	0.069
Smoking status – n (%)			1.000
Yes	5 (71)	10 (63)	
Past	2 (29)	5 (31)	
Never	0 (0)	1 (6)	
Pathology – n (%)			1.000
Adenocarcinoma	4 (57)	7 (44)	
Squamous	3 (43)	7 (44)	
Adeno-Squamous	0 (0)	1 (6)	
NSCLC	0 (0)	1 (6)	
Tumor size - Avg (min-max) mm	32 (24-48)	33 (11-74)	0.822
T stage - n (%)			
T1b		3 (18)	
T1c	4 (57)	6 (35)	
T2a	2 (29)	3 (18)	
T2b	1 (14)	2 (12)	
T3		1 (6)	
T4		1 (6)	
N stage - n (%)			0.416
N 0	7 (100)	14 (88)	
N 1	0 (0)	2 (12)	
PDL1 - median (min-max) %	1 (0-65)	2 (0-85)	0.632
Treatment initiation-Surgery interval - median (min-max) days	43 (38-52)	36 (23-62)	0.043

Conclusion: Neoadjuvant pembrolizumab for early NSCLC achieved a 27% rate of MPR, a 12% rate of pCR, with 8% rate of grade 3-4 TRAE. Two doses of neoadjuvant pembrolizumab at a three week interval, followed by surgery two weeks later, is the RP2D/S. Longer interval from treatment to surgery was associated with higher rate of MPR. Correlative studies are ongoing.

Keywords: anti-PD-1, Surgery, Neoadjuvant

OA11 EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA11.02 Treatment Outcomes of Re-irradiation Using Stereotactic Ablative Radiotherapy to Lung: A Propensity Score Matching Analysis

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Introduction: The purpose of this study was to compare the treatment efficacy and safety of re-irradiation using stereotactic ablative radiotherapy (SABR) and initial SABR for lung cancer and metastasis. **Methods:** A retrospective review of the medical records of 337 patients who underwent lung SABR was performed. Re-irradiation was defined as overlapping of the 70% isodose line of second-course SABR with that of the initial radiotherapy, and 21 patients were classified as re-irradiation group. A median dose of re-irradiation SABR was 54 Gy (range, 48 to 60 Gy), and a median fraction number was 4 (range, 4 to 6). Median time to re-irradiation was 13.7 months (range, 0.36 to 51.6 months). One-to-three propensity score matching was used to compare treatment outcomes and toxicity rate, and 63 patients were included in initial SABR group of matched cohort. **Results:** The median follow-up period of the matched cohort after SABR was 28.0 months (range, 3.48 to 95.8 months). The 1 and 2-year local control rates were 75.2% and 65.2% for re-irradiation group, respectively, and 93.2% and 88.3% for initial SABR group of matched cohort, respectively. The difference was statically significant (p = 0.019). The 1 and 2-year distant control rates were 75.9% and 51.4% for re-irradiation group, respectively, and 72.5% and 60.8% for initial SABR group, respectively. There was no significant difference between two groups (p = 0.93). The crude grade ≥2 toxicity rates were 42.9% for re-irradiation group, and 23.8% for initial SABR group (p=0.163). The 1 and 2-year freedom from grade ≥2 toxicity rates were 57.1% and 57.1% for re-irradiation group, respectively, and 81.6% and 77.8% in initial SABR group, respectively. Marginally significant difference between two groups (p=0.086) was found. In re-irradiation group, one grade 3 toxicity (pulmonary) was reported, and there was no grade 4-5 toxicity. **Conclusion:** The local control rate of in-field re-irradiation SABR was lower than initial SABR. Biological background of the worse outcome needs to be discussed by further research. Toxicities of re-irradiation SABR was manageable.

Keywords: re-irradiation, stereotactic radiation therapy

OA11 EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA11.03 Oncologic Outcomes of Patients with Resected T3N0M0 Non-Small Cell Lung Cancer

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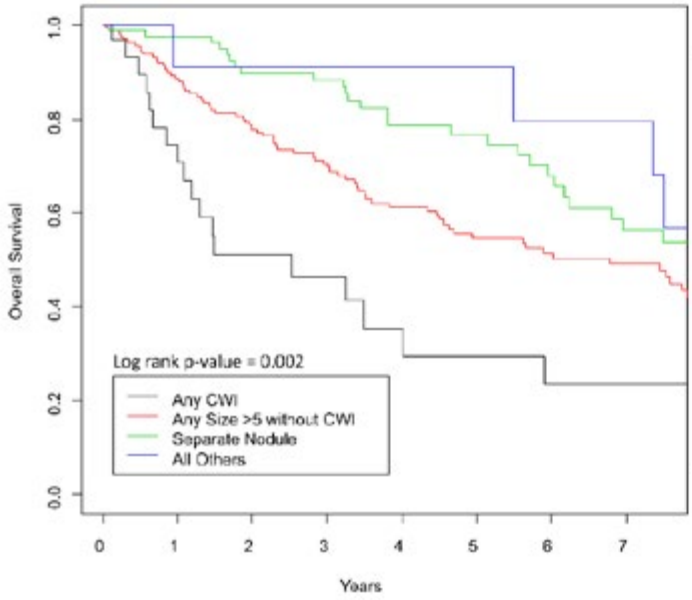
Introduction: The 8th Edition T3N0M0 category represents a heterogeneous group of Non-Small Cell Lung Cancers (NSCLC). This study aims to compare the oncologic outcomes of individual T3 features. **Methods:** Between 2001 and 2019, 293 consecutive pT3N0M0 NSCLC patients according to the 8th lung cancer TNM classification were enrolled. Neo-adjuvant chemotherapy cases and Pancoast tumors were excluded. Patients were grouped according to the T3 features in one of four categories: (1) Chest Wall Infiltration (CWI), (2) Size (> 5cm to ≤ 7cm), (3) presence of Satellite Nodule and (4) All Other T3 features. Patients with multiple features were grouped in a separate category, and then regrouped after exploring interactions between features. Any CWI was classified in Group 1 regardless of other T3 features, and Size plus any T3 feature other than CWI in Group 2. Multivariable regression models were developed to determine associations of clinical factors with oncologic outcomes. Overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan-Meier and Cox proportional hazard analyses. **Results:** Among the 293 eligible patients, 51,9 % were males with a mean age of 68 years old. Lobectomy was performed in 91,5 % of cases (n=268) and 56 % (n=164) of NSCLC were adenocarcinoma. Between the T3 categories, Size and Satellite Nodule were the most common in 59% (n=172) and 28% (n=81) of cases respectively. Local and distant recurrences occurred in 10,6% (n=31) and 14% (n=41) of patients, while 6,8% (n=20) had both types of recurrences. After multivariable adjustments: age over 65 (p=0,005), male gender (p=0,007), CWI (p=0,002), larger tumors (p=0,047) and incomplete resections (p=0,03) were associated with worse OS. The same variables were associated with worse DFS (p<0,05) except for incomplete resections (p=0,067). Patients with CWI had the worst 5-year OS (30%) followed by Size (55%), Separate Nodule (77%), and All Others (91%). Pair-wise comparisons showed that CWI had worse OS compared to each of the three other T3 categories (p< 0,05), while Size had worse OS compared to Satellite



Pair-wise Comparisons	Hazard Ratio, 95% CI	P-value
CWI vs Size	**2.32 (1.37, 3.91)**	**0.002**
CWI vs Separate Nodule	**3.79 (2.06, 6.98)**	**<0.001**
CWI vs Others	**7.56 (1.75, 32.67)**	**0.007**
Size vs Separate Nodule	**1.64 (1.03, 2.59)**	**0.036**
Size vs All Others	3.26 (.79, 13.31)	0.099
Separate Nodule vs All Others	1.99 (0.47, 8.41)	0.349

Conclusion: These results show great heterogeneity within the T3N0M0 classification confirmed by the significant OS and DFS differences between T3 features. Furthermore, pair-wise comparisons showed that CWI had the worst OS when compared to all other categories. These results raise the question whether there should be a subdivision of the T3 category in the forthcoming 9th TNM edition. Future work should focus on examining the oncologic outcomes of T3 lung cancer patients with CWI.

Keywords: NSCLC, T3N0M0, Surgical resection

OA11 EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

OA11.04 Impact of Local Control on Cause-Specific Survival After SBRT for Early-Stage NSCLC: Dynamic Prediction With Landmarking

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Introduction: Stereotactic body radiotherapy (SBRT) is an effective treatment for early-stage non-small cell lung cancer (NSCLC), especially in inoperable patients. Although previous studies have indicated that local control improves with higher doses above the biologically effective dose (BED) 100 Gy, the effect of improved local control on survival remains unclear. The purpose of this study was to assess the impact of local recurrence (LR) on cause-specific survival with a dynamic prediction model that incorporates LR as a time-dependent covariate. **Methods:** This study included 386 stage IA NSCLC patients treated with SBRT from two centers, one using a high BED of 140 Gy or more and the other using a conventional BED of 105 Gy. We developed landmark dynamic prediction models for the probability of cause-specific survival. This model provides the probability of surviving an additional 2 years at different prediction time points during follow-up, given the history of recurrent status. Baseline covariates included in the model were age, gender and tumor diameter, and the time-dependent covariates were LR and regional or distant recurrence (RDR). The interactions between prediction time points and covariates were also considered in the model. LR was defined as recurrence within the radiation field. **Results:** With the median follow-up of 4.3 years, 89 patients (23%) died of lung cancer. In a total of 127 patients who developed recurrence, 18 had LR only, 81 had RDR only, and 28 had both. The landmark model showed that age, tumor diameter, LR and RDR were significantly associated with increased odds of shorter cause-specific survival. Among these covariates, LR (adjusted odds ratio [aOR], 16.1; 95% CI, 9.7-26.7; P < .001) and RDR (aOR, 16.0; 95%CI, 11.6-22.0; P < .001)) demonstrated a strong effect on cause-specific death 2 years after the prediction time points. **Conclusion:** The dynamic prediction using landmark model showed that LR had a strong impact on subsequent cause-specific deaths. This result suggests that improving local control with higher doses is a reasonable strategy.

Keywords: dynamic prediction, early-stage non-small cell lung cancer, Stereotactic body radiotherapy

OA12.01 Genomic and Immune Cell Landscape of Response to Chemo-Immunotherapy in Malignant Pleural Mesothelioma

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Introduction: Mesothelioma is a rare and fatal cancer that has seen few treatment advances until the recent approval of combination immune checkpoint blockade. We have recently reported the clinical efficacy and safety of the phase 2 PrE0505 trial of the anti-PD-L1 antibody, durvalumab, plus cisplatin and pemetrexed chemotherapy for patients with previously untreated unresectable pleural mesothelioma (MPM; NCT02899195). **Methods:** We performed whole exome sequencing (WES), coupled with genome-wide focal and large-scale copy number aberration analysis and sequence computational deconvolution to determine mutational processes, clonal composition, enrichment in immunogenic mutations and genomic instability of MPM. In parallel, we evaluated the intra-tumoral T cell repertoire by means of T cell receptor (TCR) sequencing and assessed PD-L1 expression and CD8+ T cell density by immunohistochemistry. Clinical outcomes utilized included best radiographic response as well as landmark 12-month overall survival. **Results:** Integrated genomic, immune repertoire and functional analyses revealed that a higher immunogenic mutation burden (p=0.023) coupled with a more diverse T cell repertoire were linked with favorable clinical outcome (p=0.018), especially for epithelioid MPM. Functional studies of autologous T cells indicated that mutation-associated neopeptides were a potential driver of the anti-tumor immune response to chemo-immunotherapy. Tumor PD-L1 expression and CD8 T cell density as assessed by immunohistochemistry, were not associated with response to therapy. A trend towards enrichment in mutations in chromatin regulating genes, such as SETD2, was identified in responding MPMs. Consistent with the notion that genomic instability and large-scale copy number losses are driver events for MPM, we found that homologous recombination deficiency was a hallmark of epithelioid MPM achieving long-term survival (p=0.014). Three long term responders showed genomic near-halpoidization, which is an extreme form of whole genome loss of heterozygosity. Interestingly, patients with pathogenic germline loss-of-function alterations in cancer predisposing genes, especially those involved in DNA repair, were more likely to attain long term survival (log rank p=0.05 and p=0.032 for all patients and patients with epithelioid MPM respectively). **Conclusion:** Our findings indicate that responses to combination durvalumab with platinum-based chemotherapy are driven by the complex genomic landscape and T cell repertoire composition of MPM with potential clinical implications for patients with mesothelioma.

Keywords: mesothelioma, immunotherapy, multi-omics, genomics

OA12.02 Metformin has Divergent Effects on the Tumor Immune Microenvironment of Non-Small Cell Lung Cancer (NSCLC) Depending on Obesity

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Introduction: Improving outcomes for the growing early-stage patient pool requires developing adjuvant non-surgical therapeutic strategies, which have been traditionally focused on late-stage NSCLC. Metformin, a widely used type II diabetes drug with a long history of safety and minimal side effects, is also known to show anti-cancer activity. We have previously demonstrated that the anti-cancer effects metformin in stage I NSCLC is dependent on patient Body mass index (BMI). To gain insight into the molecular mechanism responsible for these context-dependent effects, we sought to model the effects of high-BMI status and metformin in a mouse model of lung cancer. **Methods:** Diet-induced obesity (DIO) was established by feeding C57BL/6 mice a high-fat diet for 16 weeks. Age/sex-matched control mice were fed a normal diet. Cohorts from obese and non-obese groups were injected subcutaneously with Lewis lung carcinoma (LLC) cells and subsequently monitored until established tumors were noted (~day 11). Tumor-bearing mice were then injected intraperitoneally every two days with metformin (50 mg/kg), and tumor growth was serially measured. Flow cytometry was used to measure tumor immune microenvironment and RNA-seq was used to measure gene expression of tumors in comparison populations. **Results:**

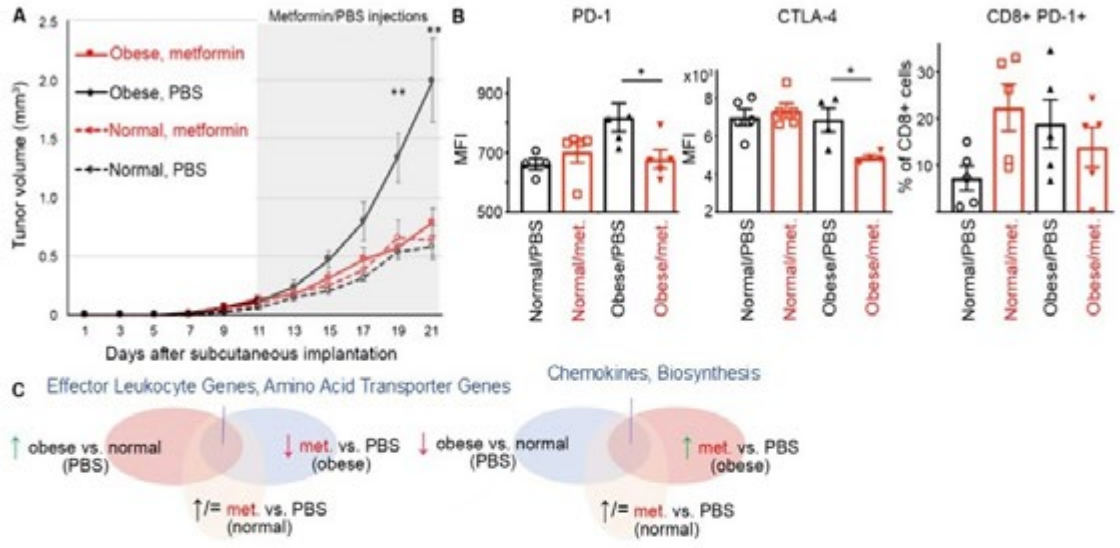

Fig. 1. Obesity-dependent effect of metformin on progression of subcutaneous Lewis lung carcinoma tumors in mice. A. s.c. LLC tumor volumes were calculated (volume = 0.5 x length x width^2) and shown are mean tumor volumes +/-SEM. **B.** Tumor leukocyte suspensions were obtained and characterized by flow cytometry. **C.** Tumor gene expression was assessed by RNASeq. Comparison groups are shown and notable results are summarized. *p<0.05,**p<0.02 Student's t test.

Figure 1 summarizes our results. Obese mice given no metformin supported robust tumor growth. However, tumor growth was suppressed in metformin-treated obese mice. In contrast, and in agreement with lung patient survival data, metformin treatment of non-obese mice did not affect tumor progression. Immune checkpoint molecules were divergently affected by metformin in obese and non-obese mice. Particularly notable were the reductions seen in the levels of PD-1 and CTLA-4 on tumor-associated regulatory (Treg) T cells in metformin-treated obese mice. The frequencies of PD-1-expressing CD8+ T cells among tumor-infiltrating lymphocytes were also reduced by metformin in obese mice compared to non-obese controls. Transcriptome analysis of gene expression in the tumors of these mice also revealed obesity-dependent effects of metformin on genes encoding factors relevant to the regulation of leukocyte memory/effector differentiation as well as genes with known roles in metabolic and biosynthetic pathways. **Conclusion:** Pro-survival and anti-tumor effects of metformin observed in high-BMI patients are operative across species and can therefore be explored mechanistically in widely used mouse models. Our results suggest that the immune-modifying effects of metformin seen in high-BMI lung cancer patients and obese mice alike may stem from unique metabolic conditions that afford optimal reshaping of the anti-tumor immune response.

Keywords: Metformin, Obesity, microenvironment

OA12.03 Combined Inhibition of SHP2 and CXCR1/2 Promotes Anti-Tumor T Cell Response in NSCLC

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Introduction: Clinical trials of SHP2 inhibitors (SHP2i) alone and in various combinations are ongoing for multiple tumors with over-activation of the RAS/ERK pathway. In addition to its potential tumor cell-autonomous actions, SHP2is have important effects on the tumor microenvironment (TME), including potentially complex effects on anti-tumor immunity. Most pre-clinical studies of SHP2is have used models lacking adaptive immune responses or rarely harbor the mutational spectrum of the cognate human disease and fail to reproduce tissue-specific immunity. To this end, orthotopic and immune-competent tumor models that better reflect human cancers might provide important insights into identifying more efficacious and rational combinational strategies that enhance immune-modulatory effects of SHP2is. **Methods:** In order to characterize the tumor cell-autonomous and non-autonomous effects of SHP2 inhibition, we conducted systematic TME analysis including multi-color flow cytometry, immune cell depletion experiments and single cell RNA-Seq in genetically engineered mouse models (GEMMs) of Kras- and Egfr-mutant non-small cell lung cancer (NSCLC). Consecutive magnetic resonance imaging (MRI) was used to evaluate the efficacy of a rational combination which reversed the adverse consequences of SHP2 inhibition on tumor-associated immune cells. Moreover, we performed RNA-seq on pre- and post-treatment biopsy samples from KRASG12C inhibitor clinical trials to see whether other RAS/ERK pathway inhibition results in the same adverse immune effects in NSCLC patients. **Results:** We found that SHP2i treatment depleted alveolar and M2-like macrophages and promoted B and T lymphocyte infiltration in Kras- and Egfr-mutant NSCLC. However, treatment also increased intratumoral granulocytic myeloid-derived suppressor cells (gMDSCs) via tumor-intrinsic, NF-kB dependent production of CXCR2 ligands. Other RAS/ERK pathway inhibitors also induced CXCR2 ligands and gMDSC influx in mice, and CXCR2 ligands were induced in tumors from patients on KRASG12C-inhibitor trials. Combined SHP2 (SHP099)/CXCR1/2(SX682) inhibition depleted a specific cluster of S100a8/9high gMDSCs, generated Klrg1+ CD8+ effector T cells with a strong cytotoxic phenotype but with also expressing the checkpoint receptor NKG2A, and enhanced survival in Kras- and Egfr-mutant models. **Conclusion:** Our study shows that inhibiting the SHP2/RAS/ERK pathway triggers NF-kB-dependent upregulation of CXCR2 ligands and recruitment of S100a8/9high gMDSCs, which suppress T cells in NSCLC. Combining SHP2 and CXCR2 inhibitors blocks this gMDSC immigration, resulting in enhanced Th1 polarization, induction of CD8+ KLRG1+ effector T cells with high cytotoxic activity and improved survival in multiple NSCLC models. Our results argue for testing RAS/ERK pathway/CXCR1/2/NKG2A inhibitor combinations in NSCLC patients.

Keywords: RAS/ERK inhibition, CXCR1/2 inhibitor, gMDSC

OA12.04 Pre-Treatment T-Cell Receptors (TCR) Repertoire in Non-Small Cell Lung Cancer (NSCLC) Patients Treated With Single Agent Immunotherapy

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Introduction: TCR repertoire plays a key role on the orchestration of the immune response. In particular, reduced pre-treatment Shannon diversity, increase clonality and increase convergence of TCRs have been suggested to reflect clonal expansion of antigen-specific T-cells in the tumour microenvironment. These are thought to be correlated with better response rate, improved progression free survival (PFS) and overall survival (OS). Here we aim to explore the above TCR repertoire features in peripheral blood of NSCLC patients (with PDL1≥50%) treated with single agent pembrolizumab in the first line setting; and correlate them with overall response rate (ORR), PFS and OS. **Methods:** We prospectively collected baseline blood from 48 NSCLC patients treated with first line pembrolizumab. High quality DNA was extracted from white blood cells and used for TCR sequencing using the Oncomine TCR Beta-SR Assay (Thermo Fisher). TCR clonality and convergence were calculated for each individual and correlated with survival using Kaplan-Meier curves and survival statistics. Multivariate analysis was carried out controlling for other variable that may influence the association of TCR repertoire and outcomes such as age, sex, ECOG, smoking status and pre-treatment neutrophil to lymphocyte ratio (NLR). **Results:** Our data matured for 29 patients only with a follow-up of at least 6 months. We observed a trend towards increased pre-treatment TCR clonality in patients with objective response to pembrolizumab and statistically significant reduced Shannon diversity (P = 0.042). Convergence did not seem to affect ORR in our cohort. Moreover, there was a significantly longer PFS in patients with reduced number of pre-treatment clones (HR = 0.54, 95%CI 0.21-1.43, P = 0.037), reduced Shannon diversity (HR = 0.52, 95%CI 0.20-1.38, P = 0.047), reduced Evenness (HR = 0.41, 95%CI 0.14-1.19, P = 0.044) and elevated clonality (HR = 2.45, 95%CI 0.84-7.11, P = 0.044). Reduced rather than increased convergence was correlated with a trend towards improved PFS. None of these parameters were statically significant in relation to OS. **Conclusion:** Increased pre-treatment TCR clonality and reduced diversity are associated with improved ORR and PFS, but not OS in NSCLC patients with high PD-L1 treated with pembrolizumab monotherapy. Further maturation of this cohort will demonstrate whether the circulating pre-treatment TCR repertoire is a prognostic factor for immunecheckpoint inhibition.

Keywords: T-CR repertoire, Non-small cell lung cancer, Immunotherapy

OA13 TOPICS OF PLEURAL MESOTHELIOMA
SUNDAY, SEPTEMBER 12, 2021 - 17:30-18:30

OA13.01 S1619 A Trial of Neoadjuvant Cisplatin-Pemetrexed With Atezolizumab in Combination and Maintenance for Resectable Pleural Mesothelioma

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This abstract is under embargo until September 12 at 09:00 Mountain Time.

OA13 TOPICS OF PLEURAL MESOTHELIOMA
SUNDAY, SEPTEMBER 12, 2021 - 17:30-18:30

OA13.02 Socioeconomic Disparities in Access to Treatment and Survival in Operable Malignant Pleural Mesothelioma in the United States

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This abstract is under embargo until September 12 at 09:00 Mountain Time.

OA13.03 Type M1 and Type M2 Macrophages Are Associated With Patient Survival in Malignant Pleural Mesothelioma

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Introduction: Previous studies have demonstrated the prognostic role of the immunological tumor microenvironment in malignant pleural mesothelioma (MPM). Tumor-infiltrating macrophages form the major component of the leucocytes in MPM tumor microenvironment. Macrophages can be divided into two main phenotypes: type M1 macrophages have an anti-tumorigenic function and type M2 macrophages a pro-tumorigenic function promoting tumor development. The macrophage phenotypes affect the biological behavior of MPM and may provide potential therapeutic targets. Thus, we aimed to spatially profile the expression of five markers expressed by macrophages in MPM tumor tissue and assess their association with patient survival. **Methods:** The study cohort consisted of tissue microarrays including samples from 76 Finnish MPM patients (71 epithelioid and 5 biphasic), including 18 patients who survived at least 60 months. We analyzed location-specific tissue expression of markers expressed by macrophages (CD68 [Dako; M0876], CMAF [Abcam; ab199424], pSTAT1 [Cell Signaling Technology; 8826], HLA-DRA1 [Abcam; ab20181] and CD163 [Abcam; ab188571]) using multiplexed fluorescence immunohistochemistry and digital pixel-based image analysis. Single marker expressions and marker combinations were measured as proportional areas to total tissue, stromal, or tumor area. Univariate Cox regression was used to assess the association between macrophage expression and time to death (all-cause mortality). **Results:** In univariate Cox regression analysis, type M2 pro-tumorigenic macrophages ($CD163^+CMAF^+$ $HLA\text{-}DRA1^-$) (Figure 1A.) were associated with shorter survival time (HR=9.54, p=0.03), whereas type M1 anti-tumorigenic macrophages ($CD68^+pSTAT1^+$ $HLA\text{-}DRA1^+$) were associated with longer survival time (HR=0.87, p=0.03). Furthermore, the presence of pSTAT1 expressing immunogenic tumor cells ($CK5^+pSTAT1^+CD68^-CD163^-HLA\text{-}DRA1^-$) (Figure 1B.) was associated with longer survival time (HR=0.97, p<0.01). **Conclusion:** The expression of type M1 macrophages and pSTAT1 expressing tumor cells were associated with longer survival and the expression of type M2 macrophages was associated with shorter survival. These may provide new immunotherapeutic targets.

Keywords: tumor microenvironment, macrophages, Mesothelioma

OA13 TOPICS OF PLEURAL MESOTHELIOMA
SUNDAY, SEPTEMBER 12, 2021 - 17:30-18:30

OA13.04 Chromosomal Rearrangements and Antigen Presentation as Predictors of Survival in Mesothelioma Treated With Immune Checkpoint Inhibitors

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Introduction: Immunotherapy has emerged as a frontline treatment option for malignant pleural mesothelioma (MPM) with the recent approval of the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab. Whereas tumors with high mutation burdens are typically responsive to immunotherapy, MPM reportedly has a very low mutation burden, which is inconsistent with other tumors related to carcinogen exposures. We previously demonstrated that chromosomal rearrangements are common and have neoantigenic potential in MPM. Herein we investigated whether chromosomal rearrangements are associated with survival in patients with MPM treated with immunotherapy. **Methods:** Pleural biopsies of progressive MPM after at least one line of therapy were obtained from patients (n=44) prior to treatment with nivolumab alone (NCT29908324) or the combination of nivolumab and ipilimumab (NCT30660511). RNA and whole genome sequencing were performed. The junctions of chromosomal rearrangements, detected by a bioinformatics package SVAtools, were used to estimate the impact on unique transcripts. Antigen presentation in each sample was determined by using normalized gene expression data and the ssGSEA algorithm in the Gene Ontology dataset in Molecular Signature Database. Associations with overall survival following immunotherapy were estimated using cox models. Based on a clear separation between groups, an overall survival outcome of 1.5 years was used to distinguish patients with and without durable survival benefit following treatment. Area under receiving operating characteristic (AUROC) was used to determine any associations with patients' survival after immunotherapy based on the 1.5-year cutoff. **Results:** While junction counts by themselves did not predict overall survival or ^{3} 1.5-year survival, we identified statistically significant interactions between antigen presentation and junctions counts using multiple antigen presentation gene sets. For example, a gene set representing the "regulation of antigen processing and presentation of peptide antigen" demonstrated a highly significant interaction with junctions (p=0.0026) and was predictive of overall survival (p=0.003). This interaction also predicted 1.5-year or greater survival with an AUROC of 0.82. While junction counts in tumors with high expression of antigen presentation gene sets were associated with improved survival outcomes, high junction counts in tumors with low expression of antigen presentation gene sets were associated with worse survival. **Conclusion:** In the context of preserved antigen presentation, chromosomal rearrangements are associated with improved survival outcomes with immunotherapy. In contrast, in the absence of effective antigen presentation, chromosomal rearrangements were associated with poor survival outcomes. With the recent approval of the combination of nivolumab and ipilimumab for the frontline treatment of MPM, our approach might be useful to identify patients who would benefit the most with frontline immune checkpoint inhibitors.

Keywords: chromosomal rearrangements, Immune checkpoint inhibitors, antigen presentation

OA14 GLOBAL DISPARITIES IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

OA14.01 Family History of Cancer and Lung Cancer: information from the Thoracic Tumors Registry (TTR study)

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Introduction: Lung cancer remains the leading cause of cancer incidence and mortality worldwide. Smoking habit has been regarded as the most important risk factor for lung cancer and therefore smoking control is considered the most effective method of prevention. Nevertheless, genetic susceptibility may also affect lung cancer risk **Methods:** The Thoracic Tumors Registry (TTR) is an observational cohort multicenter study performed in Spain, including patients with lung cancer or other types of thoracic tumors. Enrollment took place between August 2016 and June 2020. The evaluation included a review of demographic, epidemiological, clinical and molecular data. A univariate analysis was used to analyze the differences between patients with or without family history of cancer. SPSS v.26 **Results:** 12,351 patients were enrolled. 667 had unknown family history of cancer and were excluded. Of the other 11,684 patients, 5,806 had a prior cancer history and 5,878 did not. The characteristics of patients with or without family history of cancer were presented in Table 1. Some patients had to be excluded due to missing or wrong data in the age data collection. The median overall survival (OS) of patients with family history of cancer was 23 months (CI 95%: 21.39-24.61) versus 21 months (CI 95%: 19.53-22.48) in the group of patients without family history, $p < 0.001$. Table 1. Characteristics of patients with or without family history of cancer

Characteristics	Family history	No family history	P value
Age at diagnosis Mean (SD), years	63.74 (9.99)	64.87 (10.15)	P<0.001
< 50 years > 50 years	479 (53.16%) 5,267 (49.31%)	422 (46.84%) 5,414 (50.69%)	P=0.026
Sex Male Female	4,127 (71.08%) 1,679 (28,92%)	4,447 (75.65%) 1,431 (24.35%)	P<0.001
Race Caucasian Other	5,748 (99.0%) 58 (1.0%)	5,686 (96.73%) 192 (3.27%)	P<0.001
Smoking status Never smoker Ex-smoker Current smoker Unknown Passive smoking Yes No Unknown	667 (11.49%) 2,656 (45.75%) 2,454 (42.47%) 29 (0.29%) 1,084 (18.8%) 810 (14.04%) 3,912 (67.16%)	723 (12.30%) 2,787 (47.41%) 2,310 (39.30%) 58 (0.99%) 1,047 (17.97%) 1043 (17.9%) 3,788 (64.13%)	P<0.001 NS
ECOG PS PS 0-1 PS ≥2 Unknown	5,062 (87.19%) 736 (12.68%) 8 (0.13%)	4,904 (83.43%) 969 (16.49%) 5 (0.08%)	NS
Stage (NSCLC) I II III IV Limited (SCLC) Extended (SCLC) Unknown	483 (8.3%) 419 (7.2%) 1414 (24.3%) 2706 (46.6%) 292 (5%) 447 (7.7%) 45 (0.9%)	467 (7.9%) 414 (7%) 1377 (23.4%) 2877 (48.95%) 232 (3.94%) 461 (7.8%) 50 (1.01%)	P=0.01
Histology Adenocarcinoma Adenosquamous carcinoma Squamous cell carcinoma Large cell carcinoma Sarcomatoid carcinoma NOS/undifferentiated Carcinoid tumors Small cell lung carcinoma	3,098 (53.37%) 52 (0.9%) 1,369 (23.58%) 148 (2.6%) 23 (0.4%) 133 (2.3%) 33 (0.57%) 692 (11.77%)	3,109 (52.89%) 106 (1.8%) 1,442 (24.53%) 163 (2.8%) 13 (0.22%) 126 (2.14%) 24 (0.41%) 734 (12.64%)	NS
Biomarkers EGFR mutated ALK translocated ROS1 translocated KRAS detected BRAF detected PDL1 positive	483 (17.44%) 126 (5.54%) 35 (3.29%) 53 (26.37%) 15 (3.96%) 953 (54.15%)	382 (13.38%) 155 (6.76%) 30 (2.53%) 106 (29.12%) 20 (4.07%) 1000 (52.66%)	NS

NSCLC: non-small cell lung cancer; NS: non-significant; PS: performance status; SCLC: small cell lung cancer; SD: standard deviation **Conclusion:** Patients with a family history of cancer were diagnosed at a younger age and were more often women. Significant differences were found regarding tobacco habit, number of limited stage small-cell lung cancer diagnosed and overall survival.

Keywords: Family History of Cancer and Lung Cancer; Thoracic tumours Registry

OA14 GLOBAL DISPARITIES IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

OA14.02 Social Vulnerability Is an Independent Risk Factor in Patients Undergoing Surgical Treatment of Lung Cancer

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Introduction: The social vulnerability has become an object of study linked to cancer. Emerging countries like Brazil have very high levels of social inequality and the problem of vulnerability becomes even more relevant. Lung cancer is one of the most common neoplasms in the country and an understanding of the role of social vulnerability in this disease is essential for the development of specific public policies. The objective is to analyze the influence of social vulnerability on surgical treatment for lung cancer. **Methods:** Retrospective study with analysis of the Hospital Cancer Registry (RHC) database of patients diagnosed with lung cancer in the city of São Paulo, from January 2000 to December 2013. RHC is a record maintained by the Oncocentro Foundation of São Paulo that collects, through trained registrars, data from cancer hospitals in the State of São Paulo. Patients with clinical stage I and who received surgery or a combination of treatments involving surgery were selected from the sample. For the analysis of the social vulnerability, the São Paulo Social Vulnerability Index (IPVS) was used, classified from 1 to 6 (1: little and 6: a lot of social vulnerability) according to the patient's address. We use georeferencing technology to classify the individual IPVS of each patient. The main outcome was mortality at 30 days and we used a logistic regression model to calculate the odds ratio (OR) of the relevant variables. To calculate the measure of association between the independent variables and survival, we used Cox regression analysis. We considered p <0.05 as significant. **Results:** A total of 7,896 records, 11.2% (881) diagnosed with clinical stage I. Of these, 523 received surgery,t and 48% (251) died by 2019. 53.2% were male (278) the mean age was 64 years (SD 10.4). As for social vulnerability, 49.6% of patients lived in areas with very low vulnerability (IPVS 2). The most prevalent cancer was adenocarcinoma (54%) and the average time between diagnosis and treatment was 28.4 days. Using the independent variables IPVS, age, histological type, and gender, logistic regression showed that IPVS (OR 1.73; p <0.001) and age (OR 2.51; p = 0.012) are risk factors for mortality in 30 days in the population of patients with clinical stage I and who received surgical treatment. Overall survival: median of 87 months (32-0). After adjusting for the independent variables, the Cox regression showed that the IPVS (HR 1.28; 95% CI 1.12 and 1.45; p = 0.000) and age (HR 1.03; CI 95 % 1.01 and 1.04; p = 0.000) are associated with greater risk, while Gender showed an HR of 0.61 (95% CI 0.47 and 0.8; p = 0.000), indicating lower risk when associated with the female. **Conclusion:** Even when diagnosed at an early stage, the social aspects contribute to the 30-day mortality of patients undergoing surgical treatment of lung cancer. It confirms that social vulnerability, by the IPVS, is an independent risk factor in the population studied.

Keywords: lung cancer, Social vulnerability, Emerging countries

OA15 UPCOMING MOLECULAR TARGETED AGENTS FOR EGFR EXON 20 INSERTION AND MET SKIPPING MUTATION
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

OA15.01 Mobocertinib in EGFR Exon 20 Insertion–Positive Metastatic NSCLC Patients With Disease Control on Prior EGFR TKI Therapy

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Introduction: EGFR exon 20 insertions (ex20ins) occur in 4%–10% of EGFR mutations in non–small cell lung cancer (NSCLC), accounting for ~2% of NSCLC. No approved therapies specifically for EGFR ex20ins+ NSCLC are available. Objective response rates (ORRs) in previously treated patients receiving first-, second-, or third-generation EGFR tyrosine kinase inhibitors (TKIs) are <10%, with a median progression-free survival (PFS) <4 months. Mobocertinib (TAK-788), an oral EGFR TKI that specifically targets EGFR with ex20ins, holds Breakthrough Therapy Designation for patients with EGFR ex20ins+ NSCLC who previously progressed on platinum-based chemotherapy (in the United States) or who had prior chemotherapy (in China), based on preliminary phase 1/2 results. **Methods:** A phase 1/2, open-label, multicenter, study of mobocertinib (NCT02716116) evaluated a dose-expansion EGFR ex20ins+ metastatic NSCLC cohort who progressed after response or stable disease for ≥6 months on any prior EGFR TKI therapy. The primary endpoint was confirmed ORR assessed by the investigator per RECIST v1.1. Other efficacy endpoints included disease control rate (DCR), duration of response (DoR), PFS (per Independent Review Committee [IRC]) and investigator, and overall survival (OS). Patients received mobocertinib 160 mg orally once daily. **Results:** Twenty patients previously treated with EGFR TKI were enrolled, with median age of 61.0 y [range: 38–78] and Eastern Cooperative Oncology Group performance status of 0 (35%) or 1 (65%); 55% female. Median number of metastatic sites was 3.5 (range: 1–6); 10 patients (50%) had baseline brain metastases. Sixteen patients (80%) received prior platinum-based chemotherapy and 13 patients (65%) received prior immunotherapy. Prior EGFR TKIs included poziotinib (n=13), erlotinib (n=5), afatinib (n=4), and osimertinib (n=4); 11/20 patients (55%) received EGFR TKIs as most recent prior treatment. Confirmed ORR was 20% per investigator and 40% per IRC (**Table**) and 95% (19/20) had target lesion reduction per IRC. Treatment-related adverse events (TRAEs) observed in ≥20% of patients were diarrhea (90%), nausea (35%), pruritus (30%), rash (25%), anemia (25%), vomiting (20%), dermatitis acneiform (20%), and fatigue (20%). Grades 3/4 TRAEs occurred in 4 patients (20%). Serious AEs occurred in 7 patients (35%). Two patients discontinued due to AEs (10%).

Efficacy Parameter	N=20
Median follow-up, mo	14.2
Median time on treatment (range), mo	7.8 (2–21)
Confirmed ORR per IRC, n (%) [95% CI]	8 (40) [19.1–63.9]
Confirmed ORR per investigator, n (%) [95% CI]	4 (20) [5.7–43.7]
Median DoR per IRC, mo [95% CI]	13.0 [5.6–not reached]
Confirmed DCR per IRC, n (%) [95% CI]	18 (90) [68.3–98.8]
Median PFS per IRC, mo [95% CI]	7.3 [3.6–13.0]
Median OS, mo [95% CI]	Not reached [14.7–not reached]
6-mo OS rate, %	94.7
12-mo OS rate, %	78.6
Confirmed ORR per IRC in patients previously treated with TKI targeting EGFR exon 20 (poziotinib), n/N (%)*	4/13 (31)
Confirmed ORR per IRC in patients previously treated with other EGFR TKIs (afatinib, osimertinib, erlotinib), n/N (%)*	4/7 (57)

*Patients may have received ≥1 TKI.

Conclusion: Mobocertinib treatment had a clinically meaningful benefit for patients with EGFR ex20ins+ metastatic NSCLC with ≥6-month disease control on prior EGFR TKI. The safety profile was manageable, similar to other patient cohorts, and consistent with the broader class of EGFR TKIs.

Keywords: non-small cell lung cancer, EGFR tyrosine kinase inhibitor, exon20 insertion

OA15 UPCOMING MOLECULAR TARGETED AGENTS FOR EGFR EXON 20 INSERTION AND MET SKIPPING MUTATION
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

OA15.02 Phase 1 Studies of DZD9008, an Oral Selective EGFR/HER2 Inhibitor in Advanced NSCLC with EGFR Exon20 Insertion Mutations

P. Janne[1], M. Wang[2], P. Mitchell[3], J. Fang[4], W. Nian[5], C. Chiu[6], J. Zhou[7], Y. Zhao[8], W. Su[9], D..R. Camidge[10], T. Yang[11], V. Zhu[12], M. Millward[13], Y. Fan[14], W. Huang[15], Y. Cheng[16], L. Jiang[17], D. Brungs[18], L. Bazhenova[19], C.K. Lee[20], B. Gao[21], S. Qi[22], X. Yu[22], C. Deng[22], K. Chen[22], X. Ye[22], L. Zheng[22], Z. Yang[22], J.C. Yang[23]

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Introduction: Approximately 2% of Non-Small Cell Lung Cancer (NSCLC) harbors EGFR Exon20 insertion (Exon20ins) mutations. There are no approved targeted therapies for this patient population, and current available therapy only provides limited clinical benefit. DZD9008 is a rationally designed selective, irreversible EGFR/HER2 inhibitor being studied in two ongoing phase 1/2 studies (NCT03974022 and CTR20192097). **Methods:** The objectives of the phase 1/2 studies are to assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of DZD9008 in NSCLC with EGFR or HER2 mutations. Both studies include dose escalation and expansion cohorts. **Results:** Between July 9, 2019 and February 5, 2021, 97 NSCLC patients with EGFR or HER2 mutations were dosed with DZD9008 (dose range: 50 mg to 400 mg, once daily). Male/Female: 44/53; Median age 59 (32-85). Patients carry EGFR sensitizing mutation, T790M double mutation, uncommon mutation, Exon20ins or HER2 Exon20ins. DZD9008 showed approximately dose-proportional PK, with a half-life of around 50 hours. DZD9008 was well tolerated up to 400 mg (MTD) once daily. The dose limiting toxicities (DLTs) were diarrhea and cardiac arrhythmia. The most common TEAEs were diarrhea (grade 3, 5.2%) and skin rash (grade 3, 1%). Fifty-six patients carrying more than 16 different subtypes of EGFR exon20ins had $\geq$ 1 post-treatment efficacy assessment. These patients received median 2 (range 1 - 10) lines of prior therapies, including prior chemotherapy 92.9% (52/56), prior EGFR TKI 44.6% (25/56) (1 patient had poziotinib treatment), onco-immunotherapy 30.4% (17/56), VEGFR antibody 41.1% (23/56), JNJ-61186372 7.1% (4/56) and others 17.9% (10/56). Twenty-four patients (42.9%, 24/56) had baseline brain metastasis. Partial response was observed at $\geq$ 100 mg dose levels. The objective response rate (ORR) was 39.3% (22/56) across all dose levels. At the dose level of 300 mg once daily, the ORR was 48.4% (15/31), and disease control rate (DCR) was 90.3% (28/31). Responses were observed in 2 patients with prior JNJ-61186372 treatment. Anti-tumor activity was observed across different EGFR exon20ins mutation subtypes. By data cut-off, the median treatment duration was 100 days (range 1 – 422). The longest duration of response was over 6 months, and 18 out of 22 responders are still responding. In addition, PR was also observed in patients with EGFR sensitizing mutation, double mutation or HER2 Exon20ins. The updated data will be presented in the meeting. **Conclusion:** DZD9008 showed a favourable safety profile and promising anti-tumor efficacy in pre-treated NSCLC with EGFR exon20ins and other EGFR or HER2 mutations. DZD9008 is currently in phase 2 clinical development in EGFR Exon20ins NSCLC.

Keywords: DZD9008, NSCLC, Exon20 insertion

OA15.03 Amivantamab in Non-small Cell Lung Cancer (NSCLC) with MET Exon 14 Skipping (METex14) Mutation: Initial Results from CHRYSALIS

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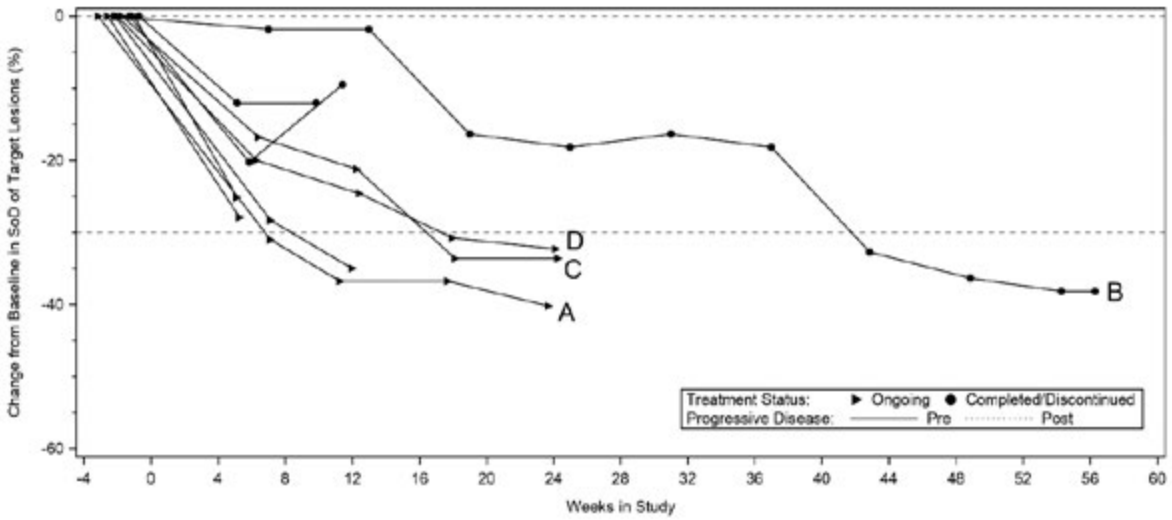
Introduction: Amivantamab, a novel, fully human bispecific antibody targeting both the epidermal growth factor receptor (EGFR) and MET, is being explored as a monotherapy in non-small cell lung cancer (NSCLC) within the CHRYSALIS study (NCT02609776), and has received Breakthrough Therapy Designation for the treatment of patients with EGFR exon 20 insertion disease, after prior treatment with platinum chemotherapy. Given the bispecific nature of amivantamab, its role in patients with MET exon 14 skipping (METex14) mutations is being explored (MET-2 cohort) in patients both naïve to and refractory to other available MET therapy. We present early results demonstrating amivantamab activity in MET-driven NSCLC. **Methods:** CHRYSALIS is an ongoing phase 1 dose escalation/dose expansion study of amivantamab in patients with advanced NSCLC. Patients with METex14 NSCLC whose disease progressed on or who declined current standard of care were treated at the recommended phase 2 dose (RP2D) of 1050 mg (1400 mg ≥80 kg) weekly in cycle 1 and biweekly thereafter. Response was assessed by the investigator using RECIST v1.1. **Results:** As of 29 Mar 2021, 16 patients with METex14 NSCLC had received amivantamab at the RP2D. Median age was 70 (range, 55–75), 69% were women, and median prior lines of therapy were 2 (range, 0–10), including prior treatment with crizotinib (n=3), capmatinib (n=1), tepotinib (n=2), and anti-MET antibody (n=1). Nine patients had at least 1 postbaseline disease assessment, 7 are pending first disease assessment; 13 remain on treatment. Antitumor activity was observed in each of the 9 response-evaluable patients, with 4 confirmed partial responses, including patients with prior anti-MET therapy (Figure). Three of the 4 responders remain on treatment (6.0–6.6+ months) with ongoing responses, and 1 discontinued after 12 months. The safety profile was consistent with previously reported experience of amivantamab at the RP2D (Sabari 2021 JTO 16(3):S108-109). Treatment-related adverse events leading to dose reduction or discontinuation occurred in 6% of patients, each. Among 7 patients who received prior MET tyrosine kinase inhibitor (TKI), baseline ctDNA demonstrated 2 patients with potential resistance mechanisms: PIK3CA mutation in one, and CDK4 and EGFR amplifications and a possible secondary MET mutation (A1251V) in the other. Five patients had no identified MET TKI resistance alteration. **Conclusion:** This report provides first evidence of amivantamab activity in MET-driven NSCLC, in addition to its previously reported anti-EGFR activity, consistent with its bispecific mechanism of action. Enrollment into MET-2 cohort is ongoing, and presentation will include updated data.

Figure. Spider Plot of Response-evaluable Patients (n=9)



Patient with cPR	Prior LOT	Prior Therapies
A	1	Cisplatin/pemetrexed
B	>5	Carboplatin/paclitaxel Carboplatin/gemcitabine Cisplatin/vinorelbine Docetaxel Nivolumab Palbociclib Crizotinib
C	2	Carboplatin/pemetrexed/pembrolizumab Pembrolizumab/bemcentinib
D	5	Carboplatin/paclitaxel/pembrolizumab Pembrolizumab Budigalimab/venetoclax DS-1062A Tepotinib

cPR, confirmed partial response; LOT, lines of therapy; SOD, sum of lesion diameters

Keywords: Amivantamab, NSCLC, MET Exon 14 Skipping

OA15.04 Telisotuzumab Vedotin (teliso-v) Monotherapy in Patients With Previously Treated c-Met+ Advanced Non-Small Cell Lung Cancer

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Introduction: Teliso-V is an anti-c-Met antibody conjugated with a tubulin inhibitor MMAE. The aim of this phase 2 trial (NCT03539536) is to explore safety and efficacy of teliso-V in cohorts (based on histopathology and EGFR mutation) and subgroups (based on c-Met expression) of patients with c-Met+ advanced NSCLC (stage 1), followed by expansion into an appropriately selected population for further evaluation of safety and efficacy (stage 2). Abstract previously submitted to, but not yet presented at AACR 2021. **Methods:** Patients had ECOG ≤ 1 with 1-2 prior lines of therapy including cytotoxic chemotherapy, immunotherapy and targeted therapy. c-Met status was determined centrally by IHC (SP44 antibody). Membrane staining ≥ 25% 3+ or ≥ 75% 1+ was considered positive for non-squamous and squamous, respectively. Teliso-V dose was 1.9 mg/kg Q2W. Primary endpoint was objective response rate (ORR) per central review in patients with ≥ 12 weeks follow-up. Secondary endpoints were duration of response, disease control rate, PFS and OS. **Results:** ORR was 35.1% in the non-squamous EGFR WT cohort (53.8% in c-Met high group and 25.0% in c-Met intermediate group; Table),but was modest in the squamous and EGFR Mu cohorts. G3 or higher AEs occurred in 50/113 (44%) patients, with most common (≥ 2%) being malignant neoplasm progression (6.2%), pneumonia (5.3%), hyponatremia (4.4%), anemia (2.7%), dyspnea (2.7%), fatigue (2.7%), increased GGT (2.7%), peripheral sensory neuropathy (2.7%), and pneumonitis (2.7%). G5 AEs investigators considered possibly related to teliso-V were sudden death, dyspnea, and pneumonitis (1 event each). **Conclusion:** ORR in non-squamous EGFR WT NSCLC was encouraging with a tolerable safety profile, and this cohort met prespecified criteria to transition to stage 2. In this cohort, ORR was highest in the c-Met high group, though also clinically meaningful in the intermediate group. Enrollment into the squamous cohort was stopped. Enrollment into the EGFR MU cohort will continue until the next interim analysis.

Table

NSCLC Group	N (Total=88)	Confirmed Responses	ORR (95% CI)
NSQ EGFR WT	37	13	35.1% (20,53)
c-Met high (≥ 50% positive, 3+ staining)	13	7	53.8% (25, 81)
c-Met int (25-49%, 3+ staining)	24	6	25.0% (10,47)
NSQ EGFR MU	30	4	13.3% (4,31)
c-Met high (≥ 50%, 3+ staining)	22	4	18.2% (5, 40)
c-Met int (25-49%, 3+ staining)	8	0	0 (-,-)
SQUAMOUS (≥ 75%, 1+ staining)	21	3	14.3% (3, 36)

Keywords: Clinical trials, Advanced non-small cell lung cancer, teliso-v

OA16 CLINICAL IMPACT OF LIQUID BIOPSY FOR PATIENTS WITH NSCLC
SUNDAY, SEPTEMBER 12, 2021 - 20:00-21:00

OA16.01 Plasma NGS At Time of Diagnostic Tissue Biopsy – Impact on Time to Treatment: Results From a Pilot Prospective Study

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Introduction: The expansion of targeted therapies has transformed the treatment landscape of advanced NSCLC, however the majority of patients do not receive guideline-recommended tumor genotyping. Molecular profiling for actionable mutations is often initiated at the first medical oncology visit leading to significant treatment delays and potentially inappropriate treatment assignments if therapeutic decisions are made prior to genomic results. The role of plasma-based genomic profiling performed simultaneously with diagnostic tissue biopsy in suspected advanced NSCLC has largely been unexplored. **Methods:** We conducted a single-arm prospective study of patients with suspected advanced (stage IIIB/IV) lung cancer based on cross-sectional imaging. Blood samples were collected at the time of tissue biopsy and sequenced using a commercial 74-gene next-generation sequencing panel. The primary outcome measure was time to treatment compared to a retrospective cohort of similar patients receiving standard of care (SOC) tissue sequencing at diagnosis or plasma-based testing at the initial oncology consult. **Results:** We analyzed comprehensive genomic profiling results from 107 newly diagnosed advanced NSCLC patients. In the prospective intervention arm, 52 NSCLC patients underwent plasma-based genomic profiling prior to a diagnostic biopsy (cohort 1). In the retrospective control arm, 55 NSCLC patients that received SOC reflex tissue genotyping (cohort 2). In cohort 1, median age was 69 years, 79% had a smoking history and 92% had a non-squamous histology, similar to cohort 2. At least one somatic variant was detected in 51/52 (98%) of pre-biopsy plasma NGS specimens. Plasma NGS identified a therapeutically informative driver mutation in 32(62%) patients (13 KRAS, 13 EGFR, 2 ERRB2, 2 MET, 1 BRAF, 1 RET). The number of driver mutations was similar in both arms. Tissue sequencing for recommended biomarkers was completed for 87% of patients in cohort 1. Concordance between tissue and plasma sequencing was 93%. Turnaround time for plasma NGS was significantly shorter compared to tissue NGS (7 vs. 28 days, $p<0.001$). Comprehensive NGS results were available prior to the first oncology visit in 85% of cases in cohort 1 vs 9% in cohort 2 ($p<0.0001$). A significantly higher percentage of patients received a specific treatment recommendation during the first oncology visit in cohort 1 compared to cohort 2 (75% vs 47%, $p=0.005$), respectively. Time to treatment was significantly shorter in cohort 1 compared to cohort 2 (12 vs. 19 days, $p=0.009$), with a shorter time to treatment in patients identified to have a specific driver mutation (10 vs. 18 days, $p=0.0007$). **Conclusion:** Our data demonstrate that plasma-based genomic profiling performed at the time of diagnostic biopsy in suspected advanced NSCLC is highly concordant with tissue sequencing and is associated with decreased time to treatment initiation compared to reflex tissue genotyping.

Keywords: Liquid biopsy, lung cancer, time-to-treatment

OA16.02 The Economic Value of Liquid Biopsy for Genomic Profiling in Advanced Non-Small Cell Lung Cancer

D. Ezeife[1], E. Spackman[2], R. Juergens[3], J. Laskin[4], J. Agulnik[5], D. Hao[1], S. Laurie[6], J. Law[7], L. Le[8], L. Kiedrowski[9], B. Melosky[4], F.A. Shepherd[7], V. Cohen[5], P. Wheatley-Price[6], R. Vandermeer[10], J. Li[7], R. Fernandes[7], A. Shokoohi[4], R. Lanman[9], N. Leighl[7]

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Introduction: Liquid biopsy (LB) detects targetable alterations in circulating tumour DNA beyond tissue testing alone (TT) in newly diagnosed advanced non-small cell lung cancer (NSCLC) patients. We estimated the cost-effectiveness of adding LB to standard TT in a public system as part of an investigator-initiated trial. **Methods:** A cost-effectiveness analysis was conducted using a decision analytic Markov model from the Canadian public payer (Ontario) perspective and a lifetime horizon in patients with treatment-naïve stage IV non-squamous NSCLC and ≤10 pack-year smoking history. LB was performed using Guardant360™ (G360), with comprehensive genomic profiling of >70 cancer-associated genes. Standard TT included single gene testing for EGFR and ALK and/or limited panel testing. Molecular testing by LB plus TT was compared to TT alone. Transition probabilities were calculated from the investigator-initiated VALUE clinical trial (NCT03576937) for patients that received systemic therapy. Costs from the Princess Margaret Cancer Centre and published literature were used, including costs for targeted therapy, chemo-immunotherapy and repeat tissue biopsy as needed. Sensitivity analyses varied costs, utilities and prevalence of genomic targets to assess uncertainty in the model. **Results:** Data for the model were derived from 146 stage IV patients, with a median age of 64 (range 23-91), 64% were female and 79% never smokers. Targetable alterations were identified in 68.5% of patients using LB and TT, compared to 52.7% using standard TT alone. For those receiving targeted therapy (N=82), median progression-free survival (PFS) was 11.4 months (95% CI: 8.3 – NR) and median overall survival (OS) was not reached. For those receiving non-targeted therapy (N=48), median PFS and OS were 9.8 months (95% CI: 4.4 – 19.5) and 19.5 months (95% CI: 10.2 – 19.5), respectively. Use of the LB + TT strategy resulted in incremental cost savings of $37,216 (95% CI: $32,158-42,171) per patient and a gain of 0.07 quality-adjusted life-years (95% CI: 0.02-0.12) compared to TT alone. Use of non-proprietary technology may increase savings up to $40,215 CAD (95% CI: $35,220 to 45,304) per patient. Major drivers of cost-effectiveness were drug acquisition costs, LB cost and prevalence of targetable alterations. **Conclusion:** The use of LB added to TT in the initial diagnosis of clinically selected patients with advanced NSCLC significantly increases the proportion of patients that can access targeted therapy and also reduces costs, primarily by avoiding inappropriate use of chemo-immunotherapy first-line.

Keywords: Liquid biopsy, NSCLC, Economics

OA16 CLINICAL IMPACT OF LIQUID BIOPSY FOR PATIENTS WITH NSCLC
SUNDAY, SEPTEMBER 12, 2021 - 20:00-21:00

OA16.03 Matched Targeted Therapy by cfDNA of CSF Beyond Leptomeningeal Metastases Progression Upon Osimertinib in EGFR-Mutated NSCLC Patients

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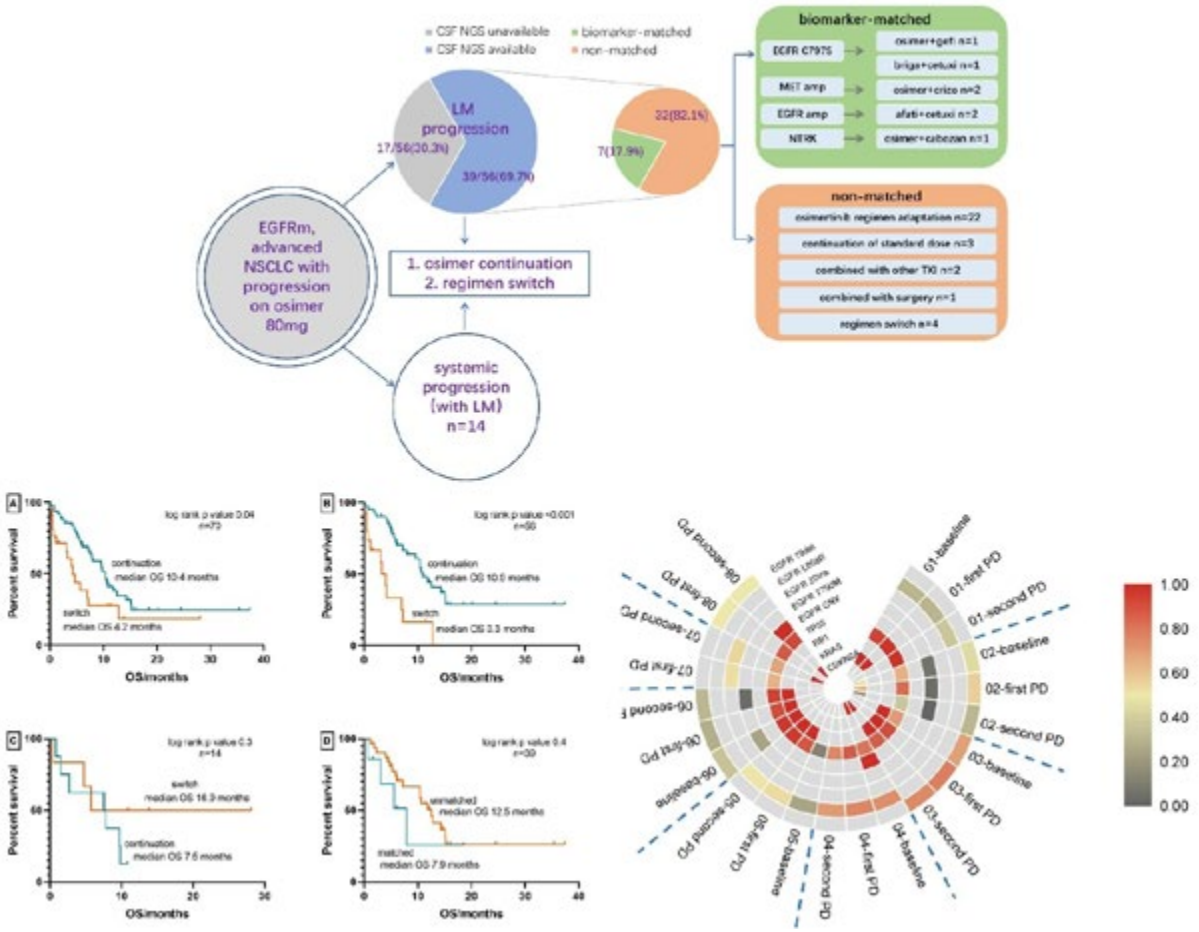
Introduction: Despite better efficacy of osimertinib for central nervous system (CNS) metastases, CNS progression is still frequently seen in EGFR-mutated NSCLC patients. Currently, clinical utility of cerebrospinal fluid (CSF) as well as subsequent treatments were unexplored after standard-dose osimertinib failure with leptomeningeal metastases (LM) progression. **Methods:** EGFR-mutated NSCLC patients who failed osimertinib 80 mg and had diagnosis of LM were included. Reasons for osimertinib failure were collected. CSF next-generation sequencing was performed where available. **Results:** A total of 112 EGFR-mutant NSCLC patients with LM who experienced osimertinib 80 mg failure were identified. Only those with LM as progression site were finally included for analysis (n=70), median age of 54 years, nearly a half female (47.1%), and predominantly never smokers (87.4%). EGFR mutations were exon 19 deletion (52.9%), L858R (41.4%) and uncommon mutations (5.7%). Among the entire cohort, continuing osimertinib had longer OS than regimen switch (10.4 versus 4.2 months, P=0.04). This benefit of continuation maintained in the LM-only progression group (10.9 versus 3.3 months, P<0.001), not in the systemic progression group (7.5 versus 16.9 months, P=0.3). Based on CSF NGS at the time of LM-only progression upon osimertinib, resistant mechanisms were found: C797S mutations, MET copy number gain, EGFR copy number gain and NTRK fusion. These patients then received matched treatments and showed a median OS of 7.9 months. Matched targeted therapies indicated no difference in OS compared with unmatched group (7.9 versus 12.5 months; P=0.4). Serial monitoring by CSF also saw dynamic changes of genetic alterations (KRAS, CDKN2A) at baseline, first and second osimertinib progression.

(Figure)



Conclusion: For patients who failed osimertinib with LM as the progression site, continuation of osimertinib demonstrated an improved OS. Besides, biomarker-matched therapy based on CSF NGS might be considered beyond LM progression upon osimertinib.

Keywords: leptomeningeal metastases, matched therapy, cerebrospinal fluid

OA16 CLINICAL IMPACT OF LIQUID BIOPSY FOR PATIENTS WITH NSCLC
SUNDAY, SEPTEMBER 12, 2021 - 20:00-21:00

OA16.04 A Combined Model of Clinical, Imaging and DNA Methylation Biomarkers to Improve the Classification of Pulmonary Nodules

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Introduction: Early detection is the key to reducing lung cancer related deaths. Accurate malignant-benign classification of pulmonary nodules is still a great diagnostic challenge. Our previous studies (DOI: 10.7150/thno.28119; 10.1172/JCI145973) have established a blood-based DNA methylation model (PulmoSeek) to tackle this problem. Here we described a novel combined model of clinical, imaging and blood-based DNA methylation biomarkers, termed "PulmoSeek Plus", to further improve the classification of pulmonary nodules. **Methods:** In a prospective-specimen collection and retrospective-blinded-evaluation (PRoBE) trial, 1,097 patients with a solitary pulmonary nodule (5-30 mm in diameter) detected by CT/LDCT and no prior history of cancer were enrolled from thoracic surgery departments. We analyzed over 60 radiomic features from CT images that quantified characteristics of pulmonary nodules. A combined clinical (age, gender, smoking status, and family history of cancers) and imaging biomarkers model (CIBM) was developed in a training set (653 malignant and 186 benign nodules) and the locked model was validated in a validation set (214 malignant nodules, 88.3% in Stage I, and 44 benign nodules). The clinical risk predictions were calculated using the Mayo model and Brock model, and the PulmoSeek model was also validated, in this validation set. A novel combined model of clinical, imaging and blood-based DNA methylation biomarkers, termed "PulmoSeek Plus", developed by the integration of the predictions of CIBM model and PulmoSeek model using logistic regression, was evaluated with 5-fold cross-validation in the same validation set. The ROC curves were compared to evaluate the diagnostic performance among the CIBM, PulmoSeek, PulmoSeek Plus, Mayo, and Brock model, pathologic diagnosis as the gold standard. **Results:** AUCs for the CIBM, PulmoSeek and PulmoSeek Plus model in the validation set were 0.85 (95% CI 0.79-0.91), 0.87 (95% CI 0.82-0.91) and 0.91 (95% CI 0.87-0.95), respectively. All three models showed improved accuracy over the Mayo model (AUC=0.60, 95% CI 0.52-0.68) and the Brock model (AUC=0.70, 95% CI 0.63-0.77). The sensitivity of the CIBM, PulmoSeek and PulmoSeek Plus model for rule out at a fixed specificity of 50.0%, were 91.6% (95% CI 0.88-0.95), 90.7% (95% CI 0.87-0.94) and 98.6% (95% CI 0.97-1.00), respectively. The sensitivity of the PulmoSeek Plus model in Stage IA1 (n=48), IA2 (n=86), IA3 (n=31) and IB (n=24) were 97.9% (95% CI 0.96-1.00), 98.8% (95% CI 0.98-1.00), 96.8% (95% CI 0.95-0.99) and 100.0% (95% CI 1.00-1.00), respectively. The sensitivity of the PulmoSeek Plus model were 100.0% (95% CI 1.00-1.00) in sub-centimeter nodules (n=111), 98.2% (95% CI 0.97-1.00) in nodules ≥10 and 20 mm in size (n=69), and 98.6% (95% CI 0.97-1.00) in nodules ≥20 and ≤30 mm in size (n=34). The PulmoSeek Plus model showed a significantly improved accuracy over the CIBM and PulmoSeek model, 90.3% (95% CI 0.87-0.94) vs 84.5% (95% CI 0.80-0.89) vs 83.7% (95% CI 0.79-0.88). **Conclusion:** PulmoSeek Plus, integration of clinical, imaging and DNA methylation biomarkers, is an accurate tool for the early detection and classification of pulmonary nodules with an overall accuracy of 90.3%, a sensitivity of 98.6% and a specificity of 50.0%, potentially reducing the rate of unnecessary invasive procedures.

Keywords: DNA methylation biomarkers, Pulmonary nodules, Malignant-benign classification

OA17.01 Core Supportive Care for People Living With Lung Cancer During COVID-19: Analyses of Specialist Lung Cancer Nursing Practice

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Introduction: Evidence now suggests that people living with lung cancer have a high susceptibility to the SARS-CoV-2 virus, experience disproportionately worse outcomes if infected with the virus, and are living with raised levels of vigilance and stress compared to people living with other cancer types. Specialist lung cancer nurses (SLCNs) have been instrumental and transformational in pandemic response management, working to ensure that this patient cohort is appropriately supported emotionally and physically, while developing and implementing policies and protocols to facilitate the provision of such support in a safe and timely manner. In this view, with a Latourian lens, a praxiographic study was undertaken with the objective of providing recommendations on core supportive care practices discrete to people living with lung cancer through the COVID-19 pandemic. **Methods:** Process mapping of pre-pandemic and mid-pandemic (3rd quarter 2020) patterns of care delivery was undertaken by the Research Committee of the Australia and New Zealand Lung Cancer Nurses Forum (ANZ-LCNF) with ANZ-LCNF members who agreed to participate in this study. A 2-stage analytical process followed. First, content analysis of pre- and mid-pandemic process maps was conducted per member participant to elucidate differences and similarities in care delivery. All data reflective of 'differences' in practice were then merged and preliminary concepts derived; the same process performed for 'similarities'. Second, a theoretically driven analysis was conducted to understand the complex work performed by SLCNs during the pandemic environment. Informed by the preliminary concepts, drawing on Latourian concepts of multiplicity, effacement, symmetry and convergence, a praxiographic teasing out of what happened for SLCNs and the patients for whom they care assembled higher-level themes reflective of practice change due to the pandemic environment. **Results:** Specialist lung cancer nurse practice, patients and health systems experienced disruption due to COVID-19 pandemic and which served to upset the complex and sometimes fragile workings of relative health-related networks. De-coupling of services, tele-practice, ambulatory expertise, and counsel reflect the ways SLCN practice has pivoted in view of such disruption. This underscores the importance of SLCNs establishing robust and functional partnerships with all entities in healthcare networks to facilitate optimal supportive cancer nurse care. **Conclusion:** COVID-19 continues to make an impact on people living with lung cancer. Analyses of pre- and mid-pandemic SLCN practice has defined recommendations for optimal supportive cancer nurse care. It is important to promote this crucial work to ensure all people living with lung cancer in this rapidly changing environment receive optimal care.

Keywords: Specialist lung cancer nurse, COVID-19 pandemic, Core supportive care

OA17.02 COVID-19 Pandemic and Mental Health Status of Lung Cancer Patients in Indonesia

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Introduction: COVID-19 pandemic has brought massive changes to various aspects of life, which create psychological distress and have led to an increase in mental health disorders, especially in patients who need regular visits to hospital as lung cancer patients. To date, there has been no data available related to depression status during the pandemic in lung cancer patients. **Methods:** We have conducted a cross sectional study in Thoracic Oncology Outpatient Clinic in Persahabatan National Respiratory Referral Hospital Jakarta, Indonesia. We ask the patients using Patients' Health Questionnaire-9 (PHQ-9) for their experience during COVID-19 pandemic. This study has been approved by ethical committee Faculty of Medicine University of Indonesia number 21-01-0053/2020. **Results:** This preliminary result consisted of only eighteen lung cancer patients, with mostly male (66.7%), living mostly in Jakarta greater area (88.9%). Stage II consist of 5.6%, stage III 27.8% and stage IV 66.7%, with current treatment are chemotherapy (72.2%), targeted therapy 22.2%, and radiotherapy 16.6%. Using validated Bahasa Indonesia PHQ-9, we found 50% of patients were experiencing depression during COVID-19 pandemics. **Conclusion:** This preliminary study showed high prevalence of depression of lung cancer patients during COVID-19 pandemics, and would influence their quality of life. We currently awaits for the final results of this study.

Keywords: COVID-19, mental health, depression

OA17.03 Clinical and Social Impact of COVID-19 Pandemic in Patients with Thoracic Malignancies

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Introduction: Evidence has accumulated indicating that lung cancer patients have represented a vulnerable population throughout the COVID-19 pandemic. Limited information is available in Latin America regarding the overall detrimental effects of depression, anxiety, and distress due to the ongoing pandemic. This study aimed to determine the prevalence and impact of psychological disorders due to the COVID-19 pandemic in the medical attention and survival of patients with thoracic cancers. **Methods:** To determine the impact of COVID-19 in the mental health of thoracic cancer patients, specialized psychiatrists and psych-oncologists performed a cross-sectional mental health evaluation in a single center between March 1st, 2020, to February 28th, 2021. For this purpose, models were developed to test the association between mental health status and delays in medical care, and a second model to test the association between delays in care and survival effects. A logistic regression model was built with binary variables describing timeliness in treatment during the COVID-19 pandemic and the DASS-21 dichotomous explanatory self-reported anxiety, depression, and stress subscales. Scientific and bioethical committees of the Instituto Nacional de Cancerología (INCan) approved this study (020/043/ICI) (CEI/1493/20). **Results:** Five hundred and forty-eight patients were eligible for the analysis. The mean age was 61.5±12.9 years, non-small cell lung cancer (NSCLC) was the most seen neoplasm (86.9%), advanced stages predominated (80%), and the majority of patients were under active therapy (82.8%). The mean DASS-21 score was 10.45, being women more affected than men (11.41 vs. 9.08, p<0.001) in the overall scale and on each subscale (p<0.001). Anxiety was reported in 30.5% of cases, followed by depression and distress in equal proportions (18%). Any change in treatment was reported in 23.9% of patients, of whom 78.6%% were due to the COVID-19 pandemic. Delays (≥ 7 days) were the most frequent treatment change in 41.9%, followed by treatment suspension at 37.4%. After adjusting for age and sex, patients with thoracic neoplasms and depression had 4,5 higher odds of experiencing delays on treatment (95% CI 1.53 to 13.23, p= 0.006). Similarly, patients with stress had 3,18 higher odds of experiencing delays (95% CI 1.0 to 10.06, p= 0.006). Anxiety was not associated with delays in care. Moreover, patients without changes in its cancer treatment had a more prolonged progression-free survival and overall survival, [HR 0.21, p<0.001] and [HR 0.28, p<0.001]. **Conclusion:** There is enough evidence to suggest that depression among patients with thoracic neoplasms is associated with treatment delays. Changes in primary treatment, especially delays due to pandemic, were associated with lower survival rates than those without changes.

Keywords: SARS-COV2, Thoracic cancers, COVID-19 pandemic

OA17.04 The Global Impact of COVID-19 on Telehealth and Care for Persons With Thoracic Cancers

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OA18 REAL WORLD DATA IN A MODERN WORLD
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA18.01 Lung Cancer in Vietnam

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Introduction: Lung cancer is an oncologic public health challenge, with widening global disparities. Characterizing nation-level resources and patterns of care is vital to dissemination of knowledge, technology and other resources needed in the global fight against lung cancer. Vietnam, a low/middle-income country with a population of 96 million, has high lung cancer incidence and mortality. **Methods:** As part of a Global Health collaboration between Vanderbilt University and the National Cancer Institute of Vietnam, we conducted an inventory of lung cancer care delivery infrastructure, patterns and outcomes of lung cancer care using data from the Vietnam National Cancer Institute and Ministry of Health. **Results:** Lung cancer is the second most common cancer and second leading cause of cancer-related deaths among Vietnamese; the most common cancer among men and fourth leading cancer among women. Approximately 15.5 million Vietnamese, mostly men, actively smoke (Table). Currently, there are no national lung cancer screening guidelines or programs in Vietnam. Approximately 30% of cases are incidentally detected via computed tomography examination; >80% are non-small cell lung cancer (NSCLC), 69% of which are adenocarcinoma; 70-80% are diagnosed at stage III or IV; 35% have EGFR, 23% KRAS and 7% ALK gene mutations. Most cancer cases are referred to provincial/central hospitals for diagnosis confirmation and first line treatment. For patients with stages I and II NSCLC, surgical resection is recommended to be performed at provincial/central hospitals. From hospital registry data, approximately 13%, 20.3%, and 74.2% of lung cancer patients receive surgical treatment, radiation therapy, and chemotherapy, respectively. Within the five largest oncology hospitals in Vietnam, there are 42 specialty lung cancer surgeons, 389 medical oncologists, 79 radiation oncologists, 50 pulmonologists, 103 radiologists, 46 pathologists, and 40 palliative care specialists. Palliative care units have been established within five provincial/central hospitals. There are currently 58 linear accelerators for 3-dimensional conformal radiation therapy in Vietnam. Older radiation techniques, such as cobalt-60 external radiotherapy machines, however, are still in use due to their low cost. The aggregate 1-year lung cancer survival rate is 42%, and the 5-year survival rate is 16%.

Lung Cancer Epidemiology and Resources for Care Delivery in Vietnam	
Variable	Statistic
Epidemiology Annual new lung cancer cases Annual lung cancer deaths Age-standardized incidence rate/100,000 Age-standardized mortality rate/100,000 Stage distribution (2016 – 2018)- % I II III IV Unknown	26,262 (2020) 23,797 (2020) Males: 27-35; Females 11 – 12 26 1 4 19 55 21
Prevalence of Current Smoking (year) Men Women	72.8% (1990); 45% (2015) 4.3% (1990); 1.1% (2015)
Cancer Care delivery infrastructure National Health Insurance system (since 1993) Number of: Comprehensive Cancer Centers (location) Hospitals with Oncology Services PET-CT scanners Linear accelerators Regional Cancer Registries (Provinces)	Population covered 77% (2015); 90% (2020) 5: National Cancer Hospital, Hanoi Oncology Hospital, Hanoi (North Vietnam); Hue Oncology Hospital, Hue City (Central Vietnam); Ho Chi Minh City Oncology Hospital, Cho Ray Hospital, Ho Chi Minh City (South Vietnam) 70 9 58 9 (Hanoi, Thai Nguyen, Hai Phong, Thanh Hoa, Hue, Da Nang, Can Tho, Kien Giang and Ho Chi Minh City).
Human resources for specialty lung cancer care Lung cancer surgeons Medical Oncologists Radiation Oncologists Pulmonologists Radiologists Pathologists Palliative care specialists	42 389 79 50 103 46 40
Patterns of care delivery: percentage of hospital registry patients using treatment modalities Surgical resection rate Radiation therapy Chemotherapy Receipt of targeted therapy Palliative care	13% 20% 74% 8% 61

Conclusion: Lung cancer is a major public health burden in Vietnam. Developing effective smoking cessation and lung cancer screening programs, as well as improvements in the quality of lung cancer care are top priorities to reduce the adverse public health impact of lung cancer in Vietnam.

Keywords: Lung cancer care, Smoking Cessation, vietnam lung cancer

OA18 REAL WORLD DATA IN A MODERN WORLD
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA18.02 Canprim Beyond Oncology Into Primary Care Cancer Distress Follow-up Study Among Outpatients

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Introduction: In developed regions distress screening for cancer patients has become a hallmark of oncology care, but it is not yet included as a quality of care metric in primary care settings. A greater understanding of psychosocial pathways beyond oncology care is vital, yet, at present, there is a lack of research among cancer outpatients in this area in Romania. Outpatients at-risk of developing cancer distress, including fear of cancer reoccurrence, represent a vulnerable group that needs to be recognized, and their quality of life, information needs, and concerns have to be identified and followed in time. **Methods:** The CANPRIM project is the first nation-wide study to build evidence focused on psychosocial burdens, distress, and pathways among cancer outpatients in primary care settings in Romania. It will develop an interdisciplinary research platform with primary care providers (PCPs) involved from 41 counties to assess psychosocial determinants of cancer outpatients' illness trajectory beyond oncology care. It aims to follow-up cancer distress, quality of life, information needs, and concerns in cancer outpatients facilitated by an innovative psychosocial assessment approach. It will study cancer outpatients most likely to benefit from future cancer distress management interventions, and it will follow them in the illness continuum from beyond oncology into primary care. Main objectives: a.) build the evidence focused on psychosocial burdens, distress, and pathways in cancer outpatients; b.) it is crucial to better understand the role and negative impact of elevated cancer distress in outpatients; c.) study cancer outpatients most likely to benefit from future cancer distress management interventions. Our specific aims are to foster cancer distress detection in primary care settings, to support in-time evaluation of the quality of life, information needs, and concerns of cancer outpatients in Romania, and to raise awareness about fear of cancer recurrence in order to reduce delayed psychosocial help-seeking among cancer outpatients with significant psychosocial risks. **Results:** The CANPRIM project will lead to an advance in scientific knowledge and understanding of cancer distress, quality of life, need for information, patients' concerns, and fear of cancer recurrence in primary care settings in Romania, based on current theories and methodological approaches concerning these research topics. Thus, the potential to build evidence in this area and to influence the psychosocial activity of primary care services providers (PCPs) is considerable. Eventually, the CANPRIM project will enhance the capacity of our current care system to deliver psychosocial services to individuals with cancer in Romania. The first results will be presented. **Conclusion:** Psychosocial assessment in primary care has the highest potential for reducing cancer distress in cancer outpatients because screening identifies patients at risk for ongoing psychological problems and unmet psychosocial care needs. In this perspective, the CANPRIM project will contribute to a better quality of care, and quality of life, for cancer outpatients in Romania. Acknowledgement.

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OA18 REAL WORLD DATA IN A MODERN WORLD
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA18.03 LUNGCOVID: SARS-CoV-2 Infection in Patients With Thoracic Tumors - Multicenter Observational Study in Portugal

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Introduction: Since the beginning of the COVID-19 pandemic, health care system was readjusted and thoracic cancer patients with COVID-19 were studied in international registries. In patients with malignant thoracic neoplasms the differential diagnosis is complex, due to the location of the disease and symptoms related to cancer. Age, smoking status, comorbidities, previous corticotherapy treatment, performance status and stage of thoracic malignancies have been described as prognostic factors. Some registries and series of COVID-19 in thoracic malignancy patients reported mortality rates of 26% (CCC-19), 32% (TERAVOLT), 39% (UKCCMP) and even 47% (Dutch Oncology COVID-19 Consortium). A national survey on the impact of COVID-19 in lung cancer patients´ treatment has been presented by the Portuguese Lung Cancer Study Group. However, a national study of COVID-19 patients with thoracic malignancies has not been done. Objectives: To access the frequency and severity of COVID-19 in Portuguese patients with thoracic malignancies, and to study clinical manifestations, intensive care admission and factors associated with a worst outcome. **Methods:** LUNGCOVID is a multicenter national observational study. Patients with primary thoracic malignancy, age 18-years-old and SARS-CoV-2 infection diagnosed by reverse-transcriptase polymerase chain reaction or antigenic test since March 2020, will be eligible. Clinicopathological characteristics will be accessed by reviewing medical records. The variables to be studied are: age, sex, performance status, smoking habits, presence of comorbidities, previous corticotherapy treatment, factors related to the underlying cancer disease (stage of the disease, histological type), treatments, previous chest radiotherapy, oncologic systemic treatment, COVID-19 symptoms, need of intensive care admission and survival. **Results:** Section not applicable **Conclusion:** Section not applicable.

Keywords: SARS-CoV-2, thoracic tumors, Outcome

OA19 SCREENING AND EARLY DETECTION: STATE OF THE ART
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA19.01 Prospective Study of Lung Cancer Screening Criteria: USPSTF2013 vs PLCOm2012 – International Lung Screening Trial (ILST) Results

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Introduction: Low-dose computed tomography lung cancer screening has been demonstrated to substantially reduce lung cancer mortality. Lung cancer screening is most effective when applied to high-risk individuals. One approach to determining eligibility is based on categorical age/pack-years/quit-years, which has been exemplified by the United States Preventive Services Task Force (USPSTF2013) eligibility criteria: age 55-80 years, ≥30 pack-years smoked, and in former smokers quit ≤15 years. Many comparative studies have found that determining screening eligibility using a validated risk prediction model, such as the PLCOm2012, is more effective. Most of these studies have been retrospective and trial based. The ILST is a large, multinational, population-based prospective study that enrolled individuals for screening if they were USPSTF criteria or PLCOm2012 positive. The aim of this study was to determine which criteria was most sensitive at identifying individuals who would be diagnosed with lung cancer and to determine which selection method led to the most total potential years of life gainable. **Methods:** A total of 5819 individuals were scan in Canada, Australia, Hong Kong and the U.K. PLCOm2012 risk ≥1.7%/6y selected exactly the same number of individuals for screening as did the USPSTF2013 criteria. For our analysis, we used this PLCOm2012 threshold for comparisons. Missing data were imputed with multiple imputations. Differences in the proportion of lung cancers detected by USPSTF versus PLCOm2012 were compared using the binomial exact method. Even though it was anticipated that the PLCOm2012 would detect more cancers, they may occur in older individuals with more comorbidities and with shorter life expectancies. Therefore, to make an objective comparison of true benefit between the two approaches, we compared the total number of life years potential gainable in lung cancer patients by each of the criteria. To do this we apply a parametric Weibull survival model which predicted median life expectancy of each participant. The model predictors of all-cause mortality included age, sex, body mass index, number of comorbidities, lung cancer status (no cancer, early stage, or advanced stage lung cancer) and four smoking exposure predictors. The differences in potential life-years were compared between criteria and confidence intervals and p-value were prepared with bootstrap resampling with 1000 re-samplings. **Results:** After a median follow-up of 2.27 years in both groups, lung cancer was diagnosed in 125 individuals who were USPSTF2013 positive and in 151 individuals who had PLCOm2012 risks ≥1.7%/6y ($p<0.001$) (N=4540 in each group). Those who were PLCOm2012≥1.7%/6y were older (65.7y vs 63.3y) and had more comorbidities (mean 3.0 vs 2.7) than those who were USPSTF positive. In the individuals diagnosed with lung cancer, the difference in total life-years potentially livable if lung cancer death was averted, PLCOm2012≥1.7%/6y minus USPSTF2013 positive) was 258.9 life-years (95% CI 34.2 to 503.3, $p=0.012$). **Conclusion:** In this prospective, multinational, population-based study, the PLCOm2012 approach selects significantly more individuals diagnosed with lung cancer. In spite of selecting individuals who were older and had more comorbidities, the overall weighted balance of life years potentially liveable if lung cancer deaths were averted significantly favours using the PLCOm2012 criteria.

Keywords: USPSTF PLCOm2012 criteria, Prospective cohort study, screening eligibility criteria

OA19 SCREENING AND EARLY DETECTION: STATE OF THE ART
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA19.02 The UKLS Trial Outcome Results: Lung Cancer Mortality Reduction by LDCT Screening Confirmed in an International Meta-analysis

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OA19 SCREENING AND EARLY DETECTION: STATE OF THE ART
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OA19.03 Differences in Detection Patterns, Characteristics, and Outcomes of Central and Peripheral Lung Cancers in Low-Dose CT Screening

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Introduction: Although low-dose computed tomography (LDCT) screening is known to be effective for the detection of lung cancers localized in peripheral lung regions at a curable stage, limited data is available regarding the characteristics and outcomes of central lung cancers diagnosed in a screening cohort. This study aimed to determine whether LDCT screening could effectively detect central lung cancers at an early stage and offer survival benefits. **Methods:** We analyzed 52,615 adults who underwent lung cancer screening with LDCT between May 2003 and Dec 2019 at a tertiary center in South Korea. Characteristics and outcomes of those diagnosed with lung cancer, stratified by screen-detection status and cancer location, were evaluated. **Results:** A total of 352 individuals (281 screen-detected, 71 non-screen-detected) were diagnosed with lung cancer. Compared to screen-detected cancers, non-screen-detected cancers tended to be centrally-located (11.4% vs. 64.8%, p<0.001). Most non-screen-detected central cancers (89.1%) had a negative result on prior LDCT screening. Multivariable regression analyses revealed that for peripheral cancers, screen-detection was associated with a significantly lower probability of diagnosis at an advanced stage (III/IV, odds ratio (OR)=0.15, 95% confidence interval (CI)=0.05–0.45) and mortality (hazard ratio (HR)=0.33, 95% CI=0.13–0.84); however, the association was insignificant for central cancers. For screen-detected cancers, central location, compared to peripheral location, was significantly associated with a higher risk of diagnosis at an advanced stage (OR=20.83, 95% CI=6.67–64.98) and mortality (HR=4.98, 95% CI=2.26–10.97). **Conclusion:** Unlike for peripheral cancers, LDCT screening did not improve early detection and outcomes of central lung cancers, indicating an important limitation of LDCT screening and the need for developing novel modalities to screen and treat central lung cancer.

Keywords: low-dose computed tomography, lung cancer screening, central lung cancer

OA19 SCREENING AND EARLY DETECTION: STATE OF THE ART
MONDAY, SEPTEMBER 13, 2021 - 17:30-18:30

OA19.04 Potential Clinical and Economic Impact of Missed Lung Nodules – A Claims Database Analysis

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Introduction: Lung cancer leads to more than 200,000 new cases and 130,000 deaths each year and comprises 25% of cancer-related deaths in the U.S. Early detection is important for survival; the 5-year relative survival rate for localized disease is 61%, compared to 35% for non-metastatic, regional disease and 6% for metastatic disease. **Methods:** To calculate the clinical and economic impact of a potential missed lung cancer diagnosis, we examined claims data in IBM® Marketscan® database between 1/1/2013 and 4/30/2020. We identified patients that had Chest Computed Tomography (CT) with no record of cancer prior to CT. We identified patients diagnosed with localized disease within 30 days following the chest CT (Group 1) and patients diagnosed with distant disease one year after the CT (Group 2). All patients had at least 30 days of continuous insurance coverage after the date of cancer diagnosis. We collected median costs of claims per patient, both total and within 30 days of diagnosis, during the study period. Clinical impact of diagnosis was evaluated as the median number of days from diagnosis to the patient's first encounter with palliative care (EPC) and grouping end of life (EOL) events using claims coded as "do not resuscitate", "cardiac arrest", "respiratory arrest", "cachexia" or "adult failure to thrive". **Results:** Group 1 consisted of 765 patients diagnosed with localized disease within 30 days of the original chest CT. Group 2 consisted of 522 patients diagnosed with distant disease one year after the original CT, with no intervening CTs between the original CT and diagnosis of distant disease. Clinical impact for Group 1 was associated with a median time to EPC of 287 days and a median of 132 days to EOL from date of diagnosis. In Group 2, the median time to EPC was 74.5 days and median time to EOL was 53 days . The economic impact of each approach was measured. Group 1 had a median 30-day cost per patient from the day of diagnosis of $12,467 and a median total cost per patient of $77,361 from date of diagnosis to the end of the study period. Group 2 had a median 30-day cost per patient of $26,184 and a median total cost per patient of $110,531. All patients with advanced disease in this study had a chest CT with no associated cancer diagnosis one year prior to ultimate cancer diagnosis. In some cases, findings of cancer may have been missed on the original CT. This evaluation allowed us to calculate the potential clinical and economic impact of missing lung nodules in chest CTs. To our knowledge, this is the first systematic use of claims data to identify these types of relevant outcomes. **Conclusion:** To help improve early diagnosis of lung cancer, peer review of CTs and the use of AI-enabled imaging technologies may facilitate early detection of lung cancer and minimize potential misses of lung cancer diagnoses. Along with analysis of claims data, these approaches hold significant promise to improve outcomes and reduce costs associated with lung cancer.

Keywords: Claims data, missed finding, lung cancer

OA20 EXPLORING TREATMENT MODALITIES AND TOOLS IN LOCALLY ADVANCED NSCLC
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

OA20.01 Long Term Survival in Operable Stage Iiia Nsclc Patients Treated With Neoadjuvant Nivolumab Plus Chemotherapy - Nadim Study

M. Provencio[1], E. Nadal[2], A. Insa[3], M.R. García Campelo[4], D. Pereiro[5], M. Domine[6], M. Majem[7], D. Rodriguez Abreu[8], A. Martinez-Marti[9], J. De Castro[10], M. Cobo[11], G. López Vivanco[12], E. Del Barco[13], R. Bernabé[14], N. Viñolas[15], I. Barneto[16], S. Viteri[17], E. Pereira[18], A. Royuela[1], M. Casarrubios[1], C. Salas[19], E.R. Parra[20], I. Wistuba[21], V. Calvo[1], R. Laza - Briviesca[1], A. Romero[1], B. Massuti[22], A. Cruz[1]

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Introduction: Neoadjuvant chemoimmunotherapy been shown to be highly effective in resectable stage IIIA NSCLC. Now we provide long term survival data **Methods:** This was an open-label, multicentre, single-arm phase 2 trial in which patients with histologically or cytologically documented stage IIIA NSCLC and Eastern Cooperative Oncology Group performance status of 0 or 1 and who were deemed locally to be surgically resectable by a multidisciplinary clinical team were treated with neoadjuvant intravenous paclitaxel (200 mg/m2) and carboplatin (area under curve 6; 6 mg/mL per min) plus nivolumab (360 mg) on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant intravenous nivolumab monotherapy for 1 year (240 mg every 2 weeks for 4 months, followed by 480 mg every 4 weeks for 8 months). Here we report progression-free survival (PFS) and Overall survival (OS) at 36 and 42 months, assessed in the modified intention-to-treat population (ITT), which included all patients who received neoadjuvant treatment, and in the per-protocol population (PP), which included all patients who had tumour resection and received at least one cycle of adjuvant treatment. **Results:** Median follow-up time was 37.9 months (95%CI: 36.7-40.7), with a 94% maturity at 36 months. Among the ITT population (N=46), 37 patients, constituting the PP population, received subsequent adjuvant therapy. Of them, 27 (58.7%) patients completed the adjuvant treatment (16 cycles), 10 (21.7%) patients received between 3 and 15 cycles of adjuvant therapy, and 9 (19.6%) patients did not receive adjuvant therapy. At the time of data cutoff (March 2021), progression disease was diagnosed in 14 patients and 9 deaths were recorded in the ITT population. Of these, three deaths corresponded to patients who did not undergo surgery and had disease progression, four deaths corresponded to patients who underwent surgery and had disease progression, and the two remaining deaths corresponded to patients who were diagnosed as being disease free but died from COVID19 infection. Notably, among patients who could not undergo surgery (N=5), one of them is still alive and with no evidence of disease. PFS at 36 and 42 months in the ITT population were 69.6% (95%CI: 54.1-80.7), in both cases. Similarly, PFS at 36 and 42 in the PP population were 81.1% (95%CI: 64.4-90.5) in both cases. The percentage of patients who were alive at 36 and 42 months in the modified ITT population were 81.86% (95% CI: 66.8-90.6) and 78.94% (95%CI: 63.1-88.6), respectively. Likewise, OS at 36 and 42 months in the PP population was 91.0% (95%CI: 74.2-97.0) and 87.3% (95%CI: 69.3-95.1), respectively. **Conclusion:** The efficacy of nivolumab in combination with platinum-based chemotherapy in patients with resectable stage IIIA NSCLC is clearly supported by long term survival data.

Keywords: NADIM trial, neoadjuvant chemo-therapy, long term survival

OA20 EXPLORING TREATMENT MODALITIES AND TOOLS IN LOCALLY ADVANCED NSCLC
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OA20.02 Pre-Treatment Levels of ctDNA for Long-term Survival Prediction in Stage IIIA NSCLC Treated With Neoadjuvant Chemo-Immunotherapy

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OA20.04 Survival of Patients with Persistent N1 or N2 Disease After Induction Therapy for Stage IIIA-N2 Non-Small-Cell Lung Cancer

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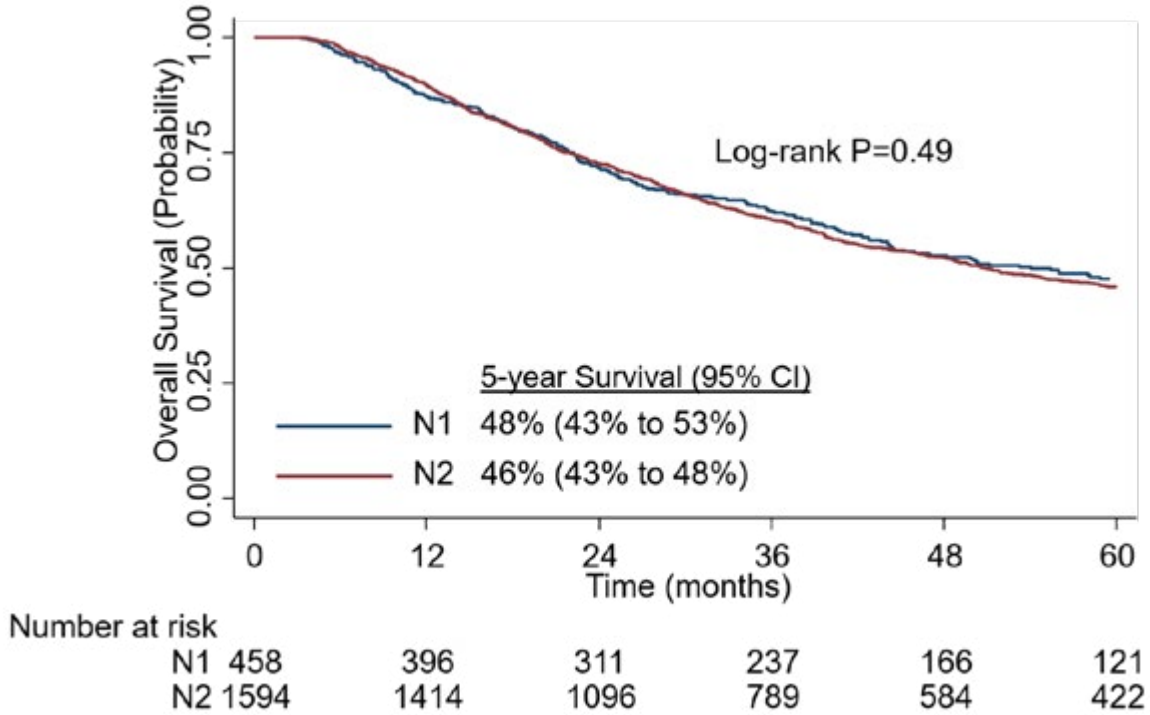
Introduction: The role of surgery for patients with stage IIIA-N2 non-small-cell lung cancer (NSCLC) who have persistent nodal disease after induction chemotherapy or induction chemoradiation is unclear. The objective of this study is to evaluate the long-term survival of patients with Stage IIIA-N2 NSCLC who undergo surgery for persistent N1 or N2 disease following induction therapy. **Methods:** Overall survival of patients with clinical T1-3 N2 M0 who underwent lobectomy after induction chemotherapy or induction chemoradiation and had pathologic N1 (pN1) or N2 (pN2). NSCLC in the National Cancer Data Base from 2004 to 2017 was evaluated using Kaplan-Meier analysis. **Results:** From 2004-2017, there were 2,230 patients that underwent lobectomy following induction therapy for cT1-3N2M0 NSCLC who were then found to have pN1 or pN2 disease. Of these patients, 1,085 (49%) received induction chemotherapy and 1,145 (51%) received induction chemoradiation. In the induction chemotherapy group, the two-year survival was 72% ([95% CI: 65%-77%]) for patients with pN1 disease and 73% ([95% CI: 70%-76%]) for patients with pN2 disease. The five-year survival was 47% ([95% CI: 39%-55%]) for pN1 disease and 45% ([95% CI: 42%-49%]) for pN2 disease. In the induction chemoradiation group, the two-year survival was 72% ([95% CI: 66%-77%]) for pN1 disease and 72% ([95% CI: 70%-75%]) for pN2 disease. The five-year survival was 48% ([95% CI: 41%-55%]) for pN1 disease and 46% ([95% CI: 42%-50%]) for pN2 disease.

Figure 1. Survival of Patients with Persistent N1 or N2 Disease After Induction Therapy for Stage IIIA-N2 Non-Small-Cell Lung Cancer



Conclusion: In this national study, the five-year survival of patients with cT1-3N2M0 NSCLC that underwent lobectomy following induction chemotherapy or chemoradiation and were then found to have persistent pN1 and pN2 disease was approximately 46-48%. These findings suggest that invasive mediastinal restaging after induction therapy for stage IIIA N2 NSCLC may not be necessary. These findings also suggest that persistent N1 and N2 disease after induction chemotherapy or induction chemoradiation for stage IIIA-N2 NSCLC should not be considered a contraindication to surgical intervention.

Keywords: stage IIIAN2, Surgery, Persistent Nodal Disease

OA20 EXPLORING TREATMENT MODALITIES AND TOOLS IN LOCALLY ADVANCED NSCLC
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

OA20.05 Neoadjuvant Chemotherapy-alone vs Chemoradiation followed by Sleeve Resection for Locally Advanced Non-Small Cell Lung Cancer

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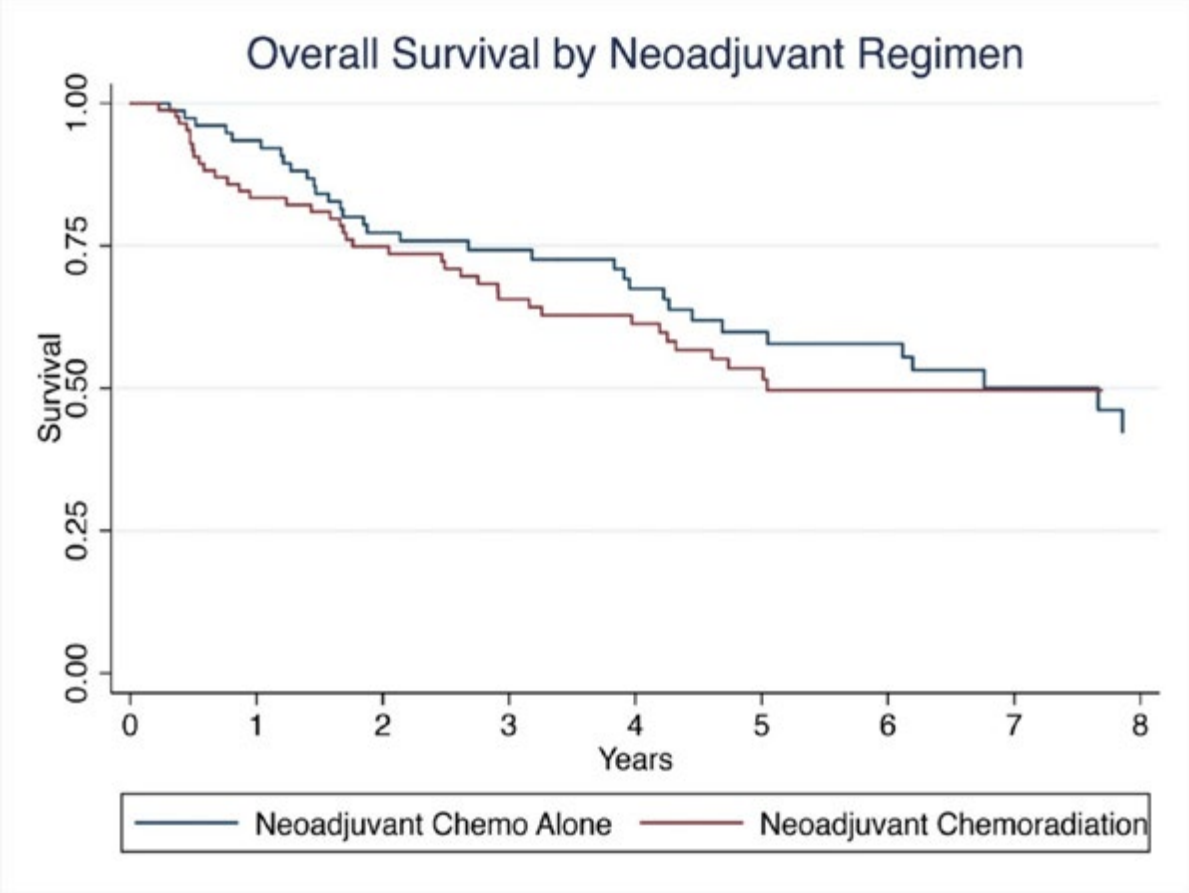
Introduction: Traditionally, neoadjuvant chemoradiation is followed by surgery in patients with locally advanced resectable non-small cell lung cancer (NSCLC). The risks and benefits of this approach are not well defined in patients requiring a sleeve lung resection. In this context, we compare the short- and long-term outcomes of neoadjuvant chemotherapy-alone versus chemoradiation followed by sleeve lung resection. **Methods:** We used the National Cancer Database to identify locally advanced NSCLC patients who received either chemotherapy-alone or chemoradiation in the neoadjuvant setting followed by a sleeve lung resection between 2006 and 2017. Our outcomes of interest were 30-day mortality, 90 day mortality, and overall survival. To minimize confounding by indication, we used propensity score adjustment, logistic regression, Kaplan-Meier survival analysis, and Cox proportional hazards models to identify associations. **Results:** Of 176 total patients, 92 (54.9%) received neoadjuvant chemotherapy-alone and 84 (45.1%) received neoadjuvant chemoradiation. Patients in both groups were well balanced in terms of age, sex, race, Charlson-Deyo comorbidity index, insurance status, median income, and education (all p>0.05). Similarly, the groups were well balanced in terms of tumor histology, and stage (all p>0.05). Patients receiving neoadjuvant chemoradiation had similar 30-day mortality (0% vs 2.2%; p=0.179), but higher 90-day mortality (11.96% vs 2.38%, P=0.015), and there was no difference in overall survival between patients receiving neoadjuvant chemoradiation compared to chemotherapy-alone (**Figure**; p=0.621). On multivariable analysis, neoadjuvant chemoradiation was associated with higher 90 day mortality (aOR=6.2; p<0.027) and not associated with overall survival (aHR=1.1 p=0.729).



Conclusion: In this first national study of patients with locally advanced resectable NSCLC requiring a sleeve lung resection, neoadjuvant chemoradiation was associated with a 5-fold increase in 90-day mortality without an overall survival benefit over neoadjuvant chemotherapy-alone.

Keywords: locally advanced non-small cell lung cancer, sleeve lung resection, neoadjuvant chemoradiation

Mini Oral Abstract Sessions

MA01 MULTIMODALITY MANAGEMENT OF ADVANCED LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

MA01.01 The Role of Surgery for M1a Non-Small-Cell Lung Cancer with Contralateral Lung Involvement

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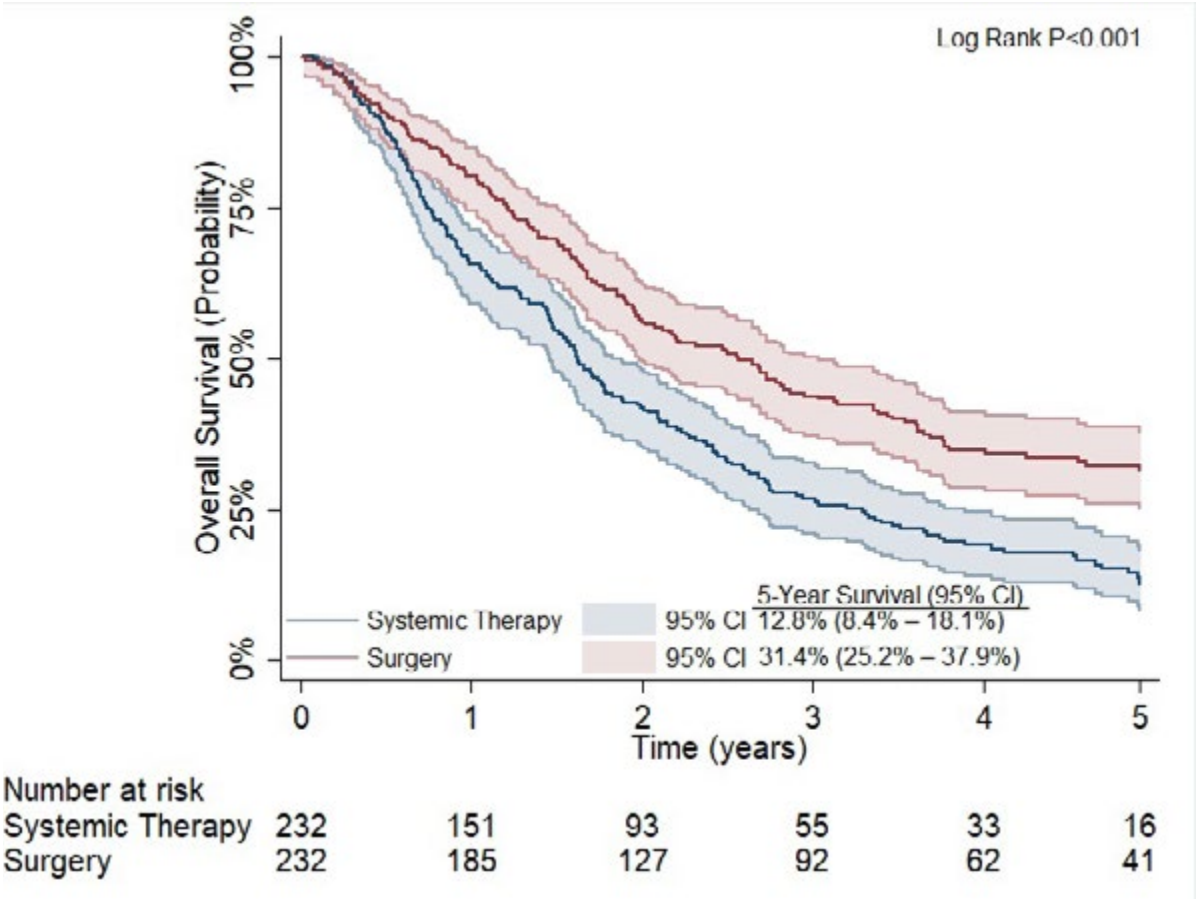
Introduction: There is limited consensus on the optimal treatment strategy for cM1a non-small-cell lung cancer (NSCLC) in the setting of contralateral lung involvement. Current National Comprehensive Cancer Network (NCCN) guidelines recommend surgery for a subset of Stage IVA that is node-negative (N0 M1a) where primary tumors present with a solitary contralateral lung nodule; however, no clear recommendations have been made for node-positive disease. This study sought to assess long-term survival of patients receiving either systemic therapy (with or without radiation) or multimodality therapy that included surgery for cM1a NSCLC with contralateral lung involvement. **Methods:** Patients with cT1-4, N0-3, M1a NSCLC due to contralateral lung involvement (i.e. additional pulmonary nodules in a contralateral lobe, contralateral pleural nodules, or direct extension into the contralateral lung or main stem bronchus) in the National Cancer Data Base from 2010-2015 were included. Long-term overall survival of patients who received surgery as part of multimodality therapy was evaluated and compared to survival of patients treated with systemic (chemotherapy, chemotherapy with immunotherapy, or immunotherapy) therapy (with or without radiation) using Kaplan-Meier analysis, Cox proportional hazards modeling, and propensity score matching. **Results:** Of the 12,313 patients with cM1a NSCLC due to contralateral lung involvement, 457 (3.7%) patients received multimodality therapy that included surgery. In unadjusted analysis, surgery resulted in better 5-year overall survival when compared to systemic treatment (34.6% [95% CI: 30.0-39.3] vs 12.1% [95% CI: 11.3-13.0], p<0.001). Multivariable-adjusted analysis demonstrated better overall survival with surgery when compared to systemic treatment (HR: 0.59, 95% CI: 0.50-0.70, p<0.001). In a propensity score-matched analysis of 232 patients who underwent surgery and 232 patients who underwent systemic treatment, well-balanced by 15 common prognostic covariates including comorbidities, T-status, and N-status, surgery was associated with better 5-year overall survival than systemic treatment (Figure 1). An additional propensity score-matched analysis of 254 patients with cN0 M1A disease demonstrated better survival in the surgery group when compared to the systemic treatment group (38.5% [95% CI: 29.5-47.5] vs 17.4% [95% CI: 10.6-25.7], p<0.001).



Conclusion: In this national analysis of patients with stage IVA NSCLC presenting with contralateral lung involvement, multimodality treatment that included surgery was associated with better overall survival than systemic treatment, supporting NCCN guidelines that recommend surgery for node-negative Stage IVA disease presenting as contralateral lung solitary nodules. In addition, the findings suggest reconsideration of surgery in a multimodality treatment setting for carefully selected node-positive cM1a NSCLC presenting with contralateral lung involvement.

Keywords: Stage IVA NSCLC, Multimodal Therapy, Contralateral Lung Involvement

MA01 MULTIMODALITY MANAGEMENT OF ADVANCED LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

MA01.02 Surgical Complexity of Pulmonary Resections Performed for Oligometastatic Non-Small Cell Lung Cancer

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Introduction: Management of oligometastatic non-small cell lung cancer (NSCLC) has rapidly evolved in recent years, with heightened emphasis on the benefits derived from local consolidative therapy (LCT). Pulmonary resection has been established as an important component of LCT, previously shown by our group to be both feasible and associated with long-term survival; however, technical aspects of such surgical procedures have not been well characterized. We sought to review the technical complexity of operations performed within a large cohort of patients with oligometastatic NSCLC. **Methods:** We identified patients treated at a single institution between 2000-2017 with stage IV NSCLC and ≤3 synchronous metastases. Patients who underwent surgical resection of the primary tumor were identified by chart review. Individual patient records were reviewed in detail, and aspects of surgical complexity were recorded. Descriptive analyses were performed. **Results:** Among 194 patients with oligometastic NSCLC, 173 (89%) received LCT, and 30 (15%) underwent resection of the primary tumor. Mean age at surgery was 60 years, and 14/30 (47%) were male. ECOG status was ≥ 1 for12 (40%), 23 (77%) were previous or current smokers, and 11 (37%) underwent induction therapy preoperatively (chemo: 10, 33%; chemoradiation: 1, 3%). Mean tumor size at surgery was 3.4 cm (1.2-7.5), and nodal disease was present in the majority of cases (N1: 9, 31%; N2-3: 7, 24%). Thoracotomy was performed in 25 (83%) patients, and procedures included 25 (83%) lobectomies, 3 (10%) pneumonectomies, and 2 (7%) sublobar resections. Operative notes were available for 27 patients, who had mean blood loss of 200 mL (50-600) and operative time of 200 minutes (72-492). Proximal pulmonary artery (PA) control was needed in 4 (15%). Sleeve resection was needed in 4 (15%), including 1 (4%) bronchial, 1 (4%) PA, and 2 (7%) double-sleeves. Unplanned procedural change was required in 2 (7%) patients (including 1 pneumonectomy). Chest wall resection, including ribs and/or sternum, was needed in 3 (11%). Lymph nodes were characterized as hard/densely adherent in 9 (33%) of procedures, and operations were described as more difficult or complex than usual in 16 (59%) cases. Despite intraoperative challenges, R0 resection was achieved in 97% (29/30) of patients, and morbidity was acceptable, with average length of stay 5.9 days (2-29), and most frequent complications being atrial fibrillation (n=7, 26%) and prolonged airleak (n=3, 11%). **Conclusion:** As surgery has emerged as an important aspect of LCT in patients with oligometastic NSCLC, healthcare teams should be prepared for the technical challenges of such cases. We have found that these operations can be performed safely, yet require frequent advanced techniques and complex resection strategies. Surgical teams should ensure that resources including time, equipment, and expertise are allocated properly in operative planning.

Keywords: Oligometastatic, Surgery, Local consolidative therapy

MA01 MULTIMODALITY MANAGEMENT OF ADVANCED LUNG CANCER
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MA01.03 PREC Multicentre Restrospective Study: A Preoperative Risk Classification for Synchronous Oligometastatic Non-Small Cell Lung Cancer

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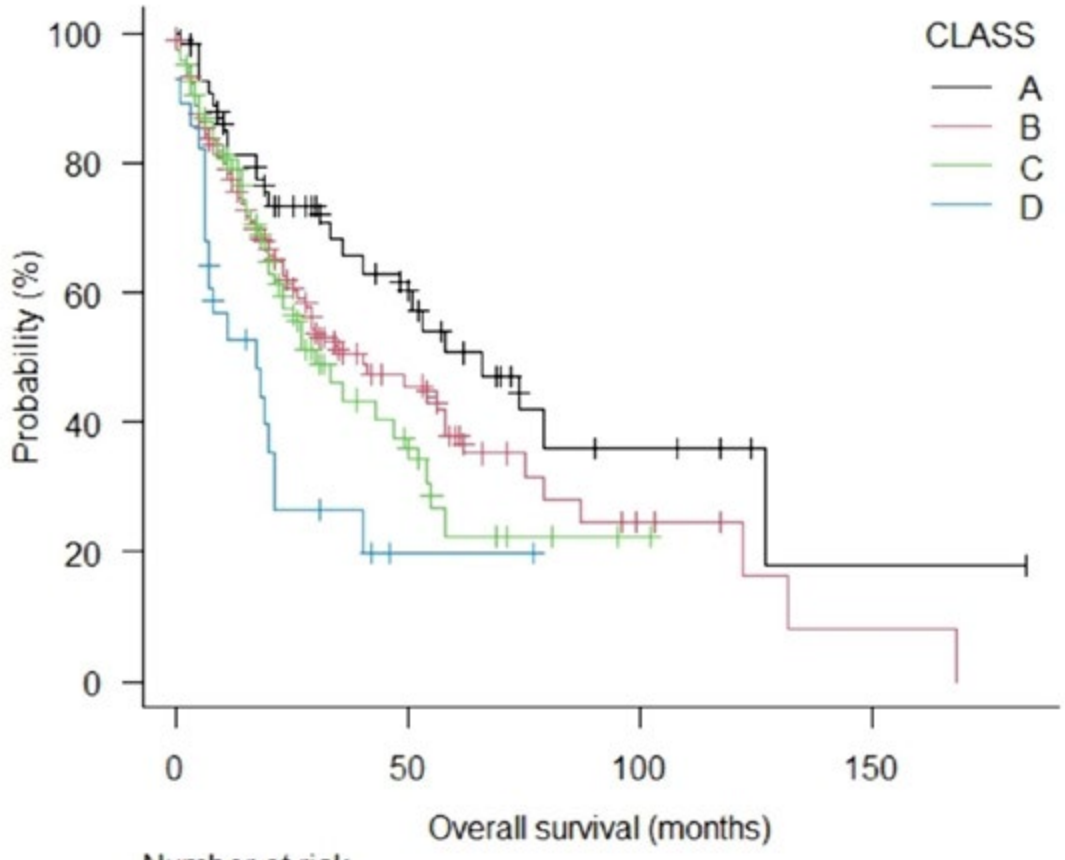
Introduction: In our previous multicentre study (Lung Cancer, 2021;154:29-35), longest survival was observed in synchronous lung oligometastatic/non pN2 disease. Aims. To identify preoperative favourable prognostic factors and to propose a preoperative classification for categorising the synchronous oligometastatic NSCLC. **Methods:** Retrospectively review of records (2005–2018). Inclusion criteria: synchronous oligometastatic NSCLC (≤5 extrapulmonary metastases), radical surgical treatment of primary tumour radical and all metastatic sites with/without neoadjuvant/adjuvant therapy. Exclusion criteria: palliative/diagnostic surgery, relapsing lung cancer, no follow-up information. Primary endpoint: identification of risk classification for oligometastatic NSCLC. Statistical analysis. Median OS/PFS were estimated by reverse Kaplan–Meier method. Stratified backward stepwise Cox regression model was employed for multivariable survival analyses. Backward elimination was performed with p-value of 0.20. Akaike information criterion was used to estimate the models' relative quality, selecting the ones with the best goodness of fit and avoiding collinearity bias. A prognostic grouping that could consider all the relevant prognostic factors simultaneously was constructed. ROC curve was generated. Hosmer-Lemeshow statistics was used for measuring OS calibration within groups. **Results:** 281 patients included (Table 1a). Data from the Cox regression model (Table 1b) was used to construct a prognostic risk classification.

Table 1a. Characteristics of the population	
Variables	No. (%)
Age (years), mean ± SD	62.7 ± 9.6
Male/female ratio	1.8
Tumour descriptor - cT1a - cT1b - cT1c - cT2a - cT2b - cT3 - cT4 Node descriptor - cN0 - cN1 - cN2	9 (3.3) 40 (14.5) 87 (31.5) 44 (15.9) 43 (15.6) 35 (12.7) 18 (6.5) 155 (56.2) 46 (16.7) 75 (27.2)
Metastasis location - Brain - Adrenal gland(s) - Contralateral lung - Bone - Subcutaneous tissue - Other sites	143 (50.9) 46 (16.4) 40 (14.2) 36 (12.8) 4 (1.4) 3 (1.1)
Histological diagnoses - Adenocarcinoma - Squamous-cell carcinoma - Others - Adenosquamous carcinoma	219 (77.9) 33 (11.7) 11 (3.9) 9 (3.2)

Table 1b. Results of Cox regression analysis for progression-free survival			
Variables	HR	95% CI	p-value
Age >65	1.37	1.00 – 1.57	0.0269
cN1/cN2	2.10	0.68 – 6.44	0.019
Lung/brain metastases	2.96	1.44 – 6.07	0.0031
Induction treatment	1.38	0.56 – 3.40	0.027

Four parameters (age, site of metastasis, clinical nodal status, and induction treatment) were used to build a risk classification (Figure): • Group A. No risk factors (age ≤65 years, lung/brain metastasis, cN0, induction treatment). • Group B. One risk factor (age >65 years or no lung/brain metastasis or cN1–2 or no induction treatment). • Group C. Two risk factors. • Group D. ≥3 risk factors. AUC was 0.56 (95% CI: 0.49–0.62), Hosmer-Lemeshow statistics was 21.3 (3 degrees of freedom, p=0.0042).



Number at risk

A	56	21	5	1
B	118	26	5	1
C	74	12	1	0
D	28	1	0	0

Conclusion: Patient selection is critical in identifying the proper subsets of oligometastatic NSCLC. After validation, this preoperative risk classification might support decision-making during the multidisciplinary team assessments and patients' selection for enrollment in future randomised trials.

Keywords: Oligometastatic, lung cancer, Surgery

MA01 MULTIMODALITY MANAGEMENT OF ADVANCED LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

MA01.05 Sintilimab, SBRT and GM-CSF for Advanced NSCLC: Safety Run-in Results of a Prospective, Multicenter, Phase II Trial

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Introduction: Several PD-1/PD-L1 inhibitors have been approved, with or without chemotherapy, in advanced non-small cell lung cancer (NSCLC). However, the objective response rate (ORR) remains limited in unselected population. Accumulating data indicated that adding stereotactic body radiation therapy (SBRT) to PD-1/PD-L1inhibitors could improve treatment efficacy in NSCLC and the anti-tumor immune response induced by SBRT may be enhanced by granulocyte-macrophage colony stimulating factor (GM-CSF), which plays a pivotal role in dendritic cell differentiation and maturation. Nevertheless, the safety and efficacy of triple combination of Sintilimab, SBRT and GM-CSF in advanced NSCLC remain unknown. **Methods:** This is a prospective, multicenter, phase II study (NCT04106180). Eligible patients (pts) were advanced EGFR/ALK negative NSCLC pts who had failed first-line standard chemotherapy. Pts received SBRT (8 Gy*3) to one lesion, followed by Sintilimab (200 mg d1, every 3 weeks) and GM-CSF (125 μg/m2 d1-d14, cycle 1) within 3 weeks after SBRT. Sintilimab would be given continuously until disease progression, unacceptable toxicity, or up to 35 cycles. To determine the tolerability of the triple combination therapy, a safety run-in phase was conducted in the first 20 enrolled pts by monitoring the dose-limiting toxicities (DLTs). Primary end point is ORR. Secondary end points are safety, out-of-field response rate, overall survival (OS), progression free survival (PFS). Here, we report the preliminary results of the safety run-in phase. **Results:** From 2019/10/16 to 2020/8/8, 20 pts were enrolled from 3 academic centers. The majority of pts were male, smoker, ECOG 1 and non-squamous NSCLC, with a median age of 61 (range, 32-71). Baseline brain, liver and bone metastasis were present in 2, 4 and 8 pts, respectively. All of the pts had more than 5 lesions at baseline, and the sites of SBRT included lung (n=11), mediastinal lymph node (n=5), liver (n=1), abdominal lymph node (n=1), pleural nodule (n=1) and vertebra (n=1). There were no DLTs. Treatment-related adverse event (TRAE) occurred in 18 pts. The most common TRAEs were fatigue (50%), fever (30%), and ostealgia (20%), and all were grade1. Only 2 grade 3 TRAEs were observed. 1 pt had G3 ALT and AST elevation, and the other experienced transient (recovered within 7 days) acute heart failure which was considered GM-CSF related. No grade 4 or 5 AE occurred. Median follow-up was 7.9 (range,1.6-16.5) months by data cut-off (2021/02/28). Partial response occurred in 7 and stable disease in 5 pts, the confirmed ORR was 35%. Median PFS was 6.9 (95% CI, 2.76-NA) months with 12 events and 1-year OS rate was 75.0% (95% CI, 58.2%-96.6%). **Conclusion:** Triple combination of Sintilimab, SBRT and GM-CSF is safe and shows promising efficacy as a novel second-line treatment for advanced EGFR/ALK negative NSCLC. The trial continues to recruit participants.

Keywords: SBRT, GM-CSF, pd-1 inhibitor

MA01 MULTIMODALITY MANAGEMENT OF ADVANCED LUNG CANCER
WEDNESDAY, SEPTEMBER 08, 2021 - 08:15-09:15

MA01.06 Effects of the Immunotherapy Era on Maintenance Outcomes in Advanced Nonsquamous NSCLC: Subgroup Analysis of ECOG 5508

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Introduction: The ECOG 5508 (E5508) study, which enrolled patients from 2010-2015, evaluated pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer (NSCLC). Results showed that single-agent bevacizumab or pemetrexed were equally efficacious in regards to progression free survival (PFS) and overall survival (OS). Combination therapy improved PFS, but the difference in OS was not statistically significant. Treatment practice changed in 2015 with the approval of immune checkpoint inhibitors for second line therapy in metastatic NSCLC with progression on or after platinum based therapy. Patients who were enrolled in E5508 later in the registration period would have most likely received immunotherapy after progression, which could potentially have had an effect on OS in these patients. A subgroup analysis was performed to evaluate this possibility. **Methods:** The 874 patients in the E5508 trial who were randomized to one of the maintenance therapy arms were divided into two groups based on registration date before or after 2014-01-01, chosen because patients who enrolled in the study in 2014 or later most likely would have been treated with immunotherapy at progression. These two groups were divided into three subgroups based on the maintenance treatment they received. OS and PFS were estimated using the Kaplan-Meier method. Cox models were performed to examine the differences among the subgroups in OS and DFS. **Results:** 444 patients were in the “Before-IO” group. This total was evenly split between the 3 maintenance subgroups. 430 patients fell into the “After-IO” group. In this group, 139, 146, and 145 patients received bevacizumab, pemetrexed, and the combination respectively. The interaction test between registration group and treatment were not significant. PFS continued to be significantly improved in both combination subgroups with no significant change by enrollment period (HR “Before-IO” 0.70, p=0.006, HR “After-IO” 0.63, p=<0.001). Median OS in the “Before-IO” group with combination maintenance was 15.8 months compared to 14.6 and 14.4 months with pemetrexed and bevacizumab respectively (HR of combination vs. bevacizumab 0.85, p=0.21), while the “After-IO” combination subgroup OS was 17 months compared to 19 and 13.3 months for pemetrexed and bevacizumab monotherapy (HR of combination vs. bevacizumab 0.97, p=0.83). **Conclusion:** There was a favorable trend towards improved OS, although not statistically significant, in the “Before-IO” combination maintenance subgroup compared to the bevacizumab subgroup. This suggests that studies that enrolled patients both before and after 2014 may have been impacted by subsequent IO treatments. There was also an increase in median OS for both the pemetrexed and combination “After-IO” groups, suggesting a broad impact on OS from immunotherapy.

Keywords: immunotherapy, Maintenance, overallsurvival

MA01.07 Prognostic Value of STK11 & KRAS Mutations and irAE Incidence in Response to Immunotherapy in Hispanics: A Multicenter Analysis

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Introduction: STK11 mutations in patients with metastatic non-small cell lung cancer (NSCLC) have emerged as a potential biomarker for relative lack of response with the use of immune checkpoint inhibitors (ICIs). Whether co-mutation with KRAS can impair or improve response to ICIs remains controversial. In addition, the incidence of immune-related adverse events (irAEs) have been shown to be predictive of response to ICIs. Here, we present a multicenter analysis of the predictive value of STK11, KRAS, and irAEs with a subset analysis based on ethnicity performed for the first time. **Methods:** Patients with stage IIIB-IV NSCLC who were treated with ICIs were identified at three independent centers: University of Miami/Sylvester Comprehensive Cancer Center, Memorial Cancer Institute/Memorial Health Care System, and Mount Sinai Comprehensive Cancer Center. Patients were prospectively tested with next-generation sequencing (NGS) that include KRAS and STK11 mutations and were evaluated for progression-free survival (PFS) and overall survival (OS). Log-rank tests were used to compare OS and PFS, chi-squared tests were used to compare proportions among variable, and Kaplan-Meier survival curves were used to report OS and PFS. Furthermore, since Hispanics are often not stratified in clinical trials, we sought to evaluate if the predictive value of these biomarkers were similar between Hispanics and non-Hispanic white (NHW) patients. **Results:** We identified a total of 703 patients, of which 63 (9%) harbored STK11 mutations. Thirty patients (48%) with STK11 mutations also harbored KRAS co-mutations. Hispanic patients comprised 26% of our cohort, while NHW comprised 61%. Compared to STK11 wild-type (WT) patients, those with STK11 mutations who received ICIs had significantly shorter OS (24.0m vs. 38.3m, p=0.035) and PFS (6.2m vs 15.3m, p=0.003). PD-L1 positivity (at least 1%) was present in 21% of patients with STK11 mutations and 50% in STK11 WT patients (p=0.0002). Interestingly, patients with both STK11 and KRAS co-mutations (S/K) in our populations had significantly improved PFS compared to patients with STK11 mutation alone (S) (16.1m vs. 4.1m, p=0.031) with similar trend with OS (32.3m vs. 21.8m, p=0.21). No significant differences were observed when S/K and S patients were categorized by ethnicity. We also observed that the occurrence of irAEs is associated with significantly improved OS (46.3m vs. 29.7m, p=0.022) without affecting PFS. Incidence of irAEs was 37% in Hispanic patients and 31% in NHW patients (p=0.043), and Hispanic patients had significantly higher rates of irAEs regardless of STK11 mutation status. In Hispanic patients without irAEs, OS was significantly shorter than that of NHW patients (22.3m vs. 32.0m, p=0.019). **Conclusion:** In our patient population, while STK11 mutation was a negative prognostic marker for ICI use, concomitant STK11 and KRAS mutations were associated with significantly improved PFS with a positive trend in OS. We also observed that occurrence of irAEs was associated with better OS in our patient population and that Hispanic patients experienced irAEs at higher rates than their NHW counterparts, although this did not translate into a significant OS benefit. Further investigation and identification of disease characteristics associated with improved outcomes with STK11 and KRAS co-mutations is warranted.

Keywords: immunotherapy, STK11, KRAS

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.01 Efficacy and Safety of Selpercatinib in Chinese Patients With RET Fusion-Positive Non-Small Cell Lung Cancer: A Phase 2 Trial

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Introduction: Selpercatinib, a first-in-class, highly selective and potent inhibitor of the rearranged during transfection (RET) kinase with central nervous system (CNS) activity, is approved in multiple countries for use in RET fusion-positive non-small cell lung cancer (NSCLC) and RET-altered thyroid cancers. Herein, we present results from LIBRETTO-321 (NCT04280081), the first study to evaluate the efficacy and safety of selpercatinib in Chinese patients with RET fusion-positive NSCLC. **Methods:** This open-label, multi-center, phase 2 study enrolled Chinese patients with advanced RET-altered solid tumors including RET fusion-positive NSCLC. Oral selpercatinib (160 mg twice daily) was administered in 28-day cycles until progressive disease, unacceptable toxicity, withdrawal of consent, or death. The primary endpoint was objective response rate (ORR; RECIST 1.1) as assessed by independent review committee (IRC). Key secondary endpoints included duration of response (DoR), CNS ORR, CNS DoR, and safety. Efficacy was analyzed in the primary analysis set (PAS), comprising patients with RET fusion-positive NSCLC whose RET status was confirmed by central laboratory, and in all response evaluable patients with NSCLC, defined as all enrolled patients with measurable disease and ≥1 post-baseline assessment. Safety was evaluated in all treated patients. Types of Analysis and Data Reporting: Data to be presented include patient demographics, baseline disease characteristics, and the main study endpoints as below: ORR (IRC-assessed) in the PAS and response evaluable subgroup; ORR (IRC-assessed) in treatment naïve vs pre-treated patients in the PAS and response evaluable subgroup; Assessment of DoR, CNS ORR, CNS DoR in the PAS; Treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, discontinuation due to TEAEs in the safety population. **Results:** As of 25 Mar 2021, 77 patients were enrolled including 47 RET fusion-positive NSCLC patients, 26 of whom were included in the PAS. Tumor responses are summarized in Table 1. In the PAS, after a median follow-up of 9.7 months the IRC-assessed ORR was 69.2% (95% CI, 48.2-85.7), and was 87.5% for treatment-naïve and 61.1% for pre-treated patients. The median DoR was not reached; at 9 months the DoR rate was 93.8%. Among all response evaluable patients with NSCLC (n=45) after a median follow-up of 10.4 months the IRC-assessed ORR was 66.7% (95% CI, 51.0-80.0). Among five patients with measurable CNS metastasis at baseline, four (80%) achieved an IRC-assessed objective intracranial response and all of them had sustained responses at 9 months. In the safety population (n=77), the most common grade ≥3 treatment-emergent adverse events (TEAEs) were hypertension (19.5%), aspartate aminotransferase increased (15.6%) and alanine aminotransferase increased (15.6%). Most TEAEs were grade 1 or 2. TEAEs led to discontinuation of selpercatinib in 5.2% (n=4; three [3.9%] considered related to selpercatinib) and dose reduction in 32.5% (n=25) of patients, and one patient died due to a TEAE considered unrelated to selpercatinib.

Table 1. Tumor responses to selpercatinib as assessed by IRC in patients with *RET* fusion-positive non-small cell lung cancer

	PAS[a] (n=26)			Response evaluable population[b] (n=45)		
	All (n=26)	Treatment naïve (n=8)	Pre-treated (n=18)	All (n=45)	Treatment naïve (n=11)	Pre-treated (n=34)
BOR, n (%)						
CR	1 (3.8)	1 (12.5)	0 (0)	2 (4.4)	2 (18.2)	0
PR	17 (65.4)	6 (75.0)	11 (61.1)	28 (62.2)	8 (72.7)	20 (58.8)
SD	7 (26.9)	1 (12.5)	6 (33.3)	13 (28.9)	1 (9.1)	12 (35.3)
SD ≥16 weeks	3 (11.5)	0 (0)	3 (16.7)	4 (8.9)	0	4 (11.8)
PD	1 (3.8)	0 (0)	1 (5.6)	2 (4.4)	0	2 (5.9)
ORR, n (%)	18 (69.2)	7 (87.5)	11 (61.1)	30 (66.7)	10 90.9)	20 (58.8)
95% CI[c]	48.2-85.7	47.3-99.7	35.7-82.7	51.0-80.0	58.7-99.8	40.7-75.4

[a]Patients with *RET* fusion-positive NSCLC whose *RET* status was confirmed by central laboratory; [b]All enrolled patients with measurable disease and at least 1 post-baseline tumor assessment; [c]Confidence intervals estimated using the Clopper-Pearson method.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; IRC, independent review committee; ORR, objective response rate; PAS, primary analysis set; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease.

Conclusion: Selpercatinib had robust and durable anti-tumor activity in Chinese patients with advanced RET fusion-positive NSCLC and was well-tolerated, consistent with previously reported results from LIBRETTO-001.

Keywords: Selpercatinib; RET fusion-positive NSCLC; China; ORR

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.02 Efficacy and Safety of Pralsetinib in Chinese Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer

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Introduction: RET fusion has been identified as an oncogenic driver in approximately 1-2% of patients with NSCLC. Pralsetinib is a highly potent and selective inhibitor of RET and oncogenic RET alterations. ARROW is a phase I/II, open-label, and first-in-human study to evaluate the safety and antineoplastic activity of pralsetinib in a variety of advanced RET altered solid tumors including NSCLC. Previously we reported the efficacy and safety results of pralsetinib in a cohort of Chinese patients with RET fusion+ NSCLC after platinum-based chemotherapy at WCLC 2020. Here we present updated results of this cohort and also report the results of pralsetinib in a cohort of Chinese NSCLC patients without prior systemic treatment. **Methods:** RET fusion+ Chinese NSCLC patients without or with prior platinum-based chemotherapy were enrolled and administered with pralsetinib 400 mg QD. The primary endpoints are the objective response rate (ORR) by blinded independent central review per RECIST v1.1 and safety profile, assessed by incidence, severity, and type of AEs in Chinese patients. The secondary endpoints include duration of response (DOR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival, and overall survival. Types of Analysis and Data Reporting: The study will present the primary endpoint BICR-assessed ORR and the secondary endpoints including DOR, CBR, DCR, PFS, and OS of pralsetinib in treatment naïve and pretreated Chinese patients with advanced RET fusion+ NSCLC. The data are expected to show whether pralsetinib has deep and durable antitumor activity in treatment naïve patients similar as previously reported in pretreated Chinese patients with RET fusion+ NSCLC after platinum-based chemotherapy, and its overall safety and tolerability. **Results:** As of 12 April 2021, 68 Chinese patients with RET fusion+ NSCLC (37 previously treated with platinum-based chemotherapy and 31 systemic treatment-naïve) received pralsetinib. At baseline, most (95.6%) patients had ECOG performance score of 1. The RET fusion partners (66.2% KIF5B, 17.6% CCDC6, 16.2% other) and the prevalence of brain metastases (33.8%) were similar to the global population. The efficacy results are shown in the table. Pralsetinib shows high ORRs in Chinese RET fusion+ NSCLC patients regardless of prior therapy. All patients treated with at least 1 dose of pralsetinib were included in the safety analysis (n=68). The most frequently reported treatment-related adverse events (TRAEs) included aspartate aminotransferase increased (80.9%), neutrophil count decreased (79.4%), anemia (67.6%), white blood cell count decreased (60.3%), and alanine aminotransferase increased (57.4%). 10.3% of patients discontinued pralsetinib due to TRAEs.

Outcome	Prior platinum-based chemotherapy treatment (n=33) [a]	No prior systemic treatment (n=30) [a]
ORR, % (95% CI) CR, % PR, % SD, % PD, % NE, % CBR, % (95% CI) DCR, % (95% CI)	66.7 (48.2 - 82.0) 3.0 63.6 27.3 3.0 3.0 84.8 (68.1 - 94.9) 93.9 (79.8 - 99.3)	80.0 (61.4 - 92.3) 6.7 73.3 6.7 6.7 6.7 86.7 (69.3 - 96.2) 86.7 (69.3 - 96.2)
Responders' outcome	Prior platinum-based chemotherapy treatment (n=22)	No prior systemic treatment (n=24)
Median time to first response (CR/PR), months (min, max) 6-month DOR rate, % (95% CI) 9-month DOR rate, % (95% CI)	1.89 (1.7 - 5.6) 77.3 (59.8 - 94.8) 50.0 (29.1 - 70.9)	1.87 (1.7 - 3.8) 76.7 (55.6 - 97.8) 38.3 (0.0 - 92.5)
[a] Efficacy population with measurable disease at baseline. CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable.		

Conclusion: Pralsetinib is a promising targeted therapy with rapid and deep clinical activity in RET fusion+ NSCLC Chinese patients regardless of prior therapies. Efficacy results are consistent with previously reported data from the global population in the ARROW trial, and in treatment naïve Chinese patients pralsetinib shows the same efficacy. Pralsetinib safety profile in Chinese patients is manageable, with no new safety signals detected. Overall, pralsetinib showed a favorable benefit-risk profile, offering a transformative medicine to Chinese RET-fusion driven advanced NSCLC patients.

Keywords: Pralsetinib, RET fusion, NSCLC

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.03 MET-Driven Acquired Resistance (AR) in Fusion-Positive Non-Small Cell Lung Cancer (NSCLC)

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Introduction: MET alterations have been characterized as oncogenic drivers and acquired resistance mechanisms in NSCLC. With the recent approval of multiple MET inhibitors in NSCLC, we sought to characterize the landscape of MET alterations as potential AR mechanisms in fusion-positive NSCLC. **Methods:** Comprehensive genomic profiling (CGP) results from tissue (n=67,016) or circulating tumor DNA (ctDNA; n=10,827) samples from 77,843 NSCLC patients were queried for ALK, RET, ROS1, FGFRs, EGFR, NTRK, BRAF, RAF1 or ERBB2 fusions, or activating ALK, RET, ROS1 or FGFR rearrangements) and concurrent oncogenic MET alterations. MET amplifications were defined as ≥4 copies above the median specimen ploidy. A subset of cases had paired samples collected ≥60 days apart with an acquired MET alteration; available treatment information was collected from the provided pathology report or reported by the treating physician. **Results:** Driver fusions/rearrangements were identified in 4.7% (3,679/77,843) of NSCLC samples. 1.7% (64/3,679; 52/3,279 [1.6%] tissue, 12/400 [3%] ctDNA) of fusion/rearrangement-positive samples (52% ALK, 13% RET, 7.8% BRAF, 7.8% FGFR3, 19% other) harbored ≥1 concurrent likely oncogenic MET alteration (73% MET amplification [median 11 copies, range 6-94], 15% MET exon 14 splice [METex14], 4.5% D1228X, 3.0% L1195X, 4.3% other). Notably, MET variants of unknown significance (VUS) were identified in 77/3,679 (2.1%) additional cases including a subset with recurrent kinase domain mutations (D1164X and R1166X). Of ALK cases with likely oncogenic co-MET alterations, EML4-ALK v1 (42%) and EML4-ALK v3a/b (27%) were most common. Three EML4-ALK cases and MET amplification (9-19 copies) also harbored an ALK resistance mutation (I1171N/S/T). Eight RET rearrangements/fusions (3 KIF5B-RET, 3 RET intron 11 rearrangements, 1 CCDC6-RET, 1 RET-KIF5B) were observed with likely oncogenic MET alterations (6 amplifications [median 12 copies, range 6-75], 1 each: METex14 splice, L1195V). Paired patient samples were available for 218 fusion/rearrangement-positive cases and 8 harbored ≥1 acquired MET alteration. 6/8 pairs had documented receipt of ≥1 interim targeted therapy, including one EML4-ALK case with a novel MET D1164N VUS acquired after treatment with alectinib, brigatinib and lorlatinib (Table). Multiple patients have since received MET targeted therapy and will be presented.

Table.
Legend: *ALK G1202R was also detected in an interim ctDNA sample post-alectinib and prior to lorlatinib. This patient is currently receiving concurrent ALK (lorlatinib) and MET (capmatinib) targeted therapy; longitudinal testing, treatment course and further on-target and off-target mechanisms of resistance will be presented. #Case report initially published (Zhu et al. JTO, 2020) and patient has since received MET targeted therapy (capmatinib) with identification of emergent MET D1228N (case report Zhu et al. JTO, in press). ± Case initially published as part of the SPACEWALK study (Lawrence et al. JTOCRR, 2021); patient subsequently received crizotinib (ALK/MET inhibitor) with response and alectinib+crizotinib with re-response.

Case	Sample type	Interval between paired samples (days)	Driver alteration	Notable acquired alterations	Interim targeted therapies
1*	tissue/liquid	722	EML4-ALK fusion	MET amplification, ALK I1171S	Alectinib (15 mos), lorlatinib (7 mos)
2	tissue/tissue	638	EML4-ALK fusion	MET amplification	None noted
3	tissue/tissue	313	EML4-ALK fusion	MET amplification	Alectinib
4#	tissue/liquid	675	KIF5B-RET fusion	MET amplification	Selpercatinib (7.5 mos), Cabozantinib (3.5 mos)
5	tissue/tissue	2,038	RET-KIF5B reciprocal fusion	MET L1195V	Unspecified RET inhibitor
6	tissue/tissue	655	EML4-ALK fusion	MET amplification	None noted
7±	tissue/tissue	214	EML4-ALK fusion	MET amplification	Alectinib (6 mos)
8	tissue/liquid	950	EML4-ALK fusion	MET D1164N (VUS)	Alectinib (16 mos), brigatinib (3.5 mos), lorlatinib (7 mos)

Conclusion: Co-occurring MET alterations were detected in 1.7% of NSCLC fusion/rearrangement-positive samples, a subset of which may represent AR to targeted therapy. The majority of were MET amplification, though known and novel point mutations were also identified, and further studies are warranted to elucidate the role of these events in driving resistance and responsiveness to available therapies and combinations.

Keywords: acquired resistance, fusion, MET

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.05 A Phase I Study of Afatinib in Combination With Osimertinib in Patients After Failure of Prior Osimertinib

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Introduction: Acquired resistance of to the initial osimertinib (OSI) therapy remains a majormain issue in thefor treatment of in patients with epidermal growth factor receptor gene (EGFR) mutation-positivemutation positive non-small cell lung cancer (NSCLC) patients. Secondary EGFR mutations or co-existing uncommon EGFR uncommon mutations have been reported as a part of the resistanceresistant mechanisms for of osimertinibOSI. Afatinib (AFA) has a broad range of antitumor activitiesy for athe variety of EGFR mutations. A Ppreclinical study suggests thatthe concurrent use of AFA with OSI may have thea potential to eradicate not only the secondary resistant clones but also the co-existing uncommon EGFR uncommon mutation clones. Dual blockage of OSI and AFA may be athe potential new approach to counteract osimertinib OSI resistance. **Methods:** This open-label phase I study enrolled patientspts with advanced EGFR -positive NSCLC who experienced exhibited progressive disease after receiving OSI. The primary endpoint was to determine the maximum tolerated dose (MTD). This phase I study was planned as a standard 3 + 3 dose-escalation study enrolling patients in receiving three differentdifferent three dose levelslevel of AFA in combination with OSI at a standard dose of 80 mg once per day. The doses of AFA once per day were planned as follows: level 1, 20 mg; level 2, 30 mg; level 3, 40 mg. The Ssecondary endpoints included the overall response rate (ORR) and survival outcomes. **Results:** A total of 13 patients were enrolled in this study. Each Six6 patients werehave been treated at levelslevel 1 and 2, and one patient was excluded because of early disease progression. At level 1, one patient experienced grade 3 diarrhea as a dose-limiting toxicity (DLT). At level 2, two patients experienced grade 3 diarrhea or and intolerable grade 2 nausea as DLTs, respectively. The MTD was defined as AFA 30 mg of AFA in combination with OSI 80 mg of OSI orally daily. The mostMost frequent adverse events were diarrhea (76.9%), anemia (76.9%), and rash (69.2%). Considering the toxicity profiles in all treatment periods, we determined that the recommended dose of AFA was 20 mg orally daily with an OSI dose of 80 mg. In all evaluable patients (n = 12), the ORR was 7.7% ([95% confidence interval (CI) 0.2%, 36.0%]) and disease control rate was 46.2% (95% CI 19.2%, 74.9%). The Mmedian progression-freeprogression free survival was 2.4 months (95% CI 1.4, -not reached). **Conclusion:** Combination therapy with OSI and AFA is tolerable for OSI-resistant EGFR-mutated NSCLC. However, the additional effect of AFA on OSI may be limited in OSI-resistant settings. Further investigation in the first-line setting is needed.

Keywords: afatinib, osimertinib, non-small cell lung cancer

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.06 Phase 1b Study of Pelcitoclax (APG-1252) in Combination With Osimertinib in Patients With EGFR TKI-Resistant NSCLC

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Introduction: Third-generation tyrosine kinase inhibitor (TKI) osimertinib is standard of care for patients with EGFR-mutant non-small cell lung cancer (NSCLC), although resistance almost inevitably develops. Pelcitoclax (APG-1252) is a dual BCL-2/BCL-xL inhibitor which exhibits synergistic anti-tumor effects with osimertinib in preclinical models of EGFR-mutant NSCLC. **Methods:** This single-arm study evaluated the safety, efficacy, and pharmacokinetics (PK) of pelcitoclax in combination with osimertinib, including dose expansion at the recommended phase 2 dose (RP2D) of pelcitoclax in patients with third-generation EGFR TKI-resistant NSCLC. Eligible patients had advanced EGFR-mutant NSCLC with prior third-generation EGFR TKI exposure. Two dose levels were planned, with pelcitoclax at 160 mg and 240 mg by IV infusion once a week combined with osimertinib at 80 mg orally daily (QD) in a 21-day cycle. **Results:** At data cutoff date of March 29, 2021, 33 patients had been treated with pelcitoclax plus osimertinib. The median age was 56 years, 55% of patients were female, and 85% had ≥ 2 lines of systemic treatment. Treatment-related adverse events included increased aspartate aminotransferase (AST; 57.6%), increased alanine aminotransferase (ALT; 51.5%), reduced platelets (36.4%), increased amylase (27.3%), increased blood creatinine (24.2%), decreased leukocytes (21.2%), anemia (18.2%), or rash (12.1%). No grade 3 AST and ALT elevation or thrombocytopenia was observed in the pelcitoclax 160 mg group. One case of dose-limiting grade 4 thrombocytopenia was observed. Thus, the RP2D for pelcitoclax was 160 mg per week plus osimertinib 80 mg QD. Of 20 efficacy-evaluable patients, a total of 3 partial responses were observed, including 2 patients with osimertinib-resistant NSCLC who had an EGFR T790M mutation. PK analysis indicated no significant difference in PK profile following coadministration of pelcitoclax and osimertinib compared to either agent alone. **Conclusion:** Combination treatment with pelcitoclax and osimertinib at RP2D was safe and feasible. Preliminary synergy and efficacy of both pelcitoclax and osimertinib were also observed in some patients with osimertinib-resistant NSCLC. Ongoing studies are investigating the efficacy of this combination in treatment-naive and second-line patients with the EGFR T790M mutation. Internal study identifier APG1252NC101; Clinical trial registration: NCT04001777.

Keywords: EGFR-mutant NSCLC, osimertinib, Pelcitoclax

MA02 RET AND NOVEL COMBINATIONS OF OSIMERTINIB
WEDNESDAY, SEPTEMBER 08, 2021 - 09:30-10:30

MA02.07 T-DM1 and Osimertinib (TRAEMOS) To Target HER2 Bypass Track Resistance in EGFRm+ NSCLC: Interim Analysis of a Phase II Trial

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Introduction: Despite high response rates to osimertinib in patients with EGFR mutation positive (EGFRm+) NSCLC, resistance inevitably develops. HER2 overexpression and amplification is detected in 13% of NSCLC-patients with acquired TKI-resistance. Previously, we showed that trastuzumab and paclitaxel in this setting is associated with a 41% ORR. Here, we evaluated the efficacy and toxicity of trastuzumab-emtansine (T-DM1) and osimertinib in patients with HER2 overexpression and/or amplification after progression on osimertinib as last line of treatment. We report a pre-planned interim analysis. **Methods:** In this multicenter single arm phase II study with a safety run-in (NCT03784599), eligible patients (≥18 years, WHO PS ≤2) with EGFRm+ NSCLC, progressing on EGFR TKI treatment and with HER2 overexpression (IHC ≥2+ in ≥10% of the cells) and/or HER2 amplification (ISH and/or NGS) were included. Patients were treated with T-DM1 3.6 mg/kg (IV infusion) every 3 weeks and osimertinib 80 mg QD. For patients with progression on 1st or 2nd generation EGFR TKIs, osimertinib monotherapy was initiated and T-DM1 was added at time of progression on osimertinib. Primary endpoints were to assess the ORR after 12 weeks and to evaluate safety of the combination treatment. In the safety run in, assessed in a classical 3+3 design, the first 3 patients received T-DM1 3.0 mg/kg. If none of these 3 patients developed a dose limiting toxicity (DLT), the T-DM1 dose was escalated to the standard dose of 3.6 mg/kg. Responses were assessed every 6 weeks according to RECIST 1.1. Treatment was continued until progression or unacceptable toxicity. Sample size was calculated using Simon's two stage minimax design (H0=41%, H1>55%, 80% power, one-sided type I error rate of 10%, sample size: 58 patients, cohort A ORR 16/36 in order to proceed to cohort B). **Results:** From January 15 2019 until April 6 2021, 27 patients were included and started with T-DM1. In the safety run in, none of the patients developed a DLT. Therefore, the study continued with osimertinib 80 mg QD and T-DM1 3.6 mg/kg IV infusion q 3 weeks. ORR and DCR after 6 weeks of treatment, evaluable in 24 patients, was 0% and 63% (16/24) respectively. One patient is not yet evaluable for the primary endpoint. ORR and DCR after 12 weeks of treatment were 13% (3/23) and 43% (10/23). DCR in HER2 IHC2+ and 3+ cohort was 36% (5/14) and 55% (5/9). Median PFS was 2.8 months (95% CI, 2.3-3.3 months), median duration of disease control was 20 weeks (range 4-47 weeks). Grade 2/3 adverse events occurred in 29%/21% of patients, including pneumonitis, LVEF decrease, fatigue, erythema and CK elevation. There were no grade 4 and 5 therapy-related adverse events. **Conclusion:** TRAEMOS is the first trial combining T-DM1 and osimertinib in patients with EGFRm+ NSCLC and progression on osimertinib to target HER2 bypass track resistance. Safety profile is favorable compared to cytotoxic chemotherapy, however this treatment strategy showed very limited efficacy. Further clinical evaluation of this regimen is not warranted.

Keywords: HER2, NSCLC, EGFR

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.01 EPICAL Trial. A Phase Ib StudyCombining Anti-Epidermal Growth Factor (EGF) Vaccination With Afatinib in EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: Stage IIIB-IV non-small cell lung cancer patients with mutations in the EGF receptor gene (EGFR) usually derive clinical benefit from to tyrosine kinase inhibitors (EGFR TKIs) but ultimately relapse. In preclinical studies, we have showed that anti-EGF antibodies generated by vaccination significantly increased the antitumor activity of TKIs in EGFR-mut cell lines, blocking EGFR, Erk1/2, Akt and STAT3 activation and delaying emergence of resistance. Based on these findings, the EPICAL trial was initiated (ClinicalTrials.gov number, NCT03623750) . **Methods:** The EPICAL was a single arm, phase 1b, single arm study to evaluate the safety and efficacy of first line anti-EGF vaccination combined with afatinib. The trial enrolled advanced NSCLC patients with sensitizing EGFR mutations confirmed in a central laboratory. Patients received 40 mg/day of afatinib and five intramuscular anti-EGF vaccinations every 14 days and then every three months until progression. Four medical centers in Spain participated, with a target enrollment of 30 patients. However, the COVID-19 outbreak forced an early termination of the study in March 2020 with only 23 patients included. Serial blood samples were collected and used to evaluate the levels of selected growth factors by ELISA and biological activity by addition of sera to in vitro cultures of EGFR-mut cells followed by Western blotting. **Results:** Of the 23 patients enrolled in the trial, nine (39%) had exon 19 in-frame deletions, twelve (52%) exon 21 substitutions and two (9%) exon 18 missense mutations. Combination treatment was well tolerated and no SAES related to anti-EGF vaccination were reported. Objective response and disease control rates were 78.3% (95%CI=53.6-92.5) and 95.7% (95%CI=78.1-99.9), respectively. At data cut-off, with a median follow-up of 11.4 months (95%CI=8.1-15.2), the median progression-free survival was 17.4 months (95% CI=13.22-NA) and median survival not reached (95% CI=15.21-NA). Median PFS for patients with exon 19 deletions and exon 21 point mutations were 13.9 months (95%CI=8.7-NR) and 17.4 months (95%CI=13.2-NR), respectively. Three months after initiation of treatment, high titers of anti-EGF antibodies were detected in all patients and serum EGF and TGFα levels were found to be significantly lower compared to baseline levels. Finally, treatment with post-vaccination patient's sera inhibited EGFR, AKT and ERK1/2 phosphorylation in EGFR-mut cells growing in vitro. **Conclusion:** The combination of an anti–EGF vaccine with afatinib is well tolerated and induces a sustained immunogenic effect. Vaccination against EGF might enhance the clinical efficacy of EGFR TKIs.

Keywords: EGFR-mutant non-small cell lung cancer, EGFR inhibitors, anti-EGF vaccination

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.02 TROPION-PanTumor01: Updated Results From the NSCLC Cohort of the Phase 1 Study of Datopotamab Deruxtecan in Solid Tumors

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Introduction: Datopotamab deruxtecan (Dato-DXd) is an antibody drug conjugate (ADC) composed of a TROP2-directed monoclonal antibody conjugated to a topoisomerase I inhibitor via a tetrapeptide-based cleavable linker. Dato-DXd demonstrated encouraging antitumor activity in patients with advanced/metastatic non-small cell lung cancer (NSCLC) in preliminary analyses from TROPION-PanTumor01. Based on this study, Dato-DXd 6 mg/kg has been selected as the recommended dose for the phase 3 TROPION-Lung01 trial. Here we report updated results in NSCLC. **Methods:** TROPION-PanTumor01 (NCT03401385) is a phase 1 dose-escalation/expansion study evaluating Dato-DXd in patients with solid tumors. Patients were unselected for TROP2 expression and had measurable disease per RECIST version 1.1; patients with stable/treated brain metastases were permitted. The primary objective was safety and tolerability. Secondary objectives were efficacy and pharmacokinetics. The primary analysis in the NSCLC cohort will be performed 6 months after enrollment of the last patient, which occurred on 06 October 2020. **Results:** As of the data cutoff (08 January 2021), enrollment in the NSCLC cohort was complete; 180 patients from the dose-escalation and -expansion phases were treated with Dato-DXd 4 mg/kg (n=50), 6 mg/kg (n=50), or 8 mg/kg (n=80). Overall, 42% of patients were aged ≥65 years and 37% had a history of brain metastases. The median number of prior therapies was 3 (range, 1-9); 83% had prior PD-(L)1 therapy and 96% had prior platinum chemotherapy. Median follow-up was 11.4 months (range, 3.1-25.9 months). Objective response rate by blinded independent central review: 4 mg/kg, 24% (12/50); 6 mg/kg, 26% (13/50); 8 mg/kg, 24% (19/80), including 4 patients (2 each at 4 mg/kg and 6 mg/kg) still ongoing treatment with responses not yet confirmed. Grade ≥3 treatment-emergent adverse events (TEAEs) regardless of causality were reported in 47% of patients across doses. TEAEs seen in ≥30% of patients included (all grade, grade ≥3) nausea (52%, 1%), stomatitis (48%, 2%), alopecia (39%, 0%), and fatigue (32%, 1%). Select TEAEs (all grade, grade ≥3) of decreased neutrophil count/neutropenia (6%, 1%) and diarrhea (16%, 0%) observed with another TROP2-directed ADC were infrequent with Dato-DXd. Drug-related interstitial lung disease, by independent adjudication, occurred in 19 patients (11%): 4 mg/kg (10%, 1 grade 1, 3 grade 2, 1 grade 3); 6 mg/kg (4%, 2 grade 2); 8 mg/kg (15%, 3 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). TEAEs leading to dose reductions/interruptions occurred in 16% and 18% of patients, respectively: 4 mg/kg, 2% and 14%; 6 mg/kg, 8% and 18%; 8 mg/kg, 30% and 21%. Treatment discontinuations due to TEAEs were observed in 15% of patients (4 mg/kg, 14%; 6 mg/kg, 10%; 8 mg/kg, 19%), including some patients with prior dose reductions/interruptions. Primary analysis results from the NSCLC cohort will be presented. **Conclusion:** Dato-DXd continues to demonstrate promising efficacy and a generally manageable safety profile in heavily pretreated patients with advanced/metastatic NSCLC for whom treatment options are limited.

Keywords: antibody drug conjugate, NSCLC, metastatic

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.03 NBTXR3 Activated by SBRT Combined with Nivolumab or Pembrolizumab in Patients With Advanced Cancers: Phase I Trial

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Introduction: Immune checkpoint inhibitors (ICIs) have led to durable responses and improved outcomes in patients with lung cancer who respond to treatment, however many patients exhibit resistance to ICIs. Overcoming this resistance is a major challenge in immuno-oncology. Emerging evidence suggests that radiation therapy (RT) can enhance the antitumor response to ICIs by producing an immunomodulatory effect. RT dose and ultimate efficacy are however limited by toxicity related to exposure of healthy tissues. NBTXR3, composed of functionalized hafnium oxide nanoparticles, is injected intratumorally and activated by RT. NBTXR3 increases RT energy deposit inside tumor cells and subsequent tumor cell death, without adding toxicity to healthy tissues. Preclinical data demonstrate NBTXR3/RT can trigger both a local and systemic anti-tumor immune response, overcome resistance to anti-PD-1 in mice bearing resistant lung tumors, and reduce development of spontaneous lung metastases. We hypothesize that NBTXR3/RT, combined with anti-PD-1 may prime the immune system to increase the proportion of ICI responders or convert ICI non-responders to responders. **Methods:** This multicenter, open-label, phase I trial [NCT03589339] is evaluating NBTXR3/SBRT/anti-PD-1 (nivolumab or pembrolizumab) in 3 cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to HN re-irradiation and (2) lung or (3) liver metastases from any primary cancer eligible for anti-PD-1. Stereotactic body RT (SBRT) is delivered at tumor-site specific doses per standard practice. The primary objective is to determine the NBTXR3/SBRT/anti-PD-1 recommended phase 2 dose in each cohort. Secondary objectives are anti-tumor response (objective response rate), safety, and feasibility of NBTXR3 injection. **Results:** Nine patients have been treated at the 22% NBTXR3 dose level, 3 with HNSCC, 4 with lung metastases and 2 with liver metastases. NSCLC was the primary cancer in 2 lung patients and 1 liver patient. HNSCC was the primary cancer in 2 lung patients and 1 liver patient. Overall tumor regression was observed in 8/9 patients, 7 of whom were anti-PD-1 non-responders, including 4 lung patients. Of particular interest, the combination of NBTXR3/SBRT/anti-PD-1 resulted in tumor regression in 6/7 patients who had progressed on prior anti-PD-1, including 3 lung patients. A complete response lasting over 1 year has been observed in the injected lymph node in 1 anti-PD-1 naïve HNSCC patient. 2 SAEs related to anti-PD-1 and possibly related to NBTXR3 (G5 pneumonitis, G4 hyperglycemia) were observed in 1 anti-PD-1 naïve HNSCC patient and considered DLTs. This patient also experienced two other SAEs (G4 diabetic ketoacidosis, G4 acute kidney injury) related to anti-PD-1. SBRT-related safety profile was as expected. NBTXR3 injection in the lung was well tolerated. Updated safety and efficacy results with additional patients and longer follow-up will be presented. **Conclusion:** Safety data from this first-in-human phase I trial evaluating NBTXR3/SBRT/anti-PD-1 in patients with advanced cancers, show NBTXR3 intratumoral injection is feasible and well-tolerated in HNSCC, lung, and liver metastases. NBTXR3/SBRT/anti-PD-1 demonstrated promising signs of efficacy and led to tumor regression in patients having progressed on prior anti-PD-1. These data support further development of NBTXR3/SBRT in combination with anti-PD-1 as well as other ICIs.

Keywords: NBTXR3, Pembrolizumab, Nivolumab

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.05 DNA Damage Response (DDR) Gene Mutations and Correlation With Immunotherapy Response in NSCLC Patients

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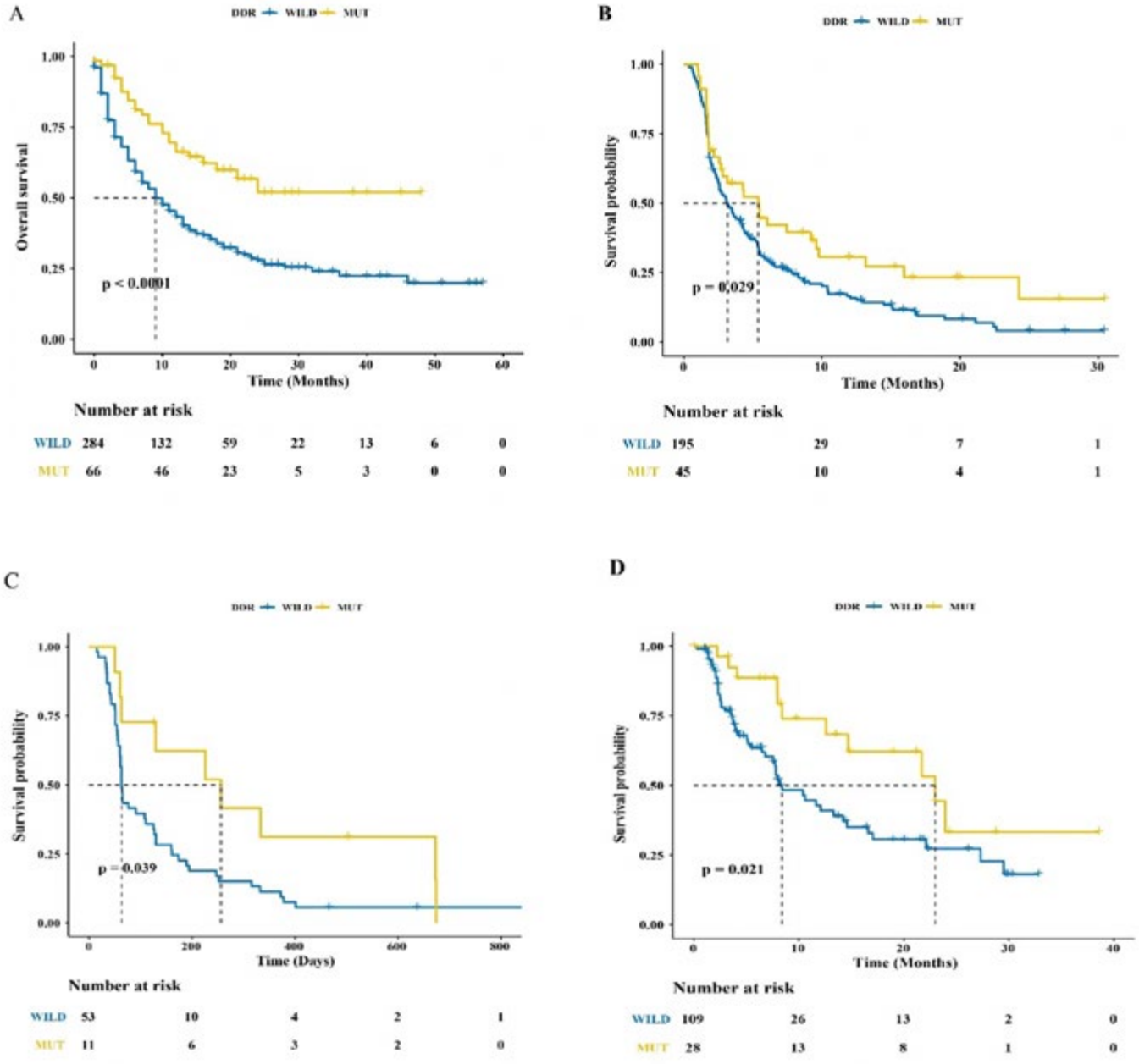
Introduction: Previous studies have shown that gene mutations in the DDR pathway are related to the efficacy of immunotherapy for advanced NSCLC. However, whether there are key genes in the DDR pathway that are positively related to the efficacy of immunotherapy in advanced NSCLC remains unclear. **Methods:** We first used a published cohort of 350 NSCLC patients from MSKCC to screen the gene mutations in the DDR pathway potentially related to the efficacy of advanced NSCLC immunotherapy, defined as the DDR-IO gene set. Then, we included 64 patients with advanced NSCLC who received PD-(L)1 inhibitor monotherapy in SYSUCC to test the predictive value of the DDR-IO gene mutations. Further, we used another cohort consisted of 137 lung cancer patients to validate our findings. In addition, we tried to explore the potential mechanism using TCGA data. **Results:** We identified a DDR-IO gene set consisting of 7 DDR pathway genes, which included ATM, BRCA2, BRIP1, MRE11, POLE, MSH2 and PARP1. In the MSKCC cohort, we found that patients with DDR-IO mutations tended to gain more survival benefit from anti-PD-(L)1 immunotherapy than DDR-IO wild-type patients (Median OS: unreached vs 9 months, $p < 0.001$; median PFS: 5.40 months vs 3.17 months, $p = 0.029$, Fig. A-B). Furthermore, we examined the predictive value of DDR-IO gene set in the SYSUCC cohort. We found that the median PFS of DDR-IO gene mutant patients was significantly better than that of DDR-IO wild-type patients (Median PFS: 256 days vs. 63 days, $p = 0.039$, Fig. C). In the 137 validation cohort, we also found that the PFS (Fig. D), ORR, DCR, and DCB rates of patients with DDR-IO gene mutations were significantly better than those DDR-IO gene mutations ($p < 0.05$). We have made a preliminary exploration of the potential mechanism by which the DDR-IO gene mutations affect immunotherapy. We found that TMB and TNB were significantly higher in NSCLC patients with DDR-IO gene mutations (TMB, $p = 0.012$; TNB, $p = 0.009$) in the SYSUCC cohort. Similar results were found in TCGA data ($p < 0.05$). In addition, the proportion of CD8+ T cells, M1 macrophages, T lymphoid follicular helper cells and activated NK cells were significantly higher in NSCLC patients with DDR-IO gene mutations ($p < 0.05$).



Conclusion: The DDR-IO gene mutation status can be helpful to predict the efficacy of immunotherapy in patients with advanced NSCLC, the mechanism of which needed to be explore by further research.

Keywords: Immunotherapy, DNA damage response pathway, Gene mutation, Non-small cell lung cancer

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.06 ctDNA Mass-Adjusted bTMB as a Predictive Biomarker in NSCLC Patients Receiving PD-(L)1 Inhibitors

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Introduction: High blood tumor mutational burden (bTMB) was significantly associated with progression-free survival (PFS) in non-small cell lung cancer (NSCLC) patients receiving atezolizumab. However, it failed to predict overall survival (OS). We hypothesized that ctDNA mass-adjusted bTMB (abTMB) might predict survival benefits in NSCLC patients receiving immune checkpoint inhibitors (ICIs) treatment. **Methods:** We collected clinical and genetic data from POPLAR and OAK trials. Genetic mutations and bTMB were determined by blood-based FoundationOne next-generation sequencing assay. Durable clinical benefit (DCB) was defined as PFS lasting ≥ 6 months. The cutoff value of abTMB for DCB prediction was calculated based on a receiver operating characteristic curve. Interaction between treatment and abTMB was assessed. National Cancer Center (NCC) cohort was used as a validation. **Results:** 853 NSCLC patients from POPLAR and OAK trials were included (n=429 for atezolizumab and n=424 for docetaxel) in this study. In the atezolizumab arm, the optimized cutoff value of abTMB for predicting DCB was 8 muts/Mb*ng. Significantly higher objective response rate (ORR) and DCB were observed in high abTMB patients than low abTMB patients receiving atezolizumab (20.5% vs. 11.0% for ORR, P=0.020; 40.8% vs. 23.8% for DCB, P<0.001). The median PFS (4.2 months vs. 2.4 months; adjusted hazard ratio [HR] for disease progression or death, 0.730; 95% CI, 0.593 to 0.900; P=0.003) and OS (15.9 months vs. 9.5 months; adjusted HR for death, 0.646; 95% CI, 0.508 to 0.822; P<0.001) of patients with high abTMB were significantly longer than those of patients with low abTMB in the atezolizumab arm. Importantly, the interaction between abTMB and treatments was significant for OS (interaction P=0.019) and PFS (interaction P=0.002). In addition, the prognostic role of abTMB was validated in the NCC cohort and high abTMB was associated with improved OS (28.5 months vs. 13.0 months; adjusted HR for death, 0.210; 95% CI, 0.049 to 0.899; P=0.035), PFS (15.5 months vs. 2.9 months; adjusted HR for disease progression or death, 0.305; 95% CI, 0.120 to 0.778; P=0.013), DCB (61.5% vs. 26.5%, P=0.041), and ORR (46.2% vs. 17.6%, P=0.065).

Table. Treatment interaction with ctDNA mass-adjusted bTMB (abTMB) for overall survival and progression-free survival in POPLAR and OAK trials

	OS			PFS		
	Adjusted HR	95% CI	*P* for interaction	Adjusted HR	95% CI	*P* for interaction
abTMB < 8	0.788	0.641-0.968	0.019	1.104	0.915-1.331	0.002
abTMB ≥ 8	0.534	0.415-0.688		0.697	0.555-0.875	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Conclusion: The ctDNA mass-adjusted bTMB was predictive of the PFS and OS benefits in NSCLC patients receiving ICIs treatment. The abTMB might be used to identify patients who will benefit from ICIs treatment.

Keywords: bTMB, NSCLC, ctDNA

MA03 BIOMARKERS FOR IMMUNOTHERAPY: ARE ALL RELEVANT?
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA03.07 Interferon-Gamma Mediated Immune Evasion: A Potential Mechanism of Resistance to Immunotherapy in Non-Small Cell Lung Cancer

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Introduction: Immunotherapy has unprecedentedly improved survival rates in patients with non-small cell lung cancer. Some patients with high tumor mutation burder, PD-1 and PD-L1 shows limited benefit from immunotherapy. Immune evasion described by immune contexture in tumor microenvironment could be potential mechanism of resistance to immunotherapy in non-small cell lung cancer. **Methods:** Data in our study were accessed from the Gene Expression Omnibus (GSE30219, GSE50081, GPL570) , The Cancer Genome Atlas (TCGA) and Immlnc database. Unsupervised hierarchical clustering was conducted to establish novel classification for NSCLC based on immune-related lncRNAs. Kaplan-Meier survival plots were utilized for survival analysis and overall survival (OS) estimation. Single sample gene set enrichment analysis and gene set variation analysis were performed to explore the landscape of tumor immune microenvironment. Gene instability and potential therapeutic effects were analyzed among three cohorts. The Tumor Immune Dysfunction and Exclusion (TIDE) algorithm mapping was applied to predict the therapeutic response to ICIs. Comparison of single nucleotide variation (SNV) and tumor mutational burden (TMB) among three identified clusters were performed through Kruskal-Wallis test. **Results:** We found that cluster A had the best prognosis by Kaplan-Meier analysis, followed by cluster B and cluster C significantly (p=0.0048). With a favorable prognosis, cluster A was marked by distinct infiltration of activated B cell, activated dendritic cell, activated CD8 T cell, central memory CD4 T cell, presented as immune-inflammed phenotype. However, in cluster B, the infiltration density of plasma cells, M1 and M2 macrophages, CD8 T cells, gamma delta T cells, myeloid-derived suppressor cells and memory CD4 T cells infiltration was significantly high as well, corresponding to immune-evaded phenotype. Cluster C had the lowest existence of immune infiltrating lymphocytes, correlated with immune-desert phenotype. Tumor mutation burden in cluster B was highest ($p < 0.001$), while lowest in the cluster A. We subsequently investigated the expression of crucial immune checkpoints among three clusters, such as PD-1, CTLA-4, CD28, and TNFRSF14, that higher expression of immune checkpoint molecules was observed highest in cluster A, followed with cluster B ($p < 0.001$).With respect to predicted response to immunotherapy, cluster B had the higher tumor immune dysfunction and exclusion score and lower predicted responders than cluster A ($p<0.001$). Cluster B had high mutation of KEAP1, LRRC7, PAPPA2, ABCA13, APOB, MUC17, NRXN1, DNAH9, SORCS1 and ZNF804A. The hub genes analyzed by Cytoscape software and String database in cluster B were STAT1, PARP9, TRIM21, OAS3. To explore potential mechanisms, activation of interferon−gamma and MHC class I signaling pathways could be detected in cluster B by Gene Ontology functional annotation analysis. **Conclusion:** In conclusion, we established a novel prognostic classification for NSCLC corresponding with classic immune inflammation, immune evasion and immune desert phenotypes, which describe tumor features in terms of immune contexture, genomic characteristics, and immune checkpoints, targeting the tumor immune microenvironment comprehensively rather than immune checkpoint and TMB alone. Our result suggested interferon-gamma mediated immune evasion could be a potential mechanism of therapeutic resistance to immunotherapy in non-small cell lung cancer.

Keywords: non-small cell lung cancer, immunotherapy, Tumor immune microenvironment

MA04.01 Multimodality Treatment and Outcome in Stage III Thymic Epithelial Tumors (TETs): A Retrospective Analysis From the French RYTHMIC Network

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Introduction: TETs are rare and potentially aggressive malignancies with high associated prevalence of autoimmune disorders (AIDs). Complete resection, pathological subtype according to WHO classification and Masaoka-Koga stage (MK) are the main prognostic factors. MK III represents a heterogeneous population without a clear optimal therapeutic approach, so we have collected outcomes of patients with MK III TETs in a large prospective registry. **Methods:** RYTHMIC is a French network for TETs composed of national and regional expert centers, with the objective of systematic discussion of patient's management at a single nationwide tumor board, based on consensual guidelines. We conducted a retrospective analysis of MK III TET patients discussed at the RYTHMIC tumor board between January 2012 and December 2019. Data were prospectively collected in a central database. Prognostic factors for disease-free survival (DFS) and overall survival (OS) were determined by Cox proportional hazards modeling. **Results:** 366 patients with a median age of 61 years (range 16-90) were included; 52% were male. 27% (n=99) of AIDs, mainly Myasthenia Gravis (n=82, 82.8%). Thymoma B2 was the most frequent (n=106, 29%) followed by B3 (n=71, 19.4%), thymic carcinoma (n=56, 15.3%), AB (n=29, 7.9%), B1 (n=28, 7.7%) and, A (n=22, 6%). Tumor invasiveness were mainly reported to lung (n=99, 27%), pleura (n=91, 25%) and pericardium (n=72, 29.7%). TNM classification was available in 60% of patients, among them: T2 (n=70, 19.1%), T3 (n=135, 36.9%), T4 (n=14, 4%). Forty-two (11.5%) and 23 (6.3%) patients reported phrenic nerve (PN) and great vessels invasiveness, respectively. Surgery was performed in 254 patients (69.4%), resection was complete (R0) in 54% including 34.6% (n=88) PN resection; mean tumor size was 72 mm (1-200 mm) post-operative radiotherapy was delivered to 97% (n=169). Among 55 patients initially considered non-surgical candidates, 36 (65.5%) underwent resection after induction chemotherapy, and 10 (2.7%) patients received with definitive radiotherapy. Recurrence was observed in 87 (26%) patients, mainly to the pleura (n=39, 45%). 10-year OS and DFS were 79% and 30%, respectively. Multivariate analysis for DFS is reported in the table 1; no statistical significance results were found for OS.

	Clinicopathological prognostic factors for DFS			
	HR	95% C.I. lower	95% C.I. upper	p-value
Sex (female)	4,951	2,094	11,708	<0,0001
Age at Dx	0,976	0,953	1,001	0,059
AID	0,791	0,295	2,123	0,642
T2	NA	NA	NA	0,046
T3	1,463	0,516	4,147	0,474
T4	10,424	1,607	67,611	0,014
Type A	7,147	0,431	118,425	0,17
Type AB	NA	NA	NA	0,982
Type B1	0,239	0,025	2,281	0,214
Type B2	2,339	0,609	8,991	0,216
Type B3	0,778	0,166	3,637	0,749
Thymic carcinoma	43,18	7,604	245,212	<0,0001
Complete resection	0,311	0,14	0,692	0,004
Adjuvant Radiotherapy	0,771	0,236	2,518	0,666
Induction Chemotherapy	0,371	0,143	0,962	0,041

Conclusion: Complete resection after induction chemotherapy improves recurrence outcome of patients with MK III TET, especially for T4. Adjuvant radiotherapy may have a positive impact on DFS. MK III TET patients not candidates for primary surgery should be systematically reassessed for resection after induction chemotherapy.

Keywords: Thymic Epithelial Tumors, stage III, complete resection, induction chemotherapy

MA04 CURRENT STATUS AND FUTURE PROSPECTS OF PLEURAL MESOTHELIOMA AND THYMOMA
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA04.02 Characteristics of Genomic Alterations in Chinese Patients with Thymic Epithelial Tumors

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Introduction: Thymic Epithelial Tumors (TETs), including thymomas and thymic carcinomas, are almost among the rarest of all cancers. Currently, the etiology and pathogenesis of TETs remain unclear, and few therapeutic options are accessible. Meanwhile, molecular-targeted treatments of TETs have met with limited success, and more potential drug-target genes needed to be understood. Herein, we presented a comprehensive analysis of the genomic characteristics of Chinese patients with TETs. **Methods:** A cohort of 30 TETs patients, including 24 (80%) thymomas and 6 (20%) thymic carcinomas cases, was enrolled from Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University from May 2018 to December 2020. NGS of targeted-450 cancer genes was performed on FFPE tumors and matched blood samples in OrigiMed (Shanghai, China) which laboratory was certified by CAP and CLIA. Genomic alterations, tumor mutational burden (TMB) and microsatellite instability (MSI) were assessed. **Results:** In total, 301 clinically relevant genomic alterations from 163 genes were identified. 91.0% of them were substitutions/indels, 4.7% truncations, 2.3% homozygous deletions, 2.0% amplifications and no rearrangements/fusions. In all patients, the top 6 most common mutation genes were MUC16 (50.0%, 15/30), ZFHX3 (36.7%, 11/30), OBSCN (30%, 9/30), ARID1B (16.7%, 5/30), PARP4 (16.7%, 5/30), and TFEB (16.7%, 5/30). Interestingly, there was no overlap of high-frequency genomic alteration between above and published TCGA patients. Moreover, mutant genes of 53.3% (16/30) patients were involved in homologous recombination repair (HRR) pathway and 26.7% (8/30) in cell-cycle pathway. 3 patients harbored potential drug-target genes, namely, 2 patients with both CDKN2A and CDKN2B homologous deletions (CDK4/6 inhibitors were recommended), and the other one with BRCA1 Y1463* (PARP inhibitors were recommended). Notably, mutations of TP53, CDKN2A and CDKN2B were only detected in thymic carcinomas, while ZFHX3 only in thymomas. It suggested that different genes may related to malignant degree of TETs. NOTCH3 and RAD50 mutations were significantly associated with younger patients ($p < 0.01$), while LRIG1 mutations tend to in older patients ($p<0.05$). Patients with GTF2I mutations had smaller tumor sizes than those wild-type patients (Median: 1.8 vs 4.8 cm, $p < 0.05$). Last but not least, TCGA published data showed that TETs had the lowest TMB among adult cancers, which was confirmed in our cohort. The median TMB was 3.3 muts/Mb, up to 76.7% (23/30) patients had TMB < 5 muts/Mb and only 2 patients had TMB > 10 muts/Mb (12.8 and 36.2 muts/Mb, respectively). In addition, all patients were MSS. **Conclusion:** Our study revealed comprehensive genomic profiling of Chinese TETs, which displayed significant difference compared with Western patients. Also, we confirmed that the thymomas and thymic carcinomas had distinct genomic features. Mutations of some genes could guide clinical targeted therapy or immunotherapy.

Keywords: Thymic Epithelial Tumors, Genomic alterations, Next-generation sequencing (NGS)

MA04.03 A Phase II Study of Palbociclib for Recurrent or Refractory Advanced Thymic Epithelial Tumor (KCSG LU17-21)

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Introduction: Thymic epithelial tumors (TETs) are rare but the most common tumor of the anterior mediastinum. Platinum-based combination chemotherapy is standard of care which is associated with a 50%-90% overall response rate (ORR) in metastatic disease. However, there is no standard chemotherapeutic option after failure of platinum-based combination chemotherapy. Genetic alterations associated with cell cycle including pRB, $p16^{INK4A}$, and cyclin D1 are commonly observed in TETs. Based on these results, we conducted a phase II trial to evaluate the efficacy and safety of palbociclib in patients with recurrent or refractory advanced TETs. **Methods:** This is a phase II multicenter, open-label, single arm study of palbociclib monotherapy in patients with recurrent or metastatic advanced TETs who failed one or more cytotoxic chemotherapy. Patients receive oral palbociclib 125mg daily for 21days followed by a 7-day break. The primary endpoint was the progression-free survival (PFS) rate at 6 months (H0=30% vs H1=48%). **Results:** Between August 2017 and October 2019, 48 patients were enrolled. The median number of previous chemotherapy was 1 (range: 1-4) and 21 (43.7%) of 48 patients received thymectomy. By WHO classification, Type A (n=1), Type B1 (n=2), Type B2 (n=8), Type B3 (n=13), Type C (n=23), and unknown (n=1). With medial follow-up of 14.5 months (range 0.8-38.2), the median cycle of palbociclib was 10 (range 1-40). The PFS at 6 months was 60% and the median PFS was 11.0 months (95% CI: 4.6-17.4). Six of 48 patients (12.5%) achieved partial response. The median overall survival was 26.4 months (95% CI: 17.4-35.4). The most common adverse events of any grade included neutropenia (62.5%), anemia (37.5%) and thrombocytopenia (29.1%). **Conclusion:** Palbociblib monotherapy is well tolerable and encouraging efficacy in patients with TETs who failed platinum-based combination chemotherapy. Updated results will be presented.

Keywords: Palbociclib, Cyclin D1, Thymic Epithelial Tumors

MA04.05 Survival Benefit of Multiagent Chemotherapy With and Without Curative Surgery for Malignant Pleural Mesothelioma

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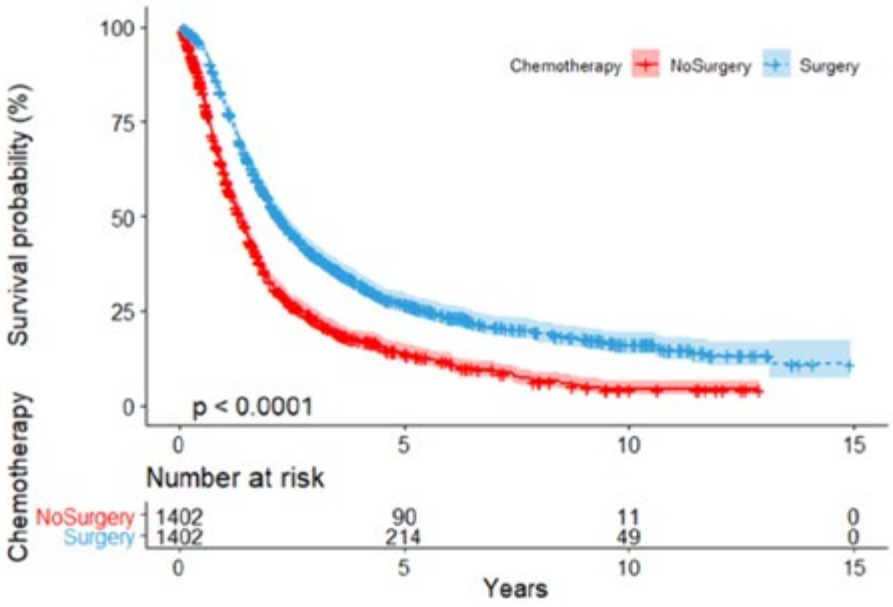
Introduction: There is limited evidence demonstrating a survival advantage of curative-intent surgery for malignant pleural mesothelioma over systemic therapy. This radical surgery (pleurectomy, decortication or extra pleural pneumonectomy) carries a significant risk of increased morbidity and mortality. We sought to evaluate if the addition of curative intent surgery is associated with better survival over multiagent chemotherapy alone in a large population-based study. **Methods:** The National Cancer Database (NCDB) was queried for patients with clinical stage I to IIIA malignant pleural mesothelioma with epithelioid or biphasic histology who underwent multiagent chemotherapy with and without the addition of curative intent surgery from 2004 to 2017. Propensity score analysis was used to adjust treatment groups by patients and tumor characteristics, socio-economic status, and facility type. Kaplan-Meier utilized for estimating survival and log-rank test used for comparison between groups. Univariable and multivariable cox regression analysis were used to estimate predictors of survival. **Results:** Between 2004-2017, we identified 4036 patients eligible for surgical treatment according to National Comprehensive Cancer Network Guidelines who received multiagent chemotherapy. A total of 1844 patients underwent surgery while 2192 did not. Propensity score yielded 1402 matched pairs. Survival estimates for 5 and 10 years with multiagent chemotherapy alone were 11.2% and 3.6%, respectively, while it was 23.9% and 14.2% when curative intent surgery was performed (figure1A). Median survival was 16 months without surgery and 22 months with surgery. Predictors for worse overall survival, after adjustment for other variables, were undergoing chemotherapy alone, older age, and male gender.



Prognostic Factors	Univariable Cox			Multivariable Cox		
	HR*	95% CI	p-value	HR*	95% CI	p-value
Treatment: Chemotherapy (Ref)	-	-	-	-	-	-
Systemic + radiotherapy	1.371	1.070, 1.756	0.0125	1.272	0.989, 1.635	0.0604
Surgery with systemic therapy	0.561	0.510, 0.617	**<.0001**	0.606	0.549, 0.668	**<.0001**
Surgery + systemic + radiotherapy	0.732	0.627, 0.855	**<.0001**	0.728	0.622, 0.853	**<.0001**
Age	1.024	1.020, 1.029	**<.0001**	1.021	1.015, 1.028	**<.0001**
Gender: Male vs. Female (Ref)	1.575	1.424, 1.741	**<.0001**	1.427	1.289, 1.580	**<.0001**
# Days on Chemotherapy	0.997	0.996, 0.998	**<.0001**	0.998	0.997, 0.999	**0.0002**

* Multivariable Cox model adjusted by race/ethnicity, insurance status, facility type and volume, Charlson-Deyo Score, and tumor stage.

Conclusion: The addition of curative intent surgery to multiagent chemotherapy is associated with a survival advantage in this large nationwide database study. The possible confounding effect of selection bias in surgical outcomes is not captured in this analysis. Results of well-designed randomized controlled trials are needed to further define the role of curative intent surgery in the treatment algorithm for malignant pleural mesothelioma.

Keywords: Mesothelioma, survival, Surgery

MA04 CURRENT STATUS AND FUTURE PROSPECTS OF PLEURAL MESOTHELIOMA AND THYMOMA
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA04.06 MicroRNAs Contribute to the Chemotherapy Response of Malignant Pleural Mesothelioma

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Introduction: Although platinum-pemetrexed chemotherapy remains the gold-standard for treatment of malignant pleural mesothelioma (MPM), to date we are still lacking true predictive biomarkers able to identify those patients who truly respond to chemotherapy. Aiming to overcome this problem, we previously performed microRNA expression profiling in tumour tissue of responders and non-responders to induction chemotherapy, which identified candidate predictive microRNAs. Candidates from this profiling are now investigated in vitro for their potential to alter the response of MPM cell lines to cisplatin and pemetrexed. **Methods:** Commercially available MPM cell lines MSTO-211H, H28, Meso1 and Mero82, and the non-malignant transformed mesothelial cell line MeT-5A were reverse transfected with mimics of microRNAs showing differential expression in responders and non-responders. In a first step, we assessed the effect of microRNA overexpression on cell growth without additional drug treatment. Next, 24h post transection, cells were treated with increasing concentrations of cisplatin or pemetrexed for 5 days, at which point IC50s were determined. Finally, transfected cells were treated with the combination of cisplatin and pemetrexed at the concentration of the respective IC50s. **Results:** Initial analyses of five candidate microRNAs revealed that overexpression of microRNAs frequently resulted in reduced cell growth of MPM cell lines, but not in MeT-5A. Specifically, overexpression of miR-380-5p resulted in at least 40% growth inhibition, overexpression of miR-221-3p or miR-30a in at least 30% growth inhibition in MPM lines. Investigating the effect on cisplatin response, we observed that in a subset of cell lines, overexpression of miR-380-5p and miR-221-3p indeed resulted in increased sensitivity to the drug. This effect was most pronounced for miR-221-3p, for which we saw significantly lower IC50 values in MSTO-211H (17.59 vs 2.65, $p<0.001$) and Meso1 (21.59 vs 5.54, $p<0.001$). Furthermore, in Meso1 cells, overexpression of miR-380-5p, also resulted in a significant increase in sensitivity to cisplatin (21.59 vs 10.36, $p=0.045$). However, neither of these microRNAs induced strong sensitisation to pemetrexed. In contrast, overexpression of miR-221-3p, the microRNA with the strongest sensitising effect towards cisplatin, in the same cell lines, appears to induce increased resistance against pemetrexed. Evaluating the effect of microRNA overexpression on the sensitivity to the cisplatin-pemetrexed doublet then showed that although cells are not sensitised to pemetrexed, the sensitising effect on cisplatin is strong enough to result in significantly reduced cell growth 5 days after treatment when compared to the drug-treatment without microRNA overexpression. For both miR-221-3p and miR-380-5p overexpression, transfected cells treated with the combination showed 50-75% lower cell growth than cells without microRNA overexpression. **Conclusion:** First in vitro investigations suggest that overexpression of microRNAs previously linked to chemotherapy-response has the potential to increase the sensitivity to cisplatin. Interestingly, current data for pemetrexed suggest that some microRNAs might render cells more resistant to this drug. However, when treated with the cisplatin-pemetrexed doublet, the sensitising effect on cisplatin seems to be the dominant mechanism, resulting in increased response to the doublet in microRNA overexpressing cells. Further studies aim to understand the underlying mechanisms responsible for the differences in response to microRNA overexpression.

Keywords: microRNAs, Mesothelioma, chemotherapy resistance

MA04 CURRENT STATUS AND FUTURE PROSPECTS OF PLEURAL MESOTHELIOMA AND THYMOMA
WEDNESDAY, SEPTEMBER 08, 2021 - 10:45-11:45

MA04.07 Clinical Characteristics and Outcomes in Patients With Malignant Pleural Mesothelioma (MPM) with COVID-19 Infection

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This abstract is under embargo until September 8 at 10:45 Mountain Time.

MA05 USING REAL WORLD AND PATIENT REPORTED DATA TO IDENTIFY GAPS AND NEEDS FOR PEOPLE WITH LUNG CANCER: IMPACTS OF THE COVID-19 PANDEMIC, TREATMENT PATTERNS, AND PSYCHOSOCIAL IMPACTS
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

MA05.01 Patients' Experiences During COVID-19: Insights From The Second Global Lung Cancer Coalition Patient Experience Survey

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Introduction: The Global Lung Cancer Coalition (GLCC) is a partnership of 41 patient organisations across 30 nations, dedicated to improving outcomes for lung cancer patients. In 2020, the GLCC conducted its first global patient experience survey, using member networks to canvas patients' opinions on their care. In 2021, the GLCC wanted to explore how COVID-19 had affected patients' experiences of lung cancer care, so determined to undertake a second survey. **Methods:** The GLCC reconvened its steering group, adding representatives from Spain and South Africa. The steering group agreed a list of 27 questions for patients and carers. Some questions from the 2020 survey were reprised, including: Whether patients feel involved in decision-making Whether patients feel treated with dignity and respect by their treatment team The survey asked new questions on: The physical and mental impact of a lung cancer diagnosis How COVID-19 had affected diagnosis and treatment pathways and patients' mental and physical health Opinions on virtual (telephone or video) consultations, where offered in place of face-to-face consultations From where patients seek information For each participating country, the agreed questions were translated into the native language. An additional survey was developed in English with a question asking respondents which country they were from, allowing English-speaking patients to participate even if not from one of the participating members' countries. Surveys were distributed via members' supporter networks, newsletters and social media. As some members felt one month was insufficient time to gather responses, the survey was kept open in the majority of countries for two months, between February and April 2021. **Results:** The survey was distributed in 17 out of the 40 countries where the GLCC has members: Argentina, Australia, Brazil, Bulgaria, Canada, Denmark, Ireland, Israel, Italy, Mexico, The Netherlands, Portugal, Spain, Taiwan, The UK, The USA and a pan-African survey. This includes four countries who didn't take part in the 2020 survey. One member said that COVID-19 meant they could not participate in the initiative because they needed to prioritise their resources to responding to patients' needs. The analysis of the findings will be undertaken in May 2021. The GLCC is keen to submit these data as a late-breaking abstract(s) for the World Conference on Lung Cancer. The GLCC plans to produce global and national reports for use in advocacy, with comparisons to 2020 data where members participated in both surveys. **Conclusion:** We are extremely grateful to all the patients and carers for their time and insights in responding to the survey, and to members for distributing the survey while occupied with supporting people with lung cancer. The findings will continue to support the GLCC's advocacy work as healthcare systems begin to recover from COVID-19. We hope they will also be useful in guiding lung cancer services and policymakers into those areas which are most important to patients and which should be prioritised as part of efforts towards recovery.

Keywords: patient experience, Survey

MA05 USING REAL WORLD AND PATIENT REPORTED DATA TO IDENTIFY GAPS AND NEEDS FOR PEOPLE WITH LUNG CANCER: IMPACTS OF THE COVID-19 PANDEMIC, TREATMENT PATTERNS, AND PSYCHOSOCIAL IMPACTS
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

MA05.02 Impact of Covid-19 on Lung Cancer Care and Utilization of Patient Support Resources

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Introduction: The COVID-19 pandemic has caused significant effects on rates of cancer diagnosis, treatment, and accessibility of cancer care (Wu et.al., World J Oncol, 2021). Barriers to seeking timely oncology care may lead to lung cancer patients being diagnosed at later stages or interruption of optimal therapy once diagnosed. This study examines the impact of COVID-19 pandemic on lung cancer care in the GO2 Foundation Care Continuum Centers of Excellence (CCCOE) network and on the utilization of patient support resources provided by the GO2 Foundation. **Methods:** An annual survey of the Care Continuum network, COE Impact Study, is conducted each summer to assess quality care metrics of lung cancer patients from diagnosis through treatment, care, and survivorship. In 2020, the impact of COVID-19 on lung cancer diagnosis and care was added to the survey. The survey is designed to deliver both quantitative and qualitative results about the impact of COVID-19 on lung cancer patients. GO2 Foundation also conducted a comparative analysis of 2020 data to prior years on the number of patients contacting GO2 Foundation for Lung Cancer's support helpline, and health care providers (HCPs) requesting educational materials to determine the impact of the COVID-19 pandemic on patient support services utilization. **Results:** A total of 27 CCCOE programs across the US participated in the survey. 60% of COE survey respondents reported a decrease in new lung cancer diagnoses during the pandemic compared to 2019. Survey respondents were also asked to report any long-term impacts they felt the pandemic would have on lung cancer care. The most frequently expressed concern was 'delays in diagnosis or treatment' as a long-term impact of COVID-19. In response to question about changes in patient attitudes due to COVID-19, most respondents reported 'fear of contracting COVID-19' from a pre-defined options list as the biggest concern among patients. There was a 35% decrease in patient and caregiver request volume on the GO2 Foundation's Helpline in 2020 compared to the previous year. There was a 13% decrease in helpline usage from quarter 1 to quarter 2 in 2020, whereas the average change in helpline usage from quarter 1 to 2 in the past 2 years was only 3%. Requests from health care providers (HCPs) for printed patient educational materials from GO2 Foundation saw a 38% decrease compared to the previous year. **Conclusion:** A majority of GO2 Foundation CCCOE programs noted a decrease in lung cancer diagnosis rates during the COVID-19 pandemic. In addition, patient support services offered by GO2 Foundation for Lung Cancer also saw a decrease in use compared to previous years. These changes highlight the far-reaching impact of COVID-19 on lung cancer diagnoses, treatments, and support services utilization by patients. Increased awareness of the pandemic's effects on lung cancer care throughout the medical community is important to prepare for meeting patient needs during the post-pandemic period.

Keywords: lung cancer, covid-19, diagnosis rates

MA05 USING REAL WORLD AND PATIENT REPORTED DATA TO IDENTIFY GAPS AND NEEDS FOR PEOPLE WITH LUNG CANCER: IMPACTS OF THE COVID-19 PANDEMIC, TREATMENT PATTERNS, AND PSYCHOSOCIAL IMPACTS
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

MA05.03 Considering the Continued Impact of the COVID-19 Pandemic on Patient Advocacy and Support Organisations

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Introduction: Over the last year, COVID-19 has been the primary focus for health systems around the world, impacting the diagnosis, treatment, and care of patients, including lung cancer patients. During this time, patient advocacy and support organisations have played an essential role in offering advice and support to patients. A year after the first lockdowns were announced in most countries, the Global Lung Cancer Coalition (GLCC) surveyed its members to understand how the pandemic has affected organisations and the support they offer to patients, and if experiences have evolved throughout the pandemic. The GLCC is a partnership of 40 patient organisations across 29 countries, dedicated to improving outcomes for lung cancer patients. This survey follows on from a GLCC survey conducted at the start of the pandemic in 2020. **Methods:** The GLCC's steering group designed a 24-question survey spanning five themes: changes in the levels of demand from patients throughout the pandemic; topics on which patients were seeking support; changes to services as a result of the pandemic; impact on organisations' finances; and lung cancer patients' access to COVID-19 vaccines. The online survey was shared with the GLCC's membership and was open for eight weeks between February and March 2021. **Results:** 19 GLCC members responded to the survey. Not every organisation answered each question. Almost two-thirds of organisations (12/19, 63%) have seen an increase in the number of patient requests throughout the pandemic, mainly via phone and helplines, email and Facebook. Organisations who saw an increase (7/12, 58%) stated that the number of requests received now is between 20-80 percent higher than at the start of the pandemic. 12 organisations (12/19, 63%) have seen a change in the types of support requested throughout the pandemic, with patients now asking for information on the availability and safety of the COVID-19 vaccine, and the impact of COVID-19 on treatment now and in the future. Most organisations (18/19, 95%) have continued to offer the new digital services introduced at the start of the pandemic, including online webinars, online emotional support groups, and more content on their website. 17 organisations disclosed how COVID-19 has impacted their income. Seven organisations (41%) have seen no change in their income during the pandemic. However, this does not reflect any fluctuations since the pandemic began. Only six (6/19, 32%) stated their national or regional government has offered support to patient advocacy organisations throughout the pandemic. Most organisations (15/19, 79%) said COVID-19 vaccines are available in their country. Whilst one organisation (1/19, 5%) stated lung cancer patients have already received their COVID-19 vaccines, almost two-thirds (12/19, 63%) expect lung cancer patients to receive their vaccines in the next six months. **Conclusion:** Patient organisations have had to be agile in the support they are offering to patients during the pandemic, responding to an increase in requests and evolving patient needs. In many cases, organisations are doing so with limited funding. More funding is required to ensure that these organisations can continue to provide patient support and, in some cases, survive.

Keywords: COVID, patient information, advocacy

MA05 USING REAL WORLD AND PATIENT REPORTED DATA TO IDENTIFY GAPS AND NEEDS FOR PEOPLE WITH LUNG CANCER: IMPACTS OF THE COVID-19 PANDEMIC, TREATMENT PATTERNS, AND PSYCHOSOCIAL IMPACTS
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

MA05.05 Treatment Patterns in Patients With EGFR-Positive Lung Cancer: A Real-World Patient-Report

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Introduction: As the lung cancer treatment landscape rapidly evolves, understanding what treatments reach which patients is critical. Capturing this information via healthcare systems nationally and internationally is challenging, however, patient-reports of treatments can help fill this gap. We aimed to learn about treatment sequencing for patients diagnosed with EGFR+ non-small cell lung cancer (NSCLC) in the real-world. **Methods:** Project PRIORITY, a patient-founded and patient-driven IRB-approved study, asked patients diagnosed with EGFR+ NSCLC to self-report all their treatments. Participants were asked, via an online survey, about the number of lines of treatment they had received, as well as specific drugs and their duration. Descriptive statistics and Sankey plots were used to explore the data. **Results:** 425 patients and caregivers completed the baseline survey; an additional 127 participants completed a longitudinal assessment. Most respondents were female (78%), 65 years or younger in age (67%), living in the US (74%), and diagnosed between 2015-2019 (84%). At time of survey completion, * 82% of **total** participants reported having stage IV non-small cell lung cancer (NSCLC). Nearly half (48%) received only 1 line of therapy, 25% received 2 lines, and 23% ≥3 lines of therapy. * 83% of **stage IV** participants received a tyrosine kinase inhibitor (TKI) as first-line therapy; osimertinib was the most common (43%), followed by erlotinib (35%). This pattern was not observed for participants residing outside the US, where erlotinib was the most frequently prescribed first-line TKI. * Most participants (96%) on first-line osimertinib did not report a second-line therapy confirming that osimertinib offers a longer PFS (within the study timeframe). Of the participants taking TKIs who reported additional lines of therapy, the most common transition was to osimertinib. In the figure, all second- and third-line pathways for participants on first-line TKIs are presented. * In addition to TKI monotherapy, second-line treatment regimens included TKI combinations with chemotherapy or radiation. Immunotherapy, though contraindicated for EGFR+ NSCLC, was also seen in second- and third-line settings Additional stratification analysis by year of diagnosis and side effects associated with sequencing will be presented. **Conclusion:** To our knowledge, this is the first report of treatment sequencing of EGFR-positive lung cancer in the era of multiple TKIs. Despite the relatively recent diagnoses of the participants in our study, our analysis highlights clear disparities in all lines of treatment where guideline recommendations for EGFRm NSCLC is not being prescribed.

Keywords: EGFR positive, Real-world data, Patient advocacy

MA05 USING REAL WORLD AND PATIENT REPORTED DATA TO IDENTIFY GAPS AND NEEDS FOR PEOPLE WITH LUNG CANCER: IMPACTS OF THE COVID-19 PANDEMIC, TREATMENT PATTERNS, AND PSYCHOSOCIAL IMPACTS
THURSDAY, SEPTEMBER 09, 2021 - 08:15-09:15

MA05.06 The Psychosocial Impact of Lung Cancer – A European Perspective

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Introduction: Lung Cancer Europe is an organisation committed to people impacted by lung cancer. Patient-centred care is about focusing on the needs of the person, and this requires understanding peoples´ experience and identifying their needs and priorities. As part of the lung cancer community, we are aware of the significant impact brought by the diagnosis of this disease. The purpose of this study was to raise awareness of the high emotional and social issues related to this disease, as reported directly by patients and caregivers. **Methods:** An online survey (patients and caregivers) was created and translated into 12 languages. It was active from May 20th-June 25th 2020. Data was collected through a self-filled online survey using the Surveymonkey® platform. A quality control check of the data was performed to identify and delete invalid answers. The data was integrated using the SurveyMonkey® analytic tools. Open questions were translated into English, aggregated and standardised into a single curated data set. A set of qualitative interviews were also undertaken with specialists. **Results:** The survey was completed by 365 people with lung cancer and 194 caregivers across 17 European countries. Adenocarcinoma was the most common diagnosis among the respondents (59.9%), with 49.2% diagnosed with Stage IV disease. Overall, 77.2% of caregivers and 52.5% of individuals with lung cancer stated that their emotional wellbeing had been negatively affected by 'quite a bit/very much'. For both, the feelings that deeply impacted their quality of life were uncertainty (62.5%), sadness (61.2%), anxiety (69.6%) and fear (59.6%). Many people with lung cancer reported impairments in physical and role functioning, fatigue, breathlessness, and pain, which affected their wellbeing. The key unmet needs reported by the participants were psychological needs (41.4%), symptom control and management (40.7%), issues related to the impact on family (32.5%) as well as rehabilitation and exercise (30.6%). There was also a lack of emotional support for patients - 42.2% felt they could not count on anyone to receive this support 'ever or only a little of the time/some of the time'. More than 80% stated that people asked them about their smoking history when they learned about their lung cancer diagnosis. Participants also confirmed some stigmatizing attitudes and behaviours from others, such as considering the person as responsible for getting lung cancer (reported by 30.9% of patients; 41.2% of caregivers) or judging the person negatively for having this disease (reported by 28.2% of patients; 24.0% of caregivers). Of those surveyed, 34.9% received some support from a patient organisation or a non-governmental organisation (NGO). The factors that were more useful for people who received this kind of support was information about the disease and treatments, and contact with other people impacted by the disease. **Conclusion:** The findings of this study stress the need to implement a friendlier, more accessible, and more holistic approach to healthcare services. There is a critical need to provide integrated psychosocial services in the lung cancer care pathway, increase awareness of patient organisations and NGOs, and fund initiatives offering 'peer to peer' support.

Keywords: advocacy, psychosocial, Europe

MA06.01 Death From Intercurrent Disease After Proton- Versus Photon-Based Chemoradiotherapy for Non-Small Cell Lung Cancer

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Introduction: Patients with locally advanced non-small cell lung cancer (LA-NSCLC) treated with chemoradiotherapy (CRT) often have cardiopulmonary comorbidities and receive significant radiation dose to normal structures. One way to reduce normal tissue exposure is with proton beam therapy (PBT). We sought to determine if PBT was associated with a reduced risk of death from intercurrent disease in this patient population. **Methods:** We retrospectively reviewed the records of 187 patients with LA-NSCLC who received definitive CRT with either PBT (n=98) or photon therapy (n=89) between December 2008 and November 2016 at a single academic center. No patient received consolidation immunotherapy as this cohort predated the results of the PACIFIC trial. Baseline patient-, tumor-, and treatment-related parameters were collected. Primary endpoint was death from intercurrent disease (DID), defined as death in the absence of disease progression. DID was compared between PBT and photon therapy groups using the cumulative incidence function and Gray's test and modelled using the Fine-Gray method. Disease progression was considered a competing event. Secondary endpoint was overall survival (OS), assessed using the Kaplan-Meier method and Cox regression. **Results:** The PBT group was older (median 69 years vs 62 years, p<0.001), had a more extensive smoking history (median 40 pack-years vs 30 pack-years, p=0.043), and had a greater burden of pre-CRT cardiovascular events (54.1% vs 34.8%, p=0.008). Median radiotherapy dose in both groups was 66.6Gy (range, 52.2-74Gy). The PBT group experienced lower mean heart dose (MHD) (median 6.7Gy vs 15Gy, p<0.001), total lung V5Gy (median 35.9% vs 48.2%, p<0.001), contralateral mean lung dose (median 0.97Gy vs 5.9Gy, p<0.001), and mean esophageal dose (MED) (median 22.1Gy vs 26.5Gy, p=0.003). Median follow-up was 28.8 months (range, 3.6-131.6 months). Following CRT, 25 patients (13.4%) experienced DID. Presumed causes of DID included: respiratory failure due to congestive heart failure, COPD, pneumonia, or aspiration (n=10), out-of-hospital cardiopulmonary arrest of unclear etiology (n=4), undifferentiated sepsis (n=2), probable radiation pneumonitis (n=1), esophagopleural fistula (n=1), and unknown (n=7). 3-year cumulative incidence of DID was 7.1% in the PBT group versus 14.6% in the photon therapy group (p=0.098). PBT (subdistribution hazard ratio [sHR] 0.25, p=0.0042), MHD (sHR 1.06/Gy, p=0.0018), and MED (sHR 1.05/Gy, p=0.019) were associated with a reduced, increased, and increased risk of DID, respectively, after controlling for age and ECOG performance status in three separate 3-variable regression models. OS was similar between the PBT and photon therapy groups (median 29 months vs 28.8 months, p=0.6; HR 1.09, p=0.6). MHD (HR 1.02/Gy, p=0.013) was associated with worse OS after controlling for age, ECOG performance status, baseline pulmonary comorbidity, and internal gross tumor volume. Patients receiving MHD >10Gy vs ≤10Gy experienced higher 3-year cumulative incidence of DID (15.6% vs 6.7%, p=0.049) and inferior OS (median 22.9 months vs 34.1 months, p<0.001). **Conclusion:** In this cohort of patients treated with definitive CRT for LA-NSCLC, PBT was associated with reduced cardiac, pulmonary, and esophageal dose and reduced risk of DID on multivariable analysis. These results suggest PBT may have a clinically meaningful benefit in this population.

Keywords: proton therapy, chemoradiation, toxicity

MA06.02 Impact of Heart and Lung Radiation Dose and Lymphopenia on Non-Small Cell Lung Cancer Outcomes

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Introduction: Lymphocytopenia may adversely affect survival. This effect has been hypothesised to be linked to heart and lung radiation and associated circulating immune cell dose. In this large single centre study of non-small-cell lung cancer (NSCLC) patients treated with radical chemo-radiotherapy (CRT), we assess the impact of lymphocytopenia in relation to heart and lung dose on survival and tumour control. **Methods:** We retrospectively analysed all NSCLC patients treated with CRT from January 2018 to December 2020. Patient, tumour and treatment characteristics, mean heart dose (MHD), mean lung dose (MLD) and relapse patterns were collected. Minimum lymphocyte count identified during and within 6 months of radiotherapy was classified 'lymphocyte nadir' and graded using CTCAEv5. EDIC, an estimate of effective radiation dose to circulating immune cells, was calculated based on Jin et al's model. EDIC = (0.12xMLD) + (0.08xMHD) + (0.45+0.35x0.85x(n/45)^0.5)) x (ITD/62x10^3) integral body dose (ITD), fractions (n) Progression free survival (PFS) and overall survival (OS) were calculated from start of treatment and associations between variables assessed using Cox regression models. **Results:** 150 of 164 patients treated with CRT had lymphocyte data. All patients received radical doses of radiotherapy with intensity-modulated radiation therapy and platinum doublet chemotherapy. 25 had adjuvant Durvalumab. Patients with ≥grade 2 lymphocytopenia at nadir (≥G2LN) had significantly worse PFS (HR=1.53, p<0.05) and OS (HR 1.69, p<0.05) than <grade 2 lymphocytopenia at nadir (<G2LN). Median OS was 26.5 and 35.1 months respectively. Patient and treatment characteristics are summarised in table 1. There was no significant difference in OS between sequential and concurrent CRT. Mean MHD and MLD were higher in patients with ≥G2LN compared to <G2LN (10.7Gy vs 7.8Gy and 13.4Gy vs 11Gy respectively) though not significantly. Larger planning target volume (PTV) was significantly associated with worse OS (HR=1.002, p<0.001) and correlated with lymphocyte nadir (Pearson r=-0.40, p<0.001). 111 patients had EDIC measures. EDIC negatively correlated with lymphocyte nadir (Pearson r=-0.237, p=0.017). Median EDIC was 2.38. EDIC ≥2.38 was associated with worse OS compared to <2.38 (19.5 vs 36.9 months respectively) (HR=1.75, p=0.067).

Table 1: Patient and treatment characteristics

	Lymphocyte nadir <Grade 2	Lymphocyte nadir ≥Grade 2
Number of patients	78	72
Median Age (range)	69 (44-85)	65 (45-87)
Stage		
IIA	1	0
IIB	6	4
IIIA	35	20
IIIB	32	40
IIIC	4	8
Histology		
Adenocarcinoma	36	40
Squamous Cell Carcinoma	38	27
Adeno/Squamous	3	0
NSCLC NOS	1	3
Large Cell Neuroendocrine	0	1
Sarcomatoid carcinoma	0	1
Delivered dose		
55Gy in 20 fractions	14	3
64Gy in 32 fractions	64	69
Chemotherapy		
Sequential	31	12
Concurrent	47	60
Adjuvant Durvalumab	12	13
PJP Prophylaxis	0	0
Progressed	38 (48.7%)	40 (55.5%)
Local	10	11
Regional	11	9
Oligometastatic	2	8
Multiple metastases	15	12
Median PFS (95% CI)	16.2 months (12.2-20.2)	10.5 months (4.8-16.2)
Died	25 (32.1%)	33 (45.8%)
Lung Cancer	17	20
Other Cause	6	8
Unknown Cause	2	5
Median OS (95% CI)	35.1months (31.7-38.5)	26.5months (15.1-37.9)
Mean mean lung-PTV physical dose (range)	11Gy (3.3-18.2Gy)	13.4Gy (5.9-20.7Gy)
Mean mean heart physical dose (range)	7.8Gy (0.3-26.2Gy)	10.7Gy (0.9-28.7Gy)
Mean maximum heart dose (range)	56Gy (0.7-68.7Gy)	59.2Gy (4.4-68.9Gy)
Mean Clinical Target Volume (range)	89.7cm^3 (3.3-394.5cm^3)	185.9cm^3 (11-586.1cm^3)
Mean Planning Target Volume (range)	344.8 cm^3 (61.5-921.8cm^3)	550.8cm^3 (136.9-1250.8cm^3)
Median EDIC (range)	1.97 (0.45-3.71)	2.54 (0.11-4.79)
Timing of lymphocyte nadir		
During or within 1 month of RT	65	71
1-6 months after RT	13	1
Tested COVID positive during data collection	0	0

Conclusion: Larger PTVs result in higher MHD, MLD and effective radiation dose to circulating immune cells, resulting in lower lymphocyte nadir which is associated with poorer outcomes. Lymphocyte nadir appears to be a surrogate for survival; we recommend closer surveillance of patients with ≥G2LN, reducing MHD and MLD to as low as possible and considering pneumocystis-jiroveci-pneumonia (PJP) prophylaxis. The additional impact of adjuvant immunotherapy would be interesting to assess.

Keywords: mean-heart-dose, mean-lung-dose, lymphocytopenia

MA06.03 Deep Learning-Based Survival Prediction for Non-Small Cell Lung Cancer Patients Undergoing Radical Radiotherapy

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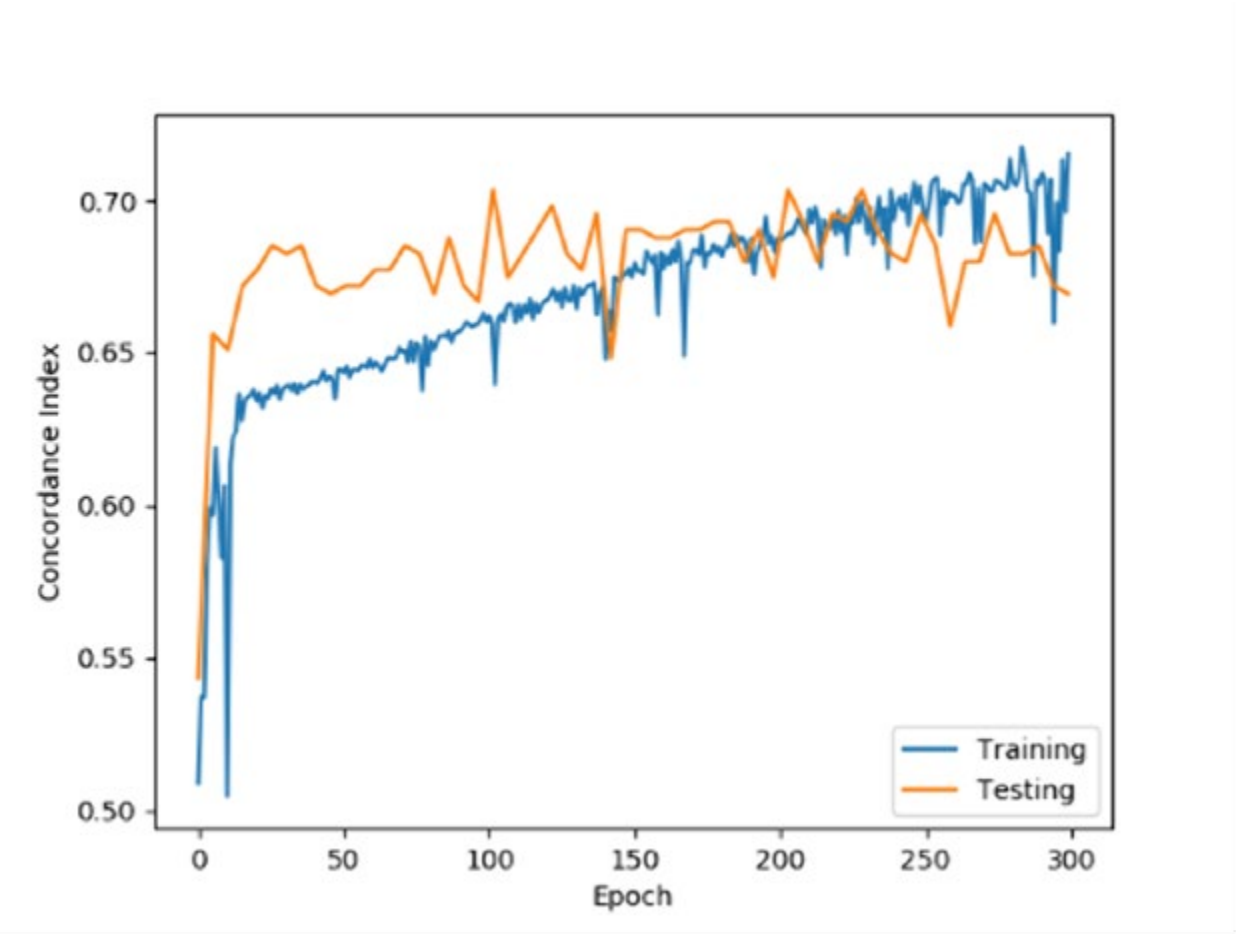
Introduction: The use of radiotherapy as part of a multimodality treatment approach has improved outcomes for patients with non-small cell lung cancer (NSCLC), though survival rates continue to lag behind those seen for many other cancers. Survival is frequently assessed using Cox proportional hazards (CPH) regression; however, this method may be too simplistic as it assumes a linear relationship between predictors and the outcome. Deep learning (DL), which employs biologically-inspired artificial neural networks, has been proposed as an alternative method to capture the complex, non-linear associations between variables required for accurate survival prediction. This method is yet to be applied to NSCLC patients undergoing radical radiotherapy, where an accurate predictor of survival would influence patient management. In this retrospective study, we built a DL-based model to predict overall survival using readily available clinical and treatment information on a large dataset of NSCLC patients who received radical radiotherapy and compared its performance against a CPH model. **Methods:** The dataset contained clinical, demographic, treatment and time-to-event survival data for 431 NSCLC patients treated with radical radiotherapy between 2010 and 2015. We built CPH- and DL-based survival prediction models using the following covariates: gender, age, time between diagnosis and treatment, planning target volume, histology, recurrence, chemotherapy and lung volume receiving ≥20 Gy. The DL-based model was implemented using DeepSurv, a deep neural network-based survival prediction algorithm. Data preprocessing included feature scaling of all covariates. The network structure comprised of an input layer, six hidden layers and a binary output layer. The number of nodes in each hidden layer decreased with depth. We used the SeLU activation function, a negative log likelihood CPH-based loss and Nesterov momentum with a learning rate of $2x10^{-3}$. We employed L1 and L2 regularisation along with dropout to prevent overfitting. The dataset was randomly divided into mutually exclusive training and testing sets at a ratio of approximately 90:10 .

We compared the performance of the CPH and DL models using the Harrell's concordance index (c-index) metric. **Results:** The DL-based survival prediction model generated a c-index of 0.703 after 200 epochs. Training and testing set performance are shown graphically (see figure). The DL method exhibited an improved c-index compared to the conventional CPH method of 0.703 vs 0.637, respective



Conclusion: We show that, using readily available clinical and treatment variables, DL-based survival analysis demonstrates superior performance over the CPH method for survival prediction in patients with NSCLC undergoing radical radiotherapy.

Keywords: Survival analysis, Deep Learning, radiotherapy

MA06 DIFFERENTIATING OUTCOMES AND IMPACT IN UNRESECTABLE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 09:30-10:30

MA06.05 Patterns of Care in Maintenance Therapy in U.S. Patients Undergoing Definitive Chemoradiation for Stage 3 Non-Small Cell Lung Cancer (NCSLC)

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MA06 DIFFERENTIATING OUTCOMES AND IMPACT IN UNRESECTABLE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 09:30-10:30

MA06.06 Treatment Recommendations for Stage III NSCLC by 3 Dutch Multidisciplinary Tumor Boards Prior To, and Following the PACIFIC Trial

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MA06 DIFFERENTIATING OUTCOMES AND IMPACT IN UNRESECTABLE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 09:30-10:30

MA06.07 Inferior Outcomes in Minority Patients with Unresectable Non-Small Cell Lung Cancer (NSCLC) After Durvalumab Consolidation Therapy

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Introduction: The PACIFIC trial demonstrated that durvalumab improved 3-year overall survival (OS) in unresectable Stage III non-small-cell lung cancer (NSCLC) following chemoradiotherapy (CRT). However, there is insufficient data on outcomes in minority populations (blacks and Hispanics) and there is no consensus on the preferred therapy after patients experience progression on durvalumab. This study aimed to evaluate the real-world outcomes of patients treated with durvalumab and subsequent therapies after disease progression. **Methods:** This was a retrospective study of 50 NSCLC patients treated in a large multi-site diverse community cancer center with CRT followed by durvalumab. Patients were evaluated for progression-free survival (PFS) after initiation of durvalumab. The PFS of minorities were also evaluated and compared with Non-Hispanic Whites (NHW). Treatment characteristics of the patients were also reviewed. Patients who received subsequent therapy after progression on durvalumab were also assessed for PFS. All PFS data was estimated using Kaplan-Meier analysis. **Results:** All patients met the criteria for the PACIFIC study. Key baseline characteristics of patients included a median age of 65 years (46-90y), 18% Blacks, 29% Hispanic and 89% with PDL-1>50%. The treatment characteristics of the patients (Table 1) were similar to the PACIFIC trial. A total of 16 patients (32%) progressed on durvalumab; the median PFS observed was 38.4 months (95% CI 11.0-38.4). The median PFS of minority populations were 8.6 months (95% CI 5.8- 38.4) versus NR (95% CI 8.13-NR) for NHW. 15 of the 16 patients who progressed received subsequent therapy; 1 died after durvalumab completion. The subsequent lines of therapy for the patients that progressed were as follows: 8(53%) immunotherapy/chemotherapy combination, 3(20%) chemotherapy only, 3(20%) targeted therapy, and 1(7%) radiation therapy. The median PFS for patients on the subsequent therapies was 9.5 months (95% CI 6.8-12.0). The median PFS for patients on immunotherapy/chemotherapy combination was 9.5 months and 8.8 months for patients on other subsequent therapies

Table 1: Results

Results	n=50
Median PFS, months (95% CI) All patients non-Hispanic whites Minority	38.4 (11.0-38.4) NR (8.13-NR) 8.6 (5.8-38.4)
12-month PFS rate (95% CI) All patients Non-Hispanic White Minority	65.9% (49-79.7) 61.7% (38.3-85.3) 47% (24.3%-71.1%)
18-months rate (95% CI) All patients Non-Hispanic White Minority	59.1% (36.7-76.1) 61.7% (38.3-85.3) 47% (24.3-71.1)
Median treatment duration, months(range)	8.1(0.4-12)
Median duration between end of RT and initiation of durvalumab, days (IQR)	37(27.5-55)
Status at cut-off date, n (%) On-going treatment Discontinued treatment	17(34) 33(66)
Treatment Discontinuation n (%) ADR Loss to follow up Disease	3(6.7) 3(6.7) 16(32) 11(22)

Conclusion: Evaluation of durvalumab consolidation in patients with advanced NSCLC finds PFS in clinical practice to be consistent with trial data. However there is a strong disparity in the PFS observed in the minority populations, these findings need to be evaluated in a larger population to determine its significance as there wasn't adequate minority representation in the PACIFIC trial. There was no significant difference between the median PFS of patients started on immunotherapy subsequent therapy and those initiated on non-immunotherapy regimens. This preliminary finding may suggest that progression on durvalumab doesn't impact survival on subsequent therapy

Keywords: Minority , Immunotherapy,nsclc

MA07.01 Dynamic Liquid Biopsy During Immunotherapy Anticipates Hyperprogression And Early Death in Advanced Non-Small Cell Lung Cancer

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Introduction: Immune checkpoints inhibitors (ICIs) have revolutionized the treatment of advanced Non-small cell lung cancer (NSCLC). However, a proportion of patients could experience detrimental effects and no predictive markers are available for their early detection. Aim of the study is to use longitudinal liquid biopsy as a tool to identify patients experiencing hyper-progression (HPD) or death within 12 weeks (early death, ED) following ICIs. **Methods:** Advanced NSCLC receiving ICIs at Istituto Oncologico Veneto were prospectively enrolled. Plasma was collected at baseline (T1) and after three/four weeks of treatment, according to treatment schedule (T2). Cell free DNA (cfDNA) was quantified and analyzed in NGS. Quantification of cfDNA and variant allele fraction (VAF) of tumor-associated genetic alterations were evaluated as static and dynamic parameter for their potential impact on outcome. The genetic alteration with the highest VAF at baseline (maxVAF) was evaluated as reference for NGS analysis. **Results:** 171 patients treated with ICIs from March 2017 to August 2019 were enrolled. Five cases matched criteria for HPD and 31 experienced ED; one case overlapped. Median OS of HPD patients was 3.8 (95%CI: 1.7-NA) versus 12.4 (95%CI: 9-13.7) months for non-HPD patients (p:0.012). Among clinical features, the presence of extra-thoracic disease was associated with the risk of experiencing ED (p:0.002). Quantification of cfDNA at T2 and its absolute variation (T2-T1) were significantly associated with the risk of ED (p:0.012, p:0.005, p:0.009), while no association with HPD was found. maxVAF relative change (T2-T1/T1) was significantly associated with the risk of experiencing HPD; Odds Ratio (OD): 8.14 (95%CI: 1.38-47.96, p:0.02). A ROC-based analysis was performed in order to define optimal cut-off values for risk definition. Patients experiencing an increase (T2-T1) of at least 4 ng/ml of cfDNA had higher risk to develop a detrimental effect and adjusted OR was 68.18 (95% CI: 5.61-828.57, p<0.001). Patients with a maxVAF relative variation (T2-T1/T1) of at least 0.2 had higher risk to develop HPD (OR: 12 (95% CI: 1.07-134.11, p= 0.044). **Conclusion:** Liquid biopsy performed early during treatment might anticipate detrimental effects of ICIs. ED and HPD were associated with different patterns of longitudinal liquid biopsy analysis. cfDNA quantification might be a simple cost-effective tool to anticipate ED, while relative change in VAF correlated with the risk of HPD. On these premises, we aim to validate a two-step risk assessment model by performing cfDNA quantification followed by NGS analysis.

Keywords: Liquid biopsy, Immune checkpoint inhibitors, biomarkers

MA07 LIQUID BIOPSY APPLICATIONS FOR IMMUNO-ONCOLOGY, TARGETED THERAPIES, AND EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

MA07.02 Evaluating Circulating Tumor DNA to Predict Overall Survival Risk in Non-Squamous Non-Small Cell Lung Cancer in IMpower150

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Introduction: A surrogate endpoint for overall survival (OS) could inform risk-based treatment decisions and provide early signals of efficacy to accelerate drug development for non-small cell lung cancer (NSCLC). We evaluated the utility of longitudinal circulating tumor (ct)DNA testing to predict OS and progression-free survival (PFS) in IMpower150, a phase III randomized controlled study of first-line (1L) chemotherapy plus atezolizumab and/or bevacizumab in patients with metastatic non-squamous NSCLC. **Methods:** Pre-treatment plasma samples from 1062 patients were retrospectively analyzed with the Blood Tumor Mutational Burden assay (Foundation Medicine Inc) at baseline; on-treatment samples from 566 patients (C2D1, C3D1, C4D1 or C8D1) were also evaluated with a custom ≈330-kb assay targeting ≈300 genes harboring baseline mutations. Clonal hematopoiesis of indeterminate potential (CHIP)/germline correction was performed for 466 patients who had evaluable peripheral blood monocyte samples, split into training (n=240) and validation (n=226) sets. ctDNA presence was quantified using different metrics (tumor molecules/mL plasma, allele frequency, number of detected variants), summarized per sample (mean, median) and across visit (difference, percent change). Associations with OS and PFS were evaluated at various landmarks using rank concordance (c-index) for individual ctDNA metrics, and jointly using the lasso model with cross-validation. Contributions of known baseline prognostic factors added to the model were then evaluated along with longitudinal metrics, including sum of longest diameter, blood tumor markers and routine laboratory data. **Results:** 204/240 patients (85%) had ctDNA at baseline and 181/240 (75.4%) had ≥1 pathogenic mutation detected. Clearance of pathogenic mutations occurred more frequently in patients who had complete or partial treatment responses (CR/PR; 39/100 [39%] clearance) than those who had stable (SD; 11/52 [21.2%]) or progressive disease (PD; 4/21 [19%]). Clearance was associated with improved PFS vs no clearance in patients with SD (median, 9.95 vs 5.1 months; HR 0.41; 95% CI 0.20-0.83) and PD (median, 2.6 vs 1.4 months; HR 0.20 [0.04-0.89]), and with numerically improved PFS in patients with CR/PR (median 10.4 vs 8.5 months; HR 0.85 [0.55-1.31]). Jointly modeling ctDNA features to predict survival showed that OS models performed better (c-index was higher and median split HR was lower) than PFS models (table). Adding clinical and biomarker features to ctDNA metrics improved OS model performance. **Conclusion:** ctDNA metrics were associated with OS and PFS in this combined 1L chemotherapy/immunotherapy/anti-angiogenesis treatment setting in patients with metastatic non-squamous NSCLC. ctDNA shows promise as a potential surrogate marker for survival, especially when combined with other biomarkers.

Model	Time point	Outcome	Performance (c-index)[a]	Top feature(s)[b] in model	Hazard ratio using median split (95% CI)
ctDNA	C3D1	PFS	0.60	Number of detected variants normalized by AF at BL	0.67 (0.50, 0.90)
ctDNA + additional features	C3D1	PFS	0.57	CYFRA 21-1 level at C3D1	0.86 (0.64, 1.15)
ctDNA	C3D1	OS	0.62	Difference in number of detected variants from BL to C2D1; number of detected pathogenic variants at C3D1; mean MTM at C3D1	0.62 (0.44, 0.86)
ctDNA + additional features	C3D1	OS	0.68	CYFRA 21-1 level at C3D1; difference in number of detected variants from BL to C2D1; CA19-9 level at C3D1	0.43 (0.31, 0.60)

AF, allele frequency; BL, baseline; CA 19-9, carbohydrate antigen 19-9 [blood tumor marker]; CYFRA, cytokeratin 19 fragment [blood tumor marker]; MTM, tumor molecules/mL plasma. [a] C-index (rank concordance) is a measure of patient-level association with a time-to-event endpoint (0.5 = random; 1.0 = perfect prediction). [b] Features that had both the highest gain (most improvement on model fitting from next-door analysis) and highest usage (selected most often by lasso).

Keywords: predictive biomarker, ctDNA variant clearance, surrogate endpoint for survival

MA07 LIQUID BIOPSY APPLICATIONS FOR IMMUNO-ONCOLOGY, TARGETED THERAPIES, AND EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 10:45-11:45

MA07.03 Paired Liquid and Tissues Biopsies to Guide Treatment for Patients That Progress on 2nd Line Osimertinib Treatment

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Introduction: Despite a high response rate and durability, resistance to osimertinib inevitably occurs in the majority of patients. Identification of resistance mechanisms may guide sequential targeted therapy. We aimed to 1) identify the resistance mechanism using paired liquid and tissue biopsies in patients that progressed on 2nd line osimertinib 2) determine progression free survival (PFS) of post-osimertinib therapy. **Methods:** From 09-2019 to 02-2021 50 patients that progressed on 2nd line osimertinib treatment were enrolled in this single-center prospective study. Patients underwent both liquid and tumor biopsies. Liquid biopsies were analyzed using AVENIO ctDNA Expanded Panel, tissue biopsies were analyzed with a targeted NGS panel and Archer FusionPlex Lung Version 1. Results were discussed case by case in a weekly Molecular Tumor Board (MTB), which led to tailored treatment advise. Post-MTB treatment was monitored every 6-8 weeks with CT. **Results:** The EGFR mutation could be detected in 37/50 plasma samples (74%) and 48/50 tumor biopsies (96%). Matched results were available for 35/50 patients (70%). For 39/50 patients (78%) ≥1 mechanism(s) of resistance could be identified in plasma and/or tissue, of which 15 showed ≥2 mechanisms of resistance. Most prevalent resistance mechanisms were MET amplification (38%) and EGFR C797S mutation (16%). Concordance between plasma and tissue will be presented separately. Following MTB discussion, 23 patients received targeted therapy and 16 patients chemotherapy. Four patients received best supportive care. Six patients continued osimertinib, three of whom received additional local ablative therapy. One patient had not yet started with chemotherapy. Targeted treatment consisted of osimertinib in combination with: dabrafenib and trametinib for BRAF V600E mutation (n=1); trametinib w/wo dabrafenib for BRAF fusion (n=3); 2nd gen EGFR TKI for EGFR G724S/L718Q mutation (n=2), 1st gen EGFR TKI for C797S mutation in trans with T790M (n=2); crizotinib for MET amplification (n=8) and ALK fusion (n=1), or combination of MET amplification and ALK fusion (n=1); T-DM1 for HER2amp/overexpression (n=5). Median PFS was 5.2 months for chemotherapy (95%CI 3.9 – 6.5 months) and 3.3 months for targeted therapy (95%CI 1.4 – 5.2 months). Median follow up was 9.1 months for chemotherapy and 7.2 months for targeted therapy. For patients receiving targeted therapy after progression on osimertinib, the number of identified resistance mechanisms had limited influence on PFS. Patients who had one resistance mechanism identified had a PFS of 5.8 months (95%CI 4.2 – 7.5 months), while this was 3.2 months for those with ≥2 resistance mechanisms (95%CI 0.2 – 6.2 months). Ten patients were biopsied after progression on targeted therapy. The mechanism of resistance that was targeted could not be detected anymore in 7/10 (70%) biopsy samples, while a new mechanism of resistance could be detected in 5/10 (50%). **Conclusion:** When paired liquid and tissue biopsies were used to guide treatment after progression on second line osimertinib, no difference in PFS was observed between chemotherapy or targeted therapy in this cohort. A relatively short duration of response to targeted therapy after progression on osimertinib may be explained by the high prevalence of multiple mechanisms of resistance, both synchronous as well as metachronous.

Keywords: tissue biopsy, osimertinib, Liquid biopsy

MA07.05 A Novel Blood-Based microRNA Diagnostic Test With Very High Accuracy for Early Lung Cancer Screening and Monitoring

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Introduction: Lung cancer is the leading cause of cancer death worldwide. Stage I lung cancers have a very good 5-year overall survival rate of about 80%, but these patients are typically asymptomatic and thus unlikely to be diagnosed. In fact, a staggering 75% of lung cancers are diagnosed at stages III and IV with a 5-year overall survival rate of only 30% and 6%, respectively. Lung cancer is in need of a good early diagnosis method. The current standard screening technique, low dose computed tomography (LDCT) has only 60% specificity, resulting in unnecessary invasive lung biopsies. We report here, the development of a serum-derived, microRNA (miRNA)-based genomic signature for potential early lung cancer diagnosis, by making use of a large public microarray dataset (Communications Biol 2020;3:134). **Methods:** The miRNA microarray dataset (1566 lung cancer patients and 2178 non-cancer controls across 2565 miRNAs) was downloaded from GEO. The data were divided into the same training and test sets as in the original publication. Linear Models for Microarray Data (limma) analysis was used to identify and rank differentially expressed miRNAs in the training set for building diagnostic models by calculating a diagnostic index using top rank miRNAs. Cross-validation was performed to determine the optimal number of miRNAs for the final diagnostic model, which was then evaluated in the test set for the diagnostic performance. **Results:** In the training set (n=416, 208 cancer vs 208 non-cancer), 10-fold cross-validation showed that a prediction model of top 4 miRNAs ranked by limma performed the best. In the testing set (n=3328, 1358 cancer vs 1970 non-cancer), the 4-miRNA prediction model demonstrated an area under the curve (AUC) of the Receiver's Operating Characteristics (ROC) analysis of 0.999, and 99% for both sensitivity and specificity (vs. 95% sensitivity and 99% specificity of the original 2-miRNA model in the original publication). The new model also showed consistently superior sensitivity than the original model in all clinical subgroups examined (Table 1). In addition, using our model the diagnostic index for post-surgery samples dropped to the level of those from non-cancer controls.

Sensitivity of the new diagnostic model vs. the original diagnostic model in relevant clinical subgroups

Clinical Subgroups	N	Original Model	New Model
Clinical stage IA	686	0.961	0.996
Clinical stage IB	285	0.937	0.996
Clinical stage IIA	146	0.973	0.979
Clinical stage IIB	61	0.967	0.984
Clinical stage IIIA	164	0.902	0.994
Clinical stage IIIB	6	0.833	1.000
Clinical stage IV	8	1.000	1.000
T stage T1a	466	0.961	0.996
T stage T1b	297	0.956	0.993
T stage T2a	435	0.936	0.991
T stage T2b	52	0.923	1.000
T stage T3	89	0.944	0.989
T stage T4	17	0.941	1.000
N stage N0	1047	0.955	0.995
N stage N1	166	0.958	0.982
N stage N2	142	0.901	0.993
Adenocarcinoma	1038	0.951	0.992
Squamous cell carcinoma	205	0.942	0.995
Small cell lung cancer	22	0.909	1.000

Conclusion: A serum-based diagnostic test with nearly perfect accuracy has been developed, which showed exceedingly better performance than LDCT. If validated in independent studies, this test has the potential for effective clinical screening of early stage lung cancers.

Keywords: lung cancer, serum microRNA, early diagnosis

MA07.06 Circulating Tumor DNA for Monitoring Minimal Residual Disease and Early Detection of Recurrence in Early Stage Lung Cancer

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Introduction: In early stage non-small cell lung cancer (NSCLC), recurrence is frequently observed and overall long-term survival remains poor. Circulating tumor DNA (ctDNA) has emerged as an effective non-invasive tool to detect/monitor minimal/molecular residual disease (MRD) and potentially guide systemic therapies to improve outcomes. **Methods:** This study included patients diagnosed with stage I-III NSCLC at the National Cancer Centre Singapore between May 2013 and June 2019. Recruited patients received standard of care management involving surgical resection with (n=15) or without adjuvant chemotherapy (n=42), followed by surveillance. Plasma samples (n=336) were collected prospectively pre- and serially post-surgery in all patients. Whole exome sequencing (WES) of NSCLC resected tissue and matched germline DNA was used to design patient-specific multiplex-PCR assays (Signatera™) to track 16 single-nucleotide variants in plasma samples. The relationship between ctDNA status and recurrence, detected by radiographic imaging was evaluated. To investigate intra-tumoral heterogeneity, WES was performed on multiple regions of the same tumor in 6 patients to identify the common variants. **Results:** The cohort consisted of 57 patients with a median age of 60 (43-83) years, of which 60% were male, 54% were non-smokers, 84% had adenocarcinoma, and 47% were EGFR mutated NSCLC. Stage distribution was 68% for Stage I and 16% each for Stage II and III. At median follow up of 33.0 (9.8-72.1) months, 11 (19%) patients had relapsed. ctDNA detection at presurgery was significantly associated with higher stage (p<0.0001), lymph node positive disease (p<0.0001),and shorter recurrence free survival (RFS; HR 5.46, 95%CI 1.21-24.6, p=0.003). In the post-surgery setting, ctDNA was detected in 7 patients, of which 100% (7/7) experienced radiological recurrence at a median of 15.4 (4.9-43.0) months. ctDNA-positivity preceded radiological findings by an average lead time of 3.8 (0-12.9) months. Longitudinally, ctDNA detection at any time point was associated with shorter RFS (HR 22.0, 95%CI 3.6-133.8, p<0.0001), while absence of ctDNA was associated with favorable outcome, corresponding to a negative predictive value of 94% (45/49 patients). Multiregional analysis of the tumor (2-6 regions per resected tumor sample) from 6 patients revealed significantly higher proportions of subclonal mutations in adenocarcinoma cases (n=3) compared to patients with squamous carcinoma (n=3). **Conclusion:** ctDNA detection during follow-up after surgery identified patients with high risk of relapse in early-stage NSCLC. Phylogenetic analysis revealed early evolutionary branching with greater proportions of subclonal mutations in adenocarcinoma subtypes that may impact clonal variant selection for ctDNA-based assays. Prospective studies are needed to assess the clinical utility of ctDNA status to guide disease surveillance and management.

Keywords: Lung adenocarcinoma, squamous cell lung carcinoma, ctDNA, molecular residual disease, mutiregion analysis, tumor-informed

MA07.07 Detecting Stage I Lung Cancer with High Sensitivity Using Genome-wide Multi-dimensional Fragmentomic Profiles of Cell Free DNA

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Introduction: Survival rate of lung cancer patients diagnosed at the early stage is about 9 times greater than that at the late stage, but approximately 60% of patients are diagnosed when metastasis has already occurred. Although cell-free DNA (cfDNA) analysis has shown great potential for liver cancer diagnosis, its detection sensitivity for lung cancer is currently unsatisfying especially for small tumors at the early stage (40% or even lower for Stage I patients). Therefore, there has been a growing demand for highly sensitive detection method of early-stage lung cancer. To this end, we performed a prospective study and established an integrated machine learning model using genome-wide multi-dimensional fragmentomic profiles of cfDNA for detecting Stage I non-small cell lung cancer (NSCLC), including adenocarcinoma (ADC) and previously understudied minimally invasive adenocarcinoma (MIA), with emphasis on small-size tumors. **Methods:** 150 NSCLC patients (ADC: 115 and MIA: 35; Stage IA: 144 and Stage IB: 6; tumor size < 1 cm: 57) and 115 healthy individuals were recruited in the training cohort. Whole-genome sequencing (~5X coverage depth) was performed for plasma cfDNA samples. A stacked ensemble learning model was constructed by integrating five machine learning algorithms and four cfDNA fragmentomic features - breakpoint motif, end motif, fragmentation size ratio, and fragmentation size distribution. The performance of the model was initially assessed in an internal validation cohort including 102 NSCLC patients (ADC: 78 and MIA: 24; Stage IA: 99 and Stage IB: 3; tumor size < 1 cm: 44) and 75 healthy individuals, and subsequently validated in an external cohort recruited from two other different centers including 40 NSCLC patients (ADC: 35 and MIA: 5; Stage IA: 36 and Stage IB: 4; tumor size < 1 cm: 14) and 40 healthy individuals. **Results:** Our model successfully yielded a sensitivity of 96% (stage IA: 96%, IB: 100%) for cancer detection at 95% specificity with an Area Under the Curve (AUC) of 99% in the internal validation cohort. Using the cutoff of prediction score at 95% specificity in the internal validation cohort, we observed a sensitivity of 93% (stage IA: 92%, IB: 100%) and specificity of 90% in the external validation cohort. When combining the two validation cohorts, a sensitivity of 95% and a specificity of 93% were achieved for early stage NSCLC detection. More importantly, our model exhibited an exceptional ability for detecting very early-stage and small-size tumors, yielding sensitivities of 96% (internal validation cohort) and 100% (external validation cohort) for MIA, and 98% (internal validation cohort) and 93% (external validation cohort) for <1 cm tumor. Finally, our model performance remained high (internal validation cohort: 94% sensitivity at 95% specificity; external validation cohort: 85% sensitivity and 93% specificity) when sequencing depth was downsampled to 1X coverage. **Conclusion:** We have established an integrated predictive model using genome-wide multi-dimensional cfDNA fragmentomic profiling for Stage I NSCLC detection. Our model demonstrated an unprecedented detection sensitivity even for MIA and small-size tumors, shedding lights on early-stage lung cancer screening in clinical practice.

Keywords: Cell-free DNA fragmentomics, Lung cancer, Early detection

MA08 DRIVER MUTATIONS AND IMMUNE PROFILES IN EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 12:00-13:00

MA08.01 Presence of High-Grade Subtype Predicts Recurrence of Stage I Lung Adenocarcinoma Only in EGFR-Mutated Patients

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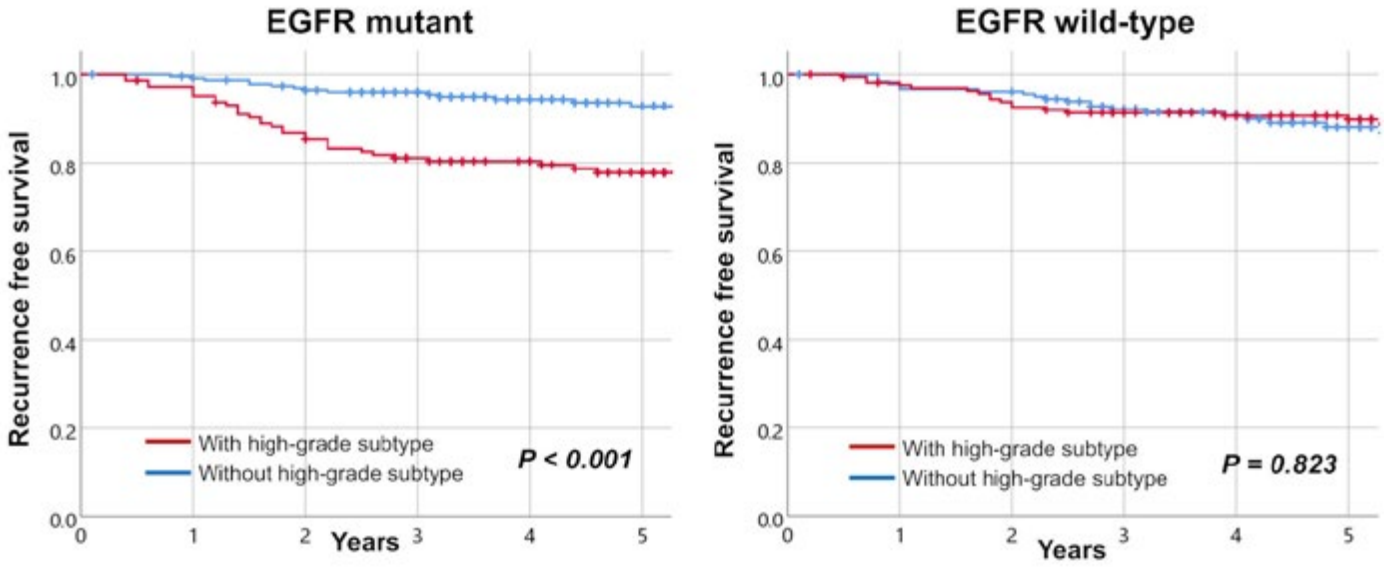
Introduction: It was reported that epidermal growth factor receptor (EGFR) mutation was a risk factor for recurrence when high-grade histological subtype (solid or micropapillary) was predominant. This study aimed to evaluate the prognostic impact of the combination of EGFR mutation and the presence of high-grade subtype, even if it was not predominant, in resected stage I lung adenocarcinoma. **Methods:** We reviewed the medical records of 721 patients who underwent curative resection for pathological stage I lung adenocarcinoma and EGFR mutation analysis. The overall survival and recurrence-free survival (RFS) were compared according to EGFR mutation status and presence of > 5% high-grade subtype component. Cox regression analyses were performed to identify prognostic factors. The covariates included in the multivariable analyses were EGFR mutation status, presence or absence of high-grade subtype, age (≥70 years), sex, smoking habit, size of invasion (>10 mm), pleural invasion, lymphatic invasion, and vascular invasion. **Results:** The median follow-up time was 5.2 years (range, 0.1–11.2 year). Of the 721 patients examined, relapse was observed in 57 (7.9%) cases and 21 patients (2.9%) died due to relapse, whereas 33 patients (4.6%) died due to other causes during follow-up. EGFR mutations were positive in 375 (52.0%) patients. EGFR mutation positivity was associated with female sex, nonsmoking status, lower consolidation/tumor ratio, absence of high-grade subtype, and absence of lymphovascular invasion. Cases with high-grade subtype showed poorer RFS in the group with EGFR mutations (5-year RFS, 77.7% vs. 92.8%, p <0.001), whereas there was no significant prognostic differences in EGFR wild-type cases between groups with and without high-grade subtype (5-year RFS, 89.7% vs. 87.9%, p = 0.823). Multivariate analysis revealed that the combination of an EGFR mutation and the presence of a high-grade subtype was an independent predictive factor for poor RFS (hazard ratio = 1.774, p = 0.016).



Conclusion: Presence of high-grade subtype predicts recurrence of stage I lung adenocarcinoma only in EGFR-mutated patients. Histological subtypes, including minor components, should be considered when evaluating the risk of recurrence in patients with EGFR-mutated lung adenocarcinoma.

Keywords: adenocarcinoma, EGFR, subtype

MA08.02 Outcomes of Early Stage ALK-positive NSCLC patients in a Real-World Cohort

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Introduction: While there has been a series of real-world studies on ALK-positive non-small cell lung cancer (NSCLC) in the advanced/metastatic setting, there are far fewer reports about the outcome of early stage ALK-positive cancer. The aim of this analysis was to study treatment patterns and outcomes in a real-world cohort of patients with ALK+ NSCLC diagnosed in stages I-III. **Methods:** All patients with stage I-III ALK+ NSCLC patients seen at Princess Margaret Cancer Centre (data cut-off date March 18, 2021) were included. Clinico-demographic, treatment and survival data were collected retrospectively. ALK has been reflexively tested across all non-squamous NSCLC for at least 9 years. **Results:** Of 47 patients presenting with early stage ALK-positive NSCLC, the median age was 61 years; 27/57% were female; 31/66% were never-smokers; 48% were Asian; 36% were Caucasian. 50% were ECOG 0, 47% ECOG 1 and only 3% were ECOG 2; 19/40% presented with stage I, 5/11% with stage II and 23/49% with stage III. When compared to our series of 115 de novo advanced/metastatic ALK-positive NSCLC patients, there were no significant differences in clinico-demographics, with the exception of ECOG PS. Among stage I patients, 16/84% were resected and three received adjuvant chemotherapy; two patients were treated with definitive curative radiation and chemoradiation respectively. All 5 stage II patients were resected and 3 patients received adjuvant chemotherapy. Stage III patients were treated with definitive chemoradiation in the majority of cases (16/70%) followed by consolidation durvalumab in 8 patients. 4/17% were resected and received adjuvant treatment. With a median overall follow-up time of 43.7 months, 32 (68%) had relapsed. The median time to relapse was 25.7 months overall (95% CI 20.2-51.4 months) and 144.4 months for stage I (n=9), 27.6 for stage II (n=4) and 14.4 months for stage III (n=19) patients. Sites of first metastatic recurrence were mainly in the lymph nodes (10/31%), pleura (8/25%), brain (6/19%), bone (5/16%) and liver (1/3%). Brain-only relapse without evidence of systemic metastatic disease occurred in 5 (15%) of cases. The patient who relapsed at 144 months after initial diagnosis developed ALK-positive brain only metastatic disease without evidence of an intervening second primary lung cancer. Among 15/32% early stage patients who have not relapsed, median follow-up time was 44.4 months. At the time of relapse, 25 were treated with an ALK-TKI as first-line treatment and only 2 (6%) with chemotherapy. Median overall survival (OS) from time of relapse was 47.0 months. Longer median time to relapse was marginally associated with improved OS after recurrence with an adjusted hazard ratio of 0.93 (95% CI: 0.86-1.01; p=0.07). **Conclusion:** The majority of our early stage ALK+ cohort relapsed with a metastatic pattern consistent with de novo advanced ALK+ disease including brain-only relapses. Time to relapse was directly correlated with stage at initial diagnosis and shorter time to relapse was associated with poorer outcome after diagnosis of advanced disease.

Keywords: early stage, ALK, treatment and recurrence patterns

MA08 DRIVER MUTATIONS AND IMMUNE PROFILES IN EARLY STAGE NSCLC
THURSDAY, SEPTEMBER 09, 2021 - 12:00-13:00

MA08.03 Adjuvant Chemotherapy for Patients with High-Risk Stage I Lung Adenocarcinoma Stratified by Epidermal Growth Factor Receptor Mutation Status

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Introduction: The purpose of this study was to evaluate the role of adjuvant chemotherapy stratified by the epidermal growth factor receptor (EGFR) mutation status in patients with stage I lung adenocarcinoma. **Methods:** Between 2010 and 2016, of 1,901 patients with pathologic stage I (8th edition) non-small cell lung cancer, 475 patients with high-risk (pT1c/T2a or positive for lymphovascular invasion) stage I lung adenocarcinoma undergoing lobectomy were identified. Propensity scores were estimated to adjust for confounding variables such as age, sex, smoking history, invasive component tumor size, visceral pleural invasion, lymphatic invasion, vascular invasion, adenocarcinoma subtype, and EGFR mutation status associated with the administration of adjuvant chemotherapy for matching. The primary endpoint was recurrence-free survival (RFS). **Results:** In patients without or unknown EGFR mutation (n = 292), 105 (36.0%) received adjuvant chemotherapy and 187 (64.0%) did not. In propensity score-matched 80 pairs, RFS was significantly better in patients who underwent adjuvant chemotherapy (5-year RFS, 86.8%) than in those who did not (5-year RFS, 70.9%; P = 0.009). In patients with EGFR mutation (n = 183), 78 (42.6%) received adjuvant chemotherapy and 105 (57.4%) did not. In propensity score-matched 64 pairs, there was no significant difference in RFS between patients who underwent adjuvant chemotherapy (5-year RFS, 75.9%) and those who did not (5-year RFS, 79.7%; P = 0.573). **Conclusion:** The role of adjuvant chemotherapy for high-risk stage I lung adenocarcinoma was different by the EGFR mutation status. EGFR mutation status should be tested in patients with high-risk stage I lung adenocarcinoma to decide the application of adjuvant chemotherapy.

Keywords: Lung adenocarcinoma, adjuvant chemotherapy, epidermal growth factor receptor mutation

MA08 DRIVER MUTATIONS AND IMMUNE PROFILES IN EARLY STAGE NSCLC
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MA08.05 Integrating Genomic and Transcriptomic Features Predict the Recurrence Risk of Stage IA Non-Small Cell Lung Cancer

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Introduction: Lung cancer remains the leading cause of cancer incidence and mortality world-wide. The mortality risk is still high in early stage because of the high relapse rates about 30–45% within 5 years after surgery. Therefore, there is an urgent need to evaluate the risk of postoperative recurrence in early-stage NSCLC. In this study, we depicted the genomic and transcriptomic characteristics in stage IA NSCLC patients and integrated a multi-omics recurrence model to stratify high risk recurrence patients to improve the prognosis. **Methods:** We prospectively enrolled 59 patients with stage IA NSCLC from 2012 to 2018 including 29 non-relapse patients and 30 early-relapse patients within 5 years. The paired adjacent non-tumor tissues for each patient were collected as negative control. DNA and RNA were co-extracted and performed with whole exon and transcriptome sequencing. CIBERSORT was used to access the proportion of immune cell infiltration. Patients were randomly allocated into training (49.2% of the samples) and validation (50.8% of the samples) sets. A LASSO (least absolute shrinkage and selection operator) Cox regression model was employed to build a prognostic classifier, which selected 10 potential predictors in the training cohort and were confirmed in the validated cohort. **Results:** The most frequently mutated genes in our cohort were EGFR (46.4%), TP53 (38.0%), TTN (35.2%) and USH2A (21.1%). Notably, USHA was enriched in relapse patients (32.3% vs 3.4%, p = 0.006). Among the early-relapse patients, copy number amplification at 2q31.1 was prevalent in the pre-relapse group ($p < 0.05$). Two patterns of clonal evolution were identified during the recurrence, including autonomous and acquired clonal evolution. Compared with non-tumor tissues, differentially expressed genes in pre-relapse affected the metabolism-associated pathways. Furthermore, post-relapse samples down-regulated antigen processing and presentation signaling pathway compared to non-relapse group. Interestingly, lower plasma dendritic cell infiltration was detected in post-relapse (p=0.008), indicating the defect of antigen presentation in recurrence. Genomic and transcriptomic features were further integrated to build a recurrence model that classified patients into low-risk and high-risk groups. A worse RFS (recurrence free survival) was observed in the high-risk group than the low-risk group in training cohort (23.8 vs 56.9 months, p =0.002) and the validation cohort (53.7 vs 65.9 months, p = 0.04). **Conclusion:** This study elucidated the recurrence risk molecular and immune microenvironment in stage IA NSCLC patients. A multi-omics recurrence model was further established to help find out the subset of patients with early stage who have the urgent need for postoperative intervention and guide therapeutic strategies.

Keywords: immune microenviroment, early stage NSCLC, recurrence predict model

MA08.06 Immune Cell Profiles as Predictors of Survival in Surgically Treated Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Curative surgical resection is the treatment of choice for early-stage and locally advanced non-small cell lung cancer (NSCLC). Locoregional N1 and N2 lymph nodes (LNs) are a site of tumor antigen presentation and T- and B-cell activation. They are removed during curative anatomic resection and provide a snapshot of the immune cell composition at the time of lymph node removal. While tumor bearing lymph nodes have been thoroughly investigated in NSCLC, little is known about the role of tumor-free lymph nodes. We evaluated immune cell populations in the primary tumor and matched tumor-bearing (tb) LNs, N2 non-tumour bearing (ntb) LNs and N1 ntbLNs in surgically treated NSCLC patients. **Methods:** We retrospectively collected archived tissue from patients with NSCLC treated between 1999 and 2019 at the Ludwig-Maximilians University in Munich, Germany. For each patient, material from the primary NSCLC tumor and matched tbLNs, N2 ntbLNs and N1 ntbLNs was obtained. H&E stainings of all samples were analyzed for morphological changes and qPCR of selected immune markers was performed. We used Cox regression models with forward selection to identify morphological factors associated with OS and PFS. **Results:** 151 NSCLC patients were included in this study: 71 with long-term disease-free survival (no local or distant recurrence for three years after surgery) and 80 patients with relapse within three years after surgery. Morphological assessment showed sinus histiocytosis and tumor-infiltrating lymphocyte density to be associated with PFS and OS, respectively. CD4 expression in N1 (HR = 0.72; p = 0.02) and N2 (HR = 0.91; p = 0.04) ntbLNs was correlated with PFS and OS, respectively. **Conclusion:** We found CD4 expression levels, tumor-infiltrating lymphocyte density as well as the increased levels of sinus histiocytosis to be beneficial for prolonged survival in this cohort. These findings should be investigated in patients treated with radiation, chemotherapy or checkpoint inhibition, particularly in the context of selection of adjuvant or neoadjuvant treatments.

Keywords: Lymph nodes, Immune cell composition, NSCLC

MA08.07 Immune Characteristics Associated With Lymph Node Metastasis in Early-Stage NSCLC Discovered via T Cell Receptor Repertoires Sequencing

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Introduction: Currently, surgical resection with lymph node dissection is the canonical treatment for early stage non-small cell lung cancer (NSCLC). However, the differentiated status of peripheral lymph nodes is usually substantive, and nondiscriminatory dissection may disrupt the immunosurveillance for tumor residual. The aim of the present study was to explore the immune characteristics of primary tumor (PT), peripheral blood mononuclear cell (PBMC), metastatic and non-metastatic lymph node (LN) via deep sequencing-based T cell repertoire analysis. **Methods:** 24 PTs, 20 PBMCs and 134 LNs which from 24 NSCLC patients were collected and performed T cell receptor (TCR) repertoires sequencing. The Shannon index and clonality were calculated for quantizing the immune status of each sample. The TCR was clustered and annotated by Gliph2 and VDJ database. Basic demographic and image data were routinely obtained. **Results:** Among 24 patients, 7 patients were deemed as metastasis-positive patients (LNMP) with 14 metastatic LNs and 25 non-metastatic LNs; while 17 patients with 95 LNs were no lymph node metastases patients (NLNMP). The clonality of PTs and PBMCs were positively correlated with the age of patients, while Shannon index was negatively correlated with age. There was no significant association in LNs either metastatic or not. LNs and PBMCs showed a higher Shannon index relative to PTs. But for clonality, LNs were significantly lower than PTs and PBMCs. Only in no lymph node metastases patients (NLNMP), the Shannon index and clonality of PTs and PBMCs were remarkably associated with that of LNs, providing evidence that the LNs of LNMP might experience immune dysfunction. Furthermore, the proportion of metastatic LNs shared with paired PT was higher than that of non-metastatic LNs ($p = 0.062$), suggesting that the immuno-interaction between metastatic LNs and PTs was disrupted because of tumor invasion. Multiple V and J genes of metastatic LNs, including TRBV6-6, TRBV10-2, TRBV12-3 and TRBJ1-2, showed superior used in comparison with non-metastatic LNs while TRBV9 completely opposite. With TCR annotating, we found that the proportion of cytomegalovirus (CMV) associated TCR in metastatic LNs was significantly higher than that of paired non-metastatic LNs or LNs of NLNMP. **Conclusion:** The metastatic LNs exhibited different immune characteristics, including lower immuno-interaction, unique V and J gene preference and higher infiltration of CMV-associated T cells. These results were useful to assess patient outcomes and develop appropriate management.

Keywords: TCR, NSCLC, lymph node metastasis

MA09 PREDICTIVE MARKERS FOR IMMUNOTHERAPY
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MA09.01 LCMC3: Immune Cell Subtypes Predict Nodal Status and Pathologic Response After Neoadjuvant Atezolizumab in Resectable NSCLC

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Introduction: In the Phase II LCMC3 (NCT02927301) trial of neoadjuvant atezolizumab in 181 patients with resectable Stage IB-IIIB NSCLC, 21% (30/144) experienced major pathologic response (MPR). This study incorporated a broad array of clinical, molecular and immunologic analyses to identify predictive biomarkers. In this study, we explored whether the immunophenotype of peripheral white blood cells would be potentially predictive of MPR and baseline nodal status. **Methods:** We performed 10-color, 60-marker IMMUNOME flow cytometry on pretreatment peripheral blood from samples processed within 72 hours with available MPR assessments, excluding patients in whom tumors had known EGFR and ALK mutations. A total of 115 pretreatment blood samples were analyzed in training (n=59) and testing (n=56) sets using an approach based on generalized additive models and regularized regression (LASSO) and correlated with MPR. Cell subsets detected in <50% of samples were excluded. An information divergence-based algorithm scored the remaining features, selecting 188 of 1163 total features for MPR correlation and 190 of 1163 features for N0 vs N1/N2 correlation. A multi-parametric model was built on the training set and validated on the testing set. Features were further filtered using either a χ^2 test for low frequency subsets or a t test or non-parametric test for more frequent subsets. Robustness of the cell subset selection was cross-validated and significance was tested in the training set. Receiver operating characteristic (ROC) curves tested the discriminative power of the selected model. **Results:** Subsets of natural killer (NK) and NK-like T cells were associated with absence of MPR. Higher frequencies of subsets of ILT2+ NKG2A+ and ILT2+ NKG2A− NK cells (ILT2+ CD3- CD56+ CD16+) and subsets of ILT2+ NK-like T cells (ILT2+ CD3+ CD56+ CD16+) in pretreatment peripheral blood were observed (area under the curve [AUC]: training set, 0.98; testing set, 0.74). Higher frequencies of subsets of NKG2D+ NK cells with or without CD355+ were significantly associated with nodal involvement. Further, higher frequencies of subsets of NKG2D+ NK-like T cells and NKG2D+ T cells were associated with absence of nodal involvement (AUC: training set, 0.97; testing set, 0.70). **Conclusion:** Lower frequencies of ILT2+NKG2A+ and ILT2+NKG2A− NK cells, and ILT2+ NK-like T cells in pretreatment peripheral blood were significantly associated with MPR in NSCLC patients treated with neoadjuvant atezolizumab, suggesting a negative role for the ILT2/HLA-G and/or NKG2A/HLA-E axis in response. NKG2D expression on NK cells correlated with nodal involvement, while expression on NK-like T cells and T cells correlated with absence of nodal involvement, suggesting a role for the NKG2D/NKG2D-L axis in tumor immune escape. These immunophenotyping data identify novel potential mechanisms of immune escape, and new potential biomarkers and therapy targets. Studies of anti-PD-L1/PD-1 effects on cross talk between immune cells in the tumor microenvironment, and other clinical and molecular features, including analysis of bulk and single cell RNAseq in a subset of the patients, are ongoing.

Keywords: immunophenotype, atezolizumab, resectable NSCLC

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MA09.02 SAKK 16/14 - T-Cell Receptor Repertoire Metrics Predict Response to Neoadjuvant Durvalumab in Patients With Stage IIIA(N2) NSCLC

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Introduction: T-cell receptor (TCR) repertoire assessment in blood and tissue has emerged as a novel predictive marker for response to immune checkpoint inhibitor therapy in advanced stage cancers. However, its relevance and predictive significance in the setting of resectable stage IIIA(N2) non-small cell lung cancer (NSCLC) has yet to be demonstrated. Here, we performed TCR sequencing in patients from the phase 2 trial SAKK 16/14 undergoing neoadjuvant chemotherapy with three cycles of cisplatin/docetaxel followed by treatment with the PD-L1 antibody durvalumab. **Methods:** A total of 127 peripheral blood samples and 67 formalin-fixed paraffin-embedded (FFPE) tissue samples were processed from 67 patients before and after neoadjuvant sequential chemo-immunotherapy treatment in the trial SAKK 16/14. Total RNA was extracted from peripheral blood and FFPE samples and used for TCR sequencing with the Oncomine TCR Beta-LR and SR Assays, respectively. TCR evenness, Shannon diversity, and TCR richness were calculated and correlated with the primary endpoint event-free survival (EFS) after 1 year, major pathological response (MPR), and nodal clearance. Tumor mutational burden (TMB) was assessed in tissue samples from extracted genomic DNA using the FoundationOne test or the Oncomine Comprehensive Assay Plus. Association between TCR metrics and clinical outcome data were analyzed using Mann-Whitney-Wilcox test. Analysis was performed using R (R Core Team, 2014). **Results:** TCR repertoire could be assessed in a total of 97 peripheral blood (47 pre- and 50 post-treatment) and 64 FFPE (15 pre- and 49 post-treatment) samples. In pre-treatment peripheral blood samples, TCR evenness (p=0.032) was associated with 1 year EFS. In FFPE post-treatment samples, 1 year EFS as well as MPR were significantly associated with increased TCR richness (p=0.0168 and 0.0134) and Shannon diversity (p=0.0278 and p=0.0334). Furthermore, nodal clearance was significantly associated with TCR richness and Shannon diversity in post-treatment tissue samples (p=0.0015, p=0.0087). In contrast, TMB was not associated with EFS, MPR or nodal clearance (p=0.91, p=0.47, p=0.52). **Conclusion:** Our results show that TCR repertoire measured in peripheral blood samples and tumor tissue may provide a useful tool for predicting risk of recurrence after neoadjuvant sequential chemo-immunotherapy with durvalumab in patients with resectable stage IIIA(N2) NSCLC.

Keywords: T-cell receptor repertoire, neoadjuvant immune checkpoint inhibitor, tumor mutational burden

MA09 PREDICTIVE MARKERS FOR IMMUNOTHERAPY
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MA09.03 Peripheral CD8⁺ T Cells Predicts Immune-Related Adverse Events and Survival in Advanced Non-Small Cell Lung Cancer Treated With Immunotherapy

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Introduction: Immune checkpoint inhibitors, which have been approved for the treatment of non-small cell lung cancer (NSCLC), often cause unique side effects, named immune-related adverse events (irAEs). Peripheral blood biomarkers have shown a great potential as predictors of clinical outcomes and irAEs due to minimal invasiveness and convenience. This study aims to determine the association between baseline subsets of lymphocytes and irAEs and clinical outcomes in advanced NSCLC patients after immune checkpoint inhibitors therapy. **Methods:** Patients with advanced NSCLC treated with immune checkpoint inhibitors at a single institution from May 2017 to October 2020 were analyzed retrospectively. Information including patient demographics, clinical characteristics and treatment patterns were collected. IrAEs were determined and graded using the Common Terminology Criteria for Adverse Events (CTCAE v.4.0). Progression free survival (PFS) and overall survival (OS) were evaluated by Kaplan-Meier survival curves. The predictive factors of irAEs were evaluated by univariate and multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was used to identify the most appropriate cutoff values of $CD8^+$ T cells to predict irAEs. The prognostic effects of $CD8^+$ T cells on PFS and OS were assessed by Cox-regression analyses. **Results:** Of 109 patients eligible for this study, 55 (50.5%) experienced irAEs and 38 (34.9%) developed multiple irAEs. Incidence of grade 3-5 toxicities were 14.7% (n = 16). The most common irAEs were skin-related (19.3%, n = 21) and endocrine-related (24.8%, n = 27) in all grades and pulmonary-related (3.7 %, n = 4) in grade 3 or higher. Baseline levels of $CD8^+$ T cells were associated with the onset of irAEs (P = 0.024). The optimal threshold of baseline $CD8^+$ T cells to predict irAEs was 193 M/L. The incidence of irAEs was higher in the high $CD8^+$ T cells group (61.3%) than in the low $CD8^+$ T cells group (20.7%, P < 0.001). Among the overall population, median PFS and median OS were 5.5months and 16.8months, respectively. Further analysis showed that higher $CD8^+$ T cells was favorably associated with significantly better median PFS (7.6 months vs. 2.6 months, P < 0.001) and median OS (25.9 months vs. 10.7 months, P = 0.010). **Conclusion:** In patients with advanced NSCLC treated with immune checkpoint inhibitors, baseline peripheral blood $CD8^+$ T cells may be a useful predictive marker of irAEs and clinical outcomes.

Keywords: immune-related adverse events, Peripheral CD8+ T cells, non-small cell lung cancer

MA09 PREDICTIVE MARKERS FOR IMMUNOTHERAPY
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MA09.05 PD1-Positive Tertiary Lymphoid Structure as a Predictive Factor of Durable Clinical Effect in Immunotherapy for NSCLC

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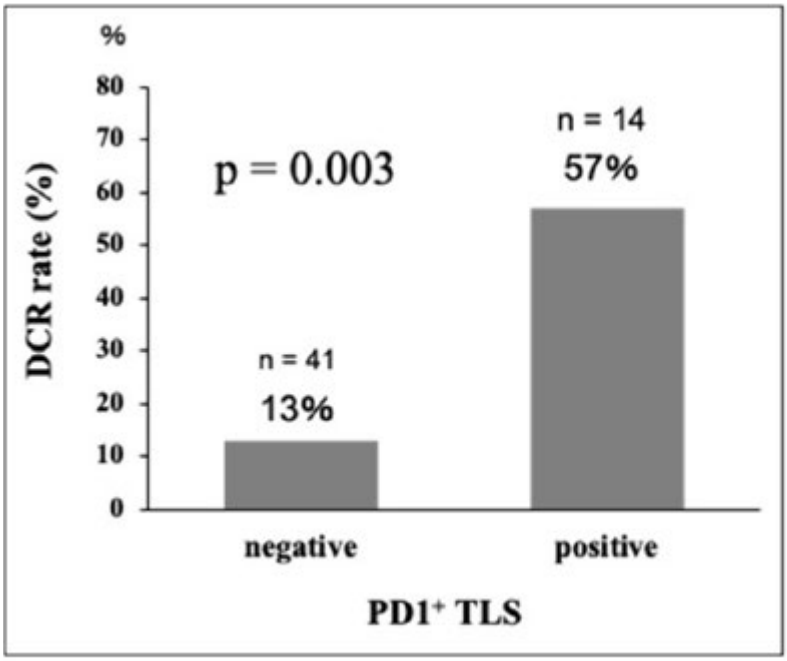
Introduction: There is urgent need for accurate biomarkers in immunotherapy (IO) for advanced or recurrent lung cancer. In 2020, tertiary lymphoid structure (TLS) of cancer tissue was reported to be related with IO response and is attracting attention as a new biomarker. In the current study, we investigated whether TLS and its lymphocyte distribution are associated with durable clinical effect (DCR) by IO in postoperative recurrent non-small cell lung cancer (NSCLC) patients. **Methods:** Between 2016 and 2019, 55 patients were treated with IO for recurrent NSCLCs. Tumor pathology and TLS were evaluated by H&E and immunohistochemical staining. DCR was defined as 'tumor maintaining stable disease or better for more than one year after IO', and the patients were divided to DCR and non-DCR group. Their clinicopathological factors, the number of TLS or tumor infiltrating lymphocytes (TIL) and lymphocytic subset in TLS were compared between the two groups. **Results:** The median age of all 55 patients was 68 years and 43 (78%) of them were men. Histological types of their tumors were 39 (71%) adenocarcinomas, 8 (15%) squamous cell carcinomas, and 3 (6%) large cell neuroendocrine carcinomas. DCR was observed in 14 (26%) patients, and included significantly younger patients (70 years old or less), more PD-L1 expression scores (TPS), more CD8-positive TIL, more PD1-positive TLS (PD1+TLS) and more immune-related adverse event (irAE, Grade 3 and more) than non-DCR group. There were not significant differences in pathological findings including histological type, pathological stage, pleural invasion, vessel invasion, predominant subtypes in adenocarcinoma. Multivariate analysis revealed that age, PD1+TLS and irAE were independent predictive factors of DCR. In DCR group, 1- and 3-year overall survival (OS) rate after IO treatment was 100 and 81%, respectively, while those in non-DCR group were 37 and 7%, respectively. Their post-IO OS curves were significantly different ($p < 0.01$).

Conclusion: We explored predictive factors for DCR in IO-treated recurrent NSCLC patients. $PD1^+$ TLS was an independent positive factor of DCR.



Keywords: immunotherapy, non-small cell lung cancer, tertiary lymphoid structure

MA09 PREDICTIVE MARKERS FOR IMMUNOTHERAPY
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MA09.06 Mature Tertiary Lymphoid Structures in Lung Adenocarcinoma Are Associated With Better Progression Free Survival

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Introduction: Prior presentations (2019): The presence of secondary follicles in early stage lung adenocarcinoma reflect disease burden Advances in cancer immunotherapy, such as immune checkpoint inhibitors, including those targeted against programmed cell death (PD-1) have refocused interest in the role of the immune response in effectively controlling lung adenocarcinoma. The presence of inducible lymphoid structures known as tertiary lymphoid structures in the tumor microenvironment has been shown to correlate with positive clinical outcome. However, the maturation states of these aggregates in lung adenocarcinoma and their potential to induce productive antitumor immune responses have completely under understood. We previously evaluated the presence and significance of secondary follicles by conventional immunohistochemistry. In this current study, we assessed the maturation states of lymphoid structures and their association with clinicopathologic features of lung adenocarcinoma. **Methods:** Seventy tumor samples from 69 patients diagnosed with lung adenocarcinoma (Stages I to III) between 2013 and 2015 were included in the study. The presence and maturation states of the lymphoid structures within the tumors were evaluated by multiplexed immunohistochemistry using five-micron sections of formalin fixed paraffin embedded tissues from 20 randomly selected tumor samples as a preliminary analysis. CD3, CD20, CD21, BCL-6, CD68, cytokeratin, and Dapi were the markers of interest. The slides were stained using the Ventana automated stainer and Opal fluorophores (480, 520, 570, 620, 690, and 780). The stained slides were scanned using the Vectra Polaris Imaging System. The images were analyzed using the InForm and QuPath softwares. The tumor samples were separated into two groups (<10 mature lymphoid structures (CD3+/CD20+/BCL-6+/CD21+ aggregates) and >10 mature lymphoid structures). Statistical analyses were formed to determine the correlations between mature lymphoid structures and tumor size, tumor grade, less mature structures (CD3+/CD20+/BCL-6+/ CD21- aggregates), progression free survival, and overall survival in lung adenocarcinoma. **Results:** The number of mature lymphoid structures correlated with the total number of lymphoid aggregates present in the tumor microenvironment (p=0.0004). Additionally, tumor samples with >10 mature lymphoid structures (9 out of 20) also had more B and T cell aggregates that expressed BCL-6 but not CD21 (p=0.0091). Tumor necrosis was absent in all of the samples with >10 mature lymphoid structures (0/9) and present in four out of eleven of the samples with <10 structures (4/11). There was no statistically significant differences in tumor size and tumor grade between tumors with <10 mature lymphoid structures and those with >10 lymphoid structures. However, progression free survival was significantly longer in patients who had >10 mature lymphoid structures in comparison with patients who had <10 mature structures (p=0.0477). **Conclusion:** A spectrum of lymphoid aggregates in different stages of maturation as functional lymphoid structures are present in lung adenocarcinoma. Higher numbers of mature lymphoid structures within the tumor microenvironment of lung adenocarcinoma may reflect the generation of productive antitumor immune responses and favorable progression free survival.

Keywords: tertiary lymphoid structures, Lung adenocarcinoma, immunotherapy

MA09 PREDICTIVE MARKERS FOR IMMUNOTHERAPY
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MA09.07 Genomic Landscape and Clinical Outcomes With Immune Checkpoint Inhibitors in NF1-Mutant NSCLC

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Introduction: NF1 encodes for neurofibromin 1, a RAS GTPase-activating protein (GAP) that regulates RAS nucleotide cycling and when inactivated can promote aberrant RAS signaling and carcinogenesis. Deleterious NF1 mutations have been previously reported in non-small cell lung cancer (NSCLC), particularly in current/former smokers, but the genomic landscape of this molecular subgroup remains incompletely characterized. Furthermore, the clinical outcomes of NF1-mutant (NF1-mut) NSCLC upon treatment with immune checkpoint inhibitors (ICI) remain unknown. **Methods:** The Foundation Medicine Inc. (FMI) NSCLC dataset (FoundationCore – N=62845) was used to analyze NF1 mutations, cancer gene co-mutations, tumor mutational burden (TMB) and PD-L1 expression in NF1-mut NSCLC. A proprietary, artificial intelligence-supported algorithm was employed to infer pathogenicity of individual NF1 mutations. Clinical outcomes upon treatment with single-agent ICI were assessed using two publicly available clinical cohorts: OAK/POPLAR (N=765) and Rizvi (N=185). Patients with known EGFR/ALK alterations were excluded. PFS was used for outcome analysis. **Results:** In the FMI dataset, inactivating somatic NF1 mutations were present in 6.9% (2805/40388) of lung adenocarcinomas (LUAD) and 7.7% (855/11041) of lung squamous cell carcinomas (LUSC). NF1-mut LUAD were significantly enriched for high TMB (TMB≥16 mutations/Mb: NF1-mut 31.3% and NF1-wild type [NF1-wt] 14.9%; P= 8E-141) and PD-L1 TPS≥1% (P=6E-10), and both LUAD and LUSC were enriched for TP53 co-mutations (LUAD P=3E-79; LUSC P=1E-5). Co-alterations in TP53 and/or CDKN2A/B were highly prevalent in NF1-mut LUAD (82.0%) and near universal in NF1-mut LUSC (95.4%). The association between NF1 mutations and high TMB was further validated in the OAK/POPLAR (P=0.002) and Rizvi cohorts (P=0.008). Importantly, in the OAK-POPLAR cohort TMB-high NSCLC patients bearing NF1-mut tumors treated with ICI exhibited markedly longer PFS compared with those harboring TMB-high NF1-wt tumors (cutoff of TMB>=16mut/Mb: PFS 9.63 vs 2.84 months, HR 0.55, P=0.054; cutoff of TMB>=10mut/Mb: PFS 4.14 vs 2.53 months, HR 0.69, P=0.119). This finding was further validated in the Rizvi cohort (cutoff of TMB>=10mut/Mb: PFS 8.33 vs 3.07 months, HR 0.52, P=0.070). Despite the small sample size, a trend for longer PFS in NF1-mut-TMB high NSCLC was also observed in the subpopulation harboring STK11/KEAP1 co-mutations (TMB>=16mut/Mb 14.36 vs <16mut/Mb 1.40 months, HR 0.13, p=0.067). **Conclusion:** Among NSCLC with high TMB, inactivating NF1 somatic genomic alterations identify a subgroup with markedly longer PFS to ICI therapy. These findings further highlight the impact of cancer gene mutations and underscore a context dependent effect of TMB on clinical outcomes from immunotherapy.

Keywords: NF1 mutation, genomics, immunotherapy

MA10 SCREENING AND EARLY DETECTION: AN OVERVIEW
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MA10.01 Prospective Evaluation of the International Lung Screening Trial (ILST) Protocol for Management of First Screening LDCT

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Introduction: The first (baseline) screening LDCT generates more early recall imaging studies or diagnostic referrals compares to subsequent screening rounds where management decisions have the advantage of information on nodule growth or appearance of new nodules. The ILST protocol (Ann Am Thorac Soc. 2020 Apr;17(4):503-512) - a personalized approach to lung nodule management is based on malignancy probability of lung nodules (N Engl J Med 2013;369:908-17). Currently, this is the only protocol that triages screenees with no lung nodule or very low risk lung nodules to biennial screening instead of annual screening. The objective of this study is to prospectively evaluate the ILST protocol for management of baseline screening LDCT and determine the potential implication if the participants were managed using the EU-NELSON or Lung-RADS protocols. **Methods:** The BC Lung Screen Trial recruited ever smokers 55 to 80 years of age who met either the $PLCO_{m2012}$ 6 years lung cancer risk ≥1.5% or USPSTF2013 criteria for screening eligibility. The participants were managed using the ILST protocol. Follow-up recommendation was triaged into one of three groups. Group 1: Routine surveillance LDCT in 12 months (1A) or 24 months (1B); Group 2: Early recall LDCT in 3 months; and Group 3: Diagnostic work-up referral. The implication of using the EU-NELSON or Lung-RADS v1.1 were compared using the largest nodule in the LDCT scan. Lung-RADS 1 & 2, 3 & 4A, 4B & 4X were combined into Group 1, 2 and 3 respectively. **Results:** 2,138 participants underwent LDCT. The minimum duration of follow-up was 18 months. The results are shown in Table 1. The proportion of participants triaged to routine surveillance (Group 1) was similar between the three protocols. However, 71% of all the participants under the ILST protocol had biennial follow-up instead of annual follow-up. The lung cancer rate (0.46%) and proportion of Stage I+II NSCLC (75%) were similar to the EU-NELSON (0.6% and 71% respectively) ($P_{\text{lung cancer proportion}}$=0.53) or the Lung-RADS protocol (0.9% and 87% respectively). The ILST protocol had the lowest early recall and diagnostic referral rates.

	ILST	Cancer	NELSON	Cancer	Lung-RADS	Cancer
Group 1: 1A. Annual Repeat	316 (14.8%)	7 (2.2%) 3 late return		1683 (78.7%)	1740 (81.4%)	19 (1.1%)
1B. Biennial	1517 (71%)	7* (0.46%)				
Annual + Biennial	183.3 (85.7%)	14 (0.76%)				
Group 2: Early Recall = 6m	234 (10.9%)	15 (6.4%)		278 (13.0%)	348 (16.3%)	16 (4.6%)
Group 3: Diagnostic Referral **	71 (3.3%)	33 (46.5%)		177 (8.3%)	50 (2.3%)	27 (54%)
Group 2+3	305 (14.3%)	48 (15.7%)		455 (21.3%)	398 (18.6%)	43 (10.8%)
Total	**2138**	**62**		**2138**	**2138**	**62**

Conclusion: The ILST lung nodule management protocol allowed most of the participants (71%) to have biennial follow up instead of annual follow-up without an increase in the lung cancer rate or proportion of advanced lung cancer. The protocol has significant implication in health care resource utilization.

Keywords: nodule management, LDCT screening, PanCan risk calculator

MA10 SCREENING AND EARLY DETECTION: AN OVERVIEW
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MA10.02 Lung Cancer Detected By Screening, Incidental Lung Nodule Program and Neither: A Prospective Observational Study

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Introduction: Early detection of lung cancer is critical for improving individual-level survival probability and population-level mortality statistics. **Methods:** We simultaneously implemented Low-Dose CT lung cancer screening (LDCT) and an Incidental Lung Nodule Program (ILNP) in a large community healthcare system. LDCT used US Preventive Services Task Force (USPSTF) 2013 eligibility criteria and Lung-RADS for decision-making; ILNP used Fleischner Society guidelines for nodule management. We compared patients diagnosed with lung cancer through LDCT and ILNP to those in our Multidisciplinary Clinic (MDC) who were diagnosed through neither program, using chi-square tests. All three programs included rigorous prospective data collection. We evaluated overall survival (OS) from date of cancer diagnosis with Kaplan-Meier analysis, proportional hazards models with hazard ratios (HR) and 95% confidence intervals (CI). **Results:** From 2015-2020, LDCT identified 130 patients from 4,797 screened (2.7%), ILNP identified 667 from 13,710 (4.9%), and MDC had 953 lung cancer patients. LDCT had less racial diversity (80% White/19% Black) versus ILNP (65%/29%) versus MDC (66%/31%) (Table 1). Lung cancer was more frequently stage I in LDCT (54%) or ILNP (49%) compared to MDC (27%; p<0.0001). Surgical resection was most frequent with LDCT (47%) followed by ILNP (40%) and MDC (32%, p<0.0001). Adjuvant treatment was most frequently used in MDC (54%) compared to LDCT (32%) or ILNP (24%, p<0.0001). We found no significant differences in treatment with radiation alone (13%/12%/10%, p=0.46) or chemotherapy alone (12%/12%/15%, p=0.31). Aggregate 3-year OS was 78% (68%-88%) LDCT versus 63% (58%-68%) ILNP versus 43% (39%-47%) MDC (p<0.0001). This translated into 63% and 35% reductions in the overall hazard of death for patients with lung cancer diagnosed by LDCT or ILNP compared to MDC (HR: 0.37 [0.23-0.60], 0.65 [0.54-0.77], Table 1). Stage-stratified survival probability was also significantly different in Stage I patients with LDCT>ILNP>MDC (p=0.0049, Table 1). Using USPSTF 2013 criteria, only 41% of ILNP and 45% of MDC lung cancer patients would have qualified for LDCT.

Table 1

Variable	LDCT	ILNP	MDC	P-value
Number of patients	130	667	953	
Age, median (Q1-Q3)	65 (60 -70)	64 (52-73)	66 (57 - 73)	<0.0001
Female sex, n (%)	2379 (50)	7603 (55)	895 (52)	<0.0001
Race, n (%)				<0.0001
Caucasian	3839 (80)	8855 (65)	1139 (66)	
Black or African American	894 (19)	4004 (29)	540 (31)	
Other	26 (1)	136 (1)	13 (1)	
Insurance (n, %)				<0.0001
Medicare	3192 (66.54)	7011 (51.14)	579 (33.72)	
Medicaid	692 (14.43)	1428 (10.42)	267 (15.55)	
Commercial	2669 (55.64)	7790 (56.82)	800 (46.59)	
Charlson Comorbidity Score				<0.0001
0	1333 (28)	5554 (41)	451 (26)	
1	2277 (48)	5106 (37)	835 (49)	
2	1187 (25)	3050 (22)	431 (25)	
Histology, n (%)				<0.0001
Adenocarcinoma	64 (49)	260 (39)	464 (45)	
Squamous	35 (27)	127 (19)	315 (33)	
Small cell	12 (9)	50 (8)	92 (10)	
Other	9 (7)	105 (16)	82 (9)	
Clinical stage, n (%)				<0.0001
I	70 (54)	329 (49)	255 (27)	
II	11 (8)	51 (8)	112 (19)	
III	18 (14)	112 (17)	254 (28)	
IV	25 (19)	106 (16)	298 (31)	
Median primary tumor size in mm, (Q1 – Q3)	20 (13 - 34)	25 (16 - 40)	35 (22 - 54)	<0.0001
Treatment				<0.0001
Surgery (+ Other Treatment Modalities)	19 (15)	63 (9)	166 (17)	
Surgery Alone	41 (32)	205 (31)	141 (15)	
Radiation	47 (36)	197 (30)	454 (48)	
Chemotherapy	56 (43)	242 (36)	591 (62)	
Postoperative mortality, N (%)				0.6778
30-days	0	23 (3.45)	8 (2.61)	
60-days	0	23 (3.45)	9 (2.93)	
90-days	0	24 (3.60)	13 (4.23)	
Years of follow-up from date of abnormal CT scan, median (Q1 – Q3)	1.56 (0.72 - 2.56)	1.79 (0.79 - 3.17)	1.02 (0.53 - 2.24)	0.0002

Eligibility for LDCT lung cancer screening, n (%)				
USPSTF 2013 criteria		273 (41)	431 (45)	<0.0001
USPSTF 2020 criteria		315 (47)	540 (57)	<0.0001
3-year OS (95% CI)				
Aggregate	78 (68, 88)	63 (58, 68)	43 (39, 47)	<0.0001
Stage I	93 (86, 100)	79 (74, 85)	64 (58, 72)	0.0049
Stage II	68 (38, 100)	57 (42, 77)	55 (45, 67)	0.7642
Stage III	70 (48, 100)	39 (29, 52)	40 (33, 49)	0.2797
Stage IV	43 (22, 87)	38 (29, 51)	22 (17, 28)	0.3331
Hazard Ratio (95% CI)			Reference	
Aggregate	0.37 (0.23, 0.60)	0.65 (0.54, 0.77)	1 (---)	<0.0001
Stage I	0.30 (0.14, 0.81)	0.64 (0.44, 0.91)	1 (---)	0.005
Stage II	0.59 (0.14, 2.46)	0.94 (0.52, 1.70)	1 (---)	0.8
Stage III	0.55 (0.17, 1.73)	1.20 (0.87, 1.64)	1 (---)	0.3
Stage IV	0.61 (0.31, 1.19)	1.00 (0.73, 1.36)	1 (---)	0.3

Conclusion: ILNP complements LDCT, identifying lung cancer in a higher proportion of patients than LDCT, even though majority of ILNP patients would not have been eligible for LDCT. ILNP provided access to early detection to a higher proportion of racial minorities. Both early detection programs led to earlier-stage diagnoses, more opportunity for surgical resection, less need for adjuvant therapy, and longer survival compared to MDC. For maximal impact on population-level lung cancer survival, ILNP should be implemented in tandem with LDCT programs.

Keywords: Early detection, LDCT screening, Incidental Lung Nodule

MA10 SCREENING AND EARLY DETECTION: AN OVERVIEW
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MA10.03 Balance Between Decreased False Positives and Delayed Diagnosis in Lung Cancer Screening

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Introduction: False positives in CT screening for lung cancer can be reduced by raising size thresholds for the definition of a positive result. The higher the threshold, the lower the false positive rate. A higher threshold will, however, delay the diagnosis in those cases which would have been detected earlier using a smaller size threshold. We wanted to determine the balance between these two competing considerations. **Methods:** We reviewed the I-ELCAP database to determine the rate of positive results for screening using increasing size thresholds for the baseline round of screening. We then determined how many cancers would have a delayed diagnosis based on higher size thresholds as well as the histology of these cancers. We then estimated the change in the curability of the cancers due to the delayed diagnoses based on the predicted size one year later. **Results:** Moving from a 6.0 mm size threshold to initiate work-up to 7.0, 8.0, and 9.0 mm, we found that the rate of positive results decreased from 102.1/1000 (10.2%) to 70.9/1000 (7.1%), 51.0/1000 (5.1%), and 39.6/1000 (4.0%). Assuming that 0.56% of the screening participants would be diagnosed of lung cancer within 1 year of baseline screening and potentially the higher thresholds would result in a delay in diagnosis of a small number (5-6%) of cancers until the next annual repeat screening, the number of cancers that would have delayed diagnosis with these higher thresholds was 0.28, 0.33 and 0.38 per 1000 screening participants. Assuming these cancers were growing with a volume doubling time (VDT) of 200 days, the anticipated absolute decrease in curability of a six-month delay in diagnosis was 1.6%-2.4%, these represent 0.005, 0.006, and 0.007 additional lung cancer deaths per 1000 screening participants for 7.0, 8.0, and 9.0 mm size threshold, respectively.

	Size threshold (mm)			
	6.0	7.0	8.0	9.0
% Positive findings [1]	10.2%	7.1%	5.1%	4.0%
# Positive findings per 1000 screening participants	102.1	70.9	51.0	39.6
# Lung cancers diagnosed within 1 year (per 1000 screening participants)*	5.6	5.6	5.6	5.6
% Cancers delayed due to increasing threshold [1]		5.0%	5.9%	6.7%
# Delayed cancers per 1000 screening participants		0.28	0.33	0.38
Additional deaths per 1000 screening participants Δ		0.005	0.006	0.007

[1] Henschke et al. Definition of a positive test result in CT for lung cancer: a cohort study. Ann Intern Med. 2013; 158(4):246-52
* Assuming 0.56% of the screening participants would be diagnosed of lung cancer within 1 year of baseline screening
Δ Deceased incurability due to 6-mo delay is estimated to be approximately 1.8% for nodule measuring 6.0-6.9 mm, 2.0% for 7.0-7.9 mm, and 2.3% for 8.0-8.9 mm

Conclusion: The magnitude of the potential loss of life due to increasing the threshold for positive results, thus delaying the diagnosis, was estimated and ranged between 0.005-0.007 deaths per thousand screening participants. This is particularly meaningful when considering the development of screening programs in countries with limited resources, as the decrease in the estimated cure rate for higher threshold of positive result should be compared with the deaths from lung cancer when not performing any screening at all which is in the range of 100 deaths per thousand screening participants.

Keywords: computed tomography, loss of life, positive finding

MA10 SCREENING AND EARLY DETECTION: AN OVERVIEW
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MA10.05 Potential of CT and PET-Based Radiomics for the Diagnosis of Lung Adenocarcinomas Indicated for Limited Resection

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Introduction: We previously developed radiomics technology using computed tomography (CT) to identify cases of preinvasive lung adenocarcinoma that may be indicated for limited resection. This study aimed to investigate whether the maximum standardized uptake value (SUVmax) on positron emission tomography (PET) has an add-on effect for this technology. **Methods:** This retrospective observational study was conducted at two medical centers. The resected pulmonary lesions were reviewed between April 2014 and March 2020. Patients with clinical stage IA lung adenocarcinomas were included. Thin-section CT images (less than 2.5 mm) were used to assess the clinical stage. For the image analysis algorithm of plain CT-based radiomics, we previously selected seven parameters: tumor volume (cm^3), volume rate of the solid component (%solid; %), mean CT value (Hounsfield units), kurtosis, skewness, variance, and entropy. In this study, a new prediction model based on multiple logistic regression comprising eight parameters (CT+PET-based radiomics) was generated, including SUVmax, after standardization to eliminate inter-facility bias. Next, stepwise variable selection was applied to the prediction model to evaluate whether SUVmax was a more important factor for identifying pathological preinvasive adenocarcinomas. A bootstrap method for randomized selection was used to assess the accuracy of the results. **Results:** A total of 262 lung adenocarcinomas were categorized into the invasive group (n = 166 [63%]) or a preinvasive group (n = 96 [37%]), the latter of which comprised adenocarcinomas in situ (n = 32 [33%]) and minimally invasive adenocarcinomas (n = 64 [67%]). Before the surgery, the mean total tumor size of the invasive group (17.0 ± 6.5 mm) was significantly greater than that of the preinvasive group (13.9 ± 5.6 mm; $p < 0.001$). The pathological T factors were Tis (n = 32), T1mi (n = 64), T1a (n = 83), T1b (n = 66), and T1c (n = 17). Although spread through air spaces (STAS) was observed in 24 specimens (9.2%), five STAS-positive cases (5.2%) were noted in the preinvasive group. Upstaging was confirmed in one patient with lymph node-positive metastasis (N1) after pathological diagnosis. However, there were no cases of upstaging among the preinvasive tumors. Before standardization, the median SUVmax was 0.6 (interquartile range [IQR], 0.00–1.40) in the preinvasive group and 1.7 [IQR, 0.99–2.85]) in the invasive group ($p < 0.001$). After a stepwise method involving the eight factors, %solid (odds ratio [OR], 0.30; 95% confidence interval [CI], 0.20–0.46; $p < 0.001$) and entropy (OR, 0.46; 95% CI, 0.32–0.67; $p < 0.001$) were selected, but not SUVmax. The area under the curve was 0.83 (95% CI, 0.78–0.88). In the bootstrapping analysis, SUVmax was never selected as a key factor compared with the original parameters of CT-based radiomics. Even when the five STAS-positive cases in the preinvasive group were reclassified into the invasive group, SUVmax did not remain a key factor in the discrimination. **Conclusion:** In the identification of cases of preinvasive adenocarcinomas for which limited resection may be indicated, SUVmax did not increase the diagnostic efficacy of the original CT-based radiomics.

Keywords: positron emission tomography, lung cancer screening, computed tomography

MA10 SCREENING AND EARLY DETECTION: AN OVERVIEW
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MA10.06 Factors Associated with Lung Cancer Screening Adherence Among Patients with Negative Baseline Nodule Finding

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Introduction: Lung cancer is the most common cause of cancer death worldwide. The National Lung Screening Trial (NLST) demonstrated a 20% reduction in mortality with low-dose computed tomography (CT) for lung cancer screening (LCS). However, that reduction was realized in patients who had a 95% adherence in three annual screens. The purpose of this study is to report adherence rates for screening in a health system and determine the factors associated with adherence in a multi-center community-based cohort with negative baseline nodule findings. **Methods:** We conducted a retrospective study of patients across a 23-hospital health care network with negative baseline LCS between January 2015 and January 2020. Exclusion criteria were incomplete data points and ineligible patients for LCS based on USPSTF recommendations. Negative LCS was defined as patients with LungRADS scores of 1 and 2. Multivariate logistic regression was used to predict LCS follow-up and adherence was defined as follow up LCS CT 11 to 15 months after prior study. Covariates considered include patient demographics, LungRADS score on screen, smoking information, screening site, median household income (based on geocoding zip code from U.S Census Bureau), and provider specialty. **Results:** Cohort included 1,668 patients with baseline screening and 507 and 264 patients with second and third screening respectively. A total of 30.4% (507/1,668) and 15.90% (264/1,660) patients were adherent on the baseline and follow up screens, respectively. Baseline and 2nd year adherence were higher among former smokers, if providers were pulmonologists and varied by screening site (table 1). 2nd year adherence also varied by patient age. Sex, ethnicity, smoking status, and household income were not significant predictors of adherence.

Total Cohort	Baseline adherence		2nd year adherence	
	OR (95%)	P-value	OR (95%)	P-value
Sex Female Male	Reference 0.88 (0.7 – 1.11)	Reference 0.29	Reference 0.81 (0.62 - 1.08)	Reference 0.15
Age 40-59 60-69 70 and above	Reference 0.85 (0.66 – 1.09) 0.76 (0.53 – 1.08)	Reference 0.22 0.13	Reference 1.08 (0.79 - 1.51) 0.98 (0.64 - 1.51)	Reference 0.62 0.94
Race White African American Asian Unknown	Reference 0.67 (0.44 – 1.02) 1.18 (069 – 1.98) 0.66 (0.38-1.09)	Reference 0.06 0.52 0.53 0.11	Reference 0.75 (0.44 - 1.24) 0.71 (0.34 - 1.39) 0.63 (0.3 - 1.21)	Reference 0.28 0.34 0.19
LungRADS score on screen 0 1 2	6.28 (0.63 – 67.56) 0.94 (0.74 – 1.19) Reference	0.10 0.63 Reference	3.77 (0.17 - 37.57) 1.01 (0.75 - 1.35) Reference	0.28 0.94 Reference
Smoking Status Current smoker Former smoker Unknown	Reference 1.29 (1.02 – 1.62) 0.29 (0.07 – 1.06)	Reference 0.03* 0.07	Reference 1.41 (1.07 - 1.87) 0.35 (0.05 - 1.77)	Reference 0.02* 0.24
Number of packs smoked 30-40 40-50 50-60 60+	Reference 1.06 (0.82-1.38) 1.25 (0.86-1.82) 1.01 (0.7-1.43)	Reference 0.64 0.24 0.96	Reference 1.12 (0.8 - 1.55) 1.7 (1.09 - 2.62) 1.28 (0.84 - 1.95)	Reference 0.51 0.02* 0.25
Site R1 R2 R3 R4 R5 R6 R7 R8 R9 R10	Reference 0.89 (0.58 – 1.39) 5.52 (2.39 – 13.1) 0.96 (0.56 – 1.62) 0.99 (0.55 – 1.74) 0.90 (0.58 – 1.41) 4.42 (2.61 – 7.6) 1.3 (0.66 – 2.53) 1.45 (0.36 – 5.17) 0.47 (0.26 – 0.85)	Reference 0.61 <0.001* 0.86 0.96 0.63 <0.001* 0.44 0.57 0.01	Reference 1.28 (0.71 - 2.42) 4.73 (1.74 - 12.45) 1.89 (0.98 - 3.78) 0.66 (0.26 - 1.59) 1.24 (0.69 - 2.36) 4.29 (2.25 - 8.53) 1.04 (0.38 - 2.63) 1.73 (0.25 - 7.65) 1.03 (0.48 - 2.18)	Reference 0.43 <0.001* 0.06 0.37 0.49 <0.001* 0.94 0.51 0.95
Median household income Below 80k/year 80-120k/year Above 120k/year Unknown	Reference 1.04 (0.8-1.35) 1.09 (0.63-1.82) 0 (NA, Inf)	Reference 0.77 0.76 0.97	Reference 1.18 (0.85 - 1.63) 0.82 (0.37 - 1.65) 0.36 (0.02 - 2.09)	Reference 0.32 0.60 0.35
Specialty Internal/Family Medicine Pulmonary Thoracic Physician Assistant / Nurse Practitioner Other	Reference 1.79 (1.38-2.34) 0.35 (0.14-0.83) 1.47 (0.79-2.71) [SGA1] 0.87 (0.45-1.6)	Reference <0.001* 0.02 0.22 0.66	Reference 1.33 (0.96 - 1.85) 0.64 (0.25 - 1.72) 0.82 (0.39 - 1.65) 0.86 (0.36 - 1.82)	Reference 0.08 0.36 0.59 0.70

Conclusion: Adherence to LCS in a multi-center community-based cohort is poor and we have identified modifiable factors that can improve screening adherence.

Keywords: LCS Adherence, LC early detection, lung cancer screening

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

MA11.01 Development of Novel EGFR Mutant NSCLC Mouse Models and Murine Cell Lines: New Tools for NSCLC Research

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Introduction: EGFR mutant lung cancer accounts for approximately 15-30% of all non-small cell lung cancer (NSCLC) cases, with the prevalence varying in different populations. A point mutation L858R and in-frame deletions in exon 19 of the EGFR gene account for the majority of all EGFR activating mutations. EGFR tyrosine kinase inhibitors (TKIs) have led to significant advances in the treatment of EGFR mutant NSCLC; however, many patients show a partial response and all eventually develop resistance. Better preclinical models are required to design rational combination therapies. Our group has used syngeneic orthotopic mouse models of NSCLC to study interactions between cancer cells and the tumor microenvironment in the lung. These approaches are limited by the availability of murine lung cancer cell lines. To our knowledge, there are currently no EGFR mutant murine lung cancer cell lines. Therefore, we developed a novel transgenic mouse strain that conditionally expresses mutant EGFR mediated by Cre-recombinase. Administration of adeno-Cre virus into the lungs resulted in the development of EGFR-driven lung tumors. **Methods:** In collaboration with the Mouse Genetics Core at National Jewish Health, we developed two novel EGFR mutant mouse models (Rosa-loxP-STOP-LoxP- EGFR L860R/del19-mC3-WPRE): one with a deletion 19 and one with an L860R mutation (equivalent to the human L858R mutation) in the mouse EGFR gene. Tumors are initiated through intratracheal injections of the adeno-Cre virus. These mice were bred with $p53^{flox}$ mice from Jackson Laboratories to increase the diversity of tumors. Tumors were harvested and submitted to histological characterization by H&E staining or processed to create cell lines. These cell lines were characterized by in vitro growth assays, western blot analyses, and sequencing to confirm their genotype and responsiveness to EGFR TKIs. Cell lines were implanted into both the flanks and lungs of mice to determine their responsiveness to EGFR TKIs. Tumor-bearing mice were imaged by CT and treated by oral gavage with the EGFR TKIs. **Results:** Intratracheal administration of adeno-Cre led to the development of multiple tumors throughout all lobes of the lung in both del19 and L860R mice. Time to tumor formation occurred within 4-12 weeks. Importantly, treatment of the mice with osimertinib resulted in tumor shrinkage and improvement in the health of mice. Moreover, we were able to successfully isolate 3 distinct cell lines (del19.1, del19.2, L860R.1) from these tumors. In vitro, these cell lines are responsive to multiple EGFR TKIs, as evidenced by a decrease in proliferation and inhibition of phospho-ERK. These cells form tumors when implanted into the flanks of nu/nu mice, del19.1-derived tumors undergo shrinkage in response to osimertinib. Orthotopically injected del19.1 cells form tumors in the left lungs of WT C57Bl/6 mice. **Conclusion:** We have developed novel mouse models as well as murine cell lines that reflect mutant EGFR-driven NSCLC which will be useful tools for studying NSCLC both in vitro and in vivo. By increasing the number of murine NSCLC cell lines, we can better recapitulate human disease to increase our understanding of NSCLC and develop novel therapeutic strategies that can be used to treat patients.

Keywords: murine EGFR cell line, EGFR mouse model, osimertinib

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
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MA11.02 Targeting HER2 Exon 20–Mutant Lung Adenocarcinoma with a Novel Tyrosine Kinase Inhibitor, Mobocertinib

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Introduction: Although pharmacologic agents targeting driver mutations in lung adenocarcinoma have led to tremendous clinical benefits for patients, human epidermal growth factor receptor 2 (HER2)-activating mutations do not have therapeutic agents and still represent an unmet clinical need. Mobocertinib is a potent tyrosine kinase inhibitor designed to target epidermal growth factor receptor (EGFR) and HER2 exon 20 insertion mutations and has reported activity in the clinic in patients with EGFR exon 20 insertionmutant non–small cell lung cancer (NSCLC). To understand the activity of mobocertinib against HER2 mutations, we conducted systematic characterization using in vitro and in vivo preclinical models. **Methods:** Ba/F3 cell lines with HER2 exon 20 insertion mutations (YVMA, G776>VC and GSP insertions) and human cell line H1781 (G776>VC insertion) were used for drug testing in vitro. Genetically engineered mouse models (GEMMs) harboring YVMA and G776>VC insertions, allograft (Ba/F3-YVMA insertion) and PDX (NSCLC YVMA insertion) were utilized for the drug testing in vivo. Gene set enrichment analysis (GSEA) was conducted based on the RNA-seq data from acquired resistant and response tumors (YVMA insertion) to explore the potential pathways involved in the resistance mechanism. Multi-parameter flow cytometry was performed to characterize the alterations in immune micro-environment under the treatments. **Results:** Mobocertinib showed less potent IC_{50} than poziotinib, comparable or slightly lower than afatinib, neratinib, and pyrotinib, and much lower than osimertinib in Ba/F3 HER2 exon 20 insertion mutant cell lines. Mobocertinib had the lowest HER2 exon 20 insertion IC_{50} / WT EGFR IC_{50} ratio of all three HER2 exon 20 insertion mutations compared with osimertinib, poziotinib, afatinib, neratinib, and pyrotinib, indicating that mobocertinib displayed the best selectivity profile in these models and could provide an improved efficacy and safety profile in clinic. Also, mobocertinib showed strong inhibitory activity in HER2 exon 20^{YVMA} allograft and PDX models. In GEMMs, while HER2 exon $20^{G776>VC}$ lung tumor had sustained complete response to mobocertinib, the lung tumor driven by the most frequent insertion type, HER2 exon 20^{YVMA}, showed only partial and transient response. From the GSEA analysis, three results were of interest to us, which are “G2M Checkpoint”, “Mitotic Spindle” and “mTORC1 Signaling”. We tested three drugs (alisertib, sapanisertib and T-DM1) for combination therapies. The combination with a second targeted agent against HER2, the antibody-drug conjugate (ADC)-like ado-trastuzumab emtansine (T-DM1) synergized with mobocertinib and provided long-term response and survival benefits in HER2 exon 20^{YVMA} tumors. In addition to the tumor cell autonomous effect, the sustained tumor growth control derives from the M1 macrophage infiltration and $CD4^+$ T cell activation. **Conclusion:** We demonstrated that mobocertinib showed a robust inhibitory activity against HER2 exon 20 insertion mutations both in vitro and in vivo. Importantly, our study provides a strong rationale for further clinical trials using mobocertinib either alone or in combination with T-DM1 to target HER2-mutant lung cancer.

Keywords: A Novel Tyrosine Kinase Inhibitor, Mobocertinib, HER2 Exon 20 Mutant Lung Adenocarcinoma, Mobocertinib and T-DM1 Combinational Therapy

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

MA11.03 Phase Separation Orchestrates EML4-ALK Signaling and Promotes Tumorigenesis

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Introduction: EML4-ALK fusion, observed in about 3-7% of human lung adenocarcinoma, is one of the most important oncogenic drivers in initiating lung tumorigenesis. Previous studies report that kinase activities of EML4-ALK are mainly dependent on dimerization or autophosphorylation of the kinase domain. Recently, emerging evidence begins to link cancer-related genes to condensate assembly, indicative of the important role of phase separation in tumorigenesis. However, it still remains largely unknown whether phase separation contributes to the oncogenic activation of EML4-ALK and how EML4-ALK fusion exactly fires downstream signaling and drives lung cancer formation. **Methods:** To understand the localization and protein properties of EML4-ALK, we transiently expressed GFP-EML4-ALK variant 1 in Hela cells, BEAS-2B cells, H2228 cells and observed multiple condensates formation through confocal microscopy. We observed the GFP–EML4-ALK condensates fusion through living cell imaging analyses. And we used fluorescence recovery after photobleaching (FRAP) assays to reveal the protein exchanges between the liquid droplets and the surroundings. To test whether the phase separation of EML4-ALK fusion exists in vivo, we took advantage of two genetically engineered mouse models (GEMMs): EML4-ALK overexpression mouse model and EML4-ALK transgenic mouse model. To study which fusion partner contributed to the phase separation of EML4-ALK, we created GFP-EML4-N and GFP-ALK-C truncation constructs. To explore whether ALK kinase activity is necessary for condensate formation, we examined the dynamics of EML4-ALK condensates after ALK inhibitor treatment through live imaging analyses. To investigate whether disruption of EML4-ALK condensates formation could affect the activation of EML4-ALK downstream signaling, we constructed the EML4-ALK21S mutant and studied the changes of downstream signaling through western blot analyses. To clarify the links between condensate formation and neoplastic transformation, we performed soft agar assay as well as in vivo tumor formation assay in nude mice. **Results:** Our study here shows that EML4-ALK variant 1 (exon 1-13 of EML4 fused to exon 20-29 of ALK) forms condensates via phase separation in the cytoplasm of various human cancer cell lines. Using two GEMMs, we find that EML4-ALK variant 1 can drive lung tumorigenesis and these murine tumors as well as primary tumor-derived organoids clearly show the condensates of EML4-ALK protein, further supporting the findings from in vitro study. We further demonstrate that mutation of multiple aromatic residues in EML4 region significantly impairs the phase separation of EML4-ALK and dampens downstream signaling pathways, especially the STAT3 phosphorylation. Importantly, it also significantly decreases cancer malignant transformation and tumor formation. **Conclusion:** We demonstrate that EML4-ALK variant 1 forms phase separation in human cancer cell lines, murine lung tumors as well as tumor-derived organoids. Our data show that the phase separation of EML4-ALK is important for firing downstream signaling, especially the STAT3 phosphorylation, and promoting tumorigenesis. These data together highlight an important role of phase separation in orchestrating EML4-ALK signaling and promoting tumorigenesis, which might provide new clues for the development of clinical therapeutic strategies in treating lung cancer patients of the EML4-ALK fusion.

Keywords: EML4-ALK, lung cancer, Phase separation

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

MA11.05 Lysyl Oxidase Inhibition Triggers Phenotypic Transition

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Introduction: Lung adenocarcinoma (ADC) to squamous cell carcinoma (SCC) transdifferentiation (AST) has been consistently observed in the clinic and associates with drug resistance in molecular targeted therapy. Our previous studies have demonstrated that LKB1 deficiency is an important trigger for AST process in the $Kras^{G12D}$/$Lkb1^{L/L}$ (KL) genetically engineered mouse model (GEMM). However, there remains largely unknown about other factors than LKB1 in contributing to AST. Using the $Kras^{G12D}$/$Trp53^{L/L}$ (KP) mouse model known to produce lung ADC only, we find that long-term treatments with the inhibitors of lysyl oxidase (LOX) sufficiently deplete collagen deposition and drive the AST process. Similar to the SCC found in the KL model, these transitioned tumors in KP model display classical squamous tumor expression patterns, e.g., they express squamous biomarkers including p63 and Keratin 14 (K14) with low or no expression for ADC biomarkers such as NK2 homeobox 1 (NKX2-1, also known as TTF1) and surfactant protein C (SFTPC). However, such pathological transition is independent of LKB1 and down-stream AMPK activation. LOX inhibition promotes excessive oxidative stress accumulation which is an important factor for driving the squamous transition. Importantly, these transitioned SCC in KP model show strong resistance to LOX inhibition in stark contrast to non-transitioned ADC. Collectively, this work uncovers an essential role of extracellular matrix remodeling in lung AST and establishes a new mouse model of AST independent of LKB1 status. **Methods:** Mice were treated at 6–8 weeks of age via nasal inhalation of adenovirus carrying Cre recombinase (2×106 PFU). Then we treated KP mice with 3-Aminopropionitrile (BAPN) or D-penicillamine (DPA) daily via intraperitoneal injection post 4 weeks of Ad-Cre infection for 6-8 weeks and then harvested mouse lungs. We use hematoxylin and eosin (H&E) staining for pathological analyses and check NKX2-1,SFTPC,K14 and P63 expression through immunohistochemistry staining (IHC). We check collagen deposition through Masson's Trichrome Collagen staining. We then analyzed whether LKB1 and its downstream signaling such as AMPK phosphorylation via real time PCR and western blot. We also check LKB1 immunostaining in mouse lung tumors. In KP mouse model, the AST process triggered by LOX inhibition was independent of LKB1 inactivation status. We test cell apoptosis and cell proliferation via cleaved caspase 3 and Ki67 IHC, respectively. ECM deprivation is a major cause of oxidative stress that contributes to the accumulation of reactive oxygen species (ROS). We then checked the level of 8- hydroxydeoxyguanosine (8-oxo-dGuo), the marker indicative of DNA oxidative modification. **Results:** Enzymatic inhibition of LOX could promote the ADC to SCC transdifferentiation in KP mice, which has wild type Lkb1 alleles. LOX inhibition results in decreased collagen deposition and ECM remodeling. Treatments with LOX inhibitors significantly increase 8-oxo-dGuo, a DNA oxidation modification marker, indicating the excessive ROS accumulation in KP ADC. **Conclusion:** Extracellular matrix remodeling drives the transdifferentiation from lung adenocarcinoma to squamous cell carcinoma and promotes drug resistance independent of LKB1 status.

Keywords: extracellular matrix remodeling, Drug resistance, Adenocarcinoma to Squamous cell carcinoma transdifferentiation

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

MA11.06 Multi-Omic Characterization of Lung Tumors Implicates AKT and MYC Signaling in Adenocarcinoma to Squamous Cell Transdifferentiation

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Introduction: Lineage plasticity, the ability to transdifferentiate among distinct phenotypic identities, facilitates therapeutic resistance in multiple cancers. In lung adenocarcinomas (LUADs), this phenomenon includes small cell and squamous cell (LUSC) histologic transdifferentiation in the context of acquired resistance to targeted inhibition of driver mutations. The incidence of transdifferentiation into squamous carcinoma in EGFR mutant tumors, the setting where this histologic shift has been most extensively described, occurs in up to 9% of cases relapsed on osimertinib and has been associated to poor prognosis. The paucity of well annotated pre- and post-transdifferentiation clinical samples has precluded the performance of informative molecular analyses: little is known about the molecular mechanisms leading to this histological transition. **Methods:** We hypothesized that multi-parameter profiling of the components of mixed histology (LUAD/LUSC) tumors, together with pre- and post-transdifferntiation clinical samples, could provide insight into factors licensing lineage plasticity between these histologies and promoting squamous transdifferentiation of LUAD. We performed detailed genomic (whole exome sequencing), epigenomic (bisulfite sequencing), transcriptomic (RNAseq) and proteomic (antibody arrays) characterization. Clinical findings were validated in preclinical models including cell lines and patient-derived xenograft treatments. **Results:** Our results suggest that LUSC transdifferentiation is primarily driven by transcriptional reprogramming rather than mutational events, and indicate that the resulting squamous tumors retain transcriptomic and methylation profiles of their previous LUAD state. We observed coordinated upregulation of PI3K/AKT, MYC and PRC2 pathway genes in the LUSC component of mixed histology tumors. Concurrent activation of PI3K/AKT and MYC induced squamous features in EGFR-mutant LUAD preclinical models, further augmented under selective pressure of osimertinib. Pharmacologic inhibition of EZH1/2 in combination with osimertinib prevented relapse and squamous transdifferentiation in an EGFR-mutant patient-derived xenograft model, and inhibition of EZH1/2 or PI3K/AKT signaling re-sensitized resistant transdifferentiated LUSC tumors to osimertinib. **Conclusion:** Our findings provide the first comprehensive molecular characterization of LUSC transdifferentiation, suggesting putative drivers and promising therapeutic targets to constrain or prevent lineage plasticity in this setting.

Keywords: Plasticity, Transformation, Squamous

MA11 NEW BIOLOGICAL INSIGHTS FOR TARGETED THERAPIES
SUNDAY, SEPTEMBER 12, 2021 - 18:45-19:45

MA11.07 Lung Squamous Cell Carcinoma Prognosis Based on Ferroptosis DNA Methylation status

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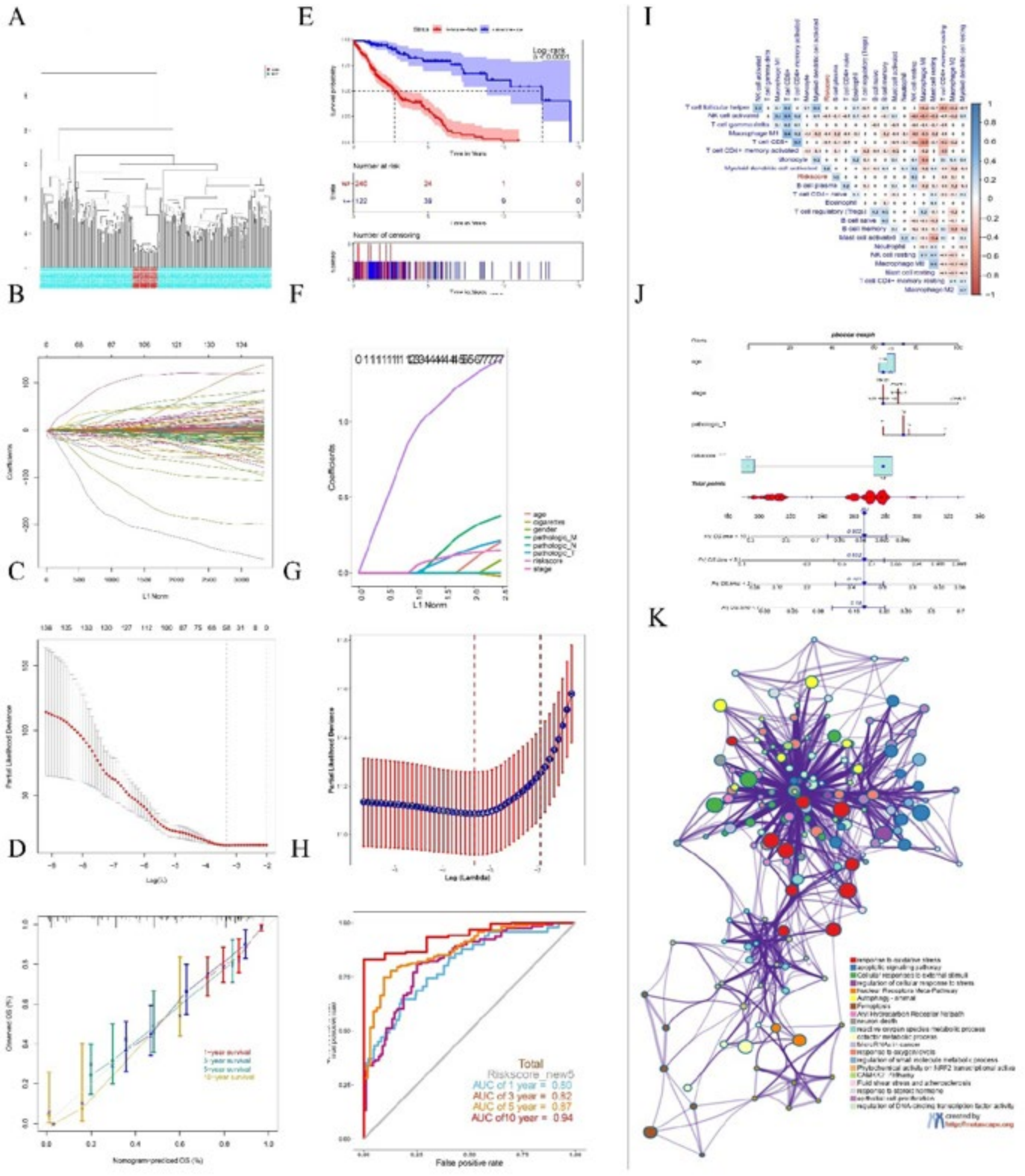
Introduction: Lung squamous cell carcinoma (LUSC) with poor prognosis is more common in elderly person and closely related to smoking. Smoking and age increasing have a certain effect on DNA methylation. Ferroptosis-related genes regulating an iron- and lipid ROS-dependent form of programmed cell death suggests critical roles for ferroptosis in cancers. However, the prognostic value of ferroptosis-related epigenetic features such as DNA methylation in LUSC needs to be studied. **Methods:** The methylation data and patient information downloaded from the TCGA database are standardized and aberrant methylated sites calculated by “ChAMP” package. 362 LUSC cases with complete OS information were randomly separated into training cohort (n = 200) and validation cohort (n = 162) with no significant differences in the age and sex (p > 0.5). Ferroptosis-related genes are collected from the FerrDb database and the methylation data of these related genes in LUSC are retrieved. Univariate Cox regression , LASSO regression and setpwise multivariate Cox hazards regression were used to establish and validate the hazards model, and the risk score was generated as previously described [Frontiers in Genetics, 2021, 12:635863.]. Then a nomogram was built based on the risks status and clinical information. **Results:** Univariate Cox regression showed a total of 137 DNA methylation sites corresponded to 109 ferroptosis related genes exhibited a significant association with patient prognosis. Function enrichment analysis revealed that these 258 genes enriched in biological pathways were closely related to cancers, such as response to oxidative stress, apoptotic signaling pathway, cellular responses to external stimuli, regulation of cellular response to stress, autophagy - animal, ferroptosis, reactive oxygen species metabolic process, response to oxygen levels and so on. Subsequently, we constructed the prognosis model containing 26 sites (cg24897291, cg11757894 , cg00170343, cg06120945, cg18287222, cg01015199, cg18245652 , cg05618386, cg17987505, cg27182551, cg13557397, cg25671164 , cg18879829, cg22341865, cg17149920, cg17197538, cg00592510, cg15590007, cg00589914, cg20229027, cg05834353, cg00738178 , cg07051257, cg08719701, cg23327734, cg12414653, cg03264601 , cg06378498, cg05170326, cg10356455, cg15871766) that can effectively predict the prognosis of LUSC patients using stepwise multivariate Cox regression analysis. This signature performed well for OS prediction with AUC of ROC 0.87 for 5 years OS prediction and significant difference of median survival time for high and low risk group.



Conclusion: Our study established a new Ferroptosis gene related DNA Methylation signature basis on the DNA methylation data form TCGA which may provide a more detailed clinical evaluation of prognosis, individualized diagnosis for LUSC patients.

Keywords: Lung Squamous Cell Carcinoma, Ferroptosis, DNA Methylation

MA12.01 A Novel Program Offering Remote, Asynchronous Subspecialist Input in Thoracic Oncology: Early Experience During a Pandemic

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Introduction: AccessHope (AH) is a program developed initially by City of Hope to provide remote subspecialist input on cancer care for patients as a supplemental benefit for specific payers and employers. While offering several platforms, the leading one has been an asynchronous model of review of medical records followed by a detailed assessment of past and current management along with discussion of potential future options in a report sent to the local oncologist. The intent of this program is that the patient can continue to have most or all management in their home environment, with the input and support of a subspecialist in that tumor type available "on demand". This summary describes an early period of development and growth of this service, focusing in cases of lung cancer, particularly relevant during the COVID-19 pandemic. **Methods:** Appropriate cases for the eligible "at risk" population were identified by a trigger list of cancer diagnoses associated with a significant degree of risk of poor outcomes that included non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Medical records were solicited from the local medical team, from which a summary narrative and chronology was developed by a team of nurses at AH. This was shared with a physician specialist in thoracic oncology from AH who wrote a summary report within several days that was sent to the local physician, followed by a direct discussion with the recipient. Using descriptive statistics, case metrics focusing on concordance with the current or proposed management plan were tracked, along with recommended changes and clinical trial options, as well as potential cost savings from suggested changes. **Results:** Over a 19-month period from 4/19 through 11/20, 110 cases were reviewed: 55% male, median age 62.5 yrs (range 33-92); 82% NSCLC (12% stage I/II, 16% stage III, 57% stage IV) and 17% SCLC (4% limited, 14% extensive). Median turnaround time for send out of report of 5.0 days. The AccessHope review agreed with the proposed or ongoing treatment in 79 (72%) cases and disagreed in 31 (28%) cases. Even with general agreement in the treatment approach, specific additional recommendations were associated with evidence-based anticipated improvements in efficacy in 76 cases (65%) and improvement in potential for cure in 14 cases (12%, only feasible in patients with curable disease). Specific recommendations associated with cost savings were identified in 14 cases (12%), associated with a total cost savings of $2,096,859. Molecular testing was ordered rarely for SCLC; for NSCLC, NGS was strongly favored and more commonly associated with more advanced stage and non-squamous histology. **Conclusion:** We have implemented a novel program of asynchronous reviews of cases of patients with lung cancer by thoracic oncology subspecialists and have demonstrated the feasibility of completing reports for a growing volume over the course of the pandemic without requiring travel and enabling patients to receive their care close to home. More than a quarter of these case reviews include recommendations associated with evidence to support improved clinical outcomes, as well as potentially significant cost savings from low value practices unsupported by evidence.

Keywords: remote care, pandemic, expert review

MA12.02 Factors Associated with Severe COVID-19 Infections in Lung Cancer Patients

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Introduction: Lung cancer patients are at increased risk of developing complications from COVID-19 disease. Real-world data may better identify lung cancer patients who are at an increased risk of developing complications while maximizing the benefit of anti-cancer therapy. **Methods:** We conducted a retrospective cohort study using the VA COVID-19 Shared Data Resource (CSDR), VA Cancer Registry, and VA Corporate Data Warehouse (CDW), which centralizes electronic health data for patients seen at VA facilities nationwide. We included patients with a diagnosis of lung cancer between October 1, 2015 and December 1, 2020, and a diagnosis of COVID-19 between February 2, 2020 and December 1, 2020. Serious SARS-CoV-2 infection was defined as the occurrence of any of the following within 2 weeks after diagnosis: (a) hospitalization, (b) ICU admission, (c) utilization of respiratory support (mechanical ventilation or intubation). Data abstracted included: age at COVID-19 diagnosis, gender, race, ethnicity, urban status, date of diagnosis of lung cancer, histology, stage, cancer treatment, individual comorbidities and most recent laboratory results prior to COVID-19 diagnosis. Patients were stratified into 3 groups: mild/moderate COVID-19 infection, serious, but non-fatal infection, fatal infection. Differences in categorical variables, were assessed using χ^2 test, while Kruskal-Wallis rank sum test was used for continuous variables. Multivariable logistic regression models were fit relative to the outcomes of interest, i.e., serious SARS-CoV-2 infection and death from SARS-CoV-2 infection. **Results:** We identified 352 lung cancer patients with COVID-19. Of these, 54 (15.3%) had severe disease and 34 others (9.7%) died. Patients who had fatal or severe infection were older than those with mild/moderate infection (median age: 74.1 and 73.8 yrs vs. 72.1 yrs; p=0.01). Patients who suffered a fatal or severe infection were also more likely than patients with mild/moderate infection to exhibit elevated creatinine levels (50.0% and 31.5%, vs. 20.5%, p = 0.003) and low hemoglobin levels (67.6% and 51.9%, vs. 39.0%, p = 0.003). In addition, 70.6% of patients who died within two weeks of SARS-CoV-2 infection suffered from diabetes, compared to 40.2% of patients with mild/moderate infection.On multivariable logistic regression, variables associated with increased odds of severe infection or death were: age (OR: 1.07; 95% CI 1.03-1.12; p=0.002), stage IV (6.06; 1.19-30.84; 0.03), elevated creatinine (2.29; 1.2-4.39; 0.01), anemia (2.02, 1.07-3.83; 0.03). Type of cancer treatment, recent surgery or radiation, chronic obstructive pulmonary disease, hypertension, diabetes, acute myocardial infection were not associated with an increased risk of severe/fatal infection. Factors associated with fatal infection included checkpoint inhibitor therapy (OR: 7.06; 95% CI, 1.21-41.11; p=0.03), diabetes (3.53; 1.9-11.46; 0.04) and abnormal creatinine level (4.48; 1.52-13.15; 0.006). **Conclusion:** Almost 25% of lung cancer patients with COVID-19 infection developed complications or died. Increasing age, stage IV disease, abnormal kidney function and low hemoglobin level were associated with a severe/fatal SARS-CoV-2 infection, while checkpoint inhibitor therapy, diabetes and abnormal creatinine levels were associated with increased mortality from COVID-19 disease.

Keywords: COVID-19 disease, risk factors, Lung cancer outcomes

MA12.03 A Thoracic Cancers International COVID 19 Collaboration Survey on Patients' Perceptions of COVID-19 (Teravolt-Paper)

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Introduction: The coronavirus disease 2019 (COVID19) pandemic has overwhelmed healthcare systems and disrupted patient care worldwide. Thoracic cancer patients are at increased risk of morbidity and mortality due to underlying malignancy and immunosuppressive anti-cancer therapies, in combination with older age, smoking habits, and pre-existing lung disease. The objective of the TERAVOLT-PAPER survey is to understand thoracic cancer patients' perceptions of the impact of COVID19 on their cancer thereby informing providers of efforts needed to encourage ongoing care. **Methods:** Adults with a diagnosis of NSCLC, SCLC, mesothelioma, thoracic carcinoid and/or thymoma from TERAVOLT-affiliated institutions and advocacy organizations were invited to complete an anonymous, multilingual web-based survey. **Results:** As of April 2021, 156 patients have participated. Of the total responses received in each survey field: 57% female, 60% over 60 years old, 64% white, 51% current or former smokers, 64% with undergraduate-level education or higher, and 38% have not received the flu vaccine in the past 12 months. 68% of respondents were on active anti-cancer treatment, majority (68%) on palliative therapy. While most (76%) reported no impact of COVID19 on their treatment schedule, those who experienced delays more commonly reported them to be at the physician's decision vs patient request (17% vs 4%). Among those with delays, 52% did not feel these delays would impact their long-term cancer care. As for 32% of respondents undergoing surveillance, 70% reported no change in their appointment schedule, 18% reported delays at the physician's decision, and 2% delays at patient request. Among those with delays, most respondents either did not feel these changes would impact their long-term cancer care (36%) or were uncertain of the impact (36%). The risk of contracting COVID19 is a major concern with 59% of respondents worrying about this "often" or "always" and 55% changing how frequently they go to their cancer center. Only 5% have considered stopping their anti-cancer therapy due to COVID19. Most respondents (60%) reported no change in the format of their appointments, compared to 20% and 14% who reported increased use of phone and video visits, respectively. Although 21% of respondents felt that having virtual appointments affected their cancer care negatively, most reported either no impact (61%) or a positive impact (13%) on their care. Regarding patient knowledge about the impact of cancer/anti-cancer therapy on risks of COVID19, 69% and 62% believed that having cancer and being on treatment increases severity of COVID19 illness, respectively. Up to 25% of respondents reported not knowing the impact of their cancer diagnosis/treatment. **Conclusion:** Despite the known impact of the pandemic on patient care, our global survey illustrates that most thoracic cancer patients do not perceive that their overall cancer care has been compromised. Virtual appointments will continue to be useful in light of patients' concerns about COVID19. Considering the high proportion of respondents indicating uncertainty, continued patient education regarding the impact of cancer and anti-cancer therapies on risks of COVID19 is critical during this challenging time. Data collection is ongoing and updates will be presented.

Keywords: thoracic cancer, TERAVOLT, COVID19

MA12.05 The Impact of the COVID-19 Pandemic on Post-Operative Outcomes of Thoracic Cancer Surgery in Canada

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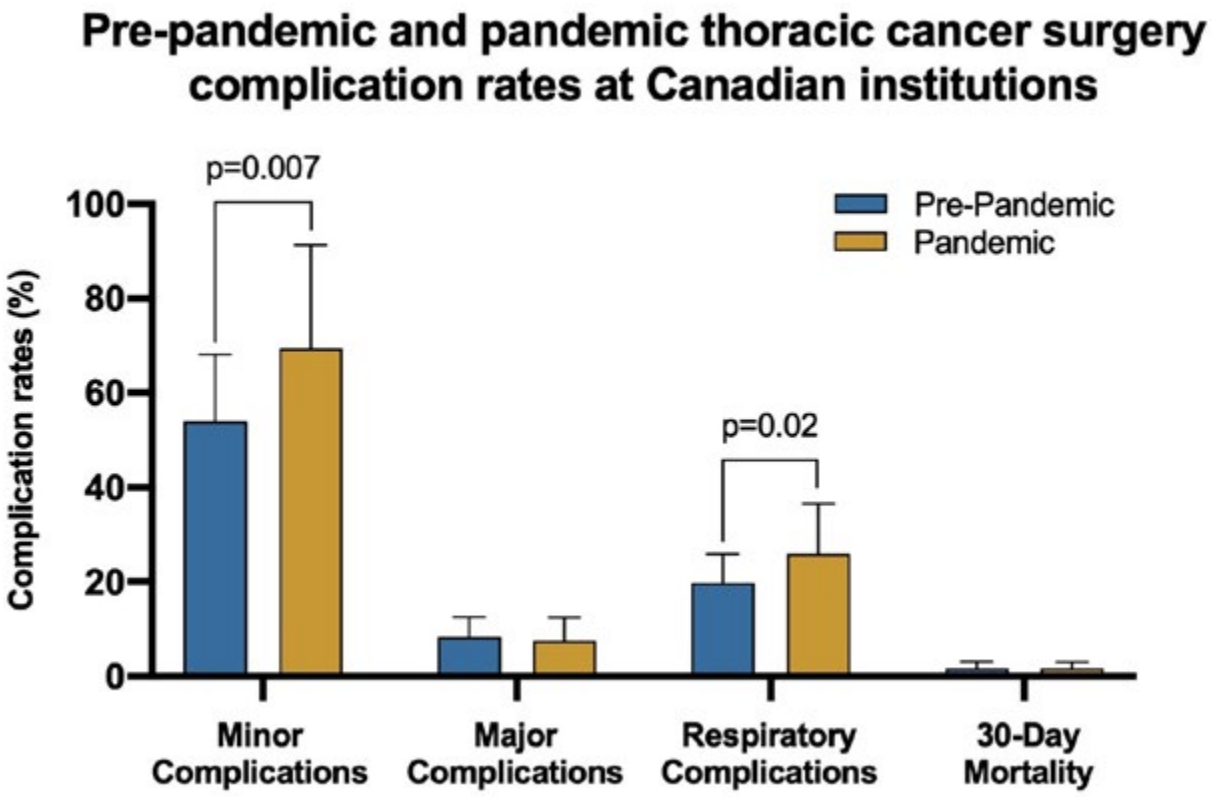
Introduction: During the COVID-19 pandemic, surgical services had to adapt their priority of operations to ensure an optimal and safe delivery of care. To minimize disease transmission and create surge capacity, elective and non-emergent procedures, including cancer operations, were initially delayed or cancelled. Studies have described an increase in post-operative complications during the pandemic for cancer patients undergoing surgery, while others have shown that thoracic surgery can be conducted safely despite this global health crisis. This study aims to understand the impact of the pandemic on post-operative outcomes of patients undergoing thoracic cancer surgery in the context of variable surgical volume and community disease prevalence. **Methods:** Adults undergoing emergency or elective surgical procedures for suspected or confirmed lung, esophagogastric, mediastinal and chest wall malignancies at 2 Canadian tertiary care centres from 2 provinces between March 2017 and February 2021 were included. The prospectively-entered Canadian Association of Thoracic Surgeons National Database was queried for patient demographic, diagnostic, operative and post-operative data. The primary outcome was complication rate (minor complications, major complications, respiratory complications, 30-day mortality). The secondary outcome was thoracic cancer surgery volume. 'Pre-pandemic' was defined as the period from March 2017 to February 2020, and 'pandemic', from March 2020 to February 2021. Descriptive statistics, t-tests and non-parametric tests were used. **Results:** A total of 3,853 patients were included. During the pandemic, 991 surgical procedures were performed. Median age was 68.0 [60.5-74.0] years. Procedures were mainly for lung cancer (73.1%), with rare emergent surgeries (2.2%). No differences were observed for diagnosis, surgical priority, operative approach or length of stay between pre-pandemic and pandemic periods. At both centres, monthly minor complication rates were significantly higher during the pandemic as compared to pre-pandemic (mean 69.4% vs. 54.0%, p=0.007). Respiratory complications were also significantly more common during the pandemic (mean monthly rate 26.0% vs. 20.0%, p=0.02). No difference was observed for major complication or 30-day mortality rates.



Conclusion: In locations with high prevalence of COVID-19, the pandemic has impacted the rate of minor complications and respiratory complications after thoracic cancer surgery, with no impact on major complications and 30-day mortality. Larger national studies could help further evaluate the correlation between various community respiratory infection rates and thoracic surgical outcomes.

Keywords: thoracic cancer surgery, post-operative complications, covid-19

MA12 THE IMPACT OF COVID-19 ON HOW WE TREAT THORACIC CANCER NOW AND IN THE FUTURE
SUNDAY, SEPTEMBER 12, 2021 - 20:00-21:00

MA12.06 Single Fraction Lung Stereotactic Body Radiotherapy Implementation in a Multi-Center Provincial Cancer Program During the COVID-19 Pandemic

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Introduction: During the COVID-19 pandemic, cancer centers worldwide were compelled to consider shortened radiotherapy regimens to minimize the risk of infectious exposure of patients and staff members. Larger institutions with multiple treatment centers may face greater challenges when developing consensus guidelines and implementing new treatment initiatives. We describe the implementation of single fraction (SF) lung stereotactic body radiotherapy (SBRT) in a multi-center provincial cancer program. **Methods:** British Columbia, Canada has a provincial cancer program with radiotherapy services distributed across six regional centers serving a population of 5.1 million people. In March 2020, coordinated provincial mitigation strategies were developed in anticipation of decreased access to radiotherapy during the COVID-19 pandemic. The provincial lung radiation oncology group identified SF lung SBRT as a mitigation measure supported by high quality randomized evidence that could provide comparable outcomes and toxicity to existing fractionated SBRT protocols. A working group of radiation oncologists and medical physicists performed a literature review and drafted provincial guidelines and procedures. The guidelines were reviewed by a group of center representatives as a component of provincial lung radiotherapy mitigation strategic planning. Individual centers were encouraged to implement SF lung SBRT as their resources and staffing would permit. Centers were then surveyed about barriers encountered during the implementation process. **Results:** A working group was created and consensus guidelines for SF lung SBRT were drafted on March 24, 2020. The working group approved and distributed the final version of the guidelines on March 26, 2020. The provincial lung radiotherapy mitigation strategy group adopted the guidelines for implementation on April 1st, 2020. Implementation was completed at the first center on April 27, 2020. Barriers to implementation were identified at 5 of 6 centers. Two centers situated in regions with disproportionately high volumes of positive COVID-19 cases cited inadequate staffing as a primary obstacle for implementation. One center experienced delays attributed to pre-scheduled commissioning of new treatment techniques. Three centers described competing priorities as reasons for delayed implementation. As of February 2021, two centers had active SF lung SBRT programs, three centers were in the process of implementation, and one center had no immediate plans for implementation because of persistent resource issues. **Conclusion:** SF lung SBRT was launched in a multi-center provincial cancer program within weeks of conception during the development of radiotherapy mitigation strategies for the COVID-19 pandemic. Although consensus guidelines were adopted quickly, the actual implementation by individual centers varied owing to differences in resource allocation and staffing among the centers. Strong organizational structures and early identification of potential barriers may improve the efficiency of adopting new treatment initiatives in large distributed radiotherapy programs.

Keywords: stereotactic body radiation therapy, pandemic, implementation

MA12.07 Oncological Procedures and Risk Assessment of COVID-19 in Thoracic Cancer Patients: A Picture From an Italian Cancer Center

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Introduction: At the end of 2019, the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) and its clinical manifestation, the coronavirus disease 2019 (COVID-19), have rapidly spread across the globe. Since then, Italy soon became one of the most affected countries. Patients with thoracic malignancies had the highest frequency of severe complications. In this challenging situation, healthcare systems modified their practice by introducing strict infection control measures to ensure optimal cancer care. This study aimed to investigate the efficacy of pre-procedure screening for COVID-19 and whether infection influenced the opportunity of patients to receive timely diagnosis and therapy. **Methods:** We retrospectively collected data of oncological procedures of patients with confirmed or suspected diagnosis of thoracic malignancies treated at Oncology Department or coming from the Emergency Department of San Luigi Gonzaga University Hospital between June 2020 and March 2021 (from the end of the first wave until the middle of the third one). According to an internal protocol, outpatients were evaluated by a clinical questionnaire and a nasopharyngeal swab (NPS) performed 24/48 hours before oncological procedures. Inpatients were tested before hospitalization and after 24, 48 hours, seven days and then in case of appearance of symptoms. Descriptive statistics were used to summarize the data. Categorial variables were summarized as counts and percentage. In this abstract we present the preliminary results. **Results:** 125 patients were included in this analysis. Median age was 72 years (range 21-83), males were 64%. At the time of the procedures ECOG Performance Status was: 0 in 46 patients (36.8%), 1 in 66 (52.8%) and 2 in 13 (10.4%). Histological types were: 108 (86.4%) NSCLC, 9 (7.2%) SCLC, 7 (5.6%) mesothelioma and 1 (0.8%) amartochondroma. The majority of patients (80%) were in stage IV. 135 programmed procedures were performed: 102 (75.5%) were diagnostic (75 lung biopsies, 21 bronchoscopy, 1 lumbar puncture, 2 thoracoscopies, 1 thoracentesis, 1 gastroscopy and 1 thoracic surgery), 25 palliative and 8 therapeutic. Eighty-nine (66%) and 46 (34%) procedures were performed in outpatients and inpatients, respectively. Of the 132 NPS performed before the procedures, 8 (6%) were found to be positive (5 for diagnostic procedures, 1 for therapeutic loco-regional procedure and 2 for exploratory bronchoscopies). The 8 positive patients were infected during the second wave (from November 2020 to January 2021). One patient was infected during hospitalization, the other ones in community. Most of patients were asymptomatic, only 2 of them had mild symptoms (fever). Six procedures were postponed (5 diagnostic, 1 palliative), an explorative bronchoscopy was canceled and a diagnostic biopsy was performed even though the patient tested positive. The median time to resolution of the infection was 17 days (range 11-36). The median delay of the procedures was 36 days (range 14-55). Four patients started systemic treatment in a median time of 40.5 days (range 21-57). **Conclusion:** Our analysis pointed out that Sars-Cov2 infection led to the postponement of a small but not negligible percentage of diagnostic and therapeutic procedures and that a structured screening for COVID-19 is critical for the best management of scheduled procedures during pandemic.

Keywords: covid-19, Lung and chest cancer, oncological procedures

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MA13.01 Camrelizumab Plus Apatinib in Treatment-Naive Patients With Advanced Non-Squamous NSCLC: A Multicenter, Open-Label, Single-Arm, Phase 2 Trial

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Introduction: Our preclinical work suggests that appropriate angiogenesis inhibition could potentiate PD-1/PD-L1 blockade, and promising anti-tumor activity was already observed with camrelizumab plus apatinib in chemotherapy-pretreated patients (pts) with advanced non-squamous NSCLC in the phase Ib/II study (NCT03083041). We hereby further investigated its efficacy in treatment-naive advanced NSCLC pts as in cohort 4 of this study. **Methods:** In this multicenter, open-label study, pts of advanced non-squamous NSCLC with EGFR/ALK wild type were enrolled. All pts, regardless of PD-L1 expression, received apatinib 250 mg orally once daily, in combination with camrelizumab 200 mg as front line setting every 2 weeks until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR), and secondary endpoints included DCR, PFS and OS. **Results:** As the cutoff date of Dec 11, 2020, 25 pts were enrolled with a median follow-up of 15.24 months (range, 2.0-20.17). The median age was 61 years old. Twelve (48%) pts were still on treatment at the time of analysis, including 4 receiving treatment beyond disease progression. Among them, 10 (40.0%) partial responses, 13 (52.0%) stable diseases, 1 (4%) progressive disease and 1(4%) not evaluable were observed. The ORR was 40.0% (10/25, 95% CI, 21.1-61.3) and DCR was 92.0% (23/25, 95% CI, 74.0-99.0). The median PFS was 11.0 months (95% CI, 7.3-14.8), while median DOR and OS were not reached. All of them had PD-L1 expression detection and 15 (60%) were PD-L1≥1%. Subgroups analysis showed similar ORR of 40.0% (95% CI, 16.3-67.7) versus 40% (95% CI, 12.2-73.8) ($p > 0.99$), and median PFS of 9.7 versus 11.0 months (HR=1.56, p=0.42) in pts with PD-L1 positive and negative tumor, respectively. The most common treatment-related adverse events of grade 3 or higher were hypertension (6 [24.0%]), increased gamma-glutamyltransferase (5 [20.0%]) and abnormal hepatic function (4 [16.0%]). Table 1. Efficacy of camrelizumab and apatinib combination in treatment-naive pts with advanced non-squamous NSCLC

	Pts	ORR, n/N	DCR, n/N	mPFS (mos, 95% CI)	mOS (mos, 95% CI)
All patients	25	40.0%, 10/25	92.0%, 23/25	11.0 (7.3-14.8)	NR (NE-NE)
PD-L1 positive	15	40.0%, 6/15	86.7%, 13/15	9.7 (0.7-15.8)	NR (NE-NE)
PD-L1 negative	10	40.0%, 4/10	100%, 10/10	11.0 (NE-NE)	NR (NE-NE)

Conclusion: Front line camrelizumab plus apatinib showed promising clinical activity with acceptable safety in pts with advanced NSCLC regardless of PD-L1 expression. A randomized phase III clinical trial (NCT04203485) is undergoing to validate the potent of this combination in front line setting.

Keywords: Camrelizumab, NSCLC, Apatinib

MA13.02 Phase II Study of Nivolumab and Ipilimumab Combined With Nintedanib in Recurrent Non-Small Cell Lung Cancer

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Introduction: Cancer-associated fibroblasts (CAFs) are a key immunosuppressive component of the tumor microenvironment (TME). Nintedanib is an oral triple kinase inhibitor that suppresses CAFs. Modulating the TME through inhibition of CAFs may represent an important synergistic approach in overcoming resistance to immune checkpoint inhibitors (ICIs). Based on these observations, we initiated a phase IB/II trial to evaluate the combination of nintedanib, nivolumab, and ipilimumab in advanced NSCLC patients. The phase IB dose-escalation results were presented at WCLC 2019 and the combination of nivolumab at 3mg/kg every 2 weeks, ipilimumab 1 mg/kg every 6 weeks, and nintedanib 150 mg once daily was declared as the recommended phase II dose (RP2D). Here we present the 1st interim analysis of phase II of the combination regimen in the ICI pre-treated patients. **Methods:** This is a single institution, investigational, non-randomized, parallel assignment phase I/II clinical trial of patients with locally advanced or metastatic NSCLC. Eligible patients can be immunotherapy naïve (Arm A) or with disease progression following immunotherapy (Arm B). Enrollment into phase II of the trial is being performed by the Bayesian two-stage design method with the primary objective of determining the efficacy of the combination regimen in NSCLC. Key secondary objectives are overall survival (OS) and progression-free survival (PFS). Descriptive statistics were used to summarize demographic and safety data. The Kaplan–Meier method with log-rank test was used for survival analysis. **Results:** 20 patients received therapy with the combination of nivolumab, ipilimumab, and nintedanib at the RP2D in the ICI pretreated cohort (Arm B). The majority of patients were female (60%) with a current or prior history of tobacco use (84%) and an ECOG performance score of 1 (90%). Adenocarcinoma was the most common histology (75%). The most common treatment-related adverse event of any grade were transaminitis, diarrhea, and pruritis, each observed in 20% (4/20) of patients. Of the 18 patients evaluable for response, 4 (22%) had a partial response (2 confirmed), 7 (39%) had stable disease and 7(39%) developed progressive disease for a disease control rate of 61%. Survival analysis showed a median PFS of 2.7 months (1.4, N.E.) and OS of 7.7 months (5, N.E.). Clinical trial information: NCT03377023. **Conclusion:** The combination of nivolumab, ipilimumab and nintedanib was well tolerated and demonstrated antitumor activity despite tumor progression on prior ICI therapy. The ICI pretreated cohort has met the predefined response criteria for the 1st interim analysis (> or = 2 responses) and will continue enrollment (with 20 additional patients) in the second stage.

Keywords: Tumor microenvironment , immunotherapy resistance , lung cancer

MA13.03 Combination of Bevacizumab + Atezolizumab (A) Who Progressed On A In Pretreated NSCLC Patients: An Open-Label, Two-Stage, Phase II Trial

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Introduction: Rapidly progressing tumors are critically dependent upon neovascularization for oxygen and nutrient supply. Vascular endothelial growth factor (VEGF) induces tumor angiogenesis, resulting in the malformed and dysfunctional vasculature within the tumor, which serves as a physical barrier for cytotoxic T cells and promotes an immunosuppressive tumor microenvironment. Anti-angiogenic treatment has demonstrated increased T cell trafficking into tumors, reduced immunosuppressive cytokines and regulatory T cells, which may overcome resistance to checkpoint inhibitors. We conducted a two-stage, phase II study to evaluate the treatment efficacy of adding bevacizumab to atezolizumab in metastatic non-small cell lung cancer (NSCLC) patients whose disease had progressed after atezolizumab monotherapy. **Methods:** NSCLC patients whose disease progressed after at least one line of platinum-based chemotherapy were eligible for study. Patients received atezolizumab 1200 mg every 3 weeks until radiographical progression (stage I). Then, bevacizumab 15 mg/kg was combined to atezolizumab 1200 mg every 3 weeks (stage II). The primary endpoint was the disease control rate (DCR) confined to stage II. **Results:** Between September 2018 and March 2020, 42 patients enrolled to receive atezolizumab monotherapy and 24 patients subsequently received atezolizumab plus bevacizumab. The median number of previous chemotherapy was 1 (range 1–3; 1: n=28 [66.7%], 2: n=12 [28.6%], 3: n=2 [4.7%]). For atezolizumab monotherapy (stage I), one (2.4%) and 15 (35.7%) of 42 patients had partial response and stable disease, respectively, leading to a DCR of 35.7% (95% confidence interval [CI], 21.6–52.0). For atezolizumab plus bevacizumab combination therapy (stage II), three (12.5%) and 18 (75.0%) of 24 patients had partial response and stable disease, respectively, leading to a DCR of 87.5% (95% CI, 67.6–97.3). For 24 patients enrolled in stage II, the median progression-free survival was 5.6 (95% CI, 4.1–7.1) months and the overall survival was 14.0 (95% CI, 10.7–17.4) months. The most common adverse events of any grade included skin rash (4, [16.7%]), pruritus (4, [16.7%]), and anorexia (3, [12.5%]). Hypertension was reported in two patients (8.3%), both with grade 2 events. **Conclusion:** Combination of bevacizumab plus atezolizumab for metastatic NSCLC patients whose disease had progressed after atezolizumab monotherapy showed a promising antitumor activity with good tolerability. Further analyses on predictive biomarker are ongoing.

Keywords: non-small cell lung cancer, atezolizumab, bevacizumab

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MA13.05 Prognostic Impact of Immune Related Adverse Events in Advanced Non-Small Cell Lung Cancer Patients with ICIs Treatment

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Introduction: Immune related adverse events (irAEs) have been reported to associate with efficacy of immunotherapy. However, no consistent association has been verified. The objective of this study is to further explore whether the appearance of irAEs after treatment with immune checkpoint inhibitors (ICIs) is associated with survival benefit in patients with advanced non-small cell lung cancer (aNSCLC). **Methods:** This is a single center retrospective cohort study of patients undergoing ICI therapy for recurrent or metastatic NSCLC during March 2015 to August 2019. Patients received ≥1 dose of ICIs and had ≥2 clinical visits were eligible for inclusion. Clinical data on patient characteristics, irAEs occurrence, and survival outcomes were abstracted from the electronic medical record of patients (LinkDoc database). The irAEs were graded (CTCAE v4.0) as per physician according to their daily clinical practice. Survival outcomes were estimated by using the Kaplan-Meier methods and compared with the Log-rank test. **Results:** Among 277 patients, most were male (72.2%) and smokers (73.3%). Median patient age was 60 (IQR: 54-67) years. Majority of tumors (83.4%) were stage IV and adenocarcinoma (61.7%) was the most common subtype. A total of 248 (89.5%) patients experienced AE (22.7% ≥ grade 3). IrAEs was observed in 51 (18.4%) patients (5.8% ≥ grade 3). The most common irAEs included hypothyroidism (3.4%), anemia (2.7%), leukopenia (1.7%), neutropenia (1.6%), fatigue (1.6%), thrombocytopenia (1.2%), and gastrointestinal disorders (1.0%). The median progression free survival (PFS) and overall survival (OS) of the patients were 6.8 (95%CI: 5.8, 8.3) and 21.5 (95%CI: 15.9, 52.4) months, respectively. As for the line of therapy, the median OS was 21.5 (15.9, NE) months in the first line patients and 18.2 (15.8, NE) months in the second line or above group. Meanwhile, the corresponding median PFS were 12.1 (5.7, 21.5) and 6.0 (5.3, 8.3) months, respectively. However, no prognostic significance of irAE incidence was observed with respect to either OS (P=0.6894) or PFS (P=0.7609) of the patients. **Conclusion:** The development of irAEs did not appear to associate with better survival of our aNSCLC patients during ICI therapy. Future studies are still needed to clarify it further.

Keywords: Immune related adverse events, Overall survival, Immune checkpoint inhibitors

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MA13.06 Improved Outcomes for Patients Developing Any Immune-Related Adverse Events in Advanced NSCLC Treated With Pembrolizumab Monotherapy

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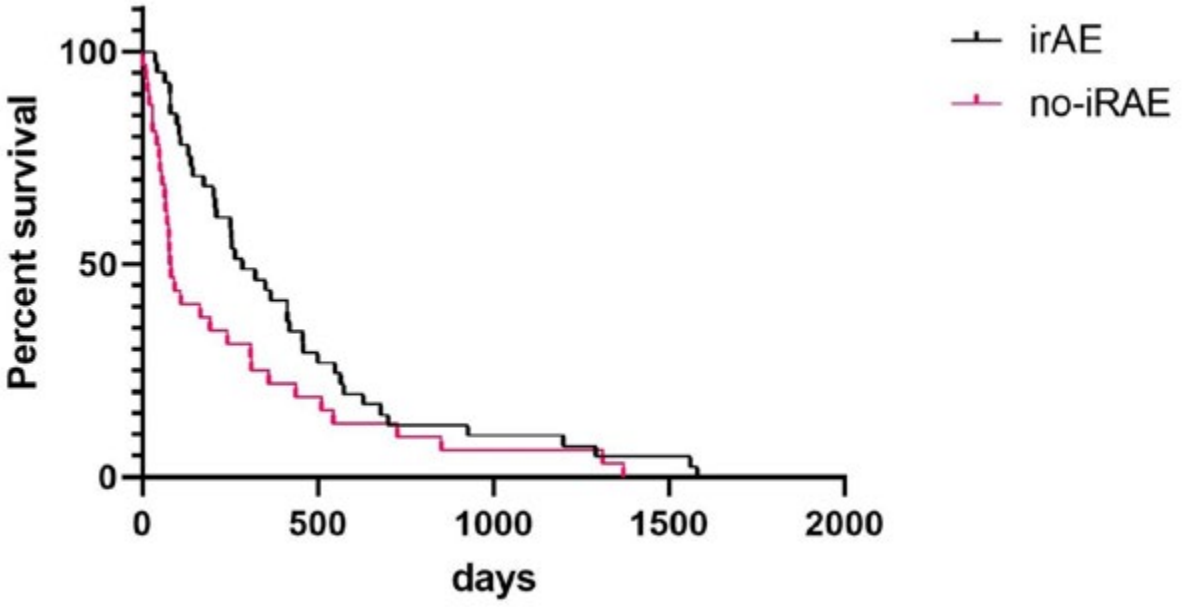
Introduction: Pembrolizumab immunotherapy is routinely used in advanced NSCLC. Immune-related adverse events (irAEs) are complications of treatment. There is little information on outcomes in patients developing irAEs. We present 7 years of experience delivering pembrolizumab monotherapy at a tertiary UK cancer centre, reporting on irAEs and outcomes. We hypothesise that the development of irAEs is associated with improved outcomes due to improved pharmacodynamic effects **Methods:** A single-centre retrospective analysis of the electronic records of NSCLC patients who received pembrolizumab monotherapy between January 2014 and December 2020. Outcomes were number and severity of irAEs and progression-free survival (PFS). **Results:** 33 out of 73 had 0 irAEs (45%), 20 had 1 irAE (27%) and 20 had >=2 irAEs (27%). 84 total irAEs were reported: skin (13), GI (13), hepatobiliary (6), endocrine (10), joint (5), cardiac (1), pulmonary (2), renal (3), and non-specific (including fatigue and nausea) (31). 12 patients had G3 irAEs (16%). These were GI (3), hepatobiliary (2), joint (2), pulmonary (2), renal (1) and 2 non-specific. 3 had G4 irAEs which were 1 each of hepatobiliary, cardiac, GI (colitis). Median time of onset of irAE was 71 days. Median PFS (mPFS) was longer for those with at least 1 irAE vs those with 0 (285 days vs 80 days, p=0.03). There was no significant difference in mPFS for those patients developing G1/2 vs G3/4 irAEs (336.5 days vs 235.5 days, p=0.51). No differences were seen in mPFS when subtyping irAEs by organ type.

Table 1 Patient demographics of study population

	n=73	%
Sex		
Male	45	61.6
Female	28	38.4
Mean Age	65	
Performance Status		
0	12	16.4
1	48	65.8
2	3	4.1
Unknown	10	13.7
Histology		
Adenocarcinoma	48	65.8
Squamous	18	24.7
Other	5	6.8
Unknown	2	2.7
PD-L1 TPS		
<10%	6	8.2
10-50%	8	11.0
>50%	51	69.8
Unknown	8	11.0
Stage		
III	17	23.3
IV	56	76.7
EGFR		
Positive	2	2.7
Negative	53	72.6
Unknown	18	24.7
ALK		
Positive	0	0.0
Negative	53	72.6
Unknown	20	27.3
Mean number of cycles	10	



Conclusion: Pembrolizumab monotherapy was well tolerated, with many experiencing no irAEs (45%). In contrast to patients with no irAEs, having at least 1 irAE was associated with improved PFS possibly indicating a surrogate marker of better pharmacodynamics activity which will require validation from a larger cohort study. An association between severity of irAE and PFS was not seen.

Keywords: Toxicities, NSCLC, immunotherapy

MA13.07 GEMSTONE-302: A Phase 3 Study of Platinum-Based Chemotherapy with Placebo or Sugemalimab, a PD-L1 mAb, for metastatic NSCLC

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Introduction: Sugemalimab is a full-length, fully human PD-L1 targeted immunoglobin G4 (IgG4, s228p) mAb. GEMSTONE-302 is a randomized, double-blind, phase 3 study to evaluate the efficacy and safety of sugemalimab or placebo in combination with chemotherapy as first-line treatment in metastatic squamous (sq) or non-squamous (nsq) NSCLC. The PFS interim analysis data as of 08 June 2020 showed that sugemalimab plus chemotherapy demonstrated a clinically meaningful and statistically significant prolongation of PFS with a well-tolerated safety profile in metastatic NSCLC patients irrespective of tumor pathology and PD-L1 expression. Sugemalimab plus chemotherapy was also associated with higher ORRs and durable responses and an OS benefit trend. Here, we report the results from the final PFS analysis and an updated OS analysis of this study. To our knowledge, this is a data report from the first randomized, double-blind, phase 3 study of anti-PD-L1 monoclonal antibody plus platinum-based chemotherapy as first-line treatment for stage IV sq or nsq NSCLC. **Methods:** Patients with Stage IV NSCLC and measurable disease per RECIST v1.1, no prior systemic treatment, ECOG PS 0-1, wild-type EGFR or ALK were randomized 2:1 to sugemalimab or placebo in combination with chemotherapy. Randomization was stratified by subtype of NSCLC (sq vs. nsq), PD-L1 expression (≥1% vs. <1%), and ECOG PS (0 vs. 1). Patients received sugemalimab (1200 mg, IV, 4 cycles, Q3W) or placebo plus chemotherapy (sq-NSCLC: carboplatin, AUC=5, IV; paclitaxel, 175 mg/m2, IV. nsq-NSCLC: carboplatin, AUC=5, IV; pemetrexed, 500 mg/m2, IV), followed by maintenance therapy with sugemalimab or placebo in sq-NSCLC patients and sugemalimab or placebo plus pemetrexed in nsq-NSCLC patients (up to 35 cycles). The primary endpoint was investigator-assessed PFS. **Types of Analysis and Data Reporting: Results:** As of 15 March 2021, amongst the 479 patients enrolled, 79 (24.7%) vs 12 (7.5%) were still on treatment in the sugemalimab+chemotherapy and placebo+chemotherapy groups, respectively. The median follow-up duration was 17.8 and 17.5 months, respectively. Compared with placebo+chemotherapy, sugemalimab+chemotherapy continued to provide longer PFS (358 events, [99.4% of the final PFS analysis], median PFS 9.03 vs. 4.90 months, stratified HR 0.48 [0.39-0.60]) and OS (198 events [55.0% of the final OS analysis], median OS 22.83 vs. 17.68 months, stratified HR 0.67 [0.50-0.90]). Twelve-month PFS rates were 36.4% vs. 14.8% and 24-month OS rates were 47.1% vs. 38.1%. ORR per investigator was 63.4% in sugemalimab+chemotherapy group and 40.3% in placebo+chemotherapy group, median DoRs were 9.82 vs. 4.37 months, respectively. Clinical benefits were observed across all the subgroups including different pathologic types and PD-L1 expression levels. Incidences of Grade≥3 TEAEs were reported in 64.1% and 61.6% of patients in sugemalimab+chemotherapy and placebo+chemotherapy groups, respectively. No new safety signals were found. **Conclusion:** In this phase 3 trial, sugemalimab was associated with a statistically and clinically significant improvement in both PFS and OS when combined with standard chemotherapy in patients with Stage IV NSCLC. These improvements were consistent in patients regardless of PD-L1 expression status or histology (squamous and non-squamous). These results support sugemalimab+chemotherapy as a potential new treatment option as the first-line treatment of patients with metastatic NSCLC.

Keywords: NSCLC, a phase III trial, PD-L1 mAb

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MA13.08 CHOICE-01: A Phase 3 Study of Toripalimab Versus Placebo in Combination With First-Line Chemotherapy for Advanced NSCLC

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Introduction: Toripalimab, a humanized monoclonal antibody against PD-1, was approved for treatment of previously treated advanced melanoma and nasopharyngeal carcinoma. Here, we report the results of CHOICE-01 (NCT03856411), a randomized, double-blind Phase 3 trial of toripalimab in combination first-line chemotherapy for advanced non-small cell lung cancer (NSCLC). **Methods:** Patients with treatment-naïve, advanced NSCLC without EGFR/ALK driver mutations were randomized (2:1) to receive toripalimab 240 mg or placebo in combination with chemotherapy (paclitaxel plus carboplatin for squamous and pemetrexed plus cisplatin/carboplatin for non-squamous NSCLC) Q3W for 4-6 cycles, followed by toripalimab/placebo for squamous and toripalimab/placebo in combination with pemetrexed for non-squamous NSCLC until disease progression, intolerable toxicity, or completion of 2 years of treatment. Stratification factors included PD-L1 tumor expression status, histopathology and smoking status. Crossover to toripalimab was allowed for patients from the placebo arm upon disease progression. Progression-free survival (PFS) and response were assessed by the investigator and by a blinded independent review committee (BIRC) per RECIST v1.1. The primary endpoint was PFS by investigator. Secondary end points included PFS by BIRC, overall survival (OS), objective response rate (ORR), and duration of response (DOR). An interim analysis and a final analysis were planned at pre-specified PFS events. **Results:** A total of 465 NSCLC patients (220 squamous and 245 non-squamous) were randomized: 309 to the toripalimab arm and 156 to the placebo arm. As of Nov 17, 2020, with a median follow-up of 7.1 and 7.0 months in the two arms, 218 PFS events were observed. At the interim analysis, a significant improvement in PFS as assessed by investigator was detected for toripalimab over placebo (HR=0.58 [95% CI: 0.44-0.77], P=0.0001), with median PFS of 8.3 vs. 5.6 months. The 1-year PFS rates were 32.6% and 13.1%. A significant improvement in PFS was observed in both

squamous and non-squamous NSCLC and in PD-L1 expression subgroups. The HR was 0.55 (95% CI: 0.38-0.83) for squamous and 0.59 (95% CI: 0.40-0.87) for non-squamous NSCLC. PFS per BIRC had similar results. The ORR was 68.7% vs. 58.9% for squamous and 58.6% vs. 26.5% for non-squamous NSCLC and the median DOR was 6.9 vs. 4.2 months for squamous and 8.6 vs 5.1 months for non-squamous NSCLC in the toripalimab and placebo arms. As of March 7, 2021, OS data was immature with a trend favoring toripalimab: median OS 21.0 vs 16.0 months (HR=0.81 [95% CI: 0.57-1.17]). The incidence of Grade ≥3 adverse events (AEs) were 76.3% vs 80.1%; AEs leading to discontinuation of toripalimab/placebo were 12.3% vs 1.9%; and fatal AEs were 5.2% vs 1.3% in the toripalimab and placebo arms, respectively. **Conclusion:** The addition of toripalimab to standard 1st-line chemotherapy in patients with advanced NSCLC showed superior PFS and ORR and longer DOR than chemotherapy alone with a manageable safety profile. These results support the use of toripalimab with chemotherapy as 1st line therapy for NSCLC patients without driver mutations regardless of histologic subtypes.

Keywords: Toripalimab, anti-PD-1, 1st line treatment for NSCLC

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MA14.01 Distribution and Detectability of EGFR Exon 20 Insertion Variants in Non–Small Cell Lung Cancer

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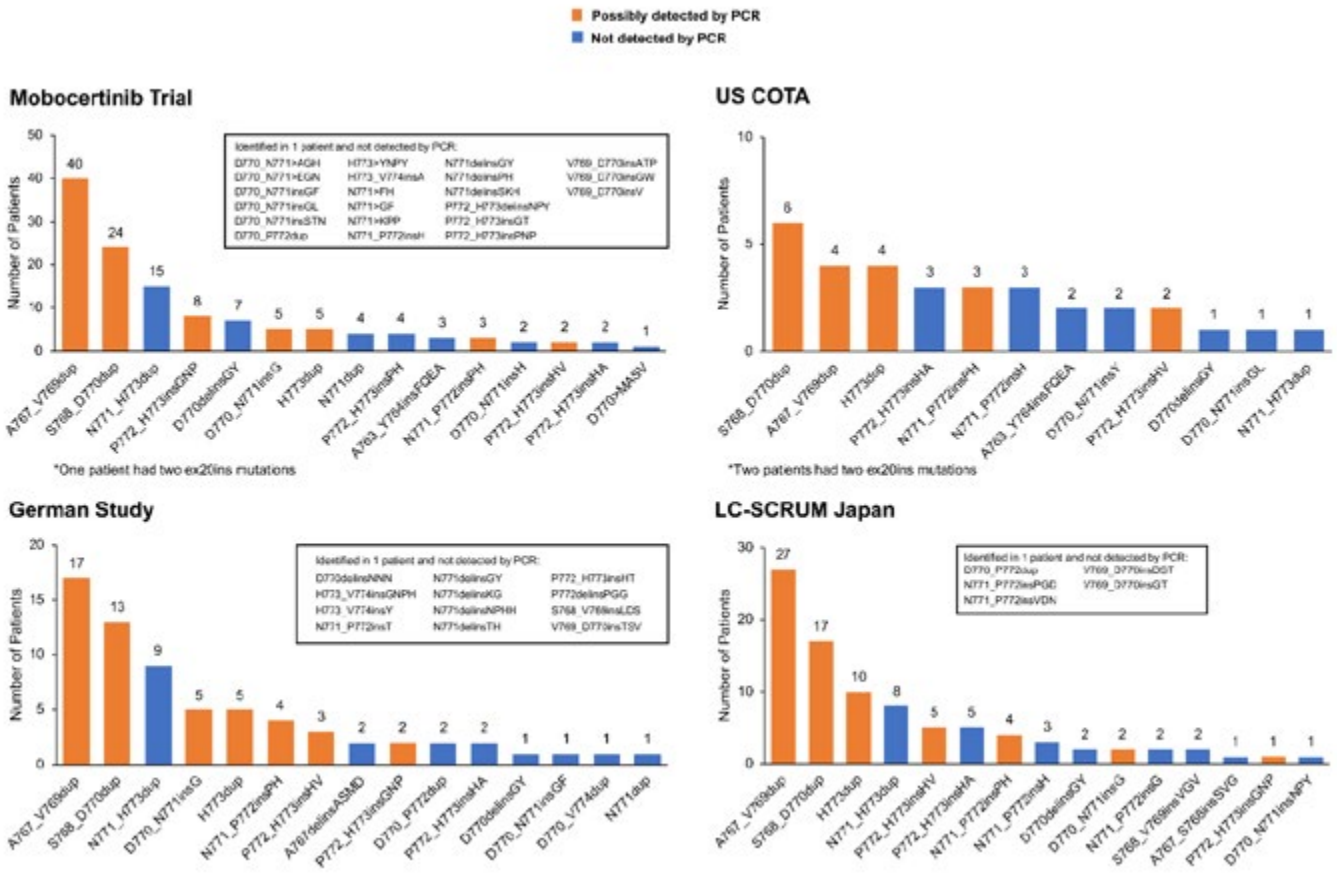
Introduction: The population of EGFR exon 20 insertion (ex20ins) mutations includes a diverse array of insertion variants and represents 5%-10% of EGFR mutations in non–small cell lung cancer (NSCLC). Specific targeted therapies are not available for patients with EGFR ex20ins+ NSCLC, regardless of insertion variant status; however, mobocertinib and amivantamab are currently in development. Identifying patients with EGFR ex20ins is challenging due to the limited coverage of polymerase chain reaction (PCR) assays and relatively recent use of next-generation sequencing (NGS). The detection of insertion variants will become more important as more drugs targeting EGFR exon 20 are being developed. Here we describe the distribution of EGFR ex20ins variants in NSCLC patients in a global clinical trial and real-world data in the United States, Germany, and Japan, and evaluate the ability of PCR versus NGS to identify EGFR ex20ins in NSCLC. **Methods:** A retrospective analysis was conducted in NSCLC patients whose EGFR ex20ins were identified by NGS/sequencing testing from a global mobocertinib trial (NCT02716116; n=145) and 3 real-world data sets: US COTA Electronic Health Record database (n=30; data cutoff 30Nov2020), chart review study across 12 academic sites in Germany (n=80), and Japanese genome screening project (LC-SCRUM-Japan; n=95; data cutoff 31Dec2019). Frequencies and percentages were calculated for each unique variant. Proportions of patients with EGFR ex20ins variants identifiable by 6 commercially available PCR kits are projected based on manufacturer-provided coverage information. **Results:** A total of 58 unique EGFR ex20ins variants were identified in this study, 36 of which were found in the mobocertinib trial, 12 variants in COTA, 27 variants in the German study, and 20 variants in LC-SCRUM. The most common variants were A767_V769dup and S768_D770dup, accounting for 33% to 46% of patients across data sets (**Figure**). Of 58 EGFR ex20ins variants, only 7 variants could have been identified by PCR tests. These PCR tests are projected to detect only 12.4% to 51.0% of patients in the trial, 13.3% to 46.7% in US COTA, 17.5% to 50.0% in the German data set, and 21.1% to 58.9% in Japan LC-SCRUM.



Conclusion: Although commonly used in clinical diagnosis, PCR has limited coverage for detecting EGFR ex20ins. It is projected that commercially available PCR kits could have missed >40% of patients with NSCLC harboring ex20ins. Given the diverse profile of EGFR ex20ins variants, NGS-based genetic testing can substantially improve their identification in NSCLC.

Keywords: exon20 insertion, next-generation sequencing, polymerase chain reaction

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MA14.02 RET Fusion Testing in Advanced Non-Small Cell Lung Carcinoma Patients: the RETING Study

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Introduction: The approval of selective RET inhibitors for patients with advanced RET fusion positive non-small cell lung carcinoma (NSCLC) means that the importance of accurately identifying those patients has never been greater. Due to the co-existance of single-gene testing and next-generation sequencing (NGS), we hypothesized that a comparison of RET fusions testing assays is urgently needed. Along those lines, the performance of RET immunohistochemistry (IHC) and RET fluorescence in situ hybridization (FISH) has recently been challenged. **Methods:** Physicians across 17 hospitals contributed to identify patients with RET fusion positive NSCLC as part of routine clinical care. In addition, RET fusion negative samples from NSCLCs diagnosed at the referral institution were also included. All tumors underwent targeted RNA-based NGS (Oncomine Comprehensive Assay v3), break-apart RET FISH (Vysis) with an automated scanning system (BioView), and RET IHC (clone EPR2871, Abcam). The material available for all tumors had been formalin-fixed and paraffin-embedded. Only cases with enough tissue available (i.e. a minimum of 50 tumor cells, as per FISH test requirements) and sufficient sequencing coverage after NGS were included. FISH and IHC results were interpreted by using previously described criteria. The NGS result was used as the gold-standard. **Results:** Analyses by the three assays was succesful in all 80 tumors. Thirty-seven RET-positive samples and 43 RET-negative NSCLCs were identified. Signet ring cells and psammomatous calcifications were frequently observed in RET-positive samples (in 30% and 27% of tumors, respectively). The most common partners were KIF5B (29/37, 78%), followed by CCDC6 (6/37, 16%). Other partners included NCOA4 (1/37, 3%) and AKAP13 (1/37, 3%). Thirty-five out of the 37 (95%) NGS-positive samples were FISH-positive (86% with a split pattern and the remaining 14% with a single 3' signal pattern). Six of those FISH-positive cases (6/35, 17%) displayed very challenging split signals (≤2 signal diameter). The two FISH-negative samples were KIF5B-RET variants that showed a narrow split (≤1 signal diameter) in 36% and 38% of tumor cells, respectively. All 43 NGS-negative tumors were also FISH-negative. Regarding RET IHC, all NGS-positive cases showed cytoplasmic staining with a mean H-score of 210 (median 210, range 5-300). Within the NGS-negative cohort, cytoplasmic staining was observed in 8 cases (19%), with a mean H-score of 9 (median 0, range 0-150). Interestingly, the two RET FISH-negative but NGS-positive samples showed relevant IHC positivity (H-score of 165 and 255, respectively). **Conclusion:** The most frequent partner in this large multicenter series of RET fusion positive NSCLCs was KIF5B. The concordance between RNA-based NGS and FISH was high, with 0% failure rate. However, the interpretation of RET FISH is very challenging due to the frequent occurrence of narrow split signals (22% in this series). RET IHC should be investigated further as an alternative method to resolve an equivocal FISH or NGS result. **Funding** This study was mainly funded by Lilly. We also thank Instituto de Salud Carlos III (ISCIII) (Fondos FEDER and Plan Estatal I+D+I 2008–2011 [PI11/02866] and 2013–2016 [PI14-01176 y PI17-01001]) and the iLUNG Program (B2017/BMD-3884) from the Comunidad de Madrid.

Keywords: lung carcinoma, Biomarker, RET

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MA14.03 Genomic Profiles and Potential Determinants of Response and Resistance in KRAS p.G12C-mutated NSCLC Treated With Sotorasib

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Introduction: Sotorasib is a first-in-class small molecule that specifically and irreversibly inhibits $KRAS^{G12C}$. In the registrational phase 2 CodeBreaK 100 trial, sotorasib showed an objective response rate (ORR) of 37.1% and a median progression-free survival (PFS) of 6.8 months in patients with KRAS p.G12C-mutated non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy and/or immunotherapy. Response to sotorasib has been observed across co-occurring mutational profiles. Here, we report preliminary data on the genomic profiles and potential determinants of response to sotorasib from an exploratory analysis of this trial. **Methods:** Baseline tissue samples were collected and analyzed for genomic alterations in KEAP1, the upstream RTK pathway, and the downstream PI3K/AKT/mTOR and MAPK pathways. Patients were categorized into the following 3 groups: early progressors (patients with an event of progressive disease and PFS of <3 months), late progressors (patients with an event of progressive disease and PFS of ≥ 3 months), non-progressors (patients with no event of progressive disease and PFS of ≥ 3 months). **Results:** A total of 126 patients were enrolled into the phase 2 trial. 65 patients with available data from baseline tissue samples were categorized per methods: 22 early progressors, 23 late progressors, and 20 non-progressors. 11 of the 65 patients had KEAP1 mutations (7 in the early progressor group, 2 in the late progressor group, and 2 in the non-progressor group). In the early progressor group, we observed mutations in EGFR, FGFR, PDGFR, RET, and MET, which were also identified in other groups. Among the patients with mutations in the MAPK pathway genes, the late progressor group was the most prevalent (43%, n=6), followed by early progressor (29%, n=4) and non-progressor (29%, n=4). Among patients with mutations in genes of the PI3K/AKT/mTOR pathway, late progressor and early progressor groups were the most prevalent (36%, n=9, each), followed by non-progressor group (28%, n=7) (summary **Table** below).

Number of patients with mutations	**Early progressors n (%)**	**Late progressors n (%)**	**Non-progressors n (%)**	**Total N (%)**
PI3K/AKT/mTOR pathway	9 (36)	9 (36)	7 (28)	25 (100)
MAPK pathway	4 (29)	6 (43)	4 (29)	14 (100)

Conclusion: In this descriptive biomarker analysis of baseline tissue specimens from the phase 2 CodeBreaK 100 trial of sotorasib in KRAS p.G12C-mutated NSCLC, diverse mutation patterns were observed. No unique genomic profiles were identified in patient groups. The presence of KEAP1 mutation was observed across all groups and was more prevalent in early progressors. These findings warrant further investigation of the longitudinal cfDNA dynamics in patients receiving sotorasib.

Keywords: biomarkers, sotorasib (AMG 510), KRAS p.G12C NSCLC

MA14.05 Clinicopathologic and Genomic Significances of the Amount of High-Grade Histologic Components in Lung Adenocarcinoma

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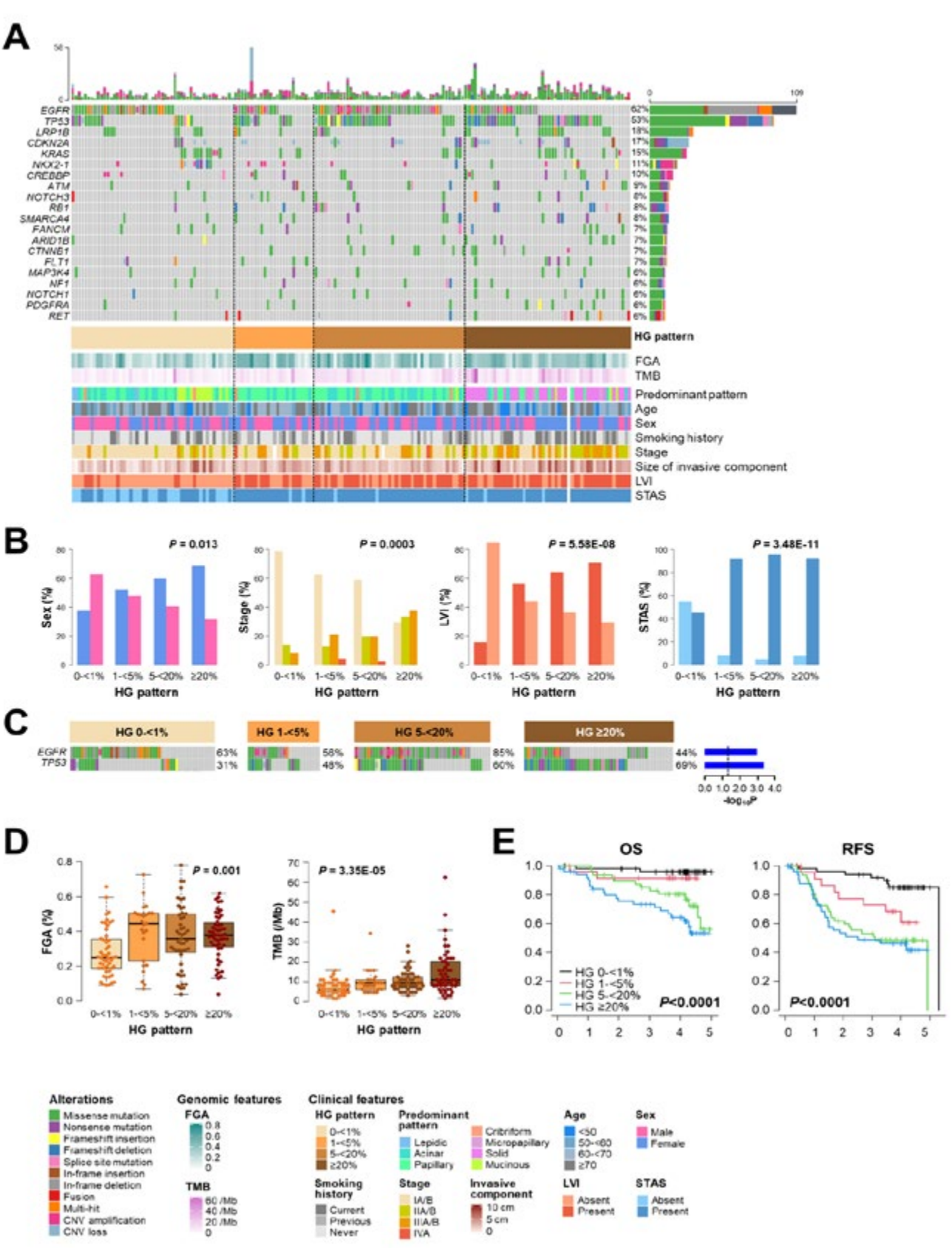
Introduction: Recent proposal of grading system for lung adenocarcinoma (LUAD) from the pathology committee of International Association for the Study of Lung Cancer emphasizes the amount of high-grade components (HGC) in the prognostic stratification of LUAD. Underlying pathobiologic features supporting the biologic significance of HGC in LUAD has not been fully evaluated yet. **Methods:** A total of 175 cases of surgically resected LUAD from January to December 2015 in Asan Medical Center were histologically evaluated. Proportions of HGCs, including solid, micropapillary, and cribriform patterns, were individually quantified, and cases were classified by the cutoff of 1, 5, and 20% according to the summated proportion of HGCs. Genomic features including the mutational profile, fraction of genome altered (FGA), and tumor mutation burden (TMB), were analyzed from the correspondent targeted next generation sequencing dataset and correlated with the HGC class. **Results:** About 14% (25/175), 27% (47/175) and 30% of the cases (52/175) had 1-<5%, 5-<20% and ≥20% of HGCs, respectively (Figure 1A). Frequencies of lymphovascular invasion was proportionally elevated when the HGCs components were elevated (P<0.0001). Remarkably, >90% of the cases harboring ≥1% of HGCs had spread-through alveolar space (STAS) (P<0.0001). The pathological stage was also elevated in all three groups with HGCs (P<0.0001) (Figure 1B). Comparison of the mutational profile revealed that the rates of EGFR mutation were significantly diminished in HGC ≥20% group only, but TP53 mutation rates were proportionally elevated when the HGCs were elevated (P = 0.001) (Figure 1C). Furthermore, FGA and TMB rates were elevated in all three groups with HGC ≥1% (FGA, P = 0.001; TMB, P<0.0001) (Figure 1D). On univariate survival analysis, both groups with HGC 5-<20% and ≥20% showed significantly inferior overall and recurrence-free survivals with similar survival lengths; HGC 1-<5% groups showed intermediate prognosis (Figure 1E). On multivariate survival analyses, HGC 5-<20% and ≥20% groups were independently associated with poor OS, but only HGC 5-<20% group was statistically significant in comparison with RFS. **Conclusion:** The clinicopathological characteristics and genomic alterations were significantly different even when ≥1% of the HGCs were accompanied in LUAD. Furthermore, both groups with 5-<20% and ≥20% of HGCs correlated with inferior survival outcomes with similar level, which implicates the clinicopathologic and genomic significance of minor HGCs in LUAD.



Keywords: Lung adenocarcinoma, Next Generation Sequencing, High-grade histologic component

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MA14.06 High Tumor Mutation Burden Predicts Unfavorable Clinical Outcome in EGFR-Mutated Lung Adenocarcinoma Treated With Targeted Therapy

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Introduction: Although high tumor mutation burden (TMB) has shown association with benefit from immune checkpoint blockade therapies, its implications in lung cancer patients with driving mutations are still unclear. The objective of this study is to determine the association between TMB and treatment outcome in epidermal growth factor receptor (EGFR)-mutated lung cancer treated with tyrosine kinase inhibitors (TKIs). **Methods:** We evaluated TMB in EGFR-mutant, lung adenocarcinoma patients who received first-line EGFR-TKIs. TMB was estimated by next-generation sequencing with a cancer gene panel (Ion AmpliSeq Comprehensive Cancer Panel). We compared the response rate (RR), progression-free survival (PFS), overall survival (OS), and frequency of secondary T790M mutation according to the different TMB groups. **Results:** Among the 131 patients who were treated with EGFR-TKIs, a total of 63 patients were eligible for the analysis. TMB was stratified by tertiles; low (≤2.13 mutations/Mb), intermediate (2.14–4.25 mutations/Mb), and high (>4.25 mutations/Mb). The TMB levels were not associated with any clinical parameters. The RR was significantly lower in the high TMB group than in the other groups (43.5% vs. 72.1% vs. 78.5%, all p = 0.01). In multivariate analysis, high TMB was independently associated with a shorter PFS in the overall population (hazard ratio [HR] = 2.64, p = 0.004), and associated with shorter OS in patients with exon 19 deletion (HR = 2.55, p = 0.041) compared with low TMB. The frequencies of secondary T790M mutation after TKI failure were not different among the different TMB groups. **Conclusion:** High TMB was associated with unfavorable clinical outcome in patients with lung adenocarcinoma treated with EGFR-TKIs. Although further large-scaled studies are required, our data suggest that high TMB may be a predictive biomarker for adverse treatment outcomes and may constitute a distinct subgroup warranting tailored therapeutic approach in this clinical setting.

Keywords: tumor mutation burden, EGFR-TKI, predictive biomarker

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MA14.07 EGFR-Mutant NSCLC With de novo or Acquired Squamous Histology: Molecular Features and Clinical Outcomes

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Introduction: Activating EGFR mutations occur predominantly in lung cancers with adenocarcinoma histology but can rarely be found in squamous tumors. Histologic "transformation" from adenocarcinoma to squamous is also seen at acquired resistance to EGFR TKIs. While squamous transformation may potentially be a driver of resistance, the biological characteristics of and treatment recommendations for squamous histology in the setting of EGFR-mutant NSCLC remain incompletely understood. **Methods:** We retrospectively identified patients seen at Massachusetts General Hospital between 2002-2021 with EGFR-mutant NSCLC demonstrating features of squamous histology on at least one biopsy. Cases were categorized into one of three groups: 'de novo squamous' (purely squamous at initial diagnosis), 'adenosquamous' (at least one biopsy demonstrating components of both adenocarcinoma and squamous histology in the same specimen, anytime in the disease course), and 'transformed' (adenocarcinoma histology at initial diagnosis with subsequent complete squamous transformation). All patients had at least one biopsy independently reviewed, and 8/10 transformed patients had both pre- and post-transformation biopsies independently reviewed by a staff pathologist. Demographics, molecular characteristics, and clinical outcomes were analyzed. **Results:** Among 565 EGFR-mutant NSCLC cases reviewed, 20 met study criteria and had archival tissue available for pathology review. Among them, 5 (25%) were classified as de novo squamous, 5 (25%) as adenosquamous, and 10 (50%) as transformed. For the transformed subgroup, 7/10 underwent transformation after first-line TKI therapy. Genotyping was available at progression on 8/10 transformed samples: 2 had EGFR T790M (both acquired) and 3 had MET amplification (1 acquired, 2 not tested at baseline); 3 had no additional resistance mechanisms. In addition, one patient had a biopsy showing T790M+ adenocarcinoma within 30 days of the biopsy showing squamous transformation. Post-transformation, 3/10 were treated with third-generation EGFR TKIs (2 T790M+), yielding a median treatment duration of 3.4 months (range 1.4-11.6), 4/10 received taxane-based chemotherapy with a median treatment duration of 10.5 months (range 0.9-13.8), and 1/10 received pemetrexed-based chemotherapy with treatment duration of 2 months. Among all 20 patients, median overall survival (mOS) from time of diagnosis was 31.5 months (95% CI [11.8-49.9]), and among transformed cohort, mOS from time of squamous transformation was 13.5 months (95% CI [0-18.6]).

Table 1. Summary of Cohort Demographics and Clinical Outcomes.

			De novo squamous	Adenosquamous	Transformed
Total N			5	5	10
Demographic Information					
	Age, Median (Range)		60 (59-63)	58 (57-76)	59 (43-76)
	Sex, No. (%)	Female	4 (80)	2 (40)	4 (40)
		Male	1 (20)	3 (60)	6 (60)
	Race, No. (%)	White	4 (80)	3 (60)	5 (50)
		Black	0 (0)	0 (0)	1 (10)
		Asian	1 (20)	1 (20)	2 (20)
		Other (or not available)	0 (0)	1 (20)	2 (20)
	Smoking History, No. (%)	Never smoker	2 (40)	2 (40)	7 (70)
		<10 pack-year smoker	3 (60)	0 (0)	2 (20)
		>10 pack-year smoker	0 (0)	3 (60)	1 (10)
	Founder EGFR Mutation	Exon 19 Deletion	2 (40)	2 (40)	6 (60)
		L858R	2 (40)	2 (40)	4 (40)
		Other (or not available)	1 (20)	1 (20)	0 (0)
	Co-occurring Resistance Mechanism at Transformation	EGFR T790M	N/A	N/A	2 (20)
		MET amplification	N/A	N/A	3 (30)
Treatment History					
	First-line treatment, No. (%)	1st- or 2nd- gen EGFR TKI	4 (80)	4 (80)	8 (80)
		3rd-gen EGFR TKI	0 (0)	1 (20)	2 (20)
	Post-Transformation Treatment, No. (%)	Carbo/taxol	N/A	N/A	4 (40)
		Carbo/pem	N/A	N/A	1 (10)
		3rd-gen EGFR TKI	N/A	N/A	3 (30)
		MET inhibitor monotherapy	N/A	N/A	1 (10)
Clinical Outcomes					
	Duration of 1st Line Therapy, Median (Range)		8.1 mos (5.1-95.8)	6.2 mos (1.5-16.5)	11.1 mos (8.1-31.9)
	Overall Survival, Median (95% CI)		12.0 mos (9.9-NR)	14.3 mos (7.4-NR)	47.8 mos (11.1-50.6)
	Time to Squamous Transformation, Median (Range)		N/A	N/A	28.3 mos (8.5-70.7)
	Survival From Transformation, Median (95% CI)		N/A	N/A	13.5 mos (0-18.6)

Conclusion: Our findings confirm the rarity of squamous transformation in EGFR-mutant cancers and suggest that co-occurring genetic drivers of resistance may be common, in distinction from SCLC transformation. Further study is needed to investigate histologic transformation in acquired resistance. Chemotherapy tailored to squamous tumors may be beneficial, though prospective trials are needed.

Keywords: EGFR, NSCLC, Squamous

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

MA15.01 Machine Learning for Prediction of Survival and Risk of Mortality in Patients with Lung Cancer Undergoing Resection

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Introduction: Machine learning predictive modelling has shown promising potential in subserving medical decision-making processes. In the present study, artificial intelligence tools were designed aiming the evaluation of surgical risk related to lung resection with curative intent in individual oncologic patients. The main objectives were to develop and validate a high-precision model for prediction of survival and risk of mortality. **Methods:** Data from 1131 patients with lung cancer who underwent lung resection with curative intent, collected from the Registro Paulista de Tratamento Cirúrgico de Câncer de Pulmão database, was employed to develop, train, and validate two machine learning models. 75% of the data (848 patients) was used as a training dataset , whereas the remaining 25% (283 patients) was used as a validation dataset. Previously to training, missing data was treated with simple imputation. The independent variables were selected based on univariate statistical methods such as cox regression and/or significance of log rank p-value. A Random Forest classification model was used for the 90-day mortality prediction model. This model had the occurrence of death within 90 days after surgery as target variable, and the predictor variables were age, gender, smoking, smoking burden, BMI, ASA, ECOG, occurrence of cardiac comorbidity, occurrence of coronary artery disease or acute myocardial infarction, current treatment for congestive heart failure, current treatment for hypertension, occurrence and type of previous solid malignant disease, occurrence of the main lesion in the right upper lobe, occurrence of the main lesion in the right upper lobe bronchus, cT (8th edition), occurrence of pleural invasion found on imaging, lymph node uptake on PET scan, and type of access to be performed. Only preoperative variables or those susceptible to planning were considered. A Random Forest Survival model was used for the survival prediction model. This model had long-term follow-up status (death or censoring) as target variable, and the predictor variables were the same as described above combined with primary lung neoplasm subtype (WHO 2015), degree of differentiation, presence of vascular invasion, occurrence of lymphatic invasion, occurrence of extracapsular involvement, free resection margins, pT (8th edition) and pathological TNM (8th edition). **Results:** For the 90-day mortality prediction model, the AUC achieved was 0.7, with an F1 score of 0.919. For the survival prediction model, the concordance index (C-Index) and the time-dependent AUC were evaluated. The performance obtained was C-Index of 0.722 and the average AUC was 0.751 for the first 110 days after surgery and 0.739 for the first 5,500 days after surgery. **Conclusion:** Both models presented AUC ≥ 0,70, and thus their performance was evaluated as satisfactory. Nonetheless, a progressive improvement is expected as more comprehensive training datasets are applied. Refined models may aid substantially in the decision between the several treatment options available for early-stage lung cancer. Moreover, the models may be converted into an online tool geared towards and accessible to all medical community.

Keywords: machine learning, Risk prediction, thoracic surgery

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

MA15.02 Association of Healthcare System Resources With Lung Cancer Screening Utilization

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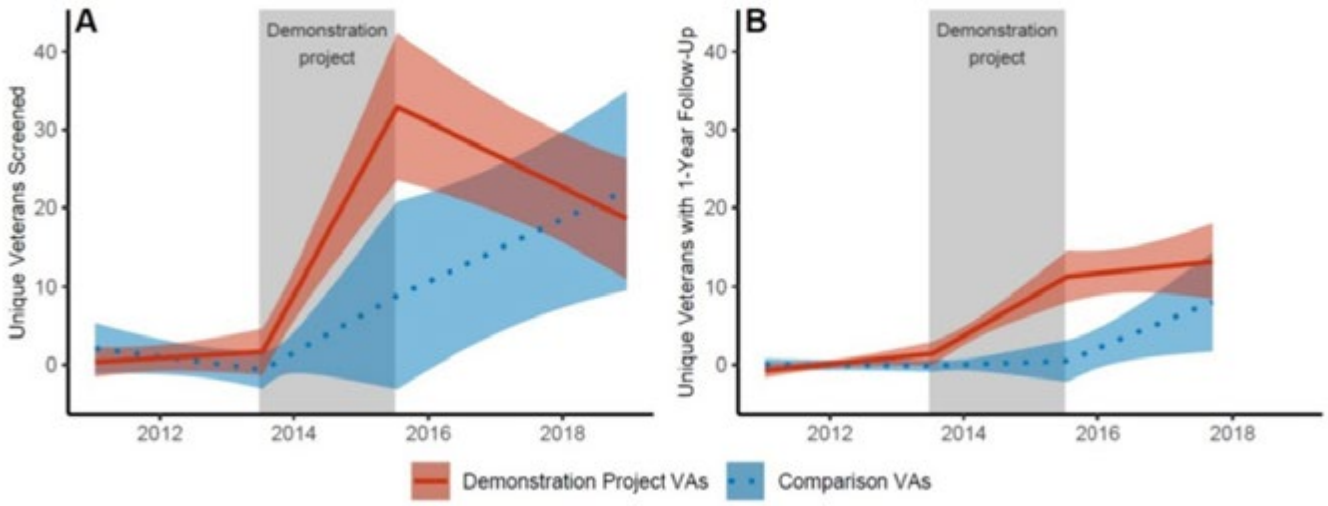
Introduction: The Veterans Health Administration (VHA) is the largest integrated healthcare system in the United States and serves 9 million Veterans. VHA issued resources from 2013-2015 including screening coordinators, a tracking system, clinical reminders, educational tools, management guidelines, and a national support network to 8 Veterans Affairs medical centers (VAMCs) as part of a demonstration project (DP). The association of healthcare system resources with lung cancer screening utilization is unknown at a national level. We hypothesized that VAMCs with healthcare system resources had higher screening rates than similar VAMCs without resources. **Methods:** The Veterans Affairs Corporate Data Warehouse provided data from 8 VAMCs that participated in the DP (DP group) and 20 comparable VAMCs that applied but were not selected (comparison group). Time periods included Pre-DP (January 2011-June 2013), DP (July 2013-June 2015) and Post-DP (July 2015-December 2018). Co-primary outcomes were unique Veterans screened per 1,000 eligible Veterans per month and those with 1-year (9-15 month) follow-up screening. Eligible Veterans were estimated using yearly counts at each VAMC in combination with the percentage of age-appropriate Veterans with eligible smoking histories found in the DP. Controlled interrupted time series and difference-in-differences analyses were performed to determine the association of healthcare system resources over time. **Results:** During the DP, the average monthly rate of unique Veterans screened increased more rapidly in the DP group than in the comparison group (by 0.91 per 1,000 eligible per month; 95% confidence interval [CI] 0.23-1.59) for an average facility-level difference of 17.3 unique Veterans per 1,000 eligible per month (95% CI 12.4-22.1). The average monthly rate of unique Veterans screened with 1-year follow up also increased more rapidly in the DP group (by 0.39 per 1,000 eligible per month; 95% CI 0.18-0.60) for an average facility-level difference of 7.1 unique Veterans per 1,000 eligible per month (95% CI 5.1-9.1). These differences were not maintained after the DP time period.



Conclusion: Resources provided by the VHA during the DP were associated with an increase in Veterans screened and one-year follow up screening. Policies that provide healthcare system-level resources would likely increase lung cancer screening reach and sustainment over time.

Keywords: healthcare resources, lung cancer screening, utilization

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
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MA15.03 Social Factors Influencing the Length of Stay in Hospital After Anatomical Resection

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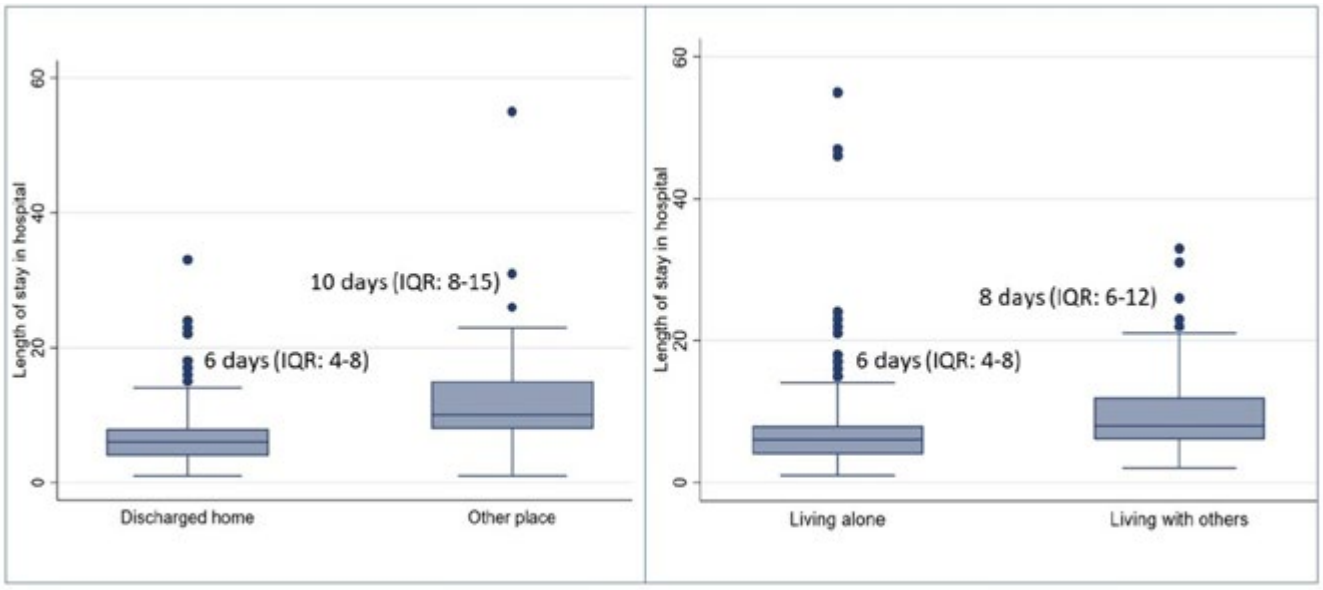
Introduction: Length of stay in hospital (LOS) is investigated in most surgical studies as quality of care measure. It represents a surrogate of procedures efficacy and safety, and it is used to compare operations or techniques. However, most studies take into consideration only clinical factors that might impair the post-operative course prolonging the LOS. The associations between social factors and post-operative outcomes is known, but not considered. We wanted to investigate whether social factors influence the LOS after anatomical lung resections for lung cancer, incorporating these non-clinical variables with established confounders, among complicated and non-complicated patients. Partial results of the study are presented at the 2021 European Society of Thoracic Surgeons meeting. **Methods:** Prospectively maintained databases on anatomical lung resections for lung cancer from two national centers, were retrospectively culled for data (January 2017-March 2021). Along with clinical factors (sex, age, performance status, FEV1, DLCO smoking status, Charlson Comorbidity Index, body mass index, surgical access, intercostal tube duration, complications), three social variables were included: living alone, place of discharge, educational level. Multiple linear regression analysis was used to determine variables that contributed to prolong LOS. Subgroup analyses were performed based on post-operative complications. **Results:** 328 consecutive patients were included. 273 lobectomies, 12 bilobectomies, 37 segmentectomies and 6 pneumonectomies were performed. Median LOS was 6 days (IQR:4-9). 119 patients (36.3%) experienced at least 1 complication (1 to 5 grade according to the Thoracic Morbidity and Mortality system). 107 patients (32.6%) lived alone, 74 (22.6%) were not discharged home (rehabilitations or other acute departments), 137 (41.8%) had an educational level below secondary school. FEV1 ($p=0.004$), chest tube duration ($p<0.0001$), performance status ($p=0.01$), surgical access ($p<0.0001$), presence of complications ($p<0.0001$), living alone ($p=0.001$) and place of discharge ($p<0.0001$) significantly influenced LOS. In the complicated group, FEV1 ($p=0.001$), intercostal tube duration ($p=0.02$), place of discharge (0.006) and living alone ($p=0.03$) were factors associated with LOS. In the non-complicated group, performance status ($p=0.001$), open approach ($p<0.0001$), intercostal tube duration ($p<0.0001$), place of discharge ($p<0.0001$) and living alone ($p=0.01$) remained associated with LOS. **Conclusion:** Social factors influence LOS after anatomical lung resections for lung cancer. LOS itself does not merely correspond to the effectiveness of surgical procedures, and its use as surrogate of quality of care should be carefully interpreted. Moreover, these results suggest the need for closer examination of patients background, anticipation and enhancement of post-surgical care (rehabilitation facilities) and may help directing health care investments in this sense.



Keywords: Lung resection, Social factors, Length of stay in hospital

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

MA15.05 Rates of Guideline-Concordant Surgery and Adjuvant Chemotherapy Among Patients in The U.S. ALCHEMIST Study (Alliance)

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Introduction: The standard of care for resectable non-small cell lung cancer (NSCLC) includes anatomic surgical resection with adequate lymph node dissection and adjuvant chemotherapy for appropriate patients. Historically, many patients with early-stage NSCLC have not received such guideline-concordant therapy. Longstanding disparities have also existed in the delivery of quality cancer care by sociodemographic factors such as race and ethnicity. This could impact interpretation of adjuvant therapy trials. In this descriptive analysis, we examined rates of guideline-concordant treatment among patients enrolled in ALCHEMIST, a large U.S.-wide screening trial to facilitate enrollment to targeted adjuvant treatment trials for resectable NSCLC, enrolling at 754 sites. **Methods:** Patients who enrolled in ALCHEMIST (Alliance A151216) from August 18, 2014-April 1, 2019 who did not enroll in a therapeutic adjuvant therapy clinical trial were included; these patients had stage IB-IIIA disease (AJCC 7th edition), with tumors at least 4 cm in size and/or positive lymph nodes. Four outcomes are reported: whether patients (1) had adequate lymph node dissection per National Comprehensive Cancer Network criteria (≥ one N1 nodal station plus ≥ three N2 nodal stations); (2) received any adjuvant chemotherapy; (3) received any cisplatin-based adjuvant chemotherapy; and (4) received at least 4 cycles of adjuvant chemotherapy. Associations between these binary outcomes and sociodemographic variables were explored using unadjusted modified Poisson regression models accounting for trial site-level correlation. **Results:** 2,834 patients were analyzed; 53.4% had adequate lymph node dissection; 57.1% received any adjuvant chemotherapy; 34.1% received any cisplatin-based adjuvant chemotherapy; and 43.7% received at least four cycles of adjuvant platinum-based chemotherapy. The distribution of treatment by key clinical and demographic characteristics is provided in Table 1; adjuvant chemotherapy was delivered more often to patients who were younger, had more advanced stage, had non-squamous NSCLC, and did not have EGFR-mutant tumors. Rates were similar across categories of race and ethnicity. **Conclusion:** Many patients with early-stage NSCLC did not receive adequate lymph node dissection or adjuvant chemotherapy despite indications for such treatment, even among patients who consented for testing to inform eligibility for an adjuvant therapy clinical trial. No substantial disparities in treatment were observed by race or ethnicity in this clinical trial cohort, contrary to historical patterns in population-based cohorts. Efforts are needed to optimize utilization of therapies with proven benefit for early-stage NSCLC. These results may inform the generalizability of clinical trials of novel therapies in the adjuvant setting. Support: U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); https://acknowledgments.alliancefound.org; Clinicaltrials.gov Identifier: NCT02194738

Keywords: lymph node dissection, adjuvant chemotherapy, ALCHEMIST

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
MONDAY, SEPTEMBER 13, 2021 - 18:45-19:45

MA15.06 Real World Trends in Treatment Patterns for Patients With Advanced NSCLC: Comparing Changes Between Younger and Older Adults

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Introduction: Care for older adults with cancer is complex as they often present with multiple comorbidities and polypharmacy, have poor performance status and limited social supports. These factors often lead to exclusion from standard therapy and clinical trials. In the past decade, treatment of NSCLC has changed due to novel therapeutics with improved tolerability due to lower adverse effect profile, leading to increased uptake of systemic therapy. The study goal is to compare the uptake of systemic therapy in adults with advanced NSCLC before and after the availability of targeted therapy and immunotherapy, and to examine the evolution in treatment patterns between younger and older adults. **Methods:** All patients with stage IV NSCLC referred to BC Cancer in 2009, 2011, 2015 and 2017 were included in the study. One-year time points were chosen based on molecular testing implementation and provincial formulary listing: baseline (2009), EGFR testing (2011), ALK testing (2015) and immunotherapy listing (2017). Age was categorized as younger (<70 years) and older (70+). Baseline demographics, disease characteristics and systemic therapy details (drug, duration, line of therapy) were collected retrospectively. Baseline characteristics will be compared by using descriptive statistics. Univariate analysis using the X^2 and Fisher's exact tests were used to compare age groups. Multivariate analysis was conducted using logistic-regression analysis.

Results:

Table 1. Comparison of systemic therapy uptake between adults <70 and 70+ years of age												
	2009			2011			2015			2017		
	<7 (n=315)	**70+ (n=271)**	**p-value**	**<70 (n=437)**	**70+ (n=366)**	**p-value**	**<70 (n=492)**	**70+ (n=534)**	**p-value**	**<70 (n=484)**	**70+ (n=522)**	**p-value**
Sex Female Male	148 (47%) 167 (53%)	131 (48%) 140 (52%)	0.80	219 (50%) 218 (50%)	175 (48%) 191 (52%)	0.52	265 (54%) 227 (46%)	267 (50%) 267 (50%)	0.24	251 (52%) 233 (48%)	245 (47%) 277 (53%)	0.13
ECOG Performance Statu at Diagnosis 0-1 2+ Unknown	117 (37%) 173 (55%) 25 (8%)	78 (29%) 168 (62%) 25 (9%)	0.1	187 (43%) 186 (43%) 64 (14%)	106 (29%) 205 (56%) 55 (15%)	<0.01	185 (38%) 240 (49%) 67 (13%)	137 (26%) 326 (61%) 71 (13%)	<0.01	169 (35%) 260 (54%) 55 (11%)	122 (23%) 330 (63%) 70 (13%)	<0.01
Histology Non-Squamous Squamous NOS	131 (42%) 33 (10%) 151 (48%)	94 (35%) 52 (19%) 125 (46%)	0.01	285 (65%) 59 (14%) 93 (21%)	215 (59%) 64 (17%) 87 (24%)	0.14	329 (67%) 73 (15%) 90 (18%)	310 (58%) 83 (16%) 141 (26%)	0.01	312 (65%) 59 (12%) 113 (23%)	311 (60%) 61 (12%) 150 (29%)	0.15
Treatment Type Best Supportive Care Chemotherapy only Any line targeted therapy Any line immunotherapy	176 (56%) 136 (43%) 2 (0.6%) 1 (0.3%)	210 (78%) 60 (22%) 1 (0.4%) 0	<0.01	206 (47%) 196 (45%) 33 (8%) 2 (0.5%)	276 (75%) 66 (18%) 22 (6%) 2 (0.5%)	<0.01	244 (50%) 159 (32%) 65 (13%) 24 (5%)	386 (72%) 95 (18%) 43 (8%) 10 (2%)	<0.01	234 (48%) 66 (14%) 88 (18%) 96 (20%)	370 (71%) 46 (9%) 50 (10%) 56 (11%)	<0.01
Lines of Therapy No treatment 1 line of therapy 2 lines of therapy 3 or more lines of therapy	176 (56%) 58 (18%) 43 (14%) 38 (12%)	210 (78%) 29 (11%) 16 (6%) 16 (6%)	<0.01	206 (47%) 86 (20%) 74 (17%) 71 (16%)	276 (75%) 44 (12%) 30 (8%) 16 (4%)	<0.01	244 (50%) 153 (31%) 56 (11%) 39 (8%)	386 (72%) 99 (19%) 29 (5%) 20 (4%)	<0.01	234 (48%) 118 (24%) 81 (17%) 51 (11%)	370 (71%) 97 (19%) 38 (7%) 17 (3%)	<0.01

Patients with EGFR mutation were 0.5%, 7%, 9%, and 12%; and ALK fusion were 0%, 0.1%, 2%, and 2% in 2009, 2011, 2015, and 2017 respectively.

Table 2. Multivariate analysis of the comparison of systemic therapy uptake between adults <70 and 70+ years of age; controlling for sex and ECOG performance status				
	<70 years		**70+ years**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
2009 2011 2015 2017	(Reference) 1.36 (1.00 – 1.86) 1.30 (0.96-1.76) 1.44 (1.06-1.95)	0.05 0.09 0.02	(Reference) 1.16 (0.78-1.72) 1.47 (1.03-2.12) 1.66 (1.16-2.40)	0.46 0.37 0.01

Conclusion: There has been an increased uptake of systemic therapy with the advent of novel therapeutics across all age groups. A significant proportion of older adults receive only best supportive care, likely influenced by poor performance status at presentation. With the introduction of new systemic therapy options including targeted and immunotherapy, more older adult patients are receiving treatment, narrowing the therapeutic gap with their younger cohort.

Keywords: Geriatric Oncology, Systemic Therapy, Real World Data

MA15 REAL WORLD FACTORS AFFECTING LUNG CANCER OUTCOMES
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MA15.07 Survival Benefit From Immunocheckpoint Inhibitors in Stage IV Non-small Cell Lung Cancer Patients ≥75 Years Old of Age

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This abstract is under embargo until September 13 at 09:00 Mountain Time.

MA16 SCLC: NEW TARGETS, BIOMARKERS, AND SYSTEMIC THERAPIES
MONDAY, SEPTEMBER 13, 2021 - 20:00-21:00

MA16.01 Subsequent Systemic Therapy After Lurbinectedin Discontinuation in Patients With Small-cell Lung Cancer

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Introduction: Lurbinectedin, a selective inhibitor of oncogenic transcription, was approved on June 15, 2020 by the US Food and Drug Administration for the treatment of adult patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Accelerated approval was based on a single-arm, open-label, phase 2 basket trial (NCT02454972). In the basket trial, lurbinectedin achieved a 35.2% overall response rate (ORR) and 9.3-month median overall survival (OS). Here, we report baseline characteristics and outcomes with lurbinectedin during the basket trial in the subset of patients who received subsequent systemic therapy. **Methods:** Adults (aged ≥18 years) with SCLC Eastern Cooperative Oncology Group performance status ≤2 and ≤1 previous platinum-containing chemotherapy regimen were eligible. Patients received lurbinectedin 3.2 mg/m^2 intraveneously once every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed ORR. **Results:** As of January 15, 2019, 47/105 (45%) patients treated with lurbinectedin received further systemic therapy after progression (1 agent: 15/47 [32%]; 2 agents: 12/47 [26%]; ≥3 agents: 20/47 [43%]). Median (range) age was 59 (44, 83) years, with 26% aged ≥65 years; 5 patients received prior immunotherapy (IO). The most common agents used as subsequent therapy were carboplatin (34%), etoposide (32%), paclitaxel (28%), and topotecan (28%); 15% received subsequent IO. Most patients with platinum-sensitive disease with chemotherapy-free interval (CTFI) between first-line platinum-based chemotherapy and lurbinectedin ≥90 days and ≥180 days received subsequent systemic therapy (31/60 [52%] and 13/20 [65%], respectively); of these patients, roughly half received further platinum-based therapy (CTFI ≥90 days: 15/31 [48%]; CTFI ≥180 days: 7/13 [54%]). Efficacy data are summarized in the **Table**. Platinum-sensitive patients with CTFI ≥90 days who received further platinum-based therapy had a median OS from the first lurbinectedin infusion of 15.9 months (12-month survival: 70.7%); those with CTFI ≥180 days had a median OS of 17.7 months (12-month survival: 100.0%). Grade ≥3 treatment-emergent adverse events (TEAEs) and serious TEAEs were reported in 20 (42.6%) and 8 (17.0%) patients receiving further systemic therapy, respectively; 1 patient discontinued treatment due to TEAE. **Conclusion:** A large proportion of patients were able to receive further therapy after progression on lurbinectedin with a promising OS, especially in platinum-sensitive patients who received further platinum-based therapy. These findings suggest lurbinectedin may extend the platinum-free interval in patients with platinum-sensitive disease; however, small sample sizes preclude firm conclusions at this time.

Table. Efficacy With Lurbinectedin

	Subsequent therapy (n = 47)	No subsequent therapy (n = 58)	All patients (N = 105)
ORR, n (%)	18 (38.3)	19 (32.8)	37 (35.2)
Median duration of response (95% CI), mo	5.5 (2.9, 6.4)	5.3 (3.5, 9.1)	5.3 (4.1, 6.4)
Median OS (95% CI), mo	11.9 (7.6, 14.9)	7.3 (4.3, 9.7)	9.3 (6.3, 11.8)

ORR, overall response rate; CI, confidence interval; mo, months; OS, overall survival.

Keywords: post-platinum chemotherapy, lurbinectedin, Small-cell lung cancer

MA16 SCLC: NEW TARGETS, BIOMARKERS, AND SYSTEMIC THERAPIES
MONDAY, SEPTEMBER 13, 2021 - 20:00-21:00

MA16.02 Platinum-Doublets as Second-Line Treatment for Relapsed Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Introduction: Second-line chemotherapy regimens for patients with relapsed small-cell lung cancer are very limited. In real world practice, re-challenge chemotherapy with first-line platinum-doublets has been commonly used in addition to topotecan or amrubicin monotherapy. However, whether platinum-doublet chemotherapy is an appropriate option as second-line treatment remains unclear. Data to generalize the efficacy of platinum-doublet chemotherapy as second-line treatment in comparison with the monotherapy regimens were of high interest. **Methods:** Studies that enrolled relapsed small-cell lung cancer and compared platinum-doublets with non-platinum-based regimens for second-line treatment were identified using electronic databases (PubMed and EMBASE) in September 2020. A meta-analysis was conducted to calculate the relative risk (RR) of objective response rate and disease control rate of the second-line chemotherapy. Subgroup analyses were conducted to focus on comparison with standard second-line regimens and sensitive relapse. Progression-free survival, overall survival and adverse events were systematically reviewed. **Results:** Based on the criteria, ten studies published between 2011 and 2020 were included in our analysis with a total of 1,222 patients: 438 treated with platinum-doublets and 784 with non-platinum-based regimens. The objective response rates for second-line platinum-doublet and non-platinum regimens were 47.3% [95% confidence interval (CI): 40.5-54.0] and 31.5% [95% CI: 22.2-40.8], respectively._Patients treated with platinum-doublets had a significantly higher objective response rate than patients with non-platinum-based regimens (RR [95% CI]: 1.527 [1.100-2.121], p=0.011), as well as disease control rate (RR [95% CI]: 1.152 [1.052-1.262], p=0.002). In a subgroup analysis comparing platinum-doublets with topotecan or amrubicin, patients treated with platinum-doublets had significantly higher objective response rate and disease control rate (RR [95% CI]: 1.663 [1.055-2.619], p=0.028 and 1.170 [1.021-1.340], p=0.023 respectively). Progression-free and overall survival appeared consistent with the tumor responses. Adverse events associated with platinum-doublets appeared acceptable compared with the monotherapies. **Conclusion:** Platinum-doublet chemotherapy as second-line treatment for patients with relapsed small-cell lung cancer can be considered as a reasonable option in comparison with non-platinum regimens.

Keywords: Small-cell lung cancer, Second-line treatment, Platinum-doublet

MA16 SCLC: NEW TARGETS, BIOMARKERS, AND SYSTEMIC THERAPIES
MONDAY, SEPTEMBER 13, 2021 - 20:00-21:00

MA16.03 CRISPR Screen Reveals XPO1 as a Therapeutic Target Strongly Sensitizing to First and Second Line Therapy in Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is an exceptionally aggressive disease comprising 13% of all lung cancer cases. With limited treatment options that typically result in transient responses, SCLC is responsible for approximately 250,000 deaths globally per year. The recent addition of immunotherapy to first-line platinum-based doublet chemotherapy appears to benefit only a small subset of patients, resulting in a 2-month increase in median overall survival. Major hurdles to improving SCLC treatment include development of rapid chemoresistance and ineffective second line therapies. The identification of more durably effective therapeutic strategies is a major unmet clinical need. **Methods:** We performed an in vitro CRISPR screen in seven SCLC cell lines, including commercially available and short term-cultured cell lines derived from patient-derived-xenografts (PDXs), representing all major SCLC subtypes. We used an in-house druggable genome library including targets for which active inhibitors, either FDA-approved or in clinical development, are available. The screen was performed with two conditions per cell line, untreated and cisplatin-treated, to identify targets whose disruption would specifically sensitize to cisplatin. Candidate targets of interest were validated genetically with independent sgRNAs in Cas9-expressing in vitro and in vivo models (pSpCTRE-PDXs) and pharmacologically, with in vitro synergy assays and PDX treatments. Signaling pathways were studied by western blot, and toxicity studies were performed in vivo, to assess the safety of the agents at pharmacologically effective doses. We performed immunohistochemistry (IHC) to assess expression of candidate targets in SCLC tissue microarrays (TMAs). **Results:** Our CRISPR screen approach revealed XPO1 (Exportin 1) as a candidate that may contribute to cisplatin resistance across all SCLC subtypes. Combination of Exportin 1 inhibitors with cisplatin demonstrated synergy in vitro, and use of cisplatin with the Exportin 1 inhibitor selinexor showed combinatorial efficacy in vivo in chemonäive SCLC PDXs representing all SCLC subtypes. This efficacy was associated with increased DNA damage and apoptosis. The combination was well tolerated in mice at the drug concentrations tested. Exportin 1 inhibition also exhibited combinatorial synergy with irinotecan, a standard agent use for recurrent SCLC, and combination of selinexor with irinotecan demonstrated substantial efficacy in SCLC PDXs derived from chemorelapsed tumors including models for all SCLC subtypes, again with manageable toxicity profiles. We found SCLC to have the highest XPO1 mRNA expression among a diverse array of tumor histologies. High XPO1 expression was confirmed at the protein level in a SCLC tissue microarray, independent of SCLC subtype. **Conclusion:** Exportin 1 is highly expressed in SCLC tumors, independent of their subtype, and its inhibition enhances sensitivity to the chemotherapeutic drugs used in first line and second line treatment of SCLC tumors. Our results provide preclinical rationale for the combination of selinexor with cisplatin or with irinotecan as first or second line treatment, respectively, of SCLC.

Keywords: SCLC, Therapy, Chemoresistant

MA16 SCLC: NEW TARGETS, BIOMARKERS, AND SYSTEMIC THERAPIES
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MA16.06 Durvalumab ± Tremelimumab + Platinum-Etoposide in 1L ES-SCLC: Exploratory Analysis of HLA Genotype and Survival in CASPIAN

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Introduction: In the Phase 3, open-label CASPIAN study, first-line durvalumab (anti-PD-L1) + etoposide and cisplatin or carboplatin (EP) significantly improved overall survival (OS) versus EP alone in patients with extensive-stage small-cell lung cancer (ES-SCLC) (data cut-off [DCO]: Mar 11, 2019): HR 0.73 (95% CI 0.59–0.91; p=0.0047). This benefit was sustained with >2 years of median follow-up (DCO: Jan 27, 2020): HR 0.75 (95% CI 0.62-0.91; nominal p=0.0032). Although not statistically significant, a numerical improvement in OS was observed with durvalumab + tremelimumab (anti-CTLA-4) + EP versus EP: HR 0.82 (95% CI 0.68-1.00; p=0.0451). Biomarkers that predict efficacy of immunotherapy are not well characterized in SCLC. As HLA expression and genotype have previously been associated with response to immune checkpoint blockade, in this post-hoc exploratory analysis, we assessed the association of HLA-I/II genotype with OS in CASPIAN. **Methods:** 805 treatment-naïve patients (WHO performance status 0/1) with ES-SCLC were randomized 1:1:1 to durvalumab + tremelimumab + EP, durvalumab + EP, or EP. The primary endpoint was OS. A subset of patients consented to provide a blood sample (collected at Day 1 pre-dose) for genetic research. Next generation sequencing was used to infer HLA typing at four-digit resolution from germline whole exome sequencing data. DCO: Jan 27, 2020. **Results:** In CASPIAN, 414 patients (52% of all treated patients) were evaluable for HLA-I/II genotype (biomarker evaluable population [BEP]). In the BEP, the HR for OS was 0.71 (95% CI 0.55–0.93) with durvalumab + tremelimumab + EP versus EP and was 0.65 (0.49–0.84) with durvalumab + EP versus EP. DQB1*03:01, an MHC class II allele (prevalence of 37% in the BEP), was associated with longer OS in the durvalumab + tremelimumab + EP arm (HR 0.59) but not in the durvalumab + EP (HR 0.93) or EP (HR 0.94) arms (Table). Presence of DQB1*03:01 was enriched in patients with OS ≥18 months in the durvalumab + tremelimumab + EP arm (odds ratio 2.28).

	Durvalumab + tremelimumab + EP (n=142)		**Durvalumab + EP (n=143)**		**EP (n=129)**	
DQB1*03:01 status	Positive	Negative	Positive	Negative	Positive	Negative
n	58	84	57	86	38	91
Median OS (95% CI)	14.9 (10.4–21.2)	10.5 (7.6–12.9)	14.7 (11.5–16.3)	14.3 (9.4–17.2)	9.7 (7.7–11.7)	10.5 (8.9–11.3)
HR (95% CI)[a]	0.59 (0.39–0.88)		0.93 (0.63–1.37)		0.94 (0.61–1.40)	
OS <18 months, n	32	62	37	55	31	73
OS ≥18 months, n	26	22	20	31	7	18
Odds DQB1*03:01 present (OS ≥18 vs <18 mo)[b]	2.28		0.96		0.92	

[a]HR <1 favors positive DQB1*03:01 status vs negative
[b]Odds ratio >1 indicates the proportion of DQB1*03:01-positive patients is higher in the OS ≥18 months subgroup than the <18 months subgroup

Conclusion: In CASPIAN, the presence of the HLA-DQB1*03:01 allele was associated with improved OS for durvalumab + tremelimumab + EP treatment. This allelic association with improved OS was not found for durvalumab + EP or EP treatments. MHC class II and CTLA-4 cooperate to determine the range of antigens the immune system can respond to and complement the antitumor mechanism of PD-L1 blockade. Further investigation is warranted to understand the role of the DQB1*03:01 allele in the tumor microenvironment.

Keywords: CASPIAN, durvalumab, tremelimumab

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MA16.07 Prognostic Value of 18F-Fluorodeoxyglucose Uptake of Bone Marrow on PET/CT in Patients with Limited Disease Small Cell Lung Cancer

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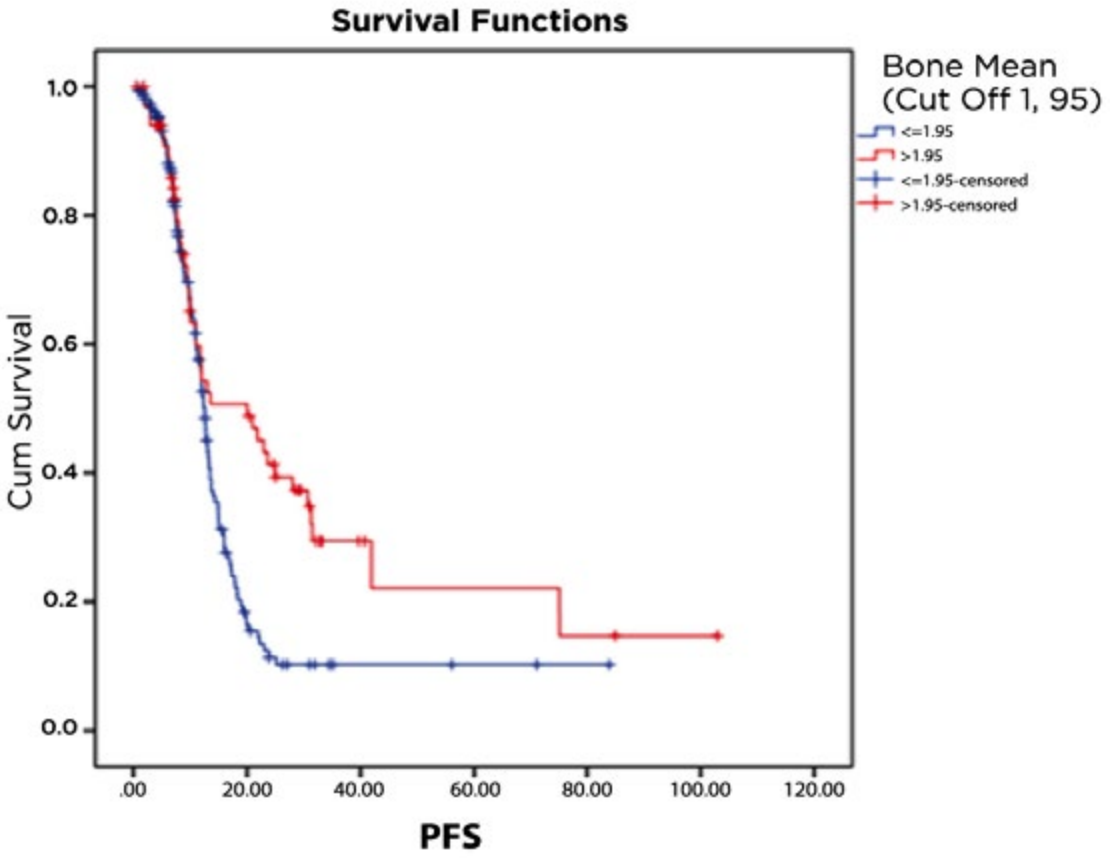
Introduction: AİM AND OBJECTİVES: Small cell lung cancer (SCLC) is a lung malignancy from the neuroendocrine cancer family with poor prognosis and metastases at the time of diagnosis. Advanced age, cachexia, low performance status, extensive disease and high lactate dehydrogenase (LDH) values are poor prognostic factors. We investigated whether 18F-fluorodeoxyglucse (FDG) uptake of bone marrow (BM) on positron emission tomography/computed tomography (PET/CT) has implications for predicting clinical outcomes in patients with limited disease small cell lung cancer (SCLC). **Methods:** 220 patients with limited-stage SCLC diagnosed between January 2010 and June 2019 were examined retrospectively in a single center. On PET/CT mean and max FDG uptake of primary tumor, mean FDG uptake of BM (BM SUV) and bone/liver ratio (BLR) were measured. FDG uptake of the BM, serum inflammation markers and other factors used in determining prognosis, overall survival (OS) and progression-free survival (PFS) were recorded and analyzed retrospectively. **Results:** BM SUV showed significant association with only PFS. It was observed that PFS was better in BM SUV mean was higher than 1,95. (p=0,03)

(figure 1)



In multivariate analysis with OS and PFS performance status of the Eastern Cooperative Oncology Group (ECOG) was observed to be a common independent prognostic factor. (p=0,001) Low stage of the disease, normal albumin values and BLR was a good prognostic factor. BM SUV mean was found to be positively correlation with primary tumor SUV max and SUV mean. **Conclusion:** Our study is the largest series in which PET / CT parameters are analyzed in limited stage SCLC patients. BM SUV mean is a parameter that can be used to predict PFS in limited-stage SCLC. BLR is an independent variable that can be used in overall survival.

Keywords: Small cell lung cancer, bone marrow FDG uptake, prognosis

MA17 DIAGNOSTICS AND PULMONOLOGY
MONDAY, SEPTEMBER 13, 2021 - 20:00-21:00

MA17.01 Reduced FEV_1 as Prognostic Factors in Patients With Advanced NSCLC Receiving Immune Checkpoint Inhibitors

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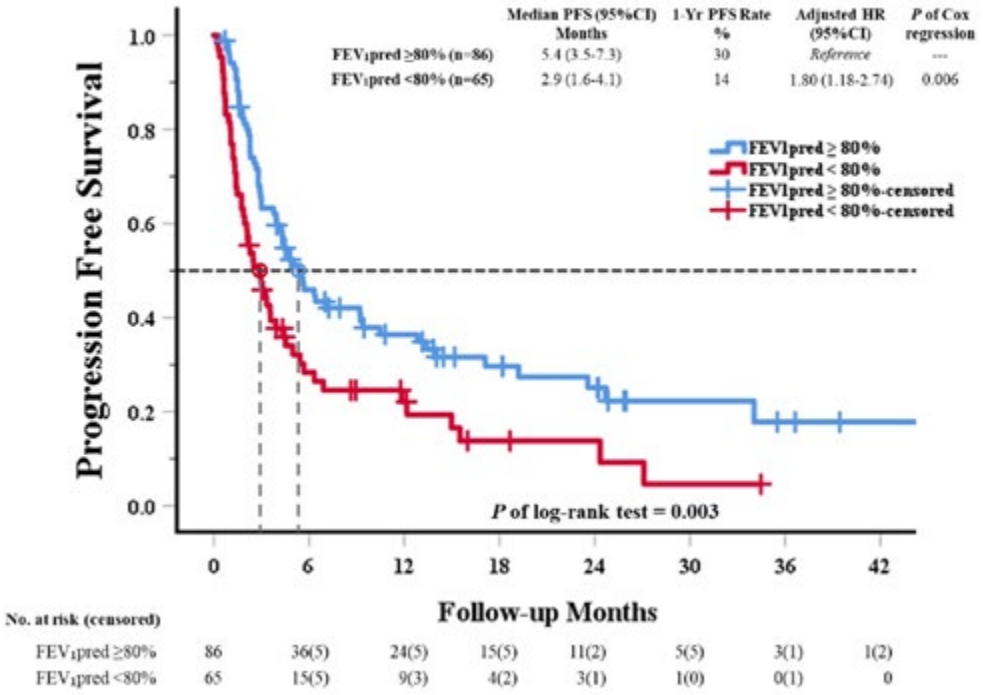
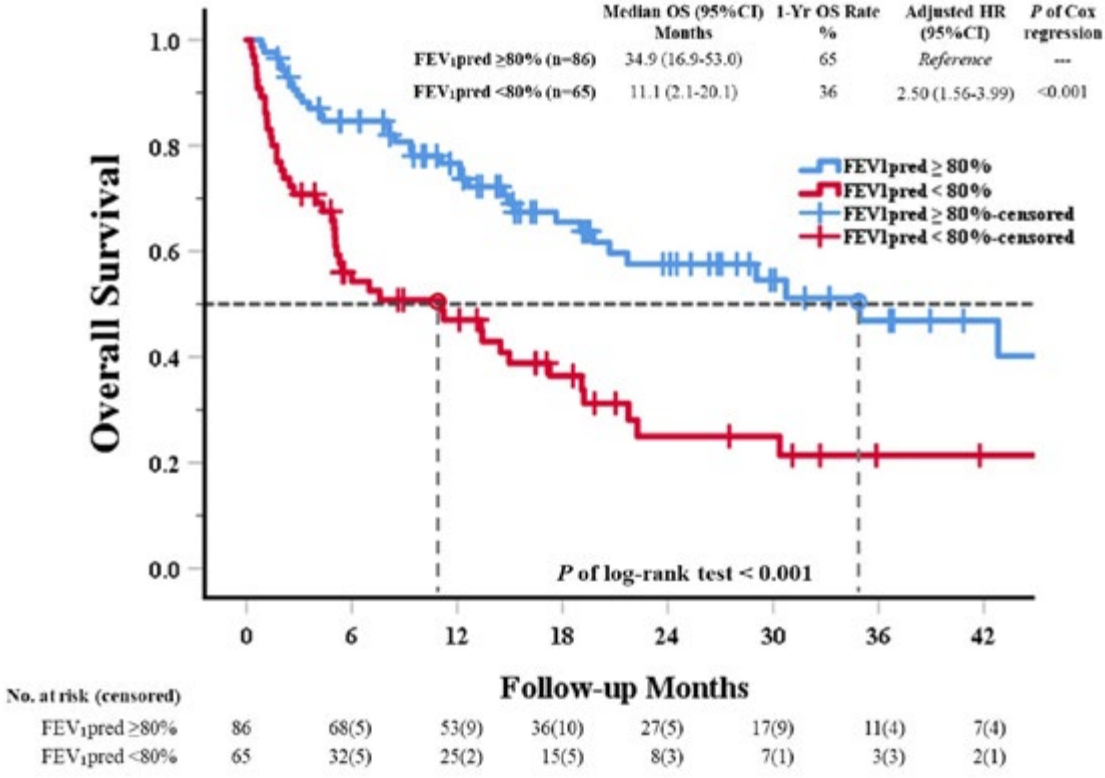
Introduction: The impact of reduced pulmonary function on patients with non-small cell lung cancer (NSCLC) receiving immune checkpoint inhibitors (ICI) is not fully elucidated. The aim of study is to investigate the influence of pulmonary function on the prognosis and treatment outcome in advanced NSCLC patients receiving ICI. **Methods:** Data were collected retrospectively from 151 patients with stage IV NSCLC who received ICI and completed spirometry before ICI therapy in Taipei Veterans General Hospital between January 2016 and December 2020. The co-primary end points were overall survival (OS) and progression-free survival (PFS) between groups divided by 80% predicted FEV_1 since ICI therapy started; the secondary outcomes were objective response rate. **Results:** Among 151 patients enrolled to this study, 67.5% of patients were men, 75.5% were adenocarcinoma, 24.5% had known targetable driver mutation, 33.8% received first-line ICI, and 62.8% received ICI monotherapy. The objective response rate was 24.5% and disease control rate was 54.3%. In multivariable analysis, patient with reduced FEV_1 had inferior PFS (50%≤ FEV_1< 80% vs. FEV_1≥80%, adjusted HR= 1.67; 30%≤ FEV_1< 50% vs. FEV_1≥80%, adjusted HR= 1.822, FEV_1< 30% vs. FEV_1≥ 80%, adjusted HR= 10.39, P=0.003), and OS (50%≤ FEV_1<80% vs. FEV_1≥ 80%, adjusted HR= 2.10; 30%≤ FEV_1< 50% vs. FEV_1≥ 80%, adjusted HR= 3.43; FEV_1< 30% vs. FEV_1≥ 80%, adjusted HR= 14.41, P<0.001). Median PFS and OS in the preserved FEV_1 group (≥80% predicted FEV_1) compared to the reduced FEV_1 group (<80% predicted FEV_1) were 5.4 vs. 2.9 months (adjusted HR= 1.80, P=0.006) and 34.9 vs. 11.1 months (adjusted HR=2.50, P<0.001), respectively. The other independent prognostic factors of OS include stage IVA disease (adjusted HR= 0.56, P=0.032), initial liver metastasis (adjusted HR= 2.15, P=0.030), and ICI monotherapy. (adjusted HR= 1.73, P=0.042)





Conclusion: Reduced FEV_1 is strongly associated with inferior clinical outcomes in patients with advanced NSCLC treated with ICI.

Keywords: Forced expiratory volume in 1 second, Immune checkpoint inhibitors, Advanced non-small cell lung cancer

MA17 DIAGNOSTICS AND PULMONOLOGY
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MA17.02 Visualization of Patterns of Lymph Node Metastases in Non-Small Cell Lung Cancer Using Network Graph Analysis

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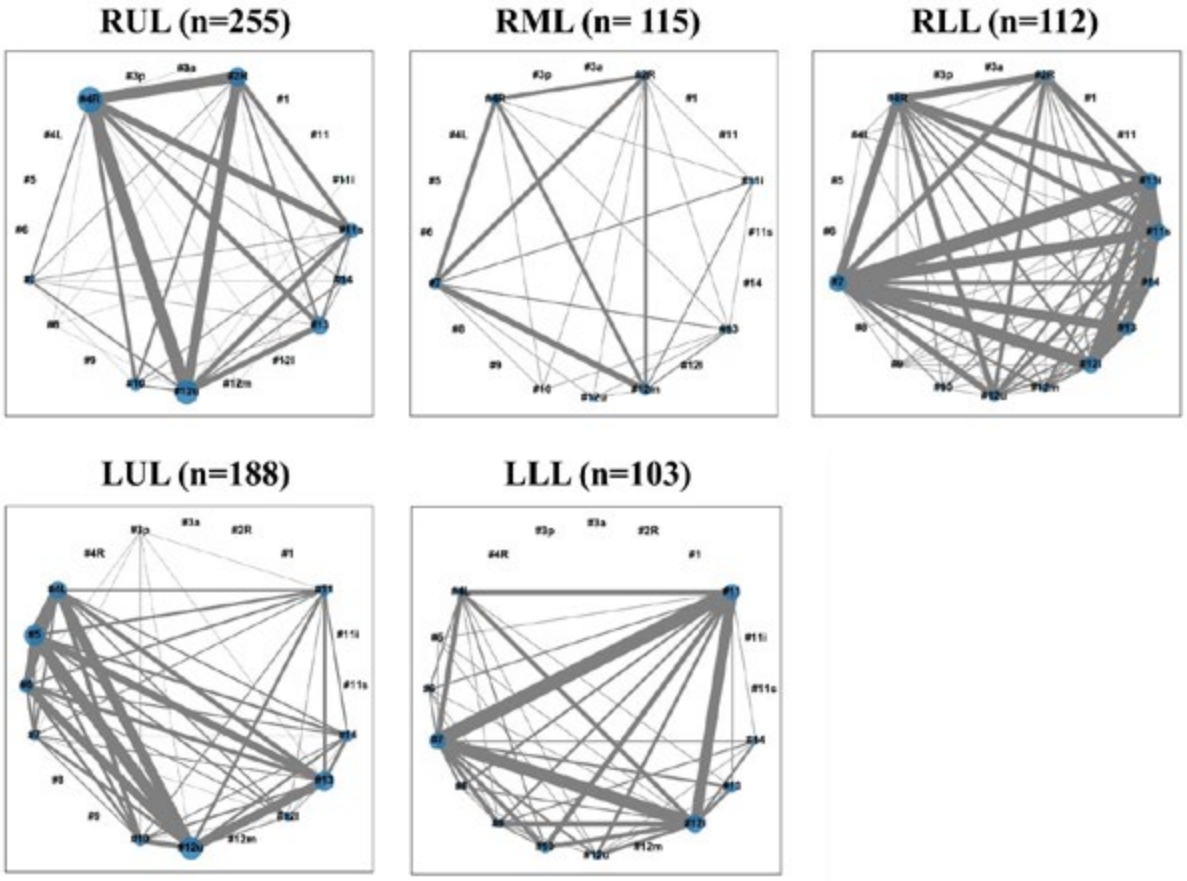
Introduction: We visualized complicated patterns of lymph node metastases in surgically resected non-small cell lung cancer. Preliminary results will be presented in Japanese at the 38th Annual Meeting of the Japanese Association for Chest Surgery on May 2021 and in English at this conference. **Methods:** Patients who underwent anatomical resection (i.e., lobectomy or pneumonectomy) with systematic mediastinal lymph node dissection for non-small cell lung cancer from Jan 2010 to Dec 2018 were included in this retrospective study. We excluded 1) neoadjuvant treatment, 2) tumor extending beyond one lobe, and 3) synchronous multiple primary lung cancer. Surgically resected lymph nodes were classified according to the IASLC lymph node map and subjected to pathological examinations. Patterns of lymph node metastases were analyzed by using network graph analysis. **Results:** The study included 783 patients with median age of 66, out of which 446 (57.0%) were men, 755 (96.4%) had lobectomies, and 564 (72.0%) had adenocarcinomas. The median number of examined lymph nodes was 20 and pathological N stage was pN0 in 428 cases, pN1 in 132, pN2 in 221, and pN3 in 2. Patterns of lymph node metastases were visualized according to the lobe (Figure 1). In the figure, lymph node stations from #1 to #14 are located on the circumference; the size of the blue dot in each station reflects the number of cases with metastases, and the thickness of the line between two lymph node stations reflects the degree of connections. In the right upper lobe (n=255), #11s/#12u N1 nodes had strong connections with #2R/#4R N2 nodes. In the right middle lobe (n=115), #12m N1 node distributed almost equally between #2R/#4R and #7 N2 nodes. In the right lower lobe (n=112), #11i/#12l N1 nodes had strong connections to #7 N2 nodes, and connections between #11i N1 node and #4R were also observed. In the left upper lobe (n=188), #12u N1 node connected equally strongly to #4L, #5, and #6 N2 nodes. In the left lower lobe (n=103), connections between #11/#12l N1 nodes and #7 N2 node were common, and connections between #11/#12l N1 nodes and #4L N2 node were also observed. We have released an interactive web application for the visualizations at http://175.41.219.167/. **Conclusion:** Network graph analysis helps us to understand patterns of lymph node metastases from the standpoint of complex network and gain new insights through a simple visualization.



Keywords: Network graph analysis, the IASLC lymph node map, lymph node metastasis

MA17.04 Leave Paraesophageal Lymph Node or Not in a Lung Cancer Surgery? A Propensity-Matched Analysis Based on Ten-Year Population.

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Introduction: Lymph node staging is closely related to outcomes of lung cancer (LC). Although paraesophageal lymph nodes (L8) are accessible in the LC surgery field, there are no guidelines indicating whether L8 must be dissected during a LC surgery. This study aims to explore the influence of L8 on the prognosis of LC and to provide reference for the diagnosis and treatment of LC. **Methods:** A single-centre cohort study with inclusion of 2962 consecutive patients who had undergone LC surgeries from 2000 to 2009. Using Propensity Score Matching (PSM) to eliminate other observed confounding, we further compared the outcomes of patients with/without L8 dissected ($L8^{D+}$/$L8^{D-}$) and of patients with/without L8 metastasis ($L8^{M+}$/$L8^{M-}$). **Results:** Before PSM, there were 2962 patients of 536 $L8^{D+}$ and 2426 $L8^{D-}$; after PSM, there were 573 patients of 215 $L8^{D+}$ and 358 $L8^{D-}$. No statistic difference was found in survival between patients with $L8^{D+}$ and $L8^{D-}$ (before PSM, P = 0.105; after PSM, P =284). Logistic regression analyses were conducted to identify L7 metastasis an independent risk factors of $L8^{M+}$ (odds ratio: 9.113, P = 0.002). In addition, we found that there was no survival difference between patients with $L8^{M+}$ and $L8^{M-}$, either (P = 0.968). **Conclusion:** The metastasis of L8 seems to have nothing to do with the prognosis of LC. Therefore, it may be not necessary to dissect L8 during LC surgeries.

Keywords: paraesophageal lymph node, Propensity Score Matching, lung cancer

MA17 DIAGNOSTICS AND PULMONOLOGY
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MA17.05 Intrapulmonary Lymph Node (LN) Retrieval With a Novel Gross Dissection Method: A Prospective, Population-Based Cohort Study

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Introduction: Ninety percent of lung cancer resection specimens have discarded LNs after standard gross dissection, 30% of discarded LNs have metastasis, including 12% of 'pN0' resections. Missed LN metastasis is associated with poor survival. In pilot studies, a novel gross dissection method increased intrapulmonary LN yield and decreased discarded LNs. We disseminated the novel dissection method to a larger group of pathology groups. **Methods:** We prospectively examined intrapulmonary LN evaluation within pathology groups serving 11 US institutions from 2009-2020. Two institutions' pathology departments initiated the novel gross dissection method in July 2012. We compared intrapulmonary LN yields and metastasis ratios with the Wilcoxon-Mann-Whitney and Chi-squared tests. Specifically, we compared between the two intervening institutions (Group A) and non-intervening institutions (Group B) prior to novel dissection initiation (baseline, July 2009-2012); between intervening institutions (Group C) and non-intervening institutions (Group D) after method initiation (July 2012-2020); and within each type of practice, comparing post-intervention to baseline (AvC and BvD). We excluded recipients of neoadjuvant therapy and sub-lobar resection; we adjusted for multiple testing using the Bonferroni method. A random subset of Group C underwent a quality-control re-dissection of the remnant resection material to examine for discarded LN. We report the rates of missed nodes, metastasis, and pN up-staging from discarded LN. **Results:** Among 3,126 resections, 34% (n=1064, 374 in A and 690 in B) were baseline. Of the remaining 66%, roughly half were performed with the intervention (C: n=967, 31%); 1095 (35%) resection specimens were examined in non-intervention pathology groups (D) (Table 1). There were no differences in total N1 LN yield or LN metastasis ratio at baseline (AvB). There was a higher metastasis ratio in C during the intervention period (C: 6.5% v D: 5.45%, adjusted $p<0.05$) but equivalent total N1 LN yields. Both intervening and non-intervening institutions increased LN yield and decreased metastasis ratio over time (AvC and BvD, all $p<0.05$). Of 250 random quality control re-dissections, 49 (19.6%) had discarded LNs; 5 specimens (2.0%) had ≥1 LN with metastasis; one person (2.0%) was up-staged. More specifically, of the 105 LN found during re-dissection, 10 (9.5%) had metastasized.

Table 1. Comparison of lymph node yield and metastasis ratios.				
Lymph Node Yields*	Baseline Intervention (A)	Baseline Non-Intervention (B)	Intervention (C)	Non-intervention (D)
N	374	690	967	1095
Lymph Node Counts (N: Median (IQR) (Range))				
Station 11-14 [AvB,AvC,BvD,CvD]	532: 0 (0-2), (0-21)	250: 0 (0-0), (0-10)	298: 0 (0-0), (0-16)	1848: 0 (0-2), (0-50)
Station 11-14 + NOS [AvC,BvD,CvD]	1385: 2.5 (1-5), (0-39)	2326: 2 (0-5), (0-29)	5754: 5 (2-9), (0-38)	5385: 3 (1-7), (0-55)
Station 10 [AvB,AvC,BvD,CvD]	526: 1 (0-2), (0-14)	842: 1 (0-2), (0-14)	1896: 1 (1-2), (0-20)	2892: 1 (1-4), (0-34)
Total N1 [AvC,BvD]	1911: 4 (2-7), (0-39)	3168: 4 (2-6), (0-30)	7649: 7 (3-11), (0-39)	8277: 6 (3-10), (0-65)
Pathologic N (N (%))[AvC]				
pNX	12 (3)	15 (2)	4 (0)	12 (1)
pN0	259 (69)	505 (73)	769 (80)	867 (79)
pN1	58 (16)	105 (15)	115 (12)	129 (12)
pN2	45 (12)	64 (9)	79 (8)	87 (8)
pN3	0 (0)	1 (0)	0 (0)	0 (0)
Metastasis Ratios (number of nodes with metastasis/ number of total nodes (%))				
Station 11-14[AvC,BvD]	60/532 (11.28)	24/250 (9.6)	15/298 (5.03)	89/1848 (4.82)
Station 11-14 + NOS [AvC,BvD,CvD]	155/1385 (11.19)	216/2326 (9.29)	401/5754 (6.97)	283/5385 (5.26)
Station 10 [AvC,BvD]	49/526 (9.32)	101/842 (12)	97/1896 (5.12)	168/2892 (5.81)
Total N1 [AvC,BvD,CvD]	204/1911 (10.68)	317/3168 (10.01)	498/7649 (6.51)	451/8277 (5.45)
*N-total number; IQR-interquartile range; Range-minimum and maximum; the superscript letters indicate which columns are statistically different at the alpha=0.05 significance level (after adjusting for multiple testing with Bonferroni correction). The comparisons tested include: AvB (baseline comparisons), CvD (intervention comparisons), AvC and BvD (within institution comparison – baseline/intervention).				

Conclusion: The novel gross dissection yielded the equivalent or more LNs, compared to conventional dissection, and outperformed in identifying LN metastasis. Missed LNs, missed LN metastasis ratios, and pN-upstaging were substantially lower than previous reports. The novel dissection method improved pN staging.

Keywords: pathologic nodal sampling, novel gross dissection

MA17 DIAGNOSTICS AND PULMONOLOGY
MONDAY, SEPTEMBER 13, 2021 - 20:00-21:00

MA17.06 Nodal Upstaging Comparison of Open, Video-Assisted Thoracoscopic, and Robotic Lung Resections Form Non–Small Cell Lung Cancer

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Introduction: Nodal staging is paramount for the treatment of lung cancer due to its role in determining the need for adjuvant therapy likewise to establish an adequate prognosis. Considering the increasing adoption of minimally invasive techniques for lung resection, it is important to determine if these methods are as effective as the open technique. Nodal upstaging has been used as a surrogate for the quality of nodal lymphadenectomy. The objective of this study was to compare nodal upstaging by open, video-assisted thoracoscopic (VATS) and robotic lung resections for non-small cell lung cancer (NSCLC) treatment. **Methods:** We retrospectively studied the registers of "Registro Paulista de Câncer de Pulmão" which is a broad multicenter databank in the state of São Paulo, Brazil. Clinical characteristics, as well as clinical and pathological staging, were collected. Patients submitted to lung resection for treatment of NSCLC were included. Patients with incomplete staging data were excluded. VATS, robotic and open techniques were compared in terms of nodal upstaging using the 7th edition of TNM staging. The primary outcome was the occurrence of nodal upstaging (N0 to N1, N0 to N2, or N1 to N2). Groups were compared using Fisher exact test for categorical variables and the t test was used to compare means of continuous variables. Multivariate analysis (logistic regression) was performed to determine factors associated with upstaging. **Results:** A total of 684 patients were included, 278 (40.64%) were submitted to open, 323 (47.22%) to VATS and 83 (12.13%) to robotic technique. Female sex was more frequent in the VATS group (open 50% vs VATS 60.99% vs robotic 48.19%; p=0.001). Patients in VATS group were older (mean age, open 62.4 vs VATS 65.97 vs robotic 63.8; p <0.001). Adenocarcinoma was the most frequent histologic type (60.96%) followed by squamous cell (18.56%) and carcinoid tumor (13.5%). Lobectomy was the most common resection (561, 82.02%) while pneumonectomy was performed in 30 (4.39%) and 78 (11,4%) were submitted to sublobar resections. Upstaging was more frequent with open technique (24,46%) followed by VATS (15.79%) and robotic (13.25%) with p=0.011. Multivariate analysis did not reveal significance for the technique as a predictor nodal upstaging (OR 0.83, p = 0.474 for VATS and OR 0.67, p = 0.301 for robotic). Factors that were associated with nodal upstaging were: descriptor T of the clinical staging (OR: 1.2, p = 0.016), descriptor N of clinical staging (OR: 3.3, p = 0.011), histological type classified as others (OR 0.25 p = 0.014), EBUS (Endobronchial Ultrasound Bronchoscopy) (OR 2.1 p = 0.003) and mediastinoscopy (OR1.8 p = 0.021). **Conclusion:** Nodal upstaging was more frequent with open resections than VATS and robotic technique; however, this difference between the techniques did not persist in the multivariate analysis when paired for possible confounding variables

Keywords: Staging, thoracic surgery, lung cancer

Featured Posters

FP01	**Early Stage/Localized Disease/Ablative Therapies**
FP02	**Health Services Research/Health Economics**
FP03	**Immuno-biology and Novel Immunotherapeutics (Phase I and Translational)**
FP04	**Immunotherapy (Phase II/III Trials)**
FP05	**Liquid Biopsy and Other Non-Invasive Diagnostic Modalites**
FP06	**Management of Lung Cancer in the Era of Covid 19**
FP07	**Mesothelioma, Thymoma and Other Thoracic Malignancies**
FP08	**Multimodality Management of Advanced Lung Cancer**
FP09	**Novel Therapeutics and Targeted Therapies**
FP10	**Palliative and Supportive Care**
FP11	**Patient Advocacy**
FP12	**Predictive Tumor Based Assays/Biomarkers/Pathology**
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FP16	**Tumor Biology and Sytems Biology: Basic Translational Science**

FP01 EARLY STAGE/LOCALIZED DISEASE/ABLATIVE THERAPIES

FP01.01 The Association of Bevacizumab with a Decreased Risk of Brain Metastases in ECOG-ACRIN E1505 in Completely Resected Stage IB-IIIA NSCLC

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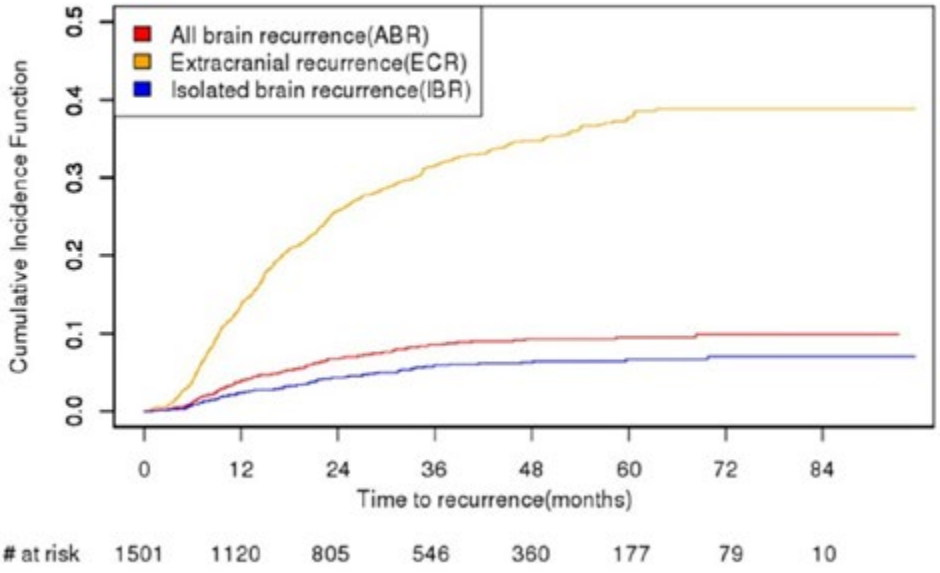
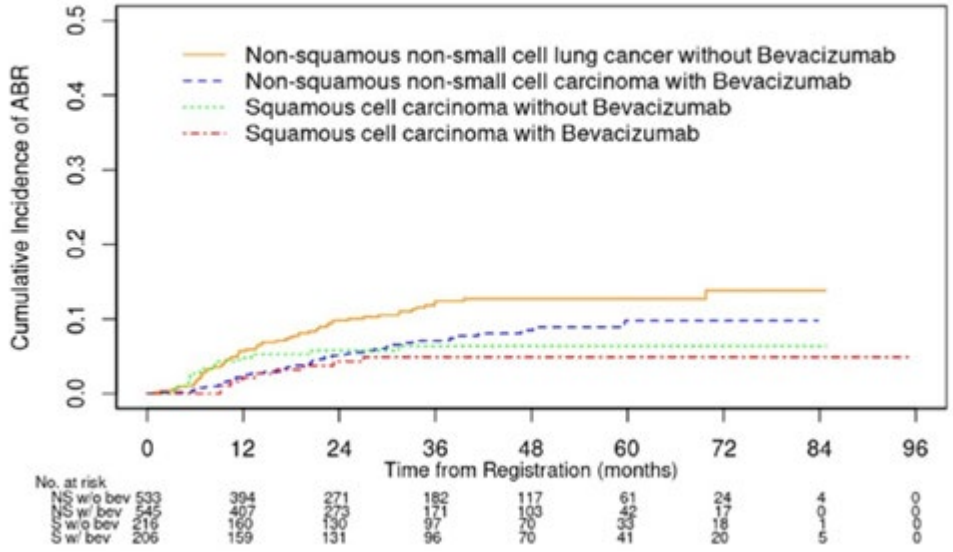
Introduction: ECOG-ACRIN E1505 was a phase III randomized trial of adjuvant chemotherapy +/-bevacizumab for patients with Stage IB (>4cm) – IIIA NSCLC. We sought to estimate the incidence/risk factors for brain recurrence as compared to extracranial recurrences (ECR). **Methods:** Among the 1501 patients enrolled, 472 developed ECR. 122 patients recurred in the brain with or without simultaneous ECR as the first recurrence site(all brain recurrences, ABR). Of the ABR patients, 84 patients presented with brain metastases without ECR (isolated brain recurrence, IBR). The cumulative incidence of recurrences was estimated after adjusting for recurrence at other sites and death as competing events. A multivariable regression model was fitted using competing risk analysis to evaluate the effect of covariates on the incidence of brain recurrence. **Results:** Median follow-up was 50.4 months. The incidence of ABR, IBR, and ECR at 6 years was 9.9%, 5.9%, and 38.8%, respectively. Bevacizumab was associated with a decreased incidence of ABR (HR=0.64; p=0.02) and IBR(HR = 0.62, p = 0.032), but there was a non-significant trend for a survival decrement in the bevacizumab arm vs control arm for both ABR and IBR. Median survivals associated with IBR, ABR and ECR were 9.5, 9.5 and 14.1 months respectively. Non-squamous histology (HR=1.87; p=0.003) was associated with ABR, and ECR was associated with NS-NSCLC histology (HR =1.79, p < 0.01), and stage/N2 involvement(HR= 1.13/1.37, both p < 0.01).





Conclusion: Bevacizumab was associated with a reduction in both IBR and ABR, but it was not associated with survival or ECR. Brain metastases whether isolated or not are associated with a lower median survival than ECR, and unlike ECR are not associated with traditional staging variables. The role of anti-angiogenesis in the prevention of brain metastases requires further exploration.

Keywords: bevacizumab, brain metastases, non-small cell lung cancer

FP01 EARLY STAGE/LOCALIZED DISEASE/ABLATIVE THERAPIES

FP01.02 A Comparative Cost Analysis Study of Robotic and Video-Assisted Lobectomy: Results of Randomized Controlled Trial (Bravo Trial)

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Introduction: Thoracic minimally invasive surgery has some proved postoperative advantages. Robotic-assisted thoracic surgery has brought relevant technical improvements with consistent equivalence in oncologic results when compared to video-assisted surgery. Despite these potential benefits of robotic surgery, the cost was still considered a limiting factor for the wide dissemination of the technique in many countries. This study evaluate the cost difference between pulmonary lobectomy in patients included in a randomized controlled trial that compared video-assisted and robotic-assisted lobectomy in lung cancer and lung metastases resection. **Methods:** Study of costs of hospital stay and follow-up of up to 90 days of patients included in the BRAVO trial, a controlled and randomized trial carried out between April 2015 and June 2017 and compared 2 surgical groups: video-assisted (VATS = 39 patients) and robotic-assisted (RATS = 37 patients) pulmonary lobectomy. Cost analysis of the 86 patients was performed using hospital micro-cost during hospitalization for pulmonary lobectomy and follow-up up to 90 days after the operation. Surgical admission costs were divided into 1- hospital costs, 2 professional services, 3 diagnostic services, 3 materials, 4 orthoses and prostheses and 5 robotic supplies. Postoperative follow up costs were obtained through the frequency of use of each of the services: emergency care, medical appointments, imaging tests, chemotherapy, radiotherapy, surgery (if was necessary reoperation), readmission and ICU stay. **Results:** There was no difference between groups in terms of demographics, preoperative clinical evaluation and cancer stage. The mean of global cost (surgery + 90-day follow-up) of patients in RATS group was R$ 35,590.41 (± 12,514.97) and in VATS group, R$ 41,066.98 (± 25,891.04), p = 0.564. The mean of surgical admission costs per patient was not different between 2 groups: VATS = R$ 32,832.86 x RATS = R$ 32,522.61, p = 0.32. While VATS group had lower cost of robotic inputs (VATS = 0 x RATS = R$ 1,479.13), endoscopic stapler loads (VATS = R$ 5,595.06 x RATS = R$ 7,023.09, p = 0.001) and materials (VATS = R$ 2024.61 x RATS = R$ 2569.49, p <0.001), RATS group had lower cost in hospital, professional and diagnostic services, without statistical significance. The total cost per patient of 90-day follow-up was higher in the VATS group (VATS = R$ 2,717.25 x RATS = R$ 1,545.76, p = 0.035). **Conclusion:** There is no difference in costs between video-ssisted and robotic-assisted lobectomy. The shorter hospital stay and the lower rate of complications contributed to lower cost of robotic surgery, despite the fact that robotic supplies still represent a weight in the final cost.

Keywords: lung cancer., robotic thoracic surgery, video-assisted thoracic surgery

FP01.03 Prevalence, Treatment Patterns and Long-Term Clinical Outcomes of Patients with EGFR Positive Resected Stage IB-IIIA NSCLC

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Introduction: The phase III ADAURA trial showed a significant disease-free survival (DFS) benefit for adjuvant osimertinib versus placebo in resected stage IB-IIIA EGFR mutated non-small cell lung cancer (NSCLC)**.** The aim of this analysis was to estimate EGFR mutation prevalence, treatment patterns and long-term outcomes in early stage (IB-IIIA) resected NSCLC patients in a real-world setting. **Methods:** From all patients with completely-resected non-squamous Stage IB-IIIA NSCLC seen at University Health Network/Princess Margaret Cancer Centre between 2012-2018, the clinico-demographic, treatment and survival data of patients with EGFR-positive cancers were collected retrospectively. Patients who had received neoadjuvant treatment were excluded. For prevalence estimation, only data from patients diagnosed 2014-2018 were included based on establishment of routine EGFR testing in early stage patients by 2014. **Results:** Prevalence of EGFR-positive NSCLC within this n=224 cohort was 32% overall (Stage IB:35%; II:24%; IIIA:38%, p=not significant). Prevalence was significantly higher in females (41% versus 22% in males), never-smokers (64% versus 19% in ever-smokers), and Asian (67% versus 29% in Caucasian) patients. Among 104 patients with EGFR-positive Stage IB-IIIA completely-resected NSCLC, median age was 67 years; the majority were female (69/66%), Asian (51/49%) or Caucasian (27/26%), and had a common EGFR mutation (86/83%); 43 (41%) had resected stage IB tumours; 35/33% had Stage II; 26/25% had Stage IIIA. Adjuvant treatment was given to 55 (53%) patients (Stage: IB, 6/14%; II, 28/80%; IIIA 21/81%); adjuvant chemotherapy was administered alone in the majority, 49/89%, while 1/2% received adjuvant radiotherapy and 5/9% received both. Median follow-up was 61 months. 63/61% patients developed disease recurrence; among stage IB, 16/37% recurred; among Stage II 25/71% recurred; and among Stage III, 22/85% recurred. First site of recurrence was solely loco-regional in 12/19%, or involved at least one metastatic site in 51/81% of patients, with first metastatic sites being lung 20/39%, pleura 17/33%, bone 8/16%, brain 8/16%, liver 4/8%, distant nodes 4/8% and adrenals 2/4%. The table below describes the survival outcomes.

Stage	**Probability of Disease Free survival at 2 years (95% CI)**	**Probability of Disease Free Survival at 5 years (95% CI)**	**Probability of Disease Free Survival at 7 years (95% CI)**
IB	0.72 (0.60-0.87)	0.61 (0.47-0.78)	0.61 (0.47-0.78)
II	0.51 (0.37-0.71)	0.17 (0.07-0.42)	0.08 (0.02-0.44)
IIIA	0.35 (0.20-0.59)	0.21 (0.09-0.46)	0.07 (0.01-0.41)
II and IIIA combined	0.44 (0.33-0.59)	0.19 (0.11-0.34)	0.08 (0.02-0.26)
Stage	**Probability of Overall Survival at 2 years (95% CI)**	**Probability of Overall Survival at 5 years (95% CI)**	**Probability of Overall Survival at 7 years (95% CI)**
IB	0.93 (0.86-1.00)	0.90 (0.80-1.00)	0.79 (0.64-0.97)
II	0.94 (0.87-1.00)	0.58 (0.42-0.82)	0.33 (0.15-0.71)
IIIA	0.89 (0.79-1.00)	0.51 (0.33-0.81)	0.43 (0.24-0.76)
II and IIIA combined	0.92 (0.86-0.99)	0.55 (0.42-0.72)	0.38 (0.23-0.60)

Conclusion: Clinico-demographic characteristics and early survival outcomes of patients with EGFR-positive NSCLC in our Princess Margaret Cancer Centre cohort were very similar to the placebo-controlled arm of the ADAURA trial. With the longer follow-up available in our cohort, we anticipate that that the placebo-controlled arm of ADAURA will also demonstrate growing numbers of recurrences and deaths.

Keywords: Survival Outcomes, EGFR+ NSCLC, Stage IB-IIIA resected

FP01.04 Prospective Observational Study of Activities of Daily Livings in Elderly Patients After Lung Cancer Surgery (JCOG1710A)

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Introduction: With the aging of general population, lung cancer incidence is expected to keep increasing, with more and more elderly patients undergoing surgical resection in developed countries. Post-operative activities of daily livings (ADL) are of critical importance to these patients and their families. However, currently available data are only on short-term surgical complications and overall survival (OS), with few studies for assessment of post-operative ADL or quality of life (QOL). The main purpose of this study is to elucidate how many elderly patients with lung cancer who underwent surgical treatment suffer from ADL deterioration, and to investigate whether it is predictable. **Methods:** This is a prospective, multi-institutional observational study, conducted by Lung Cancer Surgical Study Group of Japan Clinical Oncology Group (JCOG-LCSSG). Non-small cell lung cancer (NSCLC) patients with age of 75 or more who receive surgical resection are evaluated by Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental ADL (TMIG-IADL) and Japanese EQ-5D-5L QOL scale. TMIG-IADL is a 13-item index of competence on 3 domains (Instrumental self-maintenance, Effectance and Social role), and its standard deviation in Japanese elderly population is reported to be 3.0 points. After baseline screening evaluations before surgery, TMIG-IADL and Japanese EQ-5D-5L were collected at 6 months, 1 year, and 2 years after the operation. TMIG-IADL questionnaires are collected through the attending physicians, whereas EQ-5D-5L questionnaires are mailed by patients themselves directly to the research office. The primary endpoint is the proportion of patients alive without significant (defined as 1 standard deviation = 3 points, or more) worsening of TMIG-IADL at 6 months after surgery. The secondary endpoints include TMIG-IADL at 1 and 2 years after surgery, OS, relapse-free survival (RFS), post-operative complication, and Japanese EQ-5D-5L QOL scales. The primary endpoint and its confidence interval are estimated based on the binomial distribution. Multivariable logistic regression is performed to detect the risk factor for IADL worsening. OS and RFS are estimated using the Kaplan-Meier method. Planned sample size was 1000 to obtain the half width of a 95% CI for the primary endpoint of within 3.5%. **Results:** Between May 20, 2019, and May 29, 2020, 986 patients were enrolled from 47 institutions. One hundred and ten patients were ineligible, such as non-cancer, small cell histology or non-curative operation. The remaining 876 patients were thus eligible and followed up: male/female 491(56.1%)/385(43.9%), age 75-79/80-84/85-89/≥90 were 504(57.5%)/301(34.4%)/64(7.3%)/7(0.8%). At 6 months after surgery, 35 (4.0%) TMIG-IADL questionnaires were not retrieved, due to patient deaths (in 19), major co-morbidities (in 9), and other reasons (in 7). Therefore, the TMIG-IADL questionnaire retrieval rate was 841/876 or 96.0%, and EQ-5D-5L questionnaire was retrieved in 833/876 (95.1%). **Conclusion:** It is fully feasible to evaluate the post-operative ADL of elderly patients after lung cancer surgery, with both TMIG-IADL questionnaires (reported through surgeons) and EQ-5D-5L questionnaires (reported by patients themselves) retrieved in more than 95% of the patients. The data will be analyzed and presented at the meeting.

Keywords: Surgery, Elderly patient, Activities of daily livings (ADL)

FP02.01 Utilization and Refusal of Adjuvant Chemotherapy for Non-Small Cell Lung Cancer: A National Cancer Database Study

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Introduction: Adjuvant chemotherapy is the standard of care for resected non-small cell lung cancer (NSCLC) patients with node-positive disease and those with tumors larger than 5 cm. Despite showing survival benefits, adjuvant chemotherapy's utilization rates in the United States on a national level remain unclear. Moreover, it also remains unknown what proportion of patients refuse agent chemotherapy despite being offered. We, therefore, sought to analyze the national patterns of adjuvant chemotherapy utilization and refusal and the associated sociodemographic and clinicopathologic factors. **Methods:** This retrospective cohort study using data from the National Cancer Database included adult patients with histologically confirmed NSCLC who underwent R0 resection and were deemed to be chemotherapy eligible (node-positive disease or tumors≥5 cm) were identified. Factors associated with adjuvant chemotherapy utilization and refusal were identified using multivariable logistic regression. Joinpoint regression was used to evaluate the trends in utilization and refusal. Statistical tests were 2-sided. Statistical analysis was performed from January 1, 2021, to March 31, 2021. **Results:** Among the 44,957 patients, 24,976 (55.6%) received adjuvant chemotherapy and 18,468 did not (3,678 (8.2%) refused chemotherapy). From 2004 to 2017, the utilization of single- or multi-agent adjuvant chemotherapy increased significantly by an annual percentage change (APC) of +3.55% (95% CI, 2.60 to 4.60; P<.001). Utilization of single-agent chemotherapy decreased between 2004 to 2017 by an APC of -3.20% (95% CI, -5.50 to -0.50; P=.02); the decrease was more pronounced during the latter part of the study period, 2011 to 2017, with an APC of -10.70 (95% CI, -13.70 to -7.60; P<.001). Patients refusing adjuvant chemotherapy increased between 2004 to 2017 by an APC of +5.89% (95% CI, 4.40 to 7.40; P<.001). On multivariable analyses, factors associated with multi-agent chemotherapy utilization were private insurance (odds ratio [OR], 0.91; 95% CI, 0.85-0.96; P=.002), Midwest (OR 0.92, 95% CI, 0.85-0.99; P<.001), and nonacademic institutions (OR 0.84, 95% CI, 0.80-0.88; P<.001). Patients refusing adjuvant chemotherapy were more likely to be older (OR 1.08, 95% CI, 1.07-1.08; P<0.01), uninsured (OR 1.80, 95% CI, 1.39-2.25; P<.001), treated in the West (OR 1.44, 95% CI, 1.26-1.66; P<.001), and have higher Charlson score (OR 1.32, 95% CI, 1.18-1.47; P<.001). **Conclusion:** In this cohort study of resected NSCLC patients, we observed a lower-than-expected adjuvant chemotherapy utilization rate with almost 1/10th patients refusing adjuvant chemotherapy. Further studies are needed to understand the barriers to chemotherapy utilization and the reasons for adjuvant chemotherapy refusal in the United States.

Keywords: Utilization, Patterns of Care, adjuvant chemotherapy

FP02.02 The Impact of Sex on Non-Small Cell Lung Cancer Survival in Canada

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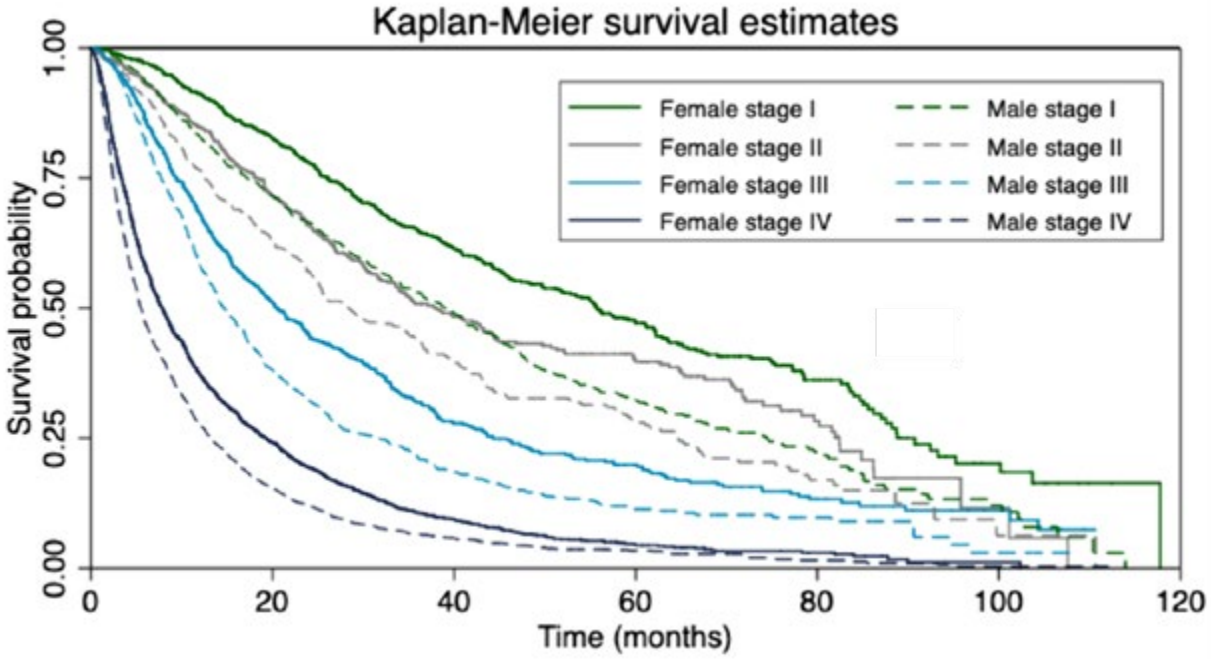
Introduction: Lung cancer is the leading cause of cancer-related death in Canada. Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases, and while new treatments have been developed, survival outcomes remain poor. Literature from outside Canada indicates differences in NSCLC survival by sex. These differences cannot be explained by differences in stage, NSCLC subtype, age, or smoking history, indicating that sex may be an independent prognostic factor. The impact of sex on NSCLC survival has yet to be thoroughly examined in the Canadian context. Here we evaluate the impact of sex on survival outcomes among a population-based Canadian cohort of lung cancer patients. **Methods:** A retrospective cohort study was completed using real-world data from the Glans-Look Lung Cancer Database (GLD). The GLD contains demographic, clinical, pathological, treatment, and outcome data for all individuals diagnosed with NSCLC in Alberta, Canada, between 2010 and 2017. Descriptive statistics were used to characterize the cohort. To analyze the impact of sex on NSCLC survival, Kaplan-Meier estimators with log rank tests were used for comparisons between cohorts grouped by sex, stage, and subtype. Overall survival was defined as time from diagnosis to death from any cause. **Results:** 8193 patients with complete data were included in analyses. Median age was 69.30 years (IQR 61.85-76.19), with 49.35% of the cohort being female. Median overall survival was 12.73 months (IQR 4.83–28.07), with 6277 (76.61%) patients deceased at end of follow-up. The highest proportion of cases (49.04%) were stage IV at diagnosis, and the most common histological subtypes were adenocarcinoma (55.35%), squamous cell carcinoma (SCC) (24.68%), and pathologically not otherwise specified (NOS) (9.79%). Survival analyses by stage indicated females had longer survival than males at every stage of diagnosis ($p<0.01$) (Figure). Analyses by subtype indicated that amongst those with adenocarcinoma, SCC, or pathological NOS, females had longer survival than males ($p<0.01$). Analyses by stage and subtype showed longer female survival for all stages of adenocarcinoma ($p<0.01$), and stage IV SCC ($p<0.01$) and pathological NOS ($p=0.02$) compared to males.



Conclusion: These preliminary analyses suggest that females with NSCLC have longer survival than males with NSCLC at all stages of disease, and within the most common histological subtypes. These analyses suggest that survival trends among Canadian NSCLC patients are similar to those seen in other western countries, and that further research is needed to elucidate the consideration of sex as an independent prognostic factor for NSCLC.

Keywords: non-small cell lung cancer, sex, survival

FP02 HEALTH SERVICES RESEARCH/HEALTH ECONOMICS

FP02.03 Factors Associated With Delayed Lung Cancer Diagnosis

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Introduction: The five-year survival rate for lung cancer is increased with localized disease, however only a small portion of patients are diagnosed at early stages. Identifying factors contributing to delayed or increased times to diagnosis can help inform clinical practice and increase early-stage diagnosis rates. **Methods:** Analysis was conducted on participant-reported data provided to the Lung Cancer Registry (www.lungcancerregistry.org) from 663 people diagnosed with lung cancer who completed an informed consent and baseline survey. Chi-square tests of association were used to assess the statistical significance of key parameters that may be associated with stage at diagnosis or time from presentation to a lung cancer diagnosis. **Results:** Of participants who had symptoms prior to diagnosis (n=500), over half of the patients (61%) reported initially presenting with their symptoms in the primary care setting with either a primary care physician, a nurse practitioner, or a physician's assistant. However, patients who reported initially presenting to an urgent care or emergency room provider were significantly more likely to be diagnosed in 3 months or less from presentation than in more than 3 months (p=0.0022). A significantly higher number of patients who were diagnosed at Stage IV, compared to earlier stages, reported initially being treated for another condition (56.9% vs 43.2%, p<.0001). Patients that reported a period of more than 3 months from initial presentation to a diagnosis of lung cancer were significantly more likely to have presented with certain symptoms including cough (p<0.001), fatigue (p=0.011), and shortness of breath (p=0.024) and to have received initial treatment for conditions other than lung cancer (p<0.001) than those diagnosed in 3 months or less. Among the patients who were treated for other conditions, those who reported a period of more than 3 months to diagnosis were also significantly more likely to have been treated first for allergies (p<0.008) or asthma (p=0.038) than those with a shorter time to diagnosis. However, initial treatment for either bronchitis or pneumonia had no significant association with time to diagnosis. **Conclusion:** These data suggest that initial treatment for more common chronic conditions such as asthma and allergies, versus more acute conditions such as pneumonia, may be a feature in cases with longer diagnosis times. Increased awareness and education about lung cancer symptoms and presentation, especially in less-traditional groups, in the primary care setting may increase timely diagnosis. This is especially important given recent observations of increasing rates of lung cancer in groups such as younger women (Jemal, A, et al., NEJM, 2018).

Keywords: diagnosis, patient reported data, care delays

FP02.04 Immunotherapy in Lung Cancer: Analysis of Patients' Awareness and Perceptions

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Introduction: Scientific advances in immuno-oncology have contributed to improved survival of lung cancer patients, and immunotherapy is part of the daily clinical practice. Due in part to these hopeful results, immunotherapy is a relatively popular subject in mass media. The scientific community has undertaken significant efforts to educate and inform patients about several aspects of immunotherapy, particularly regarding some common misconceptions, but the results are inconclusive and anecdotal. CareAcross, a digital multilingual platform which provides personalized, evidence-based support to cancer patients undertook the initiative to investigate the level of education and information of cancer patients regarding immunotherapy. **Methods:** From June 2020 to February 2021, specific questions were posed to the members of the CareAcross online platform. Members were predominantly from the UK, France, Spain, Italy or Germany, and were diagnosed with lung, breast, colorectal or prostate cancer. Their responses were correlated with other characteristics of their health profile and cancer journey. This analysis focuses on lung cancer patients, and compares the perceptions of those who have received immunotherapy vs those who have not. **Results:** Among 5589 responders, 1131 had lung cancer; 241 had received immunotherapy (21%; henceforth "IO-treated") while the rest had not (890 or 79%; henceforth "non-IO-treated"). Regarding the mechanism of action, 29% of patients responded either "do not know" or "not sure"; non-IO-treated were the least aware subgroup (33% vs 11% of IO-treated). Regarding the timing of action, 28% of patients reported knowing that immunotherapy starts working some time after treatment initiation (41% of IO-treated vs 24% of non-IO-treated). 44% of patients could not respond (22% of IO-treated vs 50% of non-IO-treated). Most patients (77%) were confident that chemotherapy causes more side-effects than immunotherapy (86% of IO-treated vs 74% of non-IO-treated) and only 3% of all believed the opposite. The main difference was observed regarding ignorance: 8% of IO-treated were unaware, compared to 23% of non-IO-treated. When comparing immunotherapy's toxicity with that of targeted therapies, more than half of all subgroups did not know. While all subgroups believed that immunotherapy was the least toxic of the two, IO-treated were the most ambivalent, resulted in a smaller gap (with 20% considering immunotherapy more toxic than targeted therapy, vs 24% for the opposite). Regarding the perception of costs to the healthcare system, 21% believe that immunotherapy costs more than targeted and chemotherapy (35% of IO-treated vs 17% of non-IO-treated). Each of the other two modalities were considered the most expensive by 12% of each subgroup, across the board. The remainder was accounted for by those who did not know (50% of all; 40% of IO-treated vs 53% of non-IO-treated) or believe they cost the same (5%; 3% of IO-treated vs 5% of non-IO-treated). **Conclusion:** The overall understanding of immunotherapy, its mechanism of action, impact, and costs, is still relatively low, even among lung cancer patients who have received such treatment. Given immunotherapy's growing applicability, these findings highlight the need for broader, continuous and frequently updated patient education initiatives. These can improve knowledge, instill confidence, reduce misconceptions, and enhance patient-clinician collaboration.

Keywords: awareness, patients, immunotherapy

FP03.02 A Phase I Trial of Atezolizumab and Varlilumab in Combination With Radiation in Patients with Metastatic Non-Small Cell Lung Cancer

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Introduction: Immunotherapy with PD-1/PD-L1 antibody is now the standard of care for the treatment of metastatic non-small cell lung cancer (NSCLC) but many tumors develop PD-1/PD-L1 resistance. We hypothesize based on existing preclinical and clinical data that combining a T-cell agonist such as varlilumab (anti-CD27 antibody) with checkpoint inhibition may be synergistic and this synergy may be potentiated further by using targeted radiation. Targeted radiation improves antigen presentation and immune infiltration and this combination may help overcoming resistance to PD-1/PD-L1 therapies for the treatment of NSCLC. We are therefore, conducting a Phase I trial to determine the safety and clinical benefit of the PD-L1 inhibitor atezolizumab and anti-CD27 antibody, varlilumab in combination with targeted radiation in patients with advanced or metastatic NSCLC. **Methods:** This single arm, open-label phase 1 trial (NCT04081688) is actively enrolling at our institution. As of 4/5/2021, 9 of the planned 15 patients have been enrolled. The primary objective is to assess the safety and tolerability of therapy with atezolizumab and varlilumab in combination with radiation in adult patients with advanced or metastatic NSCLC whose tumors have progressed on prior PD-1/PD-L1 therapy. On Day 1 of each 21-day cycle, patients receive varlilumab (10 mg/kg cycle 1 and 3 mg/kg cycle 2 onwards, IV) followed by atezolizumab (1200 mg, IV) on day 2. Radiation to a lung lesion is administered between cycle 1 and cycle 2. Secondary outcomes include ORR, CBR, median PFS and frequency of immune-related adverse events. Mandatory pre- and post-treatment tumor biopsies (of a non-irradiated lesion) will be performed to measure changes in tumor PDL1 expression, infiltrating T-cells as well as immune gene expression by Nanostring technology. Pre- and post-treatment PBMC samples will also be collected for immunophenotypic analysis using multiparameter flow cytometry.

FP03.03 ECOG PS of 0-1 and Very High PD-L1 Expression ≥90% Are Associated With Clinical Benefit From First-Line Chemo-Immunotherapy in Advanced NSCLC

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Introduction: Although chemo-immunotherapy improves clinical outcomes compared to chemotherapy in advanced non-small cell lung cancer (NSCLC), responses occur in <50% of patients, and the clinicopathologic and genomic determinants of chemo-immunotherapy efficacy are still in need of further investigation. **Methods:** Event-time distributions were estimated using Kaplan-Meier methodology. Log-rank tests were used to test for differences in event-time distributions. Cox proportional hazards models were fitted to obtain estimates of hazard ratios in univariate and multivariate models. **Results:** Among 209 patients with advanced EGFR/ALK wild-type NSCLC treated with first-line chemo-immunotherapy, median age was 64, 51.2% were women, 86.6% had history of tobacco use, and 92.4% had non-squamous histology. In the entire cohort, objective response rate (ORR), median progression-free (mPFS), and median overall survival (mOS), were 41.6%, 6.7 months, and 19.3 months, respectively. When compared to patients with a PS of 0-1 (N=183), those with a PS ≥2 (N=23) had a significantly lower ORR (15.0% vs 44.8%, P<0.01), shorter mPFS (2.2 vs 7.2 months, HR 2.01, P<0.01), and shorter mOS (3.2 vs 20.7, HR 3.37, P<0.0001) to chemo-immunotherapy. By contrast, when comparing never smokers (N=28) versus smokers (N=181) we found no differences in terms of ORR (35.7% vs 42.5%, P=0.54), mPFS (5.9 vs 6.7 months, HR 0.92, P=0.73), and mOS (26.9 vs 16.8 months, HR 1.42, P=0.20). When analyzed by increasing PD-L1 expression levels of <1% vs 1-49% vs 50-89% vs ≥90%, patients with PD-L1 expression ≥90% had the highest ORR (72.2%), the longest mPFS (16.6 months), and mOS (35.1 months) to chemo-immunotherapy (**Figure 1**). TMB had no impact on clinical outcomes. PD-L1 expression and ECOG PS were independent predictors of PFS and OS in multivariable analysis (**Figure 2**)

Figure 1

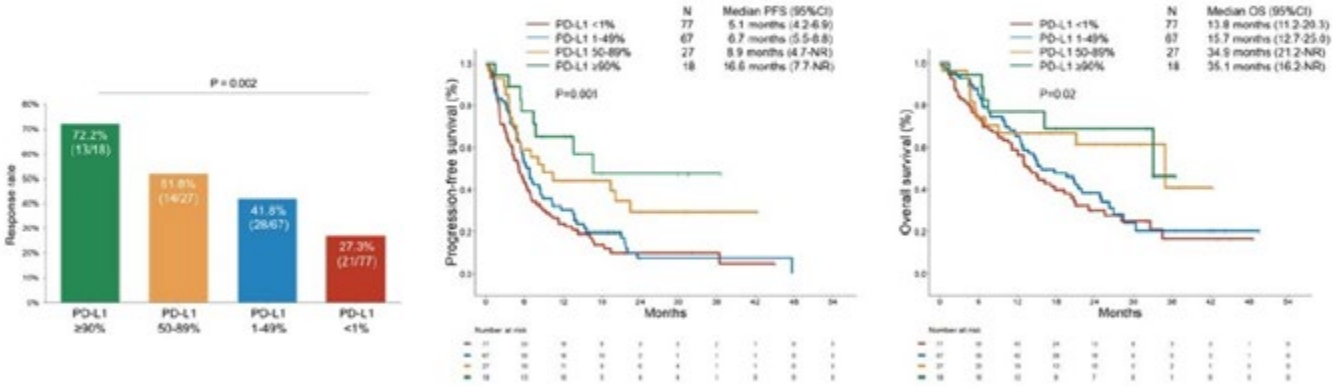

Figure 2

Progression-free survival	Univariate Hazard Ratio [95%CI]	P-value	Multivariate Hazard ratio [95%CI]	P-value
TMB	0.994 [0.971-1.017]	0.61		
PD-L1 expression	0.987 [0.982-0.993]	<0.0001	0.989 [0.982-0.997]	0.048
Age	1.01 [0.99-1.03]	0.09	-	-
Sex (female vs male)	1.21 [0.89-1.65]	0.21	1.48 [1.00-2.19]	0.049
ECOG PS (0-1 vs ≥2)	2.01 [1.28-3.16]	0.002	1.86 [1.01-3.24]	0.02
Smoking history (ever vs never)	0.92 [0.59-1.44]	0.74		

Overall survival	Univariate Hazard Ratio [95%CI]	P-value	Multivariate Hazard ratio [95%CI]	P-value
TMB	1.008 [0.984-1.017]	0.49		
PD-L1 expression	0.987 [0.982-0.993]	<0.0001	0.991 [0.982-0.999]	0.04
Age	1.02 [1.00-1.04]	0.04	-	-
Sex (female vs male)	0.88 [0.62-1.25]	0.48	-	-
ECOG PS (0-1 vs ≥2)	3.37 [2.10-5.40]	<0.0001	3.15 [1.80-5.52]	<0.0001
Smoking history (ever vs never)	1.42 [0.82-1.44]	0.20		

Conclusion: ECOG PS, smoking history, and PD-L1 expression levels may help guide treatment decisions when choosing between PD-(L)1 monotherapy vs chemo-immunotherapy as first-line option for patients with advanced NSCLC.

Keywords: PD-L1, ECOG performance status, chemo-immunotherapy

FP03.04 Dasatinib Improves the Antitumor Activity of Anti-PD-1 in NSCLC Models by Inhibiting Treg Conversion and Proliferation

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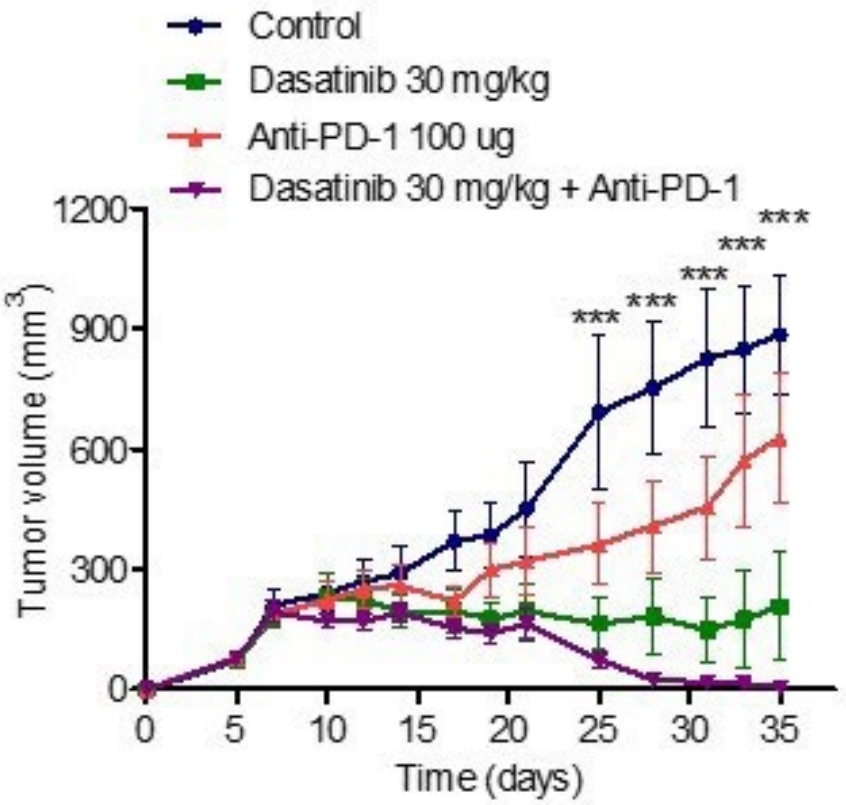
Introduction: The use of immune-checkpoint inhibitors (ICI) has greatly improved the outcome of patients with NSCLC. However, only 30-40% of patients benefit from this therapy and many of them develop acquired resistance. Immunomodulatory drugs that can reinvigorate the immune cytotoxic activity in combination with ICI (such as anti-PD-1) are a great promise to overcome resistance and improve the response to immunotherapy. Here, we evaluated the prognostic value of the SRC family kinases (SFKs), with special focus on YES1, and the immunomodulatory effect of the SFKs inhibitor, dasatinib, in combination with anti-PD-1, in two clinically relevant mouse models of NSCLC. **Methods:** A cohort of 116 NSCLC patients from University Clinic of Navarra was used to study immune infiltrates by multiplex immunofluorescence (mIF) and YES1 protein expression in tumor samples. Publicly available TCGA and Km Plotter datasets were used to study patient's survival based on SFKs expression. Syngeneic NSCLC mouse models 393P (ADC) and UNSCC680AJ (SCC) were used for in vitro and in vivo drug testing. Tumor microenvironment was characterized in 393P model by using flow cytometry and mIF. **Results:** YES1 was the most significant predictor of poor prognosis among all SFKs. Patients with high YES1 tumor protein levels showed high infiltration of CD4+/FOXP3+ cells (regulatory T cells, Tregs), suggesting an immunosuppressive phenotype. Inhibition of SFKs phosphorylation with dasatinib synergized with anti-PD1, promoting tumor regressions (87%) and the development of immunological memory that impeded tumor re-challenge in the 393P mouse model. In vivo depletion experiments showed that CD8+ and CD4+ T cells were necessary for the therapeutic effect of the combination. Moreover, dasatinib+anti-PD1 induced a very significant decrease in the number of Tregs in the tumor and blood and reduced the expression of PD1 in CD4+ and CD8+ tumor infiltrated T cells. The drop in Tregs was also confirmed by mIF in tumor sections. The anti-tumor effects of dasatinib+anti-PD-1 were validated in the UNSCC680AJ model. In functional in vitro assays, we demonstrated that dasatinib abrogated TGF-β-driven conversion of effector CD4+ T cells into Tregs and Treg proliferation through alteration of SMAD3 and STAT5 signaling pathways.



Conclusion: YES1 protein expression is associated with increased numbers of Tregs in NSCLC patients. Dasatinib synergizes with anti-PD-1 to impair tumor growth in NSCLC murine models. This study provides the preclinical rationale for the combined use of dasatinib and PD-1/PD-L1 blockade to improve outcomes of patients with NSCLC.

Keywords: Dasatinib, non-small cell lung cancer, immunotherapy

FP04.01 Nivolumab 480 mg Every 4 Weeks as De Novo Second-line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 907

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Introduction: After the initial approval of weight-based nivolumab dosing used in registrational studies for second-line advanced/metastatic non-small cell lung cancer (NSCLC), flat doses of 240 mg Q2W and 480 mg Q4W were approved in multiple countries based on pharmacokinetic modeling and clinical safety data. The clinical safety data were across multiple tumor types in patients who switched from 3 mg/kg Q2W to 480 mg Q4W nivolumab dosing, and demonstrated similar safety profiles for the two regimens. Here, we report on CheckMate 907 (NCT03090737), the first phase 2 safety study to evaluate de novo administration of nivolumab 480 mg Q4W as second-line treatment in immunotherapy-naïve patients with advanced/metastatic NSCLC. **Methods:** Adult patients with immunotherapy-naïve, histologically confirmed advanced/metastatic NSCLC, disease progression after ≥1 prior systemic regimen, and ECOG performance status (PS) 0-1 received nivolumab 480 mg Q4W over a 30-minute infusion for up to 2 years. The primary endpoint was the incidence of grade 3/4 and grade 5 treatment-related select adverse events (AEs; those with potential immunological etiology requiring frequent monitoring/intervention). Secondary endpoints included overall survival (OS), progression-free survival (PFS; investigator-assessed), confirmed objective response rate (ORR; investigator-assessed), and duration of response. **Types of Analysis and Data Reporting:** Data from the final analysis of the study, including the primary and secondary endpoints listed above, are reported. **Results:** Of 129 treated patients (median age, 63 years), 73.6% were male, 20.2% were Asian by race, 83.7% had ECOG PS 1, 77.5% had a history of smoking, 62.8% had nonsquamous histology, and 88.4% had received one prior systemic therapy. After a minimum follow-up of 26.5 months (database lock: April 9, 2021), grade 3/4 treatment-related select AEs were reported in skin and gastrointestinal categories (1 patient each); no grade 5 treatment-related select AEs were reported. The most common treatment-related select AEs (all grades) were skin (34.1%), hepatic (20.2%), gastrointestinal (14.0%), and endocrine (10.1%) events. Grade 3/4 treatment-related AEs (TRAEs) and grade 3/4 TRAEs leading to treatment discontinuation occurred in 4.7% and 1.6% of patients, respectively. Median OS was 10.6 months (95% CI, 8.3–14.7) with 1- and 2-year OS rates of 46.5% and 24.9%, respectively. Median PFS was 3.7 months (95% CI, 3.1–4.5); 1- and 2-year PFS rates were 18.9% and 10.8%, respectively. Confirmed ORR was 17.1% (95% CI, 11.0–24.7) with complete and partial responses rates of 1.6% and 15.5%, respectively. Of the 22 responders, 14 (63.6%) patients remained in response at database lock (minimum follow-up, 26.5 months). **Conclusion:** In CheckMate 907, the safety profile for de novo administration of nivolumab at a flat dose of 480 mg Q4W was comparable to that of registrational, phase 3 studies using weight-based nivolumab dosing for the second-line treatment of advanced/metastatic NSCLC; no new safety signals were identified. The efficacy profile was also similar to that of registrational studies. These results further support the de novo administration of nivolumab 480 mg Q4W.

Keywords: Nivolumab, NSCLC, De novo flat dosing

FP04.02 RATIONALE-307: Updated Biomarker Analysis of Phase 3 Study of Tislelizumab Plus Chemo vs Chemo Alone For 1L Advanced Sq-NSCLC

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Introduction: In the RATIONALE-307 trial (NCT03594747), tislelizumab plus platinum-based chemotherapy significantly improved clinical outcomes vs chemotherapy alone in treatment-naïve advanced squamous non-small cell lung cancer (sq-NSCLC). Previously, we showed superior clinical efficacy of tislelizumab plus chemotherapy vs chemotherapy alone regardless of PD-L1 expression (J Clin Oncol 38:2020[suppl; Abstr 9554]) and blood tumor mutational burden (Ann Oncol 2020;31[4]:S754–S840). Here we report the updated biomarker analysis of PD-L1 expression, tissue tumor mutational burden (tTMB) and gene expression profiling (GEP) in baseline tumor samples. **Methods:** Biomarkers were assessed in 360 patients randomized in RATIONALE-307. The association of the above-mentioned biomarkers and progression-free survival (PFS) between and within the two treatment groups was assessed using a stratified Cox proportional hazards model. P-values < 0.05 were considered statistically significant without multiplicity adjustment. **Results:** A total of 263 (73%) randomized patients had evaluable tTMB and 275 (76%) had evaluable GEP. Baseline characteristics were similar to that of the overall study population. PFS benefits of tislelizumab plus chemotherapy vs chemotherapy alone were not associated with tTMB status (**Table**). Significant treatment-specific differences in PFS were observed in patients with high expression levels of interferon-related genes, including PSMB9, HERC6, OAS2 (Interaction P-value: 0.029, 0.037, 0.025, respectively), etc., and an 18-gene tumor inflammation signature (TIS) (Interaction P-value: 0.001). High TIS score was associated with significantly longer PFS in the tislelizumab plus chemotherapy group, but not in the chemotherapy alone group. The association of TIS score and PFS was independent from PD-L1 and tTMB status. Additional analysis on GEP signatures and genomic alterations, including their association with TIS, PD-L1 expression and clinical efficacy, will be presented. **Conclusion:** This exploratory analysis of RATIONALE-307 is the first Phase 3 trial indicating a strong association between TIS score and clinical benefit of PD-1 blockade plus chemotherapy vs chemotherapy alone in sq-NSCLC. These data support TIS score as a potential predictive biomarker for PD-1 inhibitor response, regardless of PD-L1 and tTMB status.

Table: Association of biomarkers with PFS in tislelizumab plus chemotherapy vs chemotherapy alone treatment groups.

Biomarkers*	N	mPFS, Mo (95% CI) Tislelizumab + chemo vs chemo alone	PFS HR (95% CI)	Interaction P-value
PD-L1 positive	213	7.62 (6.74–11.01) vs 4.96 (4.14–5.59)	0.41 (0.28–0.60)	0.143
PD-L1 negative	136	7.56 (5.68–9.69) vs 5.45 (4.21–6.97)	0.64 (0.40–1.02)	
tTMB-high	131	9.69 (7.59–NR) vs 5.42 (4.17–5.78)	0.44 (0.27–0.72)	0.463
tTMB-low	132	6.90 (5.55–7.69) vs 5.39 (3.71–5.88)	0.57 (0.36–0.91)	
TIS-high†	138	9.79 (65.75–NR) vs 4.17 (4.04–5.55)	0.26 (0.16–0.43)	0.001
TIS-low†	137	6.9 (5.49–7.59) vs 5.78 (4.30–7.43)	0.84 (0.53–1.35)	

***PD-L1 positive: TC ≥ 1%; PD-L1 negative: TC < 1%; tTMB-high: ≥ 10 mutations/Mb; tTMB-low: < 10 mutations/Mb; TIS-high: ≥ median score; TIS-low: < median score.**

†18-gene TIS included: TIGIT, CD27, CD8A, PDCD1LG2, LAG3, CD274, CXCR6, CMKLR1, NKG7, CCL5, PSMB10, IDO1, CXCL9, HLA-DQA1, CD276, STAT1, HLA-DRB1, HLA-E. Abbreviations: CI, confidence interval; HR, hazard ratio; Mb, megabase;NMo, month; mPFS, median progression-free survival; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; TIS, tumor inflammation signature; tTMB, tissue tumor mutational burden.

Keywords: biomarkers, immunotherapy, pd-1 inhibitor

FP04.03 Clinical Benefit of First-Line Cemiplimab in Patients with Locally Advanced NSCLC: Subgroup Analysis from EMPOWER-Lung 1

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Introduction: Agents which inhibit the programmed death receptor-1 (anti–PD-1) have transformed treatment for patients with metastatic non-small cell lung cancer (NSCLC), however there is paucity of prospective clinical data investigating the use of these agents in patients with locally advanced NSCLC (laNSCLC) who are not candidates for definitive concurrent chemoradiotherapy. In the Phase 3 EMPOWER-Lung 1 Study (NCT03088540), cemiplimab, a PD-1 inhibitor, demonstrated improved overall survival (OS) and progression-free survival (PFS) in patients with advanced NSCLC and programmed cell death-ligand 1 (PD-L1) expression in ≥50% of tumor cells vs platinum-doublet chemotherapy. This study allowed the enrollment of patients with laNSCLC, in addition to those with metastatic disease, providing the largest prospective randomized evidence of first-line (1L) anti–PD-1 monotherapy in this patient population. Here, we present a post-hoc subgroup analysis of patients with laNSCLC from the PD-L1 ≥50% population in EMPOWER-Lung 1. **Methods:** In EMPOWER-Lung 1, patients were randomized 1:1 to cemiplimab 350 mg intravenous every 3 weeks or investigator's choice of platinum-doublet chemotherapy. Patients with laNSCLC were those with stage 3B/3C disease who were not candidates for definitive concurrent chemoradiotherapy. Data cut-off for this subgroup analysis was March 1, 2020. **Results:** In the PD-L1 ≥50% population of EMPOWER-Lung 1 (n=563), 87 (15.5%) patients had laNSCLC; cemiplimab (n=45) and chemotherapy (n=42). In the total laNSCLC population (n=87), median (range) age was 63.0 (31.0–81.0); male: 86.2%; non-squamous histology: 36.8%; stage 3B cancer: 79.3%; and stage 3C cancer: 20.7%. At a median follow-up of 11.6 months (interquartile range 7.2–18.2 months), cemiplimab provided significantly better PFS vs chemotherapy and numerically longer OS (not reaching statistical significance) (see Table), Objective response rates (ORR) and Kaplan–Meier estimated median duration of response (DOR) were also numerically improved with cemiplimab vs chemotherapy. **Conclusion:** In patients with laNSCLC and with PD-L1 ≥50%, 1L cemiplimab monotherapy demonstrated a significant improvement in PFS, numerically longer OS, and numerically better ORR and DOR vs chemotherapy. These results support clinical benefit provided by cemiplimab 1L monotherapy for patients with laNSCLC with PD-L1 ≥50% **Keywords:** Phase II and III Clinical Trials, Immune checkpoint inhibitors, Randomised Controlled Trials

Table. Clinical endpoint results in patients with IaNSCLC

	Cemiplimab (n=45)	Chemotherapy (n=42)
Median duration of follow-up, months (IQR)	12.2 (7.2–21.8)	11.6 (7.8–17.4)
PFS, median, months (95% CI)	8.4 (4.5–15.3)	6.2 (4.6–6.6)
HR (95% CI)	0.5 (0.3–0.9); *P*=0.0153†	
OS, median, months (95% CI)	NE (17.7–NE)	15.5 (9.6–NE)
HR (95% CI)	0.5 (0.2–1.1); *P*=0.0875†	
ORR, n, (95% CI)	20.0 (29.6–60.0)	13.0 (17.6–47.1)
CR, n, (%)	1 (2.2)	1 (2.4)
PR, n, (%)	19 (42.2)	12 (28.6)
KM estimated DOR, median, months (95% CI)‡	12.5 (6.4–21.0)	6.2 (3.4–8.5)

†Nominal *P* value.

‡Cemiplimab n=20 and chemotherapy n=13.

CI, confidence interval; CR, complete response; PR, partial response; HR, hazard ratio; IQR, interquartile range; KM, Kaplan–Meier; NE, not evaluable.

FP04.04 A Phase Ib/II Study of Imprime PGG and Pembrolizumab in Pretreated Patients With Advanced Stage Non-Small Cell Lung Cancer: BTCRC-LUN15-017

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Introduction: Imprime PGG (imprime), a β-glucan, acts as a pathogen-associated molecular pattern and creates critical "non-self" signals recognized by the innate immune system. It enhances immune cell killing, activation of antigen-presenting cells, and T cell crosstalk, thereby may increase the anti-tumor efficacy of immune checkpoint inhibitors (ICI). Imprime is safe in combination with chemotherapy at 4 mg/kg on days 1, 8, and 15 of the 21-day cycle; however, not studied with ICI in non-small cell lung cancer (NSCLC). **Methods:** A multicenter, single-arm phase Ib/II trial was conducted (NCT03003468). Patients with locally advanced or metastatic NSCLC progressed on platinum-based chemotherapy, and naïve to ICI were eligible. The protocol was modified to allow patients who previously received ICI after its approval in the 1st line setting. Tolerability was the primary objective of the phase-Ib study. Determination of progression-free survival (PFS) was the primary endpoint for the phase II study. For the null hypothesis, median PFS for the combination was 3.2 months (mo), and for the alternative hypothesis, it was 6.3 mo. **Results:** The study enrolled 35 subjects, 9 in phase Ib and 26 in phase II. Imprime was evaluated at two dose-levels, 2 and 4 mg/kg on days 1, 8, and 15 of a 21-day cycle in a 3+3 dose-escalation design. Pembro was given on day-1 of the cycle. Subjects enrolled in the phase-Ib portion were ICI naïve. Dose-limiting toxicity was not observed, and imprime dose at 4 mg/kg was selected for the phase II study. Median PFS and OS for phase Ib portion were 5.36 mo (95%CI: 1.28-27.8) and 24.21 mo (95%CI: 6.37-not reached), respectively. The objective response rate was 22.2%, with 1 complete and 1 partial response (PR). In the phase II portion, 23 of 26 patients were evaluable for PFS and OS. Fourteen (53%) subjects received ICI as their previous line of therapy. Median PFS for the phase II portion was 2.14 mo (95%CI: 1.35-5.13), and mOS was 9.79 mo (95% CI: 5.36-14.95). Of 21 response-evaluable subjects in the phase II portion, only 1 (4.8%) achieved PR, and 9 had stable disease as their best response. The bivariate analysis did not show any significant differences in outcomes based on age, gender, stage, and histology. Grade 1-2 treatment-related adverse events (TRAEs) occurring at a frequency of ≥ 5% included body aches (31%), infusion reactions (27%), fatigue (23%), and nausea (14%). Grade 3 TRAEs included infusion reactions (6%) and body aches (3%). No grade 4 or 5 TRAEs were observed. **Conclusion:** The combination of imprime and pembro is safe in patients with locally advanced or metastatic NSCLC. The addition of imprime to Pembro did not improve outcomes in the phase II portion; however, many of the participants had ICI as their prior line of therapy. Median PFS and OS were higher for patients in phase Ib who were naïve to ICI.

Keywords: immunotherapy, NSCLC, Immunomodulation

FP05.02 A Biomarker-Directed, Multi-Center Phase II Study of Molecular Response Adaptive Immuno-Chemotherapy in Lung Cancer

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Introduction: Success of immuno-oncology therapies depends on choosing patient populations likely to benefit. Current predictive biomarkers are unable to accurately identify subsets of patients that benefit from these therapies. Liquid biopsy analyses of circulating cell free tumor DNA (ctDNA) have shown promise in capturing tumor burden dynamics. Our pilot analyses provided proof of concept for the value of ctDNA in rapidly and accurately identifying patients that do not respond, and in monitoring the evolution of resistance to immune checkpoint blockade[1]. These findings suggest that ctDNA dynamics may allow patients with primary resistance to be rapidly identified and redirected to receive alternative therapies. **Methods:** This is a two stage open label phase II trial. During the first stage, treatment-naïve patients with PD-L1 TPS ≥50%, EGFR and ALK mutation negative metastatic NSCLC that are eligible to receive 1st line pembrolizumab, are enrolled. Plasma samples are prospectively collected prior to therapy initiation and every three weeks on-therapy until disease progression. Liquid biopsy analyses utilize a CLIA validated gene panel and next-generation sequencing is performed on ctDNA from plasma samples obtained at baseline, weeks 3, 6 and 9, and also baseline matched white blood cell DNA and tumor (if available). The primary objective of stage I is to identify the optimal time point for determination of ctDNA molecular response, validate concordance of ctDNA molecular response with radiologic response and establish the optimal design of the randomized stage 2 portion of the study. Secondary objectives evaluation of time to molecular response, correlation of molecular response and depth of molecular response with progression free survival and overall survival. Tertiary objectives include collection of archival tumour tissue samples from patients for additional translational research. Activated October 17, 2019, the trial has 17 of planned 50 patients enrolled in stage I. Stage II will proceed following confirmation of timing of ctDNA and correlation with clinical responses. Patients will be randomized to evaluate the potential clinical benefit of tailoring treatment to ctDNA molecular response. Key eligibility criteria for both stages I and II include: age≥18 years, ECOG performance status 0 or 1, stage IV non-squamous NSCLC, confirmed EGFR and ALK alteration negative, PD-L1 TPS ≥50% and no prior systemic or immunotherapy for metastatic NSCLC. The primary endpoint of stage II is overall response rate, as determined by RECIST 1.1 criteria. Secondary endpoints include progression-free and overall survival. Tertiary objectives are to explore ctDNA prognostic/predictive features from analyses of longitudinal blood samples. **Conclusion:** We envision that our ctDNA molecular response adaptive clinical trial will enable incorporation of liquid biopsies in immuno-oncology trial design and have broad clinical applications for the increasing number of patients treated with immunotherapy. Clinical Trial Registry Identifiers: CRI-CCTG0002/BR.36, NCT04093167. [1] Anagnostou, V, Forde, P, White JR et al., Dynamics of Tumor and Immune Responses during Immune Checkpoint Blockade in Non-Small Cell Lung Cancer. Cancer Res. 2019 Mar 15;79(6):1214-1225. doi: 10.1158/0008-5472.CAN-18-1127

Keywords: liquid biopsies, interventional clinical trial, immunotherapy

FP05.03 Multiomic, Plasma-Only ctDNA NGS Assay Developed for Minimal Residual Disease (MRD) Detection in Early-Stage NSCLC

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Introduction: Detection of minimal residual disease (MRD) by circulating tumor DNA (ctDNA) post-curative intent treatment is predictive of recurrence in NSCLC. Due to biological challenges with low ctDNA shed in early-stage disease and potential to detect non-tumor derived alterations in plasma (e.g. CHIP), most ctDNA MRD assays require a priori knowledge of genomic alterations from tumor tissue to achieve high sensitivity and specificity. Prior data from tumor-informed assays indicate ctDNA detection correlates with histologic subtype and lower sensitivity for lung adenocarcinomas compared to lung squamous cell carcinomas have been reported (Abbosh et al., 2017). We previously validated an assay (Guardant Reveal) that combines somatic and epigenomic analysis to detect ctDNA from early-stage colorectal tumors without tumor tissue or peripheral blood cells. Here we describe the expansion of this assay to detect MRD in NSCLC. **Methods:** Cell-free DNA (cfDNA) fragments are extracted from plasma, partitioned based on extent of methylation, enriched using a panel to target informative genomic and epigenomic regions, barcoded, and pooled for sequencing. Methylation status is determined non-destructively and with minimal loss of molecules, allowing sensitive genomic and epigenomic analysis of the same cfDNA fragments. A single assay with a total panel size of 5.3 Mb was developed for MRD analysis in multiple cancer types. A "ctDNA detected" result is defined by the de novo identification of tumor-derived somatic variants and/or tumor-specific contribution to methylation profile exceeding predefined thresholds, based on 1418 regions differentially methylated in NSCLC. **Results:** The assay performance was tested using 101 pre-treatment clinical samples from patients with early-stage non small cell lung cancer (NSCLC). 53% were adenocarcinoma and 39% were squamous cell carcinoma, with 8% having unknown subtype. Sensitivity for pre-treatment detection in NSCLC overall was 68.3% at 95% specificity. Additional development from larger cohorts is ongoing and data will be presented as available.

Table 1. Pre-treatment sensitivity based on histologic subtype and stage

	Adenocarcinoma N=54	Squamous cell carcinoma N=39	Unknown Subtype N=8	Combined N=101
Stage I	40.0% (12/30)	55.6% (5/9)	80.0% (4/5)	47.7% (21/44)
Stage II	83.3% (10/12)	85.0% (17/20)	50.0% (1/2)	82.4% (28/34)
Stage III	91.7% (11/12)	80.0% (8/10)	100% (1/1)	87.0% (20/23)

Conclusion: Using cancer-specific genomic and epigenomic signals combined with learning-based classifiers, we developed a method for detecting the presence of ctDNA in early-stage NSCLC patients from plasma without the need for tumor tissue. This method provides high sensitivity in both lung adenocarcinoma and squamous cell carcinoma. A plasma-only MRD assay for NSCLC offers clinical advantages by overcoming the challenges of tissue procurement, particularly following neoadjuvant therapy, and enabling faster time to results.

Keywords: Liquid biopsy, ctDNA, minimal residual disease

FP05.04 Robust Discrimination of Lung Cancer via Microbial DNA Detection and Machine Learning Classification

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Introduction: Human tissues, including tumors, are extensively colonized by taxonomically diverse microbes. Intra-tumoral microbial activity and events of cellular turnover and trafficking contribute to shedding microbial nucleic acids into the blood stream. Here we characterized microbial signatures present in primary-tumor tissue and in the blood of patients affected with different cancer types, with particular focus on lung cancer, and we demonstrated the discriminatory power of such microbial signatures for the identification and classification of lung cancer versus other cancer types. We further validated our findings using plasma-derived cell-free microbial DNA (mbDNA) to discriminate between lung cancer and cancer-free control samples. **Methods:** We re-examined The Cancer Genome Atlas (TCGA) compendium of treatment-naïve, whole genome and transcriptomic sequencing datasets to extrapolate genetic signatures of microbial origin associated with 33 different tumor types collected from 10,481 patients, which included non-neoplastic tumor-adjacent tissue and blood samples. 7.2% of TCGA sequencing reads were classified as non-human, of which 35.2% could be taxonomically classified using a reference database containing 59,974 total microbial genomes. An in-silico decontamination pipeline featuring statistical contaminant inference and historical known extraction kit contaminant removals was employed, discarding up to 92.3% of microbial taxa from the data. The decontaminated data sets were then used to train stochastic gradient-boosting machine learning models (using a 70/30 train/test split for all cancers) to discriminate between and within types and stages of cancer. **Results:** We demonstrated that mbDNA signatures from whole blood can be used to accurately classify the tissue of origin of 20 unique cancer types, including lung adenocarcinoma and lung squamous cell carcinoma. For lung adenocarcinoma we reported high discrimination between paired tumor tissue and normal-adjacent tissue (Avg. {AUROC,AUPR}={0.85,0.95}) and between primary tumor tissue and all-other cancer types (Avg. {AUROC,AUPR}={0.96,0.69}, n=32 cancer-types). We also demonstrated the high performance of blood-derived mbDNA when discriminating among TCGA cancer types: Avg. {AUROC,AUPR}={0.97,0.80}. The results from our validation study on plasma-derived mbDNA confirmed microbial signatures in blood can robustly discriminate lung-cancer samples from healthy controls: Avg.{AUROC,AUPR}={0.97,0.93}, n=94. **Conclusion:** mbDNA holds considerable promise as a truly orthogonal means of detecting and classifying lung cancer independently from host genomic alternations. Using only mbDNA signatures we have demonstrated robust discrimination between cancer-free controls and lung cancer samples and have provided early evidence of the applicability of this approach to liquid biopsy. Our continued effort on the analysis of plasma mbDNA with expanded sample cohort numbers will serve to fully validate this new class of liquid biopsy biomarkers for lung cancer detection.

Keywords: Liquid biopsy, tumor microbiome, lung cancer diagnostics

FP05.05 A Prospective Observational Study of Osimertinib Using Plasma Concentrations in NSCLC With Acquired EGFR T790M Mutation

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Introduction: Osimertinib is one of the standard treatments for the patients with EGFR mutated lung cancer. Osimertinib showed a statistically significant difference in PFS and OS when compared to first-generation EGFR-TKI. However, predictors of efficacy and safety are still unknown. At this time, we evaluated the relationship between plasma osimertinib concentrations and treatment results. **Methods:** EGFR activating mutation-positive lung cancer patients having acquired T790M resistance mutation after the 1st or 2nd generation EGFR-TKI treatment and planning osimertinib treatment entered into this study. Plasma levels of osimertinib and its metabolite AZ5104 were measured a week after the start of treatment, and at the onset of AE that required suspension or discontinuation of treatment. The concentration was measured by the HPLC method. The primary endpoint was the correlation between plasma concentration of osimertinib or AZ5104 and adverse events. The correlation between plasma concentration and treatment efficacy was one of the secondary endpoints. The number of cases was set to 40 so that a sufficient number of AE cases for analysis could be obtained. **Results:** Forty-one patients were enrolled in the study. The median age was 68 years (range 43-81), with 33 females (80%). The previous treatment history was 1 regimen in 20 patients (48.8%), and 3 or more regimens in 15 patients (36.6%). Thirty-four cases (82.9%) had CNS metastases. Overall response rate was 53.7% and disease control rate was 92.7%. Median PFS was 6.67 months. The frequency of adverse events was highest for rash, with all grades were 36.6% and G3 or higher were 2.4%. This was followed by anorexia (all grades: 31.7%), thrombocytopenia (all grades: 29.3%), anemia (all grades: 29.3%), and diarrhea (all grades: 26.8%). The frequency of drug-induced pneumonitis was of all grades: 19.5% and of G3 or higher: 2.4%. Thirty-eight cases were able to measure the trough concentrations in plasma a week after the start of treatment. The median concentration of osimertinib was 227 ng/ml and of AZ5104 was 16.5 ng/ml. The mean trough level of osimertinib in the anorexia-occurred group was significantly higher than that in the non-occurred group (385.0 ng/ml vs 231.5 ng/ml, P=0.009). Pneumonitis was not related to plasma level of the drug. In addition, the patients were divided into the quartile groups by the osimertinib trough levels (Q1, Q2, Q3, Q4 in ascending order of value), and the PFS of Q1, Q2+Q3 and Q4 were compared. The PFS of the Q2 + Q3 group was the longest compared to the Q1 group and the Q4 group. The Q1 group might be received undertreatment of osimertinib and the Q4 group tended to have more cases of discontinuation due to adverse events. Entirely, osimertinib levels were more associated with efficacies than metabolites of osimertinib. **Conclusion:** It was shown that trough concentration measurement on the 1 week after the start of osimertinib may be able to predict some gastrointestinal toxicity and efficacy. An appropriate plasma level of osimertinib may avoid some adverse events and may induce long PFS. Further analysis is required.

Keywords: osimertinib, plasma concentration, EGFR

FP06.01 Unexpected Aggressive Histological Component in Subsolid Lung Adenocarcinoma: Priority for Resection Without Delay

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Introduction: Ground glass opacity (GGO)-containing small-sized adenocarcinoma of the lung can generally be expected to have a fair prognosis after resection. However, some of such tumors might contain a histological aggressive component that is related to poor prognosis. This study aimed to identify the predictors for the aggressive histological component in GGO-containing small-sized lung adenocarcinoma to screen the patients who should undergo resection without delay in the era of COVID-19. **Methods:** Of the 2,350 patients who underwent pulmonary resection for lung cancer at our institute between 2017 and 2020, we collected data of 501 patients with GGO-containing lung adenocarcinoma with a total diameter of ≤ 2 cm. Multivariable analysis was conducted to identify predictors for the presence of histological aggressive components. **Results:** Using a historical cohort, lymphovascular invasion and predominant micropapillary or solid patterns were identified as histological aggressive components that were related to poor prognosis in stage IA adenocarcinoma. Of the included 501 cases, 36 (7.2%) had at least one histological aggressive component. A multivariable analysis showed that consolidation/tumor ratio on high-resolution computed tomography > 0.5 (odds ratio [OR], 6.08; p < 0.01), maximum standardized uptake value (SUVmax) on positron emission tomography ≥ 1.5 (OR, 3.56; p < 0.01), and smoking index > 20 pack-years (OR, 2.69; p = 0.03) were predictors for the presence of histological aggressive component, with the sensitivity of 94.4%. **Conclusion:** Consolidation/tumor ratio > 0.5, SUVmax ≥ 1.5, and smoking history > 20 pack-years were predictors for the presence of a histological aggressive component in GGO-containing small-sized adenocarcinoma. These predictors may be useful for screening patients with a potentially high risk for poor prognosis and for setting priorities for resection in the era of COVID-19.

Keywords: ground-glass opacity, consolidation/tumor ratio, prognosis

FP06.02 The Impact of The COVID-19 Pandemic on New Diagnoses of Lung Cancer: A 3-Year Review of an Irish Cancer Centre

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Introduction: The onset of the COVID-19 pandemic in March 2020 led to a disruption in cancer services worldwide. In Ireland, lung cancer is the fourth most common malignancy and the leading cause of cancer deaths. Disease stage at diagnosis and performance status are powerful prognostic factors for survival in both non-small cell (NSCLC) and small cell lung cancer (SCLC) subtypes. We review cases of lung cancer diagnosed over a consecutive three-year period to better understand the impact of the COVID-19 pandemic on this cohort of patients. **Methods:** We conducted a retrospective analysis of new cases of primary lung cancer referred to the lung cancer multidisciplinary meeting (MDM) at a tertiary referral cancer centre in Dublin, Ireland, between December 2017 and November 2020. Histological subtypes included for analysis: NSCLC (adenocarcinoma, squamous cell carcinoma, and carcinoma not otherwise specified) and SCLC. Exclusion criteria: patients without a histologically confirmed diagnosis of primary lung cancer, other histological subtypes, and patients referred for systemic anti-cancer treatment and follow-up at an external institution. We reviewed case numbers, patient demographics, disease stage at presentation, performance status at the time of diagnosis, and survival. **Results:** A total of 491 cases of lung cancer diagnosed between December ('Dec') 2017 and November ('Nov') 2020 were included for analysis. 162 cases were diagnosed between Dec 2017 and Nov 2018, 181 cases between Dec 2018 and Nov 2019, and 148 cases between Dec 2019 and Nov 2020. We compared patients diagnosed between Dec 2017 and Nov 2019 to those diagnosed between Dec 2019 and Nov 2020 to assess the impact of the pandemic: Gender: 61% vs 45% male (p=0.0013). Median age: 69 vs 67 years (p=0.26). NSCLC stage I disease 31.6% vs 22.3% (p=0.03); stage IV disease 34.4% vs 46.3% (p=0.01). SCLC extensive stage 67.3% vs 74.1% (p=0.55). Metastatic disease: 39.1% vs 51.4% (p=0.03). Performance status ≥ 2: 27.2% vs 24.4% (p=0.52). Median overall survival (mOS): 14 months vs not reached. **Conclusion:** Between December 2019 and November 2020, fewer primary lung cancer cases were diagnosed at our centre compared to the preceding two years. Of these patients, a higher number presented with metastatic disease. There was no statistically significant difference in the performance status of patients at presentation. We hypothesize that the increase in advanced stage presentations seen during the pandemic may be accounted for by the disruption to cancer services, delayed presentations due to patients following public health advice and self-isolating in response to new respiratory symptoms, and fewer patients presenting to healthcare providers due to the fear of contracting COVID-19.

Keywords: lung cancer, covid-19, pandemic

FP06.03 COVID-19: Does Thoracic Surgery Increase Mortality Rates during the Pandemic?

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Introduction: In March 2020, the Sars-Cov-2 pandemic began, and, with that, tertiary services postponed elective thoracic surgeries, believing that a post-operative thoracic surgery patient would have increased mortality for COVID-19. Accordingly, the risk of disease progression was brought to attention by medical societies since lung resections are surgeries often related to the treatment of oncological diseases. This study aims to analyze the outcome of patients that had thoracic surgery during the pandemic and evaluate the ones diagnosed with COVID-19 after lung pulmonary resection (LR). **Methods:** Data from all patients who underwent LR (lobectomy, segmentectomy, and wedge resection) by the Thoracic Surgery Service at PUCRS's Sao Lucas Hospital in Brazil during 2020 were retrospectively collected in March 2021. Information regarding etiology of the thoracic disease, type of surgical access, post-operative COVID-19 status, and evolution of the viral condition underwent descriptive analysis. **Results:** Sixty patients were submitted to LR from January to December 2020, with 3 patients going through two surgeries (two primaries lung cancer), resulting in 63 procedures. Of the 60 patients, 33 patients (55%) underwent surgery for malignant lung cancer, 25 (41.8%) for inflammatory or infectious diseases, and 2 (3.3%) for benign lung cancer. Of the 63 procedures, 27 (42.9%) were video-assisted thoracoscopic surgery (VATS), with 18 (28.6%) for early-stage cancer. During postoperative follow-up, 7 (11.7%) patients were diagnosed with COVID-19. It was established a postoperative period as up to 15 days after surgery. Four patients were infected by the new coronavirus, considering that definition. Of the 7 patients with COVID-19, two required hospitalization and died, one had worsened from associated comorbidities, and the other was diagnosed with COVID-19 8 months after surgery. The average age of patients infected in the postoperative period was 66.14 years, and the mortality rate due to COVID-19 after thoracic surgery was 3.3%. Of the 53 (88.3%) patients who were not positive for COVID-19, 2 (3.3%) died. **Conclusion:** Our data show that a small percentage of patients operated on in 2020 (11.7%) were contaminated by Sars-CoV-2 at some point after surgery, 2 of which being contaminated months after hospitalization. Given the average age of these patients and their comorbidities, it is known that they are at a higher risk for COVID-19 complications. According to the Rio Grande do Sul's Department of Health, the mortality rate for the novel coronavirus in the 60-69 age group is 5.97%. This study shows that thoracic surgery can be safely performed maintaining similar rates of contamination and mortality for the new coronavirus. Besides, it is known that choosing to postpone surgical treatment in patients with lung cancer may have a direct impact on prognosis and survival rates.

Keywords: Surgery, mortality, lung cancer

FP07.01 The MDM2/p53 Axis is a Therapeutic Vulnerability in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a rare cancer that afflicts ~3,200 new patients per year in the US and 25,576 deaths were reported worldwide in 2018. Currently there are no targeted therapies approved for MPM. Approximately 80-85% of MPM bear wild-type (WT) TP53, a key tumor suppressor subject to ubiquitylation and degradation via the E3 ligase, MDM2. Furthermore, p14ARF, a critical negative regulator of MDM2 encoded by the CDKN2A gene, is lost in up to 80% of MPM via deletion or methylation of CDKN2A. MDM2 inhibitors have been developed that result in increased p53 function to yield growth inhibition or apoptosis of tumor cells. The fact that the majority of MPM tumors bear WT TP53 and p14ARF/CDKN2A loss suggests a potential vulnerability that may be amenable to precision oncology strategies utilizing MDM2 inhibitors. **Methods:** A panel of six human mesothelioma cell lines (H28, H226, H290, H2052, H2452, MSTO211H) with defined TP53 and MDM2 status were submitted to in vitro clonogenic growth assays and immunoblot analyses with MDM2 inhibitors RAIN-32 (milademetan) and KRT-232 (AMG-232). Two MDM2 inhibitor-sensitive MPM cell lines (MSTO211H and H226) were propagated as flank xenografts in nu/nu mice and sensitivity to oral dosing with RAIN-32 was determined. **Results:**

Table

Cell Line	H28	H226	H290	H2052	H2452	MSTO211H
RAIN-32 IC_{50}, nM	32.0	25.0	19.1	9.5	7,448.0	5.5
KRT-232 IC_{50}, nM	54.8	103.0	102.7	75.3	6,333.0	24.4
TP53 status	WT	WT	WT	WT	WT, lo mRNA	WT
TP53 mRNA, rel. exp.	0.839	1.047	1.100	0.554	0.000	0.326
CDKN2A status	del	-	-	del	del	del
CDKN2A mRNA, rel. exp.	0.0000	0.0033	0.0000	0.0000	0.0002	0.0047
MDM2 mRNA, rel. exp.	0.57	0.48	0.96	0.94	0.10	0.51

The IC50 values for RAIN-32 and KRT-232 ranged from 6 - 32 nM and 24 -103 nM, respectively, in the 5 MPM cell lines bearing WT TP53, but was greater than 5 mM in H2452 cells which lack TP53 mRNA expression (see Table). Notably, the status of CDKN2A encoding the p16 cyclin-dependent kinase inhibitor and p19 ARF was null in all of the lines with undetectable mRNA levels observed. Moreover, RAIN-32 treatment (24 hr) increased p53 protein levels in the MDM2 inhibitor-sensitive lines as well as PARP cleavage. Daily oral dosing with RAIN-32 at 50 mg/kg significantly reduced the growth of both MSTO211H and H226 flank xenografts. Conclusion: MDM2 inhibitors selectivity and potently inhibit in vitro and in vivo growth of MPM cell lines bearing WT TP53. In light of the fact that there are no approved therapies following MPM treatment failure with standard cytotoxic agents or anti-PD1-based immunotherapy, the MDM2/p53 axis represents an attractive target for further clinical exploration in this disease.

Keywords: Mesothelioma, MDM2 inhibitor, TP53

FP07.02 Next Generation Sequencing Portrays Mutation Profilings of Malignant Pleural and Peritoneal Mesotheliomas

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Introduction: Malignant mesothelioma (MM) is a rare form of cancer mainly affecting the pleural and peritoneal lining. The 5-year survival rate of advanced patients is less than 1% due to the lack of effective medical therapies. To investigate the possibility of targeted therapy for MM patients, a deeper understanding of their mutation profilings is required. **Methods:** We reviewed 55 samples taken from 48 Chinese MM patients who underwent genetic testing at our institute from 2016. The samples included 33 tumor tissue samples, 19 blood samples , 2 pleural effusion and 1 ascetic fluid sample. Somatic mutation profiles were analyzed using hybridization capture based NGS, enabling the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (range 59–1021 genes). **Results:** Twenty-eight of the samples were taken from pleural mesothelioma patients, fourteen were from peritoneal mesothelioma patients and twelve were from mesothelioma patients with unknown primary sites. Similar to the previous study (Kato et al., Mol Cancer Ther, 2016), NF2 and TP53 mutations were identified in both types of mesothelioma. In our study, TP53 was the most frequently mutated gene in both pleural (30.43%, 7/23) and peritoneal (36.36%, 4/11) mesothelioma. In addition, NF2 mutation was also detected in both types (pleural mesothelioma 17.39%, 4/23; peritoneal mesothelioma 18.18%, 2/11), suggesting the possible effectiveness of mTOR inhibitors. RB1 mutation, rarely reported in MM, was also present in both types (pleural mesothelioma 8.70%, 2/23; pleural mesothelioma 18.18%, 2/11). The CDKN2A mutation detected in in both types as an actionable mutation (pleural mesothelioma 8.70%, 2/23; peritoneal mesothelioma 18.18%, 2/11). Relative to peritoneal mesothelioma, we can found EGFR (8.70%, 2/23)KRAS (8.70%, 2/23) and BRAF (4.35%, 1/23) in pleural mesothelioma samples, these patients might be also sensitive to the corresponding targeted drugs. **Conclusion:** NGS is a cost-effective tool to describe the genetic landscape of MM comprehensively, which will facilitate the development of novel therapeutics.

Keywords: NGS, mesotheliomas

FP07.03 Diagnostic Potential of Novel Mesothelioma-Specific MicroRNAs

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Introduction: One of the main challenges in diagnosing malignant pleural mesothelioma (MPM) is the differential diagnosis between MPM and other cancers, especially lung adenocarcinoma, that have metastasized to the pleura. Tissue-specific biomarkers could overcome this issue, and in particular microRNAs have been suggested to be very useful in this context, with several studies suggesting that many tissue-specific microRNAs remain to be annotated. Recently, an in-depth analysis of the TCGA small-RNA sequencing data of 87 MPM tumours identified previously undetected microRNAs that could distinguish MPM from non-small cell lung cancer (Martinez VD et al, AJRCM 2019: 61(2)). In our study, we aimed to validate these findings in an independent cohort of MPM patients and non-malignant control individuals using an alternative detection approach. **Methods:** This pilot study used diagnostic tissue specimens obtained from chemo-naïve patients who underwent diagnostic surgical procedures at the University Hospital Zurich, between 1999 and 2019. RNA was extracted from FFPE blocks of 20 patients with confirmed MPM, as well as 8 patients with a final diagnosis of non-malignant inflammatory reactions of the pleura. In addition, H28 (epithelioid) and MSTO-211H (biphasic) MPM cell lines were included. For detection of microRNAs, we designed primers for 10 novel mpm-miRs, RNU48 (reference gene), hsa-miR-16-5p and hsa-miR-21-5p (positive controls) based on the two-tailed RT-qPCR method (Androvic et al, NAR 2017: 45(15)). Mann-Whitney U Test was used to determine significance of expression differences between the two sample groups. **Results:** In initial analyses in H28 and MSTO-211H cell lines, seven of the novel mpm-miRs (mpm-miR-12, -18, -58, -65, -72, -79, 107, and -136) were detectable, as were the two positive controls. The remaining three mpm-microRNAs were undetectable with the two-tailed RT-qPCR method. Thus far, we have analysed expression of three candidates in the tissues selected for this feasibility study. We found all three mpm-microRNAs to be detectable in both MPM tissue and non-malignant pleura, suggesting expression is not limited to malignant mesothelial tissue. However, mean expression of all three candidates was significantly elevated in MPM when compared to non-malignant pleura: 23-fold (32.4 vs for mpm-miR-136, 7.5-fold (10.5 vs 1.4, $p<0.005$) for mpm-miR-18, and 10.3-fold (13.4 vs 1.3, $p<0.005$) for mpm-miR-58. Further analyses of additional mpm-miRs as well as evaluation of expression in a larger number of patients is currently underway. **Conclusion:** This preliminary study has shown that novel tissue-specific mpm-microRNAs identified from sequencing data are readily detectable in an independent series of MPM and non-malignant mesothelial tissue using a different method (RT-qPCR), with three candidates exhibiting significantly higher expression in tumour samples. Although further analyses on additional tumour (MPM and NSCLC) as well as non-malignant pleural tissue samples are required, our initial data confirm the expression of these novel tissue-specific microRNAs in MPM, highlighting the possibility that they might indeed hold diagnostic value.

Keywords: Mesothelioma, diagnosis, microRNAs

FP07.04 Effect of Tumor Treating Fields (TTFields) on DNA Damage and The FA-BRCA DNA Repair Pathway in Mesothelioma

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Introduction: Tumor Treating Fields (TTFields) are low intensity (1-3 V/cm), intermediate frequency (100-500 kHz), alternating electric fields with anti-mitotic effects on cancerous cells. TTFields therapy was clinically examined in patients with malignant pleural mesothelioma (MPM), an aggressive thoracic cancer with poor prognosis. The combined treatment of TTFields (150 kHz) with standard of care demonstrated a promising median overall survival without increases in systemic toxicity (STELLAR clinical trial). Consequently, TTFields concomitant with pemetrexed and a platinum-based chemotherapy agent are approved in the US and Europe as first line treatment for unresectable MPM. The current research aimed to elucidate the mechanism of action of TTFields in preclinical models of MPM. **Methods:** TTFields were applied using the inovitro™ system to NCI-H2052 and MSTO-211H human MPM cell lines. To investigate the effect of TTFields on DNA damage, detection of H2AX foci, a marker for DNA double strand breaks (DSB), was performed by fluorescent microscopy. Immunoblotting of cell lysates was used for determining levels of DNA damage repair related proteins. The cytotoxic effect of combining TTFields with cisplatin or pemetrexed was tested in vitro, and efficacy of concomitant TTFields, cisplatin, and pemetrexed was examined in vivo. For the animal studies, C57BL/6 mice were subcutaneously inoculated with RN-5 cells, and after 11 days of tumor development treated with TTFields or sham for 7 days, with additional injections of cisplatin and pemetrexed or vehicle. Tumor volume was determined from MRI images acquired before and after the treatment period. DNA damage within the tumor was examined in tumor slices. **Results:** TTFields at 150 kHz increased DNA DSB formation in both MPM cell lines. These effects were accompanied by increased expression of proteins involved in DNA damage-induced cell cycle arrest, p21 and p27. On the other hand, expression levels of proteins from the Fanconi Anemia (FA)-BRCA DNA repair pathway – FANCA, FANCD2, FANCJ, and BRCA1 – were reduced. Combining TTFields with standard of care chemotherapy resulted in an additive interaction for TTFields with pemetrexed, and a synergistic interaction for TTFields with cisplatin. In the animal model, tumor volume fold change was significantly decreased and levels of DNA damage within the tumor were significantly increased for the combination of TTFields with cisplatin and pemetrexed versus control. **Conclusion:** This research provides insight on the mechanism of action of TTFields in MPM. It demonstrates that TTFields elevated DNA damage, increased expression of DNA-damage related cell cycle arrest proteins, and decreased levels of FA-BRCA pathway proteins. This latter effect is further supported by the synergistic interaction displayed by the TTFields-cisplatin combination, as cisplatin-induced DNA damage requires the FA-BRCA pathway for repair.

Keywords: Tumor Treating Fields (TTFields), Mesothelioma, DNA damage

FP07.05 DREAM3R: Durvalumab With Chemotherapy as First Line Treatment in Advanced Pleural Mesothelioma - A Phase 3 Randomised Trial

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Introduction: Standard first line treatment for unresectable malignant pleural mesothelioma (MPM) is platinum-based chemotherapy with pemetrexed. Two recent, single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab and standard first line cisplatin and pemetrexed (CP) exceeded pre-specified criteria for proceeding to phase 3. DREAM3R aims to determine the effectiveness of adding durvalumab to first line CP chemotherapy in advanced MPM. **Methods:** Treatment-naïve patients with advanced MPM will be randomised (2:1) to EITHER durvalumab 1500 mg every 3 weeks plus doublet chemotherapy (cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2) every 3 weeks for 4-6 cycles, followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patient withdrawal; OR doublet chemotherapy alone for 4-6 cycles, followed by observation. The target sample size is 480 patients (320 durvalumab, 160 control) recruited over 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival is 0.70, with 2-sided alpha of 0.05, assuming a median survival of 15 months in the control group. Key inclusion criteria: MPM of any histological subtype; measurable disease as per RECIST 1.1 modified for mesothelioma (mRECIST 1.1) without prior radiotherapy to these sites; ECOG PS 0-1; and, adequate hematologic, renal, and liver function tests. Key exclusion criteria: prior systemic anticancer treatment for MPM; diagnosis based only on cytology or fine needle aspiration biopsy; contraindication to immunotherapy; and conditions requiring immunosuppressives or corticosteroids. Stratification: Age (18-70 years vs. > 70), sex, histology (epithelioid vs. non-epithelioid), and region (USA vs. ANZ). The primary endpoint is overall survival. Secondary endpoints include progression-free survival; objective tumour response (by mRECIST 1.1 and iRECIST); adverse events; health-related quality of life; and healthcare resource use. Tertiary correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutation burden, nuanced genomic characteristics, and HLA subtypes) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma. ClinicalTrials.gov Identifier: NCT04334759 and ACTRN 12620001199909.**:**

Keywords: durvalumab, immunotherapy, Mesothelioma

FP08.01 Lung Stereotactic Body Radiation Therapy for Treatment of Oligoprogressive and Oligorecurrent Metastatic Disease: A Multi-Center Analysis

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Introduction: There is growing clinical utilization of stereotactic body radiation therapy (SBRT) in the treatment of advanced lung cancer and lung metastases. In patients with limited progression, SBRT offers an ablative local therapy to address resistant clones. However, the role of lung SBRT in this setting is not well-defined. The purpose of this study is to determine clinical outcomes of SBRT for oligoprogressive and oligorecurrent intra-thoracic disease and its impact on the use of systemic therapy. **Methods:** An institutional database was queried to identify patients treated with lung SBRT for oligoprogression (OP) or oligorecurrence (OR) defined as disease progression at no more than 5 intrathoracic sites, ocurring either in the presence or absence of systemic therapy, repectively. Lung SBRT given as local consolidative therapy was excluded. Overall survival (OS), progression-free survival (PFS), and local control (LC) were estimated using Kaplan-Meier methods. Survival was measured from time of clinical progression. **Results:** 141 lung SBRT courses, comprising 172 target lesions and 118 patients were identified. 51.1% received lung SBRT for OP and 48.9% for OR. Median age at time of SBRT was 63 years. Median follow-up was 26 months for all patients. Median interval from initial diagnosis to OP/OR was 2.7 years. Primary site distribution was 45.8% lung, 11% colorectal, 9.3% head and neck, 8.5% melanoma, 8.5% sarcoma, 4.2% gynecologic, and 3.4% breast. Most patients (85.6%) received a single SBRT course; 10.2% received 2, 3.4% received 3, and 1 patient received 4 lifetime lung SBRT courses. A single progressive site was treated in 76.6% of SBRT courses, 2 sites in 22.7%, and 4 lesions for a single course. LC at 2 and 5 years were 88.5% and 86.4%. Median PFS was 7 months, 1- and 2-year PFS were 34.6% and 22.1%. Median intrathoracic PFS was 9 months, 1- and 2-year intrathoracic PFS were 40.6% and 28%. Median OS was 40 months, 2- and 5-year OS were 94.6% and 12.4%. Patients had received a median of 2 lines of systemic therapy at time of SBRT for progression. Of those who received systemic therapy, 40.3% received immunotherapy. For patients treated for OR, 47.8% remained off systemic therapy to end of follow-up, with median duration of 34.7 months. Median delay to initiation of systemic therapy was 10.7 months; 11.6% received systemic therapy immediately after SBRT. In patients treated for OP, SBRT allowed 70.8% of patients to continue treatment with the same agent, which lasted for a median duration of 6 months. 16.7% underwent a planned switch in systemic agent immediately after SBRT; and systemic therapy was discontinued in 12.5%. **Conclusion:** Lung SBRT for OP and OR is associated with durable control, with a subset of long-term survivors. SBRT both delayed the need for systemic therapy in nearly half of patients with OR, and delayed a change in systemic therapy for over two-thirds of patients with OP. These findings demonstrate the value of thoracic SBRT as a complement to systemic therapy and highlight the importance of multidisciplinary management in patients with advanced lung cancer and lung metastases.

Keywords: oligoprogression, SBRT, lung metastases

FP08.02 Artificial Neural Network-Based Tumour Recurrence Prediction in Non-Small Cell Lung Cancer Patients Following Radical Radiotherapy

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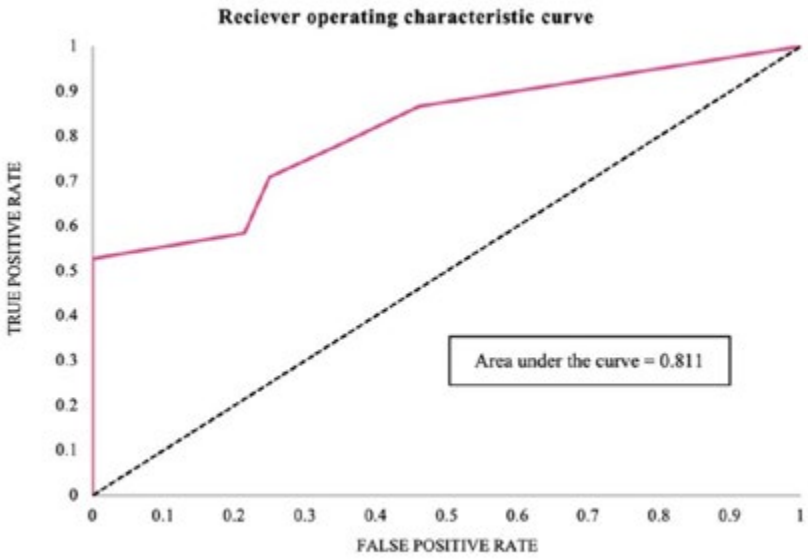
Introduction: Despite immunotherapy's addition into standard practice, progression-free survival for patients with non-small cell lung cancer (NSCLC) treated with radical radiotherapy remains disappointing. Identifying patients with a high probability of recurrence could allow modifications to treatment strategies and improve outcomes. Deep learning (DL), a subfield of machine learning in artificial intelligence, which employs artificial neural networks (ANNs) to learn complex, non-linear relationships from large datasets, has shown promise for numerous medical classification tasks. Here, we demonstrate DL's utility in predicting recurrent-NSCLC following radical radiotherapy, comparing its performance against classical logistic regression (CLR). **Methods:** Patient demographics, tumour characteristics, treatment and recurrence data were available for 451 NSCLC patients treated with radical radiotherapy between 2010 and 2015. We built CLR and DL models to predict tumour recurrence, a binary dependent variable, using the following baseline variables: age, gender, diagnosis to treatment time, planning target volume, histology, stage and chemotherapy administration. An ANN was developed and implemented using TensorFlow 2.0. Data preprocessing included the normalisation of continuous variables. The network structure comprised a fully connected input layer, four hidden layers and a binary output layer. The following parameters were used: a combination of leaky ReLU and sigmoid activation functions; binary cross-entropy loss; ADAM optimization with a learning rate of 0.0001. The dataset was randomly divided into training and testing sets at a ratio of 80:20. Metrics to compare CLR and DL performance included accuracy, precision, sensitivity, specificity, and F1 score. Also, the area under the receiver operating characteristic curve (AUC-ROC) was computed for DL. **Results:** The ANN outperformed CLR for all metrics assessed (see table) and exhibited a high AUC-ROC of 0.811 (see figure).

Metric	Logistic regression	Artificial neural network
Accuracy (%)	64.7	72.5
Precision (%)	72.4	81.3
Sensitivity (%)	66.8	70.9
Specificity (%)	61.7	75.0
F1 score	69.5	75.7



Conclusion: Using readily available clinical data, DL can predict recurrent-NSCLC following radical radiotherapy and outperforms CLR.

Keywords: Deep Learning, Classification, recurrence

FP08.03 Outcomes With Multi-Disciplinary Management of Central Lung Tumors Treated With Percutaneous High-Dose-Rate Brachytherapy

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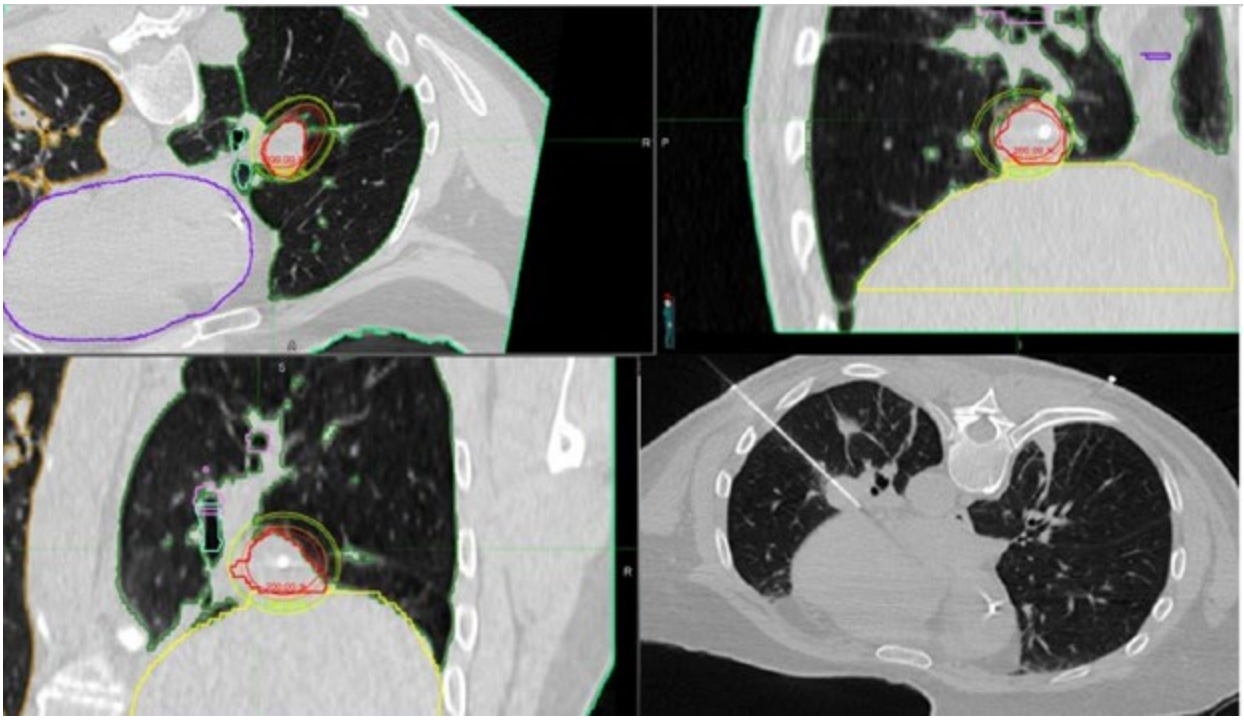
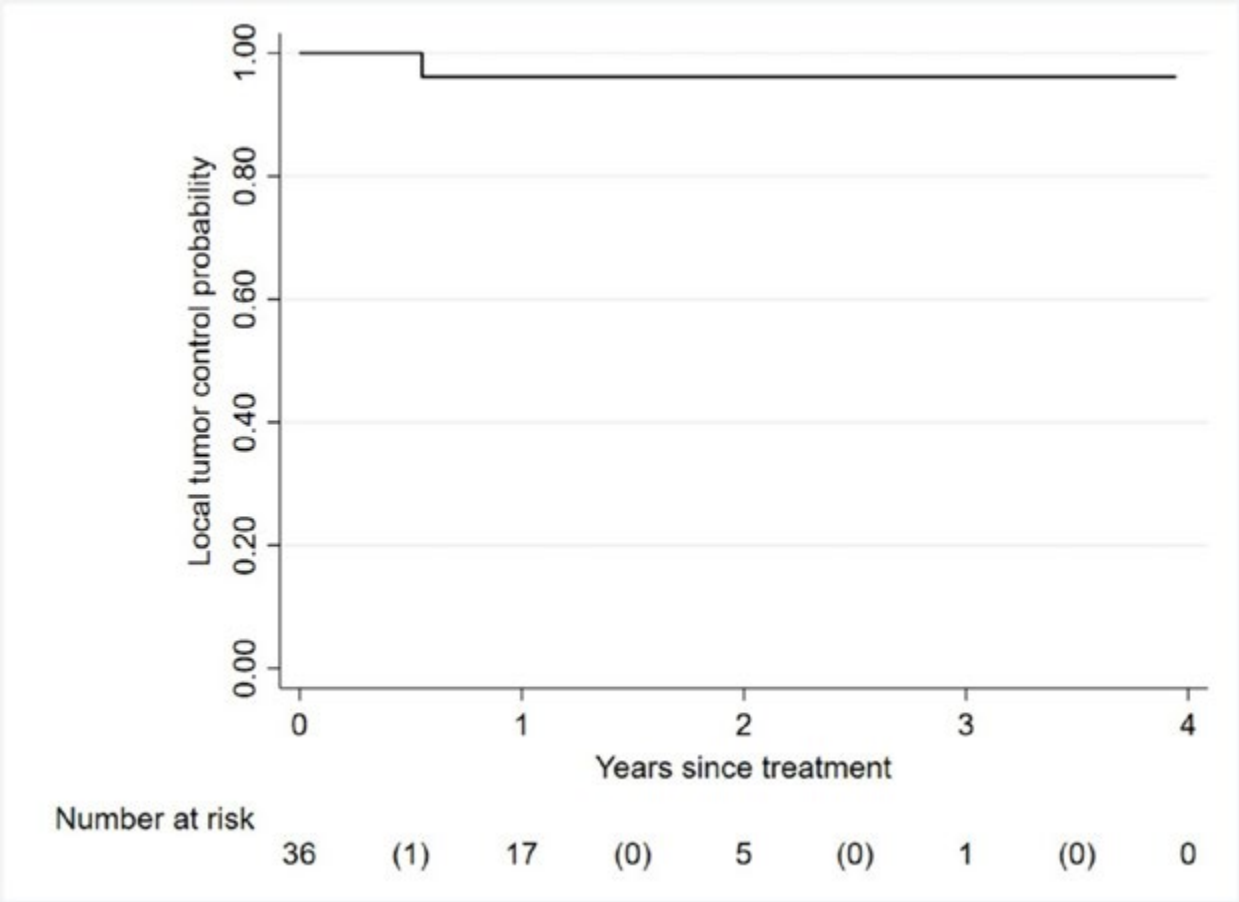
Introduction: Centrally located lung tumors present treatment challenges given their proximity to the carina and critical mediastinal structures. Therapeutic options may be limited for medically inoperable patients, particularly if they received previous thoracic radiotherapy. We introduced percutaneous high-dose rate (HDR) brachytherapy to improve the therapeutic ratio for patients with central lung tumors, and this report summarizes long-term safety and efficacy outcomes. **Methods:** From September 2015 to August 2019, the first 25 patients with 37 central lung tumors were treated with percutaneous HDR brachytherapy (Figure 1). Treatment was delivered by a multi-disciplinary team of interventional radiologists, pulmonologists, and radiation oncologists. Twenty-three patients received a median dose of 21.5Gy (range, 15-27.5) in a single fraction. Two patients received median dose of 24.75Gy (range 24-25.5Gy) over 2-3 fractions. Tumor local control (LC) was evaluated by Response Evaluation Criteria in Solid Tumors v1.1. Treatment-related toxicities were graded by Common Terminology Criteria for Adverse Events v5.0, with adverse events ≤90 days defined as acute, and those occurring after were defined as late. LC and overall survival (OS) rates were estimated by the Kaplan-Meier method



Results: Among the 37 treated central lung tumors, 88% were metastatic. Tumor location was central and ultra-central in 24.3% and 54.1%, respectively. Average tumor volume was 11.6 cm^3 (SD 12.4, range 0.57-62.8). Median follow-up was 19 months (range 3-48). The 2-year LC and OS rates were 96.2% and 65.5%, respectively (Figure 2). Four patients experienced acute grade 1-2 toxicity, whereas none developed a grade ≥3 event. The study did not identify patients with a late toxicity beyond 90 days of follow-up.



Conclusion: These data demonstrate that percutaneous HDR brachytherapy is a promising option for centrally located primary and metastatic lung tumors. Future comparisons to stereotactic body radiotherapy and other ablative techniques are warranted to expand multi-disciplinary management options.

Keywords: Central Lung Tumors, Oligometastasis, HDR Brachytherapy

FP08.04 Tumour Spread Through Air Space (STAS) In Lung Metastases

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Introduction: To evaluate the presence of tumour spread through air space (STAS) in lung metastases and its possible impact on prognosis. **Methods:** This is a retrospective study of prospectively collected data of patients (pts.) who underwent lung metastasectomy (January 2004 - December 2018) in our Thoracic Surgery division. Tissue slides were retrieved from the Pathology division for STAS evaluation of the metastatic nodule tissue. STAS was defined according to the 2015 WHO definition for lung tumors. Exclusion criteria for STAS included: cell clusters very proximal to the tumour margin; presence of neoplastic cells into the blood/lymphatic bronchial vessels; tumoural cell clusters present in incomplete or split areas of the section; presence of cell clusters distant from the tumour margin due to possible mechanical transposition. A blinded revision of all the archived tissue slides was individually performed by two trained pathologists with the aim of evaluating the presence of STAS. Discordant cases were jointly revised and discussed to reach a univocal opinion on each case. Differences between continuous and discrete variables were evaluated by t-student and Fisher's exact test or chi-square test. Overall survival (OS) was analysed using Kaplan-Meier method, log rank test, and Cox proportional hazards model. Presence of STAS was put in relation to clinical and pathological characteristics; follow-up; histology; MTS dimension; MTS site; number of subsequent metastasectomies; TNM score of the primary tumour; OS; disease free survival (DFS); time to progression (TTP) . **Results:** Three-hundred metastasectomies were retrieved of which 184 samples were considered for the study (81 pts. were excluded because lost at follow-up, 35 samples were not analysable). One-hundred and seven pts. were males (58%), 95 were smokers (56,5%), median age was 61yrs (range:16-82). STAS was found in all histotypes but was significantly prevalent in the adenocarcinoma histology ($p<0.001$). Overall, the presence of STAS seemed not to impact DFS however, in the adenocarcinoma subset, STAS was related to a worse DFS ($p<0.04$) and TTP ($p<0.05$) and STAS+ colorectal adenocarcinoma metastases were correlated to a worse TTP if compared to other STAS+ histotypes ($p<0.029$) (Fig.1).

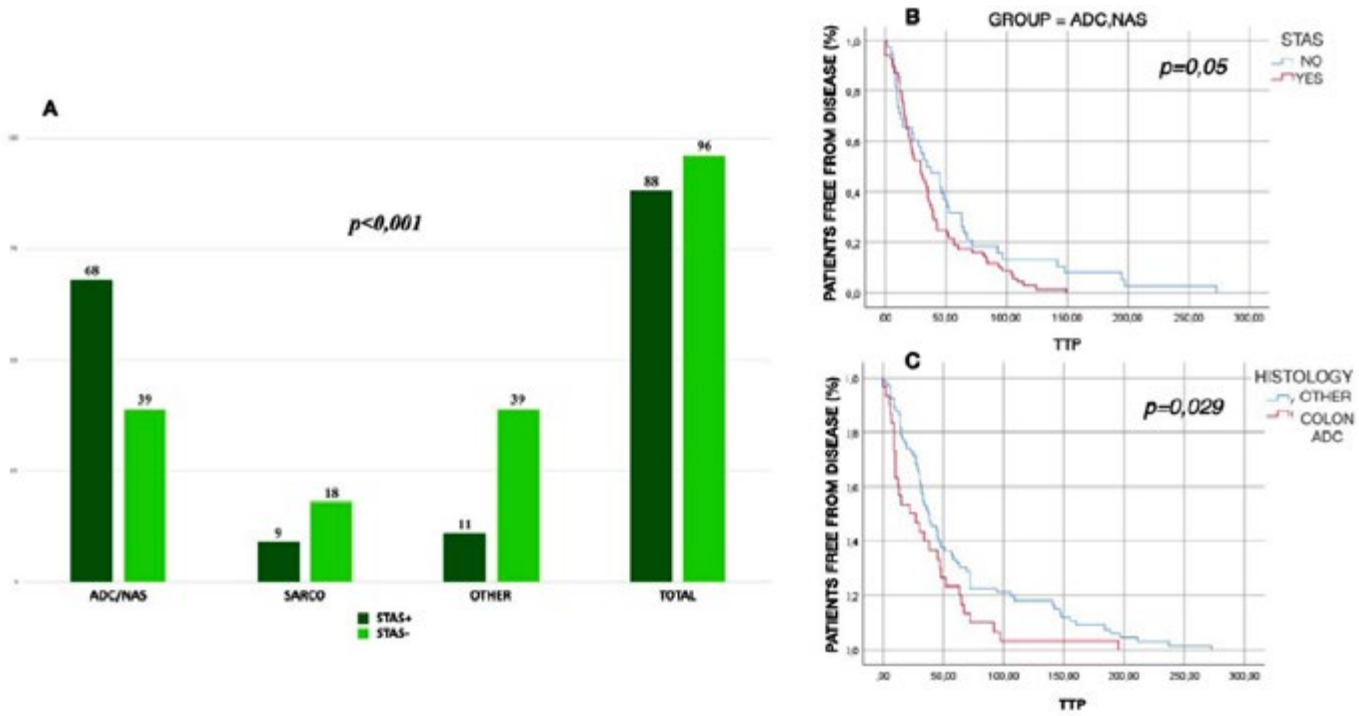

FIGURE 1. A: incidence of STAS among all histotypes; B: TTP in STAS+ adenocarcinoma group vs. other histologies; C: TTP in colon ADC vs. other histologies

Conclusion: STAS was present in lung metastases but significantly more present in the adenocarcinoma subgroup with a more aggressive behaviour, especially the colorectal one. Further studies are needed to confirm our preliminary results.

Keywords: spread through air space, STAS, lung metastases

FP09.01 Mobocertinib in Platinum-Pretreated EGFR Exon 20 Insertion+ Metastatic NSCLC Patients With/Without Prior Anti-PD(L)-1 Therapy

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Introduction: No approved, targeted therapies are available to specifically treat EGFR exon 20 insertion+ (ex20ins+) non–small cell lung cancer (NSCLC). Anti-programmed-death (ligand)-1 (anti-PD(L)-1) therapies are recommended for NSCLC patients without activating mutations as preferred therapy; however, their efficacy in EGFR ex20ins+ NSCLC is limited, with median progression-free survival (PFS) typically of 2–3 months. Mobocertinib (TAK-788) is an oral EGFR tyrosine kinase inhibitor (TKI) targeting EGFR ex20ins; it holds Breakthrough Therapy Designation for patients with EGFR ex20ins+ NSCLC who previously progressed on platinum-based chemotherapy (in the United States) or who had prior chemotherapy (in China), based on preliminary phase 1/2 results. Here we present data for platinum-pretreated patients (PPP; n=114) with/without prior anti-PD(L)-1 therapy from this study. **Methods:** The 3-part, open-label, phase 1/2, multicenter study (NCT02716116), consisting of dose-escalation/-expansion and extension cohorts, evaluated mobocertinib in patients with EGFR ex20ins+ metastatic NSCLC. PPP (from all 3 parts) had ECOG performance status 0–1, and ≥1 prior line of therapy for locally advanced/metastatic disease; patients received mobocertinib 160 mg QD. Primary endpoint was confirmed overall objective response rate (ORR) per RECIST v1.1 assessed by independent review committee (IRC). Efficacy endpoints included confirmed ORR per investigator; disease control rate (DCR), duration of response (DoR), and PFS per IRC and investigator; and overall survival (OS). **Results:** Among PPP (n=114), 43% had received prior immunotherapy. Among patients with prior anti-PD(L)-1 therapy (n=48), 32 (67%) had received ≥2 prior systemic anticancer lines; 28 (58%) received immunotherapy as part of most recent anticancer therapy. Confirmed ORR per IRC in PPP was 28% [95% CI: 20–37]; DCR was 78% [95% CI: 69–85]. Confirmed ORR per IRC was 25% in PPP with prior anti-PD(L)-1 therapy and 30% in PPP without prior anti-PD(L)-1 therapy; other efficacy endpoints are shown in the **Table**. Treatment-related adverse events (TRAEs) observed ≥10% more frequently in patients with prior anti-PD(L)-1 were nausea, fatigue, and maculopapular rash. No significant difference was observed in treatment-related diarrhea or pneumonitis/interstitial lung disease. AEs led to treatment discontinuation in 10 (21%) and 9 (14%) patients with and without prior anti-PD(L)-1 therapy, respectively.

	PPP With Prior Anti-PD(L)-1 Therapy (n=48)	**PPP Without Prior Anti-PD(L)-1 Therapy (n=66)**
Efficacy		
Confirmed ORR per IRC, n (%) [95% CI]	12 (25) [14–40]	20 (30) [20–43]
Confirmed ORR per investigator, n (%) [95% CI]	18 (38) [24–53]	22 (33) [22–46]
Confirmed DCR per IRC, n (%) [95% CI]	37 (77) [63–88]	52 (79) [67–88]
≥6-month DoR per IRC*, n (%)	7 (58)	12 (60)
Median PFS per IRC, mo [95% CI]	7.4 [5.5–21.1]	7.3 [5.4–10.2]
Median OS, mo [95% CI]	21.0 [13.1–not estimable]	24.0 [13.1–not estimable]
Safety Overview		
Any TRAE	48 (100)	66 (100)
Grade ≥3 TRAEs	28 (58)	26 (39)
Serious AEs	26 (54)	30 (45)
Dose modification due to AEs	37 (77)	36 (55)
Discontinuation due to AEs	10 (21)	9 (14)
***Per descriptive data.**		

Conclusion: Efficacy of mobocertinib was similar in patients with and without prior anti-PD(L)-1 therapies. Safety was consistent with EGFR TKI class and manageable in both populations.

Keywords: EGFR tyrosine kinase inhibitor, exon20 insertion, non-small cell lung cancer

FP09.02 Mobocertinib (TAK-788) in EGFR Exon 20 Insertion+ Metastatic NSCLC: Patient-Reported Outcomes From EXCLAIM Extension Cohort

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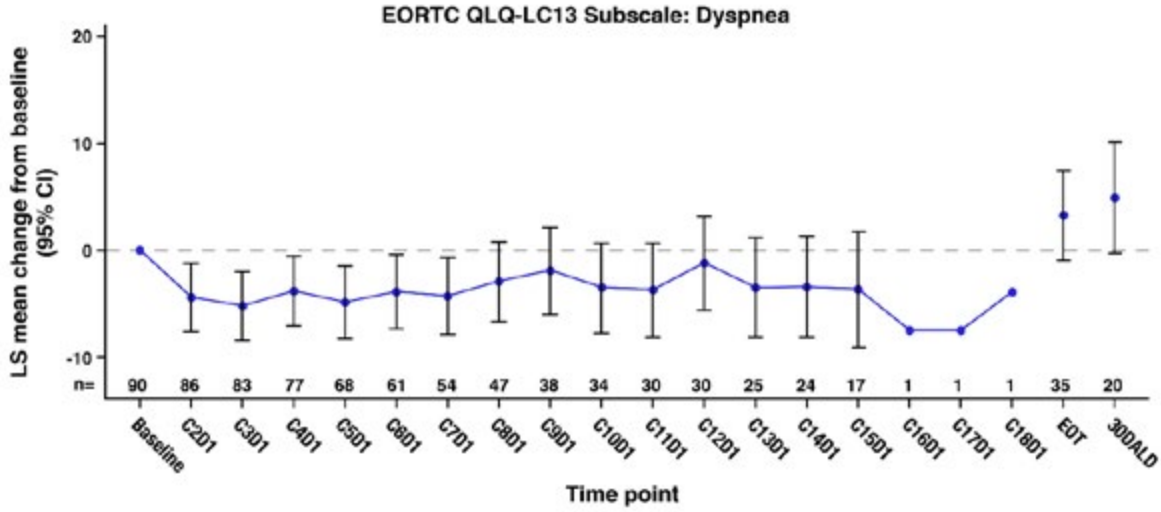
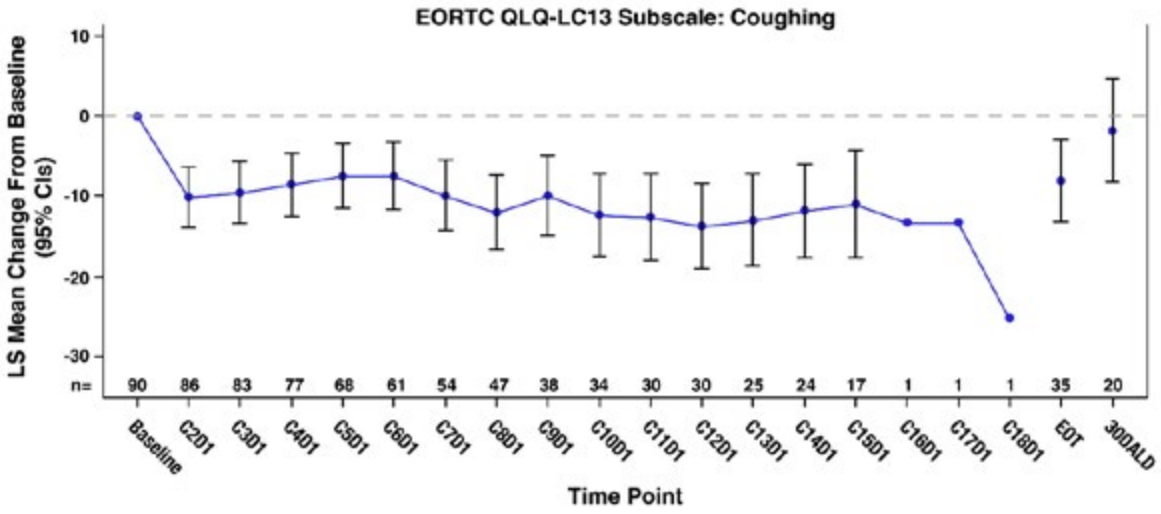
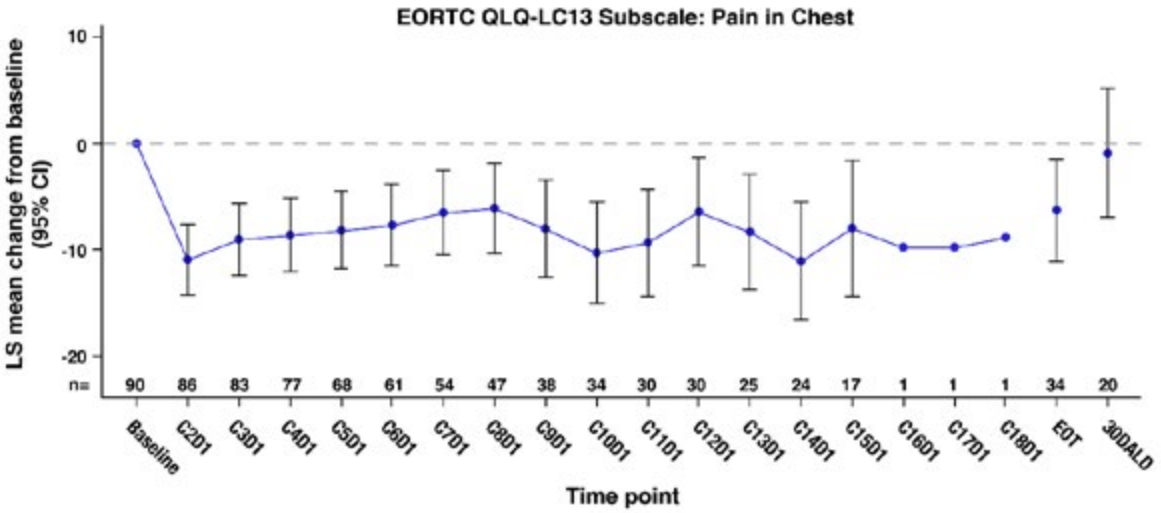
Introduction: Maintaining health-related quality of life (HRQoL) and independence in daily activities are important factors to cancer patients. Mobocertinib is an oral, first-in-class EGFR tyrosine kinase inhibitor that selectively targets EGFR exon 20 insertions (ex20ins). We previously reported that mobocertinib resulted in confirmed objective response rates (ORRs) assessed by an independent review committee (IRC) of 25% and a median progression-free survival (PFS) of 7.3 months in patients from the EXCLAIM extension cohort of the phase 1/2 study in EGFR ex20ins+ non–small cell lung cancer (NSCLC). Treatment with mobocertinib in the platinum-pretreated patients from the same study resulted in a confirmed ORR by IRC of 28% and median PFS of 7.3 months in this patient population. Here we present patient-reported outcome (PRO) data from the EXCLAIM extension cohort. **Methods:** The EXCLAIM extension cohort of the phase 1/2 multicenter study (NCT02716116) evaluated mobocertinib 160 mg orally once daily in previously treated metastatic NSCLC patients with EGFR ex20ins. PROs were assessed with European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30) v3.0, the lung cancer module (QLQ-LC13) v3.0, the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L), and select items (decreased appetite, difficulty swallowing, nausea, vomiting, diarrhea, rash, fatigue, and dry skin) from the PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE). Questionnaires were administered at baseline and selected visits before any clinical measurements, assessments, or procedures were performed. **Results:** Global health status/quality-of-life via the EORTC QLC-C30 was maintained during time on mobocertinib therapy, with most patients maintaining or improving from baseline scores (least-squares mean change -1.8 [P=0.235]). Clinically meaningful improvements from baseline in QLQ-LC13 symptom scores (defined as ≥10-point decrease in symptom scores) were observed for core lung cancer symptoms of dyspnea in 54.4% of patients, coughing in 46.7%, and pain in chest in 38.9%. Improvements were evident at cycle 2 and maintained throughout treatment (least-squares mean changes from baseline: dyspnea -3.2 [P=0.019]; cough -9.3 [P<0.001]; and pain in chest -8.2 [P<0.001]; **Figure**). Patient health status via the EQ-5D-5L was maintained throughout the study. HRQoL was maintained despite the reporting of common adverse events collected via the PRO-CTCAE, including diarrhea, dry skin, and rash. **Conclusion:** PROs for mobocertinib were favorable in previously treated patients with EGFR ex20ins+ metastatic NSCLC. Improvements in core NSCLC symptoms were observed and overall HRQoL was maintained during therapy, despite adverse events such as rash and gastrointestinal-related symptoms, including diarrhea.







Keywords: health-related quality of life, non-small cell lung cancer, exon20 insertion

FP09.03 Phase II Randomized Trial to Evaluate Prednisone Taper With or Without Nintedanib for the Treatment of Radiation Pneumonitis

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Introduction: Radiation pneumonitis (RP) is the most common limiting toxicity for definitive thoracic radiation therapy. Currently, the only standard management consists of an empiric prolonged steroid taper. Nevertheless, many patients with RP experience subsequent pulmonary exacerbations and worsening lung function leading to significant decline in quality of life. Nintedanib, a multiple tyrosine kinase inhibitor, has been shown to be effective in the treatment of idiopathic pulmonary fibrosis that shares many pathophysiological pathways with the chronic inflammation of the subacute phase of RP. This is the first prospective trial for the treatment of RP. The goal was to investigate the efficacy and safety of nintedanib in addition to a standard prednisone taper in reducing pulmonary exacerbations in patients with grade 2 or higher (G2+) RP. **Methods:** In this prospective, phase 2, randomized, double-blinded, placebo-controlled trial, patients with newly diagnosed G2+ RP were randomized 1:1 to nintedanib 150mg twice daily for 12 weeks or placebo in addition to a standard 8-week prednisone taper starting at 40mg. The primary endpoint was freedom from pulmonary exacerbations within 12 months defined as development or unexplained worsening of cough, dyspnea, hypoxia or pneumonitis lasting more than 4 days, new or worsening pulmonary infiltrates on chest CT without significant pneumothorax or pleural effusion, and exclusion of alternative causes. Secondary endpoints, including pulmonary function tests, radiographic fibrosis, quality of life, and hospitalizations will be reported in the future. Kaplan-Meier survival analysis was used to estimate probability of being free from exacerbation, with log rank test for p value and 95% confidence interval (CI). The study was closed early due to slow accrual (final enrollment 34 out of 68 planned patients). **Results:** Of 34 patients enrolled, three patients withdrew consent and one was not treated. Of the evaluable 30 patients, 18 were randomized to Arm A (nintedanib + prednisone taper) and 12 to Arm B (placebo + prednisone taper). Five patients in Arm A failed to complete treatment (three noncompliant, one dose limiting grade 2 venous thrombosis, one death). Median follow-up was 368 days. There was no statistically significant difference in freedom from exacerbation between treatment arms at one year (p=0.074) or overall (p=0.136). In Arm A, an estimated 78% of patients were free from exacerbation at 100 days (CI 61%-100%) versus 50% of patients in Arm B (CI 28%-88%), p=0.111. Median freedom from exacerbation was not reached in Arm A versus 193 days in Arm B. **Conclusion:** After the initial onset of G2+ RP, treatment with nintedanib plus prednisone taper did not significantly increase the duration of freedom from pulmonary exacerbation compared to placebo plus prednisone taper. However, there was a trend toward a benefit from nintedanib, with a notably higher freedom from exacerbation in the nintedanib arm at 100 days. Although this study was limited by low accrual, the numerical differences observed warrant further evaluation of nintedanib as an agent to prevent pulmonary exacerbations following RP. This study can serve as a benchmark for further trials studying the treatment of RP.

Keywords: pneumonitis, radiation pneumonitis, pulmonary exacerbation

FP09.04 Impact of Brain Metastasis Status on Adverse Events (AEs) Requiring Dose Reduction Among Patients Receiving Lorlatinib

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Introduction: Anaplastic lymphoma kinase (ALK)-rearranged (ALK+) and ROS1-rearranged (ROS1+) non-small cell lung cancers (NSCLC) are associated with a propensity towards central nervous system (CNS) dissemination. Lorlatinib is a third-generation tyrosine kinase inhibitor (TKI) that is approved for treatment of metastatic ALK+ NSCLC based on robust intracranial and extracranial activity. Although not approved for ROS1+ NSCLC, lorlatinib is widely used for treatment of this disease based on its promising systemic activity in the post-crizotinib setting, including among patients with brain metastasis. Compared to the first-generation ALK and ROS1 TKI crizotinib and second-generation ALK TKIs, lorlatinib has a unique side effect profile that includes neurocognitive adverse events (AEs). It remains unknown whether CNS metastases impact the lorlatinib AE profile. **Methods:** Patients with ALK+ or ROS1+ NSCLC treated with lorlatinib at a starting dose of 100 mg were identified. Patients received lorlatinib through phase I/II studies or the expanded access program at Massachusetts General Hospital between 10/2014 and 6/2019. Incidence of lorlatinib-associated AEs (Common Terminology Criteria for Adverse Events version 4.03) requiring dose reduction was compared for patients with and without brain metastases. Cognitive, mood, and speech effects were clustered to be consistent with the registrational phase I/II lorlatinib study. The following were also designated CNS AEs: hallucination, new sleep disturbance, new movement disorders, dizziness, and new onset sensory changes without neuropathy. **Results:** We identified 130 patients with ALK+ (n=97) or ROS1+ (n= 33) NSCLC treated with lorlatinib. Two-thirds of patients had received ≥2 TKIs prior to lorlatinib. A total of 106 (82%) had brain metastases and 66 (51%) had received CNS radiation, with median interval between radiation and lorlatinib of 13.8 months (range 1.0-90.9). Compared to patients with brain metastases, there was no difference in the overall rate of treatment-related AEs requiring dose reduction (47% vs 54%, p=0.652) or the frequency of dose reductions for CNS-specific AEs (33% vs 25%, p=0.627) in patients without brain metastases. The median time to onset of CNS AEs requiring dose reduction was less than 1 month for both groups. Frequency of dose reduction for non-CNS toxicity (25% vs 38%) also did not differ significantly (p=0.312) between groups. With the exception of two patients with CNS metastases who developed grade 3 cognitive disturbance, AEs requiring dose reduction in both groups were all grade 1-2. **Conclusion:** The overall rates of dose reduction and CNS-specific AEs requiring dose reduction did not differ for patients with and without brain metastases, suggesting that localization of metastases to the CNS does not enrich for the neurocognitive adverse events that distinguish lorlatinib from other ALK TKIs. Further study of risk factors predisposing to CNS toxicity from lorlatinib is indicated.

Keywords: ALK, Lorlatinib

FP10 PALLIATIVE AND SUPPORTIVE CARE

FP10.01 The Efficacy of Immunotherapy in non-Small Cell Lung Cancer Patients with Uncommon Mutations: a Real World Research from Single Site

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Introduction: Patients with uncommon mutations such as BRAF, RET, MET, ROS1 or HER2-mutated NSCLC are usually treated with targeted therapies, and immune checkpoint inhibitors have become an important treatment option for non-small cell lung cancer (NSCLC)However, efficacy of immune checkpoint drugs (ICIs) in patients harboring uncommon mutations is limited. We aim to evaluate the efficacy of ICIs in those patients in real-world settings. **Methods:** Retrospective data were collected from NSCLC patients who were BRAF, RET, MET, ROS1 or HER2 mutation positive tested by next generation sequencing (NGS) and treated with immunotherapy The clinicopathological characteristics, overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS)of patients were analyzed. **Results:** A total of 29 patients enrolled in the study, of which, median age was 59 years old, 34.5% were smokers and 79.3% were adenocarcinoma. 51.7% of the patients were treated with immunotherapy as the first line and 27.6% as second-line. Patients with BRAF, HER2, MET, RET, ROS1 mutation were 7 ,11 ,5 ,3 ,3 cases, respectively. Programmed cell death ligand 1(PD-L1) expression was assessed in 11 patients with 31.9% incidence rate for PD-L1 positive was and 20.7% for PD-L1≥50%. 24% of patients achieved partial responses with BRAF (n=2), HER2 (n=1), MET (n=2) and RET (n=2) and 58.6% (17/29) achieved stable disease (with total ORR 24.1%. The DCR was 82.8% and median PFS was 6.7 months (95% confidence interval,4.4-9.0). **Conclusion:** Patients with uncommon mutated NSCLC could benefit from ICIs. Since uncommon mutations are rare and efficacy would be different due to diverse mutation type, data from real word study would provide valuable evidence for clinical practice.

Keywords: immunotherapy, non-small cell lung cancer, uncommon mutations

FP11.01 Sustaining and Accelerating Research in Rare Oncogene-Driven Lung Cancers: Lessons From The 2020 ROS1der Research Roundtable

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Introduction: The ROS1ders, Inc. is a non-profit corporation comprised of ROS1+ patients and family members with a goal of improving outcomes for ROS1+ cancers through community, education, and research. In October 2020, The ROS1ders held two virtual facilitated "ROS1der Research Roundtables" to understand how The ROS1ders can sustain and accelerate ROS1 lung cancer research. **Methods:** The Roundtables were invitation-only and brought together members of the ROS1+ patient community with an international group of leading ROS1 clinicians and researchers from three continents. Ten out of fifteen invited researchers and clinicians were available to attend. Each two-hour Zoom meeting was facilitated by an experienced patient research advocate from the cancer advocacy community and followed the same agenda. **Results:** The Roundtable results are summarized under four themes: Barriers to ROS1 research: --Given its rarity, ROS1 cancer accounts for only a small percentage of patients seen by most hospitals and clinics. The small population does not generate many cancer models or patient specimens for research, or support accrual for Phase 3 trials. Created models may not be publicly available. --Some research centers cap the number of clinical trials they allow to be open at the same time, which means those cancers with smaller populations might not have priority. --Survivors who have/had ROS1 cancer are widely scattered making it difficult to address research questions that require collection of longitudinal data. --Research funding may be less accessible because funders believe fewer patients will benefit. Accelerating ROS1 research --Expand access to ROS1 specimens, cancer models, and study results for academic research to support successful grant submissions and preclinical research. --Leverage real-world data to support answers to most pressing questions for the ROS1 community. --Study novel mechanisms of resistance. --Explore the use of liquid biopsies and other biomarkers to rapidly evaluate patient's likely response to treatment (especially for combination therapies), estimate risk of recurrence, and detect progression early. --Expand basic research into the role of ROS1 in human biology. --Develop Patient Reported Outcome (PRO) measures to use in clinical trials of novel investigational agents. --Explore synthetic controls for trials. --Expand approach to immunotherapy translational studies. Sustaining ROS1 research --Share methods for collecting fresh ROS1 patient specimens and creating more ROS1 cancer models. --Broaden studies of drug resistance to multiple oncogene-driven lung cancers to identify common bypass mechanisms. --Build the field of ROS1 investigators. --Include funding for correlative studies in investigator-initiated trials. --Create bridges between academia and industry to develop strategic partnerships that are a "win-win." --Design smart early trials so that a preliminary read is available which, in turn, would provide rationale for a larger, randomized study. --Promote international collaborations between ROS1 researchers in different countries. Ways The ROS1ders might help accelerate research --Help generate more patient-derived ROS1 specimens and cancer models. --Enable real-world data collection and surveys. --Provide research funding for ROS1 projects. **Conclusion:** The ROS1der Research Roundtable provides a clear framework for conducting patient-partnered research to drive progress in a rare-oncogene driven lung cancer subset and has broader applicability in other rare cancers.

FP12 PREDICTIVE TUMOR BASED ASSAYS/BIOMARKERS/PATHOLOGY

FP12.01 PD-L1 Assessment in Cytology is Comparable to Histology in Predicting Treatment Response to Checkpoint Inhibitors in NSCLC

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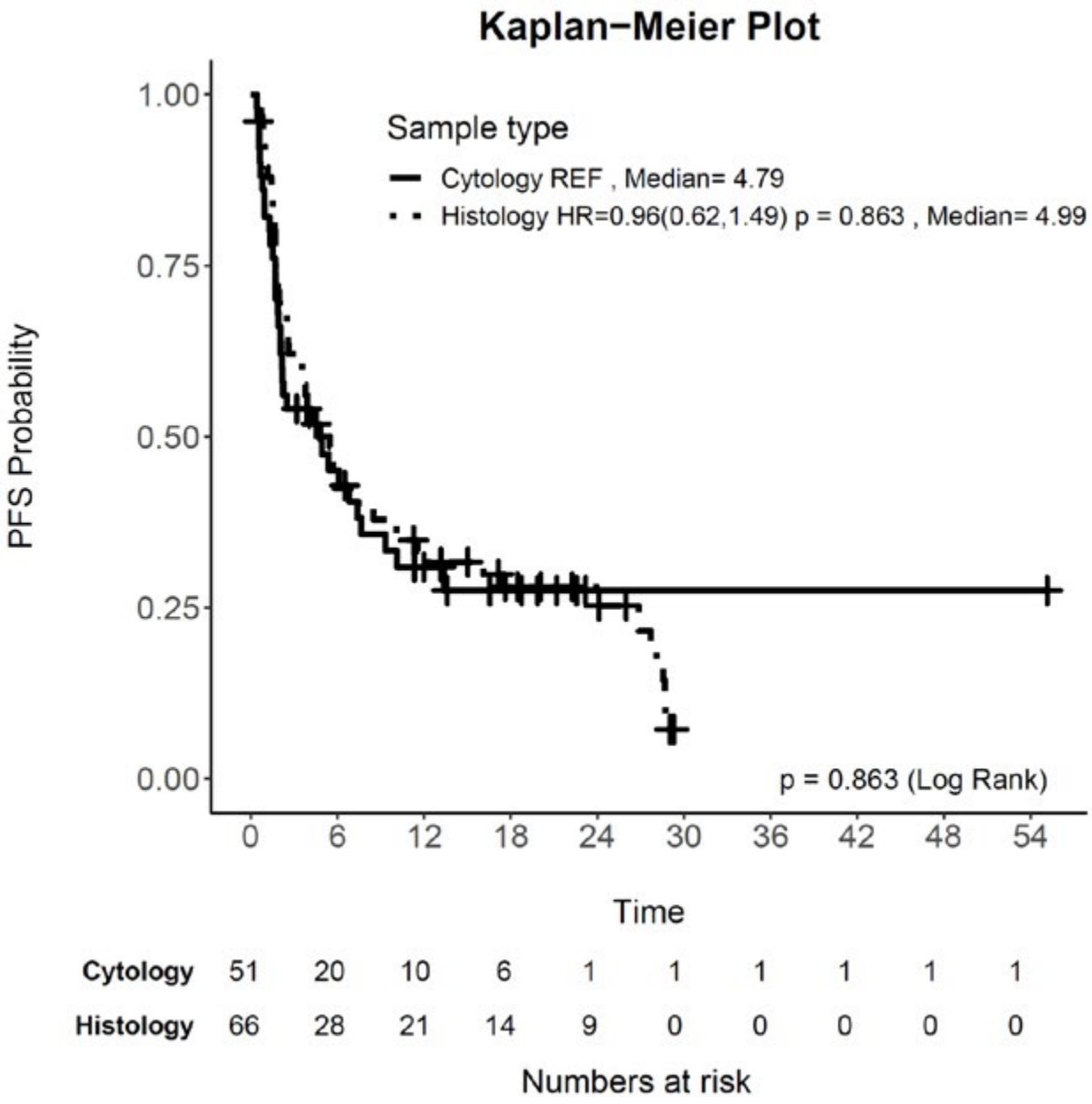
Introduction: Tumor PD-L1 expression is a key biomarker in determining first-line therapy in advanced NSCLC. PD-L1 testing was developed with histology samples; however cytology (effusions, exfoliative specimens, fine needle aspirates) is critical for diagnosis and predictive testing in a large proportion of this patient population. Prior studies indicated a similar distribution of PD-L1 expression levels and high concordance at least for the ≥50% cut-off value with PD-L1 IHC 22C3 pharmDx. We retrospectively examined the response to PD-1/PD-L1 immune checkpoint inhibitors (ICI) in patients with PD-L1 testing performed on cytology compared to histology. **Methods:** We reviewed all NSCLC cytology and histology samples tested for PD-L1 using the 22C3 pharmDx assay at the University Health Network between 2013 and 2020. PD-L1 assessment on cytology samples was conducted with formalin-fixed paraffin-embedded cell blocks if a minimum of 100 "viable" tumor cells were present. Samples were received fresh or pre-fixed with CytoLyt. A subset of patients treated with ICIs at our center was reviewed for ORR and PFS and outcomes were compared between patients with PD-L1 assessment by cytology and histology. **Results:** We identified 487 and 1683 unique patients with cytology- and histology-derived PD-L1 expression, respectively. Informative testing rates were similar between cytology and histology (91.5% vs 93.0%; p=0.27). The distribution of PD-L1 expression levels (≥50%/1-49%/<1%) was 29.8%/27.9%/42.2% for cytology and 33.6%/26.9%/39.5% for histology. Clinical data were available for 117 patients treated with single agent ICI including 51 patients with cytology- and 66 patients with histology-derived PD-L1. Baseline characteristics including age, sex, smoking history, and tumor histology were similar. There was a higher proportion of tumors with PD-L1 expression ≥50% among patients with cytology samples (76% vs 56%; p=0.03). ORR for cytology vs histology was 38% vs 35% (p=0.85). Median PFS for cytology vs histology was 4.8 months vs 5.0 months (p=0.86, Figure 1). ORR for cytology (n=38) vs histology (n=34) in the subset of patients treated with first-line pembrolizumab who had PD-L1 ≥50% expression was 43% vs 56% (p=0.35) and median PFS was 6.1 vs 9.5 months (p=0.35). **Conclusion:** Treatment outcomes to ICI are not different for patients with PD-L1 22C3 pharmDx assessment on cytology compared to histology and are comparable to those reported in clinical trials. PD-L1 test success rates and expression levels for cytology and histology were similar in cases deemed suitable for reflexive test initiation by the pathologist and support the utility of clinical biomarker testing on cytology samples.



Keywords: histology, cytology, PD-L1

FP12.02 Pembrolizumab as a Monotherapy or in Combination With Platinum-Based Chemotherapy in NSCLC: Correlation With Blood Biomarkers

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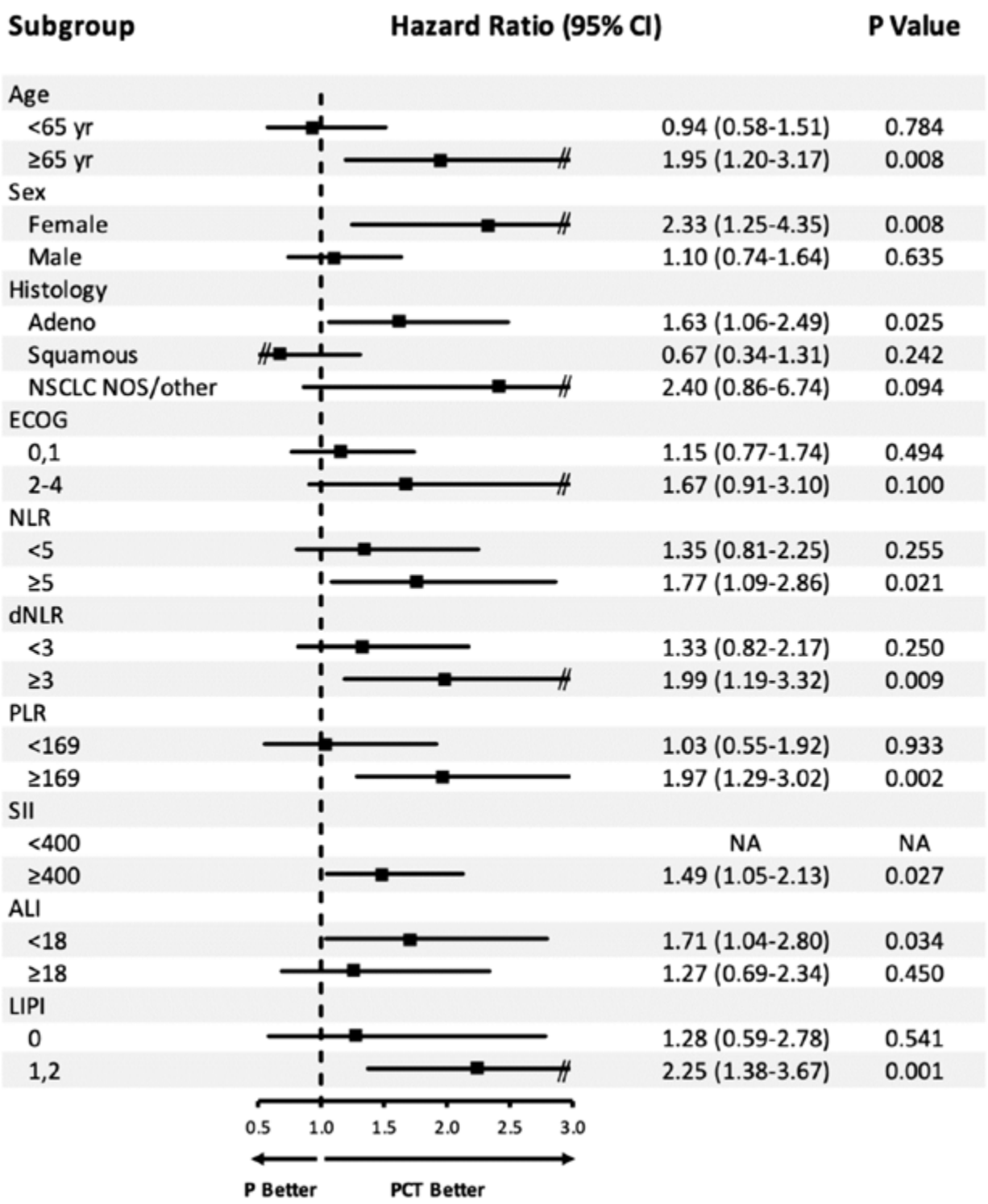
Introduction: Both pembrolizumab as a monotherapy (P) and a combination with platinum-based chemotherapy (PCT) represent standard 1st-line treatment (Tx) options for advanced NSCLC (aNSCLC) with PD-L1 tumor proportion score (TPS)≥50%. No predictive biomarkers exist to guide Tx decisions. **Methods:** 423 consecutive patients (pts) with EGFR/ALK/ROS1-wild-type PD-L1 TPS≥50% aNSCLC receiving P (group P, n=302) or PCT (group PCT, n=121) as a 1st-line Tx were identified in the electronic databases of 5 Israeli cancer centers. Overall survival (OS) was assessed in correlation with blood biomarkers (BB): NLR, dNLR, PLR, SII, LIPI, ALI. **Results:** Baseline characteristics were well balanced, except for age (p=0.0001) and ECOG PS (p=0.01) in favor of group PCT. Median OS was 13.8 months (mo) (95% CI, 11.0-18.2) and 21.3 mo (95% CI, 14.8-NR) in groups P and PCT, respectively (p=0.04). In the propensity score matching analysis (n=236; 118 pts in each group matched for age, sex and ECOG PS), mOS was 17.2 mo (95% CI, 13.2-36.5) and 21.3 mo (95% CI, 14.8-NR) in groups P and PCT, respectively (p=0.44). In group P, NLR, dNLR, PLR, LIPI, and ALI, along with age and ECOG PS significantly correlated with OS in uni- and multivariate COX regression analysis, whereas in group PCT, none of the BB demonstrated a significant correlation (a separate multivariate analysis was done for each of the BB; the model included sex, age, histology and ECOG PS - Table). In the whole cohort, OS favored PCT over P in pts≥65 years (p=0.008), females (p=0.008), NLR≥5 (p=0.02), dNLR≥3 (p=0.009), PLR≥169 (p=0.002), SII≥400 (p=0.03), ALI < 18 (p=0.03) and LIPI 1+2 (p=0.001) (Figure).

	Pts treated with P (n=302)				Pts treated with PCT (n=121)			
	Univariate analysis (HR; 95% CI)	p value	Multivariate analysis (HR; 95% CI)	p value	Univariate analysis (HR; 95% CI)	p value	Multivariate analysis (HR; 95% CI)	p value
Age (≥65 vs <65)	1.44 (1.04-2.00)	**0.029**			0.75 (0.41-1.37)	0.344		
Sex (male vs female)	0.96 (0.70-1.32)	0.793			2.07 (1.07-4.01)	**0.032**		
ECOG PS (2-4 vs 0,1)	2.69 (1.96-3.69)	**<0.001**			2.02 (1.04-3.93)	**0.038**		
Histology (sq. vs adenoca)	1.13 (0.77-1.68)	0.533			2.52 (1.27-5.01)	**0.009**		
PD-L1 TPS (≥75% vs <75)	0.91 (0.62-1.33)	0.621			0.55 (0.28-1.09)	0.085		
NLR (≥5 vs <5)	1.95 (1.41-2.70)	**<0.001**	1.74 (1.23-2.47)	**0.002**	1.56 (0.84-2.90)	0.161	1.19 (0.60-2.34)	0.618
dNLR (≥3 vs <3)	1.98 (1.43-2.74)	**<0.001**	1.91 (1.36-2.69)	**<0.001**	1.40 (0.75-2.64)	0.294	1.29 (0.66-2.51)	0.452
PLR (≥169 vs <169)	1.75 (1.24-2.48)	**0.002**	1.58 (1.10-2.29)	**0.014**	1.03 (0.53-1.99)	0.936	0.99 (0.49-1.99)	0.977
SII (≥400 vs <400)	1.41 (0.73-2.73)	0.307	1.44 (0.73-2.84)	0.295	4.36 (0.26-74.08)	0.308	NA	NA
LIPI (1,2 vs 0)	2.01 (1.35-3.00)	**0.001**	1.93 (1.27-2.94)	**0.002**	1.18 (0.52-2.68)	0.685	1.38 (0.59-3.23)	0.462
ALI (≥18 vs <18)	0.45 (0.31-0.66)	**<0.001**	0.47 (0.31-0.70)	**<0.001**	0.56 (0.28-1.10)	0.091	0.62 (0.29-1.34)	0.226



Conclusion: With the limitations of the retrospective analysis, the selected BB appear to predict outcomes with P and PCT. In order to guide Tx decisions, the results need to be validated prospectively.

Keywords: NSCLC, Blood-based biomarkers, Pembrolizumab

FP12 PREDICTIVE TUMOR BASED ASSAYS/BIOMARKERS/PATHOLOGY

FP12.03 Associations of Urinary Biomarkers of Tobacco Toxicants With Lung Cancer Incidence in Smokers: The Multiethnic Cohort Study

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Introduction: Globally, lung cancer is the second most common cancer in men and women, after prostate and breast cancer, respectively. The primary risk factor for lung cancer is smoking. However, only 11-24% of smokers develop the malignancy over their lifetime and the magnitude of risk varies across populations. The inter-individual differences in risk among current smokers may in part be due to variation in exposure to tobacco smoking-related toxicants. **Methods:** We prospectively evaluated the association of 12 urinary biomarkers of nicotine metabolism and tobacco smoking toxicants with lung cancer risk among a subcohort of 2,309 Multiethnic Cohort Study participants who were current smokers at time of urine collection. Participants were followed from the time of urine collection to one of the following endpoints: lung cancer diagnosis, death, or end of follow-up (December 31, 2017). After an average of 13.4 years of study follow-up, 140 incident lung cancer cases were diagnosed. Urinary biomarkers were normalized using a log base 2 transformation. Risk of lung cancer was estimated by the hazard ratios (HR) and 95% confidence intervals (CIs) using Cox proportional hazards models where age was the time metric. **Results:** After adjusting for decade of birth, sex, race/ethnicity, body mass index, self-reported pack-years, and urinary creatinine, we found that urinary total nicotine equivalents (TNE, a biomarker of internal smoking dose), cytochrome P450 2A6 (CYP2A6) enzymatic activity ratio (total trans-3'- hydroxycotinine/cotinine; a biomarker of nicotine metabolism), 3-hydroxypropylmercapturic acid (3-HPMA; a biomarker of acrolein) and cadmium were individually associated with an increased risk of lung cancer (p's<0.02). To assess whether the associations with tobacco toxicants were independent of smoking dose, TNE was included in these models. We found that lung cancer risk increased for every two-fold increase in levels of CYP2A6 enzymatic activity ratio (HR=1.23; =0.02), 3-HPMA (HR=1.28; p=0.007), and cadmium (HR=1.42; p=0.0003). These associations remained statistically significant even after mutually adjusting for these three biomarkers. **Conclusion:** Findings demonstrate that these three urinary biomarkers of tobacco toxicants may provide additional information on lung cancer risk that is not captured by self-report smoking history or the reference biomarker of internal smoking dose in a multiethnic population. These findings warrant replication and consideration as potential biomarkers for smoking-related lung cancer risk.

Keywords: smoking biomarkers, tobacco toxicants, lung cancer risk

FP12.04 Obesity is Associated With Greater Overall Survival in Patients With Metastatic NSCLC Receiving First-Line Pembrolizumab

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Introduction: The anti-PD1 immune checkpoint inhibitor pembrolizumab is an established treatment option for patients with metastatic non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50%. Whilst pembrolizumab therapy may lead to durable responses in some patients, a proportion of patients derive little clinical benefit from treatment. Biomarkers that predict treatment response would assist in clinical decision making in the management of metastatic NSCLC patients. The relationship between cancer and obesity is complex. The association of obesity with increased incidence, progression and mortality in some cancers but decreased mortality in others has become termed the 'obesity paradox'. Obesity can be readily assessed by measurement of the body mass index (BMI). It is unclear whether BMI measurement can be used as a biomarker in metastatic NSCLC patients. We evaluated the association between BMI and overall survival (OS) in patients receiving first-line pembrolizumab for metastatic NSCLC. **Methods:** All patients with metastatic NSCLC with PD-L1 expression ≥50% treated with first-line pembrolizumab monotherapy at a regional Scottish cancer centre were identified from the electronic patient record. Pre-treatment body measurements were used to calculate BMI (kg/m^2). Patients were classified as obese (BMI ≥30) and non-obese (BMI <30) according to widely used threshold values. The association between BMI and OS was examined using Kaplan-Meier and Cox regression methods. **Results:** Data were available for 166 patients. Median age was 69 years (IQR, 62–72 years). 23 (13.9%) patients were obese. A BMI ≥30 was associated with significantly longer OS compared to patients with a BMI <30 HR 0.47, 95%CI 0.23–0.97 (p=0.042). Survival analysis using Kaplan-Meier methods showed a greater median OS of 31.0 months in patients with BMI ≥30 compared to 11.0 months in those with BMI <30 (p=0.037).

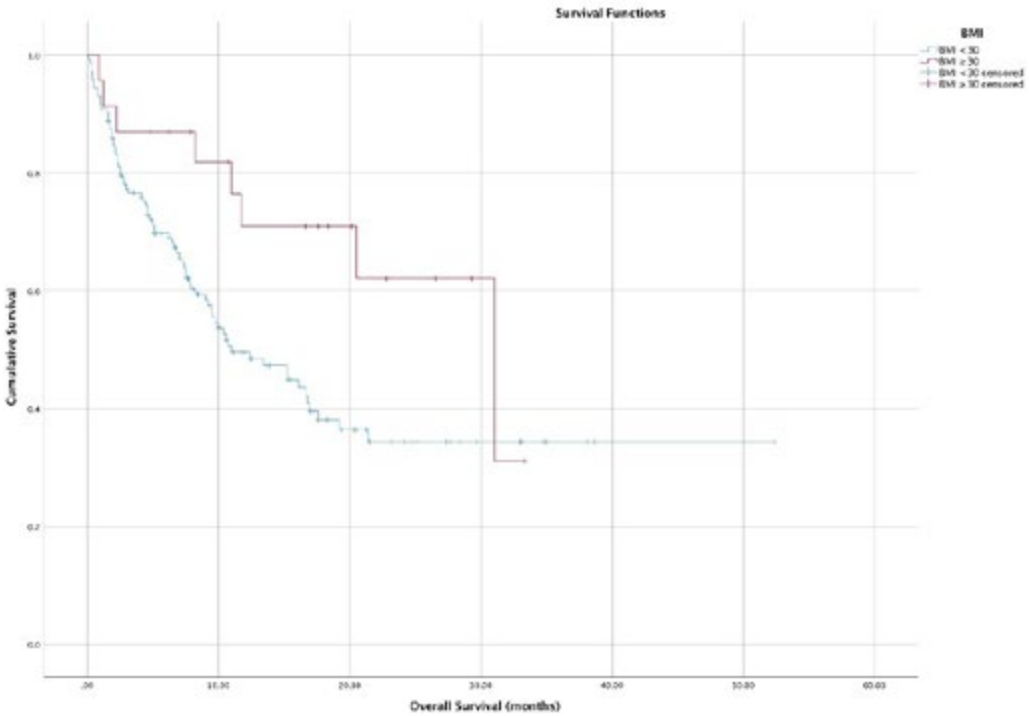

Figure 1: Kaplan-Meier analysis. Log-rank 0.037

Median survival (IQR): BMI <30, 11.0 months (6.2–15.8); BMI ≥30, 31.0 months (15.9–46.1) **Conclusion:** Obesity, defined by a pre-treatment BMI ≥30, was associated with a significantly longer OS in patients receiving first-line pembrolizumab for metastatic NSCLC with PD-L1 expression ≥50%. However, it is unclear why a high BMI is associated with a survival benefit and whether this is a true or spurious relationship. Further research on the relationship between obesity and NSCLC survival outcomes should examine possible biological mechanisms and further investigate other markers of body composition such as sarcopenia, peri-diagnosis weight loss, waist circumference and waist-to-hip ratio. It is likely that biomarkers of body composition will be more useful when utilised in conjunction with other prognostic biomarkers.

Keywords: immunotherapy, Metastatic NSCLC, BMI

FP12 PREDICTIVE TUMOR BASED ASSAYS/BIOMARKERS/PATHOLOGY

FP12.05 The Intrinsic Limitation and Clinical Impact of Mutant Allele-Specific Real-Time PCR-Based EGFR Mutation Assay in NSCLC

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Introduction: The detection of driver gene mutations, such as epidermal growth factor receptor (EGFR) mutations, plays a decisive role in the treatment of non-small cell lung cancer (NSCLC). Cobas EGFR mutation test is a mutant allele-specific real-time PCR assay that is commonly used in daily practice. It has a notable intrinsic detection limitation caused by its primer designs. Next-generation sequencing (NGS) is a comprehensive mutation assay that does not have the constraint. It will have a higher mutation detection rate but the clinical impact remains uncertain. **Methods:** We retrospectively collected archival tumor tissues from patients with stage IV NSCLC and diagnosed as EGFR wild-type by cobas EGFR mutation test. Samples were sent for FoundationOne CDx testing, an NGS study by comprehensive genomic profiling. The data collection period fell between January 1st, 2012, and July 31st, 2020. The protocol was approved by the Institution Review Board. **Results:** Total 62 patients were studied. The median age was 60 (35-86) and over two-thirds of the patients were male. 58.1% were smokers. Most histology types were adenocarcinoma (91.9%). Over half of the pathology samples were collected by needle biopsy (62.9%). Of all 62 patients, 7 patients have been detected with EGFR mutations by NGS. The false-negative rate of cobas EGFR mutation test was 11.3%. Among these overlooked EGFR mutations, 5 were exon 20 insertions and 2 were exon 19 mutations. All but one were out of the detection range of cobas EGFR mutation test. Two patients showed EGFR A763_Y764insFQEA, which has been considered as sensitive to classical EGFR tyrosine kinase inhibitors (EGFR-TKIs). Two patients (EGFR A763_Y764insFQEA and EGFR T751_I759>S) had received erlotinib during their treatment course and both of them showed stable disease with a progression-free survival of 5.9 and 10.1 months, respectively. Table Clinical characteristics and EGFR mutations

Gender	Smoking	Histology	EGFR mutation	Exon	EGFR-TKI	Response	PFS (mo)
Female	Never	Adeno.	A763_Y764insFQEA	e20ins	Erlotinib	SD	5.9
Male	Never	Adeno.	N771_P772insN	e20ins	-	-	-
Female	Never	Adeno.	V769_D770insGTV	e20ins	-	-	-
Female	Never	Adeno.	A763_Y764insFQEA	e20ins	-	-	-
Female	Never	Adeno.	L747_A750>P	e19del	-	-	-
Male	Smoker	Adeno.	H773_V774insNPH	e20ins	-	-	-
Female	Never	Adeno.	T751_I759>S	e19del	Erlotinib	SD	10.1

Conclusion: By using NGS, the false-negative rate of cobas EGFR mutation test was 11.3%. The most overlooked mutations were exon 20 insertions. A comprehensive EGFR mutation assay can provide significant benefit to NSCLC patients, especially in an area with a high prevalence of EGFR mutations.

Keywords: Next Generation Sequencing, epidermal growth factor receptor mutations, non-small cell lung cancer

FP12.06 Solid Subtype Predicts Early Bone Metastases in Sensitive EGFR-Mutated Lung Adenocarcinoma Patients After Surgery

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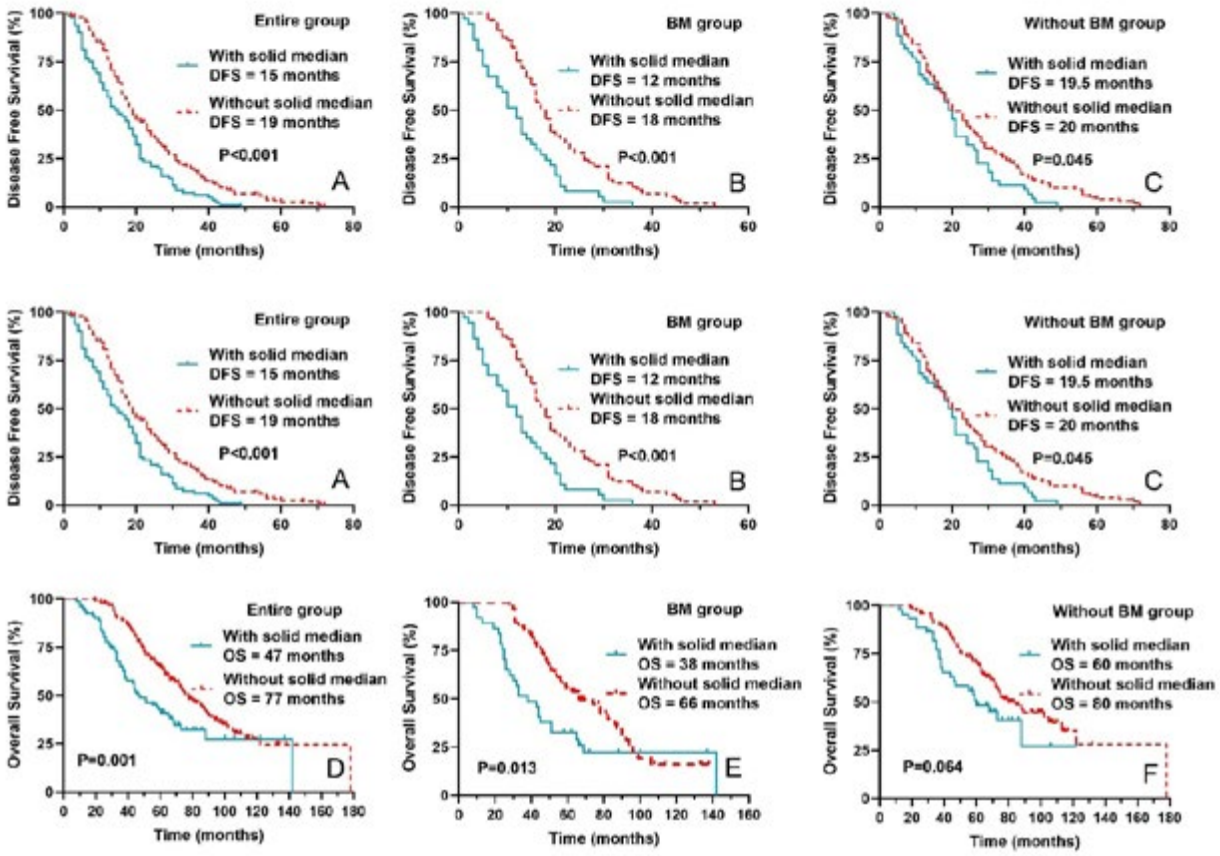
Introduction: Bone metastasis (BM) is common and associated with poor prognosis in NSCLC patients. However, valid predictors of BM remain insufficient. Solid pattern has been reported as a predictive factor in disease progression in resected NSCLC patients. This study aimed to explore the relationship between solid subtype and BM in EGFR-mutated lung adenocarcinoma patients after surgery. **Methods:** Patients with completely resected lung adenocarcinoma and sensitive EGFR mutation were included in our study. Patients with solid pattern were divided into solid-present group while the rest were in solid-absent group. CT (for chest and brain) was performed every 2-3 months. Bone scan was done every 4-6 months. BM was confirmed if one of the following criteria were fulfilled: (1) clinical or pathological confirmation of lung cancer and diagnosis of BM according to bone biopsy; or (2) pathologically diagnosed as lung cancer and with BM images. All patients received EGFR-TKI as the first-line treatment for progression after operation. Bone disease-free survival (bDFS), DFS and OS were assessed in this study. bDFS was defined as the time span between surgery and BM diagnosis. **Results:** From January 2007 to January 2017, 237 eligible patients were identified. Among them, 81 patients (34.2 %) were solid-present. BM was observed in 94 patients (39.7 %). Solid-present patients had significantly shorter bDFS than solid-absent patients (14 months vs. 27 months; P < 0.001). The difference was still significant in patients with BM as first-site (12.5 months vs. 16.5 months; P = 0.016) and non-first-site progression (16.5 months vs. 45.5 months; P < 0.001) after surgery (Figure 1). In survival analysis, solid-present group showed a significantly shortened DFS (15 months vs. 19 months; P < 0.001) and OS (47 months vs. 77 months; P = 0.001) **(Figure 2)**



Conclusion: These findings suggested that solid pattern predicted poor prognosis and early BM occurrence.

Keywords: Histologic subtype, Distant metastasis, non-small cell lung cancer

FP12 PREDICTIVE TUMOR BASED ASSAYS/BIOMARKERS/PATHOLOGY

FP12.07 Clinico-demographic Factors, EGFR status and their association with Stage at Diagnosis in Lung Adenocarcinoma Patients

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Introduction: Compared to advanced or metastatic lung adenocarcinomas, are there differences in the distribution of clinico-demographic factors such as age, sex, race, smoking status, and EGFR status in patients with earlier stage of disease at diagnosis? One large Korean study found a significant association between EGFR-mutated non-small cell lung cancers and diagnosis at an early stage; however, this and prior published studies exploring this relationship typically involved populations that were race-specific (e.g. Asians only), smoking-restricted (e.g. never-smokers only), or treatment-specific (e.g. resected cases only). We evaluated the relationship between clinico-demographic factors (including EGFR status) and stage at diagnosis in an unselected single-institutional lung adenocarcinoma sample. **Methods:** Using an institutional cancer registry, patients at Princess Margaret Cancer Centre diagnosed between 2014-2016 with lung adenocarcinomas had clinico-demographic data abstracted for a retrospective chart review. Continuous variables were compared using Mann-Whitney's U tests; categorical variables were compared through chi-squared tests. Multivariable logistic regression was used to compare these clinico-demographic variables to stage of disease. The primary analysis compared stage IV with stages I-III at diagnosis, while an exploratory secondary analysis compared stages III-IV to stages I-II. **Results:** Of the 1124 patients with lung adenocarcinomas, n=347 (30.9%) carried EGFR-mutations; 604 (54%) were female; median age was 68.8 years; 515 (46%) were Caucasian; 199 (18%) were Asian; 92 (8.2%) were of other ethnicities; 318 (28%) were of unknown ethnicities; 351 (31.2%) were never-smokers. Compared to patients with EGFR-wildtype tumors, patients with EGFR-mutated tumors were slightly younger (67.2 vs. 69.3 years; P = 0.005); more likely to be female (71.5% vs, 46.2%; P < 0.001), of Asian ethnicity (36.3% vs. 9.4%; P < 0.001), and a never-smoker (66.0% vs. 15.7%; P < 0.001). In multivariable analysis, the presence of an EGFR-mutation was not significantly associated with stage IV disease at diagnosis (OR=1.03, 95%CI: 0.76-1.40; P=0.85). However, being male (OR 1.32, 95% CI: 1.03-1.71; p = 0.031), Asian (vs. Caucasian: OR 1.58, 95% CI: 1.10-2.28; p = 0.014) or other non-Caucasian (vs Caucasian, OR 2.18, 95% CI: 1.36-3.53; p = 0.001) were independently associated with having Stage IV lung adenocarcinoma at diagnosis (vs. Stages I-III). In an exploratory analysis comparing Stage III-IV vs Stage I-II, in addition to being male or being non-Caucasian, being an ever-smoker was also associated with advanced (stage III-IV) stage disease (OR 1.45, 95% CI: 1.04-2.00; p = 0.27). **Conclusion:** In a large multiethnic Canadian patient population diagnosed with lung adenocarcinoma, no association between EGFR status and stage at diagnosis was found. However, other factors such as being male, being of a race other than Caucasian, and being an ever-smoker were independently associated with higher stage of disease at diagnosis.

Keywords: EGFR, Late Stage Disease, adenocarcinoma

FP12.08 Lung Adenocarcinomas with ROS1 Rearrangement show Diffuse Strong ROS1 Immunohistochemical Staining

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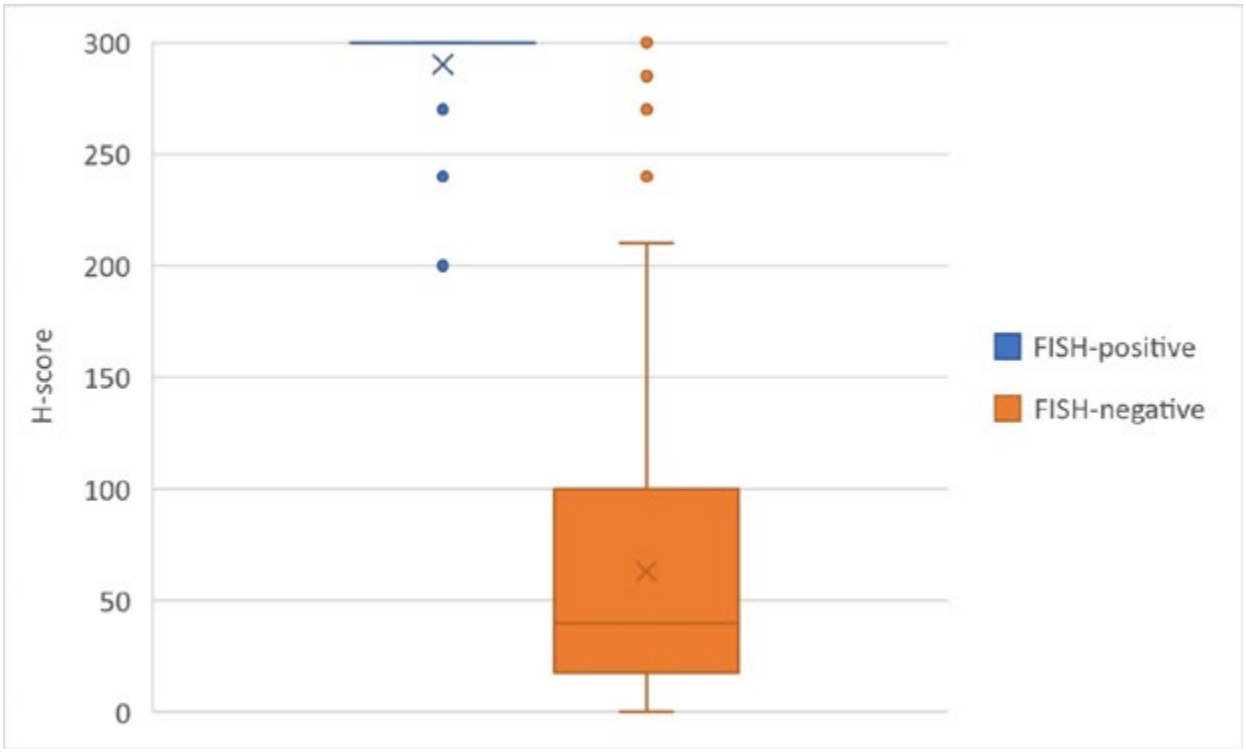
Introduction: A small proportion of lung adenocarcinomas harbour ROS1 gene arrangements and are sensitive to ROS1 tyrosine kinase inhibitors. In Australia, ROS1 immunohistochemistry (IHC) is used to screen for ROS1 rearrangements in lung adenocarcinomas followed by confirmatory molecular testing such as fluorescence in situ hybridisation (FISH), if other genetic driver alterations are negative. The optimal threshold for determining ROS1 IHC positivity is not well defined, and this study aims to determine the best threshold for ROS1 IHC screening to identify all ROS1 rearranged lung adenocarcinomas. **Methods:** 177 lung adenocarcinomas that underwent FISH testing for a ROS1 rearrangement at our hospital between 2017 and 2020 due to positive ROS1 IHC were included in the study. The degree of ROS1 IHC staining was assessed using an H-score with staining intensity (0, 1, 2, or 3+) multiplied by the percentage of positively staining cells. The FISH results and IHC H-scores were compared. **Results:** Of 177 lung adenocarcinomas cases, 32 (18%) were positive for ROS1 rearrangement by FISH and 145 (82%) were negative. FISH-positive cases had a median H-score of 300 (range 200-300; mean 290.3). FISH-negative cases had a median H-score of 40 (range 0-300; mean 63). All FISH-positive cases showed strong and diffuse positive IHC staining for ROS1. Using a threshold H-score of 200 the sensitivity of identifying ROS1 rearrangements was 100% and the specificity was 95%.

H-score range	ROS1 rearranged by FISH	ROS1 negative by FISH
≥250	29	3
200-249	3	4
150-199	0	11
100-149	0	20
50-99	0	29
0-49	0	78
Total	32	145

Table 1. Grouped frequency table showing distribution of H-scores for ROS1 FISH-positive (middle column) and FISH-negative (right column) cases.



Conclusion: Adenocarcinomas with a FISH-confirmed ROS1 rearrangement demonstrate diffuse and strong IHC staining (intensity at least 2+). Cases with weak, patchy ROS1 IHC staining were not associated with ROS1 rearrangements and in such cases FISH testing is of little to no utility.

Keywords: ROS1, Lung adenocarcinoma, molecular pathology

FP13.01 Assessment of the Fear of COVID-19 and Its Impact on Lung Cancer Screening Participation Among the Korean General Population

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Introduction: The decline in cancer screening has been reported since the beginning of the novel coronavirus disease (COVID-19) crisis. The situation could delay cancer diagnosis and increase the proportion of patients with advanced stages, which may eventually lead to dreadful effect on cancer mortality. We aimed to assess how much people's fear of COVID-19 affect the behaviors of the general population towards cancer screening. **Methods:** The Korean National Cancer Screening Survey (KNCSS) was a population-based, cross-sectional survey using a structured questionnaire, conducted annually since 2004 by the Korea National Cancer Center to investigate cancer screening rates of five major malignancies (gastric, liver, colorectal, breast, and cervix). We extracted data on 3557 cancer-free respondents aged ≥ 40 years in 2020, including sociodemographic characteristics, comorbidities, family history of cancer, self-perceived general health status, attitudes towards participating in screening, and the fear of coronavirus disease in comparison with lung cancer. We collected the information on the participation in health check-ups including cancer screening with or without schedule during the pandemic and analyzed the participation rate according to the degree of fear of COVID-19. **Results:** Among 3,557 respondents, 1066 (29.97%) people were more worried by COVID-19 than by lung cancer. 2392 (67.25%) did not participate in health check-ups, of which 573 (24.0%) had a schedule for health check-ups but did not receive. Older aged people were more likely to participate compared with those aged 40-49 years. Subjects with higher education level of undergraduate and above had higher odds of undergoing health check-ups than those with middle school level or below (OR, 1.38; 95% CI, 1.02-1.87). Regarding our main interest, we observed a significant increase ($p < 0.05$) in the proportion of non-participation with schedule when the fear of COVID-19 exceeds lung cancer. In multivariate logistic analysis, the respondents with more fear of COVID-19 compared with lung cancer showed decreased likelihood of attendance in health check-ups (OR, 0.84; 95% CI, 0.71-0.98). **Conclusion:** A considerable proportion of the general population were more worried by COVID-19 than by lung cancer, which significantly hampered their engagement in regular medical check-ups including cancer screening. This finding highlights the need for providing appropriate information to the target population of lung cancer screening to minimize disruption in cancer prevention activities.

Keywords: Cancer screening, Fear, covid-19

FP13.02 Costal Pleura-attached Noncalcified Nodules Newly Seen on Annual Low-Dose CT Screenings

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Introduction: It has previously been demonstrated that solid costal pleura-attached noncalcified nodules (CP-NCN) with average diameter<10.0 mm and lentiform, oval, semicircular (LOS) or triangular shapes and smooth margins on baseline CT do not need short-term follow-up and instead can be recommended to return for annual repeat screening. Determine whether the same criteria apply for new CP-NCNs seen on annual repeat screening rounds. **Methods:** In 111,102 annual screening scans in the International Early Lung Cancer Action Program (I-ELCAP) between 1992 and 2019, we identified 21 new solid CP-NCNs, 3.0 mm to 30.0 mm in average diameter that were lung cancer (median months to diagnosis:1.8, IQR: 1.1-4.7). In 4,425 annual screening scans in the Mount Sinai Early Lung and Cardiac Action Program between 2010 and 2019, we identified 56 new solid CP-NCNs, 3.0 mm to 30.0 mm; 55 were benign (median follow-up: 79.6 months, IQR:61.0-102.5). Shape (triangular, LOS, polygonal, round, or irregular), margin (smooth or non-smooth), pleural attachment (broad or narrow), emphysema and fibrosis within 10 mm of each CP-NCN was determined. Intra- and inter-reader agreements (B statistic) on triangular/LOS shaped solid CP-NCN with smooth margin were assessed. **Results:** Mean age of the participants with the 76 CP-NCNs was 72.2 years (SD= 8.8 at time of annual repeat CT, median pack-years of smoking was 40.2 (IQR: 27.5-53.8); 35 (46.1%) were men and 41 (54.0%) women. Size, shape, margin, and emphysema and fibrosis within a 10.0mm radius of the CP-NCNs were significant predictors of malignancy status. The median diameter of the 55 solid benign CP-NCNs was significantly smaller than of the 21 solid malignant CP-NCNs (4.2 mm vs. 11.0 mm, p < .001). Emphysema and fibrosis within a 10.0 mm radius of the CP-NCN was significant as malignant CP-NCNs more frequently had emphysema [17 (81.0%) vs. 21 (38.2%), p=.003] and fibrosis [4 (19.0%) vs. 2 (3.6%), p=.045]. CP-NCN shape, irrespective of size and margin, were significantly different between benign and malignant CP-NCNs (p=.02). Triangular shape was only seen in benign CP-NCNs (12.7% (7 of 55) vs. 0.0% (0 of 21). LOS shape in 29.1% (16 of 55) benign CP-NCNs vs. 4.8% (1 of 21) malignant ones. All CP-NCNs< 10.0 mm in average diameter with triangular or LOS shapes and smooth margins were benign after a median follow-up of 6.6 years. None of the 21 malignant CP-NCNs of any size had triangular or LOS shapes and smooth margins when they were first identified on annual repeat screening round. Intra- and interobserver agreement for triangular or LOS shaped CP-NCNs with smooth margins were almost perfect based on the B-statistic. **Conclusion:** we found that new CP-NCNs<10.0 mm with triangular, lentiform, oval or semi-circular shape and smooth margin on annual repeat rounds were all benign. Thus, for these CP-NCNs, whether identified on annual or baseline screenings, the next annual screening is recommended rather than having more immediate work-up. New CP-NCNs not meeting these criteria should continue to have more immediate follow-up as per protocol for all noncalcified nodules found on annual screenings.

Keywords: Lung cancer annual repeat screening, New costal pleura-attached noncalcified nodules, Malignancy

FP13.03 The Impact of the COVID-19 Pandemic on Lung Cancer Screening Programs in the United States

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Introduction: Multiple studies have reported a decreased rate of cancer diagnoses across the United States during the COVID-19 pandemic. This study examined data from a national network of lung cancer screening centers to understand the effects of the pandemic on screening programs. **Methods:** Lung cancer screening programs in the GO2 Foundation Centers of Excellence in Lung Cancer Screening network were surveyed between 7/16/2020 and 9/16/2020 to understand the impact of the COVID-19 pandemic on screening availability, programmatic workflow, and patient recruitment. **Results:** A total of 116 out of 346 (33.5%) lung cancer screening programs responded to the survey, comprising 423 out of 749 (56.5%) distinct screening sites in the network. 65% were community hospitals, 25% academic hospitals or affiliated teaching programs, and 7% hospital outpatient imaging programs. Collectively, the programs performed lung cancer screening by low-dose computed tomography on 125,190 patients in 2019. The median number of patients screened per program in 2019 was 726. Eighty five percent of the programs reported going on hiatus at some point in 2020 during the COVID-19 pandemic, of which all reported a duration of at least 5 weeks, and 22% reported at least 10 weeks. Screening programs also reported decreased patient volume during the pandemic with 56% reporting moderate to significant decreases in volume of new patients and 44% reporting moderate to significant decreases in existing patients (Table 1).

Table 1. Change in patient screening volume during the COVID-19 pandemic compared to pre-COVID-19

Change in Screening Volume	New Patients	Existing Patients
Significant Decrease	36%	24%
Moderate Decrease	20%	20%
Slight Decrease	22%	29%
No Change	10%	18%
Slight Increase	9%	3%
Moderate Increase	1%	3%
Significant Increase	1%	2%

Nearly all programs (91%) reported that their program infrastructure and capacity was back to pre-COVID levels. Half had incorporated telemedicine for shared decision-making visits and 44% for smoking cessation. The top three barriers cited for restoring screening volume were all patient-related: patient concerns about safety of healthcare facility (82%), increased financial barriers for patients (economic hardship/loss of insurance) (51%), and difficulty re-engaging with patients about screening (31%). **Conclusion:** The COVID-19 pandemic significantly affected lung cancer screening programs with most requiring a hiatus of five or more weeks. Screening programs reported notable decreases in patient volumes compared to pre-pandemic levels and are facing patient-related barriers to resumption of pre-COVID screening volumes. Previous network data demonstrated that lung cancer screening produces a significant stage shift to ~50% Stage I diagnoses (Copeland et al., J Oncol Pract, 2019). Consequently, the reduction in screening volumes is likely to result in more late-stage lung cancer diagnoses in the future.

Keywords: Early detection, lung cancer screening, covid-19

FP13.04 CHECK Lung Protocol: CT Lung Cancer Screening is Useful to Adjuvant Comorbid Diseases Diagnosis

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Introduction: Lung cancer screening (LCS) via chest computed tomography (CT) scans can save lives by identifying early-stage tumors. On the other hand, because cigarette smoking affects multiple systems, most participants die of comorbid smoking-related diseases, which may be unknown to the patient. Several of these diseases are treatable with an expectation of reduced mortality and improvement of quality of life. LCS scans provide information about smoking-related conditions that are not currently systematically assessed. We developed one simple free software CT scan assessment protocol (Check Lung Protocol) that evaluates the presence of six comorbid diseases during LCS. **Methods:** This study is a retrospective examination for the presence of six comorbidities of 774 low-dose CT scans from patients who underwent LCS between 2016 and 2020. Patients included met the criteria for LCS (within 55 to 80 years old at the time of enrollment, with 30 pack-years of smoking history or former smokers who quit smoking until the previous 15 years). The comorbidities searched for on scans were coronary artery calcification (CAC), sarcopenia, interstitial lung disease (ILD), emphysema, osteoporosis, and hepatic steatosis. Past medical records were reviewed to describe if these comorbidities were previously non-diagnosed. The clinic characteristics of each participant were identified as the mean of densitovolumetry values with t-test and q-square. About scans, CT data were acquired in full expiration and evaluated by two different radiologists. To validate the radiologist's interpretation, the kappa coefficient (k) was calculated to analyze the agreement index in CAC, and the intraclass correlation coefficient (ICC) to assess the correlation of the reliability of measures for liver, spleen, and bone density. **Results:** Our sample had a mean age of 64, and 602 (77.7%) were male patients. We found that 671 (86.6%) of the CT scans for LCS had at least one or more comorbidities. CAC (> 100mg) was identified in 41.9% CT scans, sarcopenia was found in 9.9%, osteoporosis was present in 44.2%, and hepatic steatosis in 40.7% of the cases. Among lung diseases evaluated, emphysema was observed in 66.3% of scans and ILD in 32.2%. New diagnoses of cardiovascular disease were made in 25% of patients, emphysema in 7%, and osteoporosis in 46%. Kappa coefficient for CAC was 0.906 ($p < 0.001$) and ICC measurements, with $p < 0.001$ for all of them, was 0.88 for liver density, 0.93 for spleen density and 0.96 for bone density. We observed a strong significant relation between sarcopenia, CAC, and mortality. **Conclusion:** Our data demonstrated a high prevalence of previously undiagnosed cardiovascular disease, emphysema, ILD, sarcopenia, osteoporosis, and hepatic steatosis in CT scans from LCS patients. Check Lung Protocol can potentially facilitate diagnoses of these additional pathologies and provide an opportunity for treatment or prevention of progression for high morbimortality conditions. Data from this study can increase the value of screening with minimal impact on LCS programs.

Keywords: lung cancer, Comorbidities, screening

FP14.01 A Phase 1b/2 Study of Autologous Dendritic Cell Vaccination in Combination With Atezolizumab in Patients With Small Cell Lung Cancer (SCLC)

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Introduction: IMpower133 trial showed a significant benefit of the combination of the anti PD-L1 antibody atezolizumab with chemotherapy over chemotherapy alone in extensive SCLC, with a 18 and 24-month landmark OS of 34% and 22% vs. 21% and 16.8%, respectively. Despite this improvement, patients achieving long-lasting remission are still uncommon. New therapeutic strategies are needed for this population. Dendritic Cells (DCs) are the most powerful antigen-presenting cells of the immune system, capable of stimulating naïve and memory immune responses. For an activating immune response, antigen presentation mediated by mature DC co-expressing costimulatory molecules (CD80, CD86, CD40) on their surface is necessary. If DCs lose these capabilities, instead of leading to an effective immune response, antigen presentation results in tolerance, which would facilitate cancer progression. DC functions are impaired in cancer patients, however with the ex-vivo modification of monocyte-derived DCs, their function can be recovered, increasing the expression of costimulatory molecules. Moreover, recent studies support that blockade of PD-1/PD-L1 functions at least in part by increasing the priming or early activation of T cell responses, rather than only reinvigorating exhausted T cells. Dendritic cell vaccination is expected to increase the tumor infiltration by tumor-specific $CD8^+$ and $CD4^+$ T cells. Atezolizumab will synergistically potentiate the specific antitumor response, by releasing T cell immunosuppression due to the binding of PD-1 checkpoint inhibitor of T cell surface to its ligand PD-L1 in tumor cells and by reinvigorating the function of the ex-vivo modified DCs. **Methods:** This is an investigator-initiated trial open at three centers in Barcelona (Spain). It is a single-arm phase 1b/2, open-label study, evaluating the combination of atezolizumab with dendritic cell vaccination pulsed with autologous tumor antigens, as maintenance treatment in patients with extensive-stage SCLC. Leukapheresis will be obtained from every patient and it will be processed in the certified facilities to obtain clinical-grade DCs pulsed with the pool of irradiated autologous tumor cell lysate. After one week of culture, fully mature DCs, which constitute the vaccine, will be aliquoted, frozen, and stored in nitrogen until its use. After completing four cycles of induction treatment with atezolizumab plus chemotherapy, maintenance treatment will consist of the administration of $10x10^6$ of matured DCs injected intradermally, up to 6 doses (maintenance phase weeks 1, 4, 7, 10, 22, and 34), in combination with atezolizumab at doses of 1200 mg every three weeks until progressive disease. In the Phase 1b safety lead-in portion, the feasibility of atezolizumab and DC vaccines combination will be evaluated, up to 6 patients, if fewer than 2 patients present limiting toxicities during the maintenance phase, treatment will be considered feasible and will be administered to 20 patients in the phase 2. Primary outcome measures will be progression-free survival and duration of clinical benefit. As exploratory endpoints the study will analyze the evolution of cytokines, circulating lymphocytes subpopulations, and DCs subsets along with treatment, as well as predictive factors of response in pretreatment tumor tissue samples. The study began enrolling patients in March 2021 and is ongoing.

Keywords: Dendritic cell, SCLC, PD-L1

FP14.02 Small Cell Lung Carcinoma's Clinical Versatility Is a Manifestation of Its Shape-Shifting Cellular Programs

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Introduction: Small cell lung carcinoma (SCLC) is an aggressive, tobacco-associated tumor characterized by rapid growth, early metastases, and initial response followed by almost invariable resistance to chemotherapy. Studies to date have not resolved the extent that diverse transcriptional programs drive SCLC and contribute to its lethality. **Methods:** We combined patient-derived xenograft (PDX) (n = 64) resources with multi-omic profiling, single-cell fluorescence tracking of ex vivo tumor cells, and mathematical and statistical models to study the topology of the SCLC transcriptional state space and its plasticity. Human tumor material and associated clinical data were obtained after informed written consent on an IRB-approved prospective registry study. Patients with a pathological diagnosis of small cell lung carcinoma and a successfully engrafted PDX were selected for further evaluation. A total of 64 patients met our eligibility criteria. **Results:** SCLC tumors are substantially more heterogeneous than previously appreciated, with most samples retaining two or more subpopulations marked by Ascl1, NeuroD1, or Yap1. Using single-cell RNA-seq profiling, we showed that the relative frequency of each state varied across tumors and tumor composition impacted clinical treatment response trajectories (e.g. Ascl1 high tumors were more likely to progress after chemotherapy [p = 0.046; Gray's test] and concomitantly had a worse overall survival [p = 0.028; log-rank test]). We measured the kinetics of state transitions using single-cell fluorescence tracking of ex vivo cells and associated single-cell dynamics with overall population trends using stochastic transition theory (i.e. Markov chains). Our results indicate that the transition rates in individual tumors were largely governed by probabilistic rules with autonomous tendencies that are critical for configuring intratumoral proportions. Critically, ATAC-seq profiling indicated a role for the epigenome in the state diversity of SCLC. Namely, there was preferential promoter accessibility to Ascl1, NeuroD1, and Yap1 in a manner consistent with gene and protein expression in the respective subpopulations. Epigenetic drugs JIB-04 and iBET-762 differentially altered Ascl1 and Yap1 state compositions across several PDX and altered chemotherapy response trajectories in these tumors. **Conclusion:** In conclusion, we have elucidated a spectrum of states in SCLC cells and quantified their dynamics, identifying cellular programs that recapitulate neuroendocrine, neural, and mesenchymal development. Our work advances a model of cellular states and program diversity in SCLC and nominates new therapeutic strategies designed to limit the plasticity, and hence versatility, of this lethal cancer.

Keywords: Phenotypic plasticity, heterogeneity, Markov chains

FP14.03 Diagnostic Accuracy in Central Pulmonary Carcinoid tumors is Dependent of Biopsy Size

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Introduction: Recently, a limited diagnostic value of preoperative biopsy for distinction between typical carcinoid (TC) and atypical carcinoid (AC) was reported, revealing 60% discordance with the gold standard of surgical resection specimen. This study investigated the influence of biopsy surface obtained with flexible bronchoscopy (FLB) and rigid bronchoscopy (RIB) on accuracy of TC and AC diagnoses. **Methods:** Biopsy-resection paired specimens of patients referred to Amsterdam University Medical Centers for either biopsy or surgical resection were retrieved. Bronchial biopsies were obtained either by flexible bronchoscopy (FLB) or rigid bronchoscopy (RIB). The definitive diagnosis was based on the resection specimen. Diagnosis according to the 2015 WHO classification, mitoses and necrosis in biopsy and resection specimen were re-evaluated by two pathologists. **Results:** After screening 298 patients, 64 biopsy-resection pairs with available tissue were included of which 34 (53%) biopsied with FLB and 30 (47%) with RIB. In 35 (55%) patients the tumor classification between the biopsy and resection specimen was concordant. The discordance in the remaining 29 cases (45%) was caused by misclassification of AC as TC in bronchoscopy specimens. This occurred predominantly in small flexible biopsies (59%, p=0.021). Of biopsies measuring <2 mm^2, 79% were classified as discordant and 52% of the discordant biopsies measured <4 mm^2, suggesting that increasing biopsy size of ≥ 4 mm^2, may lead to a drop in discordant cases by 50%. **Conclusion:** Histological classification in central carcinoid tumors is discordant in 45% of the biopsies, more often when diagnosis is made on small biopsies. Classifying bronchial carcinoid in TC or AC in biopsies < 4 mm^2 should therefore be discouraged. A cumulative biopsy surface of at least 4 mm^2 tumor is preferred to increase the diagnostic accuracy which helps in optimal treatment planning.

Keywords: Typical carcinoid; Atypical carcinoid; Biopsy size; Endobronchial therapy

FP15.01 Randomized Single-Blind Comparative Study of Midazolam Plus Pethidine Combination and Midazolam During Bronchoscopy

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Introduction: Bronchoscopy is important in the diagnosis of lung cancer. It is often uncomfortable for the patients undergoing the examination. Although analgesia and sedation are important for tolerance of bronchoscopy, the optimal drug is not clear. **Methods:** We conducted a randomized, single-blind, comparative study to evaluate the efficacy and safety of midazolam/pethidine combination (combination group) compared with midazolam alone (midazolam group) as analgesia for bronchoscopy. we randomly assigned 100 patients who were scheduled to undergo bronchoscopy for biopsy of lung tumors or mediastinal tumors. 2mg midazolam and 17.5mg pethidine were given the combination group, and 2mg midazolam and placebo were given midazolam group intravenously before the start of bronchoscopy. Patients who were more than 75 yeas old or weighted less than 45 kg received half the dose. When the sedation level was considered shallow, we added 1 mg midazolam. The primary endpoint was the patients' acceptance of re-examination assessed by visual analogue scale. The secondary endpoints were patients' subjective symptoms, dose of drugs and safety. **Results:**

Table1. Visual Analog Scale of patients' subjective pain before and during bronchoscopy

	Combination group N=47
Q1. Did you have any concerns before the test?	5.62±3.28
Q2. Was the throat anesthesia you had before the test painful?	3.92±2.94
Q3. Do you remember what happened during the inspection?	4.03±3.96
Q4. Did you feel distressed during the examination?	2.48±2.80
Q5. Did you experience any pain during the bronchoscopy?	1.10±1.88
Q6. Did you have difficulty of breathing during the test?	2.25±2.85
Q7. Did you have a cough during the bronchoscopy?	3.01±2.92
Q8. Did you feel like the examination took a long time?	3.69±2.39
Q9. How are you feeling after the test?	3.40±2.19
Q10. Do you think you could have another bronchoscopy if necessary?	3.82±2.93
Q11. Do you think you could have another bronchoscopy if necessary? (yes or no)	
Yes	38 (80.9)
No	9 (19.1)

Table 2. Objective indicators and vital signs		
Combination group	**Midazolam group**	
	N=47	N=49
Examination time (minute)	30.55±8.08	34.73±7.71
Initial dosage of midazolam (mg)	1.77±0.43	1.69±0.47
Number of additional administration of midazolam	2.06±1.45	2.63±1.35
Total dosage of midazolam (mg)	3.83±1.56	4.27±1.34
Total dosage of 2% xylocaine (mL)	18.26±3.97	19.70±3.67
Maximal systolic blood pressure (mmHg)	162.39±23.45	178.24±30.24
Highest heart rate (bpm)	104.38±16.86	105.59±17.81
Lowest MOAA/S scale	3.49±0.98	3.94±1.03
Lowest oxygen saturation (%)	92.13±3.25	90.69±5.31
Usage of flumazenil (%)		
Yes	1 (2.1)	0 (0.0)
No	46 (97.9)	49 (100.0)

Finally, we analyzed 47 patients in the combination group and 49 patients in the midazolam group. The acceptance score of re-examination was not significantly different between the two groups (3.82 vs. 4.17, p=0.547), but the visual analog scale score for physical pain was significantly lower in the combination group (Table1). Additionally the sedation level score during bronchoscopy, adverse events including maximal systolic blood pressure, the number of additional administrations of midazolam were significantly lower in the combination group (Table2). **Conclusion:** Our study has shown the efficacy and safety of the combination of midazolam plus pethidine method in the sedation for bronchoscopy. This combination method can improve tolerance of bronchoscopy.

Keywords: bronchoscopy, pethidine, sedation

FP16.01 Development and Characterization of Two Novel Squamous Cell Lung Cancer Mouse Cell Lines

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Introduction: Lung cancer is the leading cause of cancer-related death worldwide. The incidence and mortality associated with lung cancer is a major Public Health challenge in advanced societies. About 20-30% of all lung cancers are classified as lung squamous cell carcinoma (LUSC), also known as squamous cell carcinoma (SSC or SqCC) or epidermoid carcinoma. The absence of preclinical models makes LUSC disease analysis and research more challenging. The development of well-characterized cellular and molecular tools is essential for the advance in lung cancer research. In the present work, we have performed an exhaustive molecular and functional characterization of a new LUSC research model, recently developed in our laboratory. This model consists of two novel A/J mouse-derived syngeneic cell lines from NTCU-induced LUSC.In our opinion, these cell lines may become a robust tool for the study of squamous cell lung cancer in a reliable and reproducible manner. **Methods:** Carcinogenesis and cell line generation: LUSC tumors were induced by N-nitroso-tris-chloroethylurea (NTCU) (Toronto Research Chemicals) treatment applying 0.04 M NTCU by skin painting twice a week for 20 weeks to 8-week-old A/J mice. Immunohistochemical staining: Dissected tumors were fixed in 4% paraformaldehyde and embedded in paraffin. Three-micrometer-thick sections were used for tumors immunohistochemical phenotypic characterization. Exome sequencing: Whole exome sequencing was performed on extracted DNA from the tumor-derived cell lines. RNA sequencing analysis: Samples were prepared with the Illumina TruSeq Stranded mRNA kit and sequenced as reverse paired-end (50 bp) runs on the Nextseq sequencer. Tumor immunotherapy experiments: $2x10^6$ cells were subcutaneously inoculated in one flank of 8-week-old female A/J mice. When the tumors reached a volume of 75 mm^3, mice were randomized and treated intraperitoneally with 3 doses of 100 μg of anti-PD1 or anti-CTLA4. Tumor immune landscape analysis: $2x10^6$ cells were subcutaneously inoculated in one flank of 6 8-week-old female A/J mice . Thirteen days after cell inoculation, tumors were collected and processed for flow cytometry analysis. Metastasis in vivo model: Cells were transduced with a triple modality construct containing a triple fusion protein GFP, luciferase and thymidine kinase. Eight-week old female mice were inoculated in the left cardiac ventricle with 1×10^5 cells. Cells were followed by bioluminescence. **Results:** We have generated two transplantable LUSC cell lines (UN-SCC679 and UN-SCC680) derived from an N-nitroso-tris-chloroethylurea (NTCU) chemically-induced mouse model in A/J mice. Both cells lines expressed cytokeratins and p40, and lacked thyroid transcription factor 1 (TTF1) expression. Furthermore, we genetically characterized the LUSC cell lines by performing whole exome and RNA sequencing. In addition, we characterized the immune landscape of both tumors in vivo and assessed their response to immunotherapy studies combining the gold-standard checkpoint inhibitors in clinic. Finally, we studied the metastatic potential of each of these two models and confirmed that they reflect the human LUSC organotropism to the brain, bones, liver and adrenal glands. **Conclusion:** We have generated a very valuable tool for LUSC research that recapitulates the complexity of the human disease.

Keywords: LUSC, NTCU-mouse model, syngeneic cell lines

FP16.02 Genomic Characterization of Primary versus Metastatic Lung Adenocarcinoma

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Introduction: Molecular profiling has become the standard of care for patients with stage IV lung adenocarcinomas (LUAD). Although genomic alterations have been well-established as a driving mechanism of cancer development in LUAD, it remains unknown whether the clonal selection and additional genomic changes contribute to cancer metastasis. Our study is aimed to characterize the genomic landscapes in primary and metastatic LUAD through analysis of GENIE database. **Methods:** Gene sequencing data from The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE, version 8.0) were collected. A total of 7,363 samples, including 4,448 samples from primary LUAD and 2,915 samples from metastatic LUAD with comprehensive sequencing results (gene panel ≥ 275) were selected for further analysis. The prevalence and characterization of genomic alteration landscape cross primary and metastatic LUAD were analyzed. The top 10 most frequent genomic alterations and targetable alterations were compared and highlighted. **Results:** The medium mutation counts per sample was 7 in primary LUAD and 8 in metastatic LUAD. Mis-sense mutation was the most common variant classification in both primary and metastasis. TP53 (42%), KRAS (37%), EGFR (27%), STK11 (16%) and KEAP1(12%) were the most frequent alterations identified in primary LUAD. TP53 (58%), EGFR (31%), KRAS (28%), KEAP1 (15%) and STK11 (15%) were the most frequent alterations found in metastatic LUAD. KRAS, RBM10, NKX2-1, BCR, SDHC, and SYNE1 were found significantly more common in primary LUAD than those in metastatic LUAD ($P < 0.001$). By contrast, TP53, MDC1, SMARCA4 and LRP1B were much more common in metastatic LUAD ($P < 0.001$). Interestingly, EGFR exon 19 deletion (13.8% vs 10.2%, $P < 0.001$), EGFR T790M (5.0% vs 2.6%, $P < 0.001$), and T790M plus sensitizing mutation (4.8% vs 2.4%, $P < 0.001$) were found significantly higher in metastatic LUAD than primary LUAD. Primary LUAD had more frequent EGFR exon 20 insertion (2.3% vs 1.3%, $P<0.01$) and KRAS G12C mutation than metastatic LUAD (14.5% vs 11.9%, $P<0.01$). No significant differences were noticed in STK11, BRAF and MET exon 14 mutations. However, significant increase in MET (11.6% vs 5.7%, $P < 0.001$) and ERBB2 amplifications (5.7% vs 3.1%, $P < 0.01$) were found in metastatic LUAD. Similarly, ALK (14.7% vs 7.3%, $P < 0.001$), ROS1 (3.0% vs 2.0%, $P < 0.01$) and RET (3.9% vs 2.3%, $P < 0.01$) rearrangement were found more frequent in metastatic LUAD. **Conclusion:** Our study presented the landscape of genomic alterations in primary and metastatic LUAD. We found significant increases in many targetable genomic alterations in metastatic LUAD compared to primary LUAD. These findings highlighted the importance of biopsying the metastatic LUAD tumors. In addition, the potential roles of those increased genomic alterations in clonal selection or evolution of LUAD warrant further investigation.

Keywords: Lung adenocarcinomas, Primary and metastasis, Genomic alterations

FP16.03 Early Circulating-Tumor DNA EGFR Mutation Clearance in Plasma as a Predictor of Clinical Outcomes in The AURA3 Trial

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Introduction: In the phase III AURA3 trial (NCT02151981), osimertinib, a third-generation epidermal growth factor tyrosine-kinase inhibitor (EGFR-TKI), demonstrated superior efficacy compared with platinum-based doublet chemotherapy (platinum-pemetrexed) in patients with EGFR TKI-sensitizing mutation-positive (EGFRm) advanced non-small cell lung cancer (NSCLC) and T790M-mediated resistance to first- or second-generation EGFR-TKI. Herein, we further explore the association between early EGFR-mutation circulating-tumor DNA (ctDNA) clearance and clinical outcomes in both the osimertinib and chemotherapy arms. **Methods:** EGFR-mutation (Ex19del/L858R) ctDNA analysis was conducted in plasma samples with valid ctDNA results by droplet-digital polymerase chain reaction (ddPCR; Biodesix). Detectability of EGFR-mutation ctDNA at baseline (Cycle 1 Day 1), and clearance at Week 3 (Cycle 2 Day 1) and 6 (Cycle 3 Day 1) specifically in those patients with detectable EGFR-mutation ctDNA at baseline, were analyzed in relation to progression-free survival (PFS) and objective response rate (ORR) per investigator-assessed Response Evaluation Criteria in Solid Tumours 1.1. Data cut-off date for this analysis was April 15, 2016. **Results:** Among patients with a valid baseline ddPCR result, absence versus presence of EGFR-mutation ctDNA at baseline corresponded with favorable median PFS (months) in the osimertinib arm (n=209): 14.0 (95% CI 12.3, not calculable) versus 8.3 (6.8, 10.6); and platinum-pemetrexed arm (n=82): 5.8 (95% CI 4.2, 9.9) versus 4.2 (4.1, 5.6). In patients with detectable EGFR-mutation ctDNA at baseline and valid ctDNA results at Weeks 3 and/or 6, ORR was significantly better in those receiving osimertinib versus platinum-pemetrexed (Table); EGFR-mutation ctDNA clearance was also more frequently observed at both Weeks 3 and 6 in those receiving osimertinib (Table). Patients who cleared versus did not clear EGFR-mutation ctDNA at Week 3 had favorable median PFS (months) in both the osimertinib arm: 10.9 (95% CI 8.3, 12.7) versus 5.7 (4.1, 9.7); and platinum-pemetrexed arm: 6.2 (95% CI 4.0, 9.7) versus 4.2 (4.0, 5.1). A similar PFS outcome was observed for clearance at Week 6. **Conclusion:** Baseline-detectable EGFR-mutation ctDNA in patients with EGFRm NSCLC and T790M-mediated resistance to first- or second-generation EGFR-TKI was demonstrated as a poor prognostic factor. In those patients with baseline-detectable EGFR-mutation ctDNA, ctDNA clearance at Weeks 3 and 6 correlated with favorable outcomes in both treatment arms and predicted the benefit of osimertinib over platinum-pemetrexed. In this study, early on-treatment ctDNA dynamics were shown to correctly predict clinical outcomes. These data may support potential value of early ctDNA profiling in helping to inform clinical decision making and in supporting regulatory packages.

Table. ORR and ctDNA clearance status at Weeks 3 and 6 in patients receiving osimertinib or platinum-pemetrexed

Response assessment	AURA3 treatment arm* (N)	RECIST 1.1-defined response or ctDNA clearance status (n)	Comparison between treatment arms	
			Odds ratio (95% CI)	p-value (Fisher test)
RECIST 1.1-defined response in patients with baseline-detectable EGFR-mutation ctDNA and valid ctDNA results at Week 3 and/or 6				
RECIST 1.1	Osimertinib (139)	Response (97)	3.2 (1.7, 6.0)†	p=0.0004†
		Non-response (42)		
	Platinum-pemetrexed (57)	Response (24)		
		Non-response (33)		
EGFR-mutation ctDNA clearance status in patients with baseline-detectable EGFR-mutation ctDNA and valid ctDNA results at Week 3 and/or 6				
ctDNA clearance at Week 3	Osimertinib (128)	Cleared (80)	5.0 (2.5, 10.1)‡	p<0.00001‡
		Not cleared (48)		
	Platinum-pemetrexed (56)	Cleared (14)		
		Not cleared (42)		
ctDNA clearance at Week 6	Osimertinib (128)	Cleared (83)	3.2 (1.7, 6.1)‡	p=0.0007‡
		Not cleared (45)		
	Platinum-pemetrexed (57)	Cleared (21)		
		Not cleared (36)		

CI, confidence interval; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; ORR, objective response rate
RECIST 1.1, Response Evaluation Criteria in Solid Tumours 1.1
*Patients in AURA3 were randomized 2:1 to receive osimertinib or platinum-pemetrexed
†RECIST 1.1-defined response
‡EGFR-mutation ctDNA clearance

Keywords: EGFR mutation, non-small cell lung cancer, circulating-tumor DNA

FP16.04 A Nationwide Population-Based Mapping of Mutations and Gene Fusions in Lung Cancer Among Never-Smokers

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Introduction: Approximately 10-15% of all lung cancer cases arise in never-smokers. Previous studies conclude that a smoking-independent subgroup of lung adenocarcinoma with certain molecular and clinical features exists. It is well known that targetable alterations are more frequent in this group, but the nationwide population-based prevalence and spectrum of mutations and gene fusions among Swedish never-smokers have not yet been investigated. In an ongoing project within the Swedish Molecular Initiative against Lung cancer (SMIL) we characterize lung cancer in never-smokers. Herein, we report the nationwide prevalence of targetable gene fusions and MET exon 14 skipping events among over 400 Swedish never-smokers. **Methods:** The National Lung Cancer Registry (NLCR) was used to identify never-smokers that underwent lung cancer surgery in Sweden during a ten-year period (2005-2014). Patients' medical charts were reviewed to verify smoking status and to assemble clinical data. At each site, a thoracic pathologist retrieved archived surgically resected formalin-fixed paraffin-embedded tumor material, reviewed the histology of each case, and selected representative tumor tissue blocks for subsequent DNA and RNA extraction. The NanoString nCounter Elements assay was used for detection of gene fusions and MET exon 14 skipping. Mutation analysis was performed by Next Generation Sequencing (NGS) using a 26-gene exon-focused panel. **Results:** By RNA-based NanoString analysis, we detected alterations in 106 (25%) of 417 successfully analyzed tumors; 51 MET exon 14 skipping events, 35 ALK fusions, 13 RET fusions, three NRG1 fusions, two ROS1 fusions, one NTRK1 fusion, and one finding of co-occurring ALK fusion and MET exon 14 skipping. The median age at diagnosis was 71 years, 372 cases were adenocarcinomas (89%), and 288 patients (69%) were females. Mutational status obtained by DNA-based NGS was available for a subset of the tumors (n=138). Among these, 60 tumors had sensitizing mutations in either EGFR or BRAF. Since gene fusions and oncogene driver mutations are generally known to be mutually exclusive, exclusion of these cases and of an additional 26 cases with other targetable or potentially targetable mutations (mutations in EGFR exon 20, BRAF other than V600, HER2, KRAS and PIK3CA) resulted in 31 out of the remaining 52 cases (60%) having gene fusions or MET exon 14 skipping. **Conclusion:** In this nationwide population-based study on the prevalence of targetable gene alterations in lung cancer among surgically treated never-smokers, 25% of the tumors harbored gene fusions or MET exon 14 skipping. In the subset of tumors where no oncogene driver mutation had been detected by DNA-based methods, gene fusions or MET exon 14 skipping occurred in 60% of the tumors.

Keywords: Never-smoker, Gene fusion, Targetable alterations

FP16.05 Computational Omics Biology Model (CBM) Identifies Novel Biomarkers to Inform Combination Platinum Compound Therapy in NSCLC

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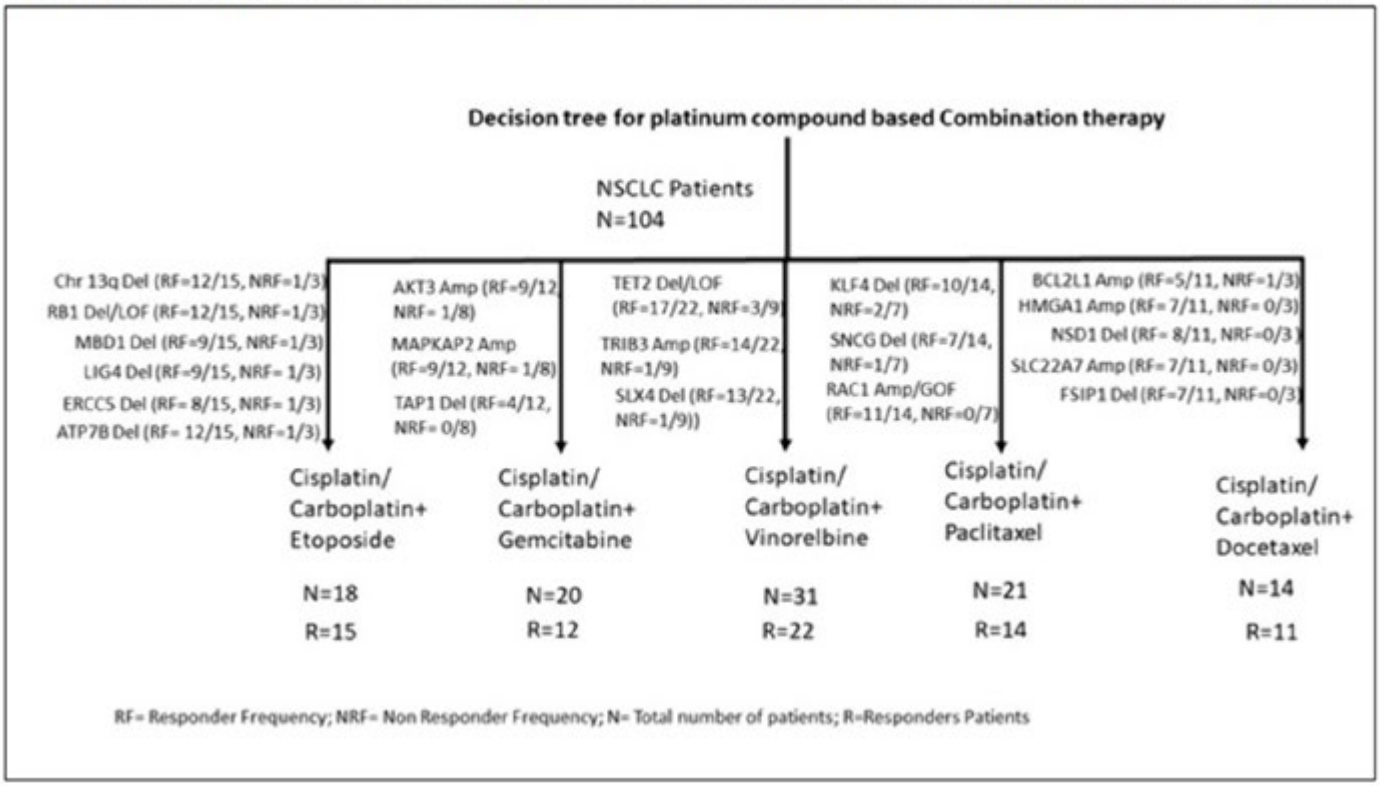
Introduction: Cytotoxic drugs are hampered by limited efficacy. Hence, a personalized treatment approach matching chemotherapy with appropriate patients remains an unmet need. Genomic heterogeneity creates an opportunity to discern key genomic aberrations and pathways that confer resistance and response to standard treatment options. We conducted a study using the Cellworks Computational Omics Biology Model (CBM) to identify novel genomic biomarkers associated with response among Non-Small Cell Lung Cancer (NSCLC) patients receiving platinum-based treatments. **Methods:** 104 NSCLC patients who received platinum-based chemotherapy were selected from TCGA: platinum-etoposide (N=18), platinum-gemcitabine (N=20), platinum-vinorelbine (N=31), platinum-paclitaxel (N=21), and platinum-docetaxel (N=14). Mutation and CNV from each case served as input for the CBM to generate a patient-specific protein network-map based on PubMed and other resources. Biomarkers unique to each patient were identified within protein network-maps. Drug impact on the disease network was biosimulated to determine efficacy score by measuring the effect of chemotherapy on the cell growth score, a composite of cell proliferation, viability, apoptosis, metastasis, DNA damage and other cancer hallmarks. Effectively, the mechanism of action of each drug was mapped to each patient's genome and biological consequences determined response. **Results:** Among the 104 patients, 74 were responders (R) and 30 non-responders (NR), determined using compete and partial response based on RECIST criteria (Figure 1). The CBM predicted clinical response with 73% sensitivity and 77% specificity. Cellworks CBM identified novel biomarkers responsible for platinum-based combination therapy response as mentioned below. +Etoposide: 13q-del, RB1-del, MBD1-del, LIG4-del, ERCC5-del, ATP7B-del +Gemcitabine: AKT3-amp, MAPKAP2-amp, TAP1-del +Vinorelbine: TET2-del/LOF, TRIB3-amp, SLX4-del +Paclitaxel: KLF4-del, SNCG-del, RAC1-amp/GOF +Docetaxel: BCL2L1-amp, HMGA1-amp, NSD1-del, SLC22A7-amp, FSIP1-del These genes contributed to drug efficacy by impacting various pathways, including DNA repair, oxidative-stress, methylation machinery, spindle formation, and mitotic-catastrophe. The aberration frequency of these genes was high among the responders within each subgroup and was very low in non-responders. Additionally, a model of clinical outcome versus the linear and quadratic function of efficacy score, drug combination and the interaction of both showed that efficacy score provides predictive information above and beyond the choice of drug combination alone (likelihood ratio chi-sq = 35.56, df=13, p-value = 0.0007).

Table

Figure 1: The optimal combination partner for platinum-based therapy determined by CBM



Description automatically generated **Conclusion:** This pilot study highlights how the Cellworks CBM biosimulation platform can help identify patients for therapy response prediction. By using novel biomarkers, a CBM-informed decision tree can be employed to identify the optimal drug combination for platinum-based therapy. We suggest that this approach be validated prospectively in a larger patient cohort.

Keywords: Multi-omics Therapy Biosimulation, Personalized Cancer Therapy, Cancer Therapy Biosimulation

Posters Presentations

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P01.01 LIBRETTO-432: A Placebo-Controlled Phase 3 Study of Adjuvant Selpercatinib in Stage IB-IIIA RET Fusion-Positive NSCLC

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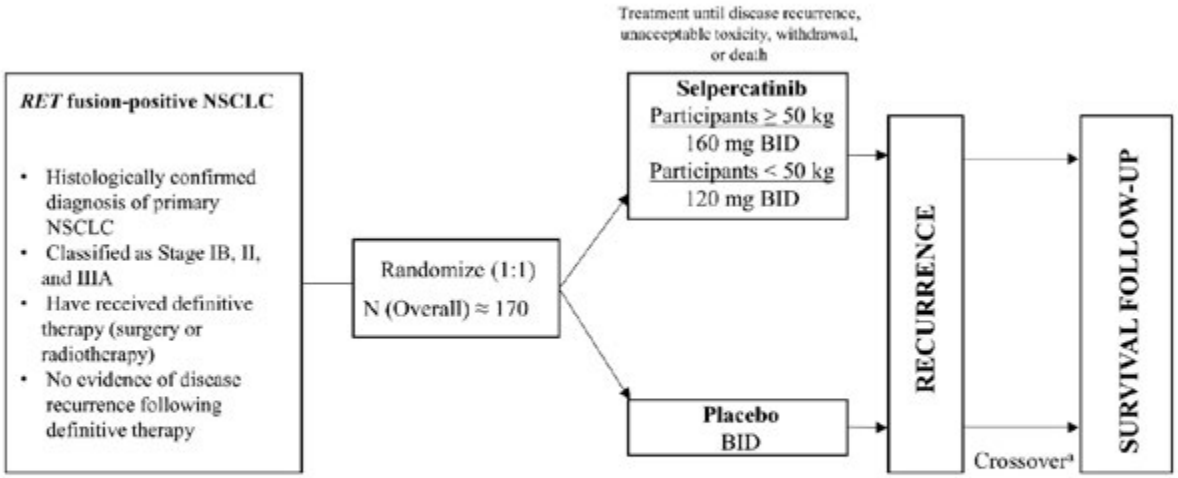
Introduction: Approximately 30% of patients diagnosed with NSCLC present with early-stage (IB-IIIA) disease. Standard treatment options for these patients are definitive locoregional therapies with/without adjuvant chemotherapy, followed by surveillance until disease recurrence. While targeted therapies are standard treatment for metastatic NSCLC with driver mutations, their use in the early-stage setting is still being characterized. Selpercatinib, a highly selective, potent and CNS active RET inhibitor, demonstrated robust and sustained antitumor activity with manageable toxicity in patients with RET fusion-positive advanced NSCLC. There is a growing evidence demonstrating that oncogene addiction in NSCLC could be actionable regardless of disease stage. LIBRETTO-432 is a Phase 3, global, multicenter, randomized, double-blind, controlled trial evaluating the efficacy and safety of adjuvant selpercatinib versus placebo in patients with RET fusion-positive Stage IB-IIIA NSCLC following completion of definitive radiotherapy or surgery with a curative intent, and other adjuvant therapy if indicated (NCT04819100). **Methods:** Patients (n≈170) will be randomized (1:1) to Arm A (selpercatinib twice daily [160mg ≥50kg; 120mg <50kg]), or B (placebo), in continuous 28-day cycles for a maximum treatment duration of 3 years (**Figure 1**). Stratification factors include disease stage (Stage IB/II/IIIA) and prior definitive therapy (surgery, radiotherapy). Crossover is allowed for Arm B patients who experience disease recurrence. Treatment will continue until disease recurrence, unacceptable toxicity, withdrawal, or death. Key eligibility criteria include age ≥18 years; histologically confirmed Stage IB/II/IIIA NSCLC; mandatory brain MRI during screening to rule out metastasis; presence of activating RET fusion in tumor by PCR/NGS (local or central testing); received definitive locoregional therapy with curative intent (surgery, radiotherapy) for Stage IB/II/IIIA NSCLC; and ECOG performance status 0-1. Maximum time allowed between definitive therapy completion and randomization must be within 26 weeks. Key exclusion criteria are presence of other known oncogenic drivers; evidence of SCLC; and evidence of disease recurrence following definitive therapy. The primary endpoint is investigator-assessed event-free survival (EFS) in the primary analysis population. EFS is defined as time from randomization until locoregional disease recurrence with histopathological confirmation, distant disease recurrence per RECIST v1.1 or histopathological confirmation, or death. Gated secondary endpoints include investigator-assessed EFS in the overall population and overall survival in both the primary analysis and overall population. Non-gated secondary efficacy endpoints include blinded independent central review (BICR)-assessed EFS, time to distant disease recurrence in the CNS assessed by investigator and BICR, and progression-free survival on the next line of treatment.

Figure 1. Trial Design of LIBRETTO-432



Abbreviations: BID = twice daily; N = number of participants; NSCLC = non-small cell lung cancer; RECISTv1.1 = Response Criteria in Solid Tumors Version 1.1.

[a]Crossover to selpercatinib allowed ONLY at disease recurrence (per RECIST v1.1 and/or histopathological confirmation).

Keywords: Selpercatinib, RET fusion-positive, adjuvant

P01.02 High Risk Factors and Benefit of Adjuvant Chemotherapy in Surgically Resected Stage IB Non–Small Cell Lung Cancer

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Introduction: Lung cancer remains the leading cause of cancer deaths worldwide. Although Stage IB disease is usually managed with upfront resection, consideration for adjuvant chemotherapy treatment is dependent on the presence or absence of high risk factors. The prognostic value of these factors and survival outcomes for these patients as reported by a national database have not been clearly elucidated. **Methods:** Patients with diagnosed NSCLC Stage IB (pT2aN0) per AJCC 7th edition between 2010 and 2016 from the NCDB were included. Non-surgical cases and cases that received radiotherapy were excluded. Univariate analyses comparing the clinico-demographic and pathologic features of those managed with surgery and observation (obs) versus surgery and adjuvant chemotherapy (CT) was performed. Multivariate analyses identified factors that influence survival and the likelihood of receiving CT. Kaplan-Meier method was performed to compare median OS. **Results:** A total of 10,669 cases (84.2% obs, 15.8% CT) were identified. The obs cohort were primarily over age 70 (50.4%); those managed with CT were primarily 50-70 years (69.3%). Cases with tumors 4-5cm (OR, 0.388, P<0.0001), pleural invasion (OR, 0.598, P<.0001), and poor tumor differentiation (OR, 0.332, P<.0001) had a decreased likelihood of receiving obs versus CT. Age over 70 (HR, 1.801, P<.0001), Medicare insurance (HR, 1.246, P<.0001), and poor tumor differentiation (HR, 1.741, p<.0001) were adverse predictors of OS for those receiving obs versus CT. Five-year survival was higher for CT (63.6%) versus obs (57.1%), median OS was 88 months versus 75 months (p<0.0001) respectively. Those with moderately differentiated tumors achieved a survival benefit of 23 months when managed with CT (**Table 1**). Median OS increased by 19 months (65 versus 84 months) for poorly differentiated tumors managed with CT (p<.0001). When visceral pleural invasion was present, median OS was 60 months (obs) and greater than 75 months (CT) (p=0.0006). Cases with tumors 4-5cm in size had a median OS of 88 months when CT was received versus 67 months when managed with obs (p<.0001). Cases managed with lobectomy experienced a survival benefit of 92 months (CT) and 76 months (obs) (p<.0001).

	Surgery and Observation (reference)			Surgery and Chemotherapy			OS Benefit (Mos)	P-value
	Median OS (Mos)	95% CI Lower Limit	95% CI Upper Limit	Median OS (Mos)	95% CI Lower Limit	95% CI Upper Limit		
Overall	75	71	77	88	83	NE[a]	13	<.0001
No pleural involvement	78	75	83	92	84	NE	14	0.0026
Visceral Pleural Invasion	60	56	71	NE	75[b]	NE	-	0.0006
< lobectomy	58	51	65	52	43	NE	- 6	0.8810
lobectomy	76	73	78	92	87	NE	16	<.0001
3-4cm	79	76	86	87	74	NE	8	0.0589
4-5cm	67	62	71	88	83	NE	21	<.0001
Moderately Diff	69	66	75	92	92	NE	23	<.0001
Poorly Diff	65	60	70	84	77	NE	19	<.0001

[a]NE= Not estimate, small sample/sparse data [b]Median OS >75 months for CT; Mos=Months CI=Confidence Interval Diff=differentiation **Conclusion:** Overall, stage IB (pT2aN0) NSCLCs managed with CT, experienced an increased median OS of 13 months when compared to the obs cohort. Cases with pleural invasion, tumors 4-5cm in size with poor differentiation might experience a survival benefit in excess of 20 months, when CT is given versus obs.

Keywords: adjuvant chemotherapy, non–small cell lung cancer, Surgical resection

P02.01 CT Integrated Bronchoscopy Manual Spraying Pigment Labeling to Localize of Small Pulmonary Nodules

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Introduction: Popularization of High Resolution Computed Tomography (HRCT) has greatly improved the detection rate of pulmonary nodules. Video Assistant Thoracic Surgery (VATS) lobectomy (sublobar lung resection in selected patients) has been the standard surgical treatment for these early stage non-small cell lung cancer. Uniportal VATS, a widely used innovative technique in minimally invasive thoracic surgery, makes less incision and also demands more precise intraoperative palpation/localization which is often challenging for small nodules. Various strategies such as the hookwire method, CT fluoroscopy-guided bronchoscopic dye marking, contrast median injection, radiotracer localization and a virtual assisted lung mapping technology (VAL-MAP). While they provide new options of nodule location for thoracic surgeons, all of these strategies require expensive hardware or software and additional two or three more doctors which are often not affordable for centers with limited resources. The purpose of this study is to develop a practically cheap method of pigment labeling for bronchoscope with no additional need of medical equipment and medical human resources. **Methods:** This is an ethic committee approved clinical trial. Medically operable patients with the HRCT detected small nodules were eligible. This nodule localization method involved a manual drawing the route by the surgeon/bronchoscopist, through a series of bronchial opening sketches and marking the leading bronchus at every bifurcation point based on the HRCT. Two to four appropriate bronchial pathways were selected for each lesion. A metal-tip catheter was inserted into a selected bronchus and advanced to the pleura. The location of the catheter tip was fluoroscopically confirmed, and 1 mL of diluted methylene blue was injected for each marking. All these procedures were completed by one doctor and one nurse. Then low dose CT scan was used to visualize the localization of the multiple markings, which were used as references in the subsequent operation. Success rate and procedure related complication are reported. **Results:** From April 2019 to July 2020, 18 lesions in 17 patients were enrolled. All surgical procedures were performed using uniportal VATS. The lesions ranged in size from 3 to 23mm, 15 (83%) were nodules of Ground Glass Opacity (GGO). The depth ranged from 0 to 19 mm. A total of 57 lung markings were planned. 54 of them (95%) were completed. Of the 3 failed markings, the target bronchus could not be accessed under the bronchoscopy because of improper angle. Fifty-two (91%) were visible during the operations. The 3 unidentified markings were in the same patient, who had been a coal miner and had a severe carbon deposition on his lung and pleura. There was no adverse event associated with this manual marking procedures. All lesions were successfully resected. In 3 patients failed multiple markings, alternative localization was used successfully. **Conclusion:** This HRCT guided manual drawing method of lesion localization is safe and effective for small nodule localization for lung cancer surgery. Results of this study appears to be better than conventional percutaneous techniques in clinically evident complications. Because it does not need special equipment, it is more suitable for developing countries with limited equipment and human resources.

Keywords: Uniportal VATS, manual drawing, bronchoscopic dye marking

P02.02 Transbronchial Microwave Ablation of Lung Nodules in the Hybrid Operating Room – Mid-Term Follow Up of a Novel Technique

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Introduction: Microwave ablation of lung nodules provides a faster, larger and more predictable ablation zone than its predecessor radiofrequency energy, while bronchoscopic ablation has theoretical advantage of less pleural-based complications than percutaneous approach. The combination of bronchoscopic approach and microwave ablation is a novel approach in local treatment of lung nodules. Mid-term results are presented here. This is an updated abstract following the presentation of early results in IASLC World Conference on Lung Cancer 2020. **Methods:** Fifty lung nodules in 42 patients who underwent electromagnetic navigation bronchoscopy microwave ablation in hybrid operating room from March 2019 onwards were retrospectively reviewed. Patients either refused surgery or had significantly high surgical risks. Eligible lung nodules were either proven lung cancers, metastases, or radiologically suspicious. Feasibility, safety and mid-term control rate of the technique were assessed. **Results:** Mean maximal diameter of lung nodules was 15.1mm (range 7-29mm), and bronchus sign was positive in 40% of them. Technical success rate was 100%, although 12 nodules required double ablation for adequate coverage. Mean minimal ablation margin was 5.55mm. There was no significant heat sink effect. Mean hospital stay was 1.74 days, 37 cases (74%) and 47 cases (94%) were discharged by post-ablation day 1 and 3 respectively. Complications included mild pain which did not require hospitalization (14%), pneumothorax requiring drainage (10%), post-ablation reaction (2%), pleural effusion (2%) and hemoptysis (2%). Median follow up is 13 months, and only 2 lesions had evidence of local recurrence, both occurring 6 months after ablation. Both of the lesions were lung metastases in the first instance and local recurrence was accompanied by widespread systemic metastases. None of treated primary lung cancers recurred. **Conclusion:** Transbronchial microwave ablation is a safe and novel ablative technique for early stage lung cancers, lung metastases or highly suspicious lung nodules in selected cases, and has an encouraging mid-term local control rate. Important selection criteria include anatomical considerations and disease factors.

Keywords: microwave ablation, transbronchial ablation, early lung cancer

P02.03 Robotic Bronchoscopy: Navigating the Change in Lung Nodule Management

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Introduction: Clinicians are inundated with findings of lung nodules from a multitude of scenarios including surveillance scans, lung screening, and emergency room evaluation. Triage of nodules to observation, biopsy and resection has been influenced by location, size, comorbidities, and technology limitations. Definitive diagnosis can alter the clinical plan but may not always be readily obtained. Nodules may represent early lung cancer, advanced lung cancer, metastatic disease from other solid tumors, or benign diagnoses. We report our experience with robotic navigational bronchoscopy as a diagnostic platform and describe the safety and utility of this technology in an academic community hospital. **Methods:** All patients undergoing navigational bronchoscopy beginning 8/1/2020 were enrolled in an IRB approved registry. Navigational bronchoscopy was performed with radial EBUS and 2D/3D imaging. Metrics including number of nodules, length of procedure, nodule characteristics, previous workup, diagnostic yield, and complications were captured prospectively on each patient. Plans for management and definitive therapy were recorded. Short term outcomes were assessed; long term outcomes are being tracked for longitudinal analysis. **Results:** We evaluated 45 patients and 58 nodules. Median number of nodules per patient was 1 (range 1 - 3). Median size of nodules was 14mm (range 5 - 44 mm). Thirty-eight patients (84%) had pre procedure PET scan. Ion was the first diagnostic intervention for 38 patients (84%). Radial EBUS was performed on all patients and confirmed navigation to the nodule in 52 of 58 (90 %). EBUS for adenopathy staging was performed simultaneously on 8 patients; no pathologic nodes were identified. Eighteen patients were scheduled for interval CT chest to continue evaluation. Nine patients had single anesthesia for diagnosis/localization/ resection; 8 had sub lobar resection and 1 had lobectomy. All patients were extubated at completion of the Ion procedures and single anesthesia cases. There were no procedure related deaths or complications. Incidence of pneumothorax was zero. Day of procedure pathology correlated with final pathology in 89%. Pathology confirmed: lung primary (16), metastatic colorectal (5), metastatic esophageal (1) lymphoma (1) and inflammatory nodules (18); navigational bronchoscopy was nondiagnostic in 4 patients. **Conclusion:** Navigational bronchoscopy is a safe diagnostic platform. In our initial experience there were zero complications in clinical scenarios which included peripheral nodules and pleural based lesions. The diagnostic yield was 89%. Accurate diagnosis established the definitive care pathway for each patient and included resection, SBRT, chemotherapy, and observation. Ion robotic assisted navigational bronchoscopy supports patient management across a range of solid tumor disease sites and facilitates decision making in our lung nodule program. The addition of Ion navigational bronchoscopy to an academic community comprehensive cancer program has expanded our ability to accurately diagnose lung nodules and guide patients to the appropriate management pathway.

Keywords: nodules, navigational bronchoscopy, early diagnosis

P02.04 Three Cases of Endoscopic Snare Resection for Tracheal and Main Bronchial Tumors

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Introduction: Tracheal and main bronchial tumors are relatively rare diseases. Primary or metastatic malignant tumors and benign tumors are also found. Even benign tumors can obstruct the airways and may require urgent treatment. We report three cases of endoscopic snare resection. **Methods:** Case 1: A 53-year-old woman examined the exacerbation of wheezing and found a tumor obstructing the left main bronchus. The snare resection was performed using a rigid bronchoscope. The tumor was Mucoepidermoid carcinoma. After snare resection she has survived for 3 years without recurrence. Case 2: A 72-year-old man had a recurrence at the stump after right upper lobectomy. The tumor obstructed his right main bronchus. The snare resection was performed under rigid bronchoscopy. After resection, radiation therapy and chemotherapy were added. Case 3: A 51-year-old woman was admitted with right renal cancer and tracheal tumor on close examination of cough. We performed snare resection under flexible bronchoscopy. The tumor diagnosed as tracheal metastasis from renal cancer. **Results:** Respiratory status was stable in all three cases, and it was possible to perform resection without PCPS. In cases 1 and 2, we considered that the tumors tended to bleed, so we used a rigid endoscope under general anesthesia. Snare excision was performed with a monopolar electric scalpel 25w of coagulation. It was possible to remove the tumor in case 1 with 3 resections and in cases 2 and 3 with only 1 resection. **Conclusion:** Snare resection is a very effective treatment method for central airway tumors. Although radical cure is rare with snare excision alone, it is possible to quickly move to next treatment because it is less invasive. Flexible bronchoscopy is adequate if the respiratory status is stable and the risk of bleeding is low.

Keywords: snare resection, tracheal tumor, bronchial tumor

P02.05 Yield of Tumor Samples With A Guide-sheath in Endobronchial Ultrasound Transbronchial Biopsy For Non-small Cell Lung Cancer

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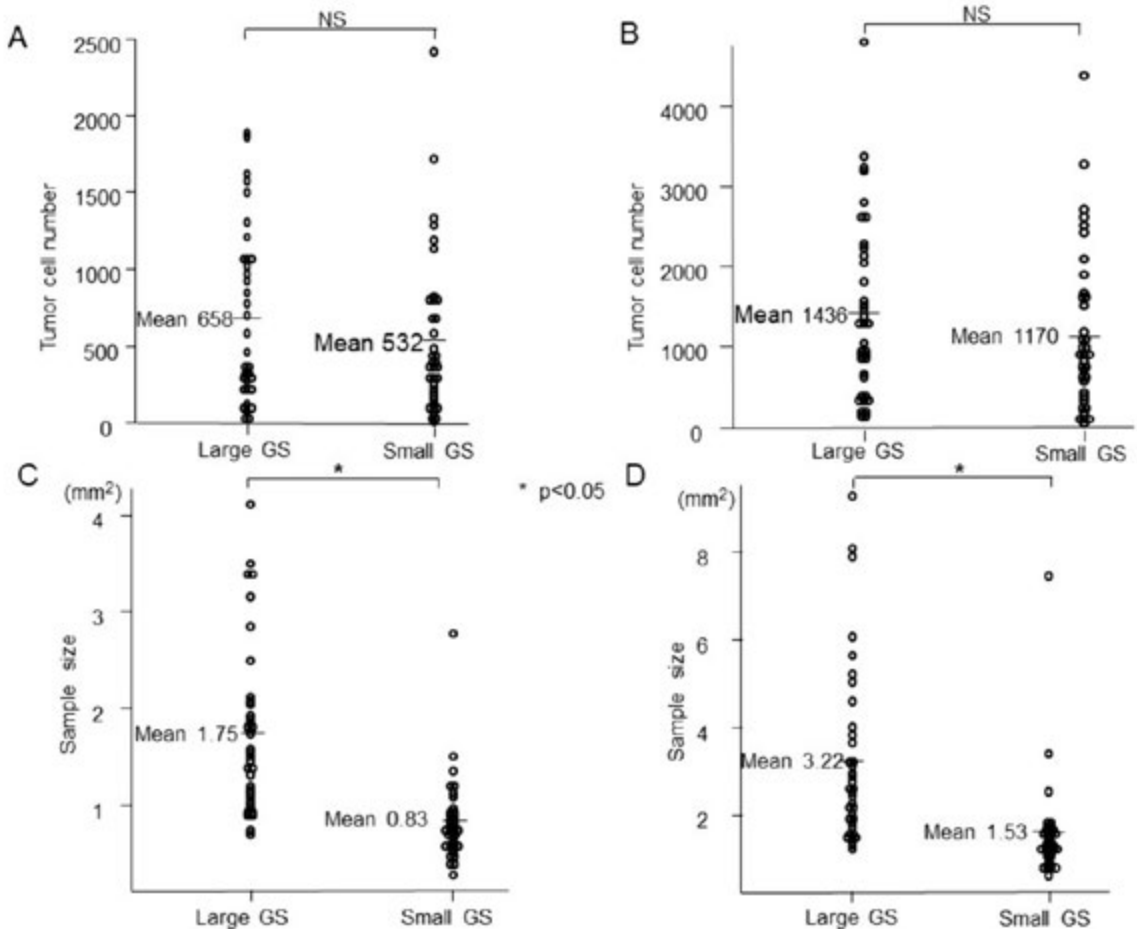
Introduction: Adequate tumor tissue is required to treatment for non-small cell lung cancer (NSCLC). Transbronchial biopsy (TBB) by endobronchial ultrasonography with a guide sheath (EBUS-GS) is useful to diagnose peripheral lung lesions. We can choose two different sizes of GS kits—large and small. The data of tumor cell number obtained by TBB using different sizes of GS are limited. It is also unclear which lesion can be diagnosed by TBB with large GS. We investigated the utility of a large GS kit to obtain many tumor cells in patients with NSCLC. We further assessed the characteristics of lesions that could be obtained by TBB with large GS. **Methods:** Patients with a peripheral lung lesion and suspected of NSCLC were prospectively enrolled. They underwent TBB with a 5.9-mm diameter bronchoscope with a large GS. When the lesion was invisible in EBUS, we changed to a thinner bronchoscope and TBB was performed with a small GS. We compared the tumor cell numbers prospectively obtained with a large GS (prospective large GS group) and those previously obtained with a small GS (small GS cohort). The primary endpoint was the tumor cell number per sample, and we assessed characteristics of lesions that could be obtained by TBB with large GS.



Results: Biopsy with large GS was performed in 55 of 87 patients (63.2%), and 37 were diagnosed with NSCLC. The mean number of tumor cells per sample of the large GS group tended to be more than that of the small GS cohort (658±553 vs. 532±526, p=0.32) (Fig.1A. B; The comparison of the counts of the slide containing the largest number of tumor cells among five samples). The mean sample size of the large GS group was significantly larger than that of the small GS cohort (1.75 mm^2 vs. 0.83 mm^2, p<0.001). (Fig.1C. D; The comparison of the largest sample size of five samples) Logistic regression analysis indicated that the bronchus generation was significantly associated with the change to a thinner bronchoscope. Of the 12 lesions involving a third or less bronchus generation, 10 (83.3%) were diagnosed by GS-TBB with large GS. **Conclusion:** There was no significant difference in tumor cell number between two sizes of GS, although the sample size obtained by large GS was significantly larger than that of small GS. The 5.9-mm diameter bronchoscope with large GS can be used for lesions involving a third or less bronchus generation.

Keywords: bronchoscopy, non-small cell lung cancer, tumor cell number

P03.01 Pathologic Response to Neoadjuvant PD-1 Inhibitors and Chemotherapy in Squamous Non-Small-Cell Lung Cancer

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Introduction: Several randomized studies have shown that the combination of programmed cell death 1 (PD-1) inhibitor and chemotherapy is efficacious as a treatment for advanced non-small-cell lung cancer (NSCLC), however, in the neoadjuvant setting, there is scarce evidence of the effectiveness and safety of the combinations in squamous NSCLC. We conducted a retrospective study to evaluate neoadjuvant PD-1 inhibitor plus chemotherapy in resectable squamous NSCLC. **Methods:** Patients from Beijing Chest Hospital, Capital Medical University between October 2019 and March 2021 treated with PD-1 inhibitors and chemotherapy for resectable squamous NSCLC were retrospectively studied. The primary objectives were to assess the pathological tumor response and safety of neoadjuvant PD-1 inhibitors and chemotherapy. **Results:** 27 patients with resectable squamous NSCLC stage IIA-IIIB were included. One to four cycles of PD-1 inhibitors (10 cases with camrelizumab, 10 cases with toripalimab, 3 cases with tislelizumab, 3 cases with sintilimab, and one case with pembrolizumab) and chemotherapy were administered prior to surgery. 15 patients (55.6%) achieved a major pathologic response (MPR), including eight (29.6%) with a pathologic complete response (pCR). 18 patients (66.6%) experienced grade 3 or higher neoadjuvant treatment-related adverse events (TRAEs), and no patient had grade 5 TRAE.

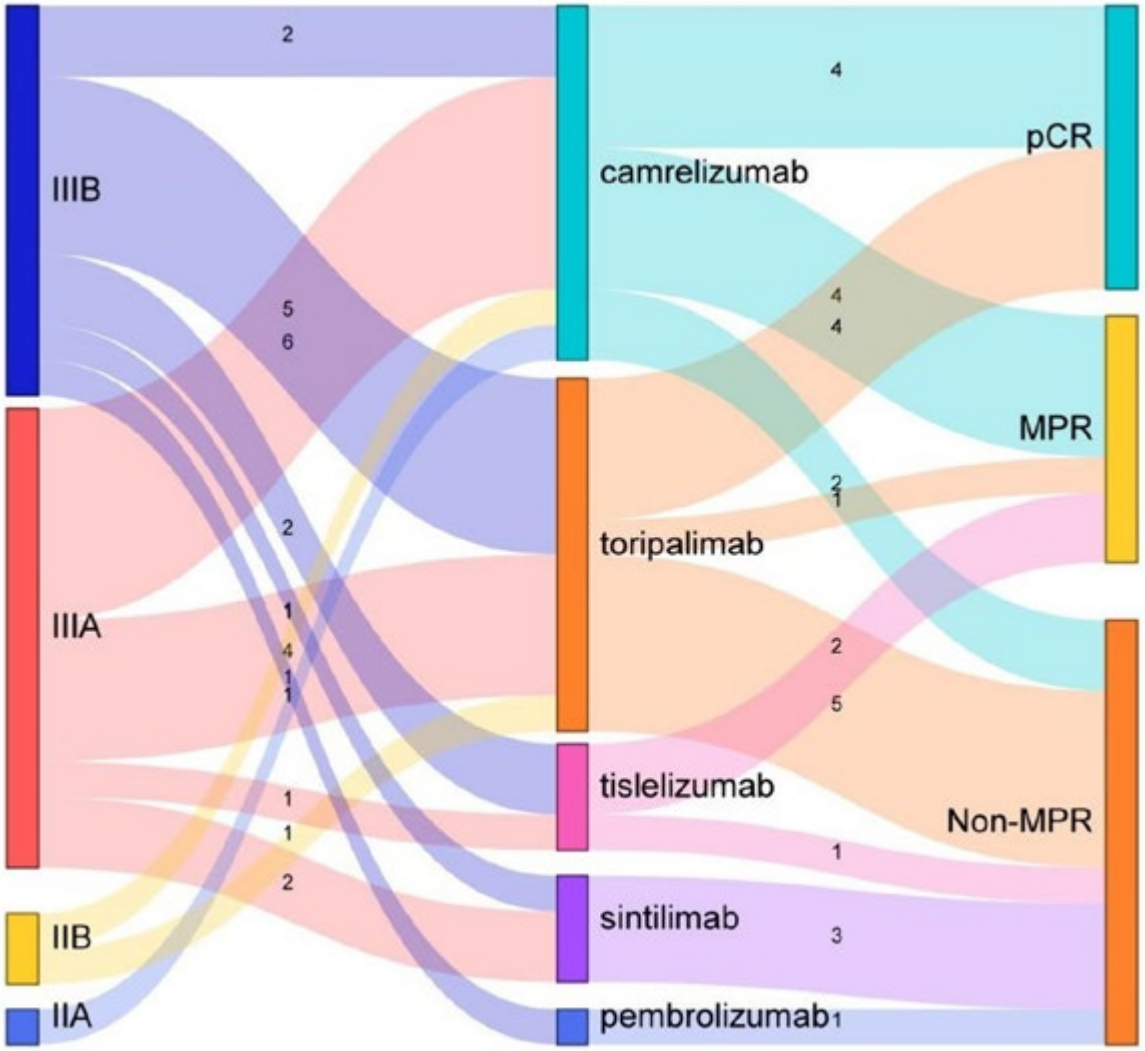

Figure: Pathological response of neoadjuvant therapy in different clinical stages

Conclusion: Neoadjuvant PD-1 inhibitors and chemotherapy is a feasible therapy in resectable squamous NSCLC. It was associated with 55.6% MPR rate and tolerable toxicity.

Keywords: Neoadjuvant immunotherapy, Squamous Non-Small-Cell Lung Cancer, programmed death-1 Inhibitors

P03.02 Osimertinib as Neoadjuvant Therapy for Resectable EGFR Mutant Non-small Cell Lung Cancer: A Real-World Multicenter Retrospective Study

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Introduction: The third-generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is well-tolerated and can improve disease-free survival (DFS) for EGFR mutant stage IB-IIIA completely resected non-small cell lung cancer (NSCLC) patients. However, limited data on osimertinib as neoadjuvant therapy for resectable, EGFR-mutant NSCLC exists. This multicenter, retrospective study aimed to investigate the efficacy and safety of osimertinib as neoadjuvant therapy in resectable patients with stage IA-IIIB NSCLC. **Methods:** The data of 13 resectable IA-IIIB EGFR mutant NSCLC patients undergoing surgery after one to three months of osimertinib neoadjuvant therapy (80mg orally daily) were retrospectively collected. **Results:** Average treatment time for osimertinib was 59.8 day prior to surgical resection. After neoadjuvant therapy of osimertinib, 2 cases reached clinial complete response, 9 reached partial response, 2 reached stable disease, with 84.6% objective response rate (ORR) and 100% disease control rate (DCR). Four patients had the data of major pathologic response (mPR) which was defined as less than 10% residual viable tumor at surgical resection. The mPR rate was 75% (3 of 4 patients). No pathological complete response (pCR) was observed. Pathological downstaging was observed in 5 patients. Treatment was well-tolerated without serious AEs or surgical complications. **Conclusion:** This retrospective study indicated that neoadjuvant therapy with osimertinib in EGFR mutant resectable IA-IIIB NSCLC patients was well-tolerated and could induce well pathological responses.

Keywords: neo-adjuvant, osimertinib

P04.01 Presence of Ground Glass Opacity Component is True Determinant of Prognosis in Clinical Stage I Non-Small Cell Lung Cancer

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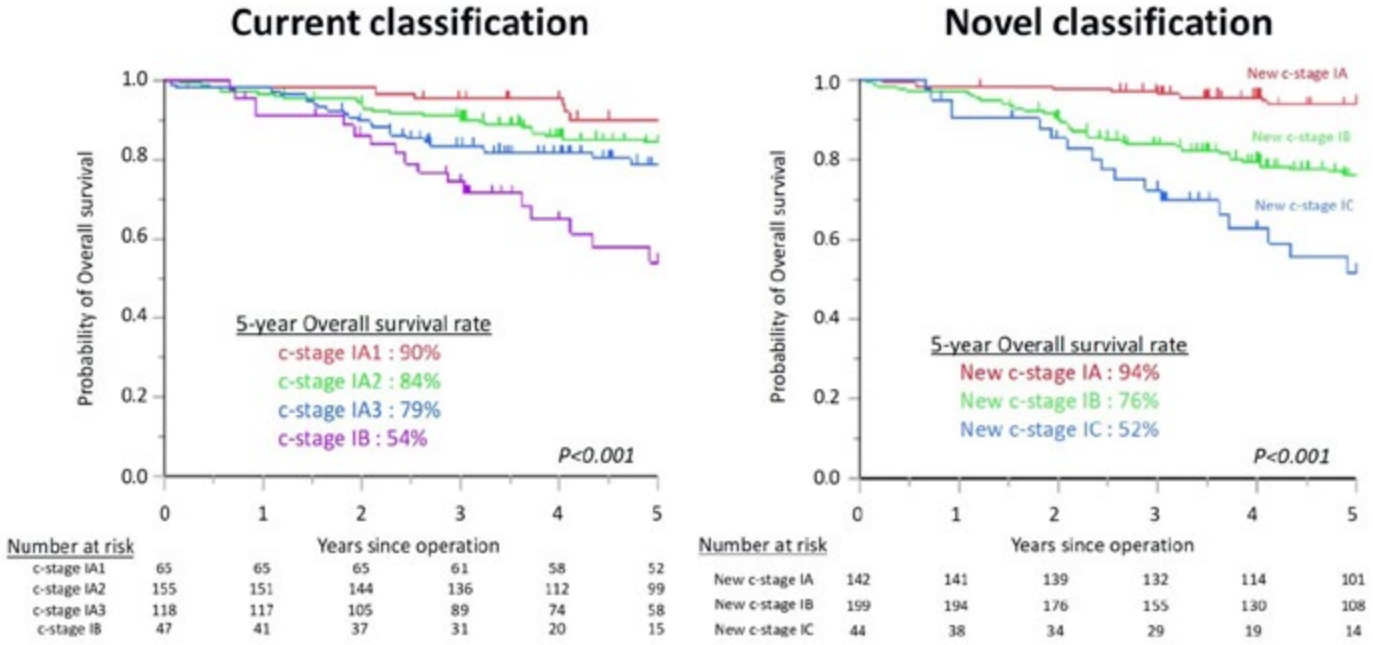
Introduction: Current Tumor-Node-Metastases (TNM) classification of non-small cell lung cancer (NSCLC) is based on the size of solid component for determination of the T factor. However, recent studies reported that the prognosis of patients who have tumors with ground-glass opacity (GGO) component (part-solid group) is significantly better than that of patients who have pure solid tumor (solid group) even if both tumors have the same diameter of the solid component. In this study, we analyzed prognosis of clinical stage I NSCLC patients and propose a new T classification that incorporates GGO status of the primary tumor. In addition, we examined if predominant pattern-based histologic grading is correlated with the prognostic difference between part-solid group and solid group. **Methods:** We retrospectively examined 385 clinical stage I NSCLC patients who underwent complete resection between 2009 through 2013. The recurrence-free survival (RFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and statistical difference was compared using the Log-rank test. A Cox proportional hazard regression analysis was performed to assess the prognostic impact of clinical or histologic factors on RFS and OS. **Results:** In our cohort, 243 (63%) and 142 (37%) patients were classified into solid group and part-solid group, respectively. The separation of the survival curves was good using the current TNM classification in the whole cohort. However, the part-solid group had a favorable prognosis irrespective of the size of the solid component. On the other hand, patients whose tumor size 3 -4 cm had a worse prognosis compared with those whose tumor size < 3cm in the solid group. Multivariate analysis confirmed above observation. Thus, we propose a novel T factor classification: IA; part solid tumors, IB; solid tumors with tumor size < 3cm, and IC; solid tumors with tumor size between 3 -4 cm. This novel classification system stratified patients' prognosis better than the current classification (Figure). On histologic evaluation, rate of the tumors with predominant pattern-based histologic grade 2/3 was higher in the solid group compared with the part-solid group. However, the part-solid group always had a better prognosis compared with the solid group in each of the subgroup divided by predominant pattern-based histologic grade.



Conclusion: Our results suggest that the presence of GGO is a true determinant of prognosis irrespective of the size of the solid component. A novel T factor classification system might be useful to predict patients' prognosis more accurately in clinical stage I NSCLCs.

Keywords: ground-glass opacity (GGO), TNM classification, early stage

P04.02 Efficacy of Multidisciplinary Team-Based Evaluation of Patients With Suspicious Pulmonary Lesions

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Introduction: The value of multidisciplinary team (MDT) meetings for cancers is well known since the late 1990's. However, there is a relative paucity of evidence that MDT meetings can improve the lung cancer care. When an indeterminate pulmonary lesion is multidisciplinary evaluated three different strategies can be explored: follow-up, pre-operative diagnostic approaches and upfront surgical resections. The aim of this study is to evaluate the prevalence of benign lesions resected by up-front surgery and that of malignant lesions surgically resected with therapeutic delay after a follow-up period in order to evaluate the efficacy of MDT meetings. **Methods:** Between January 2017 and December 2019 all patients with potentially resectable (c-stage I-IIIa) suspected lung cancer discussed at our MDT meetings were prospectively collected. The sample was divided into three groups according to the first MDT indication: DIAG group, patients with pre-operative diagnosis; SURG group, patients submitted to upfront surgery; F-U group, patients who underwent to surgical resection after a follow-up period (>6 months). **Results:** 297 patients were included and grouped as follows: 121 DIAG group (40.7%), 121 SURG group (40.7%) and 55 F-U group (18.5%). In DIAG group pre-treatment diagnosis was obtained by TTNA or EBUS-TBNA in 45 (37.1%) and 76 (62.9%) patients, respectively. In SURG group 85 lesions (70.2%) were intra-operatively diagnosed by atypical resection and frozen section, the remaining 36 (29.8%) underwent to an upfront anatomical resection. In the whole sample, a benign lesion was resected in 13 patients (4.4%) by sub-lobar resection. According to the study groups, benign lesions were found in 1 (0.8%), 10 (8.3%) and 2 (3.6%) patients from the DIAG, SURG and F-U groups, respectively (p=0.025). In 4 patients of the SURG group surgery impacted on the treatment strategy (1 usual interstitial pneumonia, 1 Wegener's granulomatosis, 2 aspergillomas). Therefore, unnecessary upfront surgery resulted in 6 patients (4.9%). Mean time intervals between the first CT scan and the surgical resection were 77 (±47 SD), 66 (±33 SD) and 416 (±504 SD) days for the DIAG, SURG and F-U groups, respectively (DIAG vs SURG p=0.044, F-U vs SURG p<0.001). Among 157 patients with p-stage I lung cancer, the 3-year survival was 72.2%, 69.7% and 77.8% for the DIAG, SURG and F-U groups, respectively (p=0.891).

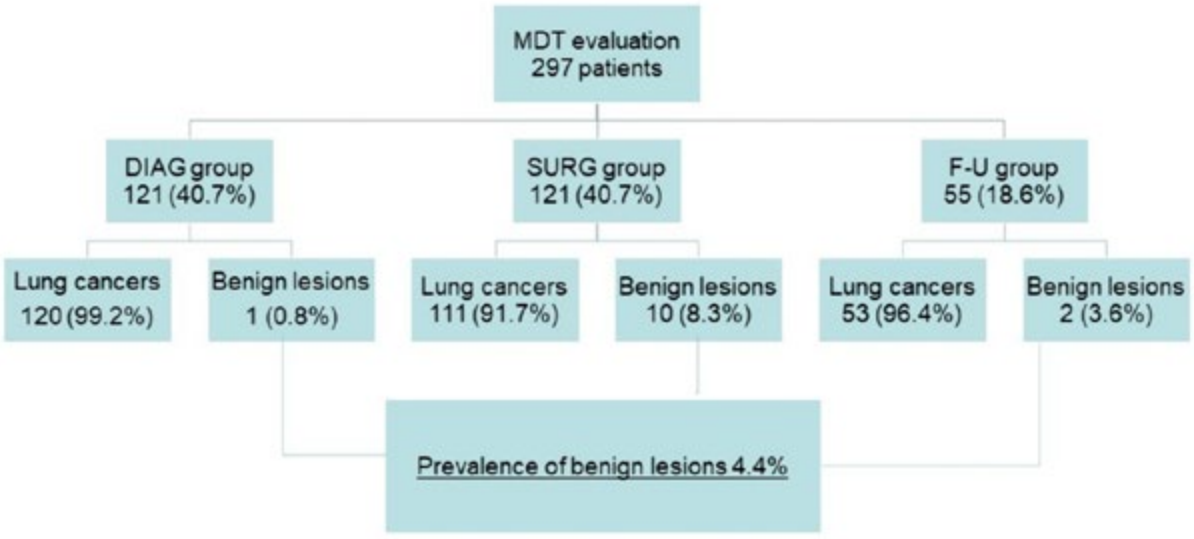

Figure 1. Flow-chart describing study groups and prevalence of benign lesions.

Conclusion: MDT assessment of indeterminate lung lesions reliably selects patients for the best diagnostic/therapeutic strategy, with an acceptable rate of diagnostic excision for benign disease and a limited number of patients submitted to delayed surgery.

Keywords: Surgery, multidisciplinary, lung cancer

P05.01 Personalized Optimization of TCP Using NTCP Based Constraints for Ultracentral Lung Tumors

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Introduction: Hypofractionated radiation of 'ultracentral' lung tumors (abutting the proximal bronchial tree/esophagus), results in high toxicity rates. Normal tissue complication probability (NTCP) and tumor control probability (TCP) models valid in early stage NSCLC have been derived; here, we apply them to evaluate whether higher TCP can be achieved while respecting NTCP constraints and study patient characteristics where TCP couldn't be improved. **Methods:** 63 consecutive patients with ultracentral NSCLC tumors treated at our center from 2008-2017 using hypofractionation were identified. Linear-quadratic equivalent dose-volume constraints on normal tissues from our 10GyX5 clinical planning criteria and NTCP model-based criteria for grade 3+ radiation pneumonitis (RP3+; guideline 5%, limit 10%), grade 2+ esophagitis (E2+; 30% limit) and lobar stenosis/atelectasis (LS; 5% guideline) were imposed. TCP at 2 years was calculated using a published model. Using open-source CERR, relative dose distributions were scaled by factors of 0.5-1.5 for four fractionations: 10GyX5, 7.5GyX8, 7GyX10, and 4GyX15. The optimal plan ($Plan_{opt}$) with the highest TCP where clinical constraints were respected was identified. For $Plan_{opt}$, predicted TCP and NTCPs for RP3+ and E2+ were compared to those for the delivered plan ($Plan_{del}$). **Results:** For 36/63 patients, TCP for $Plan_{opt}$ was higher than $Plan_{del}$ while respecting constraints. RP3+NTCP was the most frequent reason for TCP of $Plan_{opt}$ < 80% (14/24 patients; Figure 1A). Tumor volumes >40 cc were associated with problematic $Plan_{opt}$ (p=0.002) and higher RP3+NTCP values for $Plan_{del}$ (p=0.003; Figure 1B). $Plan_{opt}$ was limited by E2+NTCP in 5 problematic patients where the tumor abutted the esophagus. The remaining 5/24 patients were stopped by lung V20 or liver constraints.
RP3+NTCP for $Plan_{del}$ were similar (Figure 1C) to those of $Plan_{opt}$ (sum of square difference,SSD=42) where TCP of Planopt exceeded 80% and considerably higher (SSD=2321) than those of problematic $Plan_{opt}$s limited by the RP3+ constraint . A higher observed rate of RP3+ was consistent with higher NTCP of $Plan_{del}$. Comparing E2+NTCP of $Plan_{opt}$ vs $Plan_{del}$ (Figure 1D), esophagitis occured in 4/5 patients where E2+ was the stopping criteria, with one $Plan_{del}$ NTCP exceeding 85%.

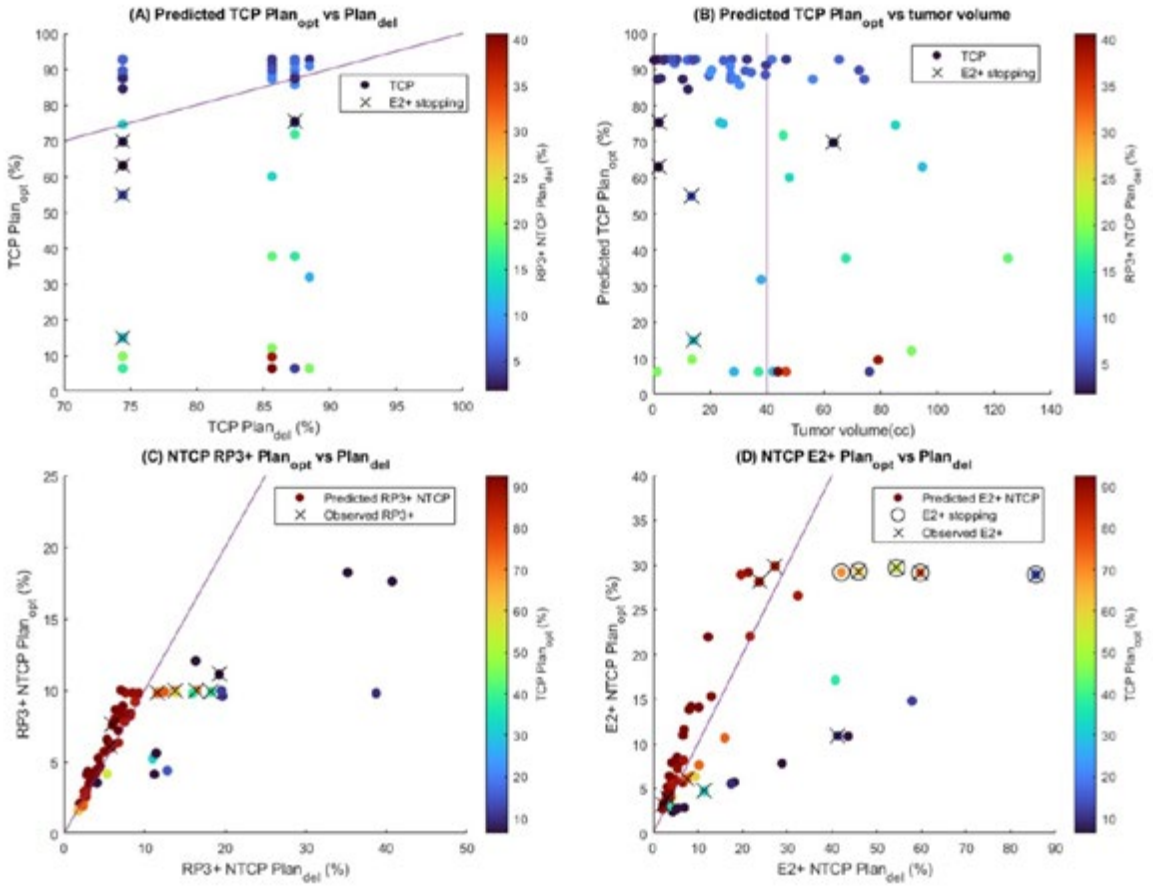

Figure 1: (A) TCP of the scaled vs delivered plan (Plan$_{opt}$ vs Plan$_{del}$) (B) TCP of Plan$_{opt}$ vs tumor volume (C) NTCP for RP3+ in Plan$_{opt}$ vs Plan$_{del}$ and (D) NTCP for E2+ in Plan$_{opt}$ vs Plan$_{del}$

Conclusion: We demonstrated the feasibility of simulated fractionation protocols yielding higher TCP while respecting NTCP in our patient cohort. In some "problematic" patients, TCP could not be improved without violating NTCP due to tumor size or proximity to esophagus. A more rigorous analysis involving treatment planning incorporating NTCP constraints is planned.

Keywords: ultracentral, TCP and NTCP, SBRT

P05.02 Does Non-Small Cell Lung Cancer Histologic Type Influence Outcomes with Single-Fraction Stereotactic Body Radiotherapy?

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Introduction: For early stage medically inoperable Non-Small Cell Lung Cancer (NSCLC) treated with fractionated stereotactic body radiotherapy (SBRT), when compared by biologically equivalent dose (BED) higher rates of local failure have been associated with squamous (SqC) histology compared to adenocarcinoma (AC) for equivalent BEDs. We sought to determine if histology outcomes differed when using single-fraction schedules (SF-SBRT). **Methods:** An IRB-approved prospective lung SBRT data registry was surveyed from 12/2009 till 12/2019 for all patients (pts) receiving SF-SBRT with minimum 6-month follow up with biopsy-proven AC or SqC excluding bronchoalveolar and "NSCLC not-otherwise specified" cases. Doses employed were either 34 Gy, planned per RTOG 0915, or 30 Gy, planned per RPCI-124407. Outcomes of interest included cumulative incidence rates of local (LF), nodal (NF), and distant (DF) failure and overall survival (OS), as well as treatment-related toxicity graded per CTCAE version 3.0. **Results:** 229 SF-SBRT pts treated over 10 years had a 2-year LF rate of 7.28%. For this analysis 113 (49.3%) met study's pathology criteria and had a 2-year LF rate of 8.41%. No association was seen between histology type and the SF-SBRT dose given: 65 pts (57.5%) had AC, of these 19 (29.2%) and 46 (70.8%) received 30 Gy and 34 Gy, respectively. Of 48 SqC pts (42.5%), 17 (35.4%) and 31 (64.6%) received 30 Gy and 34 Gy, respectively. Median follow up was 22.9 months. Patient characteristics were balanced between histologies. Median tumor size was 1.9 cm and 2.05 cm for AC and SqC, respectively. When comparing tumor features for each histology or by dose group, there were no significant (NS) differences including specifically tumor distance from the chest wall. Comparing total Ac vs. SqC cohorts, 2-year LF rates in % were 7.32 vs. 9.64, respectively (p=0.9805). In %, 2-year LF, NF, DF and OS rates for AC for 30 Gy and 34 Gy, respectively, were 10.84 vs. 6.41; 10.53 vs. 16.24; 15.79 vs. 13.04; 77.9 vs.71.2 (all NS). In %, 2-year LF, NF, DF, and OS rates for SqC for 30 Gy and 34 Gy, respectively, were 11.76 vs. 8.08; 5.88 vs. 17.94; 23.53 vs. 9.68; 70.6 vs. 77.1 (all NS). There were no grade 4/5 toxicities and NS differences in any other toxicity rate by histology or dose. For AC pts, pneumonitis rates were: 4 pts (6.2%) with grades 1-2; chest wall toxicity rates were: 7pts (10.8%) with grade 1-2 and 1 (1.5%) with grade 3. For SqC, pneumonitis rates were: 4 pts (8.3%) with grade 1-2 rates pneumonitis; chest wall toxicity rates were: 10 (20.8%) with grade 1-2 only. **Conclusion:** SqC LF rates are similar to AC's with either SF-SBRT schedule and no significant differences were seen for other outcomes or for toxicity profiles by histology and dose. This suggests equivalent efficacy for SF-SBRT doses independent of NSCLC histology

P05.03 Comparison of Stereotactic Body Radiotherapy and Radiofrequency Ablation for Early-Stage NSCLC: A Systemic Review and Pooled Analysis

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Introduction: Both stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) offer promising therapeutic options for patients with inoperable early-stage non-small cell lung cancer (NSCLC), but it is unclear which treatment would provide superior benefits for patients. In this systematic review and pooled analysis, we compare clinical outcomes and safety between SBRT and RFA for patients with inoperable early-stage NSCLC. **Methods:** Eligible studies were obtained through comprehensive search of the PubMed, Medline, Embase, and Cochrane library databases from 2001 to 2020. Original English publication of early-stage NSCLC with the treatment of SBRT or RFA were included. Local control rates, overall survival (OS) rates and adverse events were obtained by pooled analyses. **Results:** Eighty-seven SBRT studies (12811 patients) and eighteen RFA studies (1535 patients) were eligible. The local control rates (95% confidence interval) at 1, 2, 3 and 5 years for SBRT were 98% (97%-98%), 95% (95%-96%), 92% (91%-93%) and 92% (91%-93%), respectively, which was significantly higher than that for RFA: 75% (69%-82%), 31% (22%-39%), 67% (58%-76%) and 41%(30%-52%) ($P < 0.01$). As for short-term OS rates, there were no significant differences at 1 year ($P = 0.07$) and 2 years ($P = 0.42$), and the OS rates (95% confidence interval) at 1 and 2 years for SBRT and RFA were 87% (86%-88%) versus 89% (88%-91%) and 71% (69%-72%) versus 69% (64%-74%), respectively. For long-term OS rates, the rates of patients treated by SBRT at 3 and 5 years were 58% (56%-59%) and 39% (37%-40%), respectively, which was significantly superior to that by RFA: 48% (45%-51%) and 21% (19%-23%), respectively. The most frequent complication of SBRT was radiation pneumonitis (grade≥3), making up 2.6% of patients, but that of RFA was pneumothorax, making up 27.2% of patients. **Conclusion:** In comparing to RFA, SBRT is proved to have preferable local control rates and long-term OS rates but similar short-term OS rates. Prospective randomized trials with large sample sizes are warranted to compare the efficacy of SBRT and RFA.

Keywords: Radiofrequency ablation, Meta-analysis, Stereotactic body radiotherapy

P05.04 Retrospective Study on the Correlation of Central Tumour and Central Structures and the Effect on Survival for Patients Receiving Lung SABR

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Introduction: Lung Cancer is the most common cancer in the UK with non-small cell lung cancer accounts about 80% of total lung cancer cases. The current standard of care includes surgical resection with 5 years overall survival rates of 56-92% depending on the tumour size and stage. However, patients are often considered medically inoperable as a result of severe or multiple comorbidities and stereotactic ablative radiotherapy (SABR) could be offered to the patient [1] A large number of single and multi-institutional SABR phase II studies and case series, as well as two large meta-analysis, have consistently shown local control rates in excess of 90% (for biologically effective dose [BED]>100gy and 5 year overall survival rates around 40% [2] Central disease was defined as per the RTOG 0813 trial protocol, that being either the tumour is within 2 cm of the trachea, bronchi or proximal bronchial tree, or the PTV abuts the mediastinal pleura or pericardium[3] Some report suggested that SABR for centrally located lesions produces clinical outcomes similar to those for peripheral lesions when normal tissue constraints are respected [4] This study is to assess the correlation between the distance between central tumour and the central structures and the effect on survival patients receiving SABR (stereotactic ablative radiotherapy) **Methods:** Retrospective data was collected from the Weston Park Hospital lung SABR registry from January 2014 until January 2021. Survival time was calculated based on the date of starting treatment to the date of death (any cause), or last follow-up which included up to 15/1/2021 for surviving patients. Scatter plots Pearson correlation , Cox regression and independent sample T-test were used for validation. Descriptive statistical analysis was performed using SPSS16. **Results:** A total of 146 patients were collected and 43(28%) patients had tumour located less than 2cm from the central structure. At 3-4 months, almost all patients had CT follow up scan. 11 (8%) patients had complete response, 56 (38%) of the patients had partial response and 49 (34%) patients had stable disease. Unfortunately 9 (6%) patients developed progression disease on their 3 month follow up scan. The remaining patients who had recent treatment in late 2020 are still waiting to have follow up CT scan. Out of 146 patients, 28/146(19%) patients had disease recurrence and 55/146(38%) patients had died before 15/1/2021. The median overall survival time was 25.5 months. There is a relationship between overall survival and distance between the primary central tumour with p value of 0.02. The hazard of a patient experiencing the critical event/death increases by 1.24 or 24%. This implies that the death incidents are positively associated and increases with the distance of the tumour from central structure. **Conclusion:** In summary, from this study, we have demonstrated that the central location of the tumour may predict the overall survival in patients receiving stereotactic ablative radiotherapy to the lung. There may be confounding factors that influence this outcome including the size of tumour, performance status and age. More data collection and prospective data are needed to produce more robust result.

Keywords: Stereotactic ablative radiotherapy, central tumour, overall survival

P05.05 Impact of Lung Stereotactic Body Radiotherapy on Pulmonary Function Test – Experience from Tertiary Cancer Centre in India

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Introduction: Stereotactic body radiotherapy (SBRT) has proven to be an effective modality for medically inoperable early-stage non-small cell lung cancer (ES-NSCLC) and pulmonary metastases. However, the concern remains of its effect on pulmonary function test parameters especially in patients with chronic obstructive pulmonary disease (COPD). **Methods:** In this retrospective study, PFT data was evaluated for consecutively treated SBRT patients. PFT was done for all patients (unless unable to perform) at baseline and at 3-and 6-month. Baseline and post treatment PFTs at 3 and 6 months were compared and graded according to the SBRT pulmonary toxicity scale. PFT changes were also analysed according to the COPD status as defined by GOLD'S criteria. All patients underwent pulmonary rehabilitation before SBRT treatment. All patients received SBRT dose ranging from 48-60 Gy in 5-10 fractions depending upon their location. **Results:** A total of 95 patients (73 - ES-NSCLC and 22 - metastases) treated from 2010 to 2019 were included in this study. Median age was 64 years (range, 23-88), 67 - male and 39 smokers. Twenty-seven patients (28%) had baseline COPD, out of which 9 had severe and 4 had very severe COPD. Approximately 1/3rd of the patients were medically inoperable due to poor baseline PFT parameters. Baseline, 3- and 6-month PFT was available for 70, 20 and 7 patients, respectively. Baseline median forced expiratory volume in 1 second (FEV1) was 1.3 litres (range, 0.5-3.1litres) and predicted FEV1 was 64% (17%-121%), respectively. Baseline median corrected diffusion capacity for carbon monoxide (DLCO) was 6.8 mmol/min/kPa (2.3-9.9) and predicted was 72% (32-112). Baseline median forced vital capacity (FVC) was 2.1 (0.5-3.7) and predicted was 70% (22%-135%). Among evaluable patients at 3 months, there was no significant decline in median FEV1 (1.6 to 1.6 litre) and FVC (median 2.4 to 2.2 litre). Median DLCO declined from 6.6 to 5.7 and predicted from 83% to 78%. According to SBRT scale, grade 1-2 toxicity in FEV1 and FVC was seen in 9 (33.3%) and 5 (20%) patients respectively. There were no ≥ grade 3 toxicities in FEV1 and FVC. DLCO grade 1-2 toxicity was seen in 4 (21%) patients, grade 3 was seen in 1 patient. Of COPD patients, median FEV1 declined from 1.1 to 1 (10%), no change in FVC and DLCO declined from 5.5 to 4.8 (13%), respectively. Only one patient worsened in COPD grade from severe to very severe. Amongst patients who had significant drop (>10%) in FEV1 (n=3), 1 patient had baseline severe and 2 had baseline moderate COPD. **Conclusion:** SBRT treatment did not cause any significant decline in FEV1 and FVC, however, approximate 10-15% decline was seen in DLCO. SBRT is also safe in patients with severe and very severe COPD.

Keywords: ES-NSCLC, SBRT, PFT

P05 EARLY STAGE/LOCALIZED DISEASE/ABLATIVE THERAPIES - SBRT

P05.06 Clinical Application of Anatomical Landmarkers Based 3D Precise Pulmonary Nodule Localization During Thoracoscopic Surgery

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Introduction: At present, there are various methods in practice for lung nodule location, each of which has its own advantages and disadvantages. We hoped to find a more accurate, safe, effective, economical and practical method for locating lung nodules. This article aimed to study the safety and feasibility of 3D precise positioning method based on anatomical landmarks in the positioning of small pulmonary nodules. **Methods:** Patients with pulmonary nodules underwent video-assisted thoracoscopic surgery in Shenzhen Hospital of Hong Kong University were included in the study. The surgical data was retrospectively reviewed and analyzed, such as positioning time, accuracy rate, pathological results, complication rate and postoperative hospital stay. During the operation, the pulmonary nodules were accurately located by 3D precise positioning method based on anatomical landmarks (such as the rib head, the transverse process of the vertebral body, the junction of the horizontal and oblique fissure of the lung, the azygos vein, etc.), and then precisely removed to determine the nature of the pulmonary nodules. **Results:** 27 patients were included from June 2019 to April 2020: 3 males and 24 females, aged 25-76 years, with an average age of 51.8±13.7 years. There was no mortality or major surgical complications occurred in any patient within 30 days. The mean localization time was 17.6±5.8 minutes. The accuracy of localization was 96.4%. The mean diameter of pulmonary nodules was 14.0±8.0 mm, and 6.5±5.4 mm distance from visceral pleura. There was no localization related complications. The average postoperative hospital stay was 6.7 days. **Conclusion:** The 3D precise positioning method based on anatomical landmarks is safe and feasible in the positioning of lung nodules during thoracoscopic surgery for selected patients. Compared with other preoperative and intraoperative positioning methods, it can reduce the related complications. This method is accurate, safe and effective, economical, practical, easy to master, and has a short learning curve, which can be used as a reference for peers in thoracic surgery.

Keywords: 3D precise positioning method; anatomical landmarks; pulmonary nodules

P05.07 Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer Without Pretreatment Pathologic Results in a Chinese Population

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Introduction: Stereotactic body radiotherapy (SBRT) has been increasingly regarded as a reasonable option for early-stage lung cancer without pre-treatment pathologic results, but the efficiency and safety in a Chinese population remains unclear. The aim of this study is to compare survival outcomes and toxicities in early-stage lung cancer patients with or without pathologic results and to demonstrate the rationality of this treatment. **Methods:** From February May 2012 and December 2018, 110 patients treated with SBRT were retrospectively selected and divided into pathological cohort (n=55) and nonpathological cohort (n=55). Survival analysis with log-rank test was used to assess the differences of treatment outcomes, such as local control (LC), progression free survival (PFS) and overall survival (OS). **Results:** The median age was 76(range 52-93), and the median follow-up time was 57.5(range 4.3-95.1) months in cohort without pathologic results. The median age was 75(range 57-88) and the median follow-up time was 57.4(range 3.5-94) months in cohort with pathologic results. The 5-year local control, progression-free survival, overall survival rates in patients with or without pathologic biopsy were 85.1% and 91.0%, 33.2% and 59.5%, 55.6% and 52.4%, respectively. On Kaplan-Meier survival analysis, there was no significant difference between patients with pathologic results versus patients with no pathologic results in terms of LC (P= 0.954) and OS (P= 0.592). Of the 110 patients treated with SBRT, only one patient experienced grade 3 or above radiation pneumonitis. **Conclusion:** SBRT can offer a non-invasive and beneficial choice for early-stage lung cancer patients without preceding pathologic results.

Keywords: No pretreatment pathologic results, Stereotactic body radiotherapy, NSCLC

P06.01 Propensity-Matched Analysis Comparing Survival after Thoracoscopic Wedge Resection versus Segmentectomy for cT1N0 Lung Adenocarcinoma

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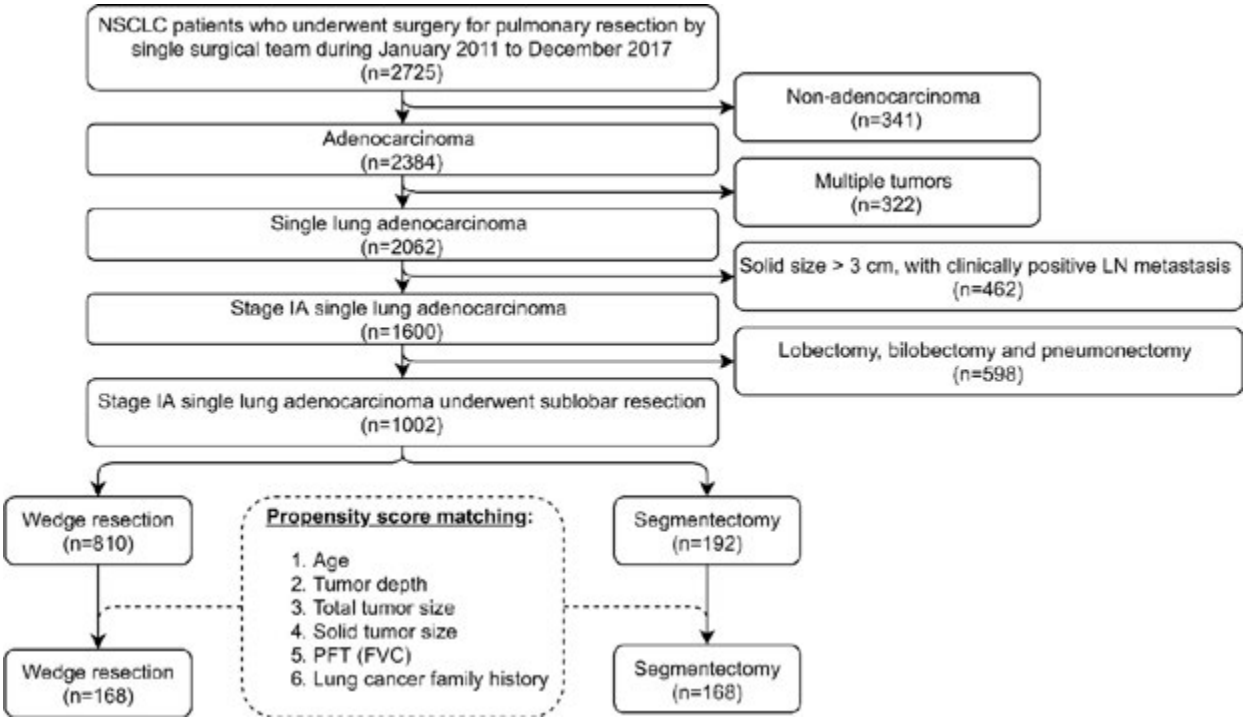
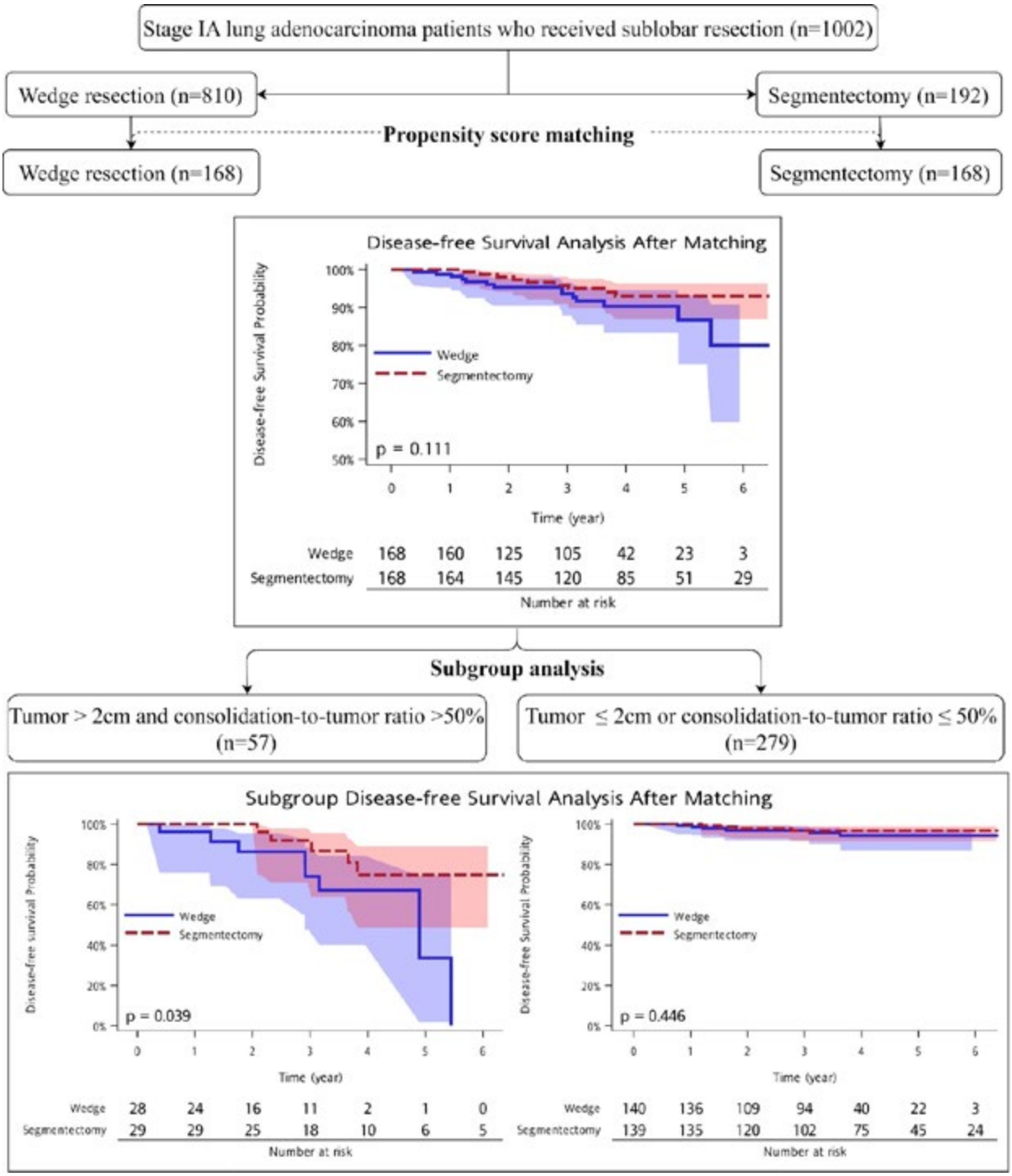
Introduction: Recently, several studies have suggested that sublobar resection may provide equivalent oncologic outcomes in selected early stage lung cancer patients while preserving pulmonary function with better perioperative outcomes. However, the choice of wedge resection or segmentectomy as a sublobar resection method in patients with cT1N0 lung cancer remains debatable. This study aims to evaluate the clinical outcomes after wedge resection and segmentectomy in patients with cT1N0 lung adenocarcinoma. **Methods:** A total of 1,002 consecutive patients with cT1N0 lung adenocarcinoma who underwent sublobar resection at our institute between 2011 and 2017 were included. A propensity score matching analysis was used for comparing the clinical outcomes between the wedge resection and segmentectomy.



Results: Wedge resection and segmentectomy were performed in 810 (80.8%) and 192 (19.2%) patients, respectively. Wedge resection resulted in better perioperative outcomes than segmentectomy. The multivariate analysis revealed that elevated preoperative serum carcinoembryonic antigen levels (p =0.018), total tumor diameter of >2 cm (p =0.012), and consolidation-to-tumor (C/T) ratio of >50% (p <0.001) were significant risk factors for poor disease-free survival (DFS). After propensity matching, no differences in the overall survival or DFS (p =0.156 and p =0.205, respectively) were noted between the two matched groups. However, subgroup analysis showed that segmentectomy was associated with superior DFS than wedge resection (p =0.039) in patients with tumor diameter of >2 cm and a C/T ratio of >50%



Conclusion: Segmentectomy is the appropriate surgical method for sublobar resection in cT1N0 lung adenocarcinoma patients and a tumor diameter of >2 cm and a C/T ratio of >50%. Wedge resection may be a safe and feasible sublobar resection method for patients with a tumor diameter of ≤2 cm or a C/T ratio of ≤50%. The results of our study need to be further validated in prospective, multi-institutional studies in other areas of the world.

Keywords: Lung adenocarcinoma, wedge resection, segmentectomy

P06.02 Incorporating Surgical Collapse in the Pathological Assessment of Resected Adenocarcinoma in situ of the Lung. A Proof of Principle Study.

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Introduction: The 8th edition of UICC/AJCC TNM classification system for non-small cell lung cancer (NSCLC) tumors recommends that size measurement of the primary tumor should be based solely on the invasive components. The distinction between adenocarcinoma in-situ (AIS) and other patterns, which are regarded as "invasive", is of the utmost importance. In AIS, surgical collapse could alter architectural patterns, e.g. papillary, thus simulating invasive growth. The purpose of this study was: a) to examine the effect of surgical collapse in hematoxylin and eosin (H&E) stained slides on the WHO classification of pulmonary adenocarcinomas and b) to examine the additional value of cytokeratin 7 (CK7) immunohistochemical (IHC) staining for recognition of surgical collapse. **Methods:** A retrospective, proof-of-principle study was performed, including early-stage NSCLC patients with resected primary adenocarcinomas, diagnosed between November 2007 and November 2010 at the Department of Pathology, Amsterdam UMC, location VUmc. H&E readings (using on average 2 slides (range 1-3)) without and with knowledge of surgical collapse were performed, blinded for clinical outcome. In a first scoring, pattern recognition according to the WHO was performed by one pathologist (HB). Subsequently, incorporating knowledge on surgical collapse, a second consensus scoring of the same slides was performed by two pathologists (HB & ET). An AIS with surgical collapse pattern was interpreted as non-invasive when a compressed pre-existing alveolar pattern was recognizable. Additionally, CK7 immunohistochemical stained slides of the same block were independently scored based on recognition of a regular collapsed pattern and monolayer of tumor cells. For survival analysis, patients with more than one tumor were categorized as 'invasive' if at least one of the tumors was invasive. **Results:** A total of 74 histological sections of 40 tumors from 33 patients were scored. After the first H&E scoring according to the WHO classification, the 5-year overall survival (OS) rate for patients with a non-invasive pattern (n=2) versus invasive pattern (n=31) was respectively 100% and 48% (p=0.18). When surgical collapse was considered, 5 invasive cases were downgraded to non-invasive AIS. The 5-year OS rate for all those non-invasive cases (n=7) remained 100% and for the invasive cases (n=26) became 39% (p=0.019). After CK7 staining the same 7 cases were scored as non-invasive. The CK7 reading was perceived as an easy tool. Noteworthy, this shift of cases to the non-invasive category did NOT affect the 100% 5-years overall survival of this non-invasive category. **Conclusion:** This proof-of-principle study shows that taking surgical collapse into account when scoring H&E and IHC-CK7 slides can enable re-classification of WHO invasive NSCLC cases into non-invasive AIS cases. In this study, the shift in recognition improved the prediction of survival outcomes, highlighting the need to recognize surgical collapse in pathological readings, as this may prevent underdiagnosing AIS.

Keywords: NSCLC, surgical collapse, adenocarcinoma in situ

P06.03 The Role of Surgery for Stage 0 Adenocarcinoma in Situ of the Lung: A U.S. National Analysis

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Introduction: Stage 0 adenocarcinoma in situ (AIS) of the lung is thought to be associated with ~100% 5-year survival after resection. However, the data for AIS are largely from Asia with few data from the U.S. In addition, there is a paucity of data on long-term survival of patients with stage 0 AIS who do not undergo any type of treatment. The objective of this study is to evaluate the long-term survival of patients who received surgery vs no treatment for Stage 0 AIS of the lung in a U.S. population. **Methods:** Overall survival of patients with AIS (TisN0M0) of the lung (with nodule size <3 cm) who underwent surgery or no treatment (i.e. no chemotherapy, surgery, radiation or immunotherapy) in the U.S. National Cancer Data Base from 2004 to 2017 was assessed using Kaplan-Meier and propensity score-matched analysis. **Results:** Of the 881 patients who were diagnosed with Stage 0 AIS, 721 (82%) underwent surgical resection while 160 (18%) underwent no treatment. In unadjusted analysis, surgery was associated with improved survival when compared to no treatment (5-year survival 91% [95% CI: 88-94%] vs 55% [95% CI: 42-67%]). When evaluating patients who had no comorbidities, surgery was still found to be associated with better survival (Figure 1a). In a propensity score-matched analysis of 92 patients who underwent surgery and 92 patients who underwent no treatment—well-balanced across 10 common prognostic covariates including comorbidities and tumor size—surgery was associated with better 5-year overall survival than no treatment (5-year survival 88% [95% CI: 76-94%] vs 60% [95% CI: 46-72%]). In an additional propensity score-matched analysis of patients with no comorbidities, surgery (n=46) was found to be associated with improved survival when compared to no treatment(n=46) (Figure 1B). In a separate propensity score-matched analysis of patients who underwent wedge (n=186) vs lobectomy (n=186) for AIS, wedge resection was associated with similar 5-year survival (92% [95% CI: 82-96%]) when compared to lobectomy (94% [95% CI: 88-97%]).

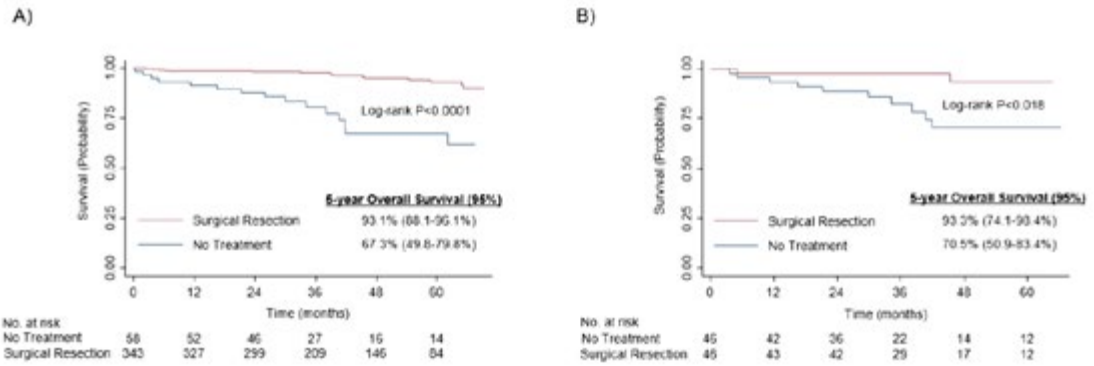

Figure 1. Surgery vs No Treatment for Stage 0 Adenocarcinoma in Situ of the Lung in Patients with No Comorbidities: Unadjusted (A) and Propensity score-matched Analysis (B)

Conclusion: In this U.S. national analysis, patients who underwent surgery for Stage 0 AIS of the lung had significantly better overall survival when compared to patients who did not undergo any type of treatment, in unadjusted, in propensity score-matched analysis and in sensitivity analysis focused on patients with no comorbidities. These results suggest that biopsy-confirmed stage 0 AIS, although indolent in nature, still warrants surgical treatment. Wedge resection for Stage 0 AIS is not associated with inferior survival when compared to lobectomy.

Keywords: adenocarcinoma in situ, ground glass opacities, AIS

P06.04 Clinical Outcomes and Pathological Characteristics of Resected ALK+ Lung Adenocarcinoma: A Single Center Retrospective Analysis

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Introduction: The data of pathological characteristics, disease free survival(DFS), recurrence patterns in resected ALK+ lung adenocarcinoma have been limited. **Methods:** Medical records of ALK+(confirmed by ALKventanaD5F3) lung adenocarcinoma patients with radical resection from April, 2017 to December, 2019 in our center were collected. High-risk pathological types(including solid predominant, micropapillary predominant and invasive mucinous adenocarcinoma), pleural invasion and vascular invasion were deemed as risk factors of recurrence in addition to TNM stage. Recurrence sites were classified into four categories based on relative positions to the primary lesion and thoracic cavity: local recurrence limited in ipsilateral thoracic cavity, intrathoracic disseminated metastasis(including pleural or pericardial effusion and metastasis in contralateral lung), extrathoracic but non-CNS metastasis and CNS metastasis. **Results:** 248 patients were included in this analysis(IA: n=119, IB: n=36, .IIA: n=7, IIB: n=31, IIIA: n=47, IIIB: n=8). Compared to patients on stage IA, higher proportions of patients on stage IB-III were found to have at least 1 risk factor of recurrence(IA:26.1% vs IB: 83.3% vs II: 86.7% vs III: 85.5%, p<0.05). With the median follow-up of 25.1 months, 29.2 months, 26.3 months, 27.1 months, median DFS were NE, NE, 43.5 months, 22.4 months for patients on stage IA, IB, II, III respectively. As for patients on stage III, those who carried at least 1 risk factor of relapse seemed to show worse DFS compared to those without(DFS: 21.8 months vs NE, 2-year DFS: 42.9% vs 70%, p=0.595). 76.5%(39/51) patients experiencing intrathoracic disseminated metastasis or extrathoracic metastasis at the time of recurrence lost second chance of radical therapy. Furthermore, Lung (16/51) was the most common recurrence site while CNS(12/51) was the most frequent organ involved when extrathoracic metastasis occurred. **Conclusion:** High proportions of patients with resected ALK+NSCLC on stage IB-III carried at least one risk factor of recurrence. More effective systemic adjuvant therapy such as adjuvant targeted therapy was urgently needed for patients on stage III especially for those with at least one risk factor of relapse. Moreover, CNS protection also needed to be taken into consideration in the adjuvant setting.

	IA	IB	II	III
2year DFS	96.6% (95%CI: 91.1%-98.7%)	94.0% (95%CI: 77.9%-98.5%)	79.2% (95%CI: 60.8%-89.6%)	46.8% (95%CI: 32.7%-59.7%)
3year DFS	96.6% (95%CI 91.1%-98.7%)	87.3% (95%CI: 62.4%-96.1%)	63.2% (95%CI: 40.3%-79.3%)	30.7% (95%CI: 15.7%-47.1%)

Keywords: pathological characteristics, recurrence, resected ALK+ lung adenocarcinoma

P06 EARLY STAGE/LOCALIZED DISEASE/ABLATIVE THERAPIES - SURGERY

P06.05 Risk Factors for Recurrence According to Site in Resected Stage I Non-Small Cell Lung Cancer

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Introduction: The rate of recurrence of non-small cell lung cancer (NSCLC) after complete surgical resection is 10–20%, even among pathological stage I cases. As the relationships between clinicopathological factors and recurrence patterns have not been clarified, the aim of this retrospective study is to clarify these relationships. **Methods:** Between May 2004 and September 2019, 1434 patients underwent complete resection for NSCLC. After excluding those with preoperative therapy, multiple lung cancers, non-invasive adenocarcinoma, or carcinoid tumors, 465 patients with pathological stage I NSCLC (TNM 8th) who underwent complete resection were evaluated. We evaluated the associations between clinicopathological factors and recurrence site. Segmentectomy and wedge resection were defined as limited resection. **Results:** The median patient age was 71 years. The 5-year overall survival rate was 77.7% and 5-year recurrence-free survival rate 72.3%. Recurrence developed in 13.1% of the patients. The median time of recurrence was 42 months. Recurrence developed in the lymph node (n = 22, 4.7%), lung (n = 19, 4.1%), and extrathoracic sites (distant metastasis) (n = 16, 3.4%), including the bone (6, 1.3%), liver (6, 1.3%), brain (4, 0.9%), and surgical margin (n = 11, 2.4%). Multivariate analysis was performed to identify the risk factors for each type of recurrence. For lymph node recurrence, limited resection ($p = 0.01$) was a risk factor. For pulmonary metastasis, older age ($p < 0.01$), higher carcinoembryonic antigen (CEA) level ($p = 0.01$), and limited resection ($p = 0.02$) were risk factors. A higher CEA level ($p = 0.01$) was a risk factor for extrathoracic distant metastasis, and older age ($p = 0.01$) and limited resection ($p < 0.01$) for surgical margin recurrence. **Conclusion:** Limited resection was related to lymph node, pulmonary metastasis and surgical margin recurrence. A higher CEA level was related to distant metastasis. Since limited recurrence could have an insufficient surgical margin, it seems that intra-thoracic recurrence tends to develop.

Keywords: recurrence, lung cancer, stage I

P06.06 Clinical Implications of Tumour Spread Through Air Spaces (STAS) In Lung Adenocarcinoma Patients Treated With Surgery

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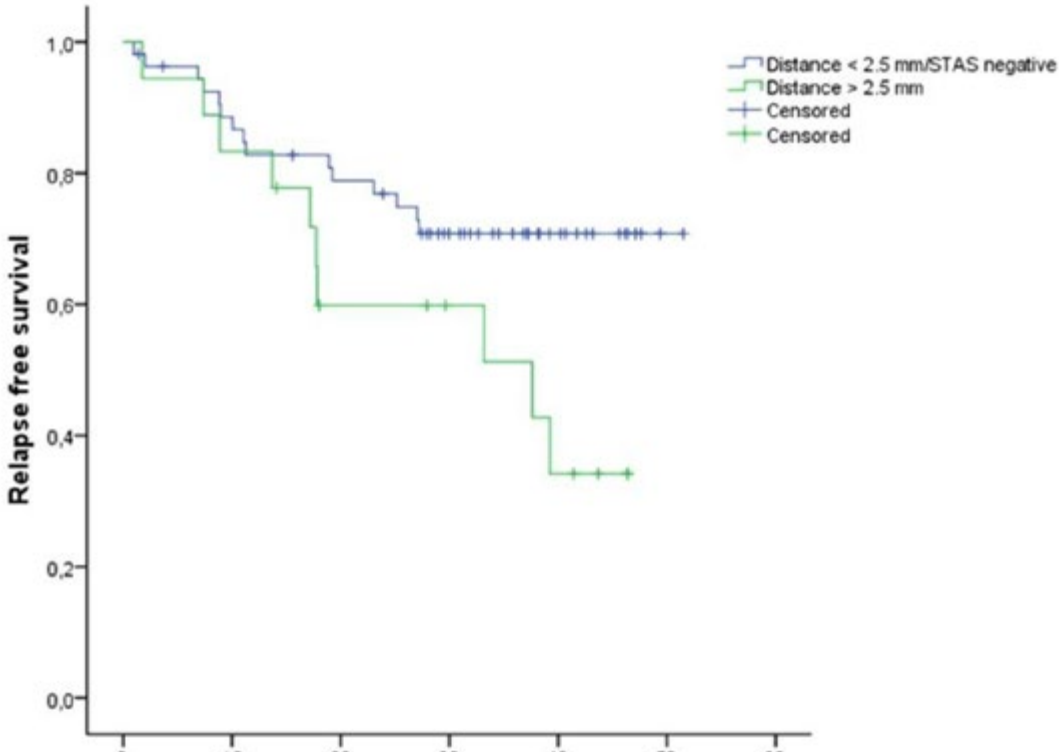
Introduction: Tumour spread through air spaces (STAS) in lung adenocarcinoma is a novel mechanism of invasion, which is important for pathologist to recognize. STAS has been proposed as an independent predictor of high risk of recurrence in patients with lung adenocarcinoma. The aim of this study was to assess the clinical implications of STAS and the distance from the edge of the tumor to the farthest STAS as prognostic factors in patients with lung adenocarcinoma treated with surgery. **Methods:** We retrospectively reviewed 73 patients with resected lung adenocarcinoma from January 2017 to December 2018 at La Paz University Hospital, Madrid (Spain). Recurrence-free survival (RFS) and overall survival (OS) were compared among patients with and without STAS. The distance from the edge of the tumor to the farthest STAS was also measured. The cutoff for this distance was 2.5 mm (according to the cutoff from the previous published studies). Survival analysis was performed using the Kaplan-Meier method. **Results:**



Distance < 2.5 mm/STAS negative	55	46	40	28	15	1	0
Distance > 2.5mm	18	15	9	7	4	0	0

The majority (n = 44, 60.3%) were males with a median age of 68 years (range 42 to 85 years). Most patients (n = 54, 73.5%) had pathological stage I, 11 patients (15.4%) had pathological stage II and 8 patients had pathological stage III (11.1%). STAS was found in 52 patients (71.2%). Regarding the distance from the edge of the tumor to the farthest STAS, 18 patients had a distance greater than 2.5 mm (24.7%). The median RFS was 48.06 months (95%CI: 33.58 – not reached). The median OS was not reached. STAS positive patients had shorter median RFS (48.06 months, 95%CI: 33.55 – 62.58) than STAS negative patients (not reached), but without statistically significant association (p = 0.06). Patients with a distance from the edge of the tumor to the farthest STAS greater than 2.5 mm had shorter median RFS (37.63 months, 95%CI: 7.55 – 67.70) than patients with a distance shorter than 2.5 mm or STAS negative (not reached), with statistically significant association (p = 0.04) (Figure 1). **Conclusion:** STAS was associated with a higher risk of recurrence. In addition, the distance from the edge of the tumor to the farthest STAS greater than 2.5 mm further increased the risk of recurrence. Further prospective studies are needed to derive definitive conclusions.

Keywords: Lung adenocarcinoma, Tumour spread through air spaces (STAS), early stage

P06.07 Learning Curve in Robotic-Assisted Thoracoscopic Pulmonary Resection: Experience of a Brazilian Surgeon

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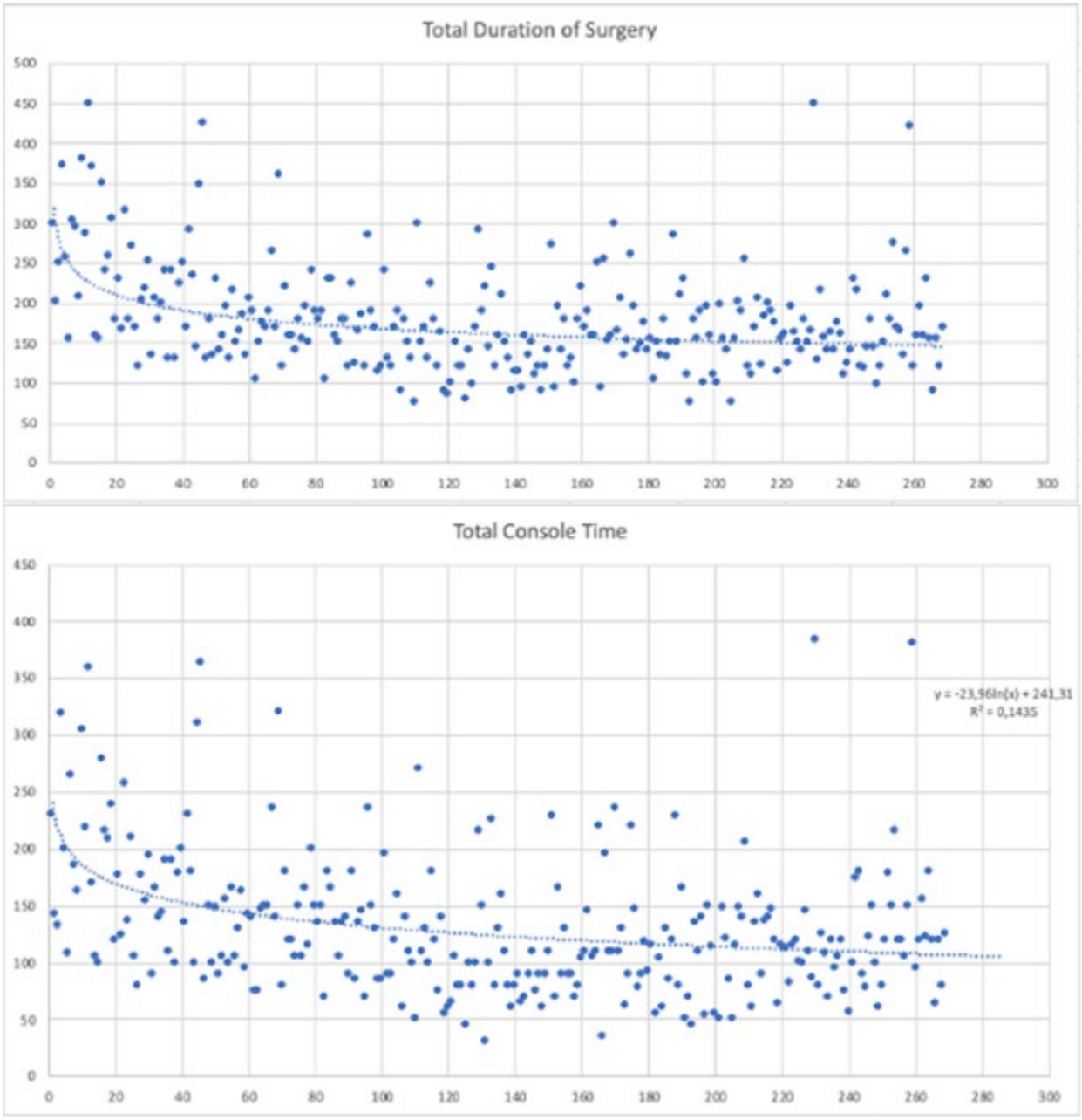
Introduction: The learning curve for robotic-assisted thoracoscopic (RATS) lung resection is yet to be defined, being suggested between 20 to 40 procedures to achieve proficiency. The generability of this data in Brazil is limited due to differences between publications' methods and the Brazilian thoracic surgeon daily practice. The aim of this study is to determine how many resections are needed for proficiency in Brazil, comparing the patients' characteristics and postoperative outcomes during the learning curve evolution. **Methods:** Retrospective study based in a prospective RATS database. We included patients who underwent anatomic lung resection performed by the main author between March 2015 and December 2020. Patients missing data regarding total duration of surgery and total console time were excluded. Scatterplots were used to determine the number of procedures to achieve proficiency. We divided the patients in tertiles, with the first one comprising the patients treated before proficiency, and the rest of them evenly distributed in the other tertiles. Subsequently we compared the groups regarding patients' characteristics and postoperative outcomes. **Results:** A total of 268 patients were included. The scatterplot revealed a learning curve of 20 procedures. There was no statistical difference regarding patients' characteristics and outcomes between the groups, except for ASA classification ($p<0.001$). There was no mortality in 30 days in our study. Lobectomy was the main resection performed, with an increase without statistical significance in the complexity of resections. The total console time and total duration of surgery decreased across the learning curve (204 to 110 minutes, $p<0.001$ and 272.50 to 157 minutes, $p<0.001$, respectively),

Patients characteristics and postoperative outcomes

Characteristics (268)	1º tertile	2º tertile	3º tertile	p value
Female sex (n=268)	6 (30.00)	65 (52.00)	70 (56.91)	0.081
Age (n=268)	67.47 [58.06-71.18]	65.72 [57.96-70.56]	66.00 [59.00-72.00]	0.817
VEF1 (%) (n=181)	81 [71-98]	88 [78.5-97]	88.5 [80-100]	0.310
Smoking history (n=257)	15 (75.00)	65 (54.62)	55 (46.61)	0.052
CPOD (n=256)	7 (35.00)	18 (15.38)	25 (21.01)	0.106
Hipertension (n=255)	12 (60.00)	56 (48.28)	57 (47.90)	0.591
Cardiac disease (n=256)	3 (15.00)	18 (15.38)	20 (16.81)	0.949
Diabetes (n=256)	3 (15.00)	17 (14.53)	23 (16.80)	0.600
Renal disease (n=256)	2 (10.00)	4 (3.42)	1 (0.84)	0.056
Diagnosis (n=252) Benign Adenocarcinoma Epidermoid Neuroendocrine tumor Pulmonary metastasis	0 (0.00) 17 (85.00) 2 (10.00) 0 (0.00) 1 (5.00)	7 (5.79) 88 (72.73) 7 (5.79) 12 (9.92) 7 (5.79)	8 (7.21) 79 (71.17) 7 (6.31) 10 (9.01) 7 (6.31)	0.817
ASA (n=255) 1 2 3	13 (65.00) 6 (30.00) 1 (5.00)	32 (27.83) 72 (62.61) 11 (9.57)	18 (15.00) 92 (76.67) 10 (8.33)	<0.001
Pathological Staging 0 IA1 IA2 IA3 IB IIA IIB IIIA IIIB	0 (0.00) 0 (0.00) 6 (31.58) 5 (26.32) 2 (10.53) 1 (5.26) 2 (10.53) 2 (10.53) 1 (5.26)	7 (6.80) 20 (19.42) 32 (31.07) 14 (13.59) 11 (10.68) 0 (0.00) 6 (5.83) 10 (9.71) 3 (2.91)	4 (5.33) 22 (29.33) 15 (20.00) 6 (8.00) 15 (20.00) 1 (1.33) 6 (8.00) 4 (5.33) 2 (2.67)	0.098
Resection (n=268) Lobectomy Lobectomy with bronchoplasty Segmentectomy Bilobectomy Pneumonectomy	20 (100.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00)	93 (74.40) 3 (3.23) 31 (24.80) 1 (0.80) 0 (0.00)	90 (73.17) 2 (2.22) 31 (25.20) 1 (0.81) 1 (0.81)	0.236
Number of lymph nodes evaluated (n=227)	12 [7,5-14]	11 [7-15]	7.5 [6-11]	0.001
Number of stations evaluated (n=226)	5 [4.5-6]	6 [5-7]	6 [5-7]	0.082
Total duration of surgery (n=268)	272.50 [204.50-327.50]	170 [130-205]	157 [132-190]	<0.001
Total console time (n=268)	204 [137.50-251.50]	130 [90-160]	110 [85-140]	<0.001
Days of chest tube drainage (n=255)	2 [1-2]	2 [1-3]	1.5 [1-3]	0.217
Length of stay (n=254)	3 [2-4]	3 [2-5]	3 [2-5]	0.820
Discharge with chest drainage (n=256)	1 (5.00)	7 (5.65)	3 (2.68)	0.485
Complications (n=257)	3 (15.00)	26 (21.14)	24 (20.62)	0.892



Conclusion: Despite the differences in the daily practice, our learning curve was comparable to the literature, achieving proficiency after 20 lung resections. The group treated more recently presented higher functional limitation, however, the safety of the procedure was stable over time, with no increase in postoperative morbidity.

Keywords: Thoracic Surgical Procedures, Robotic Surgical Procedures, Learning Curve

P06 EARLY STAGE/LOCALIZED DISEASE/ABLATIVE THERAPIES - SURGERY

P06.08 Treatment Outcome of Second Primary Lung Cancer

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Introduction: The treatment of lung cancer has advanced in recent years, and the postoperative survival period has been extended. As a result, the incidence of multiple lung cancer tends to increase. At the time of second surgery, it is necessary to examine the extent of resection in more detail. **Methods:** From patients undergoing lung resection for lung cancer at our hospital from January 2000 to December 2005, we extracted cases undergoing a second surgery as metachronous multiple lung cancer. The definition of multiple lung cancer follows that of Martini et al. We considered the postoperative course of extracted cases. **Results:** We performed lung resection 489 cases during this period. The patients consist of 272 men and 217 women. The average age was 68.2. There were 12 cases of second surgery for second primary lung cancer. At the time of first surgery, the histological types were adenocarcinoma in 10 cases and squamous cell carcinoma in 2 cases. The pathological stages were IIIA/IIA/IB/IA in 1/1/2/8 cases. At the second surgery, we performed segmental resection in 4cases and partial resection in 8 cases. 9 cases were adenocarcinoma and 3 cases were squamous cell carcinoma. Pathological stage in second surgery were IA in 9 cases and 0 in 3 cases. Two patients died of lung cancer, one died of another disease, and nine still survived. **Conclusion:** The surgery we performed for second lung cancer tended to be reduced surgery. In many cases the second primary lung cancers were detected in relatively early stage. If the secondary surgery can be performed at an appropriate timing, good prognosis can be expected.

Keywords: Multiple lung cancer, Second primary

P06.09 Lobectomy for Lung Cancer, What Is the Brazilian reality? Brazilian Society of Thoracic Surgeons Analysis

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Introduction: Minimally invasive anatomical lung resection is associated with lower post-operative complication rate and in-hospital mortality. However, learning curve is not that attractive or easy. Particularly in Brazil, the disposable devices (staplers) for this type of surgery are default for public healthcare system, prolonging learning curve Our study will evaluate the minimally invasive thoracic surgery approach (MIS) in middle-lower income country reality. **Methods:** The Brazilian Society of Thoracic Surgeons (BSTS) has a prospective database since 2015. For this analysis, all lung resections were included. Missing information in the surgery approach were excluded. A descriptive analyses and chi-square test were performed. **Results:** The BSTS has 9167 procedures registered in the database, with total of 3024 lung resections (1707 lobectomies, 91 bilobectomies, 198 pneumonectomies, 407 segmentectomies, 619 wedge resections and 2 reductions. Of the oncologic resections, 965 were lobectomy, mean age 65.2yo, 55.4% of women. Minimally invasive surgery was the approach in 587 surgeries (60.8%), 43 of them robotics (8%). Major Complication rate was 10% in MIS and 16.1% in open thoracotomy ($p<0.007$), meanwhile hospital mortality rate was 1.5% and 4.5% ($p=0.006$), respectively. The proportion of MIS was 53.9% in 2015, 54.2% in 2016, 56.9% in 2017, 56.6% in 2018, 71.4% in 2019 and 88.7% in 2020 ($p<0.001$). **Conclusion:** The proportion of minimally invasive surgery among lobectomies has increased, annually and consistent, including robotics despite the longer learning curve. MIS has a lower complication rate and mortality rate for lung cancer lobectomy compared to open thoracotomy.

Keywords: Lobectomy, minimally invasive surgery, lung cancer

P06.10 Low-Cost Video-Assisted Thoracic Surgery (VATS) Lobectomy Versus Regular VATS Lobectomy: A Propensity-Matched Study

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Introduction: The modern video-assisted thoracoscopic surgery (VATS) lobectomy demands disposable consumable endoscopic linear cutter and stapler devices for anastamosis. These pieces are associated with additional high medical costs which makes the procedure less affordable by patients. Here we have developed a new knotting method,"twining high-tension knot" to seal and cut off the bronchus and vessels instead of endoscopic staplers that can omit the use of these expensive pieces, we call it "Low-cost VATS lobectomy".The purpose of this study is to compared the safety and cost of low-cost VATS lobectomy and regular VATS lobectomy. **Methods:** This is a match paired retrospective study.The patients underwent low-cost and regular VATS lobectomy at Hong Kong University-Shenzhen Hospital were eligible. Patient data of our interest included age, sex, baseline comorbidity, lung function, disease diagnosis, tumor location, stage and histology. Perioperative features included surgical methods,procedures,operating time,intraoperative blood loss,postoperative chest drainage tube indwelling time,postoperative hospital stay,perioperative complications, the number of endoscopic staplers used during the operation, total hospitalization cost and disposable surgical consumables. The patients treated with Low-cost group was matched with the regular group. A propensity matching score was calculated with SPSS 25.0.Continuous variables were analyzed using compare means and Student's t-test or the Mann-Whitney U-test, and categorical variables were analyzed using Pearson's $\chi 2$ test or Fisher's exact test.P less than 0.05 were considered to be significant. **Results:** A total of 102 consecutive patients treated VATS thoracotomy between January 2013 and April 2020 were included in this analysis; 57 (55.9%) patients underwent regular VATS lobectomy, and 45 (44.2%) patients underwent low-cost VATS lobectomy. After 1:1 propensity score matching (PSM), the baseline demographic and clinical variables were well balanced between the two groups. There was no significant difference between the new knotting group and the regular group in operation time (256.2±87.4 vs. 252.7±73.5 min, P=0.834), intraoperative blood loss (mean, IQR: 80, 50-100 vs. 50, 30-100 ml, P=0.126), postoperative drainage tube indwelling time (mean, IQR: 3, 2-3 vs. 3, 2-3.5 days, P=0.569), hospital stay after operative (mean, IQR: 5, 4.5-7 vs. 6, 4-10 days, P=0.372), complication rate(15.6% vs. 22.2%, P=0.419) and severe complication rate (0.00% vs. 4.44%, P=0.494). The costs were significantly lower for the low-cost group procedure than the regular group procedure in the following aspects: the number of Endo-GIA stapler nails used in the operation (mean, IQR: 0, 0-4 vs. 6, 4-9, P<0.0001), the number of Endo-GIA stapler handles used in the operation (mean, IQR: 0, 0-1 vs. 1, 1-1, P<0.0001), the intraoperative one-time consumable expenses (14441.2±10554.3 vs. 29857.0±9908.4 CNY, P<0.000), and the total hospital expenses (36612.7±13915.2 vs. 57058.4±12804.1 CNY, P<0.001). Similar results were observed for lobectomy combined with wedge resection after removing the number and cost of the Endo-GIA staplers used in the wedge resection: the number of Endo-GIA stapler nails (mean, IQR: 0, 0-2.5 vs. 5, 4-6.5, P<0.0001), the intraoperative one-time consumable expenses (11830.1±7565.1 vs. 25965.4±7441.9 CNY, P<0.0001) and the total hospital expenses (34001.6±12649.1 vs. 53166.8±10966.5 CNY, P<0.001). **Conclusion:** Compare to that of regular VATS lobectomy,This new knotting technique of VATS lobectomy,which we call low-cost VATS lobectomy is the same safe and with significantly lower-cost VATS lobectomy. Additionally, this new VATS lobectomy can significantly reduce the use of consumables and the cost of the operation without increase the duration or difficulty of the operation.

Keywords: Lobectomy, Low-cost VATS surgery, twining high-tension knot

P07.01 Usage Patterns of TKIs in EGFR Mutant NSCLC: Let's Get REAL

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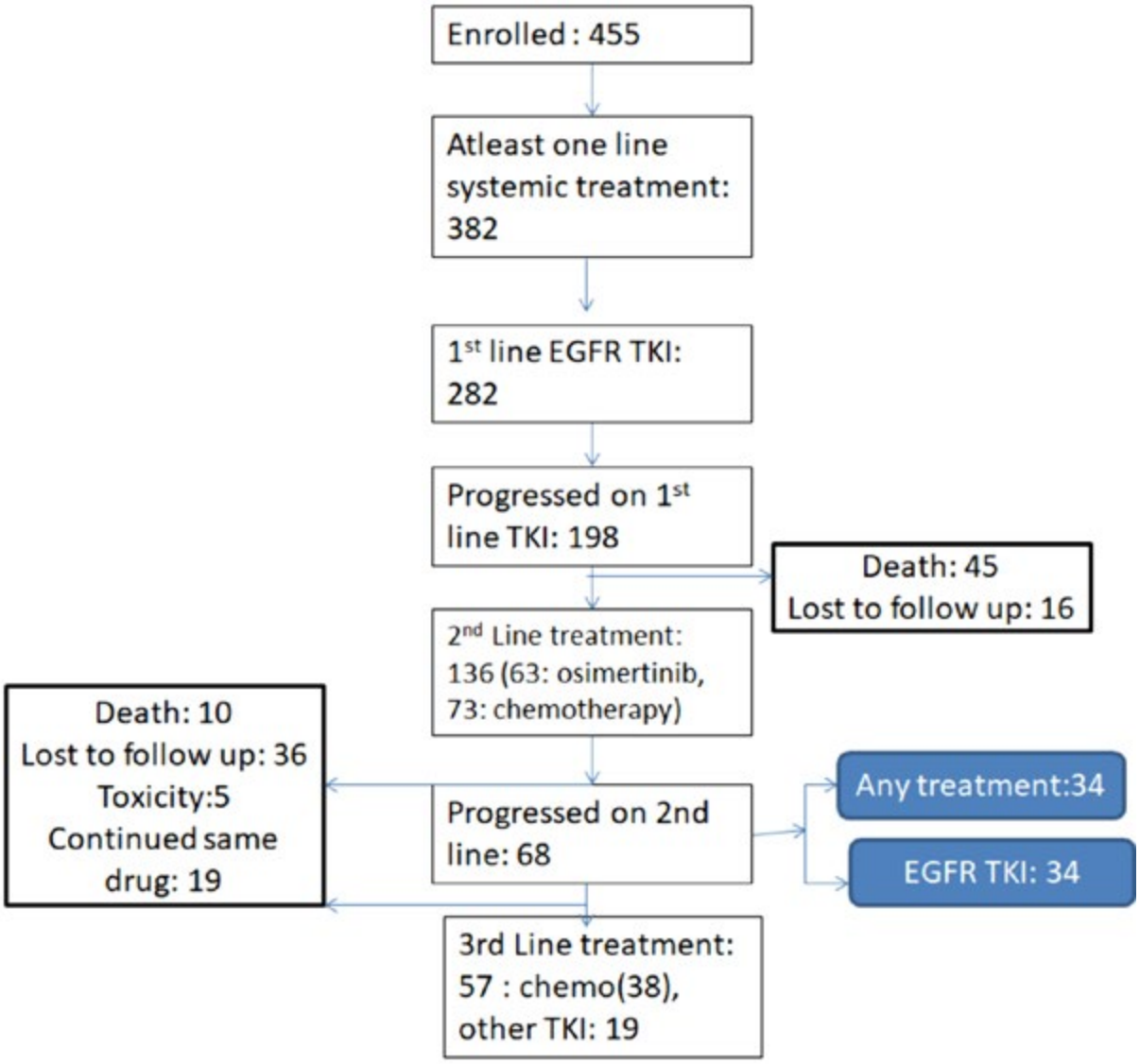
Introduction: Various treatment strategies are available which include sequencing EGFR TKIs or upfront treatment with third generation TKIs. The advantages of third generation TKIs include the OS advantage seen in the FLAURA trial. However, their widespread usage is limited by its high cost and lack of targetable resistance mechanism to osimertinib. The advantages of sequential strategy include affordability and real word applicability. However a major concern is that a substantial patient population may not take subsequent treatment. This is a single centre real world experience of treatment patterns in Indian patients with EGFR mutant advanced NSCLC. **Methods:** A total of 1350 NSCLC patients registered at our center between January 2015- March 2020 ,of which 455 patients were found to be EGFR mutant.The clinical features and demographics were retrieved from medical records. Statistical Analysis was done using R studio. **Results:**



Among 455 patients 382 (83.7%) received at least one line of systemic treatment;74 (16.3%) did not receive any treatment. Median age was 60 years (28-78years), with a male female ratio of 1.13:1. 80.2% were never smokers, and 96.4% patients (n=439) depicted adenocarcinoma histology. ECOG PS was 0-2 in 87.9% (n=400 cases). Extrathoracic metastases was present in 77.6% (n=353) patients, brain metastases at diagnosis was seen in 31.9% (n=145) cases, whereas 12.8% (n=58) patients developed later. Of the 382 patients, 282 (73.8%) received EGFR TKI as 1st line, and 100 (26.2%) received chemotherapy in 1st line. Of the 282, 198 (70.2%) patients progressed on TKI, of whom 136 (68.7%) took 2nd line treatment:73 (53.7%) chemotherapy, 63 (46.3%) received osimertinib based on T790M positivity). 68/136 (50%) progressed on 2nd line, of which 57 (83.8%) were given 3rd line treatment (38 chemotherapy, and 19 received EGFR TKIs). Among the 100 patients who received 1st line chemotherapy , 79 progressed, and 42 received 2nd line treatment (27 (34.2%) :chemotherapy, 9 (11.4%) received osimertinib and 16 (20.3%) received EGFR TKI). 35/42 (83.3%) patients progressed (15 received chemotherapy, 13 received EGFR TKIs). **Conclusion:** This real world study from India shows the real world treatment patterns of TKI usage .Inspite of major strides made in the management of NSCLC, 15 % patients upfront and 33% of patients do not receive appropriate treatment. The reasons for this could be multifactorial like poor PS, patients preference, financial and behavioral constraints etc. Every effort should be made to diagnose NSCLC when the patients PS is ok and to counsel the patients appropriately for treatment strategies.

Keywords: real world treatment patterns, TKI usage, EGFR

P07 GLOBAL HEALTH

P07.02 Real World data of Advanced Non-Small Cell Lung Cancer Patients EGFR Mutated from a Peruvian Cohort

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Introduction: Tyrosine kinase inhibitors anti-EGFR are the standard of care for NSCLC patients with sensitive EGFR mutations, however, the knowledge on the real benefit of these therapies in the real-world setting remains unclear. The aim of this study is to evaluate the characteristics and outcomes of EGFR mutated NSCLC patients treated in a real-world Latin American setting. **Methods:** Retrospective analysis of advanced NSCLC patients EGFR mutated diagnosed at Instituto Nacional de Enfermedades Neoplasicas (INEN), Lima-Peru from 2013 to 2020. Main clinical analysis, including ORR, PFS and OS, was performed only in patients who received anti-EGFR TKI (Erlotinib) at the institution. Data were collected from medical records. **Results:** During the study period, we analyzed the EGFR mutational status of 448 cases using tissue PCR or liquid biopsy in cases of insufficient material. Pathological EGFR mutations was found in 47% patients (n=211). Among these, the distribution of mutations was as follows: 61% exon 19 deletion, 25% L858R mutation, 12.6% EGFR uncommon mutations/associations, and 1.4% de-novo T790M mutation. Median age at diagnosis was 60 years (range 22-89y) and most patient were females (65.9%). Out of EGFR mutated patients, 129 (61.1%) received anti-EGFR TKI as a part of treatment at INEN, of them, 20.2% had smoking history and 24.8% biomass exposition as a main risk factor. About clinical presentation, 96 patients (74.4%) had status performance 1 (ECOG) and 37 (28.7%) presented brain metastases at diagnosis. Concerning treatment, 64.3% of patients (n=83) received TKI as first line and 35.7% as second or later line of treatment. The ORR was 86.8%. Median PFS was 14.13 months and median OS was 29.73 months. No differences in PFS and OS were found according to line of treatment (first vs second or later, p=0.69 and p=0.29 respectively) or type of mutation (exon 19 deletion vs L858R mutation vs uncommon mutations/associations, p=0.84 and p=0.50). Out of the 76 patients who progressed, half of them had T790M mutation assessment, finding 27.6% positive cases (21 patients). **Conclusion:** The proportion of EGFR mutated NSCLC in this cohort is higher than the reported in other countries outside Latin America or Asia. Our patients achieve high response rates and prolonged survival with no differences between the line of treatment or type of mutation. Results of this analysis confirm the benefit of use target therapies in the real-world setting.

Keywords: EGFR, real-world, survival

P07 GLOBAL HEALTH

P07.03 Lung Cancer Under 50 Years Old – What Reality Taught Us

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Introduction: Lung Cancer (LC) incidence increases with age and the occurrence in young patients is relatively low. The clinicopathological features are not fully explored yet. **Methods:** Retrospective analysis of LC patients' records followed in our hospital between January 2015 and January 2021. Based on a selection of patients with 50 years or less at the time of the diagnosis, we analyze their demographic features, smoking history, lung cancer characteristics, family history of cancer and survival rates. **Results:** Over this period, 725 patients were evaluated, 52 of which had 50 years or less at the time of the diagnosis. About 58% were male, with an average age of 46.7 ± 3 years. Nearly 81% had either active or past smoking habits, and 8% had asbestos exposure. Chronic obstructive pulmonary disease (23%) followed by cardiovascular disease (21%) were the most common comorbidities. In 29% of the cases, patients had a family history of cancer. In terms of presentation, 15% had pneumonia and 15% constitutional symptoms. Most of the lesions were in the right upper lobe (48%) and the histological diagnosis was made by bronchial biopsies in 31%, biopsy of metastasis in 21%, transthoracic needle biopsy in 19%, surgery in 17% and endobronchial ultrasound guided biopsy in 12%. Nearly 62% were adenocarcinoma. Regarding mutations, six were positive to EGFR, one had and ALK translocation and one ROS1. Four patients had PDL1 expression >50%. At the time of the diagnosis, most of the patients had ECOG performance status of 0/1 (40%). 60% presented stage IV disease and 13% stage IIIA. Nine patients were submitted to surgery with curative intent and nearly 54% received palliative care. 63% of the patients died. Mean survival time was 348 days. **Conclusion:** LC in younger patients presents a more aggressive behavior, greater mortality and is often detected in advanced stages. Although smoking history is still one of the major risk factors, family history plays an important role in this population too. Gene mutation assessment is mandatory for this subgroup. Early detection may be the key to achieve a better survival rate, as well as considering LC always as a possible diagnosis in younger and symptomatic patients.

Keywords: young patients, lung cancer

P07.04 Primary Lung Cancers in Patients With Head and Neck Cancer: Experience of a French Institution

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Introduction: Head and neck cancers, and lung cancers are frequent, and have a bad prognosis. In the literature, studies have analysed the relationship between these cancers. **Methods:** The aim of this study was to analyse the epidemiology of head and neck cancers, and the association with lung cancer. This study included retrospectively, all patients with head and neck cancer, and lung cancer between 2002 and 2016, in a French Institution (Institut de Cancérologie de Lorraine). All data were analysed with the SAS system, with mean, and percentages. **Results:** This study included 46 patients with head and neck cancer. Most of the patients were male, and had a tobacco, and alcohol consumption. Twenty-one patients had synchronous cancers (45,6%), and 25 had metachronous cancers (54,4%). Twenty-five lung cancers were diagnosed. Most of the secondary primary lung cancers were early, and local advanced stages. The median time before death was 41.9 months (3.7-328.2), the time before recurrence of lung cancer was 10.1 months (1.8-26.2), and the time before recurrence of head and neck cancer was 18.9 months (7.1-48.3).

	Head and neck cancers	Lung cancers
Localisation Buccal Oropharynx Larynx Hypopharynx Ethmoidal Other	12 (29.1%) 18 (39.1%) 9 (19.6%) 5 (10.9%) 1 (2.2%) 1 (2.2%)	-
Histological type Squamous cell Adenocarcinoma Small cell carcinoma	45 (97.8%) 1 (2.2%) -	23 (50%) 19 (41.3%) 4 (8.7%)
TNM stage I II III IVA IVB	7 (15.6%) ç (17.8%) 5 (11.1%) 23 (49%) 2 (4.4%)	17 (36.9%) 8 (17.4%) 10 (21.7%) 11 (23.9%) -
Treatment Surgery Chemo-radiation Radiation Chemotherapy Other or palliative care Surgery followed by adjuvant treatments	9 (20%) 9 (20%) 5 (11.1%) 7 (15.6%) 1 (2.2%) 14 (31.1%)	21 (45.6%) 3 (6.5%) 3 (6.5%) 16 (34.8%) 3 (6.5%) -

Conclusion: The diagnosis of secondary primary lung cancer in patients with head and neck cancers is frequent. Clinicians have to be aware of the risk of second primary lung cancer in head and neck cancers, in order to adapt their follow-up.

Keywords: diagnosis, lung cancer, Head and neck cancer

P08.01 Building Personalized Follow-Up Care Through AI by Bringing the Lung Cancer Patient, Data Scientist and Oncologist Together

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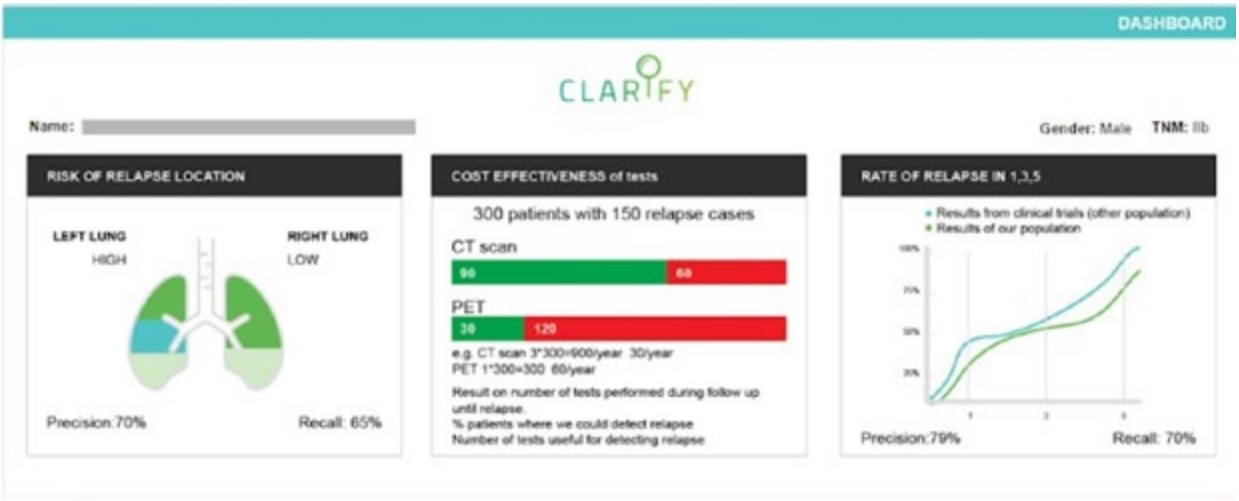
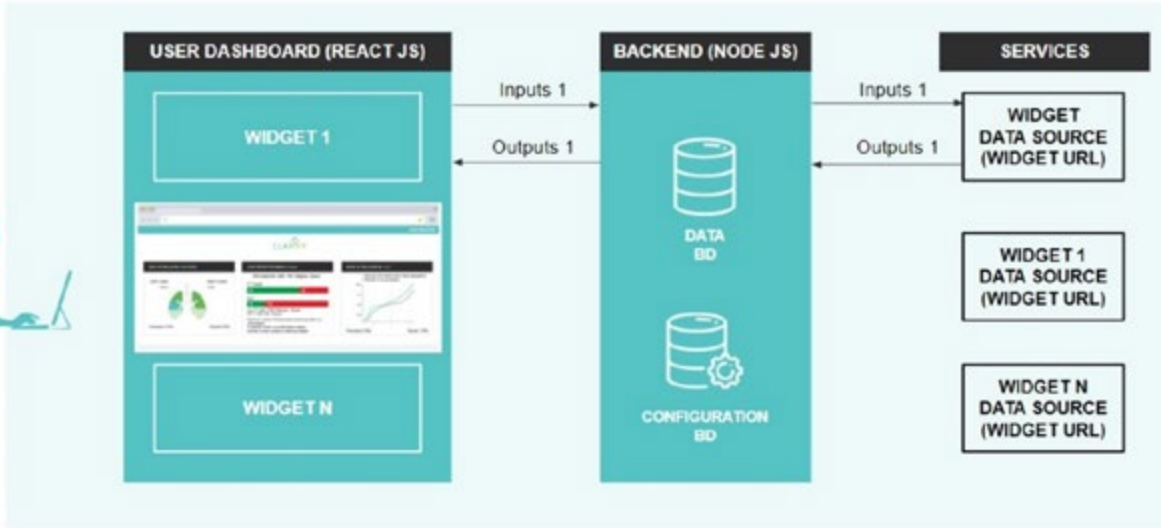
Introduction: Survival rates of lung cancer patients were rather poor until recent decades, when screening protocols, diagnostic techniques improvement and novel therapeutic options were developed. This leads to a new challenge: to increase lung cancer patients' post-treatment quality of life (QoL) and well-being. We here report on a first integration of an NLP framework for the analysis and integration of comprehensive eElectronic Health Records, genomic data, open data sources, wearable devices and QoL questionnaires, in order to determine the factors that predict poor health status and design personalized interventions that will improve the patient´s QoL. **Methods:** Patients diagnosed and treated at the Medical Oncology Department at Puerta de Hierro University Hospital were included. Eligible patients were aged >18 years old, were diagnosed with non-small cell lung cancer (all stages), and had an ECOG 0-1. Artificial Intelligence (AI) and Knowledge Discovery (KD) techniques were used to integrate heterogeneous datasets, and synthesize complex relationships within these large data sets. **Results:** A total 2052 patients were included in the study. 251.730 documents from EHR were analyzed (240.851 notes and 10.879 reports) and images from patients have been included. A total of 124 patients wore the wearable device "Kronowise 3.0" (Kronohealth SL, Spain) and QoL questionnaires were also obtained from every patient. From every patient monitoring, more than 1.000.000 data records are being analyzed, and more than 130 indicators are obtained by using expert knowledge. These heterogeneous data sources are analyzed and integrated into an interactive user interface (Figure 1). This dashboard will allow clinicians to obtain immediate and personalized information of each patient and will elaborate models based on statistical relational learning and explainable AI techniques to predict patient-specific risk of developing complications and toxicities secondary to their cancer treatments. These models will help clinicians to make evidence-based treatment and post-treatment decisions in a way that it is not possible with any existing approach. Figure 1. Project CLARIFY dashboard





Conclusion: By using AI techniques we will be able to exploit large amounts of clinical information integrated into an interactive user that will facilitate the early discovery of risk factors that may deteriorate a lung cancer patient's condition during and after treatment. It will also allow us to examine the effect of multidisciplinary interventions in order to personalize their follow-up by better assessment of their needs and eventually improve their quality of life, wellbeing, and outcome. This work was supported by the EU H2020 program, under grant agreement Nº 875160 (Project CLARIFY).

Keywords: Artificial Intelligence, knowledge discovery, personalized follow-up care

P08.02 Lorlatinib in First Line Treatment of Patients With ALK-Positive NSCLC: A Network Meta-Analysis

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Introduction: Lorlatinib, a third-generation tyrosine kinase inhibitor (TKI), showed a 72% reduction in risk of progression/death (HR 0.28: 95% CI, 0.19 to 0.41; p<0.0001) versus crizotinib in the Phase 3 CROWN study (NCT03052608). The study included previously untreated patients with anaplastic lymphoma kinase-positive (ALK+), advanced non-small-cell lung cancer. To understand the relative effects of lorlatinib compared to other treatments of interest not investigated in CROWN, we conducted a network meta-analysis (NMAs). **Methods:** We used comparator evidence, identified from a systematic literature review, to form a connected network of studies including the ALK TKIs lorlatinib (CROWN), alectinib (ALEX, ALESIA, J-ALEX), brigatinib (ALTA-1L), ceritinib (ASCEND-4, ASCEND-8), crizotinib (CROWN, ALEX, ALESIA, J-ALEX, ALTA-1L, PROFILE 1014, PROFILE 1029, eXalt3), ensartinib (eXalt3) and chemotherapy (ASCEND-4, PROFILE 1014, PROFILE 1029). The primary outcome for the analysis was progression-free survival (PFS) by independent radiologic review (IRR). Secondary outcomes (to be presented) included intracranial time to progression, objective response rate, adverse events, and overall survival. We used Bayesian, fixed and random-effects proportional hazards NMAs to derive estimates of the relative treatment effect (hazard ratios [HR]) of lorlatinib compared to the other treatments. **Results:** Fixed-effects models are presented due to the small evidence base and as these provided the best fitting models, based on DIC value. The results for PFS by IRR including all studies ranged from HR (95% credible interval) = 0.12 (0.08 to 0.19) for lorlatinib compared to chemotherapy; to 0.82 (0.36 to 1.85) for lorlatinib compared to alectinib (300 mg) [Table]. A sensitivity analysis was performed which removed studies that were solely based in Asian countries (J-ALEX, ALESIA, PROFILE1029) as this was believed to be a source of heterogeneity. The results for the analysis including only global studies ranged from 0.13 (0.08 to 0.20) for lorlatinib compared to chemotherapy; to 0.57 (0.34 to 0.95) for lorlatinib compared to brigatinib. Further sensitivity analyses using the investigator definition of PFS did not alter the conclusions of the NMA.

Treatment comparison Lorlatinib vs:	Studies	PFS HR (95% CrI)
Alectinib (600 mg)	ALEX, ALESIA*	0.61 (0.38 to 0.99)
Alectinib (300 mg)	J-ALEX*	0.82 (0.36 to 1.85)
Brigatinib	ALTA-1L	0.57 (0.34 to 0.95)
Ceritinib (750 mg)	ASCEND-4, ASCEND-8	0.22 (0.13 to 0.37)
Ceritinib (450 mg)	ASCEND-8	0.31 (0.15 to 0.66)
Ceritinib (600 mg)	ASCEND-8	0.25 (0.12 to 0.54)
Crizotinib	CROWN, ALEX, ALESIA*, J-ALEX*, ALTA-1L, ASCEND-4, ASCEND-8, PROFILE 1014, PROFILE 1029*, eXalt3	0.28 (0.19 to 0.41)
Ensartinib	eXalt3	0.55 (0.32 to 0.93)
Chemotherapy	ASCEND-4, PROFILE 1014, PROFILE 1029*	0.12 (0.08 to 0.19)
Key: CrI, credible interval; HR hazard ratio; PFS, progression-free survival Notes: *Study in Asian population only		

Conclusion: For PFS, lorlatinib reduced the hazard of progression or death compared to all other treatments based on analyses conducted using all studies when comparing to all studies. This NMA suggest that lorlatinib is an effective first line treatment for ALK+ NSCLC patients when compared to other next-generation ALK TKIs.

Keywords: Lorlatinib, Network meta-analysis, ALK-positive NSCLC

P08.03 Cost-Effectiveness of Pembrolizumab With or Without Chemotherapy for Stage IV Non-Squamous NSCLC with High PD-L1 in Switzerland

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Introduction: Until recently, chemotherapy was the only treatment option for metastatic non-squamous non-small cell lung cancer (NSCLC) without targetable mutations. The introduction of immunotherapies changed the prognosis for patients suffering from this disease. Pembrolizumab can be given as monotherapy or in combination with chemotherapy. So far, it was unclear, if and which of these treatment options is cost-effective for patients with a high programmed death ligand 1 (PD-L1) expression. **Methods:** We conducted a cost-effectiveness analysis for Switzerland, comparing pembrolizumab with and without chemotherapy and chemotherapy alone using a Markov model with a time horizon of 10 years. We used data from the KN-024 and KN-189 registration trials and the available follow-up data. Costs were assessed from a Swiss health care perspective and include further treatment lines as well as best-supportive care. **Results:** Pembrolizumab monotherapy in comparison to chemotherapy lead to a gain of 0.83 quality-adjusted life years (QALYs) and generates incremental costs of 56,585 CHF per year, resulting in an incremental cost-effectiveness ratio (ICER) of 68,580 CHF/QALY. Pembrolizumab in combination with chemotherapy resulted in a gain of 0.17 QALYs and generated incremental costs of 81,085 CHF as compared to pembrolizumab alone, resulting in an ICER of 475,299 CHF/QALY. **Conclusion:** While pembrolizumab monotherapy is cost-effective from a Swiss perspective, the combination therapy with pembrolizumab and chemotherapy is not.

Keywords: Pembrolizumab, cost-effectiveness, NSCLC

P08.04 Comparative Clinical Outcomes Between EGFR Exon20ins and Wildtype NSCLC Treated with Immune Checkpoint Inhibitors

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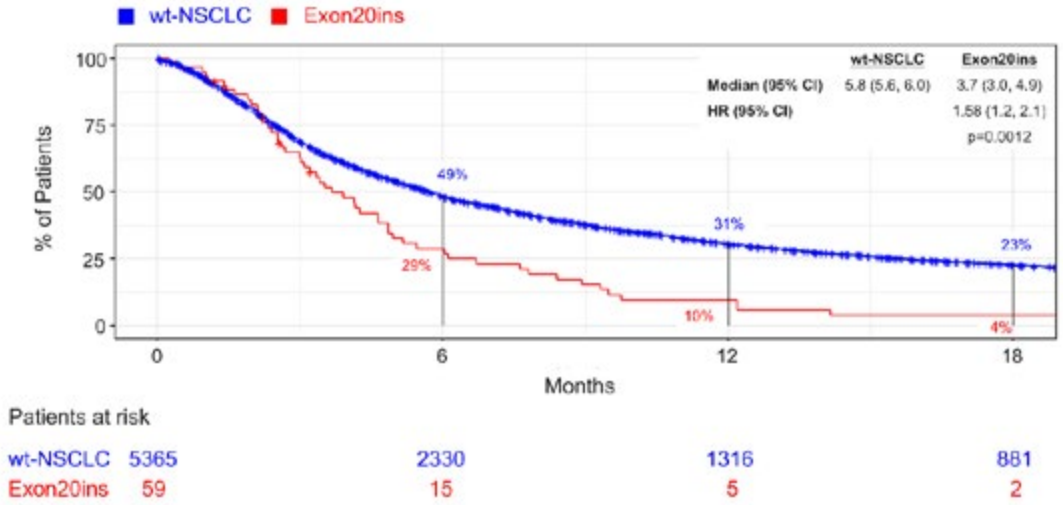
Introduction: Mutation of the epidermal growth factor receptor (EGFR) is a major oncogenic driver in non-small cell lung cancer (NSCLC), and up to 12% of all EGFR-mutant NSCLCs harbor Exon 20 insertion mutations (Exon20ins). The insensitivity of Exon20ins to EGFR tyrosine kinase inhibitors has been well documented, but the activity of immune checkpoint inhibitors (ICIs) has not been closely examined due to the frequent exclusion of patients with EGFR mutations from large immunotherapy-based NSCLC trials. **Methods:** We conducted a retrospective study to compare clinical outcomes of ICI-treated patients with EGFR Exon20ins and wildtype NSCLC (wt-NSCLC, defined as EGFR, ALK test negative). Patients with advanced NSCLC with non-squamous histology from the Flatiron Health database from 2015 to 2020 were included in this analysis. Real-world time to next therapy (rwTTNT) was the primary endpoint and analyzed using multivariable Cox proportional hazards model (covariates: age, time from advanced diagnosis to index date, time from initial to advanced diagnosis, sex, ECOG performance status, smoking history, and practice type) stratified by ICI initiation line of therapy. Overall survival was the secondary endpoint. Both endpoints were summarized by Kaplan-Meier method. **Results:** Clinical outcomes of ICI therapy were assessed in 5365 with wt-NSCLC against 59 patients with Exon20ins NSCLC. ICI treatment was received as first or second-line therapy in 25% and 41% of Exon20ins and 39% and 42% of wt-NSCLC patients, respectively. The most common ICIs received by Exon20ins and wt-NSCLC patients were nivolumab (64% and 51%) and pembrolizumab (32% and 42%), respectively. Patients with Exon20ins had a 58% increased risk of shorter time to next-line therapy compared to wt-NSCLC (adjusted hazard ratio of 1.58 [95% CI, 1.2–2.1]; p=0.0012). The median rwTTNT was 3.7 months (95% CI, 3.0–4.9) for Exon20ins compared with 5.8 months (95% CI, 5.6–6.0) for wt-NSCLC (**Figure**). At 12-months, 10% of Exon20ins patients remained on ICIs compared with 31% of wt-NSCLC patients. No meaningful difference in survival between the Exon20ins and wt-NSCLC groups was observed. **Conclusion:** ICI therapy was less effective for patients with Exon20ins compared with wt-NSCLC, although the sample size for Exon20ins NSCLC was smaller. The limited effectiveness of current treatment options for patients with EGFR Exon20ins NSCLC stress the need for new targeted therapies.

Figure: Real World Time to Next Therapy (rwTTNT)



Patients at risk

wt-NSCLC	5365	2330	1316	881
Exon20ins	59	15	5	2

Keywords: immune checkpoint inhibitor, EGFR Exon 20 Insertion, Real world

P08.05 Impact of Personal Characteristics on the Effectiveness of Immunotherapy Treatment in Late-Stage NSCLC: A Systematic Review

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Introduction: There is mixed evidence about how various personal characteristics contribute to the variability in survival in NSCLC patients after immunotherapy, as existing studies have substantial heterogeneity in clinical characteristics, tumor mutation expression, and line of therapy. Systematic reviews and meta-analyses frequently focus on randomized controlled trials (RCTs) which have limited generalizability, given their disproportionate enrollment of younger and healthier, male, and white patients in early lines of therapy. Increased use of immunotherapy globally has enabled publication of multiple observational studies with more diverse patients and more representative, real-world outcomes. This systematic review uses both RCTs and observational studies to summarize individual variations in response to immunotherapy. **Methods:** Search results from Web of Science, OVID EMBASE, and MEDLINE were evaluated, and studies on patients with locally advanced or metastatic NSCLC (>= Stage IIIB) were screened. RCTs consisting of an intervention group receiving immunotherapy and a control group that did not were included if hazard ratios (HRs) for progression-free (PFS) or overall survival (OS) were reported for at least one of age, sex, smoking status, or race. Observational studies reporting PFS or OS of patients treated with immunotherapy by one of age, sex, smoking status, or race were included. **Results:** 1124 titles and abstracts were screened, and 65 studies were selected for full text review; 18 RCTs and 17 observational studies met inclusion criteria. Among RCTs, 14/17 studies reported improved survival among those <65 years, 7/15 reported improved survival among ever-smokers, and 10/17 reported improved survival for males. Only one study reported a significant difference between races, with white patients showing improved survival. Among observational studies, 4/13 reported better survival for younger patients, 6/13 reported better survival for ever-smokers, and none reported differences by gender. Results for race were mixed, with one study reporting better survival for non-white patients, and one reporting better survival for non-Asian patients. A summary of the results is presented in Table 1.

RCTs (n=18)					
	Total # Studies Reporting	# Studies with Significant OS/PFS (groups with better OS/PFS)	Univariate Hazard Ratio Range (Min, Max)* (PFS/OS immunotherapy compared to chemotherapy		
Age (years)	17	14/17 (Patients <65); 6/17 (Patients>=65)	<65: (0.43*, 1.13) >=65: (0.45*, 1.04) 65<x<75: (0.56*, 1.06) >75: (0.74, 1.85)		
Smoking Status	15	7/15 (Ever-smokers); 2/15 (Never-smokers)	Ever-smokers: (0.54*, 0.89) Never-smokers: (0.23*, 1.69)		
Sex	17	10/17 (Male); 6/17 (Female)	Male: (0.39*, 0.97) Female: (0.29*, 1.33)		
Race	5	1/5 (White Patients)	White: (0.71*, 0.94) Black: (0.67, 0.99) Asian: (0.62, 1.31)		
Observational Studies (n=17)					
	Reference Group	Total # Studies Reporting	# Studies Reporting Significant Difference in OS/PFS (groups with higher marginal benefit/better survival from immunotherapy)	Univariate Hazard Ratio Range (Min, Max)*	
Age (years)	<65 (n=5), <60 (n=3), <70 (n=3), <75 (n=2)	13	4 (Younger Patients)	(0.84, 3.88)	
Smoking Status	Never Smokers	13	6 (Ever Smokers) 1 (Never Smokers)	(0.49, 1.06)	
Sex	Male	15	0 (No significant differences)	(0.89, 1.42)	
Race	White	3	1 (Black patients) 1 (Non-Asian patients)	(0.33, 0.90)	

Table 1: Summary of results * = Statistically significant HR from individual study **Conclusion:** The collective evidence suggests immunotherapy may provide additional survival benefit in younger patients, males, and former or ever-smokers although results are mixed. Very few studies have reported outcomes by race, and those which have are underpowered. This represents a notable gap in the literature and an opportunity to better target therapies and improve clinical practice. Evaluation of patient-level data in national registries would enable adjustment for personal and clinical characteristics that may be confounders.

Keywords: Observational Cohort Studies, Real-world data, Quality of Care

P09.01 Waiting Time and Lung Cancer Outcomes: Association and Methodological Results From a Systematic Review of Systematic and Scoping Reviews

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Introduction: Lung cancer is the leading cause of cancer death globally. Over half of lung cancer cases are diagnosed with late stage, indicating the importance of timely diagnosis and treatment for this life-threatening disease. Therefore, we conducted this systematic review of systematic and scoping reviews, to investigate the association between waiting time and lung cancer outcomes, as well as relevant methodological issues. **Methods:** Eligible articles included English-written systematic/scoping reviews and meta-analyses that investigated the impact of waiting time intervals on patient survival or disease stage at diagnosis in original studies on lung cancer. Due to the large variations in interval types, we took the Aarhus statement as reference to include articles using total diagnostic, patient, diagnostic, treatment, healthcare and total intervals, the ones generalizable in different healthcare settings across countries or regions. Articles were searched via PubMed, Embase, Web of Science, and the Cochrane Library (date range: from database inception to 6 August 2020) (PROSPERO identifier: CRD42020203530). **Results:** From 2207 publications, we included five systematic/scoping reviews published between 2002-2017; the number of their included studies ranged from 6 to 21. Study results indicated mixed associations between the time intervals and patient survival or disease stage at diagnosis, regardless of which interval was used. Specifically, more studies demonstrated no or a negative association, rather than a positive association between longer waiting times and poorer survival or later stage at diagnosis. Methodologically, reviews raised concerns of study quality, especially whether to address an important source of bias–the "waiting time paradox", where those who present with later stage disease with more severe symptoms are diagnosed and treated more promptly. One review found that only one of 21 eligible studies considered the waiting time paradox in their analyses. In addition, reviews pointed out the large variations in study characteristics (e.g., setting, region, sample population, data source). The above methodological issues may attenuate and even bias the true effect of the association results during statistical analysis, to some extent accounting for the mixed association results in studies. **Conclusion:** The results of association between waiting time intervals with lung cancer outcomes are paradoxical with the nature of cancer development and patients' journey in healthcare services. To better guide future practice and policy making, relevant research and a widespread consensus on addressing concerns in study methodologies and results are warranted, for more robust evidence of how long waiting time could be associated with poorer lung cancer outcomes.

Keywords: Time-to-treatment, lung cancer, Delayed diagnosis

P09 HEALTH SERVICES RESEARCH/HEALTH ECONOMICS - LUNG CANCER POLICY

P09.02 A Clinical Evaluation Algorithm to Define Clinical Utility of Lung Nodule Diagnosis in a Multi-Collaborator Setting Using Real World Data

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Introduction: New biomarkers for the diagnosis of indeterminate lung nodules (IPN) suspicious for lung cancer are being developed regularly. Clinically useful new diagnostic tests for IPN requires improvement in post-test risk classification to reduce subsequent testing or time to diagnosis. Therefore, measuring the activity to a diagnosis is needed. In a collaboration between Lahey Hospital and Medical Center (LHMC), representing a large screening only population, Vanderbilt University Medical Center (VUMC), a tertiary referral center with incidental and screening discovered nodules, and OneFlorida Clinical Research Consortium, a statewide network with incidental nodules, we defined an algorithm to combine real world data (RWD) from electronic health records (EHR) to measure the clinical activity necessary to diagnose an IPN. We adapted the algorithm to local environments and defined referral pattern biases for others who wish to define clinical utility using RWD. **Methods:** RWD was transformed to the Observation Medical Outcomes Partnership (OMOP) common data model. An EHR-based algorithm was coded. IPN cohorts were identified using a published algorithm or by existing registries. Chart reviews were conducted to determine the gold standard of clinical activity and to define the time to diagnosis. IPN size 6-30mm and patients aged 40-80 years were included. Clinical activity consisting of CT and PET imaging, bronchoscopies, surgeries and SBRT was identified by ICD-9/10, CPT, or site-specific procedural and diagnostic codes. Differences between algorithm and chart review results by site were measured and systematic differences in activity were investigated using correlation and Wilcoxon sign-rank tests. **Results:** A combined cohort of 1,973 patients was identified across the three sites. Full chart review occurred on 154 individuals for comparison. The EHR-based algorithm undercounted CT Imaging clinical activity (Table 1) and overestimated all other clinical activity. Spearman correlations between EHR and chart review were high for Bronchoscopy (0.94), CT Imaging (0.82) and PET Imaging (0.92), and lowest with Surgical Procedures (0.74). LHMC had the highest correlation overall between its EHR based clinical activity collection and chart review with correlations of CT Imaging (0.91), Bronchoscopy (1.00) and Surgical procedures (0.83). VUMC and OneFlorida consistently underestimated CT Imaging activity in incidental nodules.

	LHCM Algorithm/ Chart Review	**OneFlorida** Algorithm/ Chart Review	**VUMC** Algorithm/ Chart Review	**Overall** Algorithm/ Chart Review	**Overall Correlation**
CT Imaging	3.20/3.26	2.44/3.09	1.63/2.40	2.44/2.93 p<0.001	0.82
PET Imaging	-/-	0.76/0.80	0.48/0.73	0.96/0.76 p<0.001	0.94
Bronchoscopy	0.08/0.08	0.96/1.15	0.98/1.00	0.97/0.75 p=0.07	0.92
Surgical Procedure	0.20/0.24	1.80/1.35	0.30/0.25	0.82/0.64 p=0.09	0.74

Conclusion: We successfully developed an EHR-based algorithm to capture clinical evaluation activity to diagnose IPN. The algorithm was most accurate in a screening population. Systematic underreporting of CT Imaging arose among incidentally discovered nodules. Researchers seeking to determine clinical activity in IPN diagnosis must consider the method of nodule discovery when using RWD

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Keywords: clinical evaluation, Real World Data, Lung nodules

P09.03 Validation of a Real-World Mortality Endpoint for Advanced Non-Small Cell Lung Cancer Patients in China

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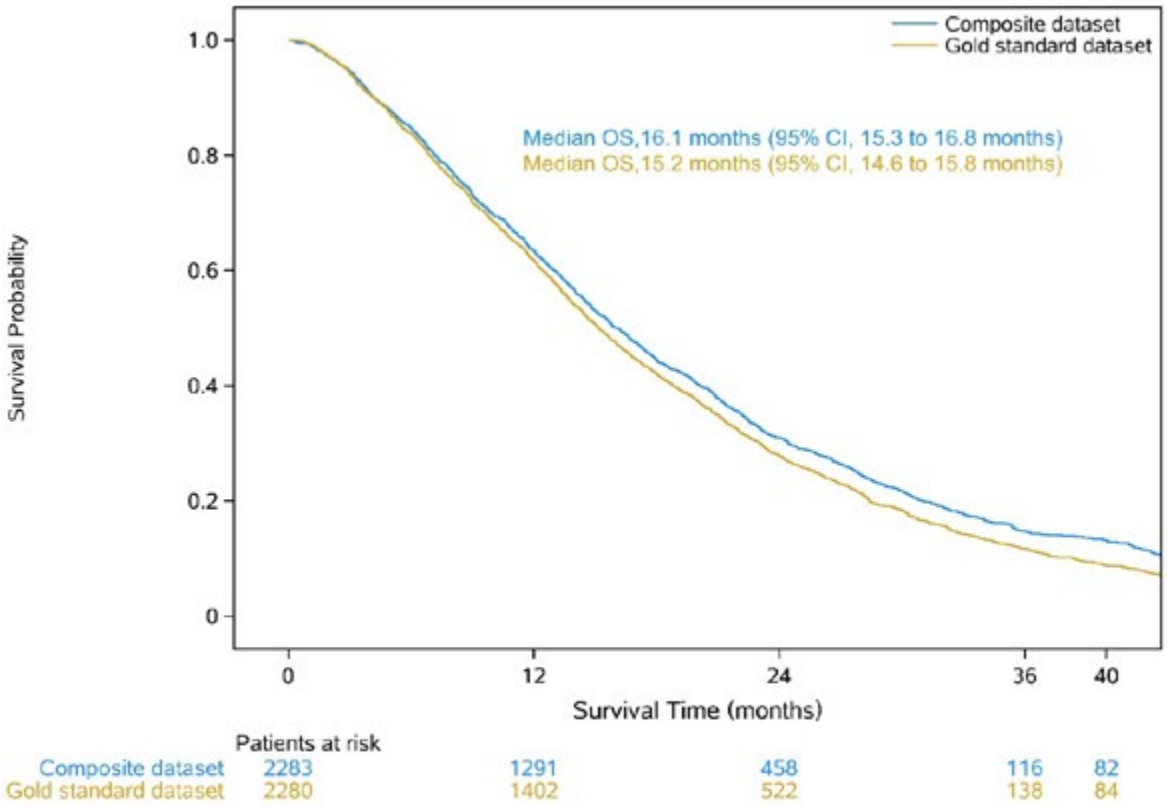
Introduction: In real-world studies, mortality data quality impacts the key endpoint, overall survival (OS). We evaluated the mortality data quality of our composite real-world dataset, benchmarked against the government-sourced data as a gold standard dataset, to develop a high-quality mortality dataset for retrospective and prospective real-world evidence. **Methods:** Patients pathologically diagnosed with advanced non-small cell lung cancer (advNSCLC) between January 2015 and December 2018 in Henan Cancer Hospital, receiving first-line systemic treatment with ≥2 medical records or 1 medical record and ≥1 follow-up were included. Patients without ID numbers who had other active primary tumors, or died within 30 days after first-line systemic treatment were excluded. The mortality data comprised of survival status (dead or alive), last survival date and death date of advNSCLC patients. Additionally, the gold standard dataset integrated the mortality data of advNSCLC patients from the Henan Provincial Cancer Center and the Henan Provincial Center for Disease Control and Prevention. Our composite dataset amalgamated the mortality data of patients from de-identified electronic health records and the LinkDoc follow-up system (contacted by the call-center and mobile application). Compared with the gold standard, data quality of the composite dataset was assessed by validity metrics, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ±30-day agreement. OS was estimated by the Kaplan-Meier survival curve. **Results:** A total of 4,844 patients were eligible. Considering the time lag of over a year of the gold standard dataset, the follow-up cut-off date was set as December 31, 2019. Consequently, the survival status of 4630 patients were analyzed. All 1218 patients with death dates in both datasets were assessed for the death date agreement. A total of 2284 patients who had records of survival time were analyzed by the Kaplan-Meier curve. Compared with the gold standard dataset, the sensitivity, specificity, PPV and NPV of the composite dataset were 82.8% [95% confidence interval (CI), 81.12-84.49], 76.8% (95%CI, 75.18-78.36), 71.8% (95%CI, 69.96-73.70) and 86.2% (95%CI, 84.81-87.57). The result demonstrated that the ± 30-day accuracy rate was 81.44% (95%CI, 79.26-83.63). The median OS were 15.2 months (95%CI, 14.6-15.8) and 16.1 months (95%CI, 15.3-16.8) in the gold standard dataset and the composite dataset (Figure 1), which was overestimated to be 5.9% in the composite dataset. Figure1. Kaplan-Meier curve of overall survival between gold standard dataset and composite dataset



Conclusion: Our high-quality composite mortality dataset was sufficient in yielding reliable real-world evidence.

Keywords: data quality, mortality information

P09.04 Evaluating Mutational Differences Between Hispanics and Asians in NSCLC

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Introduction: Hispanics living in the United States have higher rates of EGFR mutations compared with Non-Hispanic Whites. While this is similar to Asian patients living in the US, the outcomes for Hispanic patients differ. We sought to compare the variances in mutational profiles between Hispanics and Asian patients living in Los Angeles and to determine the impact of tobacco use on mutational landscape in each ethnic group. **Methods:** A total of 393 NSCLC patients treated at LAC+USC Medical Center and Norris Comprehensive Cancer Center who received comprehensive genomic profiling (CGP) were evaluated from December 2017- August 2020. CGP was done using tissue biopsies (n=211) from Caris Life Sciences (Caris) and liquid biopsies (n=224) from Guardant360 CDx from Guardant Health (Guardant). Multivariate logistic regression was performed to evaluate for role of race between Hispanics and Asians controlling for site of treatment, age at initial diagnosis, gender, and smoking. Fisher's exact test was done to evaluate for the role of KRAS mutations with regard to smoking. Survival analysis was done using the log-rank (Mantel-Cox) test. **Results:** CGP was done on 393 patients. In Hispanics (n= 90), 50.0% were male, median age of diagnosis was 62, 54.5% non-smokers, and 85.5% had adenocarcinoma. In Asians (n =142), 47.5% were male, median age of diagnosis was 65, 59.6% were non-smokers, and 83.8% had adenocarcinoma. In tissue sequenced patients, 6/22 (27.3%) Hispanics and 3/72 (4.2%) Asians had KRAS mutations while 2/22 (9.1%) Hispanics and 32/72 (44.4%) Asians had EGFR mutations. In patients sequenced by circulating tumor DNA, 9/74 (12.2%) Hispanics and 3/87 (3.4%) Asians had a KRAS mutation while 19/74 (25.68%) Hispanics and 39/87 (44.8%) Asians had an EGFR mutation. In 14 Hispanic KRAS patients, 8/14 (57.1%) had transversion mutations and 9/14 (64.3%) had TP53 comutations. In 6 Asian KRAS patients, 3/6 (50%) had transversion mutations and 2/3 (66.7%) had TP53 comutations. Logistic regression showed that race was an independent variable in KRAS (OR 4.42, 95% CI: 1.63-12.83) and EGFR mutations (OR 3.20, 95% CI: 1.70-6.19). There was a greater proportion of Hispanics smokers with KRAS mutations (14/41; 34.1%) than Asian smokers (4/58; 6.9%) (p = 0.001) Median overall survival (OS) in Hispanics was 43.3 months versus 72.4 months in Asians (p= 0.158). Hispanic EGFR patients had 39.2 months median OS compared to 71.9 months in Asian EGFR patients (p= 0.062). Hispanic KRAS patients had a median OS of 24.0 months compared Hispanic non-KRAS patients 54.7 months (p= 0.111). **Conclusion:** Our study showed a greater percentage of Hispanic patients with KRAS mutations but a greater percentage of Asians with EGFR mutations despite similar percentages in smoking and mutation distribution. There was a trend towards worse outcomes in Hispanic patients compared to Asians with similar genomic findings, and Hispanic patients with KRAS mutations compared to those without KRAS mutations.

Keywords: Real World Data, Ethnic Disparities, Disease Registries and Databases

P09.05 Variation of Treatment Recommendations for Stage III Non-Small-Cell Lung Cancer by Stage and Actionable Mutations

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Introduction: For locally advanced (stage IIIA-C) non-small-cell lung cancer (NSCLC), therapeutic options consist of definitive chemoradiation (CRT), surgery combined with neoadjuvant/adjuvant chemotherapy, and surgery combined with neoadjuvant/adjuvant CRT (trimodality therapy). However, with the introduction of immunotherapies and targeted therapies, the number of strategies to manage these patients is growing. **Methods:** A customized, IRB approved survey study was emailed to all members of the IASLC (International Association for the Study of Lung Cancer) to gauge their attitudes on practice habits. The survey collected clinical practice information including participant's country, medical specialty, type of practice, years of practice, number of lung cancer patients treated annually, and familiarity with recent phase III studies (ADAURA, FLAURA, PACIFIC, LungART). The preferred treatment regimens were also assessed for a variety of different stage III cases given the provided tumor size, location and number of lymph nodes, and presence of mutations. Variables were compared by chi-square testing. **Results:** 1,998 surveys were sent, with 87 responses received (4.4% response rate). Respondents from 31 countries included medical oncologists (48%), surgical oncologists (24%), radiation oncologists (21%), and other specialists (7%). The majority treated over 10 lung cancer patients per year (95%). Regarding stage IIIA-B disease, the distribution of recommendations for CRT, surgery combined with systemic therapy, trimodality therapy, and unanswered responses in the absence of actionable mutations was 68%, 18%, 10%, and 3%, respectively; with an EGFR mutation or ALK rearrangement it was 47%, 37%, 12%, and 3%, respectively ($p < 0.0001$). There were no significant differences based on the presence of EGFR mutation versus ALK rearrangement ($p = 0.98$). For patients without actionable mutations, the distribution of recommendations for CRT, surgery combined with systemic therapy, trimodality therapy, and unanswered responses with stage IIIA disease was 57%, 22%, 16%, and 5%, respectively; with stage IIIB disease it was 74%, 16%, 7%, and 3%, respectively ($p = 0.0005$ compared to stage IIIA); with IIIC it was 95%, 0%, 2%, and 3%, respectively ($p < 0.0001$ compared to stage IIIA); with stage III-N2 disease with 1 IASLC-defined zone it was 60%, 28%, 10%, and 2%, respectively; and with stage III-N2 disease with 2-3 IASLC-defined zones it was 64%, 21%, 12%, and 3%, respectively ($p = 0.58$ compared to 1 IASLC-defined zone). When comparing responses by physician specialty, surgical oncologists were more likely than oncologists to recommend surgery with systemic therapy for patients without actionable mutations (26% vs 11%, $p<0.0001$), but there were no significant differences between recommendations between medical and radiation oncologists ($p=0.14$). **Conclusion:** Participants in our study were more likely to recommend definitive CRT for the management of stage III NSCLC in the absence of actionable mutations. Treatment recommendations were also conditional on group stage (IIIA, IIIB, or IIIC) and physician specialty, but not on the number of involved IASLC-defined lymph node zones. Although the dominant optimal management strategy for stage III NSCLC was CRT, a notable lack of consensus was identified amongst specialists, reflecting the increased treatment options available for patients.

Keywords: Stage III NSCLC, Physician treatment recommendations

P09.06 Patient Behaviors and Attitudes Towards Lung Cancer Medication Adherence

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Introduction: Anti-cancer medications constitute a critical part of lung cancer treatment. While absolute adherence to these medication plans is not expected, there is not enough real world data to analyse and measure adherence, complicating any efforts to improve it. CareAcross, a digital multilingual platform which provides personalized, evidence-based support to cancer patients investigated patient behaviors and attitudes towards cancer medication adherence. **Methods:** During March of 2020, members of the CareAcross online platform were asked to report their level of adherence to their anti-cancer medications, and their overall attitude towards adherence. Members were predominantly from the UK, France, Spain, Italy or Germany, and were diagnosed with lung, breast, colorectal or prostate cancer. This analysis focuses on lung cancer patients. **Results:** 117 patients with lung cancer responded to the questions. Among them, 30 (26% of all responders) have not always been adherent to their treatment plans; more specifically, 20% had completely stopped taking at least one of their medications, 5% had reduced their dosage, and 3% had reduced their frequency (multiple responses were allowed). The primary reason for non-adherence of this subgroup of patients was side-effects (33%). Similarly, when adherent patients were asked about the reason that could lead them to non-adherence, side-effects accounted for even higher percentage (49%). The second reason for both groups was the treatment's perceived lack of effectiveness (30% and 21%, respectively). Among patients who completely stopped taking their medications, 45% did not replace them with anything else, 40% took alternative treatments, and 15% started taking a different medical treatment. Patients would notify their doctor in the vast majority of cases of (actual or hypothetical) non-adherence (96%). Patients were also asked to self-assess their overall adherence to medication for any health condition. Among patients who were not fully adherent to their lung cancer medication, 66% reported being adherent at least "75% of the time", compared to 88% of those who were fully adherent to their lung cancer medications. **Conclusion:** About 1 in 4 of lung cancer patients have deviated from their cancer medications, primarily due to side-effects. Most of these completely stopped taking their lung cancer medications, 40% resorted to alternative treatments, and only 15% replaced them with different medications. Patients were mostly willing to notify their doctors of any changes in their medication intake, including those who actually made changes. The level of adherence to lung cancer medications was relatively consistent with the overall level of adherence to medications for any health condition. These real world findings illustrate that adherence to lung cancer medication can be a real challenge. The fact that patients are willing to share any deviations in medication intake with their doctors presents an opportunity for constructive patient-clinician interaction on this critical topic. Moreover, the relative consistency of medication adherence across all health conditions offers the option to discuss the topic of adherence before and throughout lung cancer treatment, and potentially improve adherence levels through proactive engagement and patient education. This can be particularly impactful for the overall health of multimorbid patients taking several medications.

Keywords: patients, compliance, Adherence

P09.07 Integration of Smoking Cessation Services in Mobile Mammography and Mobile COVID Screening to Reach Rural Populations

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Introduction: Smoking cessation has been demonstrated to confer survival benefit, whereas ongoing tobacco use leads to multiple health risks. Unaided cessation is often unsuccessful. Counseling by an expert and access to pharmacotherapy can boost quit rates. Unfortunately, recruitment to cessation programs faces several barriers, particulary poor penetrance into the target population. In our region, the highest rates of smoking are in rural areas, yet tobacco cessation counseling at our institution previously occured in a centralized urban location. Two programs at our institution which routinely provide direct care to our rural, underserved population are a mobile mammography program, and mobile COVID screening/vaccine program. We aimed to integrate services with those programs and in turn demonstate ability to evaluate all patients for tobacco use, and provide point of care cessation counseling by an expert in rural setting. In addition this program would provide contact information, increase awareness, and then provide follow up contact to encourage cessation. **Methods:** A Certified Tobacco Treatment Specialist with expertise in lung cancer screening and tobacco cessation joined the mobile mammography unit and the mobile COVID-19 screening teams at rural sites 2-3 days per week. Every patient on intake was evaluated for eligibility by smoking status. All patients who were smoking were given information regarding cessation and were counseled on the importance cessation face to face by a certified tobacco treatment specialist. Telephone follow up was provided as well regarding cessation and to refer for lung cancer screening if necessary. Patients were also provided information about tobacco cessation resources with the state toll free Quitline and contact information for the screening program for family members who may benefit. **Results:** Over five consecutive months, 250 women received services through the mobile mammography program, and of these women only 9.6% (n=24/250) were currently smoking. Of the 404 patients who received services through the mobile COVID screening / vaccination program in the rural setting, 36.9% (149/404) of patients were actively smoking. None of the patients identified through either mobile program in rural areas were currently enrolled in other cessation programs. All patients received face to face intervention at the point of care by a certified tobacco treatment specialist and data was recorded for follow up telephone contact. Follow up phone calls were done to assess cessation, provide further support, and assess for eligibility for a lung cancer screening program. *as this is an ongoing project, if selected for oral or poster presentation, updated numbers could be used. **Conclusion:** As smoking cessation programs look to grow and recruit patients, those at highest risk may be in rural locations and have poor awareness or limited access to screening programs. Integrating cessation services into existing mobile screening outreach programs which already provide services to rural, underserved areas can be a way to recruit patients to a smoking cessation program, without signicant increase in resources. In a rural setting served by mobile outreach mammogram screening and/or mobile COVID-19 screening, patients are accepting of cessation resources. Further work is being done to assess the impact of these outreach interventions on cessation rates in these rural, high risk populations in order to overcome barriers to care.

Keywords: tobacco, access to care, Smoking Cessation

P10.01 Real World Data of Clinical Trial Eligibility and Outcome Analysis in Patients With Metastatic NSCLC

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Introduction: Accrual to clinical trials is a major challenge with <5% of U.S adult cancer patients (pts) enrolled in clinical trials that limits generalizability of results. There is a trend toward increasing number and complexity of inclusion criteria in lung cancer clinical trials, leading them to be more restrictive. Thus majority of pts are treated based on experience of small minority. Limited data are available regarding pt outcomes in those who would have been ineligible to receive therapy based on original clinical trial which led to treatment approval. In this study, we identified pts with metastatic Non-Small Cell Lung Cancer (mNSCLC) who received systemic therapy and reviewed eligibility of these pts for clinical trials that led to specific therapy approval, to identify outcomes among pts that would have been ineligible. **Methods:** Retrospective review of all pts with mNSCLC who had 1st line systemic therapy off protocol, at our center between August 2015-18. Descriptive statistics were used to stratify pts by age, gender, ECOG, histological subtype, mutations, regimen and eligibility status to the clinical trial protocol based on which their specific therapy was chosen. Overall survival (OS) is plotted as Kaplan-Meier curves based on eligibility, ECOG, treatment group with statistically significant p<.05 **Results:** 170 pts with a median age of 70 yrs were included. Of these, 55% were female, 81% had ECOG 0-1 while 19% had ECOG 2-3. 58 pts (35.6%) did not meet at least one eligibility criteria of the clinical trial that led to approved treatment and hence would have been ineligible. Combination chemotherapy (CC group) was used in 64% of pts, immunotherapy alone or in combination with chemo (ICI group) was used in 21% and targeted therapy (TT) in 14%. When stratified based on eligibility criteria in trials, 26% of pts with ECOG 0-1 and 77% of pts with ECOG 2-3 would have been ineligible. By treatment type, 28% of pts in CC group, 60% of pts in ICI group and 41% of pts in TT group would have been ineligible for the specific trial. OS is higher for pts who are eligible (18.7months vs 14.1m; p=.09) and with ECOG 0-1 (30.6m vs 7.3m; p=.16) as compared to pts who are ineligible and with ECOG 2-3. When median OS was compared based on if pts met the eligibility criteria, pts who met criteria had better OS compared to those who did not (18.7m vs 7.3m; p=.008). However, this difference seemed to be limited to pts who received chemotherapy (13.5m vs. 8.1m; p=.03). There were no differences in OS among pts who received ICI (not reached vs. 12.7m; p=.07) or TT (49m vs. 22.8m ; p=.1) **Conclusion:** ICI and TT trials have restrictive eligibility criteria. Interestingly, OS was same for these two groups of pts, regardless of whether they met the eligibility criteria. Pts who met the eligibility criteria for CC trials had better OS compared to pts who did not. Clinical trials have restrictive eligibility criteria and there is a potential for liberalizing these in order to make the clinical trials more generalizable.

P10.02 Improved Survival of Elderly Patients with NSCLC Treated in the Immunotherapy Era: A Historical Cohort Study

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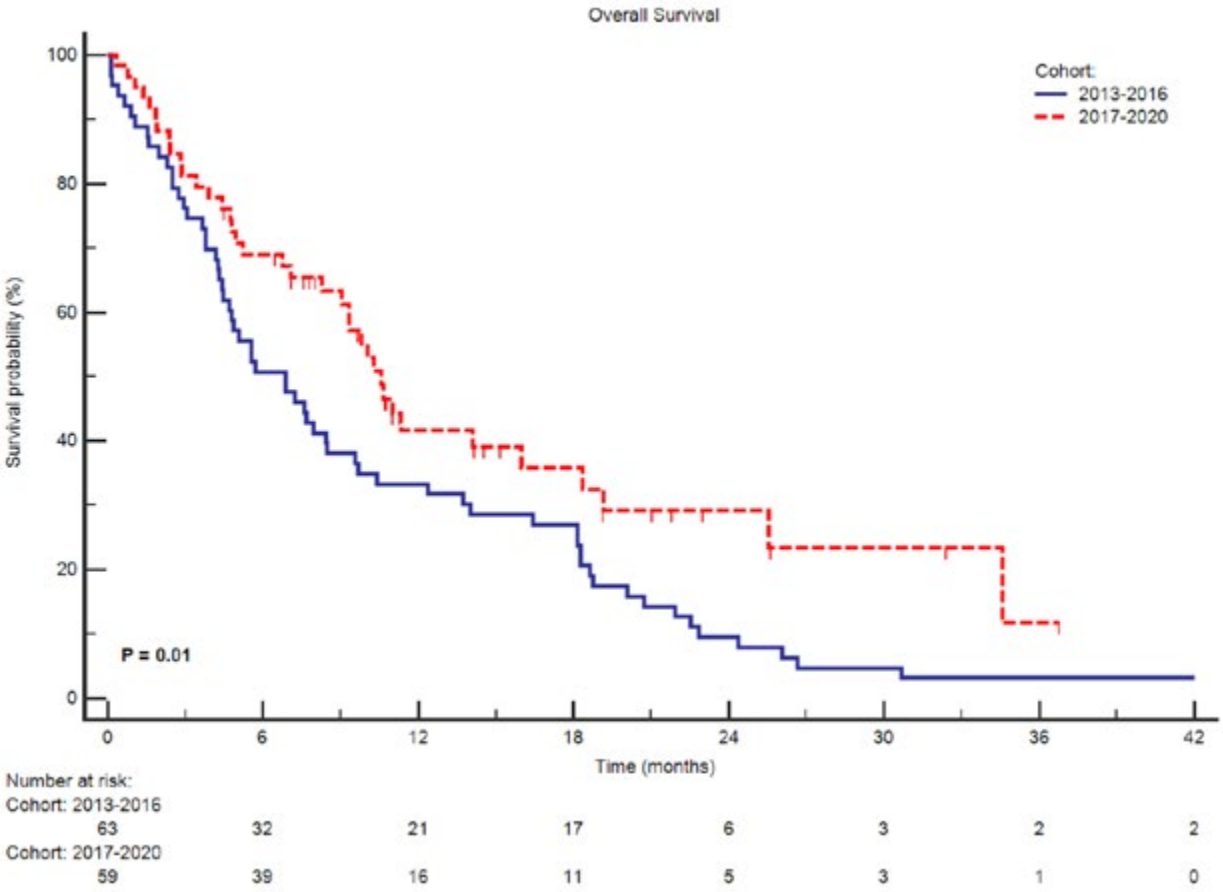
Introduction: Immune checkpoint inhibitors (ICI) have revolutionized the treatment of patients with non-small cell lung cancer (NSCLC). However, elderly patients are often under-represented in clinical trials, and the benefit of ICI in special populations remains unclear. This study aimed to evaluate treatment patterns and survival outcomes of elderly patients with NSCLC treated in the immunotherapy era compared to historical data. **Methods:** We reviewed a consecutive series of elderly patients (age ≥75) diagnosed with stage IIIB-IV non-oncogene addicted NSCLC at the University Hospital of Udine, Italy, from January 2013 to December 2020. Patients were grouped into a historical (HC, 2013-2016) and a contemporary cohort (CC, 2017-2020) according to the year of approval of ICI for the treatment of NSCLC in Italy. Baseline variables, treatment patterns, and overall survival (OS) were compared. **Results:** Overall, 180 patients were included (Table 1). The median age was 80 years (range: 75-93), 78% of patients were stage IV, and 63% had adenocarcinoma. Of note, 25% presented with a PS ≥2, and 24% with a Charlson Comorbidity Index ≥3. At baseline, a greater proportion of patients in the CC received a first-line treatment (76% vs 62%, p=0.04), a second-line treatment (47% vs 32%, p=0.09), and were aged ≥80 years (63% vs. 43%, p=0.009) compared to the HC. Among treated patients, 60% in the CC and 16% in the HC received immunotherapy. A prolonged OS was observed for the CC compared to the HC when considering all patients (8.27 vs. 4.23 months, HR 0.65, 95% CI 0.47-0.89, p <0.01) and those actively treated (10.57 vs. 6.86 months, HR 0.61, 95% CI 0.41-0.92, p =0.01, Figure 1).

Table 1

Subgroups	Whole cohort n=180 (%)	2013-2016 n=102 (%)	2017-2020 n=78 (%)	p
Age range 75-79 ≥80	 87 (48.3) 93 (51.7)	 58 (56.9) 44 (43.1)	 29 (37.2) 49 (62.8)	<0.01
Age cont. (years, median) Min-Max [25-75 percentiles]	80 75-93 [77-83]	78.5 75-89 [76-82]	80 75-93 [79-84]	0.001
Male sex	141 (78.3)	80 (78.4)	61 (78.2)	0.97
KRAS Mutated Wild type Unknown	 49 (27.2) 66 (36.7) 65 (36.1)	 31 (30.4) 31 (30.4) 40 (39.2)	 18 (23.1) 35 (44.9) 25 (32.0)	0.08
PD-L1 TPS 0 1-49% ≥50% Unknown	 24 (13.3) 12 (6.7) 21 (11.7) 123 (68.3)	 1 (0.9) 0 0 101 (99.1)	 23 (29.5) 12 (15.4) 21 (26.9) 22 (28.2)	0.49
Histology Adenocarcinoma Squamous Not otherwise specified	 114 (63.3) 51 (28.3) 15 (8.3)	 66 (64.7) 27 (26.5) 9 (8.8)	 48 (61.5) 24 (30.8) 6 (7.7)	0.80
TNM Stage IIIB IV	 40 (22.2) 140 (77.8)	 25 (24.5) 77 (75.5)	 15 (19.2) 63 (80.8)	0.39
ECOG performance status ≥2	45 (25.0)	23 (22.5)	22 (28.2)	0.43
Liver localizations	15 (8.3)	7 (6.7)	8 (10.2)	0.41
CNS localizations	16 (8.9)	10 (9.8)	6 (7.7)	0.62
Bone localizations	30 (16.7)	20 (19.8)	10 (12.8)	0.22
Adrenal localizations	27 (15.0)	19 (18.6)	8 (10.2)	0.12
Soft tissue localizations	12 (6.7)	6 (5.8)	6 (7.6)	0.63
Pleural effusion	23 (12.8)	11 (10.7)	12 (15.3)	0.36
Charlson Comorbidity Index ≥3	44 (24.4)	27 (26.5)	17 (21.8)	0.47
Charlson Comorbidity Index cont. (median) Min-Max [25-75 percentiles]	1 0-8 [0-2]	1 0-8 [0-3]	1 0-8 [0-2]	0.59
First-line treatment Best supportive care Platinum-based chemotherapy Chemo-immunotherapy Immunotherapy Single-agent chemotherapy	 58 (32.2) 54 (30.0) 1 (0.5) 15 (8.3) 52 (28.8)	 39 (38.2) 34 (33.3) 0 0 29 (28.4)	 19 (24.4) 20 (25.6) 1 (1.2) 15 (19.2) 23 (29.4)	<0.0001
Second-line treatment	44/113 (38.9)	19/60 (31.7)	25/53 (47.2)	0.09
Immunotherapy after first-line	25/113 (22.1)	6/60 (10.0)	19/53 (35.8)	<0.0001



Conclusion: In our cohort, the advent of immunotherapy had a significant impact on survival in elderly patients with NSCLC, with a higher proportion of patients treated at first and second-line.

Keywords: Real-world data, immunotherapy, Elderly patients

P10.03 Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis of Key Prognostic Factors

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Introduction: Immune checkpoint inhibitors alone or in combination with chemotherapy have become standard of care for patients with advanced non-small cell lung cancer (aNSCLC) without driver mutations. This study investigates the real-world performance of immunotherapies in the treatment of patients with aNSCLC. **Methods:** Data on patients diagnosed with aNSCLC between 1/2016 and 9/2020 who received frontline treatment with pembrolizumab alone (IO) or in combination with platinum-based chemotherapy (IO+C) within community health systems were extracted from electronic health records. The Kaplan-Meier estimator was used to assess overall survival (OS) and time-to-next treatment or death (TTNT). **Results:** Of 739 patients, 82% were White and 12% were Black; 79% had non-squamous histology. Brain and liver metastases were documented in 25% and 10% of patients, respectively; 83% of patients' tumors were tested for PD(L)-1, 80% for EGFR, and 74% for ALK. Among patients tested for PD(L)-1, 98% (295) of IO and 69% (217) of IO+C patients' tumors were positive. A greater proportion of IO than IO+C patients were female (52% vs 44%) and fewer had performance status (PS) <2 (44% vs 53%). During the median follow-up of 10 months, 24% of patients received second line therapy and 57% died. IO patients had longer median OS than IO+C patients (Table 1; p=0.02). Median OS was longer for non-squamous than squamous histology in both groups. patients with brain metastases, patients with liver metastases, and patients with PS ≥2 treated with IO had a longer median OS than patients treated with IO+C. TTNT followed a similar pattern. In Cox proportional hazards models adjusted for age, sex, race, year and stage of diagnosis, histology, brain and liver metastasis, smoking, PS, comorbidity and tumor proportion score (TPS), treatment with IO was associated with reduced mortality [HR 0.8; 95% Confidence Interval, (0.6, 1.0); p=0.02] and reduced hazard of initiating next treatment [HR 0.8 (0.7, 1.0); p=0.08]. **Table 1. Summary of findings.**

	IO		IO+Chemo	
	N	Median OS, months [95% CI]	N	Median OS, months [95% CI]
All patients	341	18 [14, 22]	398	13 [11, 15]
Squamous histology	68	12 [7, 18]	86	8 [6, 13]
Non-squamous histology	273	20 [14, 24]	312	15 [12, 17]
Liver Metastases	21	-* [3, -]	51	9 [5, 12]
Brain Metastases	90	14 [5, 18]	95	11 [7, 17]
TPS 1-49%	23	14 [4, 24]	88	11 [8, 17]
TPS ≥50%	194	15 [8, 21]	55	15 [10, 35]
TPS unknown	78	18 [14, -]	74	12 [4, 24]
PS ≥ 2	54	6 [2, 10]	50	4 [2, 6]

*Median OS was not reached. **Conclusion:** In this real-world analysis, frontline IO was associated with longer survival than IO+C. Real-world benefits of IO and IO+C were more modest than reported in clinical trials, particularly in squamous patients. While these findings must be replicated in analyses that control for imbalances in patients characteristics between the two treatment arms, real-world data provide a powerful tool for assessing treatment efficacy outside of the clinical trial setting.

Keywords: Immune checkpoint inhibitors, Survival analysis, Real-world data

P10.04 Immunotherapy-Treated Non-Small Cell Lung Cancer Patients With Sensitizing Gene Alterations: A Real World Survival Analysis

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Introduction: Mutation-specific tyrosine kinase inhibitors (TKIs) have demonstrated efficacy among patients (pts) with advanced non-small cell lung cancer (aNSCLC) with sensitizing gene alterations (GA). It is unclear how effective immune checkpoint inhibitor (ICI) therapy is among NSCLC pts with sensitizing GA, particularly after TKI failure or resistance. **Methods:** Pts with aNSCLC (stages IIIB/IV at diagnoses, or progression to metastatic disease) diagnosed 01/01/2014-06/01/2020 with sensitizing GA in EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, or RET genes were identified in community health systems, with data extracted from electronic health records. All pts were treated with at least one line of TKI. This cohort was assessed for overall survival (OS) in pts who did or did not receive ICI (either as a single agent or in combination with chemotherapy) at any time during their disease course. Sub-analyses were performed for pts with sensitizing GA in EGFR, and for pts treated with ICI after TKI therapy. **Results:** 371 TKI-treated aNSCLC pts with sensitizing GA were included in the analysis, among whom 97 (26%) were treated with ICIs. Sensitizing GA were identified in EGFR (77%), ALK (15%), ROS1 (3%), BRAF (4%), NTRK1/2/3 (<1%), MET (3%), and RET (1%) genes. Pts who were in the ICI-treated vs ICI-naive groups had similar baseline characteristics with respect to histology (non-squamous vs squamous), initial stage at diagnosis, race/ethnicity, and never-smoking history. ICI-treated pts were younger (median age 62 vs 69), and more likely to be men (41% vs 34%). Compared to ICI-naive pts, those with ICI treatment anytime had greater OS for all pts with sensitizing GA (log-rank P=0.125), as well as for pts with EGFR GA (log-rank P=0.016) (Table). Compared to ICI-naive pts, those with ICI treatment after TKI therapy also had greater OS for all pts with sensitizing GA (log-rank P=0.179), as well as for pts with EGFR GA (log-rank P=0.025). **Table 1.**

	ICI-naive			ICI- treated anytime			Log-rank P-value	ICI-treated after TKI			Log-rank P-value
	N	Died	Median OS [95% CI], months	N	Died	Median OS [95% CI], months		N	Died	Median OS [95% CI], months	
All TKI-treated patients	274	159	23.8 [20.7, 28.6]	97	62	33.5 [28.9, 44.4]	0.125	61	42	35.4 [29.7, 50]	0.179
TKI-treated patients with EGFR sensitizing GA	219	137	21.4 [18.7, 26.3]	68	43	35.4 [29.7, 50]	0.016	49	33	41.6 [29.7, 59.8]	0.025

Conclusion: Longer OS was observed in TKI-treated aNSCLC pts with sensitizing GA who received ICI compared to those who did not receive ICI at any point. This was seen within pts with any sensitizing GA, and especially within the subset of pts with EGFR GA. Further analyses into determinants of treatment response in these real world pts should be explored, along with pursuing prospective clinical trials for ICI therapy in pts with aNSCLC and sensitizing GA.

Keywords: Immune checkpoint inhibitors, Survival analysis, Real-world data

P10.05 Adherence to Treatment Recommendations From Multidisciplinary Tumor Boards

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Introduction: Due to the German National Cancer Plan, cancer centers have been established. Lung cancer centers are responsible for coordinating the care of lung cancer patients in a region and to diagnose and treat them according to the latest evidence-based knowledge. For this purpose, every patient should be discussed in a multidisciplinary tumor board. In the tumor board an individual treatment plan is discussed and treatment recommendations are given. Therefore, we investigate: 1.) how are the recommendations from tumor boards being adhered to; 2.) which factors determine the adherence of tumor board recommendations and 3.) what is the relationship between the adherence of tumor board recommendations and patient outcomes in terms of overall survival? **Methods:** Data from 1784 newly-diagnosed patients with lung cancer discussed in tumor boards in one certified lung cancer center in Northern Germany between 2014 and 2018 were documented and evaluated according to the adherence to tumor board recommendations. An analysis of the first 386 cases analyzed will be presented. Data was analyzed descriptively. **Results:** Median age of the 386 patients was 66 years (26-91 yrs) and 64% (n=247/386) of them were male. Most of the patients had an ECOG status of 0 or 1 (78%; n=301/386) and 87% of them were current or ex heavy smoker (n=335/386). 70% (n=267/386) of the patients that have been discussed in the multidisciplinary tumor board, were afterwards further treated at the same certified lung cancer center. In 79% (n=304/386) of patients, the treatment recommendations from the multidisciplinary tumor boards were completely adhered to. There were different reasons for non-adherence, e.g. patient's wish, patient characteristics and death before starting therapy. The median overall survival for the 386 patients was 13 months. Patients with a complete adherence to the multidisciplinary tumor board recommendation had an overall survival of 16 months (n=304) compared to 5 months (n=41) for patients with a partial adherence compared to 1 months (n=33) for patients with a non-adherent treatment ($p<0.001$). **Conclusion:** Preliminary results give a hint to the fact that patients with an adherent treatment after first diagnosis had a longer overall survival than patients with another therapy. More cases will be presented at the meeting using a multivariate analysis which includes patient characteristics and healthcare organizations that took over further treatment as predictors. Furthermore, the findings can be used to design interventions that improve the adherence of multidisciplinary tumor board recommendations in outpatient oncology care, optimize the quality of care, and thus potentially make a significant contribution to the implementation of the German cancer plan.

Keywords: multidiscplinary tumor board, lung cancer, adherence

P10.06 Affiliation to the Labour Market in Denmark for Patients Under 60 Years of Age After Diagnosis and Treatment for ALK-Positive NSCLC

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Introduction: Lung cancer is among the most common types of cancers in Denmark. Each year, approximately 4.600 patients are diagnosed with lung cancer and 3700 die from the disease. The majority of patients are diagnosed with NSCLC (85 %) and adenocarcinoma is the most common subtype accounting for about 40 % of NSCLC It is estimated that about 2 % of NSCLC patients in Denmark have ALK positive NSCLC **Methods:** This is a national non-interventional retrospective study. The inclusion criteria for the study group were ALK-positive NSCLC patients in Denmark diagnosed in the period 1st of January 2012 to 31st of December 2018. The individuals were identified from the National Pathology Registry (Patobank) (3). Thus, this study represents the entire diagnosed Danish ALK-positive patient population in the study period. Data were extracted from the National registries with permission from Danish Patient Safety Authority and the Danish Data Protection Agency. Based on the year of diagnosis each patient was matched by age, sex, education and location of residence region with ten controls who were otherwise randomly selected. All Danish citizens have a 10-digit personal identification number, given at birth or immigration. The personal identification number is a unique personal identifier recorded in all public registries, thus allowing linkage between these registries. Accordingly, we were able to describe the total mortality, health costs (hospital costs), sociodemographic variables (marital status, grades in school and labour market affiliation) of the patient and the control group. Labour market affiliation was classified into the following categories: in work, subsidized pensions, and died or left the country. **Results:** A total of 230 patients were identified. Of these, 25 patients were excluded as they did not meet the inclusion criteria. Of the remaining 205 patients, three patients were excluded based on chart reviews and three patients were not present in National registries. Thus, the final register study population was 199 patients with ALK-positive NSCLC. In the age group under 60 years of age we identified 61 patients with ALK-positive NSCLC and 606 controls. The number of ALK-positive NSCLC patients working decreases in the 6 months before diagnosis, with a corresponding increase in the number of subsidized patients (table). The number of patients working decreases further in the 6 months following diagnosis, after which it increases slightly. In contrast, the labour market affiliation in the control group is relatively stable. **Conclusion:** Patients under the age of 60 years with ALK-positive NSCLC have a significantly lower affiliation to the labor market at the time of diagnosis and 6, 12 and 18 months afterwards compared to a matched control group.

Keywords: Affiliation to the labour market, ALK postive NSCLC

P10.07 Real-World US Treatment Patterns and Clinical Outcomes in Advanced NSCLC After Prior Platinum Chemotherapy and Immunotherapy

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Introduction: Immune checkpoint inhibitor (ICI) therapy and platinum-based doublet chemotherapy (PDC), combined or sequentially, are the standard of care for treatment-naive patients with metastatic non-small cell lung cancer (NSCLC) without targetable driver mutations. Upon failure of these, there is a lack of data on physicians' treatment choices in this setting and their real-world effectiveness. This retrospective, observational study evaluated real-world treatment patterns and outcomes within US community oncology settings in this recently emerged post-ICI/PDC patient population. **Methods:** This study used the nationwide electronic health record (EHR)-derived de-identified Flatiron Health NSCLC database. Patients included were ≥18 years of age, diagnosed with advanced/metastatic NSCLC between January 1, 2015 and February 29, 2020. Patients were required to have had previous treatment for their advanced disease with ICI and PDC, either combined in first line (1L) or sequentially in 1L and second line (2L), and to have received treatment post-ICI/PDC. Patients were excluded if they had evidence of EGFR or ALK alterations. Patient characteristics and treatment patterns were assessed. Overall survival (OS) was estimated using Kaplan–Meier analyses and was defined as the time from the initiation of subsequent treatment following ICI and PDC until death (event) from any cause or patient censoring on the last date of activity in the Flatiron database due to lack of an event, whichever occurred first. Additional analyses by subgroups, such as histological subtype and previous ICI/PCD treatment sequence, were also conducted. **Results:** Among the 2294 patients who met the study eligibility criteria, their median age was 66 years (range: 59-73), 43.0% (n=987) were female, and 93.0% (n=2134) were treated in community-based settings. Most patients (63.2%, n=1449) had received 1L PDC followed by 2L ICI, 29.6% (n=680) 1L ICI plus PDC, and 7.2% (n=165) received 1L ICI followed by 2L PDC. Of the total sample, 29.0% (n=674) of patients received regimens containing docetaxel, mainly in combination with ramucirumab (15.0%, n=344), or as monotherapy (11.0%, n=251). The median OS was 7.29 months (95% CI, 6.90-7.66) in the overall population, 6.47 months (95% CI, 5.59-7.56) with docetaxel plus ramucirumab, and 6.74 months (95% CI, 5.65-8.48) with docetaxel monotherapy. **Conclusion:** This study reports real-world treatment patterns and survival outcomes in patients with advanced/metastatic NSCLC post-ICI/PDC. These real-world results from EHRs for patients primarily treated in community settings indicate a high unmet need for new therapies that could potentially improve outcomes in patients with advanced/metastatic NSCLC post-ICI/PDC.

Keywords: Advanced NSCLC, post-ICI and PDC, real-world evidence

P10.08 Comparing Lung Cancer in Never Smokers and Ever Smokers in Asian or Asian American Patients Treated at a Tertiary Urban Public Hospital in New York

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Introduction: The higher incidence of targetable mutations in Asian patients with lung cancer clearly suggests potentially different risk factors and underlying biology. Most of the studies regarding lung cancer in Asian patients were conducted in Asia, but limited data is known about Asian or Asian American patients in the U.S. While current lung cancer screening guidelines only affect smoker populations, expanding screening to other high risk populations is of interest. The purpose of this study is to assess various characteristics of Asian or Asian American lung cancer patients at a public hospital in New York. **Methods:** This study was conducted as a single institution IRB-approved retrospective cross-sectional study of all patients with lung cancer who are of Asian or Asian American heritage from 01/2010 to 12/2019. Demographics, smoking history, family history and clinical information including pathology were assessed and analyzed. The differences in participant characteristics were calculated using a Student T-test and rates of lung cancer and mutations were calculated with the Chi-squared statistic. **Results:** Of 166 Asian or Asian American patients diagnosed with lung cancer, 59 (36%) were never smokers, 100 (60%) were ever smokers, and 7 (4%) patients had unknown smoking history. Age at diagnosis were no different between never smokers and ever smokers (60±11.0 vs. 63.1±11.1 years, t-test p=ns), and among women there also was no difference in age between never smokers and ever smokers (61±10.8 vs. 66.5±9.6, p=ns). 44/59 (74.6%) of the never smokers were female compared to 8/100 (8%) in ever smokers (Chi-squared p<0.0001). 46/166 (28%) patients had any family history of cancer, with 13/166 (8%) having a family history of lung cancer. Family history of lung cancer in a mother, brother, or sister in never smokers was twice as high than that of ever smokers, but did not reach statistical significance (8.5% vs. 4.2%, p=ns). Stage at diagnosis comparing never vs ever smoker patients was 27.6% vs. 11.1%, (p<0.01) for stage I, 3.5% vs. 10.1% (p=ns) for stage II, 12.1% vs. 13.1% (p=ns) for stage III, and 55.2% vs. 62.6% (p=ns) for stage IV. Rates of EGFR or ALK mutations was 75% in never smokers and 33.3% in ever smokers (p<0.001). Specifically, EGFR mutations were detected in never smokers at 65.9% vs. in ever smokers at 33.3%, (Chi-squared p<0.01) and ALK fusions detected at 9.1% in never smokers vs. none in the ever smokers (p<0.05). **Conclusion:** Most of our understanding of lung cancer in Asian patients comes from data collected in Asia but less is known about lung cancer in Asians and Asian Americans in the United States and particularly on the East Coast. We found a significantly higher number of women diagnosed with lung cancer in the never smokers compared to ever smokers, and higher rates of EGFR and ALK mutations. An association with family history in certain family members with lung cancer was also observed although not significant likely due to small numbers of patients. Identifying and recognizing potential risk factors in this population could lead to additional screening guidelines particularly for Asian female never smokers.

Keywords: Asian American, EGFR mutation

P10.09 Efficacy and Toxicity of EGFR-TKI in Frail NSCLC with EGFR Mutation: A Retrospective Analysis in a Single Institution

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Introduction: EGFR-TKI is the standard treatment of care for sensitizing EGFR mutation-positive advanced non-small lung cancer (NSCLC) patients. However, the treatment strategy of first-line EGFR-TKI for frail patients has not been well established yet. In current NCCN guideline, osimertinib is preferred as first-line therapy for sensitizing EGFR mutation-positive patients regardless of their age and ECOG performance status (PS), while Japan Lung Cancer Society guideline 2020 recommends first generation EGFR-TKIs for the patients with PS 2-4. According to ASCO guideline 2021, patients with sensitizing EGFR mutation and PS 3 may be treated by EGFR-TKI monotherapy with the choice dependent on access and toxicity profile of each agent. **Methods:** We retrospectively examined 73 EGFR mutation-positive NSCLC patients of PS 2-4 or aged >75 years, who started first-line therapy of EGFR-TKI after 1st April 2015 at Osaka Toneyama Medical Center. Our aim in this research was to investigate the safety and efficacy of first-line EGFR-TKI therapy for EGFR mutation-positive NSCLC with PS 2-4 or elderly patients. Adverse events were evaluated according to the NCI-CTCAE ver.5, and the efficacy was assessed on the basis of the RECIST, ver1.1. Time to treatment failure (TTF) was defined as the days from first dose of EGFR-TKI until treatment discontinuation for any reason, and overall survival (OS) as the days from first dose until death or final follow-up. **Results:**

Patients Backgrounds				
		Osimertinib, n=19	Other TKI, n=54	
Age	≥75	17	49	
	<75	2	5	
Gender	Male	7	27	
	Female	12	27	
PS	0-1	9	31	
	2-4	10	23	
EGFR	common	18	48	
	uncommon	1	6	
Results				
Response	CR	1	0	
	PR	12	38	
	SD	2	3	
	PD	1	12	
	NE	3	1	
Response Rate		68.4%	70.3%	
Severe Adverse Events	No	8	41	
	Yes	11	13	P<0.05
TTF, Days (median)	(95% C.I.)	322 (86-702)	412 (193-493)	
	PS 0-1	646 (101-NA)	440 (206-570)	P=0.915
	PS 2-4	86 (11-NA)	332 (77-594)	

Details of severe adverse events were as below; ILD 4 (osimertinib only), liver damage 4 (osimertinib 1), skin toxicity 4 (osimertinib 2), diarrhea 4 (osimertinib 1), depression 2 (osimertinib only), QT prolongation 1(osimertinib), anorexia 1 (osimertinib). **Conclusion:** This research showed that frail patients with EGFR mutation had significantly higher possibility to develop severe adverse event during first-line therapy of osimertinib than other EGFR-TKIs.Patients with good PS (all of them were fit-elderly) who were treated by osimertinib showed better TTF than those with good PS by other EGFR-TKIs. To the contrary, patients with poor PS who received osimertinib had shorter TTF than those who were treated by other EGFR-TKIs. This result suggested that patients with PS 2-4 who received osimertinib were higher likely to experience severe adverse events at early period than patients treated by other EGFR-TKIs. First-line therapy of osimertinib could not be recommended for frail patients with PS 2-4.

Keywords: frail patients, 1st-line EGFR-TKI, adverse events

P10.10 Trends in Treatment Patterns and Survival in Advanced NSCLC Patients Treated at Frankfurt University Hospital in 2012–2018

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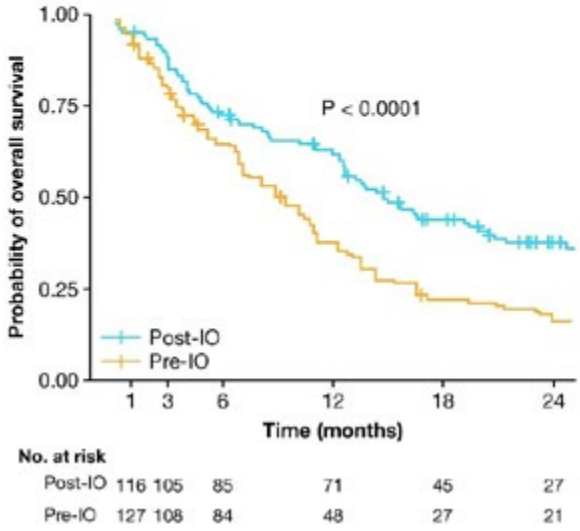
Introduction: Immuno-oncology (IO) therapy has improved outcomes for patients with advanced non-small cell lung cancer (NSCLC) versus chemotherapy in clinical trials. In Germany, immune checkpoint inhibitors have been used clinically since 2015 for patients with advanced/metastatic NSCLC without ALK/EGFR aberrations. As part of I-O Optimise, a multinational research program utilizing real-world data on thoracic malignancies, we describe the evolution of treatment patterns and overall survival (OS) for patients with advanced NSCLC treated at Frankfurt University Hospital (FUH) following the availability of IO therapies. **Methods:** This retrospective cohort study included patients with NSCLC without ALK/EGFR aberrations who received their first line (1L) of therapy at FUH between January 2012 and December 2018, with follow-up to December 2019 or death, whichever occurred first. Treatment patterns and OS are described based on histology (squamous [SQ] vs non-squamous and other [NSQ+O]) and time period (pre-IO, >12 months before anti-PD(L)1 approval as second-line [2L] therapy, vs post-IO, after anti-PD(L)1 approval as 2L therapy). Index date was the date of 1L treatment receipt. Patients receiving 1L treatment in the year between the pre-IO and post-IO periods were excluded. **Results:** During the study period, 136 (pre-IO) and 126 (post-IO) patients with NSQ+O histology and 32 (pre-IO) and 38 (post-IO) patients with SQ histology started 1L therapy. Baseline patient characteristics were similar between the pre-IO and post-IO periods; median (IQR) follow-up from 1L treatment was 9.3 (3.7-16.6) and 12.7 (4.8-20.9) months, respectively. Among NSQ+O patients, 6% received an IO therapy in the pre-IO period (all as 2L+) versus 57% in the post-IO period (22% as 1L: 13% IO monotherapy, 9% IO + chemotherapy). Median (95%CI) OS increased from 9.4 (7.1-11.1) months pre-IO to 14.8 (12.7-20.5) months post-IO. 2-year OS rate (95%CI) increased from 17% (12-25) pre-IO to 37% (29-48) post-IO (Figure a). Among SQ patients, 3% received an IO therapy in the pre-IO period (as fourth-line treatment) versus 53% in the post-IO period (29% as 1L: 16% IO monotherapy, 13% IO + chemotherapy). Median OS (95%CI) was 12.7 (9.2-18.3) months pre-IO and 10.9 (7.6-16.8) months post-IO; 2-year OS rate (95%CI) was 17% (8-38) and 15% (6-34), respectively (Figure b). **Conclusion:** These real-world results support clinical trial data on the effectiveness of IO therapies for patients with advanced NSCLC and NSQ histology in clinical practice in Germany. A larger sample size and longer follow-up are needed to better understand the impact of IO therapies in patients with SQ histology

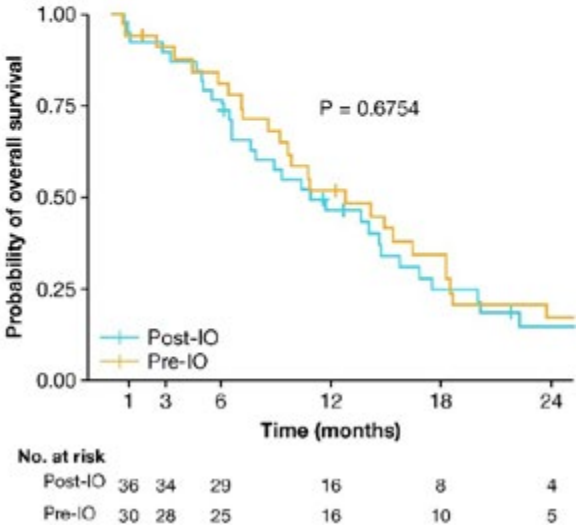
(a)

	Pre-IO N = 136	Post-IO N = 126
Censored, n (%)	15 (11)	49 (39)
Median OS, months (95% CI)	9.4 (7.1–11.1)	14.8 (12.7–20.5)
6-month OS, probability (95% CI)	0.65 (0.57–0.73)	0.72 (0.65–0.81)
12-month OS, probability (95% CI)	0.38 (0.30–0.47)	0.62 (0.54–0.71)
18-month OS, probability (95% CI)	0.22 (0.16–0.30)	0.44 (0.36–0.54)
24-month OS, probability (95% CI)	0.17 (0.12–0.25)	0.37 (0.29–0.48)



(b)

	Pre-IO N = 32	Post-IO N = 38
Censored, n (%)	5 (16)	7 (18)
Median OS, months (95% CI)	12.7 (9.2–18.3)	10.9 (7.6–16.8)
6-month OS, probability (95% CI)	0.91 (0.81–1.00)	0.76 (0.64–0.91)
12-month OS, probability (95% CI)	0.52 (0.37–0.73)	0.46 (0.33–0.66)
18-month OS, probability (95% CI)	0.34 (0.21–0.56)	0.25 (0.14–0.44)
24-month OS, probability (95% CI)	0.17 (0.08–0.38)	0.15 (0.06–0.34)



Keywords: observational cohort study, Real-world data, immune checkpoint inhibitor

P10.11 Real-World Experience With Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer at Frankfurt University Hospital

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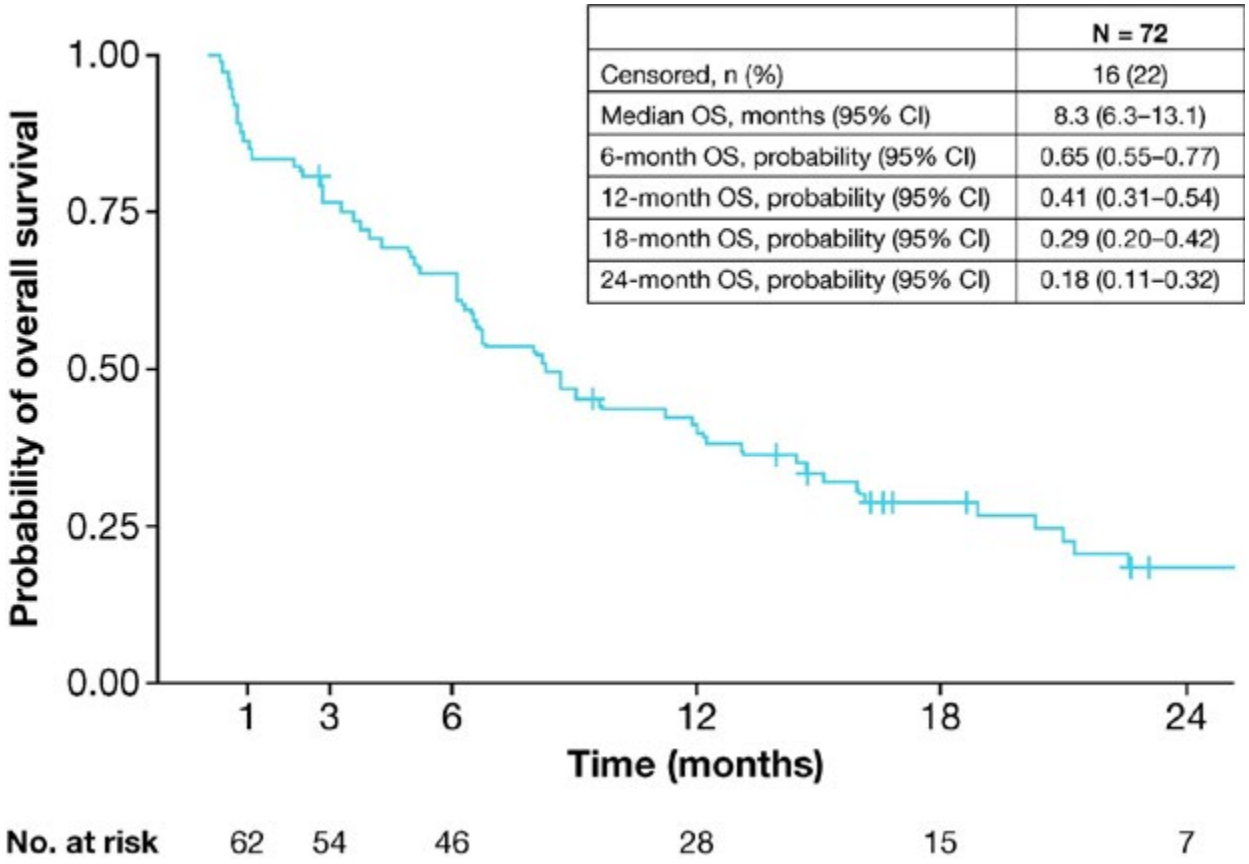
Introduction: In Germany, immune checkpoint inhibitors, including nivolumab, have been reimbursed for the second-line treatment of patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) without a confirmed anaplastic lymphoma kinase or epidermal growth factor receptor aberration since 2015 (for squamous carcinoma [SQ]; since 2016 for non-squamous carcinoma [NSQ]). Here, we describe the real-world clinical characteristics and overall survival (OS) of patients treated with nivolumab at Frankfurt University Hospital (FUH) from 2012–2019 as part of I-O Optimise, a multinational research program utilizing real-world data on thoracic malignancies. **Methods:** This retrospective cohort study included adult patients with locally advanced/metastatic NSCLC (incident stage IIIB/IV or progressed stage I–IIIA, per tumor, node, metastasis [TNM] staging) who were diagnosed between 2012 and 2018 and received nivolumab at FUH between January 2012 and December 2019, with follow-up to December 2019 or death, whichever occurred first. Change in line of therapy was defined as a change of systemic anticancer therapy regimen following progression. OS was evaluated using Kaplan–Meier methodology. **Results:** During the study period, 72 patients received nivolumab at FUH. At diagnosis, 63.9% were male; 90.3% had TNM stage IIIB/IV disease; 70.8% had NSQ, and 22.2% had SQ. At the start of nivolumab treatment, median (interquartile range [IQR]) age was 65.5 (58.0–70.0) years, 80.6% had an Eastern Cooperative Oncology Group performance score of 0–1, and 38.9% had brain metastases. 54.2% of patients were programmed death ligand 1 (PD-L1) positive (16.7% had PD-L1 ≥50%), 23.6% were PD-L1 negative, and 22.2% were not tested. 43.1% of patients started nivolumab treatment in 2018–2019. In the overall population, the median (IQR) follow-up from first nivolumab treatment was 8.3 (2.8–16.1) months. Nivolumab was received in the second-line and third- or later-line setting by 65.3% and 23.6% of patients, respectively. Overall, median OS (95% CI) was 8.3 (6.3–13.1) months; 1-year OS rate (95% CI) was 41% (31–54) (Figure). **Conclusion:** These OS results are consistent with outcomes of clinical trials and other real-world studies, and support the effectiveness of nivolumab as monotherapy for patients with previously treated advanced NSCLC in clinical practice in Germany. Future work will explore longer-term OS in this patient cohort



	N = 72
Censored, n (%)	16 (22)
Median OS, months (95% CI)	8.3 (6.3–13.1)
6-month OS, probability (95% CI)	0.65 (0.55–0.77)
12-month OS, probability (95% CI)	0.41 (0.31–0.54)
18-month OS, probability (95% CI)	0.29 (0.20–0.42)
24-month OS, probability (95% CI)	0.18 (0.11–0.32)

Keywords: NSCLC, real-world evidence, Nivolumab

P10.12 A Thorough Look at the Clinical Characteristics and Disease Burden of Lung Cancer Patients in Chinese County Area

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Introduction: Identifying the epidemiology and clinical characteristics of malignant tumors is helpful for early screening and interference. Lung cancer is one of the most common primary malignant tumors which led to high medical costs on the treatment and care. Previous literatures mainly focus on the per time or per capita cost of lung cancer patients, and the full cycle cost for lung cancer treatment remain lacked. Besides, there is still a lack of real world data from counties and remote areas. Thus, this study aimed to investigate the clinical characteristics, treatment patterns and economic burden of lung cancer inpatients from county areas in western China. **Methods:** A retrospective, observational study was conducted at Yunyang county hospital, Wanzhou district, Chongqing municipality. Lung cancer patients admitted to the hospital from Jan 2018 to Aug 2020 were selected. Data were extracted from the medical records. The demographic characteristics, clinical characteristics, clinical outcomes, medical resources consumption and disease costs of patients hospitalized for lung cancer were analyzed. A series of appropriate statistical tests were applied to the study population to examine the various outcomes. All analysis conducted with statistical analysis software R(version 3.5). **Results:** A total of 332 patients with lung cancer were finally included in the study. The average age of lung cancer patients at first diagnosis was 62.8 years old with 76.8% of male patients. 43.1% of them were farmers and 62.0% of them had a long smoking history. Of all the patients, 222 had metastatic tumors, mainly to bone, brain and liver. 181 (54.5%) patients received chemotherapy, 63 (19.0%) received targeted therapy, and only 6 (3.0%) received immunotherapy. 37 (11.1%) patients died in hospital, and the median survival time of these patients was only 0.8 years. The most common chemotherapy regimens were etoposide regimen (30.9%), paclitaxel regimen (26.0%) and docetaxel regimen (23.2%), the most common drug in targeted therapy was gefitinib (54.0%), and the most common drug in immunotherapy was camrelizumab (66.7%). The median hospitalization times of lung cancer patients was only 1, and the median hospital stay per capita was 8 days. Among 112 patients with definite tumor stage information, stage IV patients accounted for the largest ratio (59.8%). The total hospitalization cost of lung cancer patients was $1695.0 (778.5-4429.0) per person, and the average hospitalization cost was $811.2 (523.0-1434.5) per time, with the out-of-pocket rate accounting for about 28.1%. The relatively high itemized costs included western medicine expenses, imaging expenses, laboratory expenses and medical service expenses. **Conclusion:** Low early screening rate and high mortality of lung cancer are still common in county areas of western China. A depressingly high percentage of patients were presented in late stages and thus inoperable. Chemotherapy is still the main treatment for lung cancer patients in county, and most patients receive late palliative care only in the county. Thus, it is very necessary to strengthen the construction of tumor diagnosis and treatment in the county and improve the prognosis of lung cancer patients.

Keywords: disease burden, Chinese county, clinical characteristics

P10.13 Real World Outcomes for Non Small Cell Lung Cancer Treated With Checkpoint Inhibitors in Lebanon, A Multicenter Observational Study

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Introduction: Immunotherapy (IO) provides improved treatment efficacy and survival in NSCLC patients. However, data on this treatment are released from clinical trials. There is a need for a real world data experience in IO in Lebanon. The type of metastasis in for telling of response results still well unknown currently. **Methods:** In this retrospective study, 124 patients were enrolled, all were stage IIIB/IV NSCLC who received IO with nivolumab, pembrolizumab or atezolizumab at any line of treatment, and were recruited between February 2012 and august 2020. Patients with no follow up or available data, or those who received less than 6 cycles of IO were excluded. IO was continued until progression, death or unacceptable toxicity. Primary endpoints were overall survival (OS) and progression free survival (PFS) from start of IO. PFS1 or PFS2 are defined as duration from starting 1st or 2nd lines of treatment respectively to progression. for Secondary endpoints include immune related toxicity. Multivariable analysis was made on correlation of metastasis type and survival. **Results:** Across two Lebanese medical institutions (Mount Lebanon Hospital and Hotel Dieu de France Hospital-Saint Joseph university), we screened 140 patients, and included 124 patients who met the inclusion criteria. Median age at diagnosis was 69 years old, 28.5% were female, and 68.6% were at stage IV, 67.6% had adenocarcinoma and 32.4% had squamous cell carcinoma. Site of metastasis found were bone (22.8%), adrenal (20.3%), pleural (17.1%), brain (11.4%), liver (5.9%), and other (12.2%). Most patients (58.1%) had received chemotherapy alone and 41 % received immunotherapy at first line. At second line, majority of patients (77.1%) received immunotherapy. Median PFS1 was 7.55 months. Median PFS2 was 8.8 months. But no significant difference association was found between those who received chemotherapy and those who received immunotherapy as a first line (HR=1.63; p=0.542; 95% CI 0.34-7.79) or as a second line (HR=0.53; p=0.189; 95% CI 0.21-1.36). Rash was the most frequent immune related adverse events observed (16.13%) followed by pneumonitis (10.48%). No grade 3 or 4 immune related adverse events were seen during follow-up. Median OS was 14 months. A shorter overall survival was seen in patients who had bone metastasis (HR=3.23; p=0.002; 95% CI 1.53-6.82), but not those who had adrenal, brain or liver metastasis **Conclusion:** In real world, IO was well tolerated and our Lebanese data is comparable to international data. Concerning sites of metastasis and association with clinical outcome, we hypothesize that bone metastasis may influence efficacy to immunotherapy

P10.14 ctDNA and Real-World Response (rwR) in Patients With Lung Cancer From a Prospective Real-World Clinico-Genomic (PCG) study

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Introduction: Prospective real-world data studies integrated into routine clinical workflows can capture multimodal longitudinal data in patients (pts) with cancer treated in community settings. One modality is circulating tumor DNA (ctDNA), a minimally invasive, readily available test for genomic profiling, investigating resistance or monitoring disease. Using the PCG study platform to prospectively collect and link real-world clinico-genomic, imaging and outcomes data, this exploratory analysis assessed the association of longitudinal ctDNA measurement and clinical response. **Methods:** Eligible pts had metastatic NSCLC or extensive-stage SCLC and initiated systemic antineoplastic treatment, regardless of therapy line, in the Flatiron Health Network. Following consent, clinical data were collected from a nationwide Flatiron Health electronic health record (EHR)–derived de-identified database, including clinician documented assessment of disease burden change (rwR; data cutoff Sep 1, 2020). ctDNA profiling was done using FoundationOne® Liquid before treatment start, on-treatment (±14 days of first tumor assessment) and at end of therapy. In this analysis, pts had ctDNA results for ≥2 timepoints and ≥1 rwR assessment. ctDNA levels were estimated using composite tumor fraction (cTF), a metric based on aneuploidy and variant allele fraction. **Results:** As of Dec 31, 2020, 585 pts were enrolled. In the current analysis of 123 pts (31 SCLC, 92 NSCLC), median age was 67 y, 96% were current/former smokers and 70% initiated 1L therapy. Of the 92 pts with NSCLC, 73% had non-squamous (NSq) histology. Prior to therapy, median cTF was 4% (IQR, 1, 23) and was higher in SCLC vs NSCLC (49% [IQR, 5, 66] vs 2% [1, 14]; P<0.001), with 1% (0, 5; n=67) in NSq and 4% (1, 24; n=25) in Sq NSCLC (P<0.05). A significantly greater reduction in median % change in cTF on treatment from baseline was seen in pts with an rwR (rwPR, rwCR) vs those without an rwR (rwSD, rwPD) (Table) for all pts with SCLC and pts with NSCLC who had cTF of ≥1% (P<0.05).

Enrollment cTF	Pts, n	Median cTF % change (IQR)	Pts, n	Median cTF % change (IQR)
	Responder		Non–responder	
NSCLC				
All	52	-49 (-94, 12)	40	-3 (-61, 52)
≥ 1%	33	-88 (-98, -32)	30	-7 (-57, 41)
< 1%	19	27 (-22, 67)	10	15 (-79, 81)
SCLC				
All	25	-97 (-98, -76)	6	-20 (-65, -3)
≥ 1%	25	-97 (-98, -76)	5	-34 (-76, -2)
< 1%	0	0	1	-6

Conclusion: Preliminary data showed that serial ctDNA assessment in the PCG study is feasible. Pts with SCLC shed higher levels of ctDNA than pts with NSCLC, and those with rwR had strong cTF reductions close to clearance. Pts with NSCLC had varied levels of cTF at baseline and reduction in cTF, with an rwR occurring in higher ctDNA shedders. Our data encourage further studies using ctDNA response and rwR assessments to study treatment effects, early predictors for clinical outcome and to gain biological insights in the real-world setting.

Keywords: ctDNA, real-world response, prospective study

P11.01 Phase I Trial of in Situ Vaccination With Autologous CCL21-Modified Dendritic Cells (CCL21-DC) Combined With Pembrolizumab for Advanced NSCLC

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Introduction: Effective immunotherapy options are lacking for patients with advanced non-small cell lung cancer (NSCLC) who progress on a programmed cell death-(ligand)1 [PD-(L)1] inhibitor and for those that are epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement positive after progression on tyrosine kinase inhibitor (TKI) therapy. One potential approach to improve immune checkpoint efficacy in these patient populations is to promote cytolytic T cell infiltration into tumors. This can be accomplished via in situ vaccination with functional antigen presenting cells (APCs) which can take advantage of the full repertoire of tumor antigens and convert the tumor into a lymph node-like environment promoting both local and systemic T cell activation. The chemokine CCL21 promotes co-localization of naive T cells and antigen-experienced dendritic cells (DCs) to facilitate T cell activation. Our preclinical studies and phase I trial of intratumoral (IT) administration of DC genetically modified to overexpress CCL21 (CCL21-DC) revealed augmentation of tumor antigen presentation in situ, resulting in effective T cell responses and systemic antitumor immunity. However, increased PD-L1 expression was observed in a subset of patient tumors, suggesting that tumor-mediated impairment of T cell function may be forestalling a more robust CCL21-DC mediated antitumor response. Similarly, improved PD-(L)1 inhibitor efficacy may be possible with enhanced T cell infiltration and augmented APC function following IT CCL21-DC. Therefore, we are conducting a phase I trial, combining IT CCL21-DC with pembrolizumab in patients with advanced NSCLC that are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. **Methods:** This is a phase I, single institution, non-randomized, dose-escalating, multi-cohort trial followed by dose expansion. A maximum of 24 patients (9-12 escalation + 12 expansion) with stage IV NSCLC will be evaluated who have tumors accessible for IT injection and are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. Three IT injections of autologous CCL21-DC (days 0, 21, 42) will be concurrently administered with pembrolizumab, followed by q3wk pembrolizumab up to 1 year. Primary objective of dose escalation is safety and determination of maximum tolerated dose (MTD) of IT CCL21-DC (5x106, 1x107, or 3x107) when combined with pembrolizumab. Primary objective of dose expansion is objective response rate (ORR) of CCL21-DC at MTD combined with pembrolizumab. Secondary objectives include adverse event profiling and determination of drug target activity by immune monitoring studies. This trial, NCT03546361, is currently open for enrollment.

Keywords: In Situ Vaccination, NSCLC, immunotherapy

P11.02 Targeting the Tumor Neovasculature in Lung Cancer: A Phase I Study of AMG 160 in Subjects With Non-Small Cell Lung Cancer

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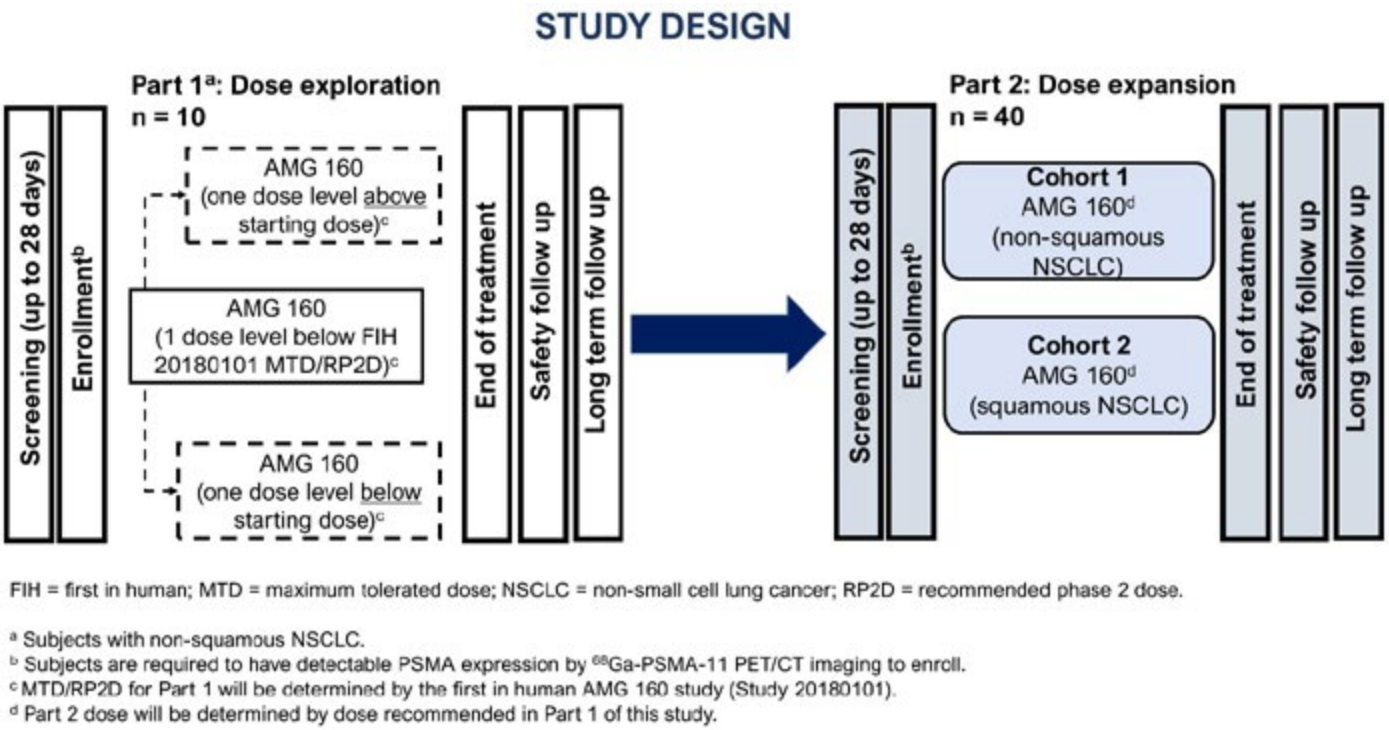
Introduction: Despite recent therapeutic advances, patients with relapsed/refractory non-small cell lung cancer (R/R NSCLC) have a dismal prognosis and there is an unmet need for more effective treatment options. AMG 160 is a half-life extended (HLE) BiTE® (bispecific T-cell engager) molecule that simultaneously binds prostate specific membrane antigen (PSMA) on tumor cells and CD3 on T cells to drive T cell-mediated lysis of tumors. The encouraging benefit-risk profile observed in an ongoing trial of AMG 160 in patients with metastatic castration-resistant prostate cancer (mCRPC) (NCT03792841) suggests a potential application for AMG 160 in patients with other PSMA-expressing tumors. In non-squamous NSCLC, PSMA is selectively expressed on the surface of endothelial cells in tumor-associated neovasculature and on the surface of endothelial and tumor cells in squamous NSCLC. Recent published studies confirm that between 49%–85% of NSCLC tumor neovasculature express PSMA. Binding of AMG 160 to PSMA-expressing neovasculature and the resulting T cell-mediated lysis may promote an anti-angiogenic effect and facilitate immune cell infiltration leading to inhibition of tumor growth. **Methods:** Primary objectives of this open-label, phase 1b study are to evaluate the safety, tolerability, and the maximum tolerated dose or the recommended phase 2 dose of AMG 160 in adults with R/R NSCLC (primary endpoints: dose limiting toxicities, adverse events); secondary objectives are to evaluate pharmacokinetics (PK) and anti-tumor activity (secondary endpoints: PK parameters, objective response as per modified RECIST 1.1 criteria, overall survival, progression-free survival, time to response or progression, duration of response). This trial will also evaluate the immunogenicity of AMG 160 and exploratory biomarkers. AMG 160 will be administered as a short-term IV infusion in a 28-day cycle until loss of clinical benefit. Key inclusion criteria: age ≥18 years; R/R, histologically confirmed stage 4 or recurrent NSCLC; evidence of progressive disease after chemotherapy and anti-PD-1 or anti-PD-L1 therapy in patients without a druggable driver mutation, or progressive disease after targeted therapies in patients with driver mutations. Detectable PSMA expression by ^{68}Gallium-PSMA-11 PET/CT imaging, and an ECOG score of 0–2 are additional key inclusion criteria. Key exclusion criteria: presence of symptomatic brain metastases, active autoimmune disease, diseases requiring chronic systemic corticosteroid or immunosuppressive therapy.The study will enroll 10 patients with R/R non-squamous NSCLC in the dose exploration phase and ≥40 patients with R/R squamous and non-squamous NSCLC in the dose expansion phase across sites in the US, Australia, and Europe.



FIH = first in human; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RP2D = recommended phase 2 dose.

[a] Subjects with non-squamous NSCLC.
[b] Subjects are required to have detectable PSMA expression by ^{68}Ga-PSMA-11 PET/CT imaging to enroll.
[c] MTD/RP2D for Part 1 will be determined by the first in human AMG 160 study (Study 20180101).
[d] Part 2 dose will be determined by dose recommended in Part 1 of this study.

Keywords: AMG 160, Phase 1b, Non-Small Cell Lung Cancer

P11.03 SHR-1316 in Combination With Fluzoparib in Relapsed Small-Cell Lung Cancer: An Open-Label, Multicenter, Two-Stage, Phase Ib Trial

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Introduction: Treatment options in second-line and beyond small-cell lung cancer (SCLC) setting are limited. This study was conducted to evaluate the safety and efficacy of SHR-1316 (a human immunoglobulin G4 antibody blocking programmed death ligand 1) plus fluzoparib (a poly(ADP-ribose) polymerase inhibitor) in treatment of relapsed SCLC. **Methods:** A single-arm, two-stage, phase Ib trial (NCT04041011) enrolled SCLC patients progressed after platinum-based treatment. In Stage 1, patients were enrolled to receive SHR-1316, 600 mg every 2 weeks plus fluzoparib 100 mg or 150 mg twice a day (6 patients for each cohort), until disease progression, unacceptable toxicity or trial withdrawal. Based on the tolerability during the first 28-day cycle and efficacy data in Stage 1, one cohort was chosen to expand to 32 patients in Stage 2. The primary endpoint was objective response rate (ORR). **Results:** From Sep 24, 2019 to Dec 10, 2020, 23 patients (pts) were enrolled, 7 pts each in stage 1, and then the 100 mg dose (recommended phase 2 dose) was expanded to 16 pts in stage 2, median follow-up duration was 4.8 months (IQR 2.8, 7.5). The confirmed ORR was 4.3% (1 of 23) and 6.3% (1 of 16) in all patients and the 100 mg dose. At the 100 mg dose, the DCR was 37.5% (6 of 16), clinical benefit was observed in 2 pts with 1 confirmed partial response and 1 prolonged stable disease (≥ 12 months), and both remained on treatment without disease progression, median progression-free survival was 1.4 months (95%CI 1.3, 2.8) and median overall survival was 6.7 months (95%CI 2.8, NR). Treatment-related adverse events (TRAEs) occurred in 21 of the 23 pts (91.3%) with the most common findings (≥ 20%) were white blood cell count decreased, anaemia, platelet count decreased, blood creatinine increased, hyponatraemia, asthenia and neutrophil count decreased; grade 3 or worse TRAEs reported in 8 pts (34.8%) including platelet count decreased and hyponatraemia (≥ 2 pts). Serious TRAEs occurred in 4 pts (17.4%), no treatment-related death occurred; none was discontinued the study treatment permanently due to TRAEs. **Conclusion:** The study combination showed moderate efficacy and manageable toxicity in relapsed SCLC patients.

Keywords: Small-cell lung cancer, SHR-1316, fluzoparib

P12.01 A Novel ^{89}Zr-α-PD-1 Immuno-PET-CT May Improve Pseudoprogression Detection in a Lung Cancer Murine Model Receiving Immunotherapy

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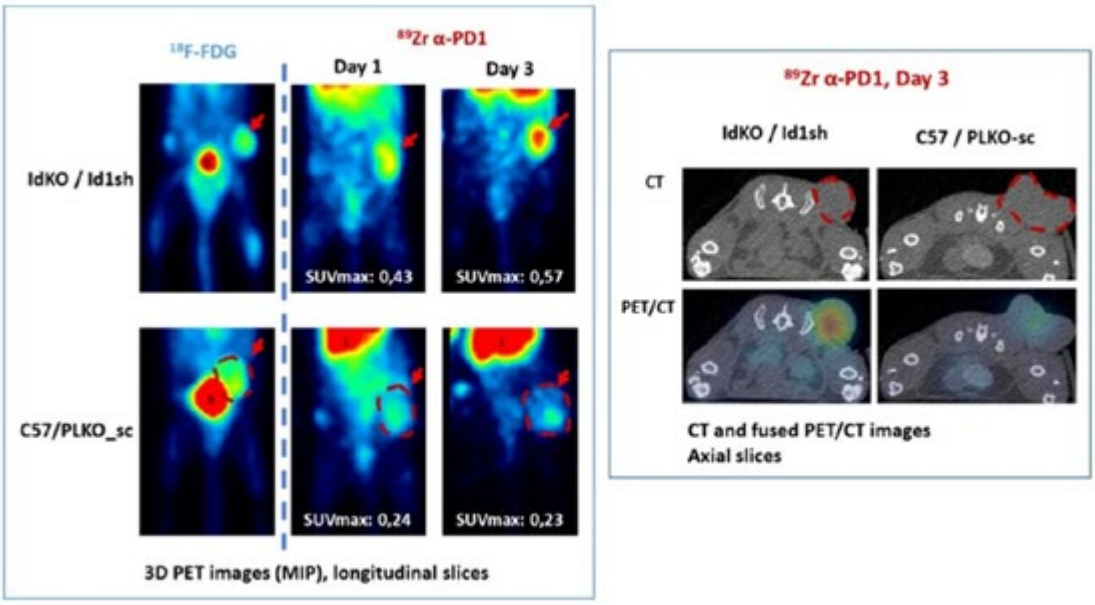
Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized lung cancer treatment improving survival of non-small cell lung cancer (NSCLC) patients. Response assessment of patients on ICIs represents a challenge since an increase in tumor size or the appearance of new lesions might not reflect true disease progression (P) but pseudoprogression (PP). Pseudoprogression has been reported in a range of 3-6% in NSCLC. Conventional 18F-FDG-PET scans do not accurately discriminate P from PP. We have recently reported the efficacy of a combined blockade of PD-1 and Id1 in a lung cancer mouse model (Baraibar et al. Cancers 2020). PD-1 is among key receptors conveying an inhibitory signal to T cells. We aimed to evaluate a novel ^{89}Zr-labelled radiotracer for micro (m)-PET-CT to detect PP in a NSCLC murine model treated with a combined blockade of PD-1 and Id1. **Methods:** Syngeneic subcutaneous tumors were generated using 1.5x10^6 Lewis Lung Carcinoma cells (with constitutive expression of Id1 or Id1 silenced) in C57BL6J and in Id1-deficient mice treated with PBS or a commercially available monoclonal antibody against PD-1 (α-PD-1) (RPM1-14, 300 µg, IP, on days 7, 10 and 14). To measure tumor growth and response to Id1-PD-1 blockade, radiotracer uptake or SUVmax, TLG and MTV were measured by ^{18}F-FDG-mPET (on days 6, 7, 10 and 14). Additionally, all animals were studied using a novel mPET radiotracer labelling the anti-PD-1 monoclonal antibody with ^{89}Zr (^{89}Zr-α-PD-1). Mice were treated with ^{89}Zr-α-PD-1 or PBS on day 14 after tumor cells injection and ^{89}Zr uptake was measured on days 14, 17 and 20 with mPET-CT following ^{18}F-FDG-mPET-CT. **Results:** ^{18}F-FDG-PET-CT SUVmax was reduced in mice under Id1 and PD-1 blockade metabolic uptake, but no significant differences were observed, underestimating the real metabolic response induced by the treatment. However, ^{89}Zr-mPET-CT showed a significantly higher ^{89}Zr uptake when Id1 was inhibited in both, tumor cells and the tumor microenvironment and mice were treated with anti-PD-1 therapy (p=0.0075), (Figure 1), suggesting an increased tumor infiltration of T cells. Tumor tissues analysis addressing the immune cells infiltration will be presented at the meeting.



Conclusion: The use of a novel ^{89}Zr-α-PD-1 immuno-PET-CT may improve pseudoprogression detection in a lung cancer murine model receiving immunotherapy. The analysis of the tumor tissues in those animals may show an increase immune cell infiltration being responsible for the antitumor response observed.

Keywords: Immuno-PET, Pseudoprogression, PD-1 blockade

P12.02 Systemic Anticancer Therapy Upregulate Plasma Levels of Damage-Associated Molecular Patterns in Patients With Advanced Lung Cancer

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Introduction: Immunogenic cell death (ICD) characterized by the release of damage-associated molecular patterns (DAMPs) from dying cancer cells may contribute to the synergistic antitumor effect of cytotoxic chemotherapy combined with an immune checkpoint inhibitor. The kinetics of circulating DAMP levels in cancer patients have remained largely uncharacterized, however. **Methods:** We evaluated the possible effects of various systemic anticancer therapy modalities on the kinetics of plasma DAMP concentrations in a prospective observational study of patients with advanced lung cancer. The plasma concentrations of high-mobility group box 1 (HMGB1), calreticulin (CRT), heat shock protein 70 (HSP70), annexin A1, and histone H3 were thus determined in 121 such patients at four time points during the first cycle of treatment. **Results:** The mean of the maximum fold change in HMGB1, HSP70, or annexin A1 concentration observed during treatment was significantly greater than the corresponding baseline value ($P < 0.005$). The maximum fold changes in HMGB1 and CRT concentrations tended to be associated with clinical response as evaluated by RECIST criteria, although the changes in the levels of these two DAMPs were not correlated, suggestive of differential induction mechanisms. Among the various treatment modalities administered, platinum-based combination or single-agent chemotherapy tended to elicit robust increases in the concentrations of HMGB1 and CRT. **Conclusion:** Serial monitoring of plasma revealed that systemic anticancer therapy increased the circulating levels of HMGB1 and CRT and that these changes tended to be associated with clinical response, suggesting that agents capable of releasing these DAMPs into plasma might induce ICD in advanced lung cancer patients.

Keywords: immunogenic cell death (ICD), damage-associated molecular pattern (DAMP), high-mobility group box 1

P12.03 The Time of Anti-PD-1 Infusion Improves Survival Outcomes by Fasting Conditions Simulation in Non-Small Cell Lung Cancer

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Introduction: Programmed cell death protein 1 (PD-1) pathway blockade represents a major breakthrough in metastatic non-small cell lung cancer (mNSCLC) treatment. However, primary and acquired resistance to PD-1 inhibition frequently occurs. Recently, we found that fasting-mimicking conditions reduced insulin-like growth factor 1 (IGF-1) levels to increase tumor immunogenicity and to sensitize lung tumors to PD-1 blockade (Ajona et al. Nature Cancer 2020). We aimed to assess whether the time of anti-PD-1 infusion, which may be associated with the fasting conditions, may correlate with clinical outcomes in mNSCLC patients. **Methods:** Consecutive mNSCLC patients treated with anti-PD-1 monotherapy or in combination with chemotherapy, between October 2013 and May 2020 were included. The hour of anti-PD-1 infusion was registered and patients were categorized in two groups. Group A: patients who received at least one of the first four treatment cycles before 12 pm and group B: patients receiving all first four cycles after 12 pm. Radiologic assessment according to iRECIST was performed every 8-12 weeks from treatment initiation. Treatment continued until disease progression, severe toxicity or death. Blood samples were collected prior to treatment initiation, second cycle administration, and at each radiological evaluation. The primary study endpoints were response rate (RR) at the first radiologic evaluation and progression-free survival (PFS). Secondary endpoints were overall survival (OS) and correlation between circulating levels of IGF-1-related proteins and clinical outcomes. **Results:** One hundred and five patients, 77 (73.3%) males, with a mean follow up of 15 months, were included. Median age was 65 (32–89). Most patients presented adenocarcinoma (70.5%) or squamous-cell carcinoma (17%). Eighty-eight patients received anti-PD-1 monotherapy and 17 patients combinations with platinum-based chemotherapy. Thirty-six patients (34.3%) were assigned to group A according to the time of immunotherapy administration and 69 to group B (65.7%). RR of 35% and 24% (p=0.079), and median PFS of 9.2 months and 3.2 months (p=0.033), respectively, were observed. The risk of progression was significantly reduced in patients who received at least one cycle before 12 pm in a multivariate model adjusted by age, gender, histologic diagnosis and treatment line [HR=0.51, 95% CI 0.29-0.91 (p=0.022)] [Figure1]

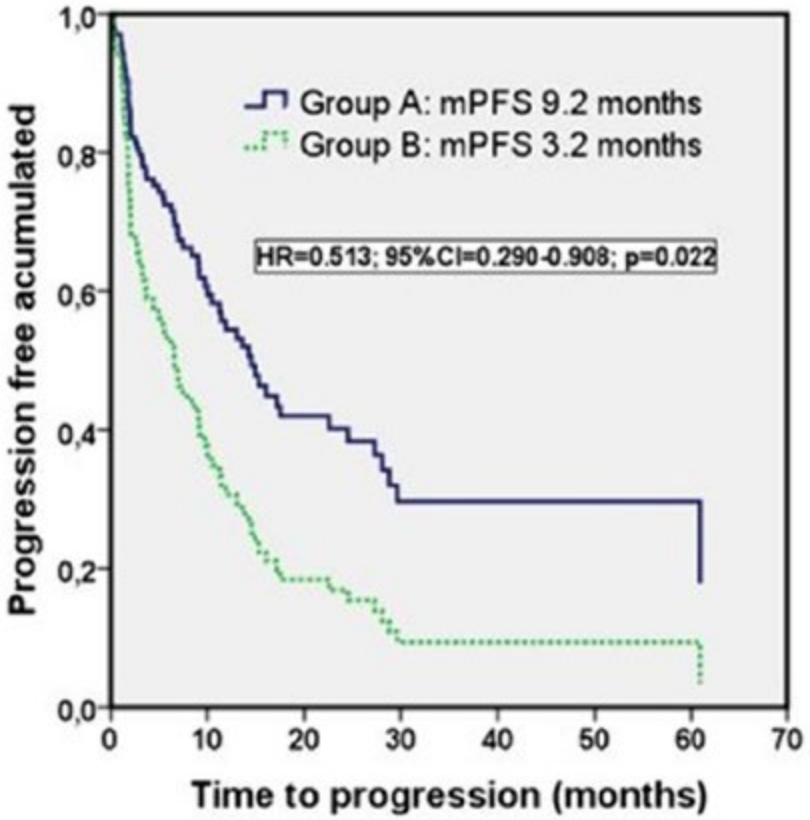

Figure 1. Progression-free (PFS) from anti-PD-1 treatment initiation according to iRECIST. Cox regression adjusted by age, gender, histologic diagnosis and treatment line

Conclusion: Anti-PD-1 treatment before 12 pm significantly improved PFS in patients with mNSCLC suggesting a correlation with fasting conditions. Overall survival and circulating levels of metabolic factors involved are being currently analyzed and will be presented at the meeting.

Keywords: non-small cell lung cancer, anti-PD-1, fasting conditions

P12.04 Radiation Mediates IDO1 Dynamic Changes in KRAS Mutation Lung Cancer Cell Lines

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Introduction: Lung cancer was the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) accounted for 85% of lung cancer, in which KARS mutation was the most common driver alterations. Radiotherapy was one of the most important treatments for lung cancer, but some studies indicated that KRAS mutation increases radiation tolerance.IDO1 is an immune checkpoint gene.The changes of IDO1 and its metabolites after radiotherapy were significantly correlated with the overall survival and metastatic risk in NSCLC. However, the changes in IDO1 activities remain unknown for patients with KRAS mutation treated with radiotherapy. **Methods:** To determine the IDO1 responsiveness of lung cancer cell lines to low dose radiation, different types of NSCLC cell lines were cultured and treated with 3Gy radiation. IDO1 protein expression levels were measured using western blot and band densities were analyzed using ImageJ software. **Results:** After radiation treatment, IDO1 protein expression levels in most lung cancer cell lines except HCC827 were decreased respectively. Interestingly, compared to the pre-treatment, the IDO1 protein levels at post-treatment were significantly decreased in KRAS mutation cell lines H460, H358, A549, Calu-1, while KRAS wild type cell lines HCC827, H1299, H226 remained slightly changes, the decreasing rates were 1.46 folds in KRAS mutation and 1.05 folds in KRAS wild type (1.460.12,1.050.01,p=0.065). IDO1 changes in adenocarcinoma A549, H460, H358 versus HCC827, H1299)was consistent with squamous cell carcinomas cell lines (Calu-1 versus H226). **Conclusion:** We found a trend of greater changes of IDO1 expression levels in KRAS mutation NSCLC cell lines compared with KRAS wild type after low dose RT. Our results indicated that low-dose radiation therapy combined with immunotherapy may be more effective for lung cancer patients with KRAS mutation.

Keywords: Radiation, KRAS mutation, indoleamine 2,3-dioxygenase 1 (IDO1)

P12.05 Neutrophil Elastase as Combined Immunotherapy Target for Treating NSCLC

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Introduction: Immunotherapy has emerged as a promising option for treating non-small cell lung cancer (NSCLC). However, immunotherapy is not equally effective for all patients. Drug resistance is also a big hurdle in treatment. Recently, cancer immune microenvironment has proved of great significance for immunotherapy. Neutrophil elastase, a protease able to degrade several extracellular matrix proteins, is encoded by ELANE gene. neutrophil elastase (NE) and neutrophil dominate airway inflammation. Sivelestat is the only approved drug working as a selective NE inhibitor. However, their direct impact on the tumor immune microenvironment is not clear. The goal of this study, therefore, was to investigate the the effects of ELANE on the NSCLC microenvironment, and the application potential of sivelestat on combination therapies to enhance the efficacy of immune checkpoint inhibitors. **Methods:** The relationship between ELANE and tumor-infiltrated immune cells was analyzed using TIMER. Immunohistochemistry was used to evaluate the density of, CD8+TILs, and CD163+ macrophages. NE from peripheral blood of NSCLC patients was determined by ELISA. The mouse model and flow cytometry were used to investigate the effects of sivelestat on the tumor-infiltrating immune cells and the efficacy of immune checkpoint inhibitors. **Results:** ELANE was significantly positively correlated with the proportion of M2 macrophages, and negatively associated the proportion of CD8+TILs. NE levels in peripheral blood of NSCLC patients was significantly positively correlated with the density of CD163+ macrophages, and negatively associated the density of, CD8+TILs. Sivelestat, which had already been marketed as a selective NE inhibitor, could increase CD8+ infiltration and reduced M2 macrophage infiltration. It can also improve the efficacy of immune checkpoint inhibitors in the mouse model. **Conclusion:** NE levels in peripheral blood could be used as potential biomarker that may predict sensitivity to immunotherapy. Sivelestat as a selective NE inhibitor already marketed, can potentially be harnessed in combination with immune checkpoint inhibitors to increase the efficacy of immunotherapy.

Keywords: neutrophil elastase, tumor microenvironment, immunotherapy

P12.06 Computational Omics Biology Model (CBM) Identifies PD-L1 Immunotherapy Response Criteria Based on Genomic Signature of NSCLC

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Introduction: PD-L1 is an immune checkpoint protein that mediates immune evasion. In Non-Small Cell Lung Cancer (NSCLC), its expression is used to predict the outcome of treatment targeting PD-1/L1. However, clinical benefits do not occur uniformly, and new approaches are needed to assist in selecting patients for immunotherapy. **Methods:** 26 patients with known clinical response to pembrolizumab were selected from publicly available data (PMID:25765070) (Table 1). Mutation and copy number aberrations from individual cases served as input into the Cellworks Omics Biology Model (CBM) to generate a patient-specific protein network map from PubMed and other online resources. Disease-biomarkers unique to each patient were identified within protein network maps. Digital drug biosimulations were conducted by measuring the effect of pembrolizumab on a cell growth score comprised of a composite of cell proliferation, viability, apoptosis, metastasis, and other cancer hallmarks. Drug biosimulations were conducted to identify and evaluate therapeutic efficacy. **Results:** Among 26 patients treated with pembrolizumab, 14 were clinical responders, defined as stable disease or partial response lasting longer than 6 months, and 12 non-responders. Notably, 9/12 non-responders were PD-L1 positive (Table 1). Cellworks biosimulation predicted response with 84.6% accuracy, 75% specificity, and 92.86% sensitivity. Positive predictive value was 81.25% and negative predictive value was 90%. CBM identified that response was influenced by pathways that impacted the tumor microenvironment (TME). Deletions of adenosine pathway genes were observed in responders, whereas CNVs for these genes were enriched in non-responders (Table 1). Loss of ENPP1, and INSIG1 and SENP2 CNV aberrations, all of which regulate the STING pathway, could play a significant role in governing immune checkpoint blockade (ICB) response. Although STK11 loss appears to be a biomarker for poor ICB response, it was equally enriched in responders (n=7) and non-responders (n=7) in this dataset. Notably, responders had STK11 mutations and chromosome 6 loss, whereas non-responders had STK11 loss with chromosome 6 wild type or gain. Finally, frameshift mutations (FSM) enhance neoepitope formation and were higher in responders (average FSM = 48) vs non-responders (average FSM = 19).

P12.07 Radiation Mediated Down-Regulation of Indoleamine 2,3-dioxygenase 1 (IDO1) Expression in Lung Cancer Cells is Associated with iNOS-NO Pathway

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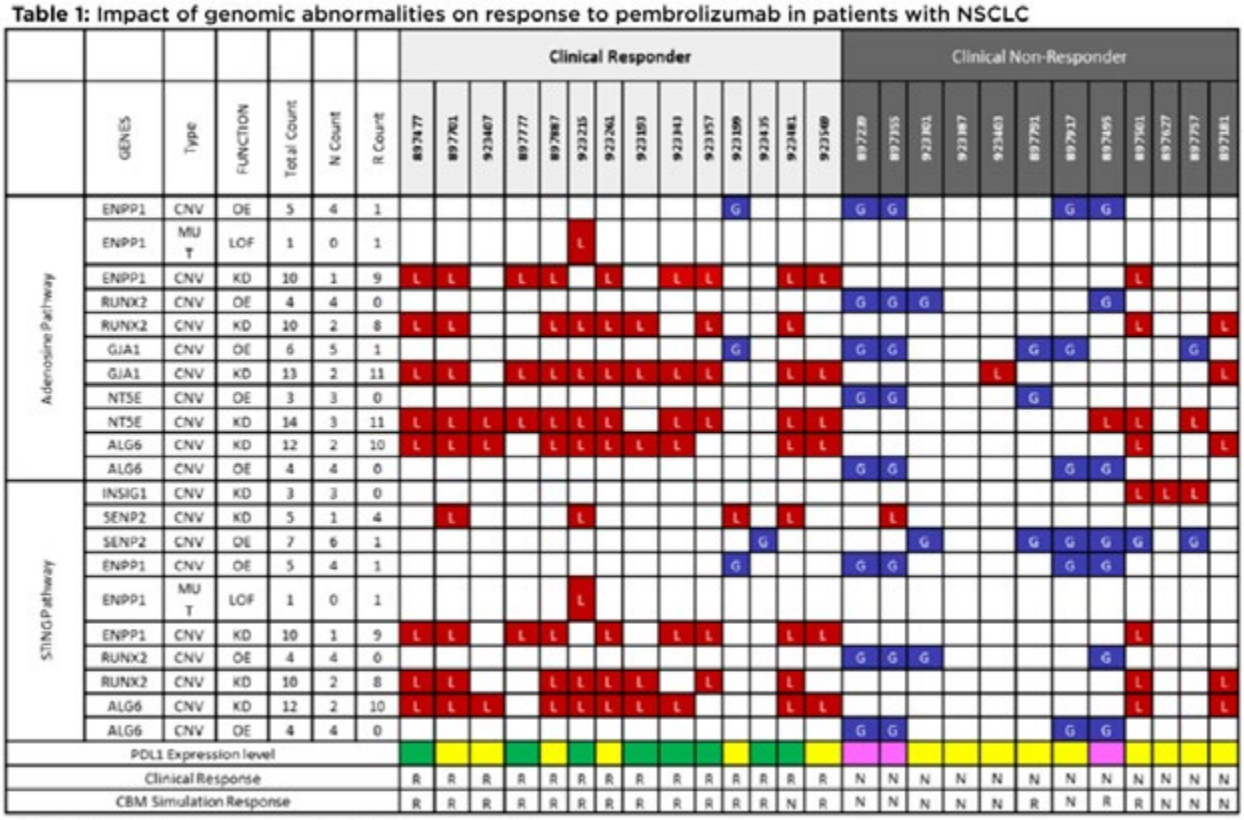
Introduction: IDO1 has been identified as an immune checkpoint gene and play an important role in tumor immunosuppression. RT can influence IDO1 and IDO1 metabolites which were significantly correlated with metastatic risk and overall survival in patients with lung cancer treated with radiotherapy. However, the molecular mechanism of how RT influence IDO1 in lung cancer is still unknown. Some studies indicate that a high level of NO can suppress the IDO1 protein synthesis, and NO was mainly mediated by iNOS, which was highly expressed after RT. Therefore, we hypothesized that radiation mediates IDO1 gene expression through iNOS-NO axis. **Methods:** Human and mouse lung cancer cell lines (H226, Calu-1, H460, H358, A549, H1650, H1975, HCC827, H1299, KLN205, TC-1, LLC) and normal endothelia cell (HUVEC) were cultured and irradiated. Cells were treated with different radiation doses(1, 3, 6 and 12 Gy)and then were collected at different times (3h, 6h,12h, 24h, 48h and 72h) post RT. RNA and protein were isolated and analyzed using qPCR and western blot to measure IDO1, iNOS, IL-1β mRNA and protein levels. iNOS, IL-1β knockout stable cell lines were generated using iNOS and L-1β gene specific designed CRISPR Cas-9 plasmids and treated with RT, and IDO1 protein levels were analyzed by western blot. Data was statistical analyzed using Graph Pad Prism8. **Results:** IDO1 mRNA and protein expression levels were decreased in most lung cancer cell lines except HCC827, which with a slightly increased IDO1 level (1.08 folds increasing) after RT. In human lung cancer cell lines, the IDO1 expression levels in KRAS mutation lung cancer cells even more significant decreased than KRAS wild type cells (1.45 folds versus 1.05 folds). In mouse cell lines, IDO1 decreased about 1.5 folds in KLN205 and TC-1 cell lines but no changes in LLC. Surprisingly, IDO1 expression level was slightly decreased in HUVEC cells after low dose RT (1.2 folds). In H456 cells, changes of IDO1 level were radiation dose dependent. Compare with low dose, higher RT dose treatment decreased IDO1 level faster and reached lowest at 3-6h post RT but IDO1 levels were recover quicker, while low dose (1 Gy) mediated IDO1 expression in a low level for longer time (48h). IDO1 levels were finally increased over pre-treatment after 72h in all dose treated cells. In addition, we verified that RT mediated high levels of iNOS and IL-1βexpression. In CRSPR cas-9 knockout iNOS and IL-1βcell lines, IDO1 expression levels were increased after radiation treatment. **Conclusion:** Our data indicated that radiation modulates down-regulation of IDO1 gene expression time and dose-dependent in lung cancer cells. Knockout iNOS and IL-1β contrarily increased IDO1 expression after RT. Therefore, the IL-1β - iNOS - NO axis might be the potential regulatory for IDO1 regulation and could be potential target in future in lung cancer radiation treatment.

Keywords: Radiation, indoleamine 2,3-dioxygenase 1 (IDO1), iNOS-NO pathway

Table 1: Impact of genomic abnormalities on response to pembrolizumab in patients with NSCLC



L = Loss, G=Gain, R=Responder, N=Non responder
PDL1 Expression level: >50% = Green, 1 to 50% = Yellow, <1%=Pink

Conclusion: Alterations of the adenosine and STING pathways play key roles in determining benefit from PD-1/L1 targeting and highlight therapeutic possibilities for improving outcome in specific patient subgroups based on PD-L1 expression. The Cellworks CBM captures a holistic picture of the TME using tumor omics and improves response prediction beyond PD-L1 testing.

Keywords: Personalized Cancer Therapy, Multi-omics Therapy Biosimulation, Immunotherapy Biosimulation

P13.01 Use of Antibiotics Is Associated With an Increase in Immunotherapy Related Adverse Effects in Patients With Non-Small Cell Lung Cancer

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Introduction: Immune check point inhibitors (ICI) are the backbone of treatment in patients with metastatic non-small cell lung cancer (NSCLC). Around 40-70% of treated patients experience either single or multisystem immune related adverse events (irAEs) leading to permanent discontinuation of ICI therapy in 10-15% of such patients, which is associated with shorter median progression free survival (PFS) and overall survival (OS). Some studies have shown that use of antibiotics in this setting is associated with increase risk of irAEs and hospitalizations. We sought to study the effects of antibiotic therapy on irAEs in advanced stage NSCLC treated with ICI (pembrolizumab, atezolziumab, nivolumab and durvalumab) therapy. **Methods:** A list of 153 NSCLC patients undergoing ICI therapy for advanced NSCLC was obtained from Mayo Clinic Florida database. A comprehensive chart review was conducted and IrAEs were diagnosed after excluding other etiologies. IrAEs were graded based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0. Type, duration and indications of antibiotic used 3 months before and after the initiation ICI therapy were recorded. Fisher's exact test (two-sided) was used to evaluate the association between antibiotic therapy and irAEs. **Results:** The median age was 66 years (IQR, 58-73) with majority being male (54.2%), white (85.6%), smoker (85.6%) with NSCLC adenocarcinoma histology (76.5%) and a good performance status, ECOG 0-1 (95%). All patients had advanced lung cancer with 92.8% with stage IV disease. Majority of the patients (69.2%) were treated with pembrolizumab. Of the 153 patients, 77 (50.4%) received antibiotics during the 3 months prior to or after initiating ICI therapy while 76 (49.6%) did not receive any antibiotics in the specified time period. The most utilized antibiotics were fluoroquinolones (36.2%) followed by penicillins (14.7%). Most common indication for antibiotic usage was respiratory tract infection (42.1%). Overall incidence of irAE was 115 (75%) with 14.7% 17 pts (14.7%) experiencing Grade 3-4 irAEs. Most common irAEs included thyroid abnormalities in 54 pts (35.2 %), hepatitis in 37 pts (24.1%), rash in 32 pts (20.9%) and colitis in 27 pts (17.6 %). Patient in the antibiotic group experienced significantly more irAEs with an odds ratio of 2.8 (95% CI 1.2-6.7, p=0.009), however there was no effect of antibiotic usage and irAEs development on PFS and OS.

Antibiotic therapy	N (%)	irAEs (%)	OR
Yes	77 (50.3%)	65 (84.4%)	2.8, (95% CI 1.2-6.7, p=0.009)
No	76 (49.6%)	50 (65.7%)	

Conclusion: Antibiotic treatment in NSCLC patients receiving ICI therapy was associated with a 2.8-fold increase risk of development of irAEs without negative impact on PFS and OS.

Keywords: NSCLC, Immunotherapy, Adverse effects, Antibiotics

P14 IMMUNOTHERAPY (PHASE II/III TRIALS) - CLINICAL TRIAL IN PROGRESS

P14.01 Phase 3 Study of First-Line Pembrolizumab ± Vibostolimab (anti-TIGIT) in Patients With PD-L1-Positive Metastatic NSCLC

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Introduction: Vibostolimab (MK-7684) is a humanized monoclonal antibody that binds to the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), blocking the interaction between TIGIT and its ligands, CD112 and CD155. Pembrolizumab, a monoclonal antibody against the PD-1 receptor, significantly improves OS versus chemotherapy in patients with previously treated and previously untreated advanced non-small-cell lung cancer (NSCLC) with PD-L1 tumor proportion score (TPS) ≥1%. In the first-in-human study (NCT02964013), the combination of vibostolimab plus pembrolizumab had a manageable safety profile and showed promising antitumor activity in patients with advanced NSCLC who were naive to anti-PD-(L)1 therapy; ORR was 31% and 25% in patients with PD-L1 TPS ≥1% and <1%, respectively. The current phase 3 study (NCT04738487) is comparing the efficacy and safety of first-line treatment with MK-7684A, a co-formulation of vibostolimab plus pembrolizumab, versus pembrolizumab monotherapy in patients with PD-L1-positive metastatic NSCLC. **Methods:** This is a phase 3, randomized, multicenter, double-blind study. Eligible patients are aged ≥18 years with pathologically confirmed, previously untreated, metastatic NSCLC with PD-L1 TPS ≥1% (centrally confirmed). Patients must have measurable disease per RECIST version 1.1, have an ECOG PS of 0 or 1, have no EGFR mutations or ALK or ROS1 gene rearrangements, and have no active or untreated CNS metastases. Patients are randomized 1:1 to receive intravenous treatment with vibostolimab 200 mg plus pembrolizumab 200 mg Q3W or pembrolizumab 200 mg Q3W for up to 35 cycles (approximately 2 years) or until disease progression, unacceptable AEs, intercurrent illness, or investigator decision. Patients who stop treatment after a CR or after completing 35 cycles and subsequently have disease progression can receive up to 17 additional cycles (approximately 1 year) of their randomized therapy. Randomization is stratified by ECOG PS (0 vs 1), PD-L1 TPS (1%–49% vs ≥50%), and region of enrollment (East Asia vs non-East Asia). The dual primary endpoints are PFS, per RECIST version 1.1 by blinded independent central review (BICR), and OS. Secondary endpoints include ORR and duration of response per RECIST version 1.1 by BICR, patient-reported outcomes, and safety. Radiographic imaging occurs at baseline, Q9W from randomization through week 54, and then Q12W until disease progression, the start of new anticancer treatment, withdrawal of consent, or death. Health-related quality of life is assessed using validated patient-reported outcome instruments including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. AEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Approximately 598 patients will be randomized. Enrollment began in April of 2021.

Keywords: metastatic non–small-cell lung cancer, Pembrolizumab, vibostolimab

P14.02 Phase III Trial of Pembrolizumab-Chemotherapy Versus Pembrolizumab in First-Line of Advanced NSCLC with PD-L1 ≥50%: PERSEE

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Introduction: Single agent antibodies against PD-(L)1 (ICI) have become since 2017 a standard of care for first-line treatment of stage IV NSCLC with PD-L1 TPS ≥50%. Recent phase III trials assessing chemotherapy-ICI combinations have shown an overall survival (OS) benefit for the combination therapy over chemotherapy alone regardless PD-L1 level of expression. In Europe, both single agent ICI and chemotherapy-ICI strategies are approved if PD-L1 TPS ≥50%. The aim of PERSEE trial is to compare head-to-head chemotherapy-pembrolizumab combinations vs. pembrolizumab monotherapy in patients with PD-L1 TPS ≥50%. **Methods:** PERSEE trial is a multicenter, prospective, open label, randomized phase III study that evaluates the superiority of chemotherapy-pembrolizumab combination over pembrolizumab single agent in first-line treatment for patients with PD-L1 TPS ≥50% NSCLC. Main inclusion criteria are stage IV or stage III NSCLC ineligible to local treatment, locally assessed PD-L1 TPS ≥50%, no known EGFR mutation or ALK or ROS1 rearrangements, ECOG performance status 0 or 1. Patients with brain metastases are included if they are asymptomatic or treated if symptomatic. Patients in the chemotherapy-immunotherapy arm receive four induction cycles once every 3 weeks with pembrolizumab 200 mg combined with cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 5 mg/mL/min, pemetrexed 500 mg/m^2 for non-squamous NSCLC or carboplatin AUC 6 mg/mL/min, paclitaxel 200 mg/m^2 for squamous NSCLC. Responders or patients with stable disease will receive pembrolizumab up to a maximum of 35 cycles and pemetrexed maintenance therapy for non-squamous NSCLC until disease progression or unacceptable toxicity. Patients in the immunotherapy alone arm receive pembrolizumab 200 mg once every 3 weeks for a maximum of 35 cycles. Primary endpoint is centrally assessed progression-free survival (PFS) according to RECIST 1.1. Secondary endpoints include overall survival, response rate, duration of response and safety. A central assessment of PD-L1 (22C3 clone) will be performed retrospectively. Assuming a hazard ratio of 0.7 for PFS in favor of chemotherapy-pembrolizumab and an expected median PFS of 7.1 months in the control group, the required sample size is 262 randomized patients (131 patients per treatment arm) for the observation of 249 events based on a 3-year recruitment period and a 5-year study period. Randomization will be stratified on tumor histology (squamous versus non squamous) and presence or absence of brain metastases. Trial will be opened in 30 centers in France and inclusions started on December 22, 2020. Recruitment is expected to end in December 2023. Clinical trial information: NCT04547504

Keywords: PD-L1 TPS ≥50%, immuno-chemotherapy, immunotherapy

P14.03 Vibostolimab Plus Pembrolizumab With/Without Docetaxel vs Docetaxel in NSCLC After Platinum Chemotherapy and Immunotherapy

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Introduction: Agents that block the interaction between the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and its ligands CD112 and CD155 have demonstrated antitumor activity in preclinical tumor models. In the first-in-human study (NCT02964013), the anti-TIGIT humanized monoclonal antibody vibostolimab (MK-7684) showed promising antitumor activity and manageable toxicity in a heavily pretreated population across multiple tumor types, particularly when combined with the PD-1 inhibitor pembrolizumab. Pembrolizumab has been shown to significantly improve OS compared with chemotherapy in treatment-naive and previously treated patients with PD-L1–positive advanced non-small-cell lung cancer (NSCLC). However, many patients present with primary or acquired resistance to immunotherapy, both in the context of monotherapy strategies or in combinations with chemotherapy. The current phase 2 study (NCT04725188) is evaluating the efficacy and safety of MK-7684A, a co-formulation of vibostolimab plus pembrolizumab, administered with or without docetaxel versus docetaxel alone in patients with previously treated metastatic NSCLC. **Methods:** This randomized, placebo- and active-controlled, parallel-group, multicenter, partial-blind study is enrolling patients aged ≥18 years with histologically or cytologically confirmed metastatic NSCLC with progressive disease after platinum-doublet chemotherapy and 1 prior anti–PD-(L)1 therapy administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. Patients must have measurable disease per RECIST v1.1, an ECOG PS of 0 or 1, and no known active CNS metastases (patients with previously treated brain metastases may participate provided they are radiologically and clinically stable). Tumor tissue from an archival or newly-obtained core or excisional biopsy must be evaluated centrally for PD-L1 expression before randomization, and local documentation of the absence of EGFR mutations or ALK or ROS1 gene rearrangements must be provided. Patients are randomized 1:1:1 to receive intravenous treatment with vibostolimab 200 mg plus pembrolizumab 200 mg Q3W (open-label), vibostolimab 200 mg plus pembrolizumab 200 mg plus docetaxel (standard-of-care dose) Q3W (blinded), or docetaxel (standard-of-care dose) plus placebo Q3W (blinded). Randomization is stratified by ECOG PS (0 vs 1), prior anti–PD-(L)1 therapy (immediate prior therapy vs no immediate prior therapy), and PD-L1 tumor proportion score (<50% vs ≥50%). Treatment continues for up to 35 cycles (approximately 2 years) of vibostolimab plus pembrolizumab, and per the locally approved label for docetaxel, or until disease progression, unacceptable AEs, intercurrent illness, or investigator decision. Patients who have SD, PR, or CR may be eligible for up to 17 additional rechallenge cycles of vibostolimab plus pembrolizumab if there is BICR verification of radiographic disease progression by RECIST v1.1 after initial treatment or first course has been completed or stopped for confirmed CR. The primary endpoint is PFS per RECIST v1.1 by BICR. Secondary endpoints are OS, ORR and duration of response per RECIST v1.1 by BICR, and safety. Radiographic imaging occurs at baseline, Q6W from randomization through week 36, Q9W through week 54, and then Q12W until disease progression, the start of new anticancer treatment, withdrawal of consent, or death. AEs are assessed by NCI CTCAE v5.0. Approximately 240 patients will be randomized. Enrollment began in April of 2021. **:**

Keywords: metastatic non–small-cell lung cancer, vibostolimab, Pembrolizumab

P14.04 A Phase 2 Multicenter Study of Iovance Autologous Tumor Infiltrating Lymphocytes (TIL, LN-145) Cell Therapy in Patients With Metastatic NSCLC

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Introduction: Patients with metastatic non-small cell lung cancer (mNSCLC) without actionable driver mutation(s) who have progressed after cytotoxic chemotherapy plus immune checkpoint inhibitors (ICI) have limited treatment options and represent an unmet need. The safety and efficacy of TIL cell therapy for mNSCLC patients who failed to respond or progressed on nivolumab has been evaluated in a Phase 1 clinical trial (Creelan B, AACR 2020), demonstrating an objective response rate (ORR) of 25% including 17% durable CRs. Of note, responders in this study had PD-L1 tumor proportion score (TPS) expression levels of 0-10%. As patients with negative or low PD-L1 expression levels are in need of therapeutic options and TIL therapy appears to offer such a therapeutic potential, we initiated the IOV-LUN-202 study, evaluating Iovance TIL cell therapy with LN-145 in patients with mNSCLC without actionable driver mutation(s), who have progressed on or following a single line of approved systemic therapy consisting of combined ICI + chemotherapy ± bevacizumab. **Methods:** IOV-LUN-202 (NCT04614103) is an actively enrolling, open-label, multi-cohort, non-randomized, multicenter Phase 2 study. Patient cohorts (n=40 ea.) based on TPS at metastatic diagnosis prior to ICI use are Cohort 1 (TPS <1%) and Cohort 2 (TPS ≥ 1%). Cohort 3 (TPS <1%; n=15), utilizes core biopsies for tumor acquisition for patients unable to undergo a surgical harvest with a 16-day Gen 3 manufacturing process. LN-145 is generated at centralized GMP facilities and the final cryopreserved infusion product is shipped to the sites. All patients receive TIL therapy consisting of nonmyeloablative lymphodepletion with cyclophosphamide (60 mg/kg x 2) + fludarabine (25 mg/m^2 x 5), followed by a single infusion of autologous LN-145 (Day 0) and up to 6 doses of IL-2 (600,000 IU/kg). Key eligibility includes: ≥ 18 yr of age; 1 prior line of therapy; ≥ 1 lesion(s) available for TIL generation and a remaining RECIST-measurable lesion; and ECOG PS of 0-1. For each cohort, the primary endpoint is ORR per RECIST v1.1. Secondary endpoints are safety, CR rate, DOR, DCR, PFS, and OS. Table 1: IOV-LUN-202 Patient Cohorts

COHORT	PATIENT POPULATION Metastatic NSCLC without an actionable driver mutation and progressive disease on or following a single line of approved systemic therapy including ICI + Chemo ± Bevacizumab	SAMPLE SIZE
1	PD-L1 TPS < 1%	N = 40
2	PD-L1 TPS ≥ 1%	N = 40
3	PD-L1 TPS < 1% / Core Biopsies	N = 15
4	Retreatment	N = undefined

Keywords: Tumor-infiltrating lymphocytes, adoptive cell therapy, non-small cell lung cancer

P14.05 Phase 2, tudy of Iovance Autologous Tumor Infiltrating Lymphocytes (Lifileucel, LN-144, LN-145, LN-145-S1) In Patients With Solid Tumors

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Introduction: The presence of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment is associated with survival outcomes in many solid tumors, including melanoma (Mel), head and neck squamous cell carcinoma (HNSCC), and non-small cell lung cancer (NSCLC). Lifileucel (LN-144), has shown efficacy with durable responses in advanced Mel (Sarnaik et al., ASCO 2020) and metastatic cervical cancer (Jazaeri et al., ASCO 2019). Activity of LN-145 in combination with pembrolizumab in HNSCC has also been demonstrated (Jimeno et al., SITC 2020). TIL therapy has shown evidence of efficacy in metastatic NSCLC in a Phase 1 study (Creelan et al., ASCO 2020). Combination of TIL and immune checkpoint inhibitors (ICIs) in ICI-naïve patients have not been previously investigated. This combination offers an alternative treatment to traditional chemotherapy in multiple indications with a one-time treatment of TIL therapy. **Methods:** IOV-COM-202 (NCT03645928) is an actively enrolling, Phase 2 global, open-label multi-cohort, non-randomized study designed to evaluate the safety and efficacy of TIL therapy as a single agent or in combination with immune checkpoint inhibitors. All patients receive either, lifileucel, LN-144 Gen 3, LN-145 or LN-145-S1 (PD-1 select TIL), which is manufactured at centralized GMP facilities generating a cryopreserved infusion product which is shipped to the treatment centers. Cohorts 1, 2 and 3 enroll Mel, HNSCC and NSCLC patients, respectively (Table 1). Patients undergo a nonmyeloablative lymphodepletion (NMA-LD) regimen prior to TIL infusion, followed by up to 6 doses of intravenous IL-2. Patients in Cohorts 1A, 2A, and 3A start pembrolizumab following tumor harvest for TIL generation, but prior to NMA-LD. Pembrolizumab is dosed per label. Patients in Cohorts 1B, 1C and 3B receive LN-145-S1, lifileucel, and LN-145, respectively. Cohort 3C patients receive a dose of ipilimumab and nivolumab prior to tumor harvest, with nivolumab continuing Q4W for up to 2 years, or until progression or unacceptable toxicity. Key eligibility includes: ≥ 18 years of age; RECIST measurable disease; ≥ 1 lesion(s) available for TIL generation; ECOG PS 0-1. Primary endpoint: ORR per RECIST v1.1. Secondary endpoints: safety, CR rate, DOR, DCR, PFS, and OS. Table 1: IOV-COM-202 Study Design

COHORT	PATIENT POPULATION	SAMPLE SIZE	TREATMENT REGIMEN
1A	Melanoma: PD-1/PD-L1 naive	N = 12	Lifileucel + pembrolizumab
1B	Melanoma: ≥ 1 prior systemic therapy(ies)	N = up to 27	LN-145-S1 as single agent
1C	Melanoma: ≥ 1 prior systemic therapy(ies)	N = up to 27	LN-144 Gen 3 as single agent
2A	HNSCC: PD-1/PD-L1 naive	N = 19	LN-145 + pembrolizumab
3A	NSCLC: PD-1/PD-L1 naive	N = 12	LN-145 + pembrolizumab
3B	NSCLC: ≥ 1 prior systemic therapy(ies)	N = 12	LN-145 as single agent
3C	NSCLC: 1 prior systemic therapy	N = up to 26	LN-145 + ipilimumab + nivolumab

Keywords: Tumor-infiltrating lymphocytes, adoptive cell therapy, non-small cell lung cancer

P14.06 Toripalimab in Combination With Bevacizumab and Platinum-Based Chemotherapy in Patients with Untreated Advanced PSC: A Phase II Study

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Introduction: Although immunotherapy has emerged as a standard treatment for advanced non-small cell lung cancer (NSCLC) without driver gene mutation, there are still insufficient data on the efficacy of immunotherapy for patients with pulmonary sarcomatoid carcinoma (PSC). Due to a high tumor mutation burden and great prevalence of programmed cell death ligand 1 (PD-L1) in PSC than other subtypes of NSCLC, immunotherapy may provide promising efficacy in advanced PSC patients. Multiple immune-monotherapy or combination with chemotherapy case studies and doublet immunotherapy based on a phase II study (NCT03022500) suggested the survival benefit of immunotherapy in advanced PSC. Blood-vessel invasion as an independent factor associated with PD-L1 expression and poor prognosis in PSC, early application of anti-angiogenesis may enhance patients' response to immunotherapy. The application of anti-programmed cell death protein 1 (PD-1) antibody combined with platinum-based chemotherapy plus anti-angiogenesis in untreated advanced PSC is worth exploring. Toripalimab, a humanized IgG4 monoclonal antibody against PD-1, achieved partial response (PR) for second-line advanced PSC in a recent case report (Jiao Y Oral Oncology 2020). Based on these pieces of evidence, we explore the combination of toripalimab with platinum-based chemotherapy and bevacizumab in patients with untreated advanced PSC. **Methods:** This is an open-label, multicenter, single-arm, phase II study that aims to evaluate the efficacy and safety of toripalimab combination with platinum-based chemotherapy and bevacizumab in patients with untreated advanced PSC. Key eligibility criteria include age 18-75 years with Eastern Cooperative Oncology Group performance status of 0-2, histologically confirmed PSC, at least 1 measurable lesion per RECIST v1.1 that not received radiotherapy, and no prior anti-PD-1 or anti-PD-L1 therapy for stage IV PSC. Patients will be excluded if they have evidence of mutations in either EGFR, ROS-1, ALK, or c-MET. 27 untreated advanced PSC patients at 5 sites will be enrolled in Chengdu city, Sichuan province of China. All patients will receive toripalimab (240 mg, d1) combined with bevacizumab (7.5 mg/kg, d1) and nab-paclitaxel (260 mg/m^2, d1 or 130 mg/m^2, d1,8) plus carboplatin (AUC= 4-5, d1) of a 21-day cycle for a maximum of 6 cycles. Patients will continue to receive maintenance therapy with toripalimab and bevacizumab until disease progression or died of two years. The primary endpoint is progression-free survival (PFS) by investigator assessment per RECIST v1.1. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS), the patient-reported outcome (PRO), and safety data per NCI-CTC AE 4.0.3. Enrollment for this trial is open in April of this year and will continue for 12 months. **Results:** Not applicable. **Conclusion:** Not applicable.

Keywords: PSC, anti-angiogenesis, Toripalimab combine with chemotherapy

P14.07 PERLA: Randomized Phase II Trial of Dostarlimab + Chemotherapy (CT) vs Pembrolizumab + CT in Metastatic Non-Squamous NSCLC

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Introduction: NSCLC remains a leading cause of cancer mortality worldwide, with poor survival prospects for metastatic disease. Front-line treatment of NSCLC has been improved by programmed cell death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. KEYNOTE-189 showed that the addition of pembrolizumab to pemetrexed and platinum-based CT significantly improved overall survival (OS) and progression-free survival (PFS) in patients with untreated non-squamous metastatic NSCLC regardless of PD-L1 expression (Gandhi New Engl J Med 2018). Promising antitumor activity was observed with dostarlimab, a PD-1 inhibitor, in a cohort of patients with NSCLC in the Phase I/II GARNET study. In GARNET, 67 patients with previously treated advanced NSCLC had an objective response rate (ORR) of 26.9% (18 partial responses) across PD-L1 tumor proportion score (TPS) categories, including patients with TPS <1%. Indirect comparison of dostarlimab data with that of pembrolizumab monotherapy in second-line NSCLC (Herbst Lancet Oncol 2016) suggests similar efficacy and safety profiles. The objective of this noninferiority study is to assess the efficacy and safety of dostarlimab plus CT versus pembrolizumab plus CT in patients with untreated metastatic non-squamous NSCLC. **Methods:** The KEYNOTE-189 trial was used as a reference for the study design of this Phase II, randomized, double-blind, 2-arm study. Eligible patients will be ≥18 years old, with histologically or cytologically confirmed metastatic non-squamous NSCLC and without known sensitizing EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available. Patients will have documented PD-L1 status by 22C3 pharmDx assay by local or central testing prior to randomization, an Eastern Cooperative Oncology Group performance status 0–1, life expectancy ≥3 months, adequate organ function, no prior treatment of metastatic disease; and will be immunotherapy naive. Patients will be randomized 1:1 to receive either dostarlimab 500 mg IV or pembrolizumab 200 mg IV every 3 weeks (Q3W) in combination with pemetrexed 500 mg/m^2 IV Q3W, and cisplatin 75 mg/m^2 or carboplatin 5 mg/mL/min (investigator's choice of CT). Carboplatin/cisplatin treatment will be discontinued after 4 cycles, whereas pemetrexed and dostarlimab or pembrolizumab treatment will continue up to a maximum of 35 cycles or until disease progression, unacceptable toxicity, or death. Patients will be stratified by PD-L1 expression (TPS <1% vs 1%–49% vs ≥50%) and smoking status (never vs former/current). The primary endpoint is ORR of dostarlimab plus CT versus pembrolizumab plus CT assessed by blinded independent central review (BICR) per RECIST v1.1. Secondary endpoints include OS, investigator-assessed PFS per RECIST v1.1, and safety. Exploratory endpoints include duration of response by BICR and investigator-assessed ORR per RECIST v1.1, correlation between PD-L1 expression and ORR, pharmacokinetics and immunogenicity of dostarlimab and potentially pembrolizumab, biomarkers correlated with response, and change in lung cancer symptoms, severity, and health-related quality of life. Enrollment has begun; approximately 240 patients will be enrolled from global sites.

Keywords: Dostarlimab, pd-1 inhibitor, NSCLC

P15.01 Phase II Prospective Study of Adjuvant Pembrolizumab in N2 Positive NSCLC Treated With Neoadjuvant CCRT Followed by Surgery

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Introduction: Nearly one third of patients with newly diagnosed NSCLC is presented at locally advanced stage. Among these patients, standard treatment option for stage IIIA-N2 subgroup is still under discussion with controversies. We hypothesize that immune checkpoint inhibitor consolidation therapy could have an additional role in prolongation of the disease-free survival (DFS) for stage IIIA-N2 NSCLC treated with neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery. **Methods:** This is a phase 2 study evaluating the clinical efficacy and safety of pembrolizumab treatment after CCRT with curative resection in stage IIIA-N2 NSCLC patients (NCT03053856). Patients were treated with five cycles of CCRT, weekly paclitaxel (50mg/m^2) and cisplatin (25mg/m^2) combined with radiotherapy (total of 44Gy over 22 fractions) followed by curative resection. Adjuvant Pembrolizumab (200mg fixed dose) is applied every three weeks up to 2 years or until disease recurrence after the surgery. The primary objective is disease-free survival. The first patient was recruited in October 2017, and this abstract reports the updated follow up data with cutoff date of March 31st, 2021. **Results:** Total of 40 patients were screened, and 37 patients received treatment. Median age was 64 years (range 39-74), and twenty-three were male (62.2%). As a curative surgery, patients received lobectomy (n=34, 91.9%), bi-lobectomy (n=2, 5.4%), or pneumonectomy (n=1, 2.7%). Adenocarcinoma was predominant (n=27, 73.0%). Activating EGFR mutation was observed in 9 patients (24.3%) and ALK fusion in 1 patient (2.7%). After the neoadjuvant CCRT, down-staging were observed in nine patients (24.3%). The total of 12 patients (32.4%) completed planned 2 years of adjuvant pembrolizumab. Among the 25 patients, 18 patients (48.6%) discontinued treatment due to disease recurrence, 4 patients (10.8%) due to the adverse events and 3 patients (8.1%) withdraw the consent. The median follow-up duration was 33.4 months (95% confidential interval [CI] 30.2-36.7), and patients received a median of 19 cycles (range 1-35) of adjuvant pembrolizumab. Disease progression was observed in 20 patients. Median DFS was 19.3 months (95% CI 12.9 – NA). DFS rate was 64.9% at 12 months, 45.9% in 24 months, and 40.8% in 36 months. Median overall survival is not reached. **Conclusion:** This study demonstrated that adjuvant pembrolizumab monotherapy in stage IIIA-N2 patients after neoadjuvant CCRT and surgery is feasible and safe with more than 40% of patients showing disease free survival at 36 months.

Keywords: adjuvant, N2, Pembrolizumab

P15.02 Toripalimab and Platinum-Doublet Chemotherapy as Neoadjuvant Therapy for Potentially Resectable Non-Small Cell Lung Cancer

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Introduction: PD-1/PD-L1 inhibitors as neoadjuvant therapy have shown promising anti-tumor activities in patients with early-stage non-small cell lung cancer (NSCLC). Here, we designed a phase II, single-arm trial to explore the antitumor activity, safety, and feasibility of neoadjuvant toripalimab plus double platinum-based chemotherapy in treatment-naive patients with potentially resectable NSCLC (ClinicalTrials.gov: NCT04144608). **Methods:** Patients with histologically confirmed potentially resectable NSCLC (IIIA-IIIB), non-driver gene mutation, were eligible. All patients received two cycles of toripalimab (240 mg d1), nab-paclitaxel (260 mg/m^2 d1) (non-squamous cell carcinoma: pemetrexed 500 mg/m^2 d1) and carboplatin (AUC 5 d1) or cisplatin (75 mg/m^2 d1) before surgery, every 3 weeks. Preoperative imaging evaluation and surgical indication evaluation were performed within 3-5 weeks after completion of neoadjuvant therapy. Patients who cannot undergo surgery will be evaluated after another 1-2 cycles of neoadjuvant therapy. Within 30 days after surgery, another 2 cycles of adjuvant toripalimab plus chemotherapy were administered, followed by toripalimab monotherapy for 13 cycles (240 mg, Q3W). The primary endpoint was R0 resection rate (defined as the number of patients undergoing surgery who achieved R0 resection divided by all the patients enrolled in this project), and the secondary endpoints were pathologic complete responses (pCR), major pathologic responses (MPR), and safety and feasibility of the neoadjuvant immunotherapy. The related biomarkers of efficacy and adverse events were determined by RNA-sequencing (RNA-seq), whole exome sequencing (WES), and T-cell receptor sequencing (TCR-seq). **Results:** As of Apr 01, 2021, a total of 18 patients were enrolled and received neoadjuvant treatment. After 2-4 cycles of neoadjuvant treatment, 15 patients (2 cycles: 12 patients; 3-4 cycles: 3 patients) downstaged and reached the surgical standards. 3 patients opted for other treatment (1 patient refused surgery, and 2 patients were unsuitable for surgery). The median age was 57 years (range: 41–70), and 13 patients (13/15, 86.7%) were men. 12 patients (12/15, 80.0%) had squamous cell lung cancer, and 8 patients (8/15, 53.3%) were identified with stage IIIB disease. For 18 patients, the R0 resection rate was 83.3% (15/18). 8 patients (8/15, 53.3%) achieved MPR, including 6 patients (6/15, 40.0%) with pCR. No patient had surgical complications. The median duration of follow-up was 6 months (range: 3-14), without any recurrences or death. Grade 3-4 treatment-related adverse events (TRAEs) were not observed, and grade 1-2 TRAEs were reported in 4 patients (4/15, 26.7%). The most common TRAEs were transaminase increased, occurring in 3/15 (20.0%) patients. **Conclusion:** The application of toripalimab in combination with platinum-doublet chemotherapy was found to exhibit good clinical efficacy and tolerability to change treatment strategy in potentially resectable NSCLC. The trial is ongoing, and the biomarker analyses will be available at the meeting.

Keywords: Neoadjuvant, Toripalimab, Potentially resectable NSCLC

P16.01 Clonal Landscape Predicts Outcome in Lung Squamous Cell Carcinoma Patients with a Low Tumor Mutational Burden

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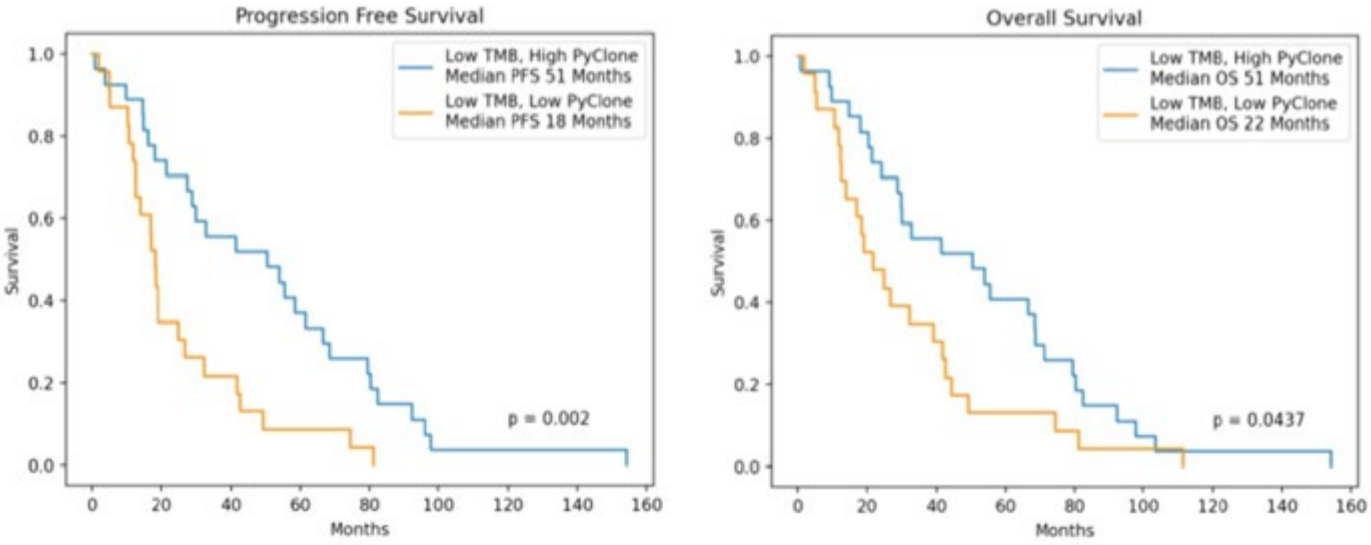
Introduction: Tumor heterogeneity metrics have become widely used in research, however none have been clinically approved. Two such methods of interest are PyClone and Mutant Allele Tumor Heterogeneity (MATH). Although PyClone has shown predictive power in manycancers, no statistically significant relationship has been found in lung squamous cell carcinoma (LUSC) . While MATH has shown clinical implications in head and neck squamous cell carcinoma. To investigate this relationship we integrated tumor mutational burden (TMB), a clinically approved biomarker for immunotherapy, MATH, and PyClone. Patients were classified as high/low if their TMB, MATH, and PyClone values were above or below their respective medians. Together these metrics may yield stronger predictive value than each metric on it's own. **Methods:** Data for 178 patients was obtained from the GDC data portal (SNV and CNV) and the cBioPortal (Clinical). Dividing the total number of somatic mutations by exom size (38Mb) yielded TMB. For PyClone, a minimum cluster size of 2 was used. MATH calculations were performed via maftools, a publicly available python library. TMB, MATH, and PyClone values were able to be calculated for 100 patients who had survival outcome data available. This cohort was composed of 57% Stage I, 24% Stage II, 16% Stage III, and 2% Stage IV patients at an average age of 69. All statistical analysis was performed in python via publicly available libraries. **Results:** Individually, TMB, MATH, and PyClone did not have a statistically significant association with outcome. MATH score did not significantly contribute to statistical power and was not used after initial assessment. Low TMB/High PyClone patients had superior PFS (51 vs. 18 months, p = 0.002, HR 0.39 CI 0.21-0.72) and OS (51 vs. 22 months, p=0.0437, HR 0.56 CI 0.32 - 0.99) than their Low TMB/Low PyClone counterparts. Low TMB/Low PyClone group was 70% Stage I, 22% Stage II, and 8% Stage III with an average age of 73. Low TMB/High PyClone group was 52% Stage I, 30% Stage II, and 18% Stage III with an average age of 68



Conclusion: TMB, MATH, and PyClone are all derived in different ways and may capture different aspects of tumor heterogeneity. When patients were classified based on median TMB and PyClone, clonal distribution measured by PyClone predicted survival in lung squamous cell carcinoma patients with a low TMB. Our study suggests interaction between TMB and clonality in predicting survival, awaiting validation with further studies.

Keywords: PyClone, tumor heterogeneity, tumor mutational burden

P16.02 Atezolizumab, Bevacizumab and Chemotherapy (IMpower150) in Stage IV Non-Small Cell Lung Cancer: The Australian Experience

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Introduction: The IMpower 150 study demonstrated that the addition of atezolizumab and bevacizumab to platinum-doublet chemotherapy resulted in significant improvement in survival, albeit with high rates of treatment-related adverse events. There are limited real world data on the efficacy and toxicity of this regimen to guide routine clinical practice particularly in pre-treated patients (pts) and in those with oncogene driven and leptomeningeal disease. **Methods:** We retrospectively assessed pts with stage IV non-squamous non-small cell lung cancer (NSCLC) treated with the IMpower150 regimen across 12 Australian sites between July 2018 and April 2021. Clinicopathologic and treatment parameters were collected. Toxicity, response rates, progression-free survival (PFS) and overall survival (OS) were analyzed. **Results:** Interim analysis included 54 pts from 3 of the 12 sites with a median follow up of 7.8 months. The median age was 60.5 years (range 33-81), 50% males, 88% were ECOG 0-1 and 61% never-smokers. 15 (28%) pts were treatment-naïve, 11 (20%) pts had 1 prior line of treatment and 28 (52%) had ≥2 prior lines of treatment. Carboplatin and pemetrexed was the most commonly used chemotherapy backbone received by 33 (61%) pts. PDL-1 status was reported in 31 (57%) pts: 35% were PDL-1 negative, 42% PDL-1 between 1 - 50% and 23% were PDL-1 > 50%. EGFR mutations were detected in 36 (67%) pts: 8 had an L858R mutation, 21 an exon 19 deletion, 3 had an exon 18 mutation and 4 had an exon 20 insertion. ALK rearrangements were detected in 3 (6%) pts. Of the remaining 15 (27%) pts 1 had a RET mutation, 6 had a KRAS mutation, 1 pt had a KRAS/TP53 mutation, 1 pt had a TP53 mutation, 1 pt had a MET/RET/TP53 mutations and 1 pt had a MET/ERBB2/PIK3CA/RICTOR/EGFR amplification. 23 (43%) pts had baseline liver metastases, 23 (43%) pts had brain metastases and 11 (20%) pts had leptomeningeal metastases. In those with leptomeningeal metastases 9 had an EGFR mutation, 1 had a KRAS G12C mutation and 1 had a TP53 mutation. In the overall population the objective response rare (ORR) was 58% including 2 pts with a complete response. The ORR for pts with liver metastases was 61%, 57% for pts with brain metastases and 36% for pts with leptomeningeal metastases. Upon progression, 15 (28%) pts received subsequent line treatment. The median PFS and OS were 5.1 months and 8.3 months respectively. The majority of toxicity events were grade 1-2 with 27 (49%) events. There were 25 (45%) grade 3 events, 2 (4%) grade 4 events and there was 1 (2%) grade 5 treatment related death. **Conclusion:** In this largely oncogene driven, heavily pre-treated population the IMpower150 regimen was efficacious and well tolerated including in patients with leptomeningeal metastases.

Keywords: IMpower150, leptomeningeal metastases, oncogene

P16.03 SWItch Maintenance PEmbrolizumab in patients with Non Small Cell Lung Cancer (SWIPE): Final Analysis

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Introduction: Pembrolizumab is indicated for first line use either as monotherapy in patients with >50% PD-L1 overexpression or in combination with platinum doublet chemotherapy, and for second line use in pretreated patients with >1% PD-L1 expression with metastatic Non Small Cell Lung Cancer (NSCLC). There are currently no data for its use as maintenance treatment. SWIPE is a prospective single arm, one stage Phase II study offering Pembrolizumab as maintenance therapy to non-progressors after first line palliative chemotherapy with NSCLC. (NCT 02705820) **Methods:** Standard inclusion and exclusion criteria for checkpoint inhibitors studies apply, however also patients with WHO Performance Status 2 and patients with PD-L1 negative tumours were allowed to participate in this study. Treatment consisted of Pembrolizumab 200 mg fixed dose every 3 weeks. Radiological assessement with CT scans every 9 weeks in the first year. The study employs a one stage phase II Fleming's design using Immune Related (IR) Progression Free Survival (PFS) at 1 year as primary endpoint. Using response hypotheses of H0 < 12 % and Ha> 25%, with a significance level α=0.05 and power 0.8, 48 patients were required to be entered into this study. **Results:** Forty-eight (48) patients were enrolled between July 2016 and March 2019. 39 males and 9 female patients. Median age 66 years (range 40-82). PS WHO 0 for 18 patients, WHO 1 for 25 patients and WHO 2 for 5 patients. Histology: adenocarcinoma in 35 patients and squamous in 13 patients. In terms of best radiological response: 1 patient had a complete radiological response and 6 patients had a partial response. The 1year IR PFS rate is 33.3% (6 month IR PFS 54.2 %). Median IR PFS is 6.3 months (CI 4.2-8.4). The 1 year RECIST PFS rate is 18.8% (6 month RECIST PFS 31.3%). Median RECIST PFS is 2.1 months (CI 0.0-4.2). The 1 year OS rate is 52.1% (6 month OS 72.9%). Median OS is 12.2 months (CI 7.8-16.6). 2 and 3 year OS is 31.2% and 22.9%. Toxicity was mainly grade 1-2, consistent with known toxicity profile of Pembrolizumab. There were three (3) grade 3 auto-immune events; one patient developed diabetes mellitus, one pneumonitis and one adrenal insufficiency, all fully recovered. There was one death during treatment due to sepsis and one due to myocardial infarction, unlikely to be related to Pembrolizumab. **Conclusion:** This maintenance Pembrolizumab study met its primary endpoint of 1 year IR PFS, providing evidence for a clinically meaningful disease control rate at 1 year in a third of patients.

Keywords: Maintenance, immunotherapy, NSCLC

P16.04 A Phase II Clinical Study Evaluating Camrelizumab Combined With Apatinib and Albumin Paclitaxel for Advanced Non-Small Cell Lung Cancer

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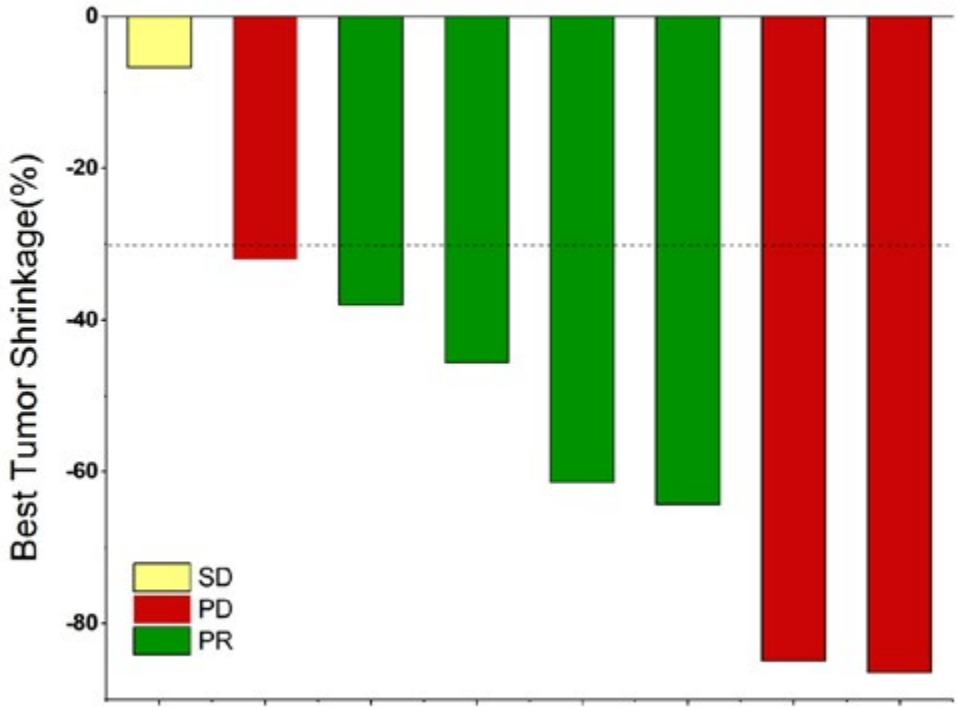
Introduction: Camrelizumab in combination with chemotherapy has been approved as first line therapy in China for NSCLC. It is becoming evident that cytotoxic chemotherapy and angiogenesis inhibitors may enhance therapeutic benefits of immune checkpoint inhibitors. CAPAP-LUNG is the first single arm, multi-center, phase II trial of Camrelizumab combined with apatinib and albumin paclitaxel without platinum for first-line treatment of non-squamous NSCLC. **Methods:** In this study, patients diagnosed with IIIB-IV non-squamous NSCLC without sensitizing EGFR and ALK alteration were enrolled to receive Camrelizumab (200mg/3w) in combination with Albumin Paclitacxel (135mg/m^2, d1, d8/3w, 4-6 cycles) and Apatinib (250mg Qd po for 5 days, take rest for 2 days every week). The primary endpoints were progression-free survival, and secondary endpoints were objective response rate (ORR) and DCR assessed by RECIST v1.1. This study is registered with ClinicalTrials.gov, NCT04459078 (follow-up is ongoing). **Results:** Between Aug 18, 2020, and Apr 1, 2021, a total of 8 patients were evaluable. The objective response rate (ORR) was 50% (4/8, 95%CI 17.5-82.6), and the disease control rate (DCR) was 62.5% (5/8, 95%CI 25.9-89.8). The research treatment was well tolerated, with 2 (15.4%) patients experiencing grade 3 treatment-related adverse events and no grade 4 treatment-adverse. Grade 3 treatment-related adverse events were decreased neutrophil count (1 [7.7%]), liver function damage (1 [7.7%]), and pulmonary infection (1 [7.7%]). It is worth mentioning that there was a female patient with poor physical condition and close to paralysis before enrollment, but after the treatment, the patient's physical condition improved and move freely.



Conclusion: Camrelizumab combined with albumin paclitaxel and apatinib showed good antitumor activity with a manageable safety profile for the first-line treatment of advanced non-squamous NSCLC.

Keywords: non-small cell lung cancer, Camrelizumab, immunotherapy

P16.05 Real World Data of First-Line Treatment With Pembrolizumab for Highly PD-L1-Expressing NSCLC

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Introduction: Programmed cell death-1 (PD-1) / programmed cell death-ligand 1 (PD-L1) inhibitors have shown efficacy for advanced non-small cell lung cancer (NSCLC) and are now standard therapies for patients with advanced-stage NSCLC. It is unknown whether pembrolizumab monotherapy (MONO) or pembrolizumab plus chemotherapy (COMB) should be selected for patients exhibiting high PD-L1 expression (tumour proportion score [TPS] of 50% or greater). However, there are few reports on the current status of first-line treatment with pembrolizumab for highly PD-L1 expressing NSCLC in clinical practice. **Methods:** This study was a retrospective, multicentre study of patients with NSCLC who received MONO or COMB as first-line treatment between December 2018 and January 2020. We reviewed the medical records of 300 patients with advanced-stage or recurrent NSCLC having PD-L1 TPS of ≥50% and no documented EGFR, ALK, or ROS1 aberrations. To control the unbalanced conditions between the two groups at baseline, we implemented a 1:1 propensity score-matched pairing method using age, performance status (PS), and PD-L1 status as adjustment factors, and the 1:1 matching yielded matched pairs of 80 patients each. **Results:** One hundred and sixty-six patients (55%) received MONO and 134 patients (45%) received COMB. The median ages were 74 (range, 52-89) and 68 (range, 45-84) years among patients who received MONO and COMB ($p < 0.01$), respectively, and the patients who received COMB had better PS (0–1) ($p < 0.01$). With a median follow-up time of 10.6 months (range, 0.1–20.6 months), the median progression-free survival (PFS) was 7.1 months (95% confidence interval [CI], 5.4–11.1) in those who received MONO and 13.1 months (95% CI, 10.2–not reached [NR]) in those who received COMB (hazard ratio, 0.64; 95% CI, 0.38–1.1). In selected subgroup analysis, the PFS benefit of COMB was observed in the population with PD-L1 TPS of ≥90% and age <75 years. Meanwhile, in the patients with PS 2, PFS was shorter in those who received COMB than that in MONO. The objective response rates were 41% (71/173) and 67.4% (91/135) in those who received MONO and COMB, respectively. Treatment discontinuation for any reason occurred in 78% (129/166) and 63% (84/134) of the patients who received MONO and COMB, respectively. Regarding severe adverse events, 36 of 166 (21.7%) patients and 28 of 134 (20.1%) patients discontinued MONO and COMB, respectively. After propensity score matching, the median PFS was 12.4 months (95% CI, 6.2–NR) and 13.0 months (95% CI, 6.6–17.1) in those who received MONO and COMB, respectively. **Conclusion:** Based on this real-world cohort, we believe that COMB may be a suitable first-line treatment for highly PD-L1 expressing NSCLC considering that COMB was not inferior to MONO in the propensity score matching analysis, and MONO may be used depending on a patient's background, such as age and PS. In the present study, the observation period was short; thus, it is necessary to extend the observation period and obtain detailed data on long-term safety and overall survival.

Keywords: treatment with pembrolizumab, advanced non-small cell lung cancer (NSCLC), high PD-L1 expression

P16.06 Comparison of Clinical Outcomes of Patients With Advanced NSCLC In Clinical Trials and in the Real World Received PD-1/PD-L1 Inhibitor

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Introduction: Although PD-1/PD-L1 inhibitors have become the standard treatment for patients with advanced non-small cell lung cancer (NSCLC), data from clinical trials are difficult to be verified in the real world. This study aims to compare the differences in population characteristics, treatment modes and clinical outcomes of advanced NSCLC patients received PD-1/PD-L1 inhibitors between the real-world (RWS) and the clinical study (RCT). **Methods:** This study enrolled 305 advanced NSCLC patients who received at least one PD-1/PD-L1 inhibitor treatment selected in the Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital Information System and the Zero Krypton database during January 2016 to September 2019. The patients were divided into RWS group and RCT group. The PD-1/PD-L1 inhibitors included pembrolizumab, sintilizumab, nivolizumab, tislelizumab, carrelizumab, teriprizumab, durvalizumab and Atezolizumab. We performed paired analysis in clinical characteristics and treatment modes. **Results:** There were 155 cases in the RCT group and 150 cases in the RWS group. The RCT group consisted of higher proportion in male (79.4%) and squamous-carcinoma type (41.3%) than the RWS group, while more patients of brain metastasis (28%) and combination therapy (50.7%) in the RWS group. The ORRs were 42.4% and 20.6% respectively in the RCT and RWS groups receiving first-line treatment with PD-1/PD-L1 inhibitors, and the difference was statistically different. Moreover, the ORRs were 42.4% and 20.6% respectively in the RCT and RWS groups receiving PD-1/PD-L1 inhibitor as second-line treatment, without statistical difference. The progression-free survival (PFS) was 15.5 vs. 13.5 months in the RCT and RWS groups (P=0.91), and the median overall survival (OS) was 25.4 vs. 33.8 months respectively (P= 0.24), with no statistical difference. After propensity match of baseline characteristics of the two groups of patients, it contained 108 patients in the RCT and RWS groups. The PFS was 13.3 vs. 13.3 months in the RCT and RWS groups (P=0.47), and the median OS was 21.1 vs. 23.2 months (P=0.58), with no statistical difference. **Conclusion:** Although more female, brain metastases and adenocarcinoma patients receiving PD-1/PD-L1 inhibitors in the real world, the clinical benefits were consistent with those in clinical trials. The results of propensity matching on the baseline characteristics of patients supported this conclusion.

Keywords: real-world, Immune checkpoint inhibitors, non-small lung cancer

P16.07 ARC-10: Phase 3 Study of Zimberelimab ± Domvanalimab vs Standard Chemotherapy in Front-Line, PD-L1-High, Metastatic NSCLC

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Introduction: Despite improvements in the clinical management of locally advanced or metastatic non-small cell lung cancer (NSCLC) that have been associated with programmed cell death protein 1/programmed death ligand (PD-[L]1) inhibition, there remains an urgent need for new treatment options to improve long term outcomes. Previous studies have shown a correlation between tumors with high expression of PD-L1 (PD-L1-high) and antitumor activity associated with anti–PD-(L)1 monoclonal antibody (mAb) treatment in patients with metastatic NSCLC. Early studies have shown that when PD-1 pathway inhibition is combined with blockade of the immunosuppressive T cell Immunoglobulin and ITIM domain (TIGIT) pathway, patients with PD-L1-high NSCLC have higher response rates and greater progression-free survival (PFS) than when the PD-1 pathway is inhibited alone. Zimberelimab is a human IgG4 mAb that targets PD-1. Domvanalimab is a humanized IgG1 mAb that targets TIGIT. This study will investigate the efficacy of zim monotherapy compared with platinum doublet chemotherapy or zim + dom in patients with PD-L1-high NSCLC. **Methods:** ARC-10 (NCT04736173) is a phase 3, randomized, multicenter, open-label study. Eligible patients are adults with treatment-naive, locally advanced or metastatic (stage IIIb or IV), squamous or non-squamous NSCLC with ≥1 measurable lesion(s) (per RECIST v1.1) and high expression of PD-L1 (TPS ≥50), no genomic tumor aberrations for which there is an approved and available therapeutic (eg, EGFR, ALK, ROS, BRAF, NTRK), and an ECOG performance score of 0–1. Approximately 625 patients will be randomized 1:2:2 into Arm A (carboplatin + paclitaxel or pemetrexed), Arm B (zimberelimab monotherapy: 360 mg intravenously [IV] once every 3 weeks [Q3W]), and Arm C (zimberelimab: 360 mg IV Q3W + domvanalimab: 15 mg/kg IV Q3W). Arm A patients may crossover to Arm B upon documented PD; however, no crossover is allowed from Arm B to Arm C. For Arm A vs Arm B, the primary endpoint is overall survival (OS) and for Arm B vs Arm C, the co-primary endpoints are investigator-assessed PFS and OS; additional endpoints include quality of life assessments and safety. Study recruitment is planned in Asia, Latin America, Africa, and Eastern Europe.

Keywords: PD-L1, TIGIT

P17.01 KEYNOTE-407 China Extension Final Analysis: Pembrolizumab Plus Chemotherapy for the Treatment of Metastatic Squamous NSCLC

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Introduction: Consistent with the global KEYNOTE-407 study, in the KEYNOTE-407 China extension study (NCT03875092), pembrolizumab + chemotherapy improved outcomes over placebo + chemotherapy in patients with previously untreated metastatic squamous NSCLC enrolled in mainland China. Median OS was 17.3 (95% CI, 14.1–NR) months for pembrolizumab + chemotherapy and 12.6 (95% CI, 9.6–not reached [NR]) months for placebo + chemotherapy (HR, 0.44 [95% CI, 0.24–0.81]). We report the protocol-specified final analysis from the KEYNOTE-407 China extension study. **Methods:** Patients aged ≥18 years with previously untreated metastatic squamous NSCLC enrolled in mainland China were randomized 1:1 (stratified by PD-L1 TPS [≥1%/<1%]) to receive pembrolizumab or placebo + carboplatin and paclitaxel for 4 cycles Q3W, then pembrolizumab or placebo for up to 35 cycles. Eligible patients with confirmed PD could cross over to receive pembrolizumab. Primary endpoints were OS and PFS per RECIST v1.1 by blinded central review. **Results:** 125 patients were randomized; 65 to pembrolizumab + chemotherapy and 60 to placebo + chemotherapy. Median (range) time from randomization to database cutoff (September 30, 2020) was 28.1 (25.1–40.9) months. 39 patients (65.0%) in the placebo + chemotherapy group received subsequent anti PD-(L)1 therapy, 38 of whom received pembrolizumab in the on-study crossover. Pembrolizumab + chemotherapy improved OS (median OS [95% CI], 30.1 [18.2–NR] months vs 12.7 [9.4–17.3] months) and PFS (median [95% CI], 8.3 [6.2–10.5] months vs 4.2 [4.0–5.4] months) compared with placebo + chemotherapy in the ITT population, irrespective of PD-L1 status (**Table**). 2-year OS and PFS rates were 56.9% and 24.2% in the pembrolizumab + chemotherapy group, and 31.7% and 3.3%, respectively, in the placebo + chemotherapy group. ORR (95% CI) was 80.0% (68.2%–88.9%) with pembrolizumab + chemotherapy vs 43.3% (30.6%–56.8%) with placebo + chemotherapy. Median DOR (range) was 7.1 (1.7+ to 29.6+) months vs 3.5 (2.4–9.0) months. 58 patients (89.2%) experienced grade 3 5 AEs in the pembrolizumab + chemotherapy group and 52 (86.7%) in the placebo + chemotherapy group. Immune-mediated AEs and infusion reactions occurred in 22 patients (33.8%) in the pembrolizumab + chemotherapy group and 6 (10.0%) in the placebo + chemotherapy group.

Table

	All patients (n = 125)	PD-L1 TPS ≥1% (n = 72)	PD-L1 TPS <1% (n = 48)
OS, HR (95% CI)	0.44 (0.28–0.70)	0.41 (0.22–0.77)	0.50 (0.25–1.01)
PFS, HR (95% CI)	0.35 (0.24–0.52)	0.30 (0.18–0.51)	0.42 (0.22–0.77)

Conclusion: Pembrolizumab + chemotherapy as first-line treatment improved OS and PFS with durable long-term benefit compared with placebo + chemotherapy in patients with squamous NSCLC, regardless of PD-L1 expression, enrolled in mainland China. These findings, consistent with those from the global KEYNOTE-407 study, support pembrolizumab + chemotherapy as first-line therapy in this population.

Keywords: Pembrolizumab, metastatic squamous NSCLC, immunotherapy

P17.02 RATIONALE 307: A Subgroup Analysis of Tislelizumab Plus Chemo vs Chemo Alone As 1L Treatment for Stage IIIB Advanced Sq NSCLC

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Introduction: Tislelizumab - a humanized, monoclonal antibody for programmed cell death protein 1 - has demonstrated significantly improved progression-free survival (PFS) and reduced risk of progression versus standard of care in advanced lung cancer (NCT03432598, NCT03594747). We conducted a Phase 3, multicenter, randomized, open-label study to assess the safety and efficacy of tislelizumab plus chemotherapy in patients with advanced squamous non-small cell lung cancer (NSCLC) (NCT03594747). Here, we report results from patients with stage IIIB disease. **Methods:** Adults in China with treatment-naïve histologically confirmed locally advanced or metastatic (stage IIIB or IV) squamous NSCLC not amenable to surgery or not suitable for chemoradiation were randomized 1:1:1 to Arm A: tislelizumab (200 mg) plus paclitaxel 175 mg/m^2 and carboplatin AUC 5 (every 3 weeks [Q3W] on day 1); Arm B: tislelizumab plus nab-paclitaxel 100 mg/m^2 (Q3W on days 1, 8 and 15) plus carboplatin (Q3W on day 1); or Arm C: paclitaxel plus carboplatin (Q3W on day 1). Paclitaxel, nab-paclitaxel and carboplatin were administered for 4–6 cycles. All treatments were administered intravenously. Stratification factors were disease stage (IIIB vs IV), and programmed death-ligand 1 expression (<1% vs 1–49% vs ≥50% tumor cells). Tislelizumab was administered until loss of benefit, withdrawal or start of new anticancer therapy. In this subgroup analysis, PFS, objective response rate (ORR) (assessed by independent review committee) and safety were evaluated in patients with stage IIIB disease. **Results:** Overall, 122/360 (33.9%) patients had stage IIIB NSCLC. Patients were randomized to Arm A (38 patients), B (40 patients) or C (44 patients). The median age was 61 years (range 34–74 years). At median follow-up time of 8.6 months across all arms, PFS was numerically longer, and ORR higher, respectively, with tislelizumab (Arms A and B) versus chemotherapy alone (Arm C) (Table, PFS: HR=0.402 [Arm A] vs 0.372 [Arm B]). The PFS benefit observed was consistent with the ITT population (Table). TEAEs (≥1) and Grade ≥3 TEAEs were similar across all arms (Table). No new safety signals were observed. Laboratory abnormalities were the most commonly reported TEAEs across all arms. **Conclusion:** In this subgroup analysis, a clinically meaningful improvement in PFS and higher ORR was observed with tislelizumab plus chemotherapy versus standard of care in patients with stage IIIB advanced squamous NSCLC. The safety and efficacy profile of tislelizumab was consistent with the overall population.

Table

	Arm A (N=38)	Arm B (N=40)	Arm C (N=44)
Number of patients discontinued from the study	5 (13.2)	5 (12.5)	5 (11.4)
Primary reason for study discontinuation			
Death	4 (10.5)	3 (7.5)	4 (9.1)
Voluntary withdrawal	1 (2.6)	2 (5.0)	1 (2.3)
Number of patients remained on study	33 (86.8)	35 (87.5)	39 (88.6)
Efficacy*	Arm A (N=38)	Arm B (N=40)	Arm C (N=44)
Median PFS in patients with stage IIIB disease, months	9.8	11.0	5.6
95% CI	5.95, NE	7.56, NE	4.17, 7.43
HR† (95% CI)	0.402 (0.215, 0.750)	0.372 (0.202, 0.686)	-
ORR, n (%)	32 (84.2)	33 (82.5)	26 (59.1)
95% CI	68.7, 94.0	67.2, 92.7	43.2, 73.7
	Arm A (N=120)	Arm B (N=119)	Arm C (N=121)
Median PFS in the ITT population, months	7.6	7.6	5.5
95% CI	5.95, 9.79	5.75, 11.01	4.21, 5.65
HR‡ (95% CI)	0.524 (0.370, 0.742)	0.478 (0.336, 0.679)	-
Safety§, n (%)	Arm A (N=38)	Arm B (N=40)	Arm C (N=43)
Patients with ≥1 TEAE	38 (100.0)	39 (97.5)	43 (100.0)
Related to any component of study treatment	37 (97.4)	39 (97.5)	43 (100.0)
Related to tislelizumab	34 (89.5)	35 (87.5)	NA
Related to any component of chemotherapy	37 (97.4)	39 (97.5)	43 (100.0)
Grade ≥3 TEAEs	34 (89.5)	35 (87.5)	34 (79.1)
Related to any component of study treatment	33 (86.8)	34 (85.0)	34 (79.1)
Related to tislelizumab	14 (36.8)	16 (40.0)	NA
Related to any component of chemotherapy	33 (86.8)	34 (85.0)	34 (79.1)
Laboratory abnormalities	25 (65.8)	24 (60.0)	18 (41.9)
Serious TEAEs	12 (31.6)	18 (45.0)	7 (16.3)
Grade ≥3	11 (28.9)	15 (37.5)	4 (9.3)
Related to any component of study treatment	8 (21.1)	10 (25.0)	6 (14.0)
Related to tislelizumab	8 (21.1)	7 (17.5)	NA
Related to any component of chemotherapy	5 (13.2)	7 (17.5)	6 (14.0)
Laboratory abnormalities	4 (10.5)	2 (5.0)	1 (2.3)
TEAEs that led to permanent discontinuation of any component of study treatment	5 (13.2)	12 (30.0)	6 (14.0)
TEAEs that led to death	0 (0.0)	1 (2.5)	1 (2.3)

Data are reported for patients in the stage IIIB NSCLC subgroup unless otherwise indicated.
*Efficacy analysis set (includes all randomized patients); †Unstratified; ‡Stratified; §Safety analysis set (includes all randomized patients who received ≥1 dose of any component of study drug).
CI, confidence interval; HR, hazard ratio; ITT, intent-to treat; NA, not applicable; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Keywords: PD-1, NSCLC, immunotherapy

P17.03 Sintilimab With Two Cycles Nab-Paclitaxel / Platinum as First Line Therapy for Advanced Squamous Non–Small-Cell Lung Cancer

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Introduction: Although immune checkpoint inhibitors (ICIs) in combination with chemotherapy has become the new stand of care in NSCLC, the optimal treatment cycles of chemotherapy is still debating. Chemotherapy is able to sensitize immune response in combination with ICIs via inducing tumor cell apoptosis and releasing neoantigen in initial combining cycles. In contrast, increasing cycles of chemotherapy might play negative roles of toxicity rather than synergetic effects. Therefore, this open-lable, multi-center, phase II study is to investigate the efficacy and safety of sintilimab in combination with short-course (two cycles) nab-paclitaxel / platinum in treatment naïve advanced squamous NSCLC patients. **Methods:** Key inclusion criteria includes: pathologically confirmed squamous NSCLC without known sensitizing EGFR/ALK/ROS1 alterations, stage IIIb-IV (AJCC 8th), unresectable or inappropriate for definitive chemo-radiotherapy, previously untreated for systemic disease, Eastern Cooperative Oncology Group (ECOG) performance status score (PS) 0 or 1, and had at least one measurable lesion per RECIST v1.1. Eligible patients will receive Sintilimab (200mg), nab–paclitaxel (260mg/m2), and cisplatin (75mg/m2) or carboplatin (AUC 5) on day 1 every 3 weeks (Q3W) for 2 cycles. Patients without disease progression (PD) will continue to receive sintilimab (200mg, day1, Q3W) maintenance until PD, intolerable toxicity, death, or for up to 2 years. Primary end point is progression free survival (PFS). Secondary end points are objective response rate (ORR), duration of response (DOR), disease control rate (DCR), overall survival (OS), safety and quality of life (QoL). **Results:** From May 2020 to March 2021, 21 patients were enrolled and treated. Median age was 65. The majority of patients were female (20/21), PS 1 (19/21), current or former smokers (16/21), and stage IV (16/21). Median follow-up is 3.19 months (range 1.38, 10.02) until Mar 18 2021. Median PFS was not reached (95%CI: 8.57mo–NA) with 4 events. 16 patients had received at least once tumor assessment. ORR was 75% (12/16) and DCR was 93.8% (15/16)among evaluable patients. Median time to response was 1.58 mo (range 1.35, 4.17), and median DOR was not arrived. At data cutoff, 16 patients (76.2%) experienced treatment emergent adverse events (TEAEs) of any-grade. Grade 3-4 TEAE happened in 3 patients: 1 with grade 3 chest distress, 1 with grade 3 neutropenia, and another with grade 4 neutropenia. Immune-related AE occurred in one patient with grade 1 increased ALT. The patient with grade 4 neutropenia had paclitaxel dose reduction during cycle 2, which was the only case of dose interruption. No TEAEs leading to treatment discontinuation or death. **Conclusion:** In this preliminary analysis, sintilimab combined with short-course nab-paclitaxel / platinum showed favorable tumor response and acceptable safety profile as first line therapy for advanced squamous non–small-cell lung cancer. Enrollment continues and more efficacy and safety data will be presented.

Keywords: Immunotherapy, Chemotherapy, Squamous NSCLC, PD-1 Inhibitor

P18.01 Treatment Efficacy of HER2-Mutant Lung Adenocarcinoma by Immune Checkpoint Inhibitors

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Introduction: Immune checkpoint inhibitors (ICIs) have dramatically improved clinical outcomes of lung cancer. However, there is limited studies focus on evaluating efficacy of ICIs for patients with human epidermal growth factor receptor 2 (HER2)-mutant non-small cell lung cancer (NSCLC). **Methods:** We conducted a multicenter retrospective study of patients with HER2-positve lung adenocarcinoma at Shanghai Pulmonary Hospital, Shanghai Chest Hospital and the First Affiliated Hospital of Wenzhou Medical University between 2016 and 2021. HER2 alteration was tested using amplification refractory mutation system (ARMS) and confirmed by DNA direct sequencing if necessary. Tumor responses, survival data and other baseline characteristics were examined. **Results:** 24 patients with HER2-mutant lung adenocarcinoma who were treated with PD-1/PD-L1 inhibitors were enrolled. The overall objective response rate (ORR) was 33.3%, disease control rate (DCR) was 83.3% and median PFS was 7.4 months. Among the 7 patients receiving ICIs as first-line therapy, 3 patients had partial response (PR) and 4 had stable disease (SD), achieving ORR of 42.9%, and DCR of 100%. As for treatment data, 5 patients received ICIs before EGFR/HER2-targeting drugs (group 1), 6 patients received ICIs after EGFR/HER2-targeting drugs (group 2) and the other 13 patients never treated with EGFR/HER2-targeting drugs until the follow-up end date (1 April, 2021) (group 3). However, there was no statistic difference of ORR or DCR between those three groups (ORR: 60% vs. 33.3% vs. 23.1%, P = 0.330; DCR: 80% vs. 100% vs. 76.9%, P = 0.444). **Conclusion:** Our retrospective study provides clinical evidence that HER2-mutant patients receiving PD-1/PD-L1 inhibitors at an early time may potentially be an effective treatment strategy to improve survival outcomes of patients with HER2-mutant NSCLC.

Keywords: HER2-mutant, PD-1/PD-L1 inhibitors, non-small cell lung cancer

P19.01 RATIONALE-303 Phase 3 Tislelizumab vs Docetaxel in Previously Treated Advanced NSCLC: China Subgroup Analysis

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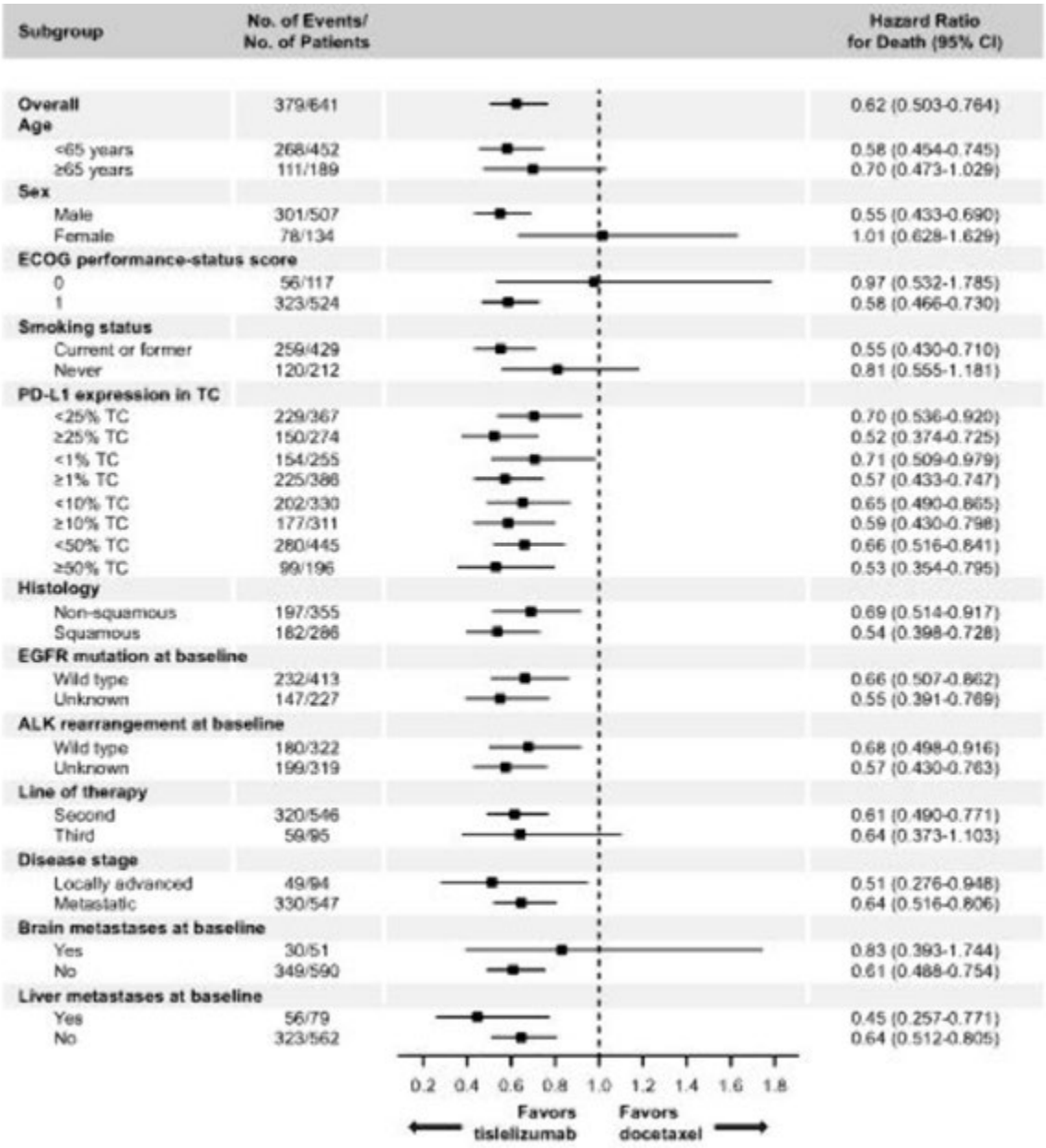
Introduction: Tislelizumab is an anti-PD-1 antibody engineered to minimize Fc R binding on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy. RATIONALE-303 (NCT03358875) demonstrated improved overall survival (OS) for tislelizumab vs docetaxel in the intention-to-treat (ITT) and PD-L1 ≥25% analysis sets with a manageable safety profile. **Methods:** Patients with squamous/non-squamous NSCLC who progressed during/after platinum-based doublet chemotherapy were randomized 2:1 to receive tislelizumab (200 mg) or docetaxel (75 mg/m^2) Q3W. Stratification factors included histology (squamous vs non-squamous), lines of therapy (2L vs 3L) and PD-L1 expression (≥25% vs <25% tumor cells). The primary endpoint was OS (ITT and PD-L1). Secondary endpoints were objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) and safety. Here, efficacy and safety of tislelizumab vs docetaxel are assessed in Chinese patients. **Results:** 641 Chinese patients were randomized. Median age was 61.0 years and 79.1% were male. Baseline characteristics were similar to the ITT population. 87.7% had discontinued treatment and 11.9% received subsequent immunotherapy. At a median follow-up of 20.7 months, OS was significantly longer for tislelizumab vs docetaxel (median OS: 17.8 vs 11.5 months; HR=0.62; P<0.0001). OS improvement with tislelizumab was observed in most subgroups (Figure). PFS, ORR and DoR were also improved for tislelizumab vs docetaxel (Table). 96.7% (tislelizumab) and 98.6% (docetaxel) of patients experienced ≥1 TEAE and 39.0% (tislelizumab) and 75.1% (docetaxel) of patients experienced a ≥grade 3 TEAE. 1.7% (tislelizumab) and 1.4% (docetaxel) experienced treatment-related TEAEs leading to death. The top three most common TEAEs were anemia, ALT increase and cough in the tislelizumab group and alopecia, anemia and neutrophil count decrease in the docetaxel group

(Table)



Conclusion: Consistent with the ITT analysis, clinical improvement was shown with tislelizumab in Chinese patients with advanced NSCLC and tislelizumab had a tolerable and manageable safety profile.

Table: Efficacy and safety

Efficacy[a]	Tislelizumab (n=423)		Docetaxel (n=218)	
Median OS, mo (95% CI)	17.8 (15.44, 20.90)		11.5 (9.43, 13.93)	
HR (95% CI)[b]	0.62 (0.500, 0.761)			
P-value[c]	< 0.0001			
Median PFS, mo (95% CI)	4.1 (3.42, 4.34)		2.3 (2.14, 3.58)	
HR (95% CI)[b]	0.61 (0.501, 0.741)			
P-value[c]	< 0.0001			
ORR, n (%)	91 (21.5)		12 (5.5)	
Median DoR, mo (95% CI)	13.5 (8.54, 21.78)		4.2 (0.56, 6.24)	
Safety[d]	Tislelizumab (n=423)		Docetaxel (n=209)	
TEAEs ≥ 15% of patients in either arm, n (%)	All grade	≥ Grade 3	All grade	≥ Grade 3
Anemia	132 (31.2)	17 (4.0)	98 (46.9)	14 (6.7)
ALT increased	98 (23.2)	3 (0.7)	38 (18.2)	0 (0.0)
Cough	93 (22.0)	5 (1.2)	36 (17.2)	1 (0.5)
AST increased	92 (21.7)	4 (0.9)	30 (14.4)	1 (0.5)
Weight decreased	77 (18.2)	4 (0.9)	21 (10.0)	0 (0.0)
Decreased appetite	69 (16.3)	5 (1.2)	46 (22.0)	2 (1.0)
Hypoalbuminemia	66 (15.6)	0 (0.0)	37 (17.7)	0 (0.0)
Constipation	55 (13.0)	0 (0.0)	38 (18.2)	0 (0.0)
Asthenia	54 (12.8)	3 (0.7)	45 (21.5)	9 (4.3)
White blood cell count decreased	20 (4.7)	1 (0.2)	72 (34.4)	46 (22.0)
Neutrophil count decreased	15 (3.5)	3 (0.7)	91 (43.5)	68 (32.5)
Leukopenia	14 (3.3)	1 (0.2)	59 (28.2)	36 (17.2)
Neutropenia	7 (1.7)	2 (0.5)	56 (26.8)	51 (24.4)
Alopecia	4 (0.9)	0 (0.0)	106 (50.7)	1 (0.5)

[a]Efficacy analysis set – China; [b]Stratified; [c]One-sided stratified log-rank test; [d]Safety analysis set - China.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DoR, duration of response; HR, hazard ratio; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Keywords: PD-1, NSCLC, immunotherapy

P19.02 Sintilimab Plus Docetaxel in Previously Treated Advanced NSCLC, Updates on Progression-Free and Overall Survival

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Introduction: Background: Our phase single-arm phase 2 study previously showed favorable efficacy of sintilimab plus docetaxel as second line therapy for advanced Chinese NSCLC patients. Here we presented the updated survival and safety data. **Methods:** Eligible patients were standard platinum doublet failure advanced NSCLC patients, who had not received any ICIs before. EGFR/ALK positive patients must be TKIs failure or intolerable. Participants would receive docetaxel (75mg/m^2, day 1) plus sintilimab (200mg, day 3) every 3 weeks for 4-6 cycles followed by sintilimab maintenance until disease progression, unacceptable toxicity, or up to 2 years. The primary end point is progression-free survival (PFS) per RECIST v1.1. Secondary end points included overall response rate (ORR), duration of response (DOR), overall survival (OS), and safety. **Results:** From 10/2019 to 11/2020, 40 patients were enrolled. Most were male (77.5%) and adenocarcinoma (87.5%). 25% (10/40) patients and 12.5% (5/40) had brain and liver metastasis at baseline, separately. Median follow-up was 9.0 months (range 1.6-16.2) as of data cut-off (2/19/2021). 13 patients temporarily suspended study treatment due to COVID-19, while 11 patients resumed treatment after documented progression-free. Among all, 9 patients were still on study treatment until data cut-off. Median PFS was 5.78 months (95%CI 4.3-8.28), and PFS rates at 6 months and 12 months were 47% and 23%. Median OS was 12.45 months (95%CI 5.82-12.62). 12 months OS rates was 64%. Of the 37 evaluable patients, ORR is 32.43% (95%CI 18.01%, 49.79%), DCR is 89.19% (95%CI 74.58%, 96.97%). Median DOR was 6.46 months (95% 1.28, NA). Median TTR (Time to Response) was 3.89 months (95% 1.61, 4.99). Efficacy of key subgroups are presented in Table 1. Table 1. Selected subgroup analysis of Sintilimab Plus Docetaxel efficacy in Treated NSCLC

Subgroup	Category	N	ORR%(95%CI)	mPFS months(95%CI)
Histological type	Adenocarcinoma	35	33.33(17.96,51.83)	5.78(4.14,8.28)
	Squamous cell carcinoma	5	25(0.63,80.59)	8.46(2.3,NA)
Smoking status	YES	22	30(11.89,54.28)	5.72(3.02,6.51)
	NO	18	35.29(14.21,61.67)	8.28(4.14,9.36)
Brain/meningeal metastasis	NO	30	31.03(15.28,50.83)	5.78(3.55,8.77)
	YES	10	37.5(8.52,75.51)	6.51(1.58,NA)
Driver gene mutation	KRAS +	6	25(0.63,80.59)	6.51(2.96,NA)
	EGFR-and TP53+	19	37.5(15.2,64.57)	5.78(3.55,9.36)
Best overall response of first-line treatment	PR	6	40(5.27,85.34)	5.22(2.3,NA)
	SD	13	41.67(15.17,72.33)	8.77(4.3,NA)
	PD	11	45.45(16.75,76.62)	8.28(1.58,NA)
First-line treatment (EGFR wild type)	Chemotherapy	24	36.36(17.2,59.34)	8.28(4.3,12.62)
	Chemotherapy +Bevacizumab	12	36.36(10.93,69.21)	5.72(1.77,6.01)
Best overall response of study treatment	PR	11	-	NA(5.52,NA)
	SD	21	-	4.86(3.55,6.01)
Maximum change of target lesions from baseline	≤ 20%	19	-	8.77(5.78,NA)
	≤0%	29	-	8.28(5.52,12.62)
	>0%	8	-	2.37(1.02,NA)

Median treatment duration was 4.4 months (range 0.1-13.9). Overall, 72.5% (29/40) patients had experienced treatment-related adverse events (TRAEs), including 15% (6/40) grade ≥3 TRAEs. No AEs led to treatment discontinuation or death. The most common TRAEs were leukopenia (32.5%), neutropenia (17.5%), alopecia (12.5%), lymphopenia (7.5%), fatigue (7.5%) and diarrhea (7.5%). 27.5% (11/40) patients experienced potential immune related AEs (irAEs), including 1 grade 3 gamma-glutamyltransferase increase, 1 grade 2 hypothyroidism and 3 grade 2 pneumonitis. **Conclusion:** This is the first study of a PD-1 inhibitor plus chemotherapy in advanced Chinese NSCLC patients who had failed first-line standard therapy. The encouraging efficacy and tolerable safety profile suggest a potential role of this combination in second-line setting. Clinical trial information: ChiCTR1900027634.

Keywords: non-small cell lung cancer, combination chemoimmunotherapy, second line

P21.01 Selected ctDNA Panel Gene Sequencing for Neoantigen Discovery and Survival Prediction in Patients With Stage IV Non-Small Cell Lung Cancer

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Introduction: Tumor neoantigens are ideal targets for immunotherapy with current work largely limited on the whole-exome sequencing data from tumor tissues which are often limited by tissue availability. The ctDNA is now widely used for genomic testing of selected panel genes but has not been tested for neoantigen assessment. The purposes of this study were to study 1) whether is it possible to discover tumor neoantigens through panel gene sequencing of ctDNA, and 2) whether the tumor neoantigens of ctDNA has significance on the prognosis. **Methods:** Patients with metastatic lung cancer for genomic sequencing results were eligible. Paired plasma, white blood cells and tumor biopsies tissue (if available) were tested by commercial vendors (the Nanjing Shihe Jiyin Bio Inc. or ShenZhen HaploX Bio Co.). After screening for non-synonymous mutations by targeting NGS, 8-11 length amino acids containing the mutation site were queried using the MHCflurry, MHCnuggetsI, MHCnuggetsII, NNalign, NetMHC, PickPocket, SMM, SMMPMBEC and SMMalign to predict the binding affinity of mutant peptides to the high-frequency HLA class I alleles in East Asian population, including HLA-A*24:02, HLA-A*11:01, HLA-A*02:01, HLA-B*40:01, HLA-B*46:01, HLA-B*51:01, HLA-C*07:02, HLA-C*01:02, HLA-C*03:04. Finally, the mutant peptides with binding affinity less than 500nM were selected as candidate neoantigens. Disparities in patient survival were analyzed by multivariate Cox regression models. Multivariate correlation analysis was performed using Pearson models. $P < 0.05$ were significant. **Results:** Between March 2020 and January 2021, a total of 49 patients with stage IV lung cancer were recruited. The ctDNA or tissue tumor DNA of 11 patients were sequenced by a commercially available 425-gene NGS panel from Shihe. The sequencing results of the remaining 38 patients were obtained using the 680-gene NGS panel from HaploX. Of all 49 patients, 45 had tissue samples and 48 had baseline blood samples. In the baseline ctDNA sequencing results, 70.1% patients had at least one genomic alteration. A total of 12 mutant genes with mutation frequency greater than 10% among all detected mutant genes, especially the mutation frequency of TP53 was as high as 68%. Based on the mutation sequencing data of these two companies, three common candidate neoantigens namely TP53c.818G>A (p.R273H), EGFRc.2573T>G (p.L858R) and KRASc.34G>T(p.G12C) were identified. Although the same gene, but 86% of the neoantigens differed from patient to patient. TP53 ($r=0.362$, $P=0.011$) and KRAS mutants ($r=0.3$, $P=0.036$) were significantly correlated with the maximal somatic variant allelic frequency (maxVAF), but had no significant correlation with overall survival (All $P>0.05$). The EGFR mutant was not significant for MaxVAF but significant for better survival ($P=0.089$). **Conclusion:** This prospective study demonstrated that it is feasible to study tumor neoantigens through ctDNA panel sequencing data performed by commercial vendors. Although most of the neoantigens are individual, the hotspot candidate neoantigens of the driver were universal in some populations and therefore can be ideal targets for neoantigen immunotherapy. Moreover, the candidate neoantigens identified such as TP53c.818G>A and KRASc.34G>T were significantly associated with the maxVAF which is a known factor significant for survival outcome of NSCLC.

Keywords: neoantigen, NSCLC, ctDNA

P21.02 Real-World Concordance Between Tumor Mutational Burden From Blood and Tissue in Lung Cancer and Other Cancers

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Introduction: Tumor mutational burden (TMB) is increasingly being utilized in the clinic to decide whether cancer patients should receive immunotherapy. Traditionally, TMB has been calculated from biopsied tissue samples, also known as tissue TMB (tTMB), and current FDA approval for using pembrolizumab in patients with TMB ≥10 mut/MB is based on tissue next-generation sequencing (NGS) results. However, tTMB requires a biopsy or a resection, and often yields insufficient amounts of DNA. Thus, TMB derived from circulating tumor DNA (ctDNA) from blood samples, also known as blood TMB (bTMB), has now been developed for use in the clinic. Currently, real-world concordance between tTMB and bTMB is not yet well understood. **Methods:** From October 2020 to March 2021, cancer patients who had both tTMB (Tempus) and bTMB (Guardant360) results were selected. From these patients, those who were treatment-naive or treatment refractory at the time of blood sample collection were selected for final analysis, as patients responding to treatment may have had altered TMB due to the treatment. **Results:** A total of 39 patients were included in our study, where 25 patients (64.1%) had lung cancer and 14 patients (35.9%) had other cancers, including esophageal, gastric, appendiceal, pancreatic, breast, ovarian, cervical, endometrial, uterine, thymic, thyroid, and maxillary cancer. Median bTMB of 9.6 mut/MB was higher than median tTMB of 3.7 mut/Mb, and the distributions of bTMB and tTMB differed significantly (Wilcoxon signed-rank V=14.5, n=39, p<0.001). bTMB was positively correlated with tTMB in the total study population (Pearson r=0.684, p-value<0.001; Spearman ρ=0.564, p-value<0.001) as well as in the lung cancer subgroup (r=0.645, p-value=0.001; ρ=0.454, p-value=0.023) and the other cancer subgroup (r=0.627, p-value=0.016; ρ=0.692, p-value=0.006). The bTMB:tTMB ratio at 10 mut/Mb tTMB was 2.1:1, 2.1:1, and 1.7:1 for the total study population, lung cancer subgroup, and other cancers subgroup, respectively; this is in comparison to the previously reported ratio of 1.6:1 for non-small cell lung cancer (Rizvi et al., 2020 JAMA Oncol)

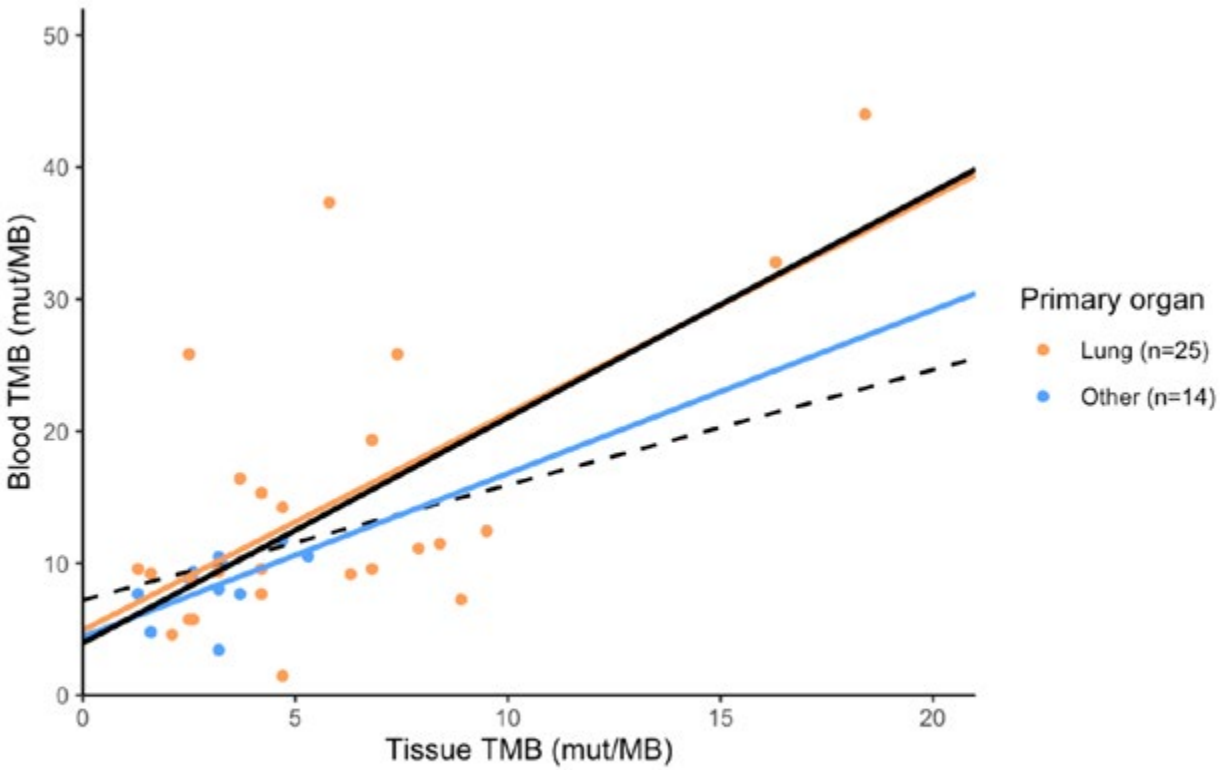

Figure 1. Correlation between tissue and blood tumor mutation burden (TMB).
Solid line represents the regression line for all 39 patients;
colored line represents the regression line by cancer types;
dashed line represents the regression line reported by Rizvi et al. (2020)

Conclusion: bTMB was positively correlated with tTMB, and median bTMB was higher than median tTMB. The bTMB:tTMB ratio of lung cancer may differ from other types of cancer. Future studies with more patients and different modalities of TMB calculation may help define the optimal bTMB threshold for receiving immunotherapy, which may be different from the tTMB threshold.

Keywords: immunotherapy, tumor mutational burden

P22.01 Personalized ctDNA Assay for MRD Detection and Treatment Response Monitoring in a Patient With Metastatic Lung Cancer

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Introduction: Treatment paradigms for metastatic lung cancer with high PD1/PDL-1 expression involves continued treatment with immune checkpoint inhibitors until disease progression or toxicity. Current strategies to monitor patients' disease status is limited to radiological imaging, which can be challenging due to associated high costs, exposure to ionizing radiation, and long duration between scans. There are currently limited options for biomarkers to use for treatment response monitoring, however personalized circulating tumor DNA (ctDNA) assays have emerged as a reliable method with lower limits of detection, particularly over static commercial panels. **Methods:** A 68-year-old male with a remote history of bladder and prostate cancers, presented with a hemorrhagic right adrenal mass that was found to be metastatic lung adenocarcinoma. Extensive imaging modalities found evidence of diffuse lymphatic involvement throughout the neck, mediastinum, and left adrenal gland, however, no discrete lung mass was identified. The patient had ctDNA testing performed using a static panel at the time of diagnosis, which identified indel discrepancies within P53 and EGFR and both the static panel and a personalized, tumor-informed ctDNA assay (Signatera™ bespoke mPCR NGS) were used at the time of recurrence. **Results:** At the time of right adrenalectomy and diagnosis of metastatic lung adenocarcinoma, the patient was found to be positive via static panel for P53 and EGFR mutations. The patient was enrolled in HALO-107-101 trial for 10 months and was eventually switched to commercial pembrolizumab treatment. While on treatment, the patient's ctDNA status as monitored via a static panel showed negative findings. After a brief loss to follow-up (8 months) and discontinuation of pembrolizumab, the patient's ctDNA status was assessed using the static panel and the personalized, tumor-informed ctDNA assay. The static panel revealed the originally identified splice site indels, suggesting disease recurrence and correlated with a new 3.7 cm left adrenal gland mass found on CT scan. ctDNA assessment performed using the tumor-informed assay revealed elevated ctDNA levels at 48.81 MTM/ML. This prompted re-initiation of patient's treatment with single agent pembrolizumab. Re-assessment of ctDNA using a static panel performed after one month indicated a negative result, while the tumor-informed assay showed a decline in ctDNA level (0.20 MTM/mL) but remained positive. Subsequent serial testing performed with the static panel showed negative results, while the tumor-informed assay showed consistently positive results (1.14 MTM/mL, 0.92 MTM/mL), which correlated with partial response on repeat imaging. Based on the continued ctDNA positivity, the decision was made to continue maintenance with pembrolizumab therapy and follow ctDNA monitoring and imaging. **Conclusion:** Identifying molecular residual disease and monitoring changes in ctDNA levels via a personalized, tumor-informed assay is of great significance, especially for metastatic patients being treated with immunotherapy. The Signatera assay can detect disease burden at levels ten-fold lower than static panels and equates to detecting one mutant allele in a pool of ten thousand normal alleles. This has practical, clinical implications for early identification of microscopic residual disease as well as real-time monitoring of response to therapy.

Keywords: ctDNA, molecular residual disease, lung, adenocarcinoma, immunotherapy

P22.02 Combined Use of CYFRA 21-1, CA125 and CRP Predicts Survival of Metastatic NSCLC Patients With Stable Disease

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Introduction: While overall survival (OS) is the gold standard for assessing treatment efficacy in NSCLC, computerized tomographic (CT) scans are used to evaluate tumor response. Peripheral blood diagnostic biomarkers may be used to complement imaging, but are still not incorporated into standard of care. We evaluated the ability of tumor antigen related biomarkers to predict survival in NSCLC patients (pts) with stable disease (SD) by RECIST 1.1 after two treatment cycles. **Methods:** In the PhIII IMpower150 trial (NCT02366143), 1202 chemotherapy-naïve pts were randomized (1:1:1) to receive: atezolizumab (A) + carboplatin + paclitaxel (ACP), bevacizumab (B) + CP (BCP), or atezolizumab + bevacizumab + CP (ABCP) given q3w. 750 pts with CT data after two cycles (~6 weeks post treatment initiation) and with available serum samples ≤14 days from CT (from all three arms) were included in this analysis; cytokeratin 19 fragment 21-1 (CYFRA 21-1), cancer antigen (CA) 125 and C-reactive protein (CRP) serum levels were measured using cobas® systems. Risk prediction for progression free survival (PFS) and OS were compared using Cox regression models and Kaplan–Meier curves. Biomarker cut-offs were optimized to obtain maximum risk differences between responder and non-responder groups. Cox proportional hazard models, based on single or combination biomarkers, were evaluated using hazard ratios and C-index. **Results:** When SD pts were classified as high- or low-risk using derived biomarker cut-offs, combination of CYFRA 21-1 + CA125 ± CRP had greater prognostic value than any individual biomarkers for both OS and PFS. Using the optimized cut offs, survival probabilities were similar between high-risk SD vs PD pts and low risk SD vs PR pts (**Table**). For OS and PFS, respectively, combination of CYFRA 21-1 + CA125 ± CRP and CYFRA 21-1 + CA125 enabled risk determination for each of the three treatment arms with a C-index of 0.683.

	Blood Biomarker (measured at 6 weeks)	OS				PFS		
		C-index	HR (SD high- vs low-risk)	HR (SD low-risk vs PR)	HR (SD high risk vs PD)	C-index	HR (SD high vs low-risk)	HR (SD low-risk vs PR)
Single marker	CYFRA 21-1	0.650	2.487	0.897	0.715	0.631	2.732	0.820
	CA125	0.653	2.880	0.833	0.885	0.623	2.506	0.814
	CRP	0.604	1.631	1.125	2.088	0.559	1.371	1.250
Two marker	CYFRA 21-1 + CA125	0.674	3.275	0.847	0.986	0.645	2.966	0.825
Three marker	CYFRA 21-1 + CA125 + CRP	0.683	3.579	0.852	1.067	0.646	3.019	0.827
	HR based on optimized cut off. HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response							

Conclusion: Whilst not predictive for treatment efficacy, a biomarker score using two/three markers combined (CYFRA 21-1 + CA125 ± CRP) can determine risk for future OS and PFS in NSCLC pts with SD at the first CT scan after treatment initiation.

Keywords: non-small cell lung cancer, CA125, CYFRA 21-1

P22.03 Role of Circulating Tumor Cell Subpopulations in Operable Non-Small Cell Lung Cancer Diagnosis and Prognosis

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Introduction: Lung cancer is an aggressive disease with high mortality rate worldwide. Surgical intervention is the most effective treatment; therefore, prompt diagnosis is fundamental to cure this neoplasm effectively. Low-dose computed tomography (LDCT)-based screening programs were proven a valid approach to further increase patients survival rate, but false positives may occur and controversies still exist in the management of subjects with indeterminate or premalignant nodules. Furthermore, some patients may experience disease recurrence and conventional prognostic factors are not able to pinpoint patients at high risk accurately. In this context, the non-invasive measurement of circulating biomarkers represents a desirable opportunity. Here, we report the results of our pilot study on circulating tumor cell (CTC) detection in operable non-small cell cancer (NSCLC) patients. **Methods:** Blood samples, collected from healthy volunteers (N=10), nodule-negative high-risk individuals (N=7) at first LDCT, and NSCLC patients (N=74) before surgery, were enriched for CTC using a size-based approach (Isolation by Size of Epithelial/Tumor cells, ISET®). Cytological samples obtained on porous membranes were stained with May-Grünwald Giemsa (4 membrane spots, corresponding to 4 mL of blood) and analyzed by a referral cytopathologist, without knowledge of the disease status and outcome. Cells with features of malignancy were identified according to the classical morphological criteria used for cytological samples. Spike-in experiments with commercially available lung cancer cell lines helped to optimize the workflow and to verify that the formation of artifacts during the filtration procedure did not occur. **Results:** Overall the CTC detection rate in patients was 60% and did not show significant differences between patients with early (I-II, N=52) and advanced stage (III-IV, N=22). Cells with features of malignancy were not detected in lung cancer-free donors. In addition to the classical CTC presenting as physically isolated events (single CTC, sCTC) within the size-based enriched fraction of cells, we identified a subpopulation of clusters of CTC and leukocytes (hetCLU), mainly monocytes (55.3%), neutrophil granulocytes (10.5%) and lymphocytes (10.5%), detected with an overall frequency of 31%, without substantial differences between the two cohorts. The status of both CTC subsets (overall median (IQR) number of CTC/4 mL in CTC+ve cases: 2 (1-3)) did not correlate with the patients' clinico-pathological features. Interestingly, the prevalence of sCTC and the presence of hetCLU predicted the risk of disease recurrence (median (IQR) follow-up time: 28 (11.8-33.5) months) within the cohort of early stage (HR 95%CI: 5.15 (1.10-24.33), p-value=0.0009, for cases with ≥2 sCTC, and 3.99 (0.47-33.57), p-value=0.0216, for cases with ≥3 sCTC) or advanced stage (HR 95%CI: 3.44 (0.76-15.50), p-value=0.0129) tumors, respectively, while neither the grading nor the lymph-node status were able to predict the risk of recurrence. **Conclusion:** The CTC detection rate obtained in operable NSCLC patients by the ISET® technique was encouraging if considering the small amount of blood analyzed compared to other works, thus laying the foundation for further trials in the diagnostic setting. Interestingly, the prevalence of two distinct subpopulations of CTC informed postoperative prognosis. Based on our observations, the biological and clinical significance of both sCTC and hetCLU in non-metastatic NSCLC would deserve further investigation.

Keywords: non-small cell lung cancer, circulating tumor cells, biomarkers

P22.04 Prospective Validation of an Eight Gene mRNA Signature in Plasma for the Diagnosis of Early Stage Lung Cancer

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Introduction: Non-small cell lung cancer (NSCLC) is usually diagnosed at stages IIIB-IV, with a median overall survival that does not exceed two years. In contrast, patients diagnosed at early and locally advanced stages (I-IIIA) can undergo surgery and have a significantly better prognosis. Imaging technologies often detect lung nodules of unknown significance that pose a diagnostic challenge. Based on a 76-patient training cohort, we developed a first mRNA expression signature in plasma that discriminates healthy individuals from early-stage patients with AUC=0.98. Here, we aimed to expand the training cohort and prospectively validate the final signature in the clinical setting. **Methods:** The training cohort will enroll 200 patients with suspected lung cancer who undergo any type of diagnostic test, including bronchoscopy, fine needle aspiration, percutaneous biopsy or surgical biopsy. Circulating-free RNA (cfRNA) is isolated from the plasma using an automatic extraction method (Qiasymphony, Qiagen). Purified cfRNA is quantified using Qubit®, retrotranscribed and pre-amplified with 14 cycles using the Low RNA Input Amplification kit (NanoString Technologies). Gene expression analysis is performed on the nCounter platform using the PanCancer IO360™ panel (NanoString Technologies), which can detect 770 transcripts related to tumor biology, micro-environment and the immune system. **Results:** The training cohort has included 126 patients so far; plasma samples have been successfully analyzed by nCounter in all cases. Ongoing analysis reveal differential patterns of gene expression in localized stage NSCLC patients versus healthy controls. A bioinformatics recursive feature elimination algorithm has selected an 8-gene signature with an area under the ROC curve of 0.89. The signature scores derived from the algorithm are significantly different between the healthy and cancer cases. **Conclusion:** Plasma RNA expression signatures can be a useful tool to guide clinical decision in patients with pulmonary nodules suspected of malignancy, orienting towards surgery or observation.

Keywords: Early detection, Liquid biopsy, Gene Expression

P22.05 Dynamic Monitoring of Blood Samples by PEAC Technology for Early-Stage Lung Cancer Patients After Surgery

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Introduction: To explore the application of PEAC technology for dynamic monitoring of blood ctDNA in early-stage lung cancer patients after surgery, and to identify biomarkers from lung cancer-associated class I driver mutations for recurrence monitoring after lung cancer surgery. **Methods:** 20 mL blood samples were collected from each lung cancer patient at the 6th and 12th months after surgery. The PEAC method was used for genetic testing of ctDNA in the blood samples. The detection results were further compared with the mutation profiles of tumor tissues collected during surgery. **Results:** A total of 60 lung cancer patients were enrolled in this study. At present, all 60 patients had completed blood testing at month 6 after surgery, and 14 patients had completed blood testing at month 12. The genetic testing of tissues showed that all 60 patients had positive testing results, including 47 with EGFR mutation, 5 with KRAS mutation, 5 with ALK fusion, 1 with NRAS mutation, 1 with BRAF mutation, and 1 with PIK3CA mutation. At month 6, seven patients were tested positive for gene mutations based on the blood samples, four of which had results consistent with the tissue, and the remaining three patients had important lung cancer-related class I driver mutations. Seven patients had their blood samples tested positive for mutations at month 12 and these patients had negative testing results at month 6. Four of these seven patients had testing results consistent with the tissue, and the remaining three patients also had significant class I lung cancer-related driver mutations. **Conclusion:** Dynamic monitoring of blood samples by PEAC technology in early-stage lung cancer patients at the 6th and 12th months after surgery can identify lung cancer-related class I driver mutations as biomarkers used for dynamic surveillance.

Keywords: ctDNA, dynamic monitoring, recurrence monitoring

P22.06 Prognostic Value of Circulating Tumor Cells in Patients With Small Cell Lung Cancer Receiving Front-Line Treatment

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Introduction: Small cell lung cancer (SCLC) is characterized by aggressive progress and initial response to chemotherapy but rapid development of relapse. circulating tumor cells (CTCs) may provide an opportunity for dynamic monitoring of treatment response and disease progression. **Methods:** Patients aged 18 years and older with pathologically confirmed and previously untreated SCLC, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 were enrolled. All participants received 4-6 courses of chemotherapy (cisplatin and etoposide). Serial blood samples were collected before chemotherapy initiation, after two treatment cycles, at the end of treatment and on disease progression. CTCs and circulating tumor epithelial cells (CTECs) levels were analyzed using subtraction enrichment technique. The expression of Epithelial-to-Mesenchymal Transition maker vimentin and stem cell marker CD44 on CTCs and CTECs were also evaluated by immunostaining FISH. Associations of CTCs, CTECs and their subpopulations with clinical factors and prognosis were determined. **Results:** Thirty-three patients were enrolled between November 2018 and January 2020. The median age of the patients was 63 years (range 43-69). 24 (72.7%) were males. Sequential samples were available from 30 and 26 patients before chemotherapy initiation and after two treatment cycles, respectively. Blood samples of all the former three time points were collected from only 14 patients because of the epidemic of COVID-19. At baseline, CTCs were detected in 29 (96.7%) patients, and CTECs were less detected (22, 66.7%). Both vimentin and CD44 positive CTCs were detected in only 8 participants at all detecting points. Interestingly, there is an increasing tendency of the CTCs level after two chemotherapy cycles, although the differences in the absolute number and detection incidence of CTCs and CTECs before and after treatment were not statistically significant (table). Almost all of the CTCs or CTECs were demonstrated to be aneuploid through chromosome 8 centromere probe (CEP8) analysis. Unfortunately, neither the absolute number nor variance of CTCs/CTECs seem to be able to predict chemotherapy response according to our current data.

Table. CTCs and CTECs level at baseline and after two chemotherapy cycles

	Baseline	Post-treatment	Wilcoxon test
CTCs (median)	8 (range 0-30)	9.5 (1-98)	p>0.05
CTECs (median)	1.5 (0-8)	1 (0-42)	p>0.05

Conclusion: SCLC showed a high incidence of CTCs detection in our study cohort, consistent with previous reports. While the predictive value of CTCs and CTECs needs to be further explored.

Keywords: Small cell lung cancer, Front-line treatment, circulating tumor cells

P23.01 Integration of Metabolomics and Transcriptomics to Reveal Metabolic Disorder in Early Lung Cancer for Non-invasive Diagnosis

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Introduction: Lung cancer (LC) is one of the most common cancers worldwide. To date, most LC patients are diagnosed at the advanced stage owing to the lack of obvious symptoms and the limitations of current clinical diagnostic techniques. Therefore, developing a new technique for early LC screening is of great importance. **Methods:** In this study, saliva samples from a total of 150 volunteers including 89 early LC patients, 11 advanced LC patients and 50 healthy controls were collected and analyzed by ultra-low noise tip-enhanced laser desorption ionization mass spectrometry (TELDI-MS) platform. The detailed procedure for the metabolic analysis of saliva samples is shown in Figure 1. RNAseq data from LC and adjacent normal tissues were obtained and performed pathway enrichment analysis based on differentially expressed genes

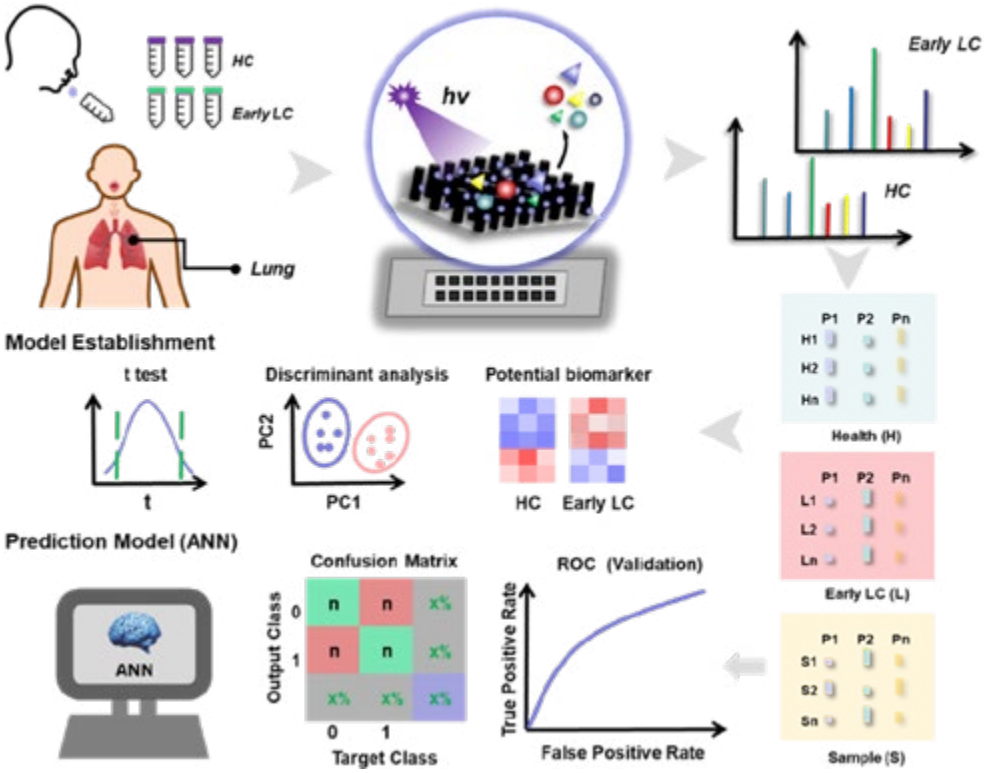

Figure 1. The workflow of metabolic analysis of saliva samples. **Results:** For each batch of samples, the whole analytical process only takes ~15 min and around 264 peaks could be reliably detected in each sample (Figure 2A). After statistical analysis, 23 metabolites were verified to be related to the dysfunction of amino acid and nucleotide metabolism in early LC (Figure 2B). Notably, the disorder of amino acid biosynthesis and metabolism has been identified by the integration of transcriptomics and metabolomics (Figure 2C). Based on the selected metabolites, early LC patients could be clearly distinguished (Figure 2D). With the established model, the sensitivity and specificity for early LC screening were 100% and 96% (Figure 2E)

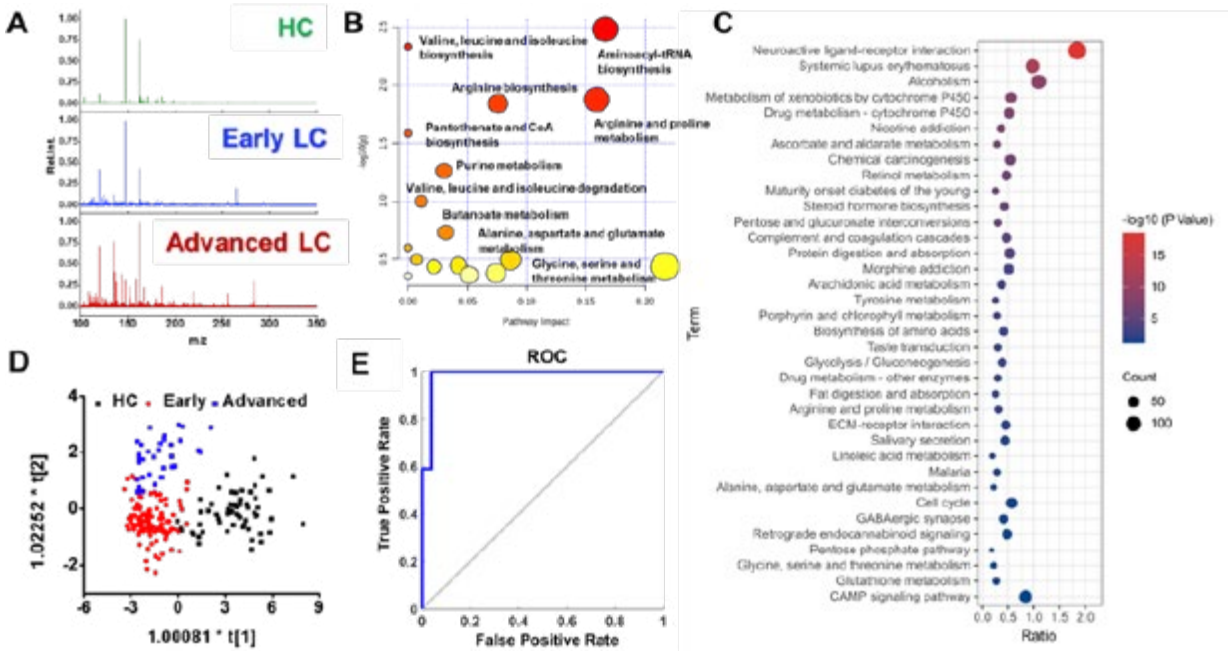

Figure 2. (A) The representative mass spectra of three groups. (B) Impact pathway analysis of differential metabolites. (C) KEGG analysis of differential genes. (D) OPLSDA result. (E) ROC curve for early LC diagnosis in the validation set. **Conclusion:** The ultra-low noise TELDI-MS platform displayed satisfactory ability to uncover early LC related metabolite biomarkers, that may help develop a non-invasive screening tool for early LC.

Keywords: Non-invasive diagnosis, early stage lung cancer, Salivary metabolomics

P23.02 Digital Multiplexed circRNA Analysis From Plasma-Derived Extracellular Vesicles of Lung Cancer Patients

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Introduction: Lung cancer stands as the leading cause of cancer-related death worldwide. The limitations of conventional techniques such as bronchoscopy or computed tomography makes early diagnosis challenging and consequently leads to a low survival rate. Liquid biopsies are emerging as an alternative to the current tissue/image-based techniques for early detection. Circulating molecules, such as DNA, RNA or proteins, can either be freely present, or can be extracted and analyzed from circulating extracellular vesicles (EVs), platelets, or circulating tumor cells (CTCs). Circular RNAs (circRNAs) are a novel type of regulatory RNAs featuring stable structure and high tissue-specific expression. Aberrant circRNA expression plays an important role in carcinogenesis and tumor progression. Exosomes have been demonstrated to be enriched with circRNAs; therefore, circRNAs could potentially be used as liquid biopsy-based cancer biomarkers in order to improve the diagnosis and treatment of the disease. However, to the best of our knowledge, multiplexing techniques such as nCounter have never been rested in this setting. Here, we aimed to determine if nCounter can be used to analyze circRNA expression in plasma-derived EVs and to develop circRNA signatures to discriminate early-stage lung cancer patients from non-cancer controls. **Methods:** Blood was processed within 8 hours and centrifuged for 20 minutes at 120xg at room temperature (RT). The platelet rich-plasma was separated and centrifuged for 20 minutes at 360xg at RT. The miRCURY Exosome Serum/Plasma Kit (Qiagen) was used to isolate plasma EVs, which were characterized by western blot (Calnexin -, Flotillin +, CD9 +) and cryo-electron microscopy (EM). Resulting EVs were treated with RNAse A (Sigma-Aldrich) to remove cell-free RNA prior to extraction of total RNA with TRI Reagent (MRC). Overnight hybridization and nCounter FLEX processing were performed following NanoString protocols after a pre-amplification step with the Low RNA Input Amplification Kit (NanoString). Expression analysis was carried out based on a custom panel of 85 circRNAs related to the biology of the disease. **Results:** In a pilot study, the custom-made nCounter panel was able to detect circRNAs from plasma EVs of both early-stage lung cancer patients (n=4) and non-cancer controls (n=4). Different circRNAs were found dysregulated in cancer patient EVs compared to non-cancer controls, particularly circ_001569, which shows a 4-fold downregulation. Machine learning methods selected a 4 circRNA expression-based signature able to accurately discriminate early-stage lung cancer patients from non-tumor controls in this limited set of samples. Plasma sample collection from 200 individuals is currently ongoing and results will be updated at the time of the meeting. **Conclusion:** The nCounter platform can be used to analyze circRNA in plasma-derived EVs. While more samples are currently being collected to increase the statistical power of the study, preliminary results indicate that EV-circRNA-based signatures can be useful to identify early-stage lung cancer patients.

Keywords: liquid biopsies, circRNAs, lung cancer

P23.03 Novel Serum Extracellular Vesicles Based miR-153-3p Biomarker Combined to a Prediction Model for Determining Early-Stage Lung Cancer

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Introduction: Lung cancer (LC) is a highly heterogeneous tumor with being the lead cause of cancer incidence and mortality. Hence, the targeting of the early-stage lung cancer (ESLC) at initial stages within <20mm size of lung nodules (LNs) is crucial for the detection and therapeutics advancement of LC. The study aims to discover novel circulating serum extracellular vesicles (sEVs) miRNA biomarkers associated with radiomics-clinical features for developing a prediction model, and tackling early-stage lung cancer and differentiating from benign lung nodules (BNs). **Methods:** The study included a population of three different groups, such as ESLC, BNs and Healthy individuals for sEVs-miRNA profiling via next-generation sequencing (NGS) in 9 serum samples. We identify and validate the top-most sEVs miRNA in a single independent cohort of these three groups by RT-PCR (n=143), and further comparison to acknowledge the detection and diagnosing efficacy by receiver operating characteristic-area under the curve (ROC-AUC) phenomenon. Moreover, the radiomics-clinical signs were combined with sEVs miRNA biomarker by logistic regression analysis to develop a radiogenomics based prediction model. **Results:** According to our preliminary result of NGS, we had chosen the most significant ESLC vs BNs group's upregulated miRNA, which was miR-153-3p. Further, the sEVs miR-153-3p biomarker for three groups found in the discovery stage was validated by RT-qPCR in the 143 subjects. The ROC-AUC of sEVs miR-153-3p for ESLC vs BNs group was 0.737 ($p<0.0001$) compared to ESLC vs Healthy and BNs vs Healthy groups, which were 0.759 ($p<0.0001$), 0.513(>0.05) respectively. Meanwhile, the present study had correlated all the data of sEVs biomarker and radiomics-clinical signs in multiple logistic regression analyses to predict the probabilities of ESLC, which represented the outstanding efficacy by ROC-AUC of 0.920 (95% CI:0.8668~0.9744)($p<0.0001$). The most significant radiomics predictors were LNs types, LNs Size, Diameter, Calcification and Lobulation as per the final prediction model. **Conclusion:** The present study discovered and validated the novel sEVs miR-153-3p in three groups of ESLC, BNs and Healthy population within <20mm size of LNs. Consistently, the radiogenomics model combined with sEVs miR-153-3p biomarker was not only representing the potential diagnostic probabilities of ESLC but also discriminating the ESLC from BNs. Further, sEVs miR-153-3p and the model may need to be validated into a large cohort before introducing as a liquid biopsy-based prediction model for ESLC.

Keywords: early-stage lung cancer, predication model, circulating exosomes

P23.04 Serum Biomarkers Enhance Prognostic Value of Computed Tomography (CT) in Patients With Non-Small Cell Lung Cancer (NSCLC)

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Introduction: CT is currently the method of choice for assessing treatment response in patients with NSCLC. Biomarkers are still not incorporated into the standard of care due partly to the absence of a compelling use case for combining biomarkers and CT. The Lung Cancer Multi-Marker study assessed biomarkers and biomarker combinations in patients with NSCLC. Within this study, a subcohort was analyzed to determine the predictive value of serum biomarkers in monitoring treatment success in patients with stable disease (SD) on CT scan after the first two cycles of therapy. **Methods:** The study enrolled adults with stage III/IV NSCLC (adenocarcinoma or squamous cell carcinoma [SCC]) and Eastern Cooperative Oncology Group performance score 0–2 with a treatment plan for ≥4 cycles of chemotherapy, tyrosine kinase inhibitors (TKI) and/or immune checkpoint inhibitors. The analyzed subcohort included patients with CT data available after 2 cycles. Serum biomarker (CEA, ProGRP, NSE, CYFRA 21-1, SCC, CA15-3 and CA125) levels were measured via electrochemiluminescence immunoassays after cycle 2. Risk prediction for progression-free survival (PFS) and overall survival (OS) were compared using Cox regression models and Kaplan–Meyer curves. Biomarker cut-offs separated patients with SD into high- and low-risk groups and were optimized to obtain the maximum risk differences (lowest log-rank p-value) between groups. Cox proportional hazard models were based on a single biomarker or combinations of 2–3 biomarkers. For combined population of adenocarcinoma and SCC, the models also included an interaction term between histology and each biomarker. Prognostic models were evaluated using hazard ratios and C-index. **Results:** Of 387 patients with NSCLC, 225 patients had complete clinical and biomarker data and PR (n=130) or SD (n=98) at the first CT scan after cycle 2; n=35 patients had progressive disease (PD). Patients received chemotherapy (75.1%), TKI (12.4%) or immune-checkpoint inhibitors (9.3%) as first-line therapy. In patients with PR or SD at the first CT scan, progression was very similar indicating poor prognostic performance of CT for PFS. When patients with SD were split into high- and low-risk groups using biomarker median value, CYFRA 21-1 had the highest prognostic value for adenocarcinoma and CA125 for SCC. Combining CYFRA 21-1, CA125 plus an interaction term between the biomarker and tumor histology, resulted in a greater prognostic value than either biomarker alone in patients with SD. Addition of a third biomarker, CEA, further improved the prognostic value. These combinations were used in a Cox model that included patients with PR, patients with PD, and patients with SD stratified in a high-risk and a low-risk group. Using an optimized cut-off, patients with SD assigned to the biomarker high-risk group had a similar survival probability to patients with PD. Patients with SD assigned to the biomarker low-risk group had a similar survival probability to those with PR. **Conclusion:** Biomarkers can provide further guidance in patients with CT-assessed stable disease and separate them into high- and low-risk groups for PFS and OS.

Keywords: non-small cell lung cancer, CA125, CYFRA 21-1

P23.05 Chromosome 3p22.1 and 10q22.3 Amplification in Different Subtypes of Lung Adenocarcinoma

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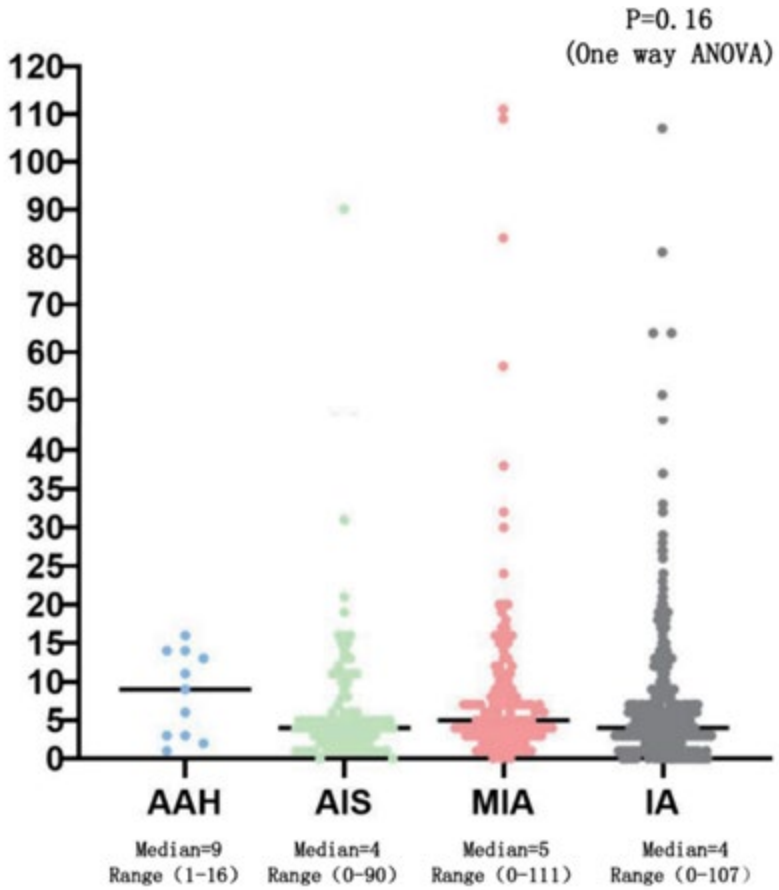
Introduction: Aneuploidy is one of the pervasiveness recognized features of cancer, but how aneuploidy influences tumorigenesis is still under investigation[1]. We previously demonstrated 3p22.1 (GC20) and 10q22.3 (surfactant protein A1 and A2, SP-A) were amplified in NSCLC by FISH. In this study, we evaluate the cytological changes of 3q22.1 and 10q22.3 amplification in different lung adenocarcinoma (AC) subtypes. **Methods:** A total of 754 patients with AC were enrolled in the study, 100 patients were with adenocarcinoma in situ (AIS), 151 patients were with minimally invasive adenocarcinoma (MIA), and 503 patients with invasive pulmonary adenocarcinoma (IA). Besides, we have found 11 individuals were with precursor lesions of atypical adenomatous hyperplasia (AAH), 10 ml of peripheral blood was obtained from each participant before surgical resection. The amplification of 3p22.1 and 10q22.3 of individuals with different AC subtypes was acquired by 4 color fluorescence in situ hybridization (FISH) assays. **Results:** The median quantitation of cells with 3q22.1 and/or 10q22.3 amplification were 9, 4, 5, and 4 for AAH, AIS, MIA, and IA (P=0.16), respectively. Besides, 11/11 (100%), 98/100 (98%), 148/151 (98%), and 468/503 (93%) patients were found to have at least one cell with 3q22.1 and/or 10q22.3 amplification in the AAH, AIS, MIA, and IA cohorts. **Figure 1.** quantitation of cells with 3q22.1 and/or 10q22.3 amplification in patients with adenocarcinoma.



Conclusion: Although no variations of aneuploidy were discovered in different subtypes of AC, 3q22.1 and/or 10q22.3 amplification have been found to present thought out the entire development cycle of AC, even in precursor lesion of AAH, and can be detected via peripheral blood. The consistency of chromosome 3q22.1 and 10q22.3 amplification found in peripheral blood indicated that this method might be an ideal biomarker for early lung adenocarcinoma.

Keywords: Liquid biopsy, lung cancer, Amplification

P24.01 Turnaround Time and Variant Prevalence of a Blood-based KRAS Test in Patients With NSCLC

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Introduction: Mutations in KRAS have historically been a harbinger of poor prognosis in patients with non-small cell lung cancer (NSCLC). These patients may have better outcomes using novel KRAS-targeting therapies currently in development, particularly if rapid turnaround, blood-based, KRAS mutation testing can identify treatment-eligible patients and help expedite time-to-treatment. A commercially available blood-based genomic test identifies the three most common KRAS mutations in NSCLC, G12C, G12V and G12D (KRAS G12C/V/D). This analysis reports blood-based test turnaround time and detected KRAS G12C/V/D prevalence both in commercial use and in a real-world clinical setting. **Methods:** The INSIGHT observational study (NCT03289780) has enrolled over 3,500 NSCLC patients at any stage and line of therapy at 33 US sites since 2017. Subjects received a blood-based genomic test (GeneStrat®, Boulder, CO) before therapy initiation. Circulating tumor DNA was analyzed using Droplet Digital PCR, with clinical sensitivity of 88%, specificity of 100%, and tissue concordance of 96% for KRAS G12C/V/D (Mellert 2017). From INSIGHT, 3451 patients had KRAS mutation testing and were eligible for turnaround time analysis. In the commercial setting, over the same time period as INSIGHT, 25148 patients received KRAS mutation testing and were eligible for turnaround time analysis. **Results:** Turnaround time decreased steadily over the years both commercially (from 35.28 hours in 2017 to 28.19 hours in 2021) and in INSIGHT (from 34.36 hours in 2017 to 29.05 hours in 2021). Among patients receiving KRAS testing, 2402 (8.15%) commercial and 336 (9.67%) INSIGHT tested positive for one of the three variants of KRAS mutation (KRAS G12C/V/D+), in line with other blood-based test results (Nacchio 2020). G12C was the most common mutation in the commercial population (49.66% KRAS G12C+) and INSIGHT (56.25% KRAS G12C+) followed by G12D (28.75% KRAS G12D+ commercial, 24.11% KRAS G12D+ INSIGHT). Among the 3337 INSIGHT patients whose KRAS testing, histology, smoking, and full staging information was available, KRAS mutation prevalence was highest in late stage (8.31% of patients tested at Stage IIIB and 12.97% at Stage IV). Interestingly, KRAS mutations were also detected in early-stage patients, including 2 patients at Stage IA (0.95% tested) and 4 each at Stages IIA (4.55% tested) and IIB (2.88% tested). Among advanced stage (IIIB/IV) patients, Ever-Smokers had higher prevalence of KRAS G12C/V/D (280/2071 tested, 13.52%) compared to Never-Smokers (9/269 tested, 3.35%). INSIGHT patients with advanced NSCLC with non-squamous histology had a higher prevalence of KRAS G12C/V/D (271/1756 tested, 15.43%) compared to squamous (18/584 tested, 3.08%). Very few co-mutations with KRAS were detected in the commercial setting in EGFR (27/1564 tested, 1.73%), BRAF (3/1556 tested, 0.19%), and ALK (2/1413 tested, 0.14%), and none were detected in INSIGHT. Conclusion: Blood-based genomic KRAS testing has rapid (<30 hour) turnaround both commercially and in a real-world clinical setting, enabling detection of 3 common KRAS mutations across stage of NSCLC. The size of the INSIGHT biobank moreover enabled detection of low percentage events such as early stage KRAS mutations. This blood-based genomic test may help guide treatment selection and promote expedited time-to-treatment for patients with KRAS G12C/V/D+ NSCLC.

Keywords: KRAS in NSCLC, Turnaround time, Blood-based genomic testing

P24.02 Unique Efficacy of Ensartinib on Different ALK Fusion Subtypes Evaluated by Plasma ctDNA

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Introduction: FDA has approved second generation ALK inhibitors such as alectinib, ceritinib, brigatinib for ALK-positive metastatic non-small cell lung cancer (NSCLC). Ensartinib, a next generation ALK TKI approved by NMPA in China, showed comparable efficacy to other ALK TKIs in the post-crizotinib setting. Precision therapy and clinical management need to know resistance mechanisms of TKIs and their efficacy on different ALK fusion subtypes and ALK secondary mutations. In this analysis, we investigated the unique efficacy of ensartinib on different mutations via ctDNA analysis. **Methods:** Plasma samples from progressive disease NSCLC patients after crizotinib treatment were prospectively collected for ctDNA analysis at baseline. Plasma DNA was analyzed using a 212-gene next generation sequencing (NGS) panel. ctDNA amount was defined as the sum of variant allele fraction (VAF) of ALK fusions and mutations. **Results:** A total of 178 patients had evaluable ctDNA at baseline. The detection rate of ALK fusions at baseline was 50.6% (90/178), among which 93.3% (84/90) were ALK-EML4 fusions. The ALK-EML4 V1 and V3 subtypes accounted for the highest proportion of all ALK fusion subtypes, with frequencies of 40% (36/90) and 31.1% (28/90), respectively. The median PFS of V1 and V3 subtypes were 5.5 (4.2, 7.7) and 6.6 (4.1, 9.8) months, respectively, compared with a median PFS of 16.1 months in ALK fusion-negative patients. Log-rank tests showed no significant difference in the efficacy of ensartinib against V1 and V3 subtypes, which differs from the results of the ALEX and ALTA-1L studies, indicating that ensartinib has different efficacy characteristics from other second-generation ALK-TKIs. In addition, patients with detectable ALK fusions or mutations were divided into high and low groups according to their ALK ctDNA levels, and the high-level group was found to have shorter median PFS compared to low-level group (4.2 vs 9.3 months). Consistent results were also obtained when analyzed for ALK fusion V1 and V3 subtypes, respectively. **Conclusion:** Consistent with previous reports, ensartinib showed high clinical efficacy. In particular, the similar efficacy of ensartinib between V1 and V3 subtypes and its non-inferior efficacy on the low-level ctDNA group differentiate ensartinib from other ALK-TKIs and provide directions for future clinical trial validation.

Keywords: ALK fusions, ctDNA, ensartinib

P24.03 Dynamic Circulating Tumor DNA Interim Results From The ALKternate Clinical Trial

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Introduction: The ALKternate clinical trial is a proof-of-concept study enrolling patients with advanced ALK-rearranged NSCLC, harboring secondary resistance to 2ndgeneration ALK-inhibitor therapy (Trial in Progress#1012). Patients receive induction lorlatinib and at confirmed disease control enter an active phase alternating lorlatinib with crizotinib testing the hypothesis that via altering selection pressure and suppressing emerging resistance clones, sustained sensitivity to lorlatinib and improved disease control may be achieved. **Methods:** Patients prospectively enrolled in ALKternate receive sequential plasma sampling, analyzed real-time via the Resolution Bioscience ctDx™ NGS liquid biopsy platform. Results are correlated with prior therapy, clinical and radiological course on trial. Interim censor date was April 07, 2021. **Results:** 14 patients have been screened for trial, 3 screen failed, 2 due to ctDNA confirming non-ALK drivers, 1 without prior resistance. N=2/11 were ineligible for the alternating arm due to primary lorlatinib resistance. N=6/9 proceeding to alternating ALKi had baseline CNS disease. The ALK fusion variant was identified in N=7/9, 1+ ALK KDMs in N=7/9, 1+ ALK bypass variants (co-occurring) in N=6/9. The variant allelic frequency (VAF) of ctDNA decreased in N=7/9, N=2/9 harboring MET amplification. Complete temporal ctDNA VAF data will be presented via stream-plots accompanying the results of Table 1, as in Figure 2. At immature median(m) follow-up 12.1mo, m-time on alternating therapy is 7.8mo. In those with persisting positive ctDNA at 6mo, time to treatment failure (TTTF) was 6.1mo and not reached in those with no detectable ctDNA. All with PD on alternating (N=5/9) crossed-over to continuous lorlatinib, PFS 5.6mo. Table 1. ALKternate patient plasma sequential ctDNA profiles

Patient ID	Prior Treatment	Baseline plasma ctDNA		6 Month Plasma		PD ALT ALKi Plasma		PD CONT Lorlat Plasma	
1	crizotinib alectinib	*EML4-ALK* V1		*Primary resistance lorlatinib*		N/A		*EML4-ALK* V1	*TP53* V216VM
2	crizotinib ceritinib alectinib	*EML4-ALK* V1 *ALK* S1206A	*BRAF* L597V *EGFR* amp *MET* amp *RICTOR* amp *TP53* deletion	ND		ND		*EML4* ALK V1 *ALK* L1196M	*BRAF* L597V *EGFR* amp *ERBB2* frameshift *KEAP1* A27G? *MET* amp *TP53* A159V *TP53* deletion
3	chemotherapy crizotinib ceritinib chemotherapy	*EML4-ALK* V3	*EGFR* amp *MET* amp *TP53* R342P *TP53* deletion	EML4-ALK V3		N/A		N/A	
4	alectinib *Screen fail*	*EGFR* V536M *EGFR* amp *ERBB2* E286K *ERBB2* amp *KEAP1* R71L	*MET* R731Q *PIK3CA* E39K *PTEN* R173F *RET* A877T *RICTOR* amp *TP53* R273L *TP53* del			N/A		N/A	
5	alectinib		*KIF5B-ALK* *ALK* V1180L *ALK* I1171S *EGFR* amp	ND **Figure 2**, continues 20+ mo ALT therapy		N/A		N/A	
6	crizotinib alectinib	ND		ND		N/A		N/A	
7	alectinib	*EML4-ALK* V2 *ALK* L1196Q *ALK* L1196M *ALK* LL1195LM *ALK* I1171N	*EGFR* amp	*EML4-ALK* V2 *ALK* L1196M		*EML4-ALK* V3 *ALK* G1202R	*EGFR* amp *TP53* R175L *TP53* frameshift	*EML4-ALK* V2 *ALK* L1196M *ALK* LL1195LM *ALK* I1171N	*EGFR* amp *TP53* deletion
8	alectinib	*EML4-ALK* V3 *ALK* G1202R	*EGFR* amp *TP53* R175L *TP53* splice *TP53* frameshift	*EML4-ALK* V3 *ALK* G1202R	*EGFR* amp *TP53* frameshift	*EML4-ALK* V3 *ALK* G1202R	*EGFR* amp *TP53* frameshift	*EML4-ALK* V3 *ALK* G1202R	*EGFR* amp *TP53* R175L *TP53* frameshift *TP53* splice
9	crizotinib, alectinib, chemotherapy	*ALK* G1202R	*TP53* P72A	*TP53* P72A		*TP53* P72A		*ALK* G1202R *ALK* I1151M	*TP53* P72A *TP53* L130F
10	crizotinib alectinib	*EML4-ALK* V3 *ALK* G1202R	*ERBB2* R103Q *TP53* S315C *TP53* S241F	*EML4-ALK* V3 *ALK* G1202R *ALK* G1269A *ALK* F1174L *ALK* F1164L *ALK* D1203N	*EGFR* amp *STK11* T71M	*EML4-ALK* V3 *ALK* G1202R *ALK* G1269A *ALK* F1174L *ALK* F1164L *ALK* D1203N	*EGFR* amp *STK11* T71M	N/A	
11	alectinib *Screen fail*	*KRAS* G12C *KEAP1* E343K *SKT11* P281P?		N/A		N/A		N/A	
12	alecinib	*EML4-ALK* V1 *TP53* R249T		*Primary resistance lorlatinib*		N/A		N/A	
13	crizotinib alectinib	*EML4-ALK* V5 *ALK* G1269A *ALK* I1171M		ND		N/A		N/A	
14	alectinib *Screen fail*	ND		N/A		N/A		N/A	

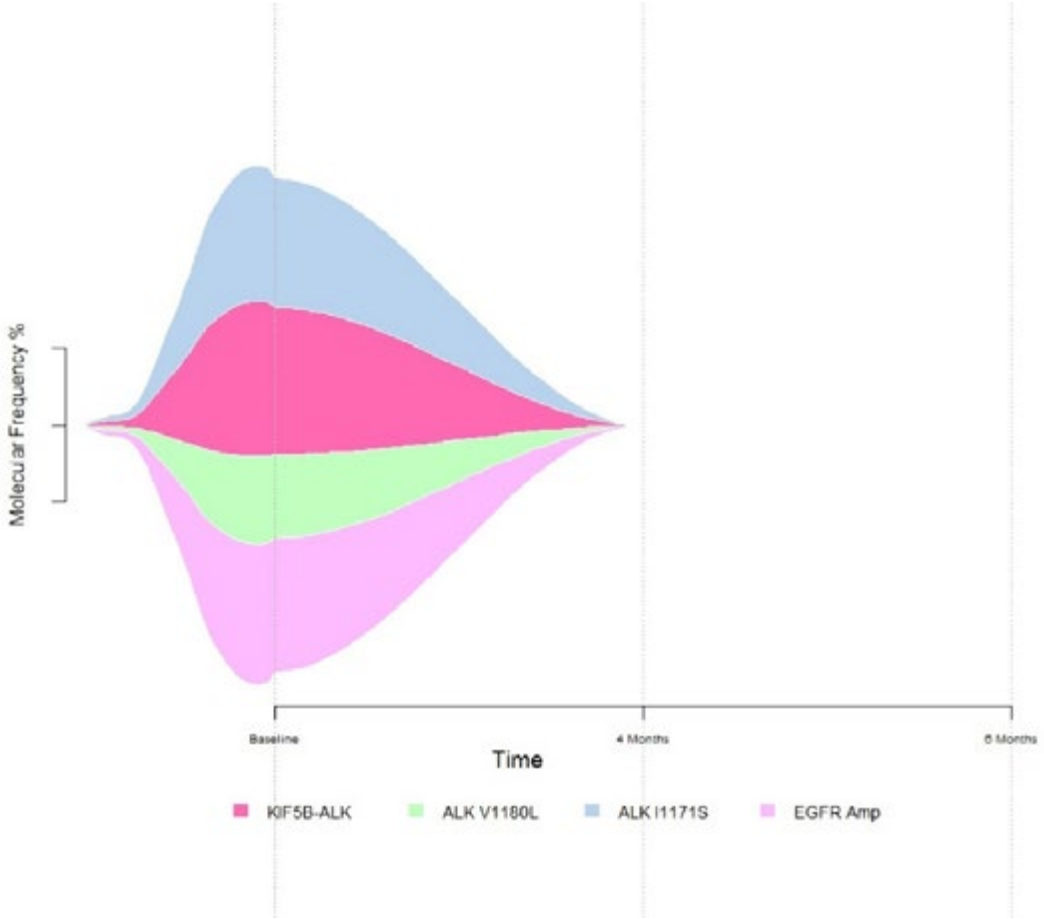

Figure 2. ALK5 VAF stream-plot **Conclusion:** Preliminary analysis of the ALKternate clinical trial dynamic plasma ctDNA profiles on alternating therapy indicate the inherent genetic heterogeneity in ALK NSCLC at drug resistance and with clearing of plasma ctDNA when alternating ALK-inhibitor therapy, an efficacy advantage is suggested.

Keywords: Drug resistance, ALK, ctDNA

P24.04 Concordance of Tissue and Cell-Free DNA-Based Next-Generation Sequencing in Patients With Lung Adenocarcinoma

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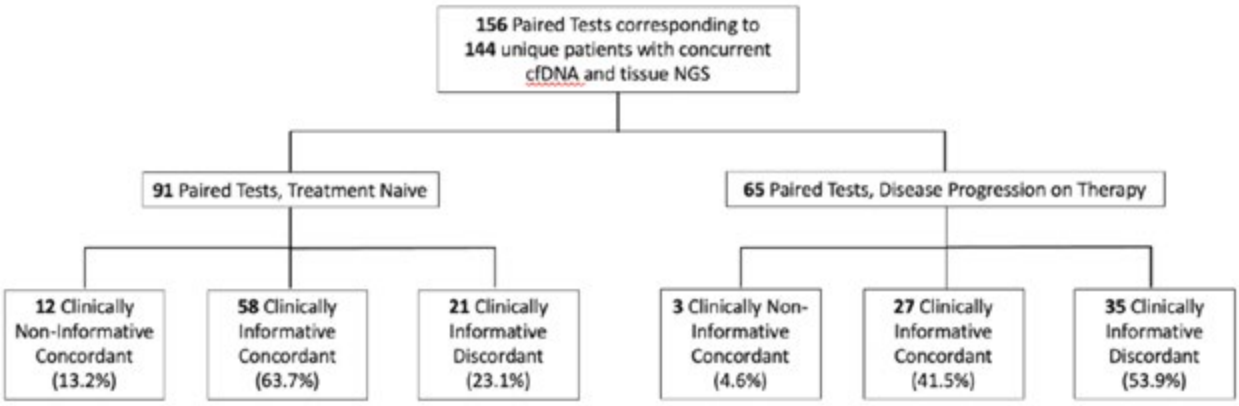
Introduction: Panel-based next-generation sequencing (NGS) to detect targetable somatic genetic events is guideline-recommended initial diagnostic testing in lung adenocarcinoma. Tissue biopsy has a number of limitations, including expense and biopsy-related adverse events. “Liquid biopsy” uses blood-based NGS on cell-free DNA (cfDNA). Prior investigations have demonstrated high rates of concordance at initial diagnosis. However, concordance at time of progression remains unknown. **Methods:** We retrospectively evaluated patients with non-small cell lung cancer treated at University of Chicago Medicine who received both cfDNA- and tissue-based NGS at diagnosis and/or progression. Paired tests were collected within 24 weeks and without an intervening therapeutic change. cfDNA-based NGS testing was performed using Guardant360 (Guardant Health; Redwood City, CA). Tissue-based NGS testing was performed using UCM-OncoPlus (University of Chicago Medicine; Chicago, IL) or FoundationOne CDx (Foundation Medicine; Cambridge, MA). Clinically informative mutations included those in the EGFR, ALK, RET, NTRK, MET, BRAF, KRAS G12C, ROS1, ERBB2, TP53, and RB1 genes. Clinically informative concordance was defined as both tests generating clinically informative results leading to the same clinical action. If one test identified a clinically informative result that the other failed to, this was deemed clinically informative discordance. Clinically non-informative tests were ones that failed to identify mutations in the aforementioned genes. **Results:** We identified 156 paired tests corresponding to 144 unique patients with NSCLC. Among the 156 paired tests, 85 (54.5%) were clinically informative concordant results, 56 (35.9%) were clinically informative discordant results, and 15 (9.6%) were clinically non-informative concordant results. Among patients with clinically informative results (n= 141), the rate of concordance among paired tests was 73.4% (n=58/79), compared to 43.5% (n=27/62) among samples collected at progression (p-value = 0.0003). Among the 56 clinically informative discordant results, actionable mutations were identified by tissue-based NGS in 39 instances (68.4%) compared to 18 (31.6%) on liquid biopsy. The most common clinically informative genetic events identified on liquid biopsy but not by tissue biopsy included EGFR T790M (n=10) and TP53 mutations (n=3). Tissue biopsy identified EGFR exon 19 deletion (n=6) and EGFR missense mutations (n=6) that were missed by liquid biopsy.



Conclusion: In this single-center, retrospective study, we demonstrate that while the rate of concordance at initial diagnosis was approximately 75%, the rate of discordance in the tests exceeds 50% at progression. On the basis of these data, we recommend both tissue and liquid biopsies at time of diagnosis and disease progression.

Keywords: next-generation sequencing, Liquid biopsy, Cell Free DNA

P24.05 Using Liquid Biopsies to Guide First-Line Therapy Decisions in Patients With Metastatic Non-Small Cell Lung Cancer

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Introduction: Liquid biopsies (LB) are non-inferior to tissue biopsies (TB) to identify actionable genetic aberrations (AGA) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC). Importantly, LB are able to report next generation sequencing (NGS) results faster than TB NGS and overcome the logistical barriers of finding, preparing and shipping tissue samples. A disadvantage of tissue NGS is insufficient sample for sequencing (QNS), tumor heterogeneity and turn-around time (TAT). This study aimed to illustrate that LB can be used in front line treatment decision making for pts with mNSCLC. **Methods:** This is a retrospective review of 165 pts within the Memorial Cancer Institute who were diagnosed with mNSCLC and received, at the same time, a TB NGS and LB NGS between 7/1/2015 and 6/30/2020. Pts were excluded if biopsies were not performed within one month of each other or the testing modality to guide treatment decision was not determined. Data collected included: demographics, biopsy TAT, biopsy type used to make the initial treatment decision, QNS rate, date of disease progression and death, and AGA detection. Descriptive statistics and logistic regression analysis were calculated for all pts. **Results:** Of the 165 evaluated pts, 88 (54%) were female, 84 (51%) older than 65 years, 90 (55%) Non-Hispanic Whites (NHW) and 47 (28%) non-smokers. TB was found to be QNS for NGS for 20 (12%) biopsies. AGA (EGFR, ALK, ROS1, NTRK, BRAFv600, RET, METexon14) were detected in the LB for 11 out of these 20 tumors (55%). In 98 pts (59%) TB did not find any AGA, while LB found 64 AGA (65%) in this group. Also LB did not detect ctDNA or no AGA were reported in 74 pts, while TB was able to find 20 AGA (27%) in this group. Fifty-four pts received targeted therapy in the first-line setting based on genotyping results: 40/54 (74%) were guided by LB NGS versus 14/54 (26%) guided by TB NGS. For 115 pts (68%) the treatment decision to initiate front line therapy in mNSCLC was made with LB results compare with 50 pts (32%) with TB, with the main reason being that the LB results were reported first. The median TAT for liquid NGS was 9 days compared with 32 days with tissue NGS ($p<0.0001$). The median time to initiating therapy was 9 days with liquid NGS vs 33.5 days with TB NGS (p-0.0004), and most of the delays after obtaining the results came due to insurance authorization. More than 90% of the pts with an AGA identified by liquid NGS were able to start therapy within 11 ± 5 days. PFS was similar if the treatment decision was based on LB NGS or TB NGS for comparable treatment groups. **Conclusion:** NGS performed by LB is a great complement to identify AGA in newly diagnosed pts with mNSCLC mainly when the TB NGS is QNS, and LB might be incorporated as standard of care to guide first-line therapy decisions when available. A prospective study with a larger sample size is warranted to validate these results**.**

Keywords: actionable genes, Next Generation Sequencing, liquid biopsies

P24.06 Resistance Mechanisms Exploring of NSCLC With Central Nervous System Metastases Using Liquid Biopsy of Cerebrospinal Fluid: A Real-World Study

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Introduction: Liquid biopsy using circulating tumor DNA (ctDNA) has been widely used in clinical practice to detect genomic alterations in non-small cell lung cancer (NSCLC). Due to the blood-brain barrier, the sensitivity of the plasma ctDNA sequencing is limited in NSCLC patients with central nervous system (CNS) metastases. Previous research has suggested that cerebrospinal fluid (CSF)-cell free DNA (cfDNA) could reveal the unique genetic profiles of intracranial metastases and guide the clinical treatment of NSCLC patients with CNS metastases. However, the potential utility of CSF as a source of liquid biopsy to explore the resistance mechanism in the real-world setting has not yet been examined. **Methods:** A total of 90 NSCLC patients with CNS metastases who had previously received targeted treatment with EGFR tyrosine kinase inhibitors (TKIs) or ALK-TKIs were retrospectively enrolled in this study. Among them, 31 patients were resistant to first or second-generation EGFR-TKIs, 54 were resistant to osimertinib and 5 were resistant to ALK-TKIs. For all patients, CSF samples were collected in a real-world setting. All samples were subjected to the targeted next-generation sequencing of 1021 cancer-relevant genes. **Results:** We successfully tested 90 CSF samples of these 90 patients. Somatic mutations were identified in 96.67% (87/90) of samples in CSF cfDNA. The most common genes seen in them were EGFR, TP53, CDKN2A, CDKN2B, LRP1B, CARD11, RB1 and IL7R. Actionable EGFR, ALK, KRAS, ERBB2, MET, and BRAF mutations were detected in 95.56% (86/90) of the CSF samples. In exploring the mechanisms of TKI-resistance, EGFR-TKIs sensitizing mutations were not detected in the CSF cfDNA in 7.06% (6/85) of patients with EGFR-TKIs resistance. 49 patients (57.65%) harbored concurrent mutations that may limit the efficacy of EGFR-TKIs, including EGFR T790M/C797S mutation, activation of bypass signaling pathways, PI3K-AKT-mTOR gene alterations, EGFR amplification, and TP53 exon8 mutation. Known EGFR-TKIs resistance mechanisms such as EGFR T790M, PI3K-AKT-mTOR signaling-related genomic alteration, ERBB2 mutation and MET amplification was detected in 3, 3, 1 and 4 patients who were resistant to first or second-generation EGFR-TKIs. EGFR C797S, EGFR L718Q, PI3K-AKT-mTOR signaling-related genomic alteration and MET amplification was detected in 1, 1, 5 and 6 patients who were resistant to osimertinib. EGFR amplification and TP53 exon8 mutation were identified in 27 and 8 patients with EGFR-TKIs resistance, though whether it would result in EGFR-TKIs resistance was still controversial. Co-occurrence of resistance mechanisms were observed in 16 patients including 2 patients without EGFR-TKIs sensitizing mutations. Known ALK-TKIs resistance mechanisms such as ALK G1269A and EGFR mutation was detected in 2 patients who were resistant to ALK-TKIs. **Conclusion:** This real-world study verified that the liquid biopsy using CSF showed high potential to identify actionable mutations and to explore the underlying resistance mechanisms for NSCLC patients with CNS metastases. CSF can be used as a source of liquid biopsy to facilitate the broad exploration of potential resistance mechanisms in clinical practice.

Keywords: NSCLC, cerebrospinal fluid, resistance mechanism

P24.07 An Ultra-Sensitive Protocol for ctDNA Mutation Detection With Application in Lung Cancers

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Introduction: To establish an ultra-high sensitivity protocol for ctDNA mutation detection in blood samples, i.e., PEAC followed by NGS (PEAC+NGS), to achieve the desirable results of targeted panel sequencing and the sensitivity of digital PCR. The PEAC+NGS protocol was proposed to achieve high concordance between the matched blood and tissue samples from patients with early-stage lung cancer. **Methods:** The cfDNA extracted from blood samples was enriched by PEAC technique, and the obtained products were amplified by a second round PCR process to add the adapter sequences used for NGS sequencing. The PEAC+NGS protocol was applied to the blood samples of 46 lung cancer patients, including 36 patients in stage I and II, and 10 patients in stage III and IV. The testing results were used to evaluate the performance of PEAC+NGS in blood ctDNA testing and its consistency with the testing results of matched tissues. **Results:** The PEAC+NGS protocol can simultaneously detect over 40 variant forms of five genes, i.e., EGFR, KRAS, NRAS, BRAF, and PIK3CA, which are closely associated with lung cancer. With a sequencing depth of over 10,000×, PEAC+NGS can achieve the ability to detect ctDNA variant at 0.01% allele frequencies, and 100% detection specificity. In 36 blood samples from patients with stage I and II lung cancer, 9 cases were detected as positive for mutations and 27 cases were negative by PEAC+NGS. The 9 blood samples with positive ctDNA variants also had positive results in matched tissue samples, while 11 of the 27 negative cases had positive testing results in matched tissues. The concordance between tissue and blood samples of stage I and II patients was 55.6%. Accordingly, for the 10 patients in stage III and IV, two blood samples detected as negative by PEAC+NGS also had negative results in the tissue; while among the remaining 8 patients that were tested positive in tissues, only one was failed to be detected by PEAC+NGS on the blood sample. The concordance between the blood and tissue samples was thus 90% for stage III and IV patients. **Conclusion:** We established an ultra-sensitive protocol for ctDNA mutation detection in blood samples, PEAC+NGS, which achieved 55.6% concordance in matched blood and tissue samples from patients with stage I and II lung cancer, and 90% concordance in stage III and IV lung cancer patients. These results demonstrate the great value of PEAC+NGS in clinical ctDNA testing.

Keywords: ctDNA, high sensitivity, Liquid biopsy

P24.08 Lung Cancer Diagnosis in Absence of Adequate Tissue Molecular Analysis in Metastatic Disease by NGS Analysis of Plasma cfDNA

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Introduction: Although molecular analysis of tumor material is standard of care in patients with metastatic non-squamous non-small cell lung cancer, this is not always feasible. In daily practice it can be difficult to obtain tumor tissue or there may be insufficient tissue available for molecular investigation. This leaves possible targeted-treatment options unidentified in a subset of patients. **Methods:** In 2019, Erasmus MC Cancer Institute launched the project Lung Cancer Diagnosis – cfDNA (LCD-cfDNA). Hospitals in the Comprehensive Cancer Network Southwest (The Netherlands) were given the opportunity to submit plasma samples from patients in whom adequate molecular analysis in tumor tissue was not possible. Blood was collected in Cellsave preservative 10mL vacutainer tubes (CellSearch, Menarini Silicon Biosystems, Castel Maggiore, Italy) and plasma cfDNA isolation was performed by QIAmp Circulating Nucleic Acid Kit (QIAGEN). NGS analysis was conducted by semiconductor sequencing with the Ion S5 System (Thermo Fisher Scientific) and cfDNA library preparation was performed using the Oncomine Lung cfDNA Assay v1 (Thermo Fisher Scientific). Results were discussed in the Thoracic Oncology Molecular Tumor Board and reported to the referring physician. **Results:** Between January 1st 2019 and January 1st 2021, plasma samples from 55 patients were submitted and analyzed. In 2 samples (3.6%), an activating EGFR aberration was detected (an exon 19 deletion in one patient; patient started on EGFR-TKI with response, and an exon 20 insertion in another patient; no treatment yet). In 4 cases (7.3%) a KRAS p.G12C and in 1 case (1.8%) an activating BRAF mutation (p.G466V) was identified in plasma (possible target for treatment in the near future). In 21 samples (38.2%) other aberrations were detected, which did not affect the choice of systemic therapy (other KRAS, TP53 and PIK3CA mutations). No mutations were found in 27 cases (49.1%). Table: Detected aberrations (per sample)

1	EGFR p.E746_A750del
2	EGFR p.P770_V771insG; TP53 p.R209Qfs*7
3	BRAF p.G466V; TP53 p.E339*
4	KRAS p.G12C
5	KRAS p.G12C; TP53 p.R267W
6	KRAS p.G12C; KRAS p.Q61H; TP53 p.R202C
7	KRAS p.G12C
8	KRAS p.G12D
9	KRAS p.G12D; PIK3CA p.E545K
10	KRAS p.G12V; TP53 p.C275F
11	KRAS p.G12V
12	TP53 p.G244V
13	TP53 p.R283C
14	TP53 p.Y205*; PIK3CA p.E545K
15	TP53 p.G266V
16	TP53 p.Y234C; TP53 c.672+1G>T; p.?
17	TP53 p.R249S
18	TP53 p.R158H
19	TP53 p.S215R
20	TP53 p.P278L
21	TP53 p.R283H
22	TP53 p.P278S; TP53 p.G279E; TP53 c.375+3_375+4insG; p.?
23	TP53 p.R267Q
24	TP53 p.C238F; TP53 p.C275S
25	TP53 p.Y163C
26	TP53 p.R248W
27	TP53 p.S241F
28	TP53 p.V272G

Conclusion: For patients in whom molecular analysis on tissue cannot be performed, NGS analysis of cfDNA in plasma provides an opportunity to detect driver mutations for subsequent targeted therapy.

Keywords: molecular testing, NSCLC, cfDNA

P24.09 Association Between Circulating EGFR Mutant Tumor DNA and Tumor Lesion Glycolysis in Patients with EGFR Mutated Metastatic Lung Adenocarcinoma

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Introduction: Monitoring the circulating tumor DNA (ctDNA) in EGFR-mutated metastatic lung adenocarcinoma (MLA) patients (pts) recently has been established as a reliable tool for therapy guidance. Tumor lesion glycolysis (TLG) measurement on an 18F-FDG-PET/CT scan gives information for tumor metabolic activity and tumor volumetric data at the same time point. We proposed that dynamic TLG assessment together with ctDNA measurement at time of response evaluation will give additional information about treatment choices. **Methods:** Plasma samples were collected at the baseline and at the response evaluation and were analyzed for EGFR mutations with the cobas EGFR Mutation Test. All 18F-FDG-PET/CT scans were performed on a combined PET/CT scanner. In all scans, TLG (g/ml x cm ^{3}) was calculated for all evaluable lesions according to the Positron Emission Tomography Response Criteria in Solid Tumors 1.0 guideline (Wahl et al, 2009). Descriptive and correlation analyses were done by SPSS v. 16.0. **Results:** Thirty-four TLG and ctDNA measurements were performed of 9 pts (women/men - 8/1) with MLA and EGFR activating mutations (exon 19 del/exon 21 L858R point mutation- 7/2). With Osimertinib as first and second (and consequent) lines therapy were treated 3 and 6 pts respectively. In addition, 7 pts received chemotherapy. Nine symptomatic progressions (sPD) had mean TLG of 231,9 g/ml x cm ^{3}, while seven asymptomatic PD (aPD) had mean TLG of 154,28 g/ml x cm ^{3}. Responders (11 measurements) had mean TLG of 60,44 g/ml x cm ^{3}. A positive Spearman correlation was found between presence of EGFR mutations on ctDNA and high levels of TLG (r = 0, 28, p = 0,04). In 5 out of 7 cases with aPD there were no EGFR mutations on ctDNA. **Conclusion:** Low patient's numbers preclude firm conclusions. EGFR mutated patients with metastatic lung adenocarcinoma have higher levels of Tumor lesion glycolysis while they symptomatically progressed in comparison to the patients with asymptomatic progression. EGFR mutations on circulating tumor DNA correlate with tumor response and Tumor lesion glycolysis.

Keywords: Metastatic Lung Adenocarcinoma, Circulating Tumor DNA, Tumor Lesion Glycolysis

P24.10 Identification of ctDNA using MassARRAY Technology in a Cross-Sectional Study of NSCLC Patients

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Introduction: Accessing tumour tissue material from non-small-cell lung cancer patients can be challenging, and often limiting. Therefore, non-invasive means of assessing tumour material is becoming increasingly more important. Circulating tumour DNA (ctDNA), sampled through a blood sample is appealing for the patient, and can be performed serially over the course of treatment. Recent advances in ctDNA have led to the development of sensitive tehcniques which have high specificity, rapid turn around time and are cost-effective. **Methods:** Here, we describe a cross sectional study for profiling the blood samples of 103 NSCLC patients for 74 variants in ctDNA across a panel of actionable lung cancer mutations using the UltraSEEK lung Panel (Agena Biosciences). **Results:** Our study showed tumour and blood concordance in the detection of KRAS mutations (G12C, G12D, G12A/V, G12R, G12RC, Q61H) in 17/27 (63%), EGFR mutations (e746_a750del, T70M, L861Q) in 14/20 (70%) with additional PIK3CA mutations across both cohorts. In patients without sufficient tissue for mutational assessment, 12/56 (21.4%) presented with plasma mutations across EGFR, KRAS and PIK3CA. Where ctDNA mutations were measured longitudinally (n=4 patients), the individual mutations mirrored the response to therapy/progression of disease. **Conclusion:** This study demonstrates the utility of detecting clinically actionable mutations in the blood samples of NSCLC patients at the time of presentation, and over the course of therapy. This can be a promising tool to determine actionable mutations, when tissue biopsy material can be limiting.

Keywords: ctDNA, Liquid biopsy, MassArray

P24.11 Cell-Free Tumor DNA (ctDNA) Utility in Detection and Monitoring EGFR Mutations in Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Recent studies have demonstrated the utility of cell-free tumor DNA (ctDNA) from plasma as an alternative source of genomic material for detection of sensitizing and resistance mutations in NSCLC. We hypothesized that plasma level of ctDNA is an effective biomarker to provide non-invasive, and thus a less risky method to determine new resistance mutations and to monitor response to treatment and tumour progression in lung cancer patients. **Methods:** This prospective cohort study was approved and conducted at the Peter Brojde Lung Cancer Centre, Montreal. Blood was collected in STECK tubes at 4 time points. DNA was extracted from plasma and ctDNA was analyzed for the presence of mutations in the EGFR gene using the COBAS® EGFR v2 qPCR (Roche) test. **Results:** 75 pts were enrolled in the study. 23 pts were TKI-naïve and 52 were already receiving first line TKI treatment. The original EGFR mutation (OM) was identified in 35 (48%) of pts at the time of enrollment with significantly higher detection rates in TKI naïve pts compared to TKI-treated group, 70% vs 37% (p=0.012). Detection of original mutation at the study baseline was negative predictor of PFS and OS (table 1). 50 patient eventually progressed on 1st line TKI, and 34/50 were tested for T790M resistance mutation. The (T790M) was detected in 27/34 (70.5%) pts. All 27 patients were treated with osimertinib in 2nd line and responded to treatment. At the time of progression detection of T790M significantly correlates with re-appearance of OM (p=0.001). Table 1. PFS and OS in EGFRm advanced/metastatic patients treated with TKI

EGFR mutation (1st ctDNA)	Median PFS (95% CI) months	Median OS (95% CI) months
Detected n=34	19.9 (12.2 – 27.7)	34.1 (18.9 – 49.4)
Not detected n=38	23.4 (13.9 - 32.9)	48.2 (35.8 – 61.1)
Overall n=72*	21.4 (17.8 - 24.9)	42.0 (34.4 – 49.5)
P value	0.06	0.003

Conclusion: Plasma ctDNA is a noninvasive patient-friendly test which can be used to detect EGFR mutations in NSCLC pts. Monitoring of OM during TKI treatment can potentially identify response and progression of the disease. Further larger prospective studies are needed to determine the utility and cost effectiveness of plasma testing to monitor disease progression and help guide treatment decisions.

Keywords: NSCLC, EGFR Mutations, ctDNA

P24.12 Biomarker Testing for Advanced Lung Cancer by Next-Generation Sequencing in Elderly Patients.

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Introduction: The Next Generation Sequencing (NGS) -based assay to find an actionable driver in non-small cell lung cancer is a modality with increasing use in clinical practice with an economic impact in developing countries. With a long list of actionable targets, limited tissue samples, and arduous single gene assays, the NGS alternative for extensive testing in clinical practice is attractive and useful even in the elderly population, in order to avoid turnaround time delays as well as allocate patients in target therapies avoiding toxic treatments. We present here our experience with NGS-based biomarker testing, focusing on patients with Non-small cell lung cancer (NSCLC) older than 75 years. **Methods:** A retrospective observational study was conducted. Consecutive stage-IV NSCLC patients with NGS predictive biomarker testing were included. Predictive biomarker testing was performed in each patient/case using either Foundation Liquid biopsy™ Solid Tumor DNA or Oncomine Focus Assay™ on Ion-Torrent sequencing platforms. Molecular testing was carried out in the setting of the Hospital Italiano de Buenos Aires, Argentina in patients with unresectable/advanced NSCLC and >75 years old. **Results:** 36 patients were older than 75 years with a median age of 79.5 years (r75-90) being 63.8% men (23/36). Within the analyzed >75-year cohort, 36% were non-smokers, and regarding the histological subtype, 91% of them were adenocarcinoma. Focusing on the elderly population, the following molecular alterations were found: EGFR (n=9, 25%), KRAS G12C (n=4, 11.1%), c-Met mutation or amplification (n= 3, 8%), rearrangements in ALK (n=2, 5.5%) and ROS-1 (n=1, 2.7%). None actionable molecular alterations were found in 18 patients (50%). Molecular alterations with approved drugs were detected in 36% of patients. Adding the possibility of entering a clinical trial, an expanded access or compassionate use program, the prevalence rises to 53%. Only 5.5% (2 patients) of this group did not access the drug due to clinical deterioration. **Conclusion:** This is a relevant study for elderly population with stage IV NSCLC describing the mutational landscape of lung cancer patients on cancer biology and treatment outcome. Our study demonstrates the clinical utility of NGS testing for identifying actionable variants and treatment decision-making in advanced lung cancer in elderly population.

Keywords: Next Generation Sequencing, Non-small cell lung cancer, elderly patients

P24.13 Circulating Tumor Cells Predict Prognosis Following First-Generation EGFR-TKI Treatment in EGFR- and TP53-Mutant Non-Small Cell Lung Cancer

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Introduction: For advanced non-small cell lung cancer (NSCLC) with EGFR mutations, first-generation EGFR-TKIs have become the first-line standard treatment. Co-mutation of EGFR and TP53 may be indicated EGFR-TKI resistance, shorter PFS and OS. This study isolates and quantifies circulating tumor cells (CTCs) and evaluates patient prognosis before and after first-line treatment with EGFR-TKIs in advanced NSCLC with EGFR and TP53 mutation. **Methods:** Patients with advanced NSCLC with EGFR and TP53 mutation were treated with a first-generation EGFR-TKI using a standard daily dose. Continuous blood samples were collected at baseline (CTCs-d0) and 28 days (CTCs-d28), and the isolation by CTCBIOPSY® was used to detect CTCs. The CTCs results were divided into favorable (< 5 CTCs) and unfavorable (≥ 5 CTCs) groups. **Results:** The median progression-free survival (PFS) of patients in the favorable group was significantly longer at baseline and after 28 days of treatment compared to those in the unfavorable group ($p = 0.0055$; $p = 0.0003$). After treatment, the PFS of patients with reduced CTCs was significantly better than those with no significant change in CTCs ($p = 0.014$). Patients with CTCs-d0 ≥ 5 and CTCs-d28 ≥ 5 had significantly lower PFS when compared to those with CTCs-d0 < 5 and CTCs-d28 < 5, respectively. **Conclusion:** This study confirmed for the first time that CTC count is closely correlated with prognosis in EGFR- and TP53-mutant advanced NSCLC following first-line treatment with first-generation EGFR-TKIs.

Keywords: Gefitinib, NSCLC, circulating tumor cells

P24.14 Validation of Companion Diagnostics for the Identification of Patients with EGFR Exon20ins NSCLC for Amivantamab Therapy

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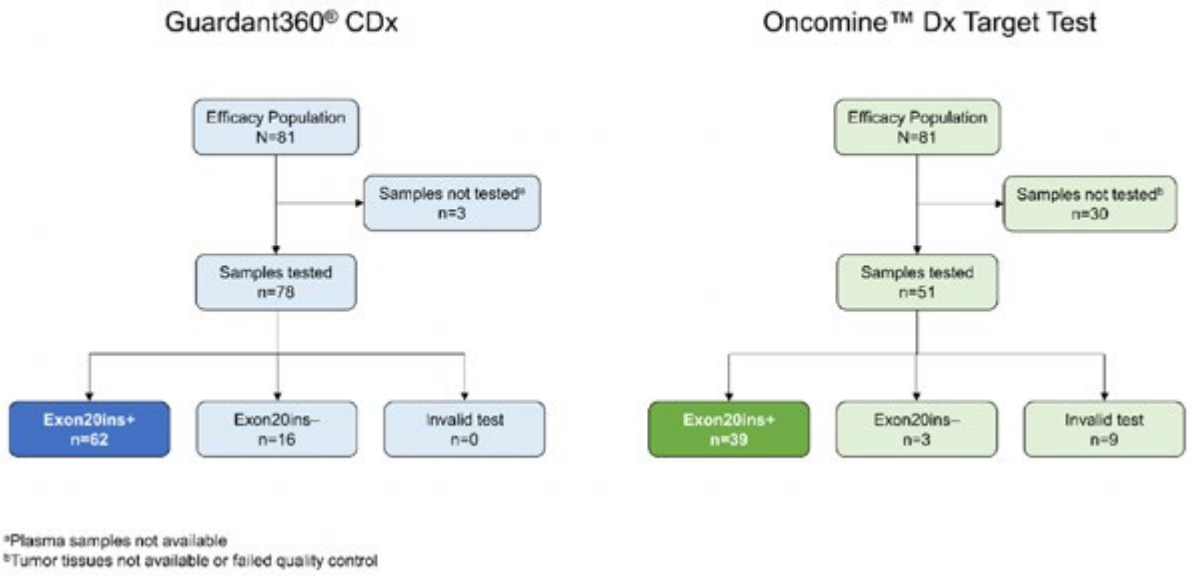
Introduction: Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity, targets activating/resistance EGFR mutations and MET mutations/amplifications. In the ongoing CHRYSALIS study (NCT02609776), amivantamab demonstrated antitumor activity in patients with EGFR exon 20 insertion (Exon20ins) disease. To identify patients likely to benefit from amivantamab therapy, we clinically validated 2 novel candidate companion diagnostics (CDx) for detecting Exon20ins variants in tumor tissue and plasma, with combined coverage of >100 variants. **Methods:** Banked plasma and tumor samples from the CHRYSALIS efficacy population (first 81 patients enrolled with EGFR Exon20ins NSCLC who had progressed on platinum chemotherapy) were tested using Guardant360® CDx and Oncomine™ Dx Target Test (ODxT). Overall response rate (ORR) of patients identified by Guardant360 CDx and ODxT was compared with that observed in the CHRYSALIS efficacy population. Agreement analysis was performed using samples with a valid CDx result from the CHRYSALIS study and samples from supplementary populations. **Results:** Of the 81 CHRYSALIS efficacy population patients, 78 plasma and 51 tissue samples were tested. Guardant360CDx identified 62 positive (16 negative) and ODxT identified 39 positive (3 negative) for EGFR Exon20ins mutation (Figure). Demographic and baseline characteristics were similar between CHRYSALIS, Guardant360 CDx, and ODxT populations. Agreement with local tests used for enrollment demonstrated high adjusted negative predictive value (99.6% and 99.9%) and positive predictive value (100% for both) for Guardant360CDx and ODxT, respectively. Comparable ORRs were observed in CHRYSALIS, Guardant360CDx, and ODxT populations (Table). ORR in Exon20ins patients identified by either Guardant360CDx or ODxT (39%) resembles that observed in the CHRYSALIS study (40%; Table). **Conclusion:** EGFR Exon20ins mutations identified by either plasma-based Guardant360CDx or tissue-based ODxT demonstrate the robust antitumor activity of amivantamab. Both tests provide accurate, comprehensive, and complementary approaches to identifying patients who could benefit from this targeted therapy.

Figure. Patient Sample Disposition



[a]Plasma samples not available
[b]Tumor tissues not available or failed quality control

Table. Overall Response Rates

EGFR Exon20ins Population	ORR[a]	n / N
CHRYSALIS efficacy population	40%	32 / 81
Guardant360 CDx	39%	24 / 62
ODxT	46%	18 / 39
ODxT or Guardant360 CDx	39%	28 / 72
ODxT and Guardant360 CDx	48%	14 / 29
ODxT but not by Guardant360 CDx	40%	4 / 10
Guardant360 CDx but not by ODxT	30%	10 / 33

[a]Partial response or better
ODxT, Oncomine Dx Target Test; ORR, overall response rate

Keywords: Companion Diagnostics, Amivantamab, EGFR Exon 20 Insertion

P25.01 Efficacy of Weekly Paclitaxel-Bevacizumab Combination in Advanced NSCLC: AVATAX, A Retrospective Multicentric Study

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Introduction: With the growing role of immunotherapy (ICI) as first-line setting for advanced NSCLC, strategies must be redefined after failure. The combination paclitaxel-bevacizumab showed in the ULTIMATE trial a significant superiority versus docetaxel as second or third-line treatment. Limited restropective studies has demonstrated unexpected efficacy of chemotherapy after prior progression on ICI. This combination could be use as salvage treatment following ICI. **Methods:** This multi-centric retrospective study identified patients treated with the combination paclitaxel-bevacizumab in metastatic non-squamous NSCLC as second-line therapy or beyond. Main objectives were to describe safety and efficacy of this combination, with a special attention to the sub-group treated just after ICI. **Results:** From January 2010 to February 2020, 314 patients started the paclitaxel-bevacizumab combination : 55% male, with a median age of 60 years, 27% with a performance status ≥2, 45% with brain metastases. A majority of patients were treated in second (20%) and third-line (39%), and 28% were treated just after ICI failure (88/314). Objective response rate (ORR) was 40% and disease control rate was 77 %. Median progression-free survival (PFS) and overall survival (OS) were 5,7 months [IQ,3,2–9,6] and 10,8 months [IQ,5,3–19,6] respectively. All grades adverse events concerned 82% of patients, including 53% asthenia and 39% neurotoxicity, and 25% of patients continued a monotherapy alone due to toxicity. Median PFS for patients treated after ICI failure (ICI+) was significantly superior compare to those not previously treated with ICI (ICI-) : 7,0 months [IQ,4,2–11,0] vs 5,2 months [IQ,2,9–8,8] p (log-rank)=0,01. There was not statistically significant difference in term of OS between this two groups. In multivariate analysis, factors associated with superior PFS were previous ICI treatment (ICI+) and performance status. **Conclusion:** This study confirms an acceptable toxicity profile associated with interesting efficacy of the combination paclitaxel-bevacizumab as second-line treatment or beyond for non–squamous NSCLC patients, particularly after progression with ICI.

Keywords: NSCLC, immunotherapy, Paclitaxel bevacizumab

P25.02 Concurrent Chemoradiotherapy With Cisplatin + S-1 for Locally Advanced Non-Small Cell Lung Cancer: IPD Meta-Analysis

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Introduction: Determining the most appropriate chemotherapy regimen to accompany thoracic radiotherapy is of the utmost importance for keeping up to speed in the fast-changing environment of stage III non-small-cell lung cancer (NSCLC) treatment. We conducted the individual-patient-data (IPD) meta-analysis of comparing "S-1 plus cisplatin" versus "other third-generation anti-cancer agent plus cisplatin" regimens to determine whether S-1/cisplatin was the ideal choice for treatment accompanied by RT. **Methods:** A thorough search was performed using multiple electronic databases. We integrated the IPD of each trial and analyzed the resulting meta-database. The primary endpoint was overall survival (OS) and the secondary endpoints included progression-free survival (PFS), objective response rate (ORR), toxicities, and treatment delivery. Subgroup analyses were done based on baseline characteristics. Statistical analyses were stratified by trials. **Results:** Three randomized trials (WJOG5008L, SPECTRA, and TORG1018) were identified; CDDP/S-1 was compared to CDDP/VNR, CDDP/PEM, and CDDP/DTX in the WJOG5008L, SPECTRA, and TORG1018, respectively. Of 316 patients enrolled in the 3 studies, 159 received S-1/cisplatin (SP), and 157 were assigned to non-SP chemotherapy. The median OS for the SP arm was 48.2 months (mo), and that of the non-SP arm was 42.4 mo. The combined HR for overall survival by the fixed-model was 0.895 (95%CI, 0.638-1.256), with no evidence of heterogeneity among the trials (test for heterogeneity, p=0.87; I2=0). The median PFS for the SP arm and non-SP arm was 12.8 mo and 14.0 mo, respectively. The corresponding HR for PFS by the fixed-model was 1.022 (0.776-1.347), with an evidence of moderate heterogeneity among the trials (test for heterogeneity, p=0.16; I2=0.46).The ORRs were 69.7% (62.1%-76.7%) and 70.9% (63.7%-78.1%) in the SP and the non-SP arms. The incidents of grade3-4 leukopenia and neutropenia in SP (37.1% and 33.3%) were significantly lower than that in the non-SP arm (65.6% and 61.8%) (p<0.01). However, the grade3-4 non-hematological toxicities detected no significant difference between them. Of the patients who received more than 2 courses of chemotherapy, a dose reduction was needed in 26 (17.9%) and 42 (27.4%) in the SP and non-SP arms, respectively (p=0.049). A total of 108 patients in the SP arm and 110 in non-SP arm had cancer recurrence, and no marked tendency was found in the relapse site. The proportion of patients receiving subsequent chemotherapy was 95.3% in the SP arm and 81.8% in non-SP arm (p=0.0098). **Conclusion:** No marked difference was confirmed in the OS, PFS, or ORR between SP and non-SP arms. SP had a significantly lower myelosuppression and better treatment compliance as chemotherapy regimen for concurrent chemoradiation in locally advanced NSCLC.

Keywords: S-1, IPD meta-analysis, locally advanced non-small-cell lung cancer

P26.01 Detecting Oligo-Metastatic/Progressive Disease in Advanced EGFR-Mutant NSCLC: PET/CT and Conventional Imaging Methods

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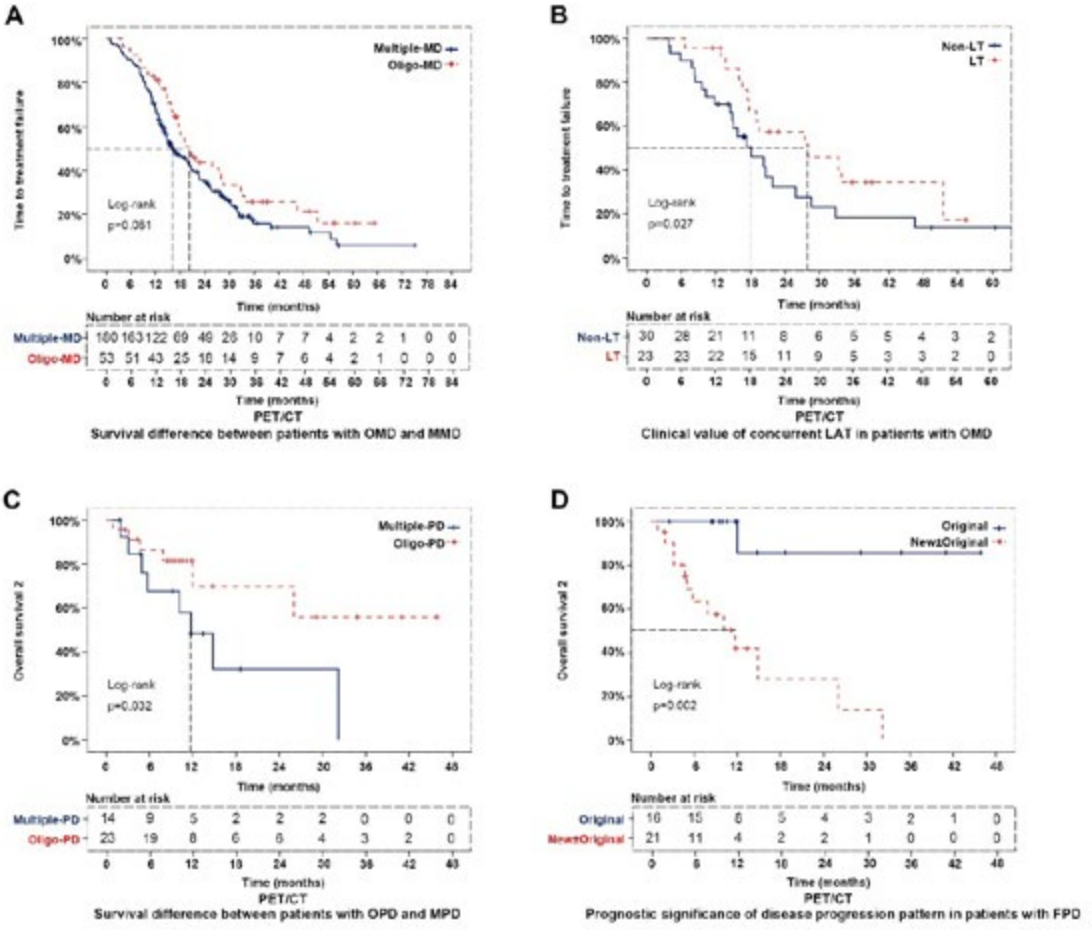
Introduction: Local ablative therapy (LAT) could potentially prolong patient's survival in advanced EGFR-mutant non-small cell lung cancer (NSCLC) receiving first-line EGFR tyrosine kinase inhibitors (TKIs) and harboring oligo-metastatic/progressive (OMD/OPD). However, the exact frequency of OMD/OPD and the optimal imaging method for identifying patients with OMD/OPD remain controversial. **Methods:** Consecutive cases with first-line EGFR-TKI treated metastatic EGFR-mutant NSCLC were retrospectively screened and those receiving PET/CT or complete conventional imaging methods (CIM), including brain MRI, chest CT, abdomen ultrasound or CT and bone scintigraphy, at baseline were included. OMD/OPD was defined as metastases/progressions documented at a maximum of 5 lesions (all thoracic lymph nodes as one lesion) and 3 organs, otherwise was referred to as multiple-metastatic/progressive disease (MMD/MPD). **Results:** OMD was detected in 53 (22.7%) of 233 patients evaluated by PET/CT and 29 (18.2%) of 159 patients evaluated by CIM at baseline. Among the patients evaluated with baseline PET/CT, time to treatment failure (TTF) tended to be longer in patients with OMD than those with MMD (p=0.061) and concurrent LAT significantly prolonged TTF in patients with OMD (28.0 vs 18.1 months, p=0.027). However, this was not the case among the patients evaluated with baseline CIM. With a median follow-up of 24.2 (range, 1.1-117.6) months, initial disease progression (FPD) was documented in 297 patients, 147 (49.5%) of whom had adequate imaging scans to comprehensively analyze the tumor distributions at FPD. OPD was detected in 23 (62.2%) of the 37 patients evaluated by PET/CT at both baseline and FPD (PET/CT group), 16 (39.0%) of the 41 patients evaluated by CIM at both baseline and FPD (CIM group), and 23 (33.0%) of the 69 patients evaluated by PET/CT at baseline and CIM at FPD (PET/CT-CIM group), respectively. The post-progression overall survival (OS2) was significantly longer for patients with OPD than those with MPD (p=0.032) in the PET/CT group, but was similar in the other two groups. Disease progression only at the originally existed sites (original PD) was detected in 43.2%, 26.8% and 65.2% of patients with FPD in the PET/CT, CIM and PET/CT-CIM group, respectively. Patients with only original PD had significantly longer OS2 (p=0.004) in the PET/CT group, but was not the case in the other two groups.



Conclusion: PET/CT has better performance in detecting OMD/OPD in first-line EGFR-TKI treated advanced EGFR-mutant NSCLC. Patients with PET/CT-detected OMD may benefit from appropriate LATs.

Keywords: EGFR mutation, non-small cell lung cancer, Oligo- metastatic disease

P26.02 A Phase II Trial of Neoadjuvant Osimertinib for Surgically Resectable EGFR-Mutant Non-Small Cell Lung Cancer: Updated Results

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Introduction: The third generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is well-tolerated and effective for first-line treatment of metastatic EGFR-mutant non-small cell lung cancer (NSCLC). Adjuvant osimertinib therapy also significantly decreases the risk of disease recurrence for patients with surgically resected (stage IB-IIIA) EGFR-mutant NSCLC. The benefit of neoadjuvant osimertinib for the treatment of surgically resectable EGFR-mutant NSCLC is unknown. The use of neoadjuvant targeted therapies in oncogene-driven NSCLC may offer the advantages of increased pathologic response rates as well as more favorable toxicity profiles compared to cytotoxic chemotherapy. These trials also offer the opportunity to identify mechanisms underlying cancer cell persistence despite optimal oncogene-targeted therapy. This abstract is an update of https://doi.org/10.1016/j.jtho.2019.08.1209. **Methods:** This is an ongoing multi-institution phase II trial of neoadjuvant osimertinib (NCT03433469), which aims to enroll 27 patients with surgically resectable stage I-IIIA (AJCC V7) EGFR-mutant (exon 19 del or L858R) NSCLC. Eligible patients are treated with one to two 28-day cycles of osimertinib 80 mg orally daily followed by surgical resection. The primary endpoint of the study is major pathological response (mPR) rate. Secondary endpoints include safety, unanticipated delays to surgery, surgical complication rate, pathological response rate (0-49% residual viable tumor), pathological complete response rate (pCR), unconfirmed objective response rate, rate of lymph node downstaging, disease-free survival (DFS), and overall survival (OS). **Results:** As of April 2021, 13 patients with early-stage (6 stage IA/B, 2 Stage IIA/B, and 5 Stage IIIA) EGFR-mutant (7 exon 19 del, 6 L858R) NSCLC have been enrolled and treated with osimertinib for an average of 59 days prior to surgical resection. The mPR rate was 15% (2 of 13). The pathological response rate was 69% (9 of 13). No pCR's were observed. Partial radiographic responses (PR) were observed in 46% (6 of 13) of patients and stable disease (SD) in 7 patients (100% DCR). Lymph node downstaging was achieved in 4 of 5 patients (80%) with positive lymph nodes detected prior to treatment. DFS and OS data are immature. Treatment was well-tolerated without SAEs and all patients proceeded to surgical resection without unscheduled delay or surgical complications. One patient developed grade 2 treatment-related pneumonitis that resolved without steroid treatment. Pre-treatment tumor biopsies were available for targeted exome sequencing analysis of ~ 500 cancer-related genes from 7 patients. Loss of function mutations in RBM10 were identified in 3 of 4 (75%) tumors that showed no evidence of pathological response to osimertinib treatment. **Conclusion:** Interim analysis of this phase II study indicates that neoadjuvant osimertinib treatment in surgically resectable, EGFR-mutant NSCLC is well-tolerated without unforeseen delays in surgery and can induce pathological responses and lymph node-downstaging of disease. However, major pathological responses are rare and complete pathological responses to neoadjuvant osimertinib are not observed. RBM10 mutations were observed in the majority of tumors that did not exhibit a pathological response to osimertinib. Combination therapy approaches, as are being studied in the NeoADAURA trial (NCT04351555), are likely needed to achieve clinically meaningful major pathological response rates in EGFR-mutant lung cancers.

Keywords: osimertinib, EGFR, Neoadjuvant

P27.01 Patterns of Care and Outcomes in Clinical T3N0M0 Non-Small Cell Lung Cancer Without Invasion of Other Structures

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Introduction: Non-small cell lung cancers (NSCLC) measuring 5-7 cm without evidence of invasion of other structures, nodal disease or metastasis are staged cT3N0M0 and clinical stage group IIB. Primary treatment is ideally surgical but many patients are non-operable and optimal non-surgical management is controversial. We set out to examine treatment patterns in these patients and associated outcomes. **Methods:** Data from the National Cancer Database (NCDB) for patients with biopsy proven cT3N0M0 NSCLC, as per the American Joint Committee on Cancer (AJCC) staging system 8th edition, from 2004-2015 were collected. Patients with 5-7 cm tumors staged cT2b in the AJCC staging system 7th edition but who would be classified T3 in the 8th were included. Patients were excluded if they had tumor invasion of adjacent structures, satellite nodules, underwent local ablation or did not undergo treatment with definitive intent. Pearson's chi-squared test and multivariate logistic regression analyses were used to assess the distribution of demographic, clinical, and treatment factors. After propensity-score matching with inverse probability of treatment weighting, overall survival (OS) was compared between treatment regimens using Kaplan-Meier analyses and doubly-robust estimation with multivariate Cox proportional hazards modeling. **Results:** We identified 9,928 patients with cT3N0M0 (AJCC 8th ed) NSCLC without invasion of other structures or satellite nodules. Of these 5,426 (55%) underwent resection. Among 4,402 patients who were treated non-operatively but received chemotherapy (CMT) or radiotherapy (RT), only 957 (22%) were treated with the non-operative standard of care (SOC) regimens of stereotactic body radiotherapy (SBRT) +/- adjuvant CMT or concurrent chemoradiotherapy (cCRT). We defined SOC SBRT as 48- 60 gray (Gy) in 3-8 fractions with BED10 $\geq$ 100 Gy and SOC cCRT as 60-70 Gy in 30-35 fractions with concurrent CMT. The only factors associated with receipt of a SOC regimen were male sex and treatment at an academic/research program or integrated network cancer program as compared to community cancer programs. Importantly, in this non-surgical group, receipt of any SOC treatment was associated with an overall survival (OS) benefit (HR 0.83, P<0.01, 95%CI 0.76-0.90) after propensity score matching. Among 957 patients treated with SOC therapies 505 (53%) received cCRT and 452 (47%) received SBRT. Only 22 patients treated with SBRT (5%) received adjuvant CMT. Among patients treated with a SOC therapy**,** factors associated with SBRT as opposed to cCRT included age over 65, Medicare insurance, living 50-200 miles from care, and treatment in the West-North-Central, West-South-Central or Pacific regions of the United States. Black patients and those treated at community cancer programs were less likely to receive SBRT. There was no OS difference between receipt of SBRT and cCRT (HR for SBRT 1.00, P=0.99, 95% CI 0.84-1.19). **Conclusion:** We identified characteristics associated with receipt of various treatments in patients with AJCC 8th ed cT3N0M0 NSCLC measuring 5-7 cm without invasion of adjacent structures. In patients treated non-surgically receipt of SOC therapy with SBRT or cCRT was associated with an OS advantage compared to non-SOC regimens. There was no OS difference between the non-surgical standard of care regimens of SBRT and cCRT.

Keywords: SBRT, T3N0M0 NSCLC, Patterns of Care

P27.02 Associating Cardiac Plaque Accumulation With Cardiac Toxicity and Overall Survival In Locally Advanced Non-Small Cell Lung Cancer

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Introduction: Patients undergoing post-operative radiation therapy (PORT) for locally advanced non-small cell lung cancer (NSCLC) are at risk for cardiac toxicity. The volume of baseline cardiac plaque may be a risk factor for cardiac toxicity. The purpose of this study was to assess a relationship between the amount of plaque and the dose to the identified plaque volume with cardiac toxicity and overall survival (OS). **Methods:** Of the 285 LA-NSCLC patients consecutively treated in our department with PORT from 2004 to 2017, 133 patients with non-contrast enhanced CT simulation scans for PORT planning were included. Prescriptions ranged from 45-66.6Gy in 1.8 or 2.0 Gy fractions. The pericardium and aorta were auto-segmented using Deep Learning and the volume inside of those structures with Hounsfield Units (HU) >130 - according to the Agatston plaque score - was segmented via HU thresholding. All plaque segmentations were qualitatively post-processed to exclude port catheters, other high HU devices and image artifacts. Two plaque volumes were identified: the volume within the pericardium (PlaquePeri) and the volume within the aorta and the pericardium (PlaqueAll). Both PlaquePeri and PlaqueAll volumes and the mean dose to those volumes were tested for association with cardiac toxicity using logistic regression analysis. Cardiac toxicity was defined as major adverse cardiac events (MACE: myocardial infarction, new onset heart failure, cerebrovascular event or percutaneous coronary intervention; n=14/133), and as arrhythmic, valvular and/or pericardial events (MACE+; n=24/133). In addition, the plaque volumes, their mean doses, MACE and MACE+ events were tested for association with OS using Cox Proportional Hazard modeling. Also, the association between the mean heart dose (MHD) and MACE, MACE+ as well as OS was explored. All doses were fractionation-corrected using α/β=3Gy. The significance level was adjusted for four multiple tests and was denoted at p=0.013. **Results:** The population median (range) volume of PlaqueAll was 0.52 (0-16) cm3, of which the majority resulted from aortic plaque (Aorta: 0.30 (0-14) cm3 vs. Pericardium: 0.03 (0-7.2) cm3). None of the investigated variables were associated with MACE or MACE+. For OS, the only predictor was MHD (HR: 1.1 (95%CI: 1.0-1.1); p=0.0008), whereas among the plaque variables, PlaqueAll presented with the lowest p-value (0.05). **Conclusion:** Neither the volume of cardiac plaque nor the plaque mean dose was associated with cardiac toxicity or OS. In contrast, there was a strong association between the mean heart dose and OS. The causality of the association between increasing heart dose and OS is likely multifactorial and remains an open question.

Keywords: plaque, cardiac toxicity, Overall survival

P27.03 Increase in Overall Survival for Locally Advanced NSCLC Patients From 2010 to 2018 - A Registry Based Study in Denmark

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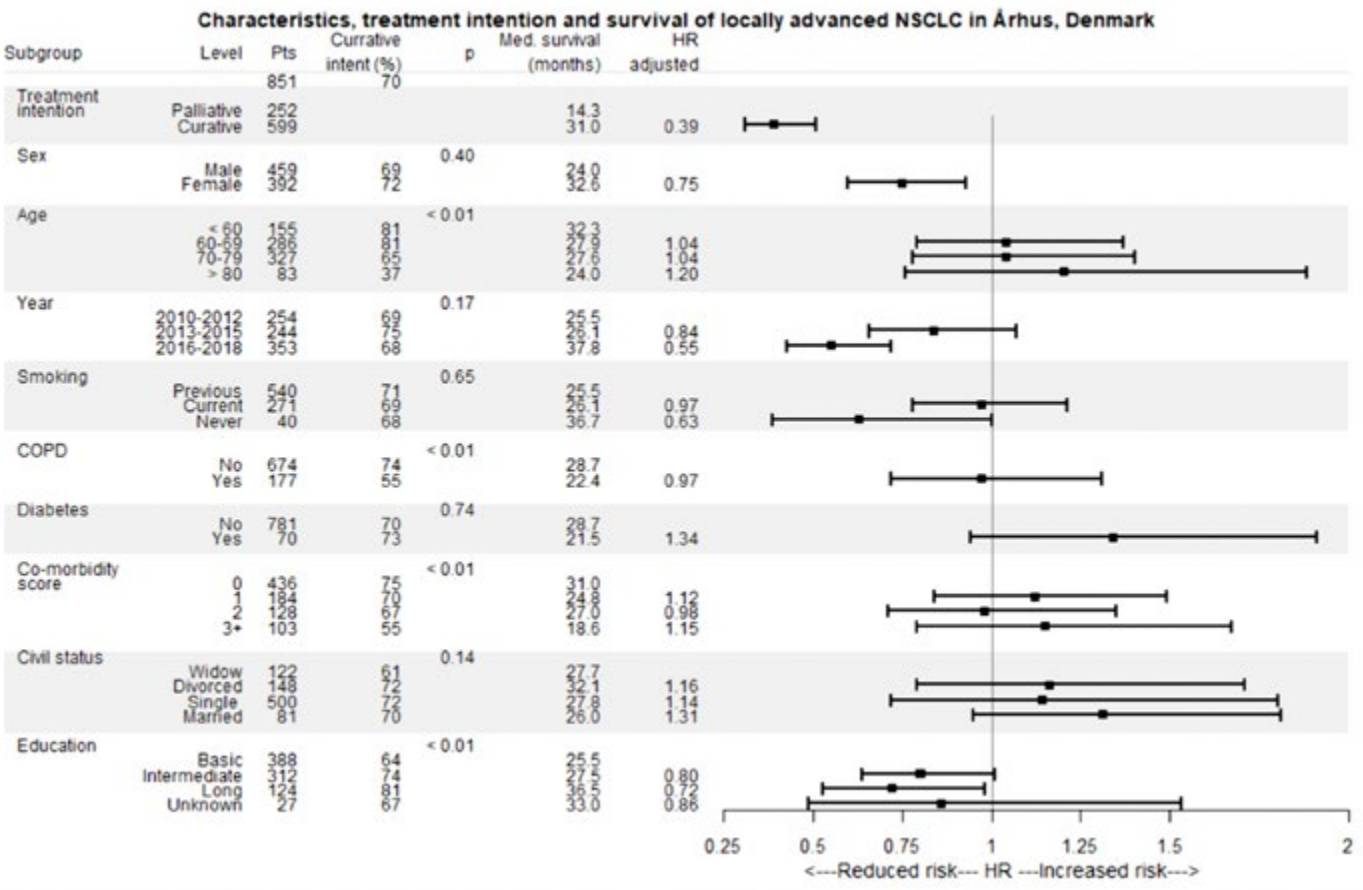
Introduction: Standard of care for NSCLC patients with unresectable disease has remained largely unchanged, either curatively intended chemoradiotherapy (CRT) followed by active surveillance, or palliative treatment. However, overall survival has improved recently, possibly due to more targeted patient selection and improved diagnostic imaging, new radiation modalities, and increased subsequent lines of treatment. Here, we describe treatment patterns and survival in the real world for stage III NSCLC patients diagnosed in the county of Aarhus, Denmark. **Methods:** Data on stage III NSCLC patients, diagnosed 2010-2018, were obtained from a regional clinical cancer database, with active follow-up until 1st July 2020. Patient level and tumor related data were linked to socioeconomic position and vital status from national mandatory registries. Planned treatment intention at diagnosis, i.e. curative vs. palliative, was recorded and stratified by in the analysis. Treatment patterns and overall survival were estimated using time-to-event methods. **Results:** Overall, 851 stage III NSCLC patients were included. 599 patients (70%) were initially treated with curative intent, while 252 (30%) initiated palliative treatment (Table 1). Factors related to curative intent were: age <70 years vs >80 years (81% vs 37% curative intent), no co-morbidities vs ≥3 (75% vs 55%), and higher vs basic education (81% vs 64%). Sex, year of primary diagnosis, smoking status and civil status were not associated with treatment intention. In patients who initiated treatment with curative intent, 27% had surgery, 68% radiation and 81% chemotherapy. Cisplatin and carboplatin were found to be equally frequently used (40% each). In patients who initiated palliative treatment, radiation was used in 78%, chemotherapy in 62% and immune therapy in 12%. Over the study period, median survival increased by 12 months (25.5 to 37.8 months), corresponding to a 45% risk reduction of death. Overall survival was strongly correlated to treatment (HR: 0.39 curative vs palliative intent), female sex (HR 0.75), higher education (HR 0.72), and most recent years of primary diagnosis (2016-2018) (HR 0.55).



Conclusion: This study has demonstrated improved survival of stage III NSCLC patients of approximately one year over the study period. Despite a dismal prognosis, a high proportion of patients are treated with curative intent. The positive trend in survival could reflect targeted work with more precise staging and radiation planning in place in Aarhus. The study also demonstrate the importance of selection of patients for curative CRT, with the most important determinants of treatment intention being age and prevalence of co-morbidities.

Keywords: Treatment patterns, survival, Curative and Palliative intent

P27.04 Clinical Outcomes for Patients With Stage III NSCLC and STK11 or KEAP1 Genetic Alterations

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Introduction: Identification of mutations via next generation sequencing (NGS) associated with worse outcomes could potentially improve prognostication and more clearly identify risk/benefit ratios for specific treatments in a given patient. STK11 and KEAP1 mutations have been recently shown to be associated with worse outcomes in patients with advanced disease receiving immunotherapy, however data regarding patients with unresectable stage III NSCLC who received consolidation durvalumab is limited. We sought to establish the prevalence of such mutations in stage III NSCLC and compare outcomes in a real-world cohort. **Methods:** We retrospectively identified patients with unresectable stage III NSCLC who received consolidation durvalumab following chemoradiation between January 2017 and March 2021 at our institution using a clinical research query tool. We then cross-matched this list with one generated from a comprehensive genomic testing data warehouse solution to identify those who also underwent NGS. Basic demographics, disease-related variables (including PD-L1 expression, TMB, and presence of other known oncogenic driver alleles), and treatment history were captured. Individuals with a STK11 or KEAP1 mutation were placed into one group, while those who were wild type for both genes were placed into the other group. Progression-free survival (PFS) and overall survival (OS) from the time of durvalumab initiation were analyzed using the Kaplan-Meier method and log-rank test. **Results:** We identified 128 individuals who had a diagnosis of stage III NSCLC and received durvalumab, however of these only 29 had also undergone NGS and were eligible for inclusion. Of these 29, the median age was 66 (IQR: 59, 74), 11 (37.9%) were female, 23 (79.3%) were Caucasian, 4 (13.8%) were African American, and 7 (24.1%) had squamous histology. Median PD-L1 expression was 9% (IQR: 0, 35), and median TMB was 8 mut/Mb (IQR: 4, 10). Other than pack-years (median 46 vs 6, p=0.03), no statistically significant differences in baseline characteristics were seen between the mutation and non-mutation groups (p>0.10). Median follow-up time was 20.6 (95% CI: 11.8, 35.9) months. Of the 29 patients, 7 (24.1%) were found to have mutations in STK11 while 5 (17.2%) were found to have mutations in KEAP1; two patients had co-mutations and thus 10 (34.5%) patients overall had at least one mutation. Median PFS was 6.6 (95% CI: 0.9, 9.7) months in patients with a STK11 or KEAP1 mutation and 9.6 (95% CI: 2.8, 22.7) months without such mutations (p=0.40). Median follow-up was 20.4 (95% CI: 8.9, 34.4) months in patients with mutations and 26.1 (95% CI: 15.4, 37.6) months in patients without mutations (p=0.89). Median OS was NR (95% CI: 0.9, NR) in patients with mutations and 24.5 (95% CI: 15, NR) in patients without mutations. **Conclusion:** No statistically significant differences in PFS or OS were seen in patients with either a STK11 or KEAP1 mutation receiving consolidation durvalumab for unresectable stage III NSCLC, however our analysis may be underpowered due to a low number of patients receiving NGS testing. Further analysis with a larger sample could potentially have prognostic and therapeutic implications, particularly if certain mutations are shown to have reduced benefit with immunotherapy.

Keywords: biomarkers, immunotherapy, NSCLC

P27.05 High Body Mass Index (BMI) Is Associated With Better Outcomes in Mexican Patients With Advanced Non–Small Cell Lung Cancer (NSCLC)

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Introduction: Population studies suggest that high body mass index (BMI) correlates with a reduced risk for death from some cancer like melanoma. The aim of our study was to evaluate the influence of high BMI on long-term overall survival (OS) in Mexican patients with advanced NSCLC. **Methods:** We evaluated 146 patients with advanced lung cancer (IIIB and IV) who were treated for locally advanced NSCLC. Demographic and clinical data were collected. BMI was estimated at diagnosis in routine screening evaluation before systemic treatment. They were stratified into two BMI groups ≧30kg/m2 and <30kg/m2 . Overall survival was analyzed by BMI group. Kaplan-Meier survival analysis and the log-rank test were used to calculate OS. Univariate and multivariate analysis to identify variables associated with OS was assessed using Cox regression model **Results:** Baseline patient characteristics and treatment parameters were similar between high BMI and no high patients. Among the included patients, the median age was 63.39 (range: 29-86 years), 49.2 % patients were females and 50.8 % were males. High BMI was associated with improved overall survival 38 vs 25 months p=0.047. There were no difference in overall survival between patient with overweight (25–29.9 kg/m2) and normal weight (18.5-24.9 kg/m2) counterparts (26 vs 25 months, p = 0.67) **Conclusion:** High BMI patients in this retrospective study had significantly improved survival relative to no high BMI patients. Our data suggest that the protective effect of obesity in locally advanced NSCLC. Additional studies are needed to clarify the mechanisms and possible concomitant factors underlying the obesity in NSCLC as dietary and lifestyle interventions.

Keywords: Body mass Index, survival, lung cancer

P27.06 Multiscale NSCLC Tumor Growth Knowledge-Based Model Reproduces Tumor-Non-Progression under Gefitinib

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Introduction: Non-small cell lung cancer (NSCLC) is the leading form of lung cancer and adenocarcinoma (LUAD) its most common histotype. Tumor size, part of the TNM-staging, is important for prognosis and treatment guidance. Response to Tyrosine Kinase Inhibitors, e.g. Gefitinib, is altered with certain epidermal growth factor receptor (EGFR+) gene mutations making time-to-progression (TTP) predictions difficult. We therefore developed an in silico EGFR+LUAD model to characterize tumor size and TTP in advanced-stage adenocarcinoma patients (IIIb or higher) with EGFR mutations (exon19-deletion (E19+) or exon21-L858R-substitution (E21+)). The model is a mechanistic representation of tumor evolution upon Gefitinib administration, including tumor heterogeneity, age, gender, initial clinical stage and smoking status as covariates. **Methods:** Three-step in silico model development:

1. Model Building using a Knowledge and a Computational Model (CM): Pathophysiology of EGFR+LUAD was characterized with seven sub-models: mutational burden, EGFR downstream pathways, tumor growth and heterogeneity, Gefitinib PK/PD, treatment-induced resistance and clinical outcome. For each sub-model, relevant biological entities and their functional relationships were extracted from scientific papers and translated into ordinary differential equations (ODEs). The CM has 43 variables, 170 parameters and 18 to 83 ODEs reflecting intra-tumor heterogeneity.
2. Calibration with information from scientific literature: Spheroids, xenografts and clinical results were used for stepwise calibration.
3. Validation against published data: Patients[1] (n=159) had E19+ or E21+ mutations and were treated with Gefitinib (250mg/day orally). A Virtual Population with equivalent baseline characteristics was simulated using the calibrated CM. Kaplan-Meier curves show tumor non-progression over time. Validation metrics: (1) "Raw-Data-Coverage" expressing the fit with the 95% prediction interval (PI) of the simulated curve (computed by bootstrapping), (2) Comparison of bootstrapped simulated survival curves (n=159) with log-rank tests (LR) for statistical significance (α=0.05). **Results:** Coverage of the model simulations with raw data was 95.92%. Proportion of non-significant bootstrapped LR tests comparing the observed curve with simulated curves was 88.43% (Figure 1).

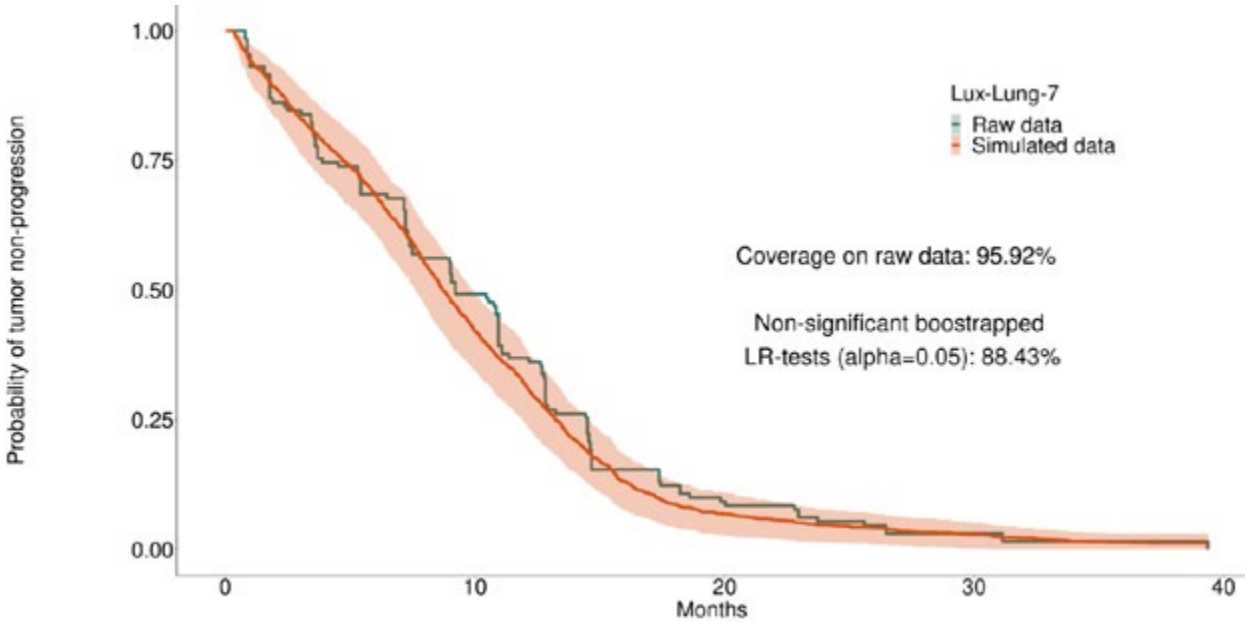

Figure 1: Tumor-non-progression of observed raw (green) and simulated data (red). Coverage with the 95%-PI of the simulated curve (orange area) represents goodness-of-fit. **Conclusion:** We reproduced a clinical trial of advanced-stage EGFR+LUAD patients treated with Gefitinib. We created a modular, reusable, multiscale Knowledge-Based model adaptable to also test the efficacy of other treatments and drug combinations on tumor-non-progression. This enables us to identify best responders and to optimize trial designs in silico. References [1]: Paz-Ares L, et al. Ann Oncol. 2017.

Keywords: LUAD, MechanisticModelling, InSilicoClinicalTrial

P27.07 Pancoast Tumour Presenting as Lower Limb Weakness; Would You Recognise It?

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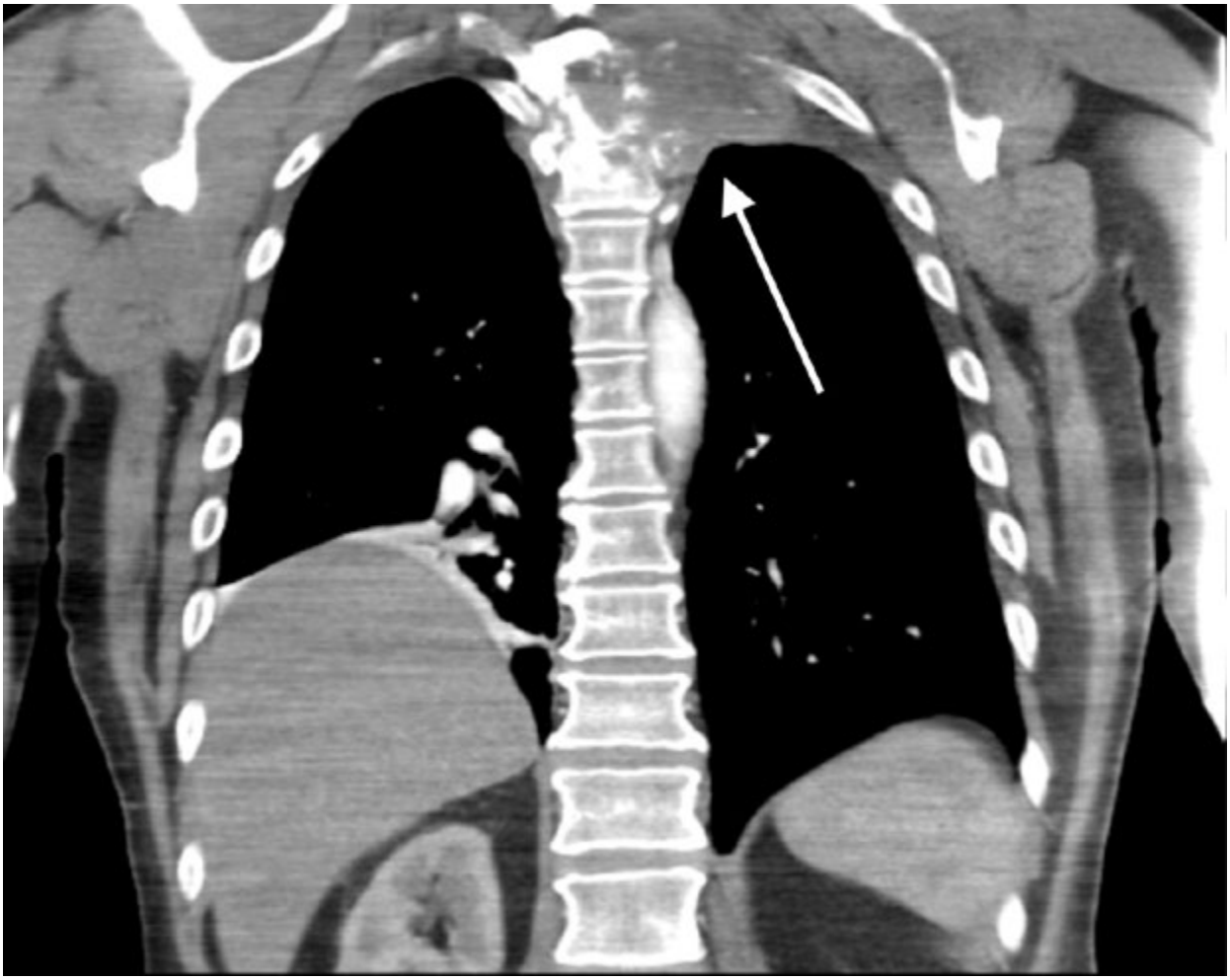
Introduction: Pancoast tumours were an obscure entity until Henry Pancoast first described them in the 20th century. This tumour typically involves the apical chest wall and thoracic inlet structures. To characterise a lesion as a Pancoast tumour, it must arise from the lung apices and cause neurological dysfunction. It may present as pain in the shoulder girdle and arm (along C8, T1 and T2 dermatomes), weak or atrophied hand muscles and Horner's syndrome, a constellation of symptoms collectively known as Pancoast Syndrome. These tumours that form 5 per cent of all the NSCLC (Non-small cell lung carcinoma) are often not detected early and have a high predilection for metastasis leading to an overall poor prognosis.

The following clinical case study accurately describes a Pancoast tumour's signs and symptoms and emphasises the need for its early recognition by retaining a high index of suspicion even in the most routine of circumstances. **Methods:** A 56-year-old man presented to the emergency department with sudden onset of left leg weakness associated with mild sensory loss. Further questioning revealed clumsiness of the left hand. The initial impression was that of a stroke, but the CT head was found to be unremarkable. It was only later that examination revealed a classical Horner's syndrome; miosis, partial ptosis and hemifacial anhidrosis, raising suspicion of an apical pathology. The chest radiograph was deemed normal, and hence a CT scan of the chest was requested, which showed a left-sided Pancoast tumour. A Subsequent MRI revealed cord compression at T2-T3 levels with tumour infiltration into the left brachial plexus. CT guided biopsy confirmed lung adenocarcinoma with distant spread.



Results: He underwent five cycles of radiotherapy, during which he developed neuropathic pain, particularly along the left shoulder and upper chest. His left-sided Horner's syndrome improved clinically. The left fingers' clumsiness did not worsen, and he continued to use his left hand despite some residual weakness but permanently lost bilateral leg function due to spinal cord metastasis. **Conclusion:** This case demonstrates the significance of a thorough medical history (including smoking) and examination while assessing patients with seemingly unrelated symptoms. The presence of "normal" physical and imaging studies should provoke the clinician to think of an alternative possibility. The inability to include Pancoast tumour in the differential diagnosis most commonly causes a delay in diagnosis and management.
Early recognition is the key since the prognosis is directly dependent on timely treatment, which affects patients' survival rate with lung adenocarcinoma.

Keywords: Pancoast tumour, Horner syndrome, Non-small cell lung carcinoma

P27.08 Accurate Positioning Technology for Lung Cancer Radiotherapy

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Introduction: The study found that the translation error caused by the rotation angle of patients in the positioning was most affected by the distance between the target and the rotation axis. In order to reduce the translation error and rotation error of patients, the positioning point should be selected as close to the tumor site as possible. For this purpose, a novel localization system was developed in this study to accurately place the positioning point inside the tumor. **Methods:** The patient with the positioning beads placed on the left/right sternoclavicular joints and the xiphoid was shaped by a vacuum pad for CT simulation. By superimposing and matching the surface of the virtual patient model with the real patient through HoloLens2, and with the help of the virtual tumor diaplay on the surface of the patient, the positioning point was correctly palced inside the tumor. 90 patients who received lung cancer radiotherapy at Shanghai Pulmonary Hospital were randomly evenly divided into three groups: control group 1, control group 2 and experimental group. In the control group 1, the positioning technician determines the positioning of the body surface points based on the description of the doctor on the received positioning sheet. Each patient in the control group 2 received a CT scan at the time of localization to determine the location of the tumor, and then CT simulation was performed. The experimental group used our new accurate positioning technology for lung cancer radiotherapy to determine body surface markers. Statistical analysis of the central movement of the radiotherapy plan in the control group and the experimental group, and the time taken for radiotherapy positioning. **Results:** In control group 1, 19 patients (63.3%) were labeled with centers outside the radiotherapy target.In control group 1, the mean deviation between the location center and the tumor center was 5.56cm In control group 2, the mean deviation between the location center and the tumor center was 3.20cm. The center points determined in the experimental group were all within the radiotherapy target area, and the average deviation of the distance between the location center and the tumor center in the experimental group was 2.84 cm. Patients in the experimental group did not need to move the bed again. **Conclusion:** The results of our study showed that the new lung cancer precise positioning technology improved the precision of positioning compared with the existing positioning technology, significantly shortened the simulation positioning time, reduced the number of patients repeated CT, and reduced the case of bed shifting again, which is worthy of clinical promotion.

Keywords: positioning point, radiotherapy, positioning

P28.01 Real-World Experience (RWE) of Consolidation Durvalumab After Concurrent Chemoradiotherapy (CCRT) In Stage III NSCLC

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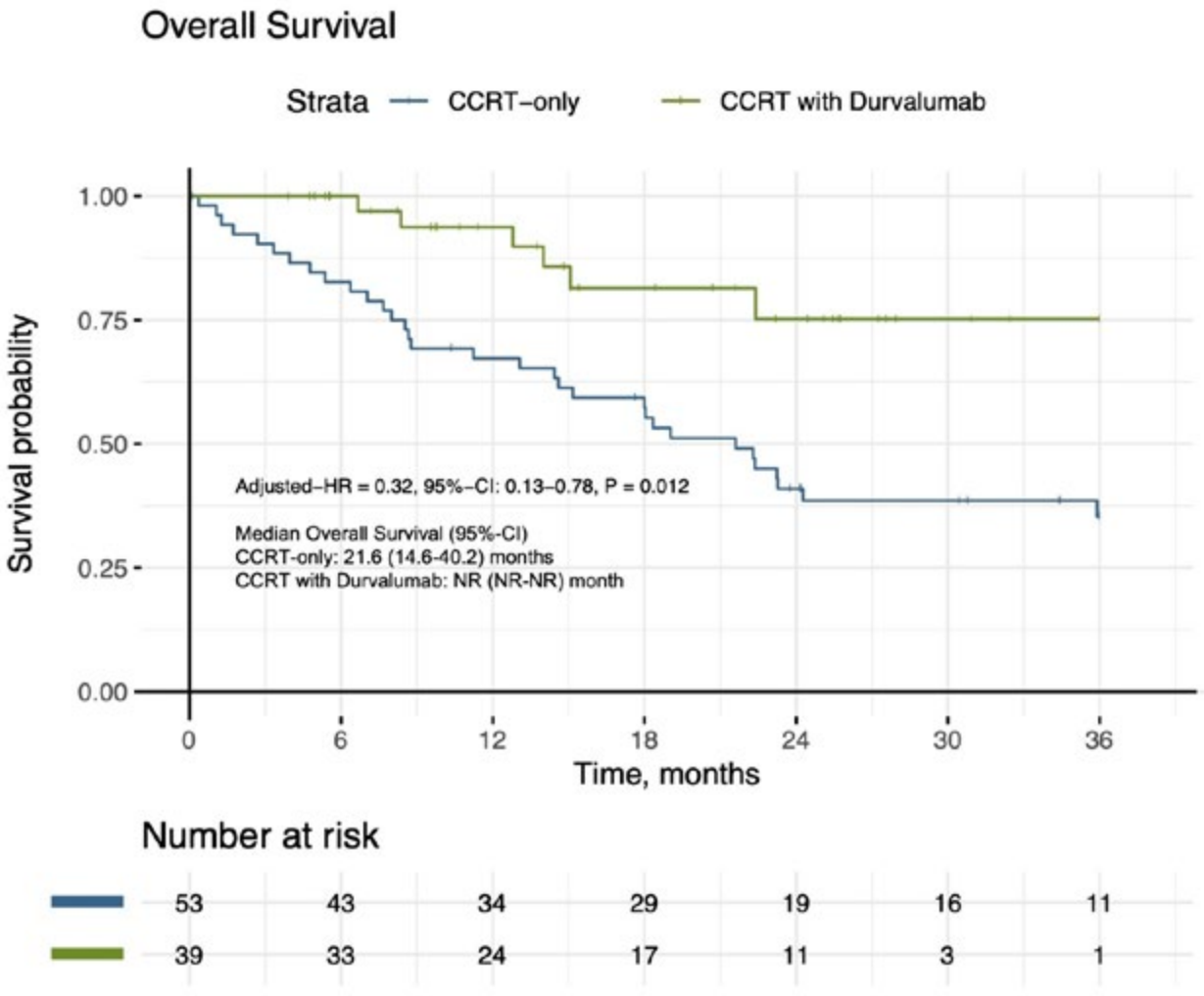
Introduction: Durvalumab consolidation is associated with improved progression-free survival (PFS) and overall survival (OS) following CCRT in unresectable stage III non-small cell lung cancer (NSCLC). Given the heterogeneity of stage III NSCLC patients, it is crucial to evaluate the efficacy and safety of durvalumab when used in the real-world setting. **Methods:** We described the outcomes of 2 cohorts of unresectable stage III NSCLC patients in a tertiary institution in Asia: one cohort received definitive CCRT alone, another cohort had durvalumab consolidation following CCRT. Primary endpoints were PFS and OS, secondary endpoints were locoregional relapse rate, distant relapse rate and safety. **Results:** Between January 2013 to August 2020, 95 patients were enrolled: 56 received CCRT alone and 39 received durvalumab consolidation following CCRT. The median age was 65 years, 78% male, 73% Chinese, 96% ECOG PS 0-1, 37% current smokers, 44% stage IIIA disease, 53% adenocarcinoma histology, 33% harboured EGFR mutations, and PD-L1 tumour proportion score (TPS) was >/=1% in 66% of patients. Median PFS was 22.7 months (95% CI 11.3 to NR) for durvalumab cohort, and 8.9 months (95% CI 6.0 to 29.2) for CCRT-alone cohort (HR 0.64, 95% CI 0.34-1.21, p=0.173). Median OS was not reached at time of analysis for durvalumab cohort and 21.6 months (95% CI 14.6-40.2) for CCRT-alone cohort (HR 0.32, 95% CI 0.13-0.78, p=0.012) (Figure). The locoregional relapse rate and distant relapse rate were 19.6% vs 5.1% (p=0.004) and, 37.5% vs 20.5% (p=0.004) in the CCRT-alone cohort and durvalumab cohort respectively. In the durvalumab cohort, 59% of patients experienced immune-related adverse events (IrAEs) of any grade. Pneumonitis (28.5%), skin toxicity (25.6%) and myositis (12.8%) were the most common IrAEs reported. Grade 2+ pneumonitis was detected in 25% of patients. Median time to onset of pneumonitis was 46 days. Six patients were subsequently rechallenged with durvalumab with no recurrence of pneumonitis. Both EGFR mutation positive and EGFR wild-type (WT) patients benefitted from durvalumab consolidation compared to CCRT alone, with improved PFS at 17.5 vs 10.9 months and 11.8 vs 4.5 months respectively.



Conclusion: In this RWE, durvalumab consolidation post CCRT was associated with a statistically significant improvement in OS and a numerically longer PFS. Larger sample size and longer follow-up are needed to confirm the findings. Patients with WT EGFR and sensitizing mutations had prolonged PFS from addition of durvalumab after CCRT. Active surveillance and appropriate management for pneumonitis are crucial while receiving durvalumab consolidation.

Keywords: Durvalumab, stage III NSCLC, pneumonitis

P28.02 Beyond PACIFIC: Outcomes and Toxicity According to Durvalumab Dosing Schedule Every 2 versus 4 Weeks

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Introduction: Durvalumab 10 mg/kg every 2 weeks for one year after chemoradiation has improved progression-free survival (PFS) and overall survival (OS) in unresectable stage III non-small cell lung cancer (NSCLC). Subsequently, a 20 mg/kg four-weekly regimen was approved based on pharmacokinetic data. We performed a retrospective analysis to compare both regimens in terms of outcomes and toxicity. **Methods:** We reviewed the medical records of all NSCLC patients treated with curative-intent chemoradiation followed by durvalumab from March 1st, 2018 to December 31, 2020 at BC Cancer, British Columbia, Canada. The four-weekly dose was introduced in April 2020. Durvalumab dosing schedule, toxicity, progression pattern and survival data were collected. Patients were divided according to the dosing schedule that was used for the majority of treatment. Comparisons were made using Chi-square and independent t tests. Logistical regression was conducted to identify predictive factors for dosing schedule. Kaplan Meier curves and log-rank test were used to analyze overall survival. **Results:** 158 patients were included in the two-weekly group and 47 patients were included in the four-weekly group (table 1). Median follow-up was 19.8 months and 11.1 months, respectively. The only significant difference between groups was age. Non-squamous histology and stage IIIA were predominant. Most patients received Carboplatin and over 90 % completed both chemotherapy (≥ 2 cycles) and radiation (≥60 Gy). Multivariate analysis including age, sex, smoking history and type of platinum identified age as the only predictive factor for the four-weekly regimen. After April 2020, 71.1% of patients received the four-weekly schedule. Median OS was not reached, but 12-month survival was 92.8 % in the two-weekly group and 93.0 % in the four-weekly group (p = 0.9).

Table 1 Patients characteristics

	Two-weekly (n=158)	Four-weekly (n=47)	p value
Age, years	66 ± 8	69 ± 6	0.02
Ethnicity Asian Non-Asian	10 (6.3 %) 148 (93.7 %)	4 (8.5 %) 43 (91.5 %)	0.6
Smoking history Current Past Never	65 (41.1 %) 78 (49.4 %) 15 (9.5 %)	19 (40.4 %) 24 (51.1 %) 4 (8.5 %)	1.0
Auto-immune disease	7 (4.4 %)	5 (10.6 %)	0.1
Histology Squamous Non-squamous Other	54 (34.2 %) 94 (59.5 %) 10 (6.3 %)	15 (31.9 %) 29 (61.7 %) 3 (6.4 %)	1.0
Stage* IIB IIIA IIIB IIIC IVA	1 (0.6 %) 88 (55.7 %) 58 (36.7 %) 10 (6.3 %) 1 (0.6 %)	2 (4.3 %) 23 (48.9 %) 18 (38.3 %) 3 (6.4 %) 1 (2.1 %)	0.4
PD-L1 TPS < 1 % 1-49 % ≥ 50 % Unknown	22 (13.9 %) 18 (11.4 %) 41 (25.9 %) 77 (48.7 %)	4 (8.5 %) 7 (14.9 %) 13 (27.7 %) 23 (48.9%)	0.7
Platinum type Cisplatin Carboplatin	66 (41.8 %) 92 (58.2 %)	15 (31.9 %) 32 (68.1 %)	0.2
≥ 2 cycles of chemotherapy	145 (91.8 %)	44 (93.5 %)	0.7
Radiation Dose, Gy Dose ≥ 60 Gy	59 ± 2 150 (94.9 %)	60 ± 2 46 (97.9 %)	0.4 0.4
Chemoradiation completion to durvalumab start, days	46 ± 25	42 ± 19	0.4

According to IASLC 8th TNM classification. Data are expressed as n (%) and mean ± SD. PD-L1 = programmed death-ligand 1, TPS = tumor proportion score, Gy = grays.

Conclusion: Two-weekly and four-weekly durvalumab administration were similar regarding overall survival in this cohort of advanced NSCLC patients previously treated with curative-intent chemoradiation. After availability of the four-weekly schedule, physician uptake was significant indicating acceptance of the pharmacokinetic data to support the dose timing. Time to treatment failure, progression pattern and toxicity analyses are in progress.

Keywords: adjuvant, durvalumab, NSCLC

P28.03 Durvalumab Adjuvant to Chemoradiation for Patients With Locally Advanced Non-Small Cell Lung Cancer: Real World Experience

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Introduction: Approximately one third of patients with non-small cell lung cancer (NSCLC) are diagnosed with locally advanced disease (LA-NSCLC). The standard treatment for patients with unresectable disease has been concurrent chemoradiation. The prognosis has been poor with median progression-free survival of approximately 8 months and 15% 5-year overall survival. The PACIFIC trial evaluated the effect of one year adjuvant treatment with durvalumab for patients who did not progress after chemoradiation, and presented favourable progression-free survival for patients receiving durvalumab compared with placebo in September 2017. **Methods:** Following the first presentation of the PACIFIC-data, a named-patient use (NPU) program was established. From December 2017 to November 2018 a total of 41 patients were included in the program. Of these, 35 patients started treatment with durvalumab. After November 2019, durvalumab as implemented in routine practice. **Results:** Six patients included did not start durvalumab treatment. The reasons were: Progression, osteomyelitis, pneumonitis, poor performance status, discovery of a metastasis that was erroneously not detected during the initial diagnostic work-up and surgery of the lung tumour. Of the 35 patients starting treatment with durvalumab, the mean days from completion of chemoradiation to start of durvalumab was 68 days, only 2 patients started earlier than 21 days. 19 patients (54%) completed one year of treatment. Of the 16 patients that discontinued treatment, eight stopped due to progression and eight due to side effects. The side effects leading to discontinuation were infusion reaction (n=1), fatigue (n=2), elevated liver enzymes (n=1), pneumonitis (n=3), worsening of psoriatic rash (n=1). **Conclusion:** Real-world data of durvalumab adjuvant to chemoradiation was generally well tolerated. Completion of treatment was (54%) and comparable to that seen in the PACIFIC trial (49%). Time from end of chemoradiation to start of durvalumab treatment was longer than seen in the PACIFIC trial and also longer than seen after introduction of durvalumab in the routine practice. This was in line with recommendations in the NPU program. At the time, there was no data on the importance of early start of durvalumab. The time to start of durvalumab decreased during the program period. After introduction of durvalumab in routine treatment, most patients start within 3 weeks if they don't have side effects that prevent an early start. Patients are followed with regards to future relapses and updates will be presented.

Keywords: immunotherapy, durvalumab, chemoradiation

P28.04 Pneumonitis With Durvalumab Following Concurrent Chemoradiotherapy

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Introduction: Durvalumab consolidation is currently the standard of care for treatment of unresectable stage III non-small cell lung cancer (NSCLC) after concurrent definitive chemoradiation. In our clinical practice and based on more recent reports, clinically significant immune-mediated pneumonitis seems to occur at a higher rate than that seen in trials reaching up to 19%. It is unclear whether chemotherapy regimen influences this risk, though some reports cite taxane-based therapy is associated with increased incidence of radiation pneumonitis. We compared the incidence of clinically significant pneumonitis (≥ grade 2) amongst different chemotherapy regimens to help predict patients at higher risk of pneumonitis. **Methods:** This is a retrospective analysis of patients with NSCLC treated at Moffitt Cancer Center who received durvalumab therapy following chemoradiation. Charts of patients were reviewed and pertinent data points were collected including baseline demographic characteristics, stage of disease, lymph node involvement, chemotherapy regimen received with concurrent radiation, the radiation dose and fractions received, the duration of durvalumab use, and the incidence of pneumonitis requiring intervention and/or discontinuation. We performed a multivariable logistic regression for this analysis with outcome of pneumonitis and covariates of chemotherapy drug (adjusting for smoking status, lymph node and regional radiation dose). **Results:** 119 patients were included in the analysis. Data was stratified according to chemotherapy regimen into taxane-based vs non-taxane-based regimens. None of the patients had a pre-existing autoimmune condition. Average duration of receiving durvalumab was about 8 months (248 days). Only 9 patients were never smokers. The average pack years for smokers was 47.1 and 39.9 for the group that received taxanes vs non-taxanes, respectively. N2-3 disease was seen in 78.3% of the taxane group and 84.0% of the non-taxane group. The rest had N0-N1 disease. More patients in the taxane group had squamous histology (50.7%) compared to the non-taxane group (14.0%). Grade ≥2 pneumonitis occurred in 30.3% (36) of patients of which 9 were grade 3-4. 34.8% of patients receiving taxanes developed grade ≥2 pneumonitis vs 24.0% of patients receiving non-taxanes OR (95% CI) 1.67 (0.72-3.88) (p=0.23). See table 1 for adjusted OR for smoking status, lymph node and radiation dose. Table 1

		Pneumonitis Grade 2 or above		
Covariate	Level	Odds Ratio (95% CI)	OR P-value	Type3 P-value
Chemotherapy drug	Taxane	1.67 (0.72-3.88)	0.230	0.230
	Non-taxane	-	-	
Smoking Status	Active	0.93 (0.16-5.49)	0.940	0.570
	Ex	1.48 (0.27-7.98)	0.652	
	Never	-	-	
Lymph node	N2/N3	1.38 (0.48-3.92)	0.548	0.548
	N0/N1	-	-	
Regional Radiation Dose cGy		1.00 (1.00-1.00)	0.883	0.883

Conclusion: Clinically significant pneumonitis in patients receiving durvalumab occurs at a higher rate than in clinical trials. The observed difference in incidence of pneumonitis between patients receiving taxane vs. non-taxane-based chemoradiation regimens (adjusted for smoking, involvement stage, and radiation dose) was not statistically significant.

Keywords: NSCLC, durvalumab, pneumonitis

P29.01 Deformable vs. Rigid Registration in Evaluating Composite Doses to Central Organs at Risk in Thoracic Reirradiation

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Introduction: Reirradiation is increasingly used to manage recurrent lung cancer manifestations in the chest. With reirradiation, high cumulative doses to Organs at Risk (OARs) can lead to potentially life threatening toxicity. Currently, there is no consensus on how to best accumulate radiation doses over time. Rigid Image Registration (RIR) and Deformable Image Registration (DIR) are often utilized in this setting, with DIR adding potential benefit in accounting for often large changes in chest anatomy after the initial treatment. The purpose of this study is to compare composite doses to central OARs as determined by RIR vs. DIR, and determine its significance in the safety and feasibility of thoracic reirradiation. **Methods:** Fourteen patients received thoracic reirradiation with overlap of the originally irradiated area. Twelve patients had one course of reirradiation, one had two, and one had three. Of the 31 total treatments, 19 utilized SBRT (15-52 Gy in 4-8 fractions; median 48 Gy) and 12 conventionally fractionated radiotherapy (30-66.6 Gy in 10-33 fractions; median 52.5 Gy). Twelve patients received at least one course of SBRT. The median interval between treatments was 16 months. RIR of initial and reirradiation planning CTs was performed using commercial registration software via box-based alignment independently to spine and carina. Corresponding composite dose distributions were used to calculate maximum doses to trachea, proximal bronchial tree (PBT), esophagus, great vessels, and spinal cord. This same process was repeated via DIR for each patient, using the rigid registrations to spine and carina as starting points. Ten corresponding anatomic landmarks were identified on each planning CT to assess accuracy of DIR. Dosimetric differences between RIR and DIR were then calculated separately for spine- and carina-based alignments. **Results:** Mean absolute differences (Gy) ± SDs and ranges in the maximum doses between RIR- and DIR-based registrations for spine- and carina-based alignments were, respectively, for trachea 2.05 Gy ± 3.22 (0.01 - 12.01), 2.02 Gy ± 2.74 (0.01 - 8.97); PBT 5.04 Gy ± 10.67 (0.03 - 40.80), 4.35 Gy ± 10.39 (0.02 - 39.53); great vessels 0.53 Gy ± 0.69 (0.01 - 2.54), 0.72 Gy ± 1.27 (0.02 - 4.99); esophagus 0.57 Gy ± 0.65 (0.01 - 2.00), 1.11 Gy ± 2.01 (0.03 - 6.34); and spinal cord 0.45 Gy ± 0.51 (0.02 - 1.50), 0.56 Gy ± 0.49 (0.03 - 1.49). A difference of at least 10 Gy was observed in 2 cases for spine based alignments, and a single case for carina based alignments for PBT. **Conclusion:** This study represents a comprehensive comparison of composite doses to centrally located OARs in thoracic reirradiation with rigid vs. deformable registrations. The observed differences demonstrate the importance of accounting for anatomic changes by using DIR to determine the composite dose. Applying DIR is particularly important if high cumulative doses to central structures are expected.

Keywords: Reirradiation, radiotherapy

P29.02 Early GLS Changes Detection After Chemoradiation in Locally Advanced NSCLC

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Introduction: Chemoradiation is the standard treatment in locally advanced NSCLC (LA-NSCLC) patients and thanks to recent combination with immunotherapy, median survival has reached unexpected improvements. In this new scenario, survivorship questions have become unmet needs, preventing toxicity a clear goal of the most current research. Cardiotoxicity is linked to thoracic irradiation with clinical manifestations such as pericardial disease, ischemic heart disease, nonischemic cardiomyopathy, valvular disease, conduction abnormalities, and arrhythmias. The aim of this study is to evaluate early cardiac function variation after chemoradiotherapy (CRT) in LA-NSCLC through the multimodal use of advanced imaging methods such as 2D speckle tracking echocardiography (STE) to explore the associations between early cardiac effects risk factors and late adverse events. **Methods:** This trial is a prospective, observational cohort study. At the beginning of the combined treatment, all patients with LA-NSCLC undergone screening tests with clinical history, physical examination, blood chemistry (including lipid dosage, cardiac markers as Troponin I, Prohormone of Brain Natriuretic Peptide, Creatine Kinase MB, Reactive C- Protein), 12-leads ECG, echocardiographic examination. A weekly evaluation was detected during treatment with ECG and cardiac marker assays. ECG, echocardiographic examination and strain evaluation was performed at month 1 (M1) and months 3 (M3) after the end of CRT. **Results:** Thirty-four patients have been enrolled. The median age was 69.5 years (range, 43-87). The median follow-up was 27.8 months with a minimum value of 20.5 months. Sixty-two percent of patients were in stage IIIA. Adenocarcinomas and squamous carcinomas were equally represented. Radiation therapy was delivered with a median total dose of 60 Gy with conventional fractionation. All patients were treated with concurrent chemoradiation and in 65% of cases it was a platinum-based regimen. None of the bio-humoral markers changed during CRT from basal values to last week of treatment. No change of normal values of QTcB and QTcF were recorded throughout the treatment. No difference was recorded between normal baseline values and at months 3 for mean End-Diastolic Volume (EDV; 109.5 vs. 102.4, p=0.099) and mean End-Systolic Volume (ESV; 48.5 vs. 48.4, p=0.967). Echocardiography Global Longitudinal Strain (GLS) and Ejection Fraction (EF) progressively decreased from baseline to M1 and M3. There was a strict correlation between GLS and FE reductions (at M1: p=0.034; at M3: p=0.018). No correlations emerged between GLS or EF and bio-humoral markers, QTcB and QTcF, the total EQD2 dose, the use of concurrent platinum-based chemotherapy, all risk factors such as hypertension, diabetes, dyslipidemia, familiarity, the Body Mass Index, age, smoking, all drug therapies intake and ASCVD score. No patients died of cardiovascular complications. Eight patients (23.5%) had a cardiovascular event at a median follow-up of 15.8 months after CRT and in all but one patient heart rhythm problems were recorded. Hearth failure affected one patient. **Conclusion:** The presented data show that GLS reduction is an early sign that occurs after the end of chemoradiation for LA-NSCLC. Future trials are needed to identify variables that can increase risk of cardiac events in this setting of patients in order to implement adequate damage prevention strategies.

Keywords: cardiac toxicity, Global Longitudinal Strain, chemoradiation

P29.03 Thoracic Organs at Risk (OARs) Contouring Variations and Consensus in Radiation Therapy for Non-Small Cell Lung Cancer

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Introduction: To ensure the high quality of clinical trials in the direction of radiotherapy, it is necessary to ensure that the organs at risk (OARs) are consistently contoured and in comply with the protocol definition. This work aimed to quantify the differences in OAR contouring on the same example patient by experts of multiple hospitals and generate a consensus guideline for the OAR contours for future work of multi-center clinical trials. **Methods:** The participating investigators/Centers were physically participated clinical trial training workshop/Global Collaborative Oncology Group (GCOG) semiannual meeting help on December 19, 2020, and those provided personal information to GCOG and submitted the contoured structures to data collection center provided by the meeting sponsor (Varian Med. Inc). The participating experts were provided with the same de-identified cases of stage III NSCLC and instructions of structure contouring and plan assessment criteria according to RTOG1106. Required OARs included lungs with minus gross tumor volume, heart, spinal cord, esophagus as well as brachial plexus. The reference OAR contours were generated by the PI of RTOG1106 and the leading author of the RTOG OAR atlas. The differences between contours from the hospitals and the Standard OAR contours were evaluated by the dice similarity coefficient (DSC). OAR variation of a stage I NSCLC were also assessed. Contouring variations were discussed and consensus were generated at the workshop through discussion with the participating experts. Post-workshop contours were further assessed for consistency. **Results:** A total of 35 centers participated the workshop, 29 of them with completed structures were eligible for the DSC analysis. Following the given instructions and atlas, this group showed a reasonable degree of consistency for lung and heart contours with mean DSC of 0.90 (range 0.37-0.99) and 0.94 (0.62-0.98), respectively. Spinal cord contours showed the largest variation among institutions. with a mean DSC of 0.64 (range 0.20-0.82). The mean DSC of the brachial plexus and esophagus were 0.85 (range 0.80-0.89) and 0.81 (range 0.22-0.91), respectively. Contours after workshop training are being collected now, results, final consensus contours and dosimetric significance will be reported at the meeting. Review of limited submitted centers showed some improvement in concordances. Consensus atlas will be presented at the presentation.

Conclusion: This study demonstrated contouring variations of five thoracic organs between 29 hospitals and the standard OAR contours showing a reasonable mean concordance but wide range of variation from the atlas contours, Improvement in consistency after training workshop suggests a value of training. Future work of multi-center clinical trials should give atlas and provide onsite training for better quality control.

Keywords: NSCLC

P29.04 Treatment Plan Parameters and Toxicity Following Chemoradiotherapy and High-Dose Radiotherapy in Stage III Non-Small Cell Lung Cancer

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Introduction: Concurrent chemoradiotherapy (cCRT) is preferred in fit patients due to a better survival. However, concerns about toxicity result in a recommendation for sequential chemoradiotherapy (sCRT) or radiotherapy (RT) alone in elderly and patients having serious co-morbidities. We studied intensity modulated radiation therapy planning parameters in the patients who received radical radiotherapy and explored the associations with radiation toxicity and survival. **Methods:** An ethics-approved database containing details of all patients with a stage III NSCLC treated in accordance with the ESMO guidelines between 2015-2017 was accessed. Patients treated using cCRT, sCRT or RT to a dose≥50Gy in ≥15 fractions were selected, excluding those who subsequently underwent surgery or had prior radiotherapy to thorax/neck. The planning objective was to limit the volume of total lung receiving ≥20Gy (≤35%), and to limit both the total and contralateral lung V5Gy as much as possible (<60% and <45%, respectively). **Results:** 129 patients fulfilled our study inclusion criteria, with a median follow-up time of 21 months (Table 1). Mean total and contralateral lung V5Gy were 41% and 16%. The incidence of radiation pneumonitis was generally low with 19% developing grade 2 and only 3% developing grade 3-4 pneumonitis. The incidence of grade≥2 and grade 3 esophagitis was 44% and 14%, respectively. All esophagitis events occurred within 90 days after treatment, and rates of grade 3 esophagitis were 14%, 11% and 14% respectively for the cCRT, sCRT and RT alone cohort. OS for cCRT, sCRT and RT were 29.0, 16.5 and 17 months. Cardiac events were recorded in 16 (12%) patients. Univariate and multivariate logistic regression analysis showed V50Gy esophagus and mean lung dose as significant predictors for grade ≥2 esophagitis (OR=1.055; 95%CI 1.018-1.091; p=0.004 and OR=1.024; 95%CI 1.003-1.044; p=0.027). Doses to the heart (V20Gy, V25Gy, V40Gy, V60Gy and mean heart dose), lungs (V20Gy, V25Gy, V5Gy contralateral lung and mean lung dose) and esophagus (V20Gy, V40Gy, V60Gy) were not associated with overall survival (OS). No significant predictors for pneumonitis grade ≥3 and cardiac events were found.

Table 1. Patient and radiotherapy characteristics (n=129)	
Patient characteristics	N (%)
Age, median (IQR)	67 (33-90)
Male	68 (53%)
Smoking history	125 (97%)
Treatment	
cCRT	64 (50%)
sCRT	44 (34%)
RT	21 (16%)
Radiotherapy technique	
hIMRT	4 (3%)
hVMAT	88 (68%)
FullVMAT	37 (29%)
PTV cm^3, median (range)	578 (48-2053)
Radiotherapy characteristics	Median (range)
PTV mean dose Gy	65.9 (10.6 – 70.2)
Mean lung dose Gy	13.7 (1.2 – 22.0)
Mean lung dose ipsilateral Gy	28.7 (0.5 – 48.0)
Mean lung dose contralateral Gy	3.7 (0.2 – 16.8)
V5Gy lung %	41 (14 – 78)
V10Gy lung %	31 (11 – 53)
V15Gy lung %	26 (9 – 44)
V20Gy lung %	22 (5 – 37)
V25Gy lung %	20 (0 – 33)
V5Gy contralateral lung %	16 (0 – 70)
V20Gy esophagus %	63 (0 – 100)
V40Gy esophagus %	46 (0 – 94)
V50Gy esophagus %	38 (0 – 92)
V60Gy esophagus %	16 (0 – 83)
V65Gy esophagus %	0.2 (0 – 36)
Mean heart dose (Gy)	13.6 (0.5 – 44)
V40Gy heart %	14.4 (0 - 60)

Abreviations: cCRT: concurrent chemoradiotherapy, sCRT: sequential chemoradiotherapy, RT: radiotherapy alone, hIMRT: hybrid intensity modulated radiation therapy, hVMAT: hybrid volumetric modulated arc therapy, full VMAT: full volumetric modulated arc therapy, PTV: planning target volume, V5Gy/V10Gy/V15Gy/V20Gy/V25Gy lung: percentage of the lung received at least 5/10/15/20/25Gy, V5Gy contralateral lung: percentage of the contralateral lung received at least 5Gy, V20Gy/V40Gy/V50Gy/V60Gy/V65Gy esophagus: percentage of the esophagus received at least 20/40/50/60/65Gy

Conclusion: The use of an IMRT/VMAT technique for high-dose radiotherapy in stage III NSCLC that focused on sparing the contralateral lung resulted in just a 3% incidence of pneumonitis grade≥3, and rates of high-grade esophagitis in a real-world patient population that were comparable with that reported in published studies with highly-selected fit patients. None of the cardiac, lung and esophageal dosimetric parameters correlated with OS.

Keywords: IMRT planning parameters, radical radiotherapy, locally advanced non-small cell lung cancer

P29.05 Gross Tumor Volume Contouring Variations in Radiation Therapy of Non-Small Cell Lung Cancer

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Introduction: Accurate delineation of gross tumor volume (GTV) is utmost important for precision radiation therapy and quality ensure of GTV compliance with the protocol definition is essential for multi-center clinical trials. This work aimed to exam GTV delineation by multicenter experts and quantifies the differences in the same one patient with stage III non-small cell lung cancer (NSCLC). **Methods:** The eligible investigators/Centers were physically participated clinical trial training workshop/ Global Collaborative Oncology Group (GCOG) semiannual meeting help on December 19, 2020, and those provided personal information to GCOG and submitted the contoured structures to data collection center provided by the meeting sponsor (Varian Med. Inc). The participating experts were provided with the same de-identified cases of stage III NSCLC) and instructions of contouring and plan assessment according to RTOG1106. The reference contours of CT based gross tumor volume (GTV) and PET based metabolic tumor volume (MTV) were delineated by the PI of RTOG1106 and the leading author of the RTOG lung Target atlas. The differences between contours from the participating MD investigators and the PI of RTOG1106 were evaluated by the dice similarity coefficient (DSC). Pre- and post-workshop performance will be compared. **Results:** A total of 35 centers participated the workshop, 29 of them with completed GTV structures were eligible for this DSC analysis. As shown on the table, the mean DSC of the GTV was 0.87 (range 0.64-0.93). The DSC of 9 hospitals was greater than 0.90, 15 hospitals were between 0.85 and 0.90, 2 hospitals were between 0.80 and 0.85, 2 hospitals were between 0.70 and 0.80, and 1 hospital was between 0.60 and 0.70. Variations were discussed and consensus contours were generated. Of 3 centers submitted post-workshop, the DSC improved by an average of 1%. Variations of CT GTV and metabolic tumor volumes of primary tumor and nodal diseases pre and at mid-treatment as well as changes after workshop will be presented at the meeting. Mid-treatment MTV variations as well as changes in the tumor target volume will be reported at the meeting. **Conclusion:** Despite of being given the atlas, this study demonstrated more than 10% GTV variations from the reference GTV in 20/29 centers, suggesting an urgent need of training workshop on this topic. GCOG is in the process of generating a consensus target delineation guideline by meticulous analysis of the variations and extensive discussion of representative international experts in NSCLC, aiming to provide a reproducible reference for the GTV delineation work multi-center clinical trials.

Keywords: NSCLC

P29.06 Both Endostar and Amifostine Reduced All the Incidence of Pneumonitis Above Grade 2 in Chemoradiotherapy With Locally Advanced NSCLC

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Introduction: The acceptable treatment strategy currently in the treatment of locally advanced non-small cell lung cancer (LA-NSCLC) patients is combination treatment, but concurrent chemoradiotherapy (CCRT) has been associated with significant toxicities. The aim of this study was to assess the ability of Endostar and amifostine (AM) to reduce the incidence of chemoradiotherapy-induced pneumonitis above grade 2 in patients with stage III NSCLC. **Methods:** Patients with locally advanced NSCLC from December 2008 to December 2017 were retrospectively analyzed. A total of 122 patients with stage III non–small-cell lung cancer received weekly vinorelbine12.5mg/m2, d1,8 and carboplatin AUC=2 concurrently with radiotherapy 60Gy(CRT group) , and Endostar in combination with chemoradiotherapy group (ECRT group) which received Endostar intravenous drip for 1–14 days (every 3 weeks) concurrently with CRT. Patients were assigned at registration to amifostine (AM) 400 mg IH third times per week or no AM during chemoradiotherapy according to the threshold of 25% for V20 in both lungs. Standard toxicity about pneumonitis end points were also collected by CTC4.0. **Results:** There were 76 cases in the CRT group and 46 cases in the ECRT group. The occurrence rate of pneumonitis above grade 2 in the CRT group was 25.0%, while the occurrence rate in the ECRT group was 13.0%. There were statistically significant difference in the occurrence rate of pneumonitis above grade 2 between the two groups (P<0.05). And, The occurrence rate of pneumonitis above grade 2 with two-lung V20>25% patients in the no AM was 31.7% and in the AM group was 14.8%. There were statistically significant difference in the occurrence rate of pneumonitis above grade 2 between the two groups (P<0.05). V20 subgroup analysis showed that the occurrence rate of pneumonitis above grade 2 with two-lung V20<25% patients in the ECRT group was lower than in the CRT group all no AM, and the difference was statistically significant (P<0.05). **Conclusion:** Both Endostar and Amifostine may reduce all efficiently the incidence of pneumonitis above grade 2 in locally advanced non-small cell lung cancer patients receiving concurrent chemoradiotherapy.

Keywords: Endostar, Amifostine, pneumonitis

P29.07 A Phase Ib Trial of Neoadjuvant Low-Dose Radiation Therapy, Chemotherapy, and Durvalumab for Potentially Resectable Stage III NSCLC

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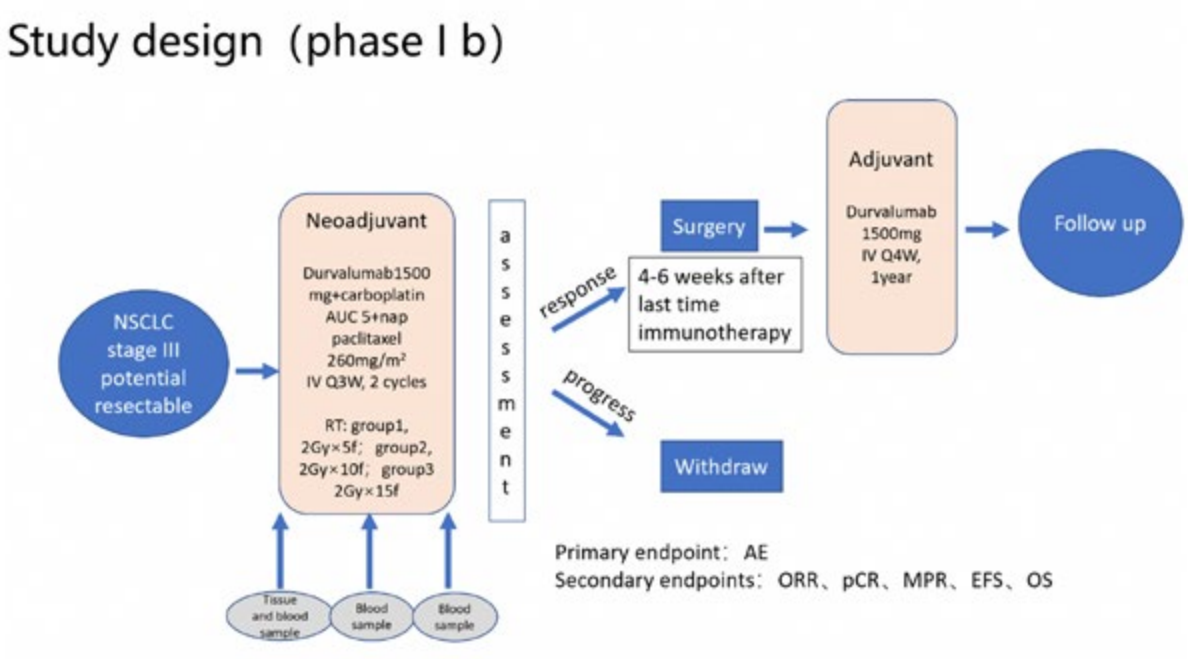
Introduction: Although PACIFIC regimen definitive concurrent chemoradiotherapy (CRT) followed by Durvalumab consolidation therapy is considered the standard of care for most of the stage III NSCLC patients, neoadjuvant immunotherapy combined with chemotherapy followed by surgery has shown the trend to be considered for some potentially resectable patients. The rationales for the neoadjuvant treatment are tumor regression effect before surgery, early eradication of micrometastasis. Recently we also find some clinical trials exploring the adding of 45 Gy in 25 fractions radiation to the combination of chemotherapy and immunotherapy neoadjuvant therapy and we could see the safety is the most concern, especially the pneumonitis incidence. Low-dose radiation therapy could help control the toxicity induced by radiation and has a synergic effect with immunotherapy. The aim of this phase Ib study is to assess the safety and feasibility of the combination of the concurrent low-dose radiation therapy, chemotherapy, and Durvalumab neoadjuvant therapy, to explore which radiation dose is the best among our three designs and evaluate if the combining neoadjuvant therapy could further improve MPR in the meantime no severe toxicities especially the grade 3-4 pneumonitis would happen. **Methods:** 9 eligible patients with histologically confirmed NSCLC (potentially resectable clinical stage III according to the American Joint Committee on Cancer 8th staging system) are enrolled. Patients receive Chemo (Day1 and 22 nanoparticle albumin-bound paclitaxel 260 mg/m2 and carboplatin AUC 5) and durvalumab (Day 1 and 22, 1500mg) and radiotherapy of 10 Gy in 5 fractions, 20 Gy in 10 fractions, 30 Gy in 15 fractions respectively in our three groups from Day1, followed by surgery. After surgery, patients are suggested to be treated with durvalumab for one year (every 4weeks, 1500 mg). The primary endpoints are safety and tolerability. The secondary endpoints are objective response rate (ORR), event-free survival EFS), overall survival (OS), pathologic complete response (pCR), and major pathologic response(MPR) in the primary tumor. biomarker analysis of PD-L1 using cancer tissue and LIPI (Lung Immune prognostic Index), ctDNA using blood sample will be conducted pre-and post- neoadjuvant and post-surgery.



Keywords: stage III nonsmall cell lung cancer, neoadjuvant immunotherapy, low dose radiation therapy

P29.08 Evaluation of the Prognostic Marker of PD-L1 Expression After Combined Radiochemotherapy in Patients With NSCLC Stage III

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Introduction: The PACIFIC study showed that patients with locally advanced, unresectable, NSCLC after radio-chemotherapy derived a benefit in progression-free survival and overall survival when treated with durvalumab, a PD-L1-inhibitor vs. placebo. This effect was limited to patients with a PD-L1 expression of >1%. In patients with PD-L1 expression of <1%, no benefit was seen partly due to the fact that the outcome in the control arm was surprisingly favorable. Thus, it could be speculated that lack of PD-L1 expression confers a favorable outcome after radio-chemotherapy in stage III NSCLC. To address the question, whether the prolonged OS in the control group with lack of PD-L1 expression was reproducible we analyzed the OS in group of 101 patients with stage III NSCLC homogeneously treated with radio-chemotherapy and not progressing after radio-chemotherapy. In all patients, PD-L1 expression was evaluated retrospectively and the outcome in the group of PD-L1 <1% and PD-L1 >1% was compared. **Methods:** Clinical data and tumor characteristics were systematically captured from the data base bank of the certified lung cancer center, including PD-L1-score. In case, PD-L1 expression had not been evaluated, the available tissues samples were sent for PD-L1-testing to Hematopathology Hamburg, after informed consent of the surviving patients had been obtained. The clinical parameters comprise age, gender, histology, smoking history, ECOG-status, type of first line treatment, Albumin, CRP, PFS and OS. **Results:** The study showed that the expression of PD-L1 is independent from gender and histology. The median OS of the patients with an expression of PD-L1 <1% was 27 months (KI 15.9 – 38.1) and with an expression ≥1% 19 months (KI 11.3 – 26.7, however this difference was not statistically significant with a p value of 0.781). The median PFS of the patients with an expression of PD-L1 <1% was 9 months (KI 6.2 – 11.8) and with an expression ≥1% 10 months (KI 6.0 – 14.0), also not being statistically significant with a p value of 0.180. The blood parameters serum CRP, albumin and CRP/albumin-ratio had no significant impact on the OS. **Conclusion:** This study showed that the assumption of lack of PD-L1 expression after radio-chemotherapy conferring good outcome vs. PD-L1 expression >1% couldn't be approved in our patient cohort.

Keywords: NSCLC, stage III, PD-L1

P30.01 Extended Resections for Advanced Stages T3/T4 NSCLC After Neoadjuvant Treatment: Conclusions of SAKK Pooled Analysis (16/96, 16/00, 16/01)

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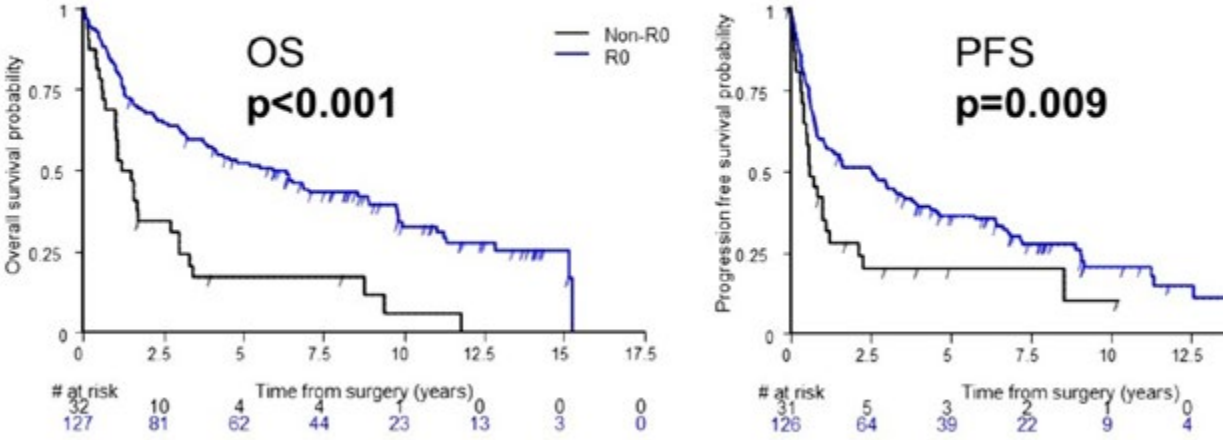
Introduction: Surgical treatment of patients with T3/4 locally advanced NSCLC including single or multilevel N2 remains a matter of debate across countries. Several trials have demonstrated that selected patients benefit from surgery, when radical (R0) resection can be achieved. We aimed to assess resectability and outcome of resections for locally advanced T3/T4 tumors after induction treatment with chemo- or sequential chemoradiotherapy in a pooled analysis of three prospective multicenter clinical trials. **Methods:** The analyses included individual patient data of 197 patients with locally advanced (T3/T4) NSCLC out of all 368 stage III NSCLC patients enrolled in phase III SAKK 16/00 and phase II SAKK 16/06 and SAKK 16/01 trials. Patients were treated with induction chemotherapy(cisplatin, docetaxel) or chemo-radiation therapy (cisplatin, docetaxel +/- radiation (44 Gy in 22 fractions in 3 weeks)) followed by resection. Resectability, safety and long-term outcomes are reported, according to 8th TNM classification. **Results:** Median age was 60 (28-76) years with 67% of patients were male. 38/197 patients were not considered for resection for medical (80%) due to progressive disease in above 70% of patients or technical (20%) reasons. 159 anatomical lung resections (with 36 extended resections) and systematic lymphadenectomy were performed with 80% (127/159) R0 rate (30/36 R0 extended resections) after previous mediastinal staging in 99%(157/159) of patients. Pathological complete response occurred in 13.2% (21/159). Overall 30- and 90 day mortality were 3% (5/159) and 7% (11/159), respectively. Morbidity was reported in 32% (51/159) with more than 70% (36/51) being a complications of minor grading. The 3-, 5-, 10-year overall (OS) after extended- vs. not extended resections were 61% [95% confidence interval (CI): 43-75], 45% [95%CI: 27-59], 29.5% [95%CI: 13-48] and 54.2% [95%CI: 45-62.6], 45.7% [95%CI: 36.7-54.3] and 26.8% [95%CI: 18.4, -35.8], respectively. In the multivariate analysis R0 resection was confirmed to be the most important factor influencing OS and PFS (hazard ratio (HR) 0.417 [95%CI: 0.262, 0.664, p<0.001) and (HR 0.602 [95%CI: 0.375, 0.965], p=0.035) respectively (figure). **Conclusion:** Surgery for T3/T4 tumors is highly effective after neoadjuvant chemo-or chemoradiation therapy in most cases and results in a 80% R0 rate with low mortality. OS is similar for extended and non-extended resections with a survival rate of approximately 45% at 5 years and 28% at 10 years.



Keywords: Locally advanced lung cancer, surgery, multimodality treatment, survival

P30.02 Salvage Surgery in Patients With Locally Advanced Non-Small Cell Lung Cancer – Outcomes and Longtime Results

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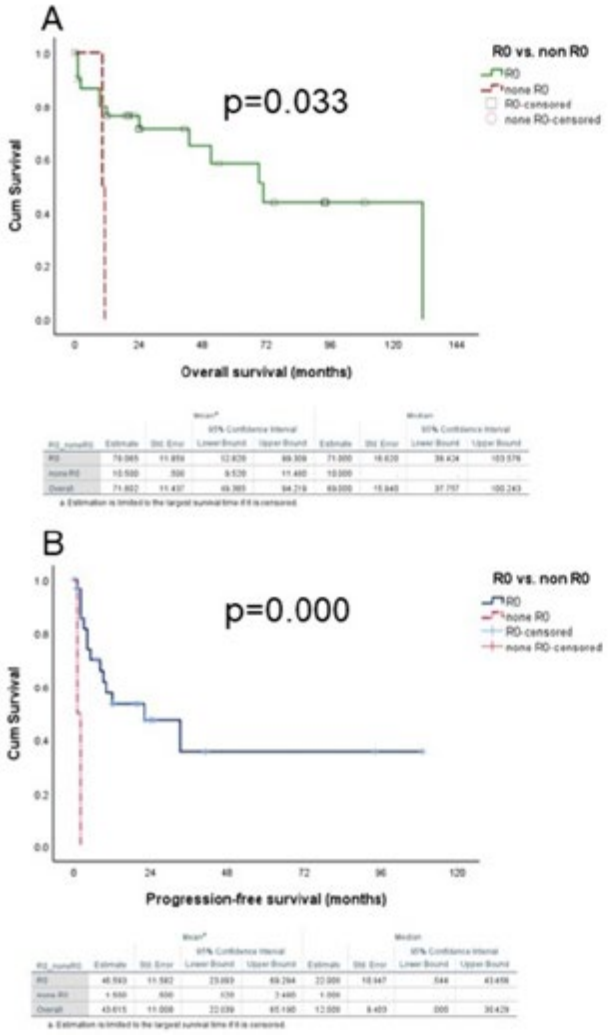
Introduction: In patients with stage IIIB or IV non-small cell lung cancer (NSCLC), current guidelines recommend a combination of systemic treatment including chemotherapy, targeted- or immunotherapy with definitive radiotherapy. Nevertheless, relapses still occur in >30% within 2 years. In selected patients with local tumor recurrence or residual disease after response, so-called "salvage resection" can be performed with curative intent. Since previous reports on this approach are scarce and candidate selection remains challenging, we aimed to assess the outcomes of salvage surgery. **Methods:** We retrospectively identified 33 patients with initial stage IIIB or IV NSCLC who underwent salvage lung resection in curative intent between time period from 2001 to 2021 and included only patients if this resection was not part of the first line treatment approach. **Results:** Median age was 62 (38-78) years with 54% of patients were male. 7 patients had stage IIIB and 24 had stage IVA and 2 stage IVB. Anatomical lung resections with 22 lobectomies/bilobectomies (with 8 extended), 1 segmentectomy and 10 extended pneumonectomies were performed and R0 resection was achieved in 93.9% (31/33) patients. The histology revealed 26 adenocarcinomas, 4 squamous carcinomas and 1 large cell carcinoma with pathological complete response in 8/33 cases. Morbidity rate was 33.3% (11/33) with 5/33 minor (Grade II) and 7/33 major (Grade IIIA-V) complications. 30- and 90-day mortality was 0% and 12% (4/33). Median overall survival (OS) were 5 years [95%CI: 3.37; 6.62] respective 69 months [95%CI: 49.4; 94.2] and progression-free survival (PFS) were 2 years [95%CI: 0.0; 4.55] respective 12 months [95%CI: 0.0; 30.42]. R0 resection of the primary tumor was an independent factor influencing OS and PFS (71 months [95%CI; 38.4; 103.6, p=0.033] and 22 months [95%CI; 0.54; 43.46, p=0.000) respectively (figure). **Conclusion:**



Salvage surgery can provide promising OS and PFS in selected patients with stage IIIB/IV NSCLC. Further analyses for adequate patient selection is necessary for adequate allocation.

Keywords: Locally advanced lung cancer, salvage surgery, multimodality treatment

P30.03 Impact of Visceral Pleural Invasion (VPI) and lymphovascular Invasion (LVI) on Stage I Non-Small Cell Lung Cancer (NSCLC) Outcomes

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Introduction: Stage I patients (pts) have 5-year survival ranging 50-75% suggesting heterogeneity within. While American Joint Committee on Cancer 8th edition upstages tumors with visceral pleural invasion (VPI) to IB, other histological features specifically lymphovascular invasion (LVI) are not accounted for in current staging. However, there is data to suggest that LVI increases risk for recurrence. Guidelines such as NCCN recommend consideration of adjuvant chemotherapy for patients with VPI and LVI despite convincing data to support this. We conducted a retrospective study of patients with stage I lung cancer who had LVI and/or VPI to understand their outcomes. **Methods:** 267 resected stage I cases from 2015-2019 were included. Medical records were reviewed for demographics, smoking history, histological features, TNM staging (AJCC edition 7), disease recurrence, systemic treatment, and date of death. Data lock occurred January 2020. Patients were considered lost-to-follow-up if their last visit occurred in 2018 or earlier. Chi-square test was used to compare proportions. **Results:** Median age was 69 years (range 44-91). Majority were female (58.4%), smokers (77.9%), & had adenocarcinoma (77.5%). 142 (53.2%) pts had lobectomy while 125 (46.8%) had sub-lobar resection. 216 (80.9%) were pathological stage Ia and 51 (19.1%) were stage Ib. 33 (12.0%) had chemotherapy. Recurrence & death from any cause occurred in 25 (9.3%) & 19 (7.1%) pts respectively. Median follow-up (FU) of the total cohort was 22.4 months (mos) (range 0.0-75.1 mos), with 23.9 mos (0.0-75.1) for pts with stage Ia disease and 26.1 mos (range 1.2-62.9) for patients with stage Ib. 83 (31.1%) pts were considered lost to follow up, of those 64 (24.0%) were with stage Ia disease and 19 (7.1%) with stage Ib disease. Data comparing LVI/VPI positive to negative populations is presented in the table below.

	LVI/VPI status	Adjuvant Chemo No. (%)	Recurrence No. (%)	P value	All-Cause-Mortality No. (%)	P value
Stage Ia N=216	+ N=21 (9.7%)	3 (22.1%)	4 (22.2%)	P= 0.032	3 (14.3%)	P=0.126
	- N=195 (90.2%)	13 (6.7%)	12 (6.2%)		11 (5.6%)	
Stage Ib N=51	+ N= 29 (56.8%)	9 (31.0%)	1 (3.4%)	P= 0.034	4 (13.8%)	P=0.271
	- N= 22 (43.1%)	8 (36.4%)	5 (22.7%)		1 (4.5%)	

Conclusion: More stage Ib pts were found to have VPI and/or LVI on pathology than Ia pts (p=0.00001), & more LVI/VPI positive (of stage Ia and Ib) pts received adjuvant chemotherapy (p=005535). Limitations include retrospective nature, sample size, and accuracy of follow-up. A multivariate analysis was not performed due to small sample size.

Keywords: visceral pleural invasion, lymphovascular invasion, non-small cell lung cancer

P30.04 Clinical Research on Patients With Surgically Resected Lung Adenocarcinoma Lesions: Are Heterogeneous GGNs Different From Part Solid Nodules?

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Introduction: To evaluate the natural course of patients with surgically resected lung adenocarcinoma (Ad) lesions with heterogenous GGN, and clarify the difference between heterogeneous GGNs and part solid nodules. **Methods:** 507 patients with proven lung Ad were retrospectively reviewed. Preoperative lung Ad lesions were investigated, and were classified into pure GGN, heterogeneous GGN, part solid nodule and solid nodule group. The disease-free survival (DFS) and Overall survival (OS) of the patients were also investigated. **Results:** All of the 58 heterogeneous GGNs were found only in patients with postoperative stage IA. The numbers of the other types including solid nodule, part solid nodule, and pure GGN in stage IA were 55, 197, and 11, respectively. In part solid nodule group, recurrence of lung Ad and death from the primary disease was observed in 13 (6.6%) and 7(3.6%) of 197 patients, respectively. There was no recurrence of lung Ad in heterogeneous GGN group. Heterogeneous GGNs were significantly associated with longer DFS than part solid nodules (p=0.042). On the other hand, there was no significant difference between heterogeneous GGNs and part solid nodules (p=0.134) in OS. **Conclusion:** Heterogeneous GGNs were associated with longer DFS than part solid nodules.

Keywords: computed tomography, Lung adenocarcinoma, Heterogeneous ground glass nodule

P31.01 Impact of COVID-19 on Lung Cancer Diagnosis and Treatment: A Retrospective Chart Review

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Introduction: The large burden of COVID-19 on health care systems worldwide raised concerns among medical oncologists about the impact of COVID-19 on the diagnosis and treatment of lung cancer patients. In this retrospective study, we investigated the impact of the COVID-19 pandemic on lung cancer care using a set of quality indicators before and during the COVID-19 era. We assessed diagnosis and treatment patterns. We also examined the timeliness of lung cancer care. **Methods:** This retrospective chart review was conducted at the Peter Brojde Lung Cancer Centre, Montreal. We compared patient diagnoses and treatment patterns before the COVID-19 pandemic (011-03-2019 to 01-03-2020) and during the pandemic (30-03-2020 to 28-02-2021). The study was approved by the Research Ethics Board (REB). **Results:** New lung cancer diagnoses decreased by 34.7% (170 vs. 111) during the pandemic. Demographics revealed slightly more advanced stage disease diagnosed during the pandemic (56%) versus before the pandemic (52%). Treatment patterns revealed an increase in the utilization of radiosurgery as the first definitive treatment (23%) during the pandemic vs. before pandemic (4 %) and a decrease in both systemic treatment (47% vs. 57%) and surgery (30% vs. 39%) during COVID-19. There was no significant delay in starting chemotherapy and radiation treatment during the pandemic compared to pre-COVID time. However, we observed a delay to lung cancer surgery during pandemic time. **Conclusion:** COVID-19 seemed to have a major impact at our lung cancer centre on the diagnoses and treatment patterns of our lung cancer patients. Diagnoses of lung cancers dropped off significantly during the pandemic. Many oncologists fear that they will see an increase in newly diagnosed lung cancer patients in the coming year as vaccination rates continue to increase. In addition, treatment patterns seemed to indicate a decrease in surgery and an increase in radiosurgery. This study is still ongoing and further data will be collected and analyzed to better understand the total impact of COVID-19 pandemic on our patient population.

Keywords: lung cancer, chart review, covid-19

P31.02 Impact of COVID-19 Pandemic in Spanish and Portuguese Lung Cancer Patients

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Introduction: In late 2019 a new pandemic disease was identified, COVID-19, caused by a new coronavirus - SARS-CoV-2. Among the risk population are cancer patients but the repercussions on these patients were probably greater because of diagnosis and staging delays. Thus, the objective of this study will be to assess the impact of COVID-19 on lung cancer patients (pts) newly diagnosed in three Portuguese and three Spanish general hospitals, in 2020 and to compare the data with the previous two pre-pandemic years. **Methods:** Newly diagnosed lung cancers pts were evaluated, between the years 2018 and 2020, in 6 hospitals (3 Portuguese and 3 Spanish). The pts's age at diagnosis, performance status, exposure to tobacco, date of diagnosis, stage of the disease, histological type of tumour, first therapeutic decision and date of death were evaluated and were compared. **Results:** A sample of 2419 pts was collected, 1334 from Portugal (55,15%) and 1085 from Spain (44,85%). We observed a decrease in lung cancer diagnosis in 2020 compared to previous years, mainly in Spanish hospitals - 855 in 2018, 829 in 2019 and 735 pts in 2020. The median age at diagnosis was 68 years old, being the majority men (73,7%), with active or prior smoking exposure (83%), adenocarcinoma as tumour histologic type (57,5%), and the samples were remarkably similar regarding these characteristics, and the only difference between years observed was the smoking history with less smokers and an increase of ex-smokers in 2020. Most pts had advanced disease at diagnosis (stage III, 22,6%, or IV, 59,4%), without an increase in 2020. In 2020, Portuguese pts presented more with ECOG PS $\geq$ 2 than in previous years – 25,6%, in 2018, 28,5% in 2019 and 36,8% in 2020. When assessing the amount of newly diagnosis by month, there was a significant decrease in 2020 and specially during the waves of COVID-19. The primary therapeutic decision was active treatment in most of the patients (80,4%), but best supportive care alone was taken more often in Portugal over the 3 years (p<0,001) and increased in 2020 (25,6% in 2018, 24,7% in 2019, and 29,9% in 2020). Mortality in 1st trimester after diagnosis was identical, even if we observe it at the 1st, 2nd, and 3rd months. **Conclusion:** In the COVID-19 pandemic year of 2020, the new diagnosis of lung cancer in these hospitals of the Iberian Peninsula decreased comparing with the two previous years. The patient's characteristics were very similar between the years analysed, with the exception of a worsening ECOG PS for Portuguese patients in 2020. The treatment decision of best supportive care was proportionally higher in Portugal and increased in 2020 versus in Spain, but it was not observed more mortality in 1st trimester after diagnosis.

Keywords: lung cancer, covid-19

P31.03 The Impact of the COVID-19 Pandemic on a Thoracic Tumor Unit of a Tertiary Hospital in Spain

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Introduction: Coronavirus disease 2019 (COVID-19) pandemic has irrupted in the worldwide scenario as a major challenge for healthcare systems. The fear to the disease and the necessity of assigning resources to this new issue may have impacted oncological healthcare. The aim of this study is to evaluate the impact of this pandemic in a Thoracic Tumor Unit of a third level hospital in Spain. **Methods:** We collected data from the healthcare activity in the Thoracic Tumor Unit of Hospital Universitario Puerta de Hierro Majadahonda in two temporal periods, the first one between January 01, 2019 and July 31, 2019; and the second one between January 01, 2020 and July 31, 2020. We included patients with diagnosis of lung cancer, thymic carcinoma and malignant pleural mesothelioma. We focused specifically in new diagnosis of cancer, inpatients activity and new patients included in clinical trials. **Results:** The number of patients with new thoracic cancer diagnosis decreased a 9.9% in the second period, with no significant differences between the type of tumor diagnosed (p = 0.757) nor in number of patients diagnosed with stage IV (p = 0.769). Hospital admissions were reduced in a 47.0%, with significantly more inpatients with stage IV thoracic cancer (p = 0.018). We observed significant differences in the main diagnosis at admission (p = 0.045) and a significant decrease in hospitalization length (6.33 vs 4.59 days, p = 0.019). Clinical trials recruitment was reduced in a 15% (20 vs 17 patients recruited in clinical trials). Results regarding outpatients and inpatients activity respectively are resumed in Table-1 and Table-2.

Table-1. Outpatients' activity

	2019	**2020**	**P**
New diagnosis	101	91	
Age (median years, range)	68.0 (38.0-99.0)	67.0 (25.0-99.0)	0.957
Sex	M: 69 (68.3%) F: 32 (31.7%)	M: 64 (70.3%) F: 27 (29.7%)	0.763
Tumor type	Lung: 101 (100.0%) Thymic and mesothelioma: 0 (0%)	Lung: 91 (100.0%) Thymic and mesothelioma: 0 (0%)	0.757
Stage IV	56 (56.6%)	49 (54.4%)	0.769
Lung cancer histology	Adenocarcinoma: 45 (44.6%) Squamous cell carcinoma: 22 (21.8%) Small cell lung carcinoma: 21 (20.8%) Large cell lung carcinoma: 3 (3.1%) NOS: 10 (9.9%)	Adenocarcinoma: 46 (50.5%) Squamous cell carcinoma: 18 (19.8%) Small cell lung carcinoma: 16 (17.6%) Large cell lung carcinoma: 1 (1.1%) NOS: 10 (11.0%)	0.757
Clinical trial recruitment	20	17	

Table-2. Inpatients' activity

	2019	2020	P
Hospital admissions	132	70	
Age (median years, range)	65.0 (42.0-83.0)	69.0 (55.0-84.0)	0.073
Sex	M: 100 (75.2%) F: 33 (24.8%)	M: 47 (67.1%) F: 23 32.9%)	0.223
Tumor type	Lung: 132 (100.0%)	Lung: 70 (100.0%)	0.467
Lung cancer histology	Adenocarcinoma: 57 (43.18%) Squamous cell carcinoma: 36 (25.76%) Small cell lung carcinoma: 26 (19.70%) Large cell lung carcinoma: 1 (0.76%) NOS: 14 (10.6%)	Adenocarcinoma: 27 (38.57%) Squamous cell carcinoma 17 (24.29%) Small cell lung carcinoma: 15 (21.43%) Large cell lung carcinoma: 1 (1.43%) NOS: 10 (14.9%)	0.594
Stage IV	88 (67.20%)	58 (82.86%)	0.018*
Main diagnosis	Infections: 29 (21.97%) Cardiocirculatory disorders: 9 (6.82%) Metabolic disorders: 11 (8.33%) Gastrointestinal disorders: 16 (12.12%) Respiratory disorders: 20 (15.15%) Genitourinary disorders: 3 (2.27%) CNS disorders: 11 (8.33%) Progressive disease: 23 (17.42%) New diagnosis: 2 (1.52%) Programmed admission: 8 (6.06%)	Infections: 26 (37.14%) Cardiocirculatory disorders: 4 (5.71%) Metabolic disorders: 7 (10.0%) Gastrointestinal disorders: 9 (12.86%) Respiratory disorders: 16 (22.86%) Genitourinary disorders: 1 (1.43%) CNS disorders: 3 (4.29%) Progressive disease: 3 (4.29%) New diagnosis: 1 (1.43%) Programmed admission: 0 (0%)	0.045*
Mean time in hospital (days)	6.33	4.59	0.019*
Fatality rate for inpatients with COVID-19 and lung cancer during period of study	27.27% (3/11)		

Conclusion: COVID-19 pandemic significatively impacted on the healthcare activity of a Thoracic Tumor Unit, reducing diagnosis, hospital admissions and clinical trial recruitment. More follow-up time is needed to determine if the healthcare impact of this pandemic will have an effect on thoracic cancer patients' mortality.

Keywords: COVID-19, lung cancer, hospital

P31.04 Global Impact of COVID-19 on NSCLC Surgery: Initial Analysis of the CovidSurg-Cancer Study

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Introduction: The CovidSurg portfolio of studies collected data on 190,261 patients from 2006 hospitals in 120 countries, including all surgical specialties. We report data regarding surgery for NSCLC in patients at risk of perioperative COVID-19 infection and in COVID-19 affected thoracic surgery hospitals. **Methods:** Anonymised data, entered prospectively into a web-based database for a three month period in each unit from the first impact of COVID-19, were retrieved. Comparisons were made between patients developing perioperative COVID-19 infection, postoperative pulmonary complications (PPCs) (a composite outcome measure of pneumonia, ARDS, respiratory failure and need for respiratory support), and 30-day mortality. Univariate analyses examined differences between groups. Stepwise multivariate binary logistic regression determined independent predictors. **Results:** 1,486 patients underwent NSCLC surgery in 83 hospitals across 28 countries between March and July 2020. Preoperative factors associated with perioperative COVID-19 included male gender, underlying respiratory disease, advanced cancer stage, open surgery and absence of a dedicated COVID-free surgical pathway. Perioperative COVID-19 was associated with a 30-day mortality rate of 26%, higher re-operation rate, critical care utilisation and complications (Table 1). In multivariate analyses (Table 2), independent predictors of perioperative COVID-19 included male gender (OR 2.06), pre-existing respiratory disease (OR 2.82), open surgery (OR 2.32), and the lack of a COVID-19 free surgical pathway (OR 3.07). The strongest independent predictor of PPCs was perioperative COVID-19 (OR 7.4), which also predicted 30-day mortality (OR 11.6, Table 2)

Variable	N	Peri-operative 30-day COVID-19 Infection		p-value[2]	q-value[3]
		No, N = 1,412[1]	Yes, N = 74[1]		
Sex	1,486			**0.005**	0.007
Female		733 (52%)	26 (35%)		
Male		679 (48%)	48 (65%)		
COPD	1,486	398 (28%)	32 (43%)	**0.005**	0.007
Respiratory Disease	1,486	478 (34%)	38 (51%)	**0.002**	0.003
Previous COVID-19	1,431			**<0.001**	<0.001
No		1,378 (99%)	33 (82%)		
Probable - clinically suspected		6 (0.4%)	3 (7.5%)		
Yes - proven with laboratory test or CT thorax		7 (0.5%)	4 (10%)		
Pre-op Non-Invasive Ventilation	1,460	0 (0%)	2 (4.2%)	**0.001**	0.002
Pathological Stage	1,262			**0.019**	0.019
Stage 0		10 (0.8%)	1 (2.6%)		
Stage 1		799 (65%)	16 (42%)		
Stage 2		203 (17%)	9 (24%)		
Stage 3		188 (15%)	11 (29%)		
Stage 4		24 (2.0%)	1 (2.6%)		
Approach	1,460			**0.002**	0.003
Open		395 (28%)	21 (44%)		
VATS/RATS		945 (67%)	21 (44%)		
VATS/RATS converted to Open		72 (5.1%)	6 (12%)		
Pathway	1,486			**<0.001**	<0.001
COVID-19 free surgical pathway		371 (26%)	5 (6.8%)		
Hospital with no defined pathway		1,041 (74%)	69 (93%)		
COVID-19 CRITCON level	1,460			**0.002**	0.003
Level 0 - Normal		218 (15%)	17 (35%)		
Level I - Low surge		508 (36%)	11 (23%)		
Level II - Medium surge		537 (38%)	14 (29%)		
Level III - High surge		149 (11%)	6 (12%)		
COVID suspected at the time of surgery?	1,459	31 (2.2%)	6 (12%)	**<0.001**	0.002
Reoperation	1,486	68 (4.8%)	9 (12%)	**0.012**	0.013
Post-operative Level of Care	1,460			**0.015**	0.015
Enhanced Ward Monitoring		285 (20%)	5 (10%)		
HDU		361 (26%)	11 (23%)		
ICU		231 (16%)	16 (33%)		
Ward		535 (38%)	16 (33%)		
30-day Mortality	1,486			**<0.001**	<0.001
Alive		1,402 (99%)	55 (74%)		
Dead (0-7 days post-operative)		1 (<0.1%)	3 (4.1%)		
Dead (8-30 days post-operative)		9 (0.6%)	16 (22%)		
Length of Hospital Stay (days)	1,460	5.00 (3.00 – 7.00)	9.00 (5.00 – 14.25)	**<0.001**	<0.001
Acute Kidney Injury	1,486	22 (1.6%)	8 (11%)	**<0.001**	<0.001
Acute Respiratory Distress Syndrome	1,486	6 (0.4%)	10 (14%)	**<0.001**	<0.001
Pneumonia	1,486	118 (8.4%)	26 (35%)	**<0.001**	<0.001
Post-operative Pulmonary Complication	1,486	139 (9.8%)	34 (46%)	**<0.001**	<0.001
Pulmonary Embolism	1,486	5 (0.4%)	3 (4.1%)	**0.006**	0.007
Sepsis	1,486	19 (1.3%)	7 (9.5%)	**<0.001**	<0.001

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

[3] False discovery rate correction for multiple testing

Figure 1. Significant Pre and Post-operative Factors stratified by Post-operative COVID-19 Infection (Univariate Modelling)

Characteristic	Peri-operative COVID-19 Infection			Post-operative Pulmonary Complication			30-day Mortality		
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Respiratory Disease									
No	—	—		—	—		—	—	
Yes	2·82	1·52 to 5·34	**0·001**	1·41	0·99 to 2·00	0·056	3·35	1·11 to 11·3	**0·038**
Previous COVID-19									
No	—	—							
Probable - clinically suspected	15·5	2·87 to 70·7	**<0·001**						
Yes - proven with laboratory test or CT thorax	27·2	6·15 to 109	**<0·001**						
Sex									
Female	—	—		—	—				
Male	2·06	1·10 to 4·02	**0·027**	1·56	1·10 to 2·24	**0·013**			
Pathway									
COVID-19 free surgical pathway	—	—							
Hospital with no defined pathway	3·07	1·26 to 9·31	**0·025**						
Approach									
a). VATS/RATS	—	—		—	—				
b). VATS/RATS converted to Open	3·72	1·29 to 9·37	**0·008**	3·35	1·79 to 6·05	**<0·001**			
c). Open	2·32	1·21 to 4·47	**0·011**	2·34	1·62 to 3·38	**<0·001**			
COVID-19 CRITCON level									
Level 0 - Normal	—	—							
Level I - Low surge	0·31	0·13 to 0·69	**0·005**						
Level II - Medium surge	0·43	0·19 to 0·93	**0·031**						
Level III - High surge	0·60	0·20 to 1·54	0·309						
Diabetes									
No				—	—				
Yes				1·62	1·01 to 2·53	**0·040**			
MDT									
Decision for non-surgical treatment as optimal choice				—	—		—	—	
Decision for non-surgical treatment but suboptimal				0·00		0·983	0·00		0·997
Decision for surgical treatment				0·75	0·14 to 6·02	0·754	0·03	0·00 to 0·33	**0·002**
Decision for surgical treatment (compromised due to COVID-19)				4·53	0·66 to 42·7	0·142	0·00		0·989
Reoperation									
No				—	—				
Yes				2·98	1·62 to 5·27	**<0·001**			
`COVID positive`				7·40	3·95 to 13·9	**<0·001**	11·6	3·73 to 36·3	**<0·001**
Post-operative Pulmonary Complication									
No							—	—	
Yes							21·5	5·91 to 93·9	**<0·001**
Acute Respiratory Distress Syndrome									
No							—	—	
Yes							7·88	1·55 to 47·1	**0·016**
`Length of Hospital Stay (days)`							0·94	0·87 to 1·00	0·101
Sepsis									
No							—	—	
Yes							4·34	0·79 to 23·3	0·085

[1]OR = Odds Ratio, CI = Confidence Interval

Figure 2. Significant Independent Predictors of Post-operative Outcomes in COVIDSurg Lung Cancer Cohort (n = 1460)

Conclusion: Modifiable factors exist which are associated with a lower rate of COVID-19. These include utilisation of COVID-19 minimised pathways and avoidance of thoracotomy. Analysis of COVID-related protocol deviations and longer term outcomes is ongoing.

Keywords: Surgery, non-small cell lung cancer, covid-19

P31.05 SARS-CoV-2 and Lung Cancer: Pandemic Impact in Diagnosis, Staging and Management

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Introduction: All restrictions and social isolation imposed by the COVID-19 pandemic did not prevent the evolution of non-infectious diseases, interfering in the diagnosis and the beginning of the treatment for other pathologies. This study aims to measure the impact caused by the pandemic on the diagnosis and staging of lung cancer in patients who underwent lung resection (LR) in 2020 compared to 2019, as well as to describe the epidemiological profile of these patients. **Methods:** In this retrospective study, data from patients who underwent LR (lobectomy, segmentectomy, wedge resection, and pneumonectomy) by PUCRS's Sao Lucas Hospital Thoracic Surgery team in Brazil within 2019 and 2020 were collected from medical records in March 2021. Only primary lung cancer patients were included. A descriptive analysis was performed. **Results:** There were 144 LR analyzed, 80 in 2019 and 66 (45.83%) in 2020. The number of LR due to primary lung cancer was 42 (52.5%) in 2019 and 30 (45.45%) in 2020. The comparison between years indicates a reduction of 28.57% in the number of LR. Of the 30 surgeries in 2020, 23 were lobectomies (76.66%), 3 segmentectomies (10%), 1 wedge resection, and 3 pneumonectomies. The incidence of lobectomies in men decreased 35.29% (17 in 2019; 11 in 2020) and remained stable in women (13 in 2019; 12 in 2020). The average age of patients who were subjected to LR was 61.57 in 2019 and 57.9 in 2020. In cancer patients, the average age was 59.9 (61.9 in 2019; 57.98 in 2020). The incidence of adenocarcinoma was 29 in 2019 (69%) and 19 in 2020 (63.3%), being the most prevalent histological type. According to our review, clinic staging (CS) for lung cancer with the highest incidence in the two years analyzed was IA2, with 26.6% of cases in 2020 and 28.5% in 2019. CS IIA corresponded to 20% in 2020 and 9.5% in 2019, IIB 16.6% in 2019 and 6.6% in 2020, IA1 16.6% in 2020 and 2.38% in 2019, IA3 19% in 2019 and 13.3 % in 2020. Of the 42 patients who were performed LR for primary cancer in 2019, 17 (40.47%) underwent video-assisted thoracoscopic surgery (VATS), and from 29 (55.17) in 2020, 16 were VATS. **Conclusion:** In general, the pandemic and its restrictions of access to tertiary diagnostic and treatment centers decreased the number of patients. There was a reduction of 28.57% in the number of procedures performed for primary lung. Most patients continued to receive a CS IA2 diagnosis, however, the percentage of diagnosis in CS IIA had grown. This percentage is worrying, as it shows that patients took longer to receive adequate treatment or were unable to make an early diagnosis. On the other hand, the average age of diagnosis decreased in 2020, which may indicate early diagnosis perhaps related to incidental findings in COVID19 CT scans. Our lower number of VATS is related to the lack of endoscopic staples in public healthcare system.

Keywords: public healthcare, Surgery, lung cancer

P31.06 Impact of Covid-19 Infection on Lung Cancer Patients: Experience in Latin-American Country ACHOCC-19L Study

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Introduction: Worldwide literature has evidenced that patients with cancer and COVID-19 have a worse prognosis. Registries such as TERAVOLT have shown aditionally, that patients with thoracic cancer have a higher mortality. We aimed to describe the characteristics demographics and outcomes in patients with lung cancer in colombian national cohort of patients with cancer and infection for COVID-19. **Methods:** The ACHOCC-19L registry is a multicenter observational study composed of a cross-sectional component and a prospective cohort component. Eligibility criteria were the presence of lung cancer and COVID-19 diagnosis confirmed with RT-PCR. Follow-up of 30 days was completed. Clinical data were extracted of the multicentric register of cancer and covid-19 in Colombia (ACHOCC-19 study), collected from Apr 1, 2020 until Oct 31, 2020. Data on demographics, oncological history and comorbidities, COVID-19 diagnosis, and clinical outcomes were described. The primary outcome was 30-day mortality from all causes and secondary outcome was asymptomatic disease during the follow up. Associations between demographic or clinical characteristics and outcomes were measured with odds ratios (ORs) with 95% CIs using multivariable logistic regression. The absolute frequencies of the observing events <4 will be reported as a value, and 4 or greater as a percentage. **Results:** 37 patients were included. They represent 5% of Global ACHOCC-19 cohort. 54% died during the follow-up and 29,7% was asymptomatic. The summary of the variables according to the outcomes is summarize in the Table 1. In relation to the patients who died, 60% were older than 60 years, 60% was male, 30% had COPD, 40% arterial Hypertension, 70% metastatic disease, 50% without specific cancer treatment, 75% received antibiotic and 75% steroids for Covid-19 infection. All patients with severe disease that received invasive ventilation died and, 69% died in hospital and did not have advanced support. About the asymptomatic population 54,5% were older than 60 years, 72.7% female, 9% had COPD, 45,5% arterial hypertension, 81,8% metastatic disease, 40% received cytotoxic and 30% no cytotoxic anti-cancer treatment. In the logistic regression analysis, age older than 60 years (OR 1, 48, 95% 0,359-6,135), male sex (OR 3,052, 95% 0,762-12,217), and having COPD (OR 2,536, 95% 0,472-13,614) behaved as a risk factor for mortality, but none was statistically significant.

Table 1. Descriptive analysis of demographic and clinical variables

Variable	Global (n:37)	Died (n:20)	No Died (n:17)	Asymptomatic (n:11)	Symptomatic (n26)
Age </=60 Years >60 Years	16(43,3%) 21(56,7%)	8 (40%) 12 (60%)	8 (47%) 9 (53%)	5 (45,4%) 6 (54,5%)	11 (42,3%) 15 (57,6%)
Sex Male Female	18(48,6%) 19(51,4%)	12 (60%) 8 (40%)	6 (35,3%) 11 (64,7%)	3 (27,3%) 8 (72,7%)	15 (57,7%) 11 (42,3%)
COPD Yes Not	9(24,3%) 28(75,7%)	6(30%) 14(70%)	3 (17,6%) 14 (82,4%)	1 (9%) 10 (91%)	8 (30,7%) 18 (69,3%)
Arterial Hypertension Yes Not	16(43,2%) 21(56,8%)	8 (40%) 12 (60%)	8 (47,1%) 9 (52,9%)	5 (45,5%) 6 (54,5%)	11(42,3%) 15 (57,69%)
ECOG 0 1 2 3 4	5(14,7%) 10(29,4%) 11(32,5%) 7(20,6%) 1(2,9%)	1 3(15,8%) 7 (36,8%) 7 (36,8%) 1	4 (26,6%) 7 (46,6%) 4 (26,6%) 0 0	4 (40%) 5 (50%) 1 0 0	1 5 (20,8%) 10 (41,6%) 7 (29,1%) 1
Metastatic disease Yes Not	27(73%) 10(27%)	14(70%) 6(30%)	13(76,5%) 4(23,5%)	9(81,8%) 2(18,2%)	18(69,2%) 8(30,8%)
Histology Adenocarcinoma Squamous cell Small cell	30(81,1%) 2(5,4%) 5(13,5%)	14 (70%) 2 (10%) 4 (20%)	16 (94,1%) 0 1	10 (91%) 0 1	20 (76,92%) 2 4 (15,38%)
Treatment Type No Treatment Cytotoxic Treatment No-cytotoxic Treatment	15(44,1%) 9(26,5%) 10(29,4%)	9 (50%) 4 (22,2%) 5 (27,8%)	6 (37,5%) 5 (31,3%) 5 (31,3%)	3 (30%) 4 (40%) 3 (30%)	12 (50%) 5 (20,8%) 7 (29,2%)
Antibiotic Treatment Covid-19 Yes Not	18(48,6%) 19(51,4%)	15 (75%) 5 (25%)	3 (17,6%) 14 (82,4%)	- -	- -
Steroids Treatment Covid-19 Yes Not	18(48,6%) 19(51,4%)	15 (75%) 5 (25%)	3 (17%) 14 (83%)	- -	- -
Course of illness Asymptomatic Mild Hospitalized without invasive ventilation Hospitalized With invasive ventilation	11(31,4%) 2 11(31,4%) 11(31,4%)	0 0 7 (36,8%) 11 (57,8%)	11 (68,7%) 2 4 (25%) 0		

Conclusion: In our study, lung cancer patients have high mortality by Covid-19 infection as has been described in worldwide literature. Age, COPD, ECOG >2 and male sex are factors for worse prognosis.

Keywords: covid 19, outcomes, lung cancer

P32.01 Clinical Screening for COVID-19 in Asymptomatic Patients With Lung Cancer: Brazilian Experience From a Single Institution

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Introduction: Covid-19 pandemic is being a disaster in Brazil. The lack of massive testing in early 2020, incomplete lockdowns and a slow vaccination campaign have contributed to impressive 4000 daily deaths in April 2021 and more than 300.000 deaths since the first case. The impact on lung cancer patients is still unknown. In order to decrease risks, we performed active screening for COVID-19 on all lung cancer patients who were asymptomatic for COVID-19 and has being treated in our Cancer Center. **Methods:** All lung cancer patients scheduled to receive chemotherapy, immunotherapy or both were invited to collect an anterior nasal swab specimen for COVID-19 testing with real-time reverse transcription polymerase chain reaction (RT-PCR) two days before drug administration. A triage for symptoms (including fever, cough, headache, loss of taste, coryza and shortness of breath) was done before the test in order to exclude symptomatic patients. If a positive RT-PCR was detected, the infusion was postponed and the patient monitored and treated if necessary. **Results:** From June 2020 to January 2021, we screened 32 asymptomatic patients with lung cancer for COVID-19. Our studied population consisted of 17 females (53.1%) and 15 males (46,8%), most of them were caucasians (29 [90.6%]), with a median age of 68 y.o., presented an ECOG of 0 and 1 (31 [96.8%]), had a previous history of smoking, (21 [65.6%]) and they had more than two comorbities (21 [65.6]). Adenocarcinoma was the most prevalent histological type (23 [71.8%]), followed by squamous cell carcinoma, (7 [21.8%]). Most patients (65.6%) were in stage 4, and 46.8% scheduled to receive chemotherapy (fig1). The test was positive in only one (3.1%) patient, who required hospitalization due to acute respiratory failure; the patient did not respond satisfactorily to the treatment of COVID-19, and eventually died. **Conclusion:** While Brazil continues to be the epicenter of deaths for COVID-19 in the world and worse, no massive vaccination will be available in the near future, the pandemic is still a massive problem for our health system. Lung cancer patients should be a priority group for vaccination. Unfortunately, this procedure is not a reality so far. Despite having only one patient that tested positive for COVID-19 in our dataset, somehow denoting a more engagement for social distancing in cancer patients, such triage and active screening program have to be routinely recommended to increase safety for all lung cancer patients who are currently under systemic therapy.

Keywords: covid-19, screening, asymptomatic

P32.02 2020 in Hindsight: Newly Diagnosed Lung Cancer Patients in the Time of COVID-19 at a Tertiary Canadian Cancer Centre

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Introduction: The COVID-19 pandemic has had significant secondary impacts on healthcare services worldwide, including delays to non-essential procedures and surgeries. Early efforts to reduce the spread of COVID-19 across Canada resulted in up to 45% fewer visits to family physicians and medical specialists between March and June of 2020 (National Physician Database, 2020, Canadian Institute for Health Information). In the context of cancer care, this may have resulted in fewer new cancer diagnoses as a consequence of limited access to a family physician or diagnositic services, and delayed time to surgery or treatment. We sought to study the immediate consequences of the COVID-19 pandemic by comparing the experience of newly diagnosed lung cancer patients in 2020 with those diagnosed in 2018 at a single Canadian tertiary cancer care centre. **Methods:** Patients seen for new primary lung cancer diagnosis at the Tom Baker Cancer Centre in Calgary Alberta, Canada in 2018 and 2020 were identified using the institutional Glans-Look Lung Cancer Research (GLR) database. Demographic, clinical, treatment and outcome data were extracted from the GLR and patients grouped by diagnosis year to evaluate differences between those diagnosed prior to (2018) and during (2020) the COVID-19 pandemic in Canada. **Results:** While a more comprehensive comparison between the 2018 and 2020 cohorts will be presented, a preliminary analysis of demographic and clinical data suggests a similar categorization of variables: Approximately 50% NSCLC (adenocarcinoma), 20% NSCLC (squamous cell carcinoma), and 15% SCLC. The majority of diagnoses in both cohorts were metastatic, although this trended lower in the 2020 cohort. Univariate analysis will be performed to confirm these and other demographic, clinical, and treatment differences, and to compare survival to determine whether diagnosis and/or treatment in 2020 is independently prognostic of outcome. Additionally, we will compare diagnosis of lung cancer across similar quarterly periods during 2018 and 2020 to determine if heightened local pandemic restrictions had an impact on total diagnoses or time to (or uptake of) treatment. **Conclusion:** Ongoing analysis of the 2020 cohort will allow quantification of any differences between 2020 and 2018 diagnosis year cohorts to determine if the events of the COVID-19 pandemic in our region had significant impact on lung cancer diagnoses, patient management or outcome.

Keywords: clinical data, covid-19, diagnosis

P33.01 Air Leak Due COVID-19 in a Lung Cancer Patient

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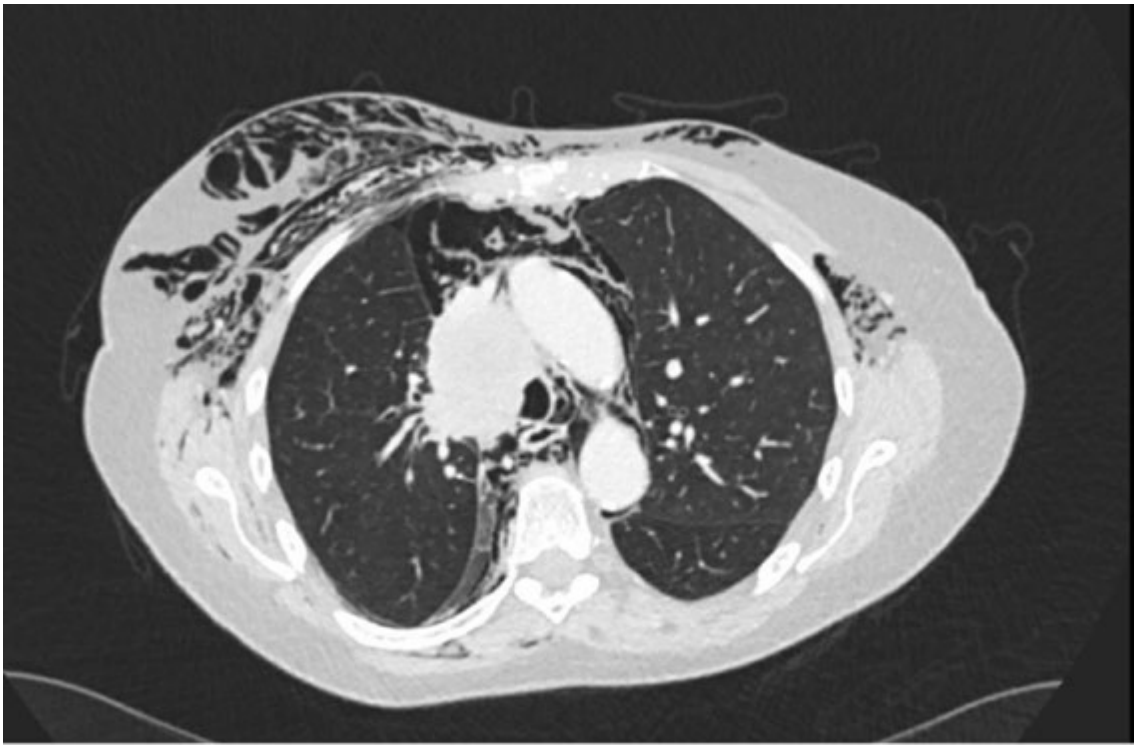
Introduction: Covid-19 causes widespread pneumonitis which carries high mortality and morbidity in patients with lung cancer. About 1% of patients will develop a pleural complication of Covid-19, which is often in the form of pneumothorax or pneumomediastinum. Case series have described these as adverse prognostic markers. **Methods:** We describe the case of a 76-year-old woman who was diagnosed in early December 2020 with T4 N2 M0 right upper lobe lung cancer. Her performance status was 0. Whilst awaiting an EBUS, in late Dec 2020, she presented with haemoptysis and facial swelling. A swab PCR was positive for Covid-19. She underwent an urgent CT scan (Figure 1) which showed widespread surgical emphysema and pneumomediastinum without pneumothorax. There was no associated pneumonitis. The lung cancer had not grown in size.



Results: She was significantly hypoxic with oxygen saturations of 90% on a 15L non-rebreathe bag. There was no intervention possible and a patient centred decision was made for palliation of symptoms. Her chosen place of death was at home: she was thus discharged with community support and died within 24 hours. **Conclusion:** Pneumothoraces can be drained with intercostal tubes, and surgical emphysema can require subcutaneous tunnelled drains. However, pneumomediastinum and surgical emphysema due to Covid-19 carries a poor prognosis (even without a lung cancer diagnosis) [unpublished local data] unless mechanical ventilation is possible (1). Air leaks in the context of Covid-19 are rare. Isolated pneumothorax and pneumomediastinum are not adverse prognostic signs, but the development of pneumothorax, surgical emphysema and pneumomediastinum on mechanical or non-invasive ventilation might be as 12 of the 14 cases locally have died. Large data sets must be analysed to confirm these findings References 1. European Respiratory Journal Nov 2020, 56 (5) 2002697; DOI: 10.1183/13993003.02697-2020

Keywords: covid-19, lung cancer, pneumomediastinum

P33.02 Day Case Thoracococoscopy With IPC Insertion

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Introduction: Northumbria Healthcare NHS Foundation Trust runs a large pleural service. Local anaesthetic medical thoracoscopy (LAT) is a well-established procedure in undiagnosed pleural effusions. Patients were traditionally admitted for a mean of 3.4 days and had a large bore drain inserted post LAT with pleurodesis. The Covid-19 pandemic has forced day case LAT provision with IPC placement without pleurodesis to minimise transmission risk. We describe our experience. LAT is performed in theatre under conscious sedation. **Methods:** All notes of patients requiring day case LAT between July 2020-Feb 2021 were analysed. Basic demographics and outcomes were collected. A descriptive analysis of the data was performed. **Results:** 17 patients underwent day case LAT. All had negative pre-operative Covid-19 swabs: mean age 70.8 years (range 34-82), 12 male,5 female. Diagnoses included 5 lung cancers, 6 mesotheliomas and 4 fibrinous pleuritis. The lung did not deflate, not enabling biopsies in 2. Non-malignant diagnoses are currently presumed. 14 IPCs and 2 large bore drain were inserted due to 2 immediate complication (surgical emphysema). 1 patient developed an empyema within 30days. 9 out of the 11 IPCs have already been removed due to pleurodesis occurring (mean number days 60. All were discharged on the same day except the two requiring further drain insertion. **Conclusion:** We have thus transformed our service after more than a decade of providing LAT as an inpatient service. This is a small cohort of patients but proves the feasibility and safety of day case LAT with massive reduction in inpatient stay. The Covid-19 pandemic has transformed our service but for the better. Further qualitative work should elucidate the acceptability of such a pathway for patients.

Keywords: lung cancer, covid-19, medical thoracoscopy

P34.01 6-Weekly vs 3-Weekly Pembrolizumab – Toxicities and Tolerance in The COVID-era

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Introduction: Pembrolizumab is a novel immunotherapy which blocks the immunoregulatory receptor PD-1 on T-cells, preventing tumours evading the immune system. It enables the immune system to detect and destroy malignant cells, and has proven to be highly successful in the treatment of a range of cancers including non-small cell lung cancer (NSCLC). However, when the COVID-19 pandemic hit the United Kingdom in March 2020, fears of vulnerable lung cancer patients acquiring the virus while attending hospital for their pembrolizumab led to the decision to switch to a newly licenced dosing regimen. This dosing regimen involved giving a higher dose of 400 mg pembrolizumab, and a longer interval of 6 weeks between doses, compared to the standard doses of 200 mg or 2 mg/kg given every 3 weeks. Concerns of staff regarding toxicities of the new regimen led to the development of this study. **Methods:** All patients with advanced NSCLC who had been treated with at least one cycle of pembrolizumab between the 01/09/19 and 08/01/21 by the oncology department in Ninewells Hospital, Dundee, were included in this retrospective study. The patients were divided into two groups based on whether they had been treated with pembrolizumab 200mg every 3 weeks, or 400mg pembrolizumab every 6 weeks. The data collected from patients was age, gender, dose and number of cycles of pembrolizumab, reported toxicities and their grading, and any reasons for stopping pembrolizumab. The database Chemocare was used to identify patient toxicities, and these were graded using the “Guideline for the Management of Immunotherapy Toxicities in Adult Haematology and Oncology patients” published by the North Cancer Alliance, and then cross-referenced with the Common Terminology Criteria for Adverse Events guidance (CTCAE) . Further information regarding toxicities was obtained using the databases Wisdom and ICE. **Results:** 42 NSCLC patients had received 200mg pembrolizumab every 3 weeks and 46 patients received 400mg pembrolizumab every 6 weeks. In the 3-weekly group, 38 patients (90.5%) reported some level of toxicity after starting on pembrolizumab. In the 6-weekly group, 35 patients (76.1%) reported some level of toxicity. In both groups the most common toxicity was fatigue, followed by shortness of breath, skin rash, nausea, and itch. There were 4 cases (9.5% of patients) of Grade 3-5 toxicities in the 3 weekly pembrolizumab group (severe skin reaction, two cases of colitis and bursitis) and 5 cases (10.9% of patients) of Grade 3-5 toxicities in the 6-weekly dosing group (two skin reactions, pneumonitis, colitis and severe fatigue). **Conclusion:** The results of this study demonstrated that there was no difference in the number of grade 3-5 toxicities experienced in either group. Clinicians can be reassured that patients are not being put at increased risk of toxicities due to the change to 400mg given every 6 weeks as a result of the COVID-19 pandemic. There was a higher number of toxicities reported overall in the 3-weekly pembrolizumab dosing group, however this may be due to other factors such as reduced patient contact as a result of the COVID pandemic, leading to underreporting by patients.

Keywords: Pembrolizumab toxicities, covid-19

P34.02 The Inhibitory Effect of Cisplatin, Paclitaxel, and Pemetrexed on the Growth of PC9GR Cells During the COVID-19 Pandemic

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Introduction: Lung cancer patients have a significantly higher risk of contracting COVID-19, and interactions with the healthcare system during cancer therapy can put patients at risk. Preliminary studies in COVID-19 patients with severe disease found a reduction in the number and function of natural killer (NK) cells. Other studies in COVID-19 patients reported acute respiratory distress syndrome (ARDS) due to the extreme release of inflammatory cytokines. Besides, adverse effects of chemotherapy, such as chemotherapy resistance and the escalation of cellular senescence can worsen the condition of patients with COVID-19. Considering these facts, we evaluated the growth-inhibitory effects of three commonly used chemotherapy drugs, cisplatin, pemetrexed, and paclitaxel, in gefitinib-resistant non-small cell lung cancer (PC9GR) cells and investigated the underlying mechanism. **Methods:** In this study, flow cytometry (FCM) was used to profile the activity and function of human NK cells. An enzyme-linked immunosorbent assay (ELISA) was performed to quantify cytokine levels. PC9GR cells were treated with cisplatin, paclitaxel, or pemetrexed as monotherapy for 72 h and then evaluated with a cell viability assay, a reactive oxygen species (ROS) assay, a terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, SA-β-Gal staining, and Western blotting. **Results:** We demonstrated that NK cell dysfunction was linked to the reduced NK-mediated elimination of PC9GR cells. The PC9GR cells showed the marked secretion of IL-6, IL-8 and VEGF cytokines, which was connected to the activation of the inhibitory signaling pathway of NK cells. We found that paclitaxel was the most potent growth inhibitor, cisplatin had an intermediate growth inhibitory effect, and pemetrexed induced a minimal growth inhibitory effect in PC9GR cells. These growth inhibitory effects were observed to be associated with ROS-mediated DNA damage, which led to the activation of apoptotic caspases. Surprisingly, paclitaxel was the strongest remover of senescent cells; pemetrexed had an intermediate effect, and cisplatin removed the lowest number of senescent cells. **Conclusion:** In light of these findings, paclitaxel may have a better therapeutic effect than cisplatin or pemetrexed on PC9GR cells, suggesting that paclitaxel could offer a novel therapeutic approach for the treatment of gefitinib-resistant non-small cell lung cancer during the COVID-19 pandemic.

Keywords: NK, covid-19, PC9GR

P34.03 Lung Cancer Patients and COVID-19 in a District General Hospital in the UK

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Introduction: Covid-19 carries high morbidity and mortality in certain patient groups such as lung cancer patients. Whilst nationwide databases such as the UK Coronavirus cancer monitoring project help in providing large scale epidemiological data, local data informs local practice. **Methods:** We identified all patients with thoracic malignancies diagnosed with Covid-19 infection via swab polymerase chain reaction (PCR) testing from March to Dec 2020 through a comprehensive search of the local hospital databases. Local Caldicott approval was granted (RPI-1294). Demographics and outcomes were analysed. **Results:** 17 patients were identified. All were white Caucasian, mean age 72.4 year with a median WHO performance status of 2. 2 were at stage 1 disease, 3 stage 2,3 stage 3, 9 at stage 4 (TNM classification). 1 was small cell, 1 mesothelioma, 1 neuroendocrine lung cancer, the rest were non-small cell lung cancers. 3 had received chemotherapy in the last 3 months, none had recent radiotherapy. 4 tested positive on routine swabs and were simply observed. 13 were admitted to hospital with Covid-1: only 1 received level 2 care (CPAP). All others were for ward-based care. COPD and hypertension were the commonest comorbidities (both in 7 patients). 6 developed widespread pneumonitis and respiratory failure and died. 4 others developed patchy infiltrates and had associated bacterial infection. All died. **Conclusion:** This cohort spanned the first and second wave. Steroids were administered in 14 patients and only 1 of the survivors. Mortality in this small group of patients (probably reflecting shielding advice) was 76% if admitted to hospital, which is very high. Larger studies are required to verify this but reinforces that lung cancer patients are very vulnerable to Covid-19.

Keywords: lung cancer, covid-19

P34.04 Chemo-Immunotherapy in Non-Small Cell Lung Cancer (NSCLC) – Real World Data from a Tertiary Oncology Centre

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Introduction: Non-Small Cell Lung Cancers (NSCLC) are the most common type of lung cancers. Advanced NSCLC usually carries a poor prognosis. The era of targeted therapy and immunotherapy has seen an improvement in prognosis with increasing progression free survival (PFS) and overall survival (OS). The aim of this audit was to assess the median PFS and toxicity profile for patients on combination chemo-immunotherapy (chemo-IO) in our centre. **Methods:** In this retrospective analysis, all patients with a diagnosis of NSCLC who had received chemotherapy with Pembrolizumab combination for the period July 2019 to June 2020 were included. Electronic records were reviewed for age, histology, PD-L1 status, number of cycles of treatment, toxicities and scan results. **Results:** A total of 61 patients were screened. Of these, 59 patients received chemo–IO combination treatment during this period and therefore met the criteria for assessment. Adenocarcinoma was the most predominant histology 67.8% (n=40), with squamous histology accounting for 20.3% (n=12), NSCLC and pleomorphic histology made up the rest. 44.1% (n=26) were PD-L1 negative, 50.8% were PDL1 positive (n=29) and the rest were insufficient or borderline. WHO performance status of all patients were recorded with 25.4% (n=15) PS 0, 72.8% (n=43) PS 1, 1.6% (n=1) PS 2. 27 patients met the criteria for assessment of PFS. In the non-squamous cohort, median PFS was 6.5 months and in the squamous cohort 5 months. Overall median PFS was 6.5 months (range 1-17) for both groups. Looking at PFS by age, patients aged over 70 years (n=21) had a median PFS of 8.25 months and those aged between 60 to 70 years (n=25), 6.5months. At present, 37% (n=22) remain on Chemo-IO treatment, with 63.6% (n=14) being aged over 60. Treatment was discontinued in 8.4% (n=5) due to toxicities. 60% (n=3) had grade 3 fatigue, 20% grade 3 nephritis (n=1) and grade 2 pneumonitis in 20% (n=1). 2 patients died whilst on treatment. **Conclusion:** Our calculated median PFS is not in keeping with trial data. Reasons for the data falling short could be due to the small number of patients. This has likely been impacted by the COVID-19 pandemic and delays in patients reaching Oncology for treatment. Other reasons could include increased frequency of scanning whilst patients are admitted into hospital for other reasons. It appears patients aged over 60 years tend to do better on the combination treatment with better outcomes and fewer toxicities. Overall survival cannot be estimated yet as data is still immature. Larger real world data sets would be needed to ascertain the true potential of Chemo-IO combination in advanced lung cancer.

Keywords: Chemo-IO,NSCLC, COVID-19

P34.05 Three Birds, One Stone: IVIG Use in Hypogammaglobulinemia, Checkpoint Inhibitor Pneumonitis, and Persistent COVID-19

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Introduction: A 64-year-old man with CLL complicated by acquired hypogammaglobulinemia and COVID-19 pneumonia in 07/2020 was diagnosed with metastatic NSCLC in 08/2020 and underwent three cycles of pembrolizumab, resulting in stable disease. Frequent hospital admissions for respiratory failure with various infections including persistent COVID-19 positivity complicated his overall course. He received monthly IVIG infusions for hypogammaglobulinemia from 11/2020 to 12/2020 which were discontinued due to an allergic reaction. In 01/2021, he was admitted for possible refractory pneumonia. Initial work-up was unremarkable, with negative cultures and no response to broad spectrum antibiotics. Bronchoscopy revealed only rhinovirus positivity. Steroids were initially deferred due to recent strongyloidiasis. He developed a progressively worsening acute hypoxemic respiratory failure and was transferred to the ICU. CT imaging revealed widespread ground glass opacities and interstitial changes. He was then started on high-dose methylprednisolone (2 mg/kg/day) with significant clinical improvement. Given his initial dramatic response to high-dose steroids and CT scan findings, his respiratory failure was attributed to a grade 4 checkpoint inhibitor pneumonitis (CIP). He then developed increased oxygen requirements, with CT findings concerning for rapidly progressive pulmonary fibrosis despite high-dose steroids. **Methods:** Information obtained by Epic electronic medical records. **Results:** Given concern for refractory CIP, escalation of immunosuppression or re-challenge with IVIG was discussed; however, these were initially deferred due to concern for infection or allergic reaction, respectively. He continued to deteriorate, requiring 15 L oxygen, with discussion of hospice. Ultimately, he opted for a re-challenge with IVIG 500 mg/kg and showed rapid improvement of pulmonary fibrosis as seen in Figure 1. Five days after the initial IVIG dose, the patient was discharged home on 3 L oxygen. Two months later at last known follow-up, he had experienced one further hospitalization and was alive at home.

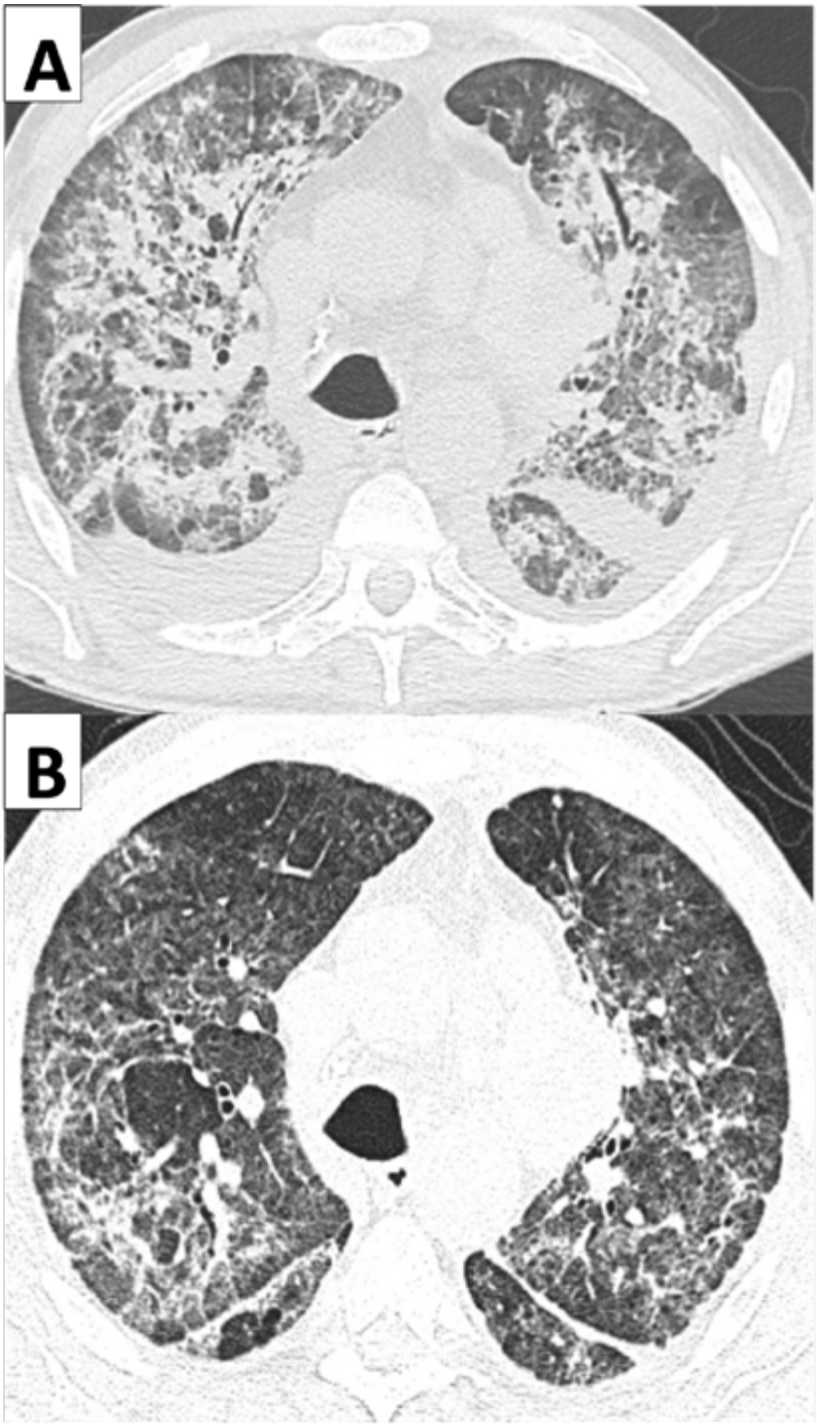

Figure 1 CT Chest scans, pre (**A**) and post (**B**) IVIG administration **Conclusion:** There is concern for increased risk and severity of CIP after COVID-19 infection due to 'priming.' A similar case report mentioned rapidly progressive, fatal CIP in a patient with small cell lung cancer on PD-1 immunotherapy following COVID-19. Our patient's case was further complicated by hypogammaglobulinemia, leading to a persistent COVID-19 infection and inflammatory state. IVIG has been described as a potential treatment for refractory CIP with low level supportive evidence. This case report is among the first to describe severe CIP with COVID-19 which had a dramatic response to IVIG therapy resulting in significantly decreased pulmonary fibrosis and oxygen requirements.

Keywords: checkpoint inhibitor pneumonitis, covid-19, NSCLC

P34.06 Antiproliferative Effects of Paclitaxel on PC9-MET Cells During the Coronavirus Disease 2019 Pandemic

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Introduction: Coronavirus disease 2019 (COVID-19) poses a great challenge for the treatment of cancer patients. It presents as a severe respiratory infection in aging individuals, including lung cancer patients. COVID-19 may be linked to the progression of aggressive lung cancer. In addition, the side effects of chemotherapy, such as chemotherapy resistance and the acceleration of cellular senescence, can worsen COVID-19. Given this situation, we investigated the role of paclitaxel (a chemotherapy drug) in the cell proliferation, apoptosis, and cellular senescence of gefitinib-resistant non-small-cell lung cancer (NSCLC) cells (PC9-MET) to clarify the underlying mechanisms. **Methods:** PC9-MET cells were treated with paclitaxel for 72 h and then evaluated by a cell viability assay, DAPI staining, Giemsa staining, apoptosis assay, a reactive oxygen species (ROS) assay, SA-β-Gal staining, a terminal deoxynucleotidyl transferase dUTP nick-end labeling assay and Western blotting. **Results:** Our results revealed that paclitaxel significantly reduced the viability of PC9-MET cells and induced morphological signs of apoptosis. The apoptotic effects of paclitaxel were observed by increased levels of cleaved caspase-3 (Asp 175), cleaved caspase-9 (Asp 330) and cleaved PARP (Asp 214). In addition, paclitaxel increased ROS production, leading to DNA damage. Inhibition of ROS production by N-acetylcysteine attenuates paclitaxel-induced DNA damage. Importantly, paclitaxel eliminated cellular senescence, as observed by SA-β-Gal staining. Cellular senescence elimination was associated with p53/p21 and p16/pRb signaling inactivation. **Conclusion:** Given these findings, paclitaxel may be a promising anticancer drug and offer a new therapeutic strategy for managing gefitinib-resistant NSCLC during the COVID-19 pandemic.

Keywords: Paclitaxel, PC9-MET, covid-19

P35.01 YB-1 is a Key Player in Aggressive Behaviour and Chemoresistance in Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is characterised by aggressive growth and frequent resistance to chemotherapy, poor prognosis for patients and limited therapeutic options. To establish potential new therapy targets, a better understanding of the MPM biology underlying these malignant behaviours is crucial. One potential candidate is the multifunctional oncoprotein YB-1, which is often overexpressed in various cancers and associated with aggressiveness, metastasis and poor outcome. **Methods:** YB-1 expression was analysed by qPCR or western blot in cell lines, and in patient material by immunohistochemistry. YB-1 overexpression was achieved by a doxycycline-inducible, retroviral construct, which was stably introduced into MPM cell lines. YB-1 knockdown was performed using YB-1 specific siRNA. For inhibition of YB-1 phosphorylation, the RSK inhibitor BI-D1870 was used. Effects of drug interaction (CI values) were calculated using the CompuSyn software. Cell migration was assessed by live cell videomicroscopy followed by manual single cell tracking and analysis using ImageJ and DiPer software, respectively. For the zebrafish model, RFP-expressing MPM cells were injected into 48 hour old larvae, imaged after 1 and 2 days and the number of cells in the tail was manually counted. **Results:** We previously reported that YB-1 is up-regulated in MPM cell lines compared to non-malignant controls. In this study we analysed MPM tissue (n>120) and normal pleura (n=3) specimens for YB-1 expression. While all control samples were negative, tumours showed a heterogeneous YB-1 expression. YB-1 knockdown decreases MPM cell migration and invasion, hence we evaluated the impact of YB-1 overexpression on these phenotypes. MPM cell lines (n=6) which overexpress YB-1 in a doxycycline-inducible manner showed significantly increased cell scattering and migration. Furthermore, YB-1 overexpression lead to significantly higher migratory capacity in vivo using a zebrafish xenograft model. Additionally, when tumour spheroids were co-cultured with endothelial cells, YB-1 overexpression led to a significantly more extensive formation of gaps in the endothelial layer. Finally, since we found that YB-1 knockdown not only decreases cell growth in vitro and in vivo but also decreases the expression of LRP1 and ABCC1, two genes involved in drug resistance, we combined YB-1 knockdown as well as inhibition of YB-1 phosphorylation via an RSK inhibitor with cisplatin chemotherapy. Our data showed highly synergistic combination effects (CI values: 0.1 – 0.5) for several cisplatin doses in combination with either YB-1 siRNA or the RSK inhibitor. **Conclusion:** In this study we report a deregulated YB-1 expression in MPM tumor specimens compared to non-malignant controls. Our data show an important role of YB-1 in the regulation of cell migration and invasion in vitro and in vivo, which are key characteristics of MPM. Additionally, YB-1 knock down as well as pharmacological inhibition of YB-1 phosphorylation not only reduce MPM cell growth but also sensitise cells to cisplatin chemotherapy. These findings contribute to a better understanding of the biology of MPM and highlight YB-1's potential as a therapeutic target.

Keywords: YB-1, Mesothelioma

P36.01 Primary Acinic Cell Carcinoma of Bronchial Ground Origin: A Case Report

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Introduction: Primary acinic cell carcinoma of the lung is an extremely rare disease. Also known as Fechner's tumor, this condition was first reported by Fechner et al. in 1972. The accurate diagnosis of primary pulmonary acinic cell carcinoma is difficult and relies on comprehensive evaluation of clinical, histological and immunohistochemical features. **Methods:** A 49-year-old male patient was referred to our hospital because of an abnormal infiltration shadow in the left lower lung field detected on a chest radiograph during a medical check-up. Chest computed tomography revealed a nodal mass shadow 10mm in size, in segment 8 of the left lower lobe. Bronchoscopic examination revealed a polypoid tumor at B8. Transbronchial biopsy was performed and the tumor was diagnosed as a bronchial gland adenoma. **Results:** The patient underwent video-assisted thoracic segmentectomy to achieve complete resection of the tumor. Macroscopically, the tumor was a solitary mass measuring 14×10×8 mm in size with substantial cut surface and showed no intraparenchimal growth. Histopathological examination revealed a polypoid projection in the bronchial space. Adeno-type cancer cells with monomorphous nuclei invade the bronchial wall tissue in association with tubule or acinus-like space formation. The cytoplasm of the tumor cells is plump and eosinophilic with granularity or clear. No direct invasion into the lung parenchyma was observed. Immunohistochemical staining revealed that the tumor cells were positive for PAS, lactoferrin, and HMG-45MI. The features are consistent with acinic cell carcinoma of bronchial gland origin. Electron microscopy showed that the acinus-forming tumor cell possess well-developed mitochondria and round-surfaced endoplasmic reticulum, in association with active luminal secretion. Rounded, electron-dense secretory exocrine granules, ranging from 150 to 340 nm in size, are noted mainly in the apical cytoplasm. Fat vacuoles are noted in some tumor cells. Microvillous intracytoplasmic lumina are occasionally noted. Bundles of intermediate filaments and desmosomal attachments are also seen. These features are consistent with acinar cell nature of the cells. Fourteen years since the surgical resection, no apparent recurrence or metastasis has been detected. **Conclusion:** We experienced an extremely rare case of primary bronchial acinic cell carcinoma diagnosed based on clinical information, histopathological features, immunogistopathological staining profile, and electron microscopy features. The limited number of reports on this type of tumor have revealed that the outcome after surgical resection is favorable due to its low-grade malignant potential. Likewise in this case, the patient remained free of recurrence for over 14 years after surgery.

Keywords: case report, Acinic cell carcinoma, bronchial ground origin

P36.02 A Case of Recurrent Giant Malignant Solitary Fibrous Tumour of the Pleura: An Elephant in the Room?

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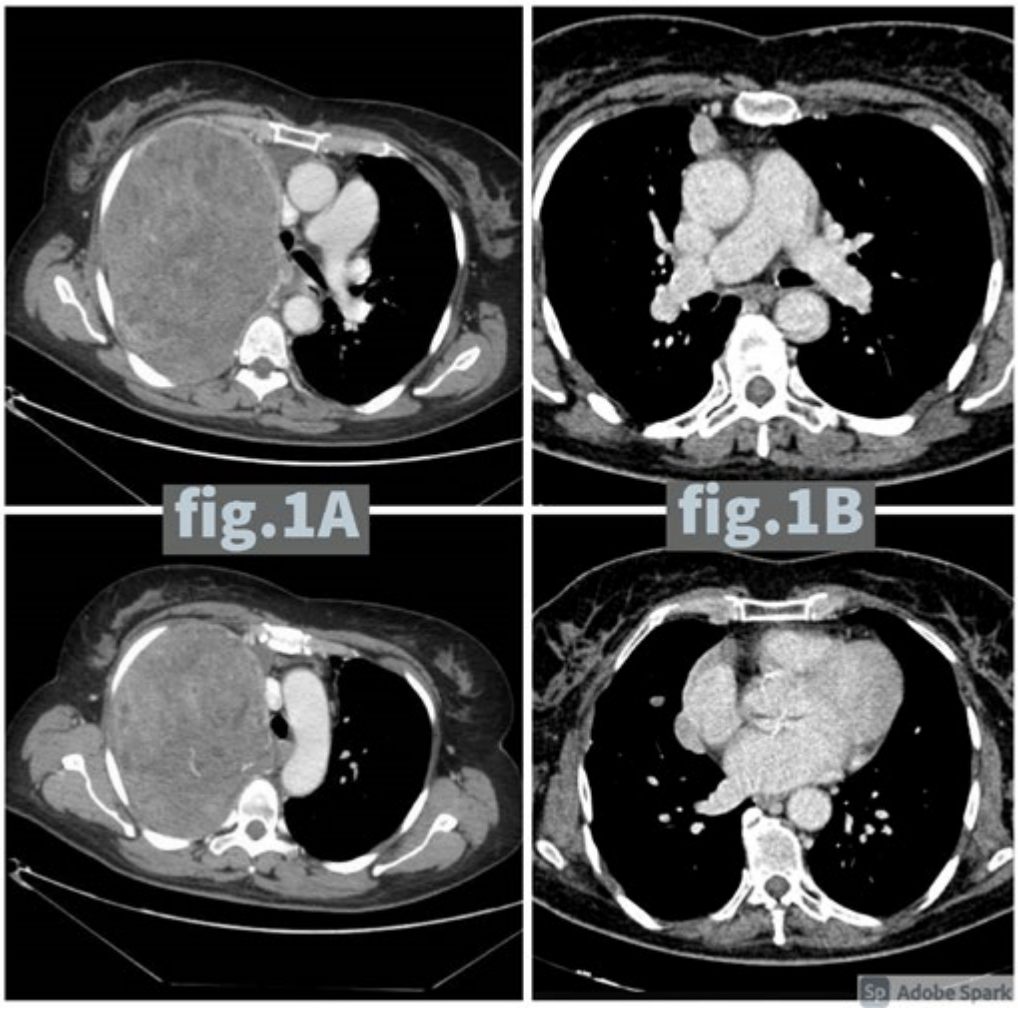
Introduction: Solitary fibrous tumor of the pleura (SFTP) is a rare soft tissue neoplasm, accounting for 4% of chest tumors. The biological behavior of SFTP is generally benign, with 10-15% of SFTP that show malignant features with unpredictable long-term behavior. **Methods:** A 59-year-old Caucasian woman with no history of previous malignancies or comorbidities arrived at our institution with cough, increasing dyspnoea, and chest pain. A chest CT scan showed a giant intra-thoracic mass (25x16x16 cm) partially occupying the right hemithorax (fig.1A). Total body 18F-FDG/PET-CT showed a very inhomogeneous mass pattern, with necrotic areas and areas with various patterns of enhancement. A transthoracic FNAB revealed pulmonary SFTP. After cardio-respiratory complete assessment and tumor board evaluation, the patient underwent surgical excision of the mass en-bloc with right upper lobe by thoracotomy.



Results: Microscopically, the tumor showed solid spindle cells with high mitotic activity (5 mitoses/10 HPF), high Ki67 expression, and CD34, bcl2, and STAT6 positive. According to England's criteria, the diagnosis was indicative of a giant malignant SFTP, and the tumor had a Tapias score of 5, which indicated a high risk of recurrence. The postoperative course was uneventful, and the patient was discharged on 8th postoperative day. Due to R0 resection, no adjuvant radiotherapy or chemotherapy was administered, and a strict follow-up was conducted. After 72 months of follow-up, the patient experimented local pleural recurrences (fig.1B) traded with surgical excision in re-thoracotomy. The histopathological analysis showed eight lesions with a median diameter of 1.5 cm, microscopically composed by spindle cells with 10 mitoses/10 HPF, STAT6+, CD34+. Although R0 resection was achieved, adjuvant chemotherapy was administered. A genome sequencing with the next generation approach was performed on the primary lesion and the recurrent disease. **Conclusion:** SFTP is a rare neoplasm with unpredictable biological behavior. The surgical resection represents the gold standard if complete resection can be reached. The recently introduced Tapias score can be helpful to assess the risk of recurrence: a strict and long-term follow-up should be conducted in case of a high score (>3). In case of local relapse, surgical excision remains the best therapeutic option.

Keywords: solitary fibrous tumor of pleura, malignant SFTP, lung resection, surgery

P36.03 Rapidly Progressed Anaplastic Carcinoma in the Anterior Mediastinum Successfully Treated With Gene-Targeted Therapy

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Introduction: Tumors that develop in the anterior mediastinum include thymoma, thymic cancer, teratomas, and embryonic cell tumors. The majority of anterior mediastinal tumors are benign and often remain asymptomatic. We report a case of an anterior mediastinal malignant neoplasm with rapid progression in a matter of days . **Methods:** A 44-year-old man presented to the local hospital with chest pain, fever, and dyspnea on exertion. He had noticed left chest pain two weeks earlier, and subsequently, fever and respiratory distress developed. **Results:** Chest contrast-enhanced computed tomography (CT) revealed a mediastinal mass shadow and bilateral pleural effusion. He was referred and admitted to our hospital for further investigation. On physical examination, the neck was supple, without thyromegaly nor lymphadenopathy, and breath sounds were clear but decreased on the left. The thyroid hormone level was within the normal range, and no atypical cells were found in the peripheral blood smear. Repeated contrast-enhanced CT showed a 10-mm round low-attenuation area on the left lobe of the thyroid gland, and there were multiple flat mass shadows consisting of a heterogeneous concentration and showing a contrast effect on the margin in the anterior mediastinum. The mass had extensively infiltrated the cardiac sac. After admission, his pleural effusion increased, blood pressure decreased, and anemia progressed. On the fifth hospital day, the patient underwent video-assisted thoracoscopic surgery for biopsy of the anterior mediastinal mass. Immunohistochemical evaluation of the mediastinum-biopsy specimen revealed anaplastic carcinoma, whereas the primary site was not identified. After the surgery, he was placed on a high-flow nasal cannula, and the bilateral drainage of bloody pleural effusion was continued. Although his performance status was 4, the patient received triple therapy with carboplatin, nab-paclitaxel, and pembrolizumab, according to the treatment guidelines for non-small cell lung cancer; however, the tumors continued to increase in size. Multiplexed genetic sequencing panels of the tumor specimen revealed BRAF-V600E mutation positivity, and the patient initiated receiving dabrafenib and trametinib. After the treatment, the mediastinal tumor reduced in size, and his general condition improved in weeks. The patient was discharged with a prescription for dabrafenib and trametinib after 3 months of hospitalization. At a follow-up conducted 6 months after discharge, he was well, with no respiratory symptoms. **Conclusion:** We described a case of anterior mediastinal anaplastic carcinoma that had progressed rapidly. The combination of the detection of a BRAF-V600E mutation and gene-targeted therapy may have contributed to rescuing the patient with poor performance status.

Keywords: anterior mediastinum

P37.01 The Results of Multimodal Treatment With Extrapleural Pneumonectomy for Female Epithelioid Malignant Pleural Mesothelioma

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Introduction: Our first choice is extrapleural pneumonectomy (EPP) followed by hemithoracic radiation and chemotherapy for operable malignant pleural mesothelioma (MPM). If EPP is inappropriate, pleurectomy/decortication followed by chemotherapy is performed. Wolf and Sugarbaker, et al. reported that women with epithelial MPM treated with EPP demonstrated a survival advantage (Ann Thorac Surg. 2010. 90:949-956). Our results of multimodal treatment with EPP for female epithelioid MPM are presented. **Methods:** Among 60 consecutive EPP cases for MPM from 2006 to 2019, epithelioid type was 40 (67%), biphasic type was 15, sarcomatoid type was 2, and special variant was 3. Nine patients (Table) of female epithelioid MPM were reviewed retrospectively. The survival data were updated in March 2020. Overall survival from the treatment start was calculated using Kaplan-Meier method. **Results:**

Age at EPP	Side	p TN	p Stage	EPP time	EPP year	Prognosis: Period after EPP
51	L	T3N0	III	7 h	2007	Alive: 12 Y 11 M
58	R	T3N0	III	6 h	2011	Dead: 5 Y 11 M
68	R	T3N0	III	8 h 48 m	2011	Dead: 1 Y 4 M
58	L	T1bN0	Ib	5 h 52 m	2011	Dead: 5 Y 2 M
60	R	T3N0	III	6 h 43 m	2012	Dead: 5 Y 9 M
62	R	T1bN0	Ib	7 h 23 m	2012	Alive: 8 Y 3 M
46	R	T2N2	III	8 h 56 m	2015	Dead: 1 Y 4 M
60	L	T2N2	III	6 h 36 m	2016	Alive: 4 Y 4 M
57	L	T4N1	IV	6 h	2016	Dead: 1 Y 1 M

Median age at EPP was 58 years old (46 - 68). Right side was 5 cases, and left side was 4 cases. Median EPP time was 6 hours 39 minutes (5 h 52 m - 8 h 56 m). No blood transfusion during EPP was in 3 cases (33%). 90-day-mortality was zero, and no patient died less than one year after EPP. Regarding IMIG (international mesothelioma interest group) pathological TNM, T4N1M0 was in 1 case, T3N0M0 was in 4 cases, T2N2M0 was in 2 cases, T1bN0M0 was in 2 cases. IMIG p-Stage was IV in 1 case, III in 6 cases, and Ib in 2 cases. Pathologically, two station mediastinal lymph nodes were metastatic in 2 cases, and two station lung lymph nodes were positive in 1 case. Adjuvant 45-50.4 Gy hemithoracic radiation was completed for 9 patients (100%). Chemotherapy was given for 8 patients (89%). Postoperative median follow-up period was 8 years and 9 months (4 y - 12 y 11 m). Although many advanced cases were treated, the 5-year survival and median survival were 67% and 70 months. Five of nine patients survived longer than 5 years after EPP. The death causes were MPM in 4 patients, cerebral infarction in 1 patient, and influenza in 1 patient. **Conclusion:** The 5-year survival rate was 67%, and median survival time was 70 months. Although many advanced

cases have been treated, the results of this multimodal treatment with EPP for female epithelioid MPM are excellent, and there have been many long survivors.

Keywords: extrapleural pneumonectomy, female, malignant pleural mesothelioma

P37.02 Improving Outcomes in Malignant Pleural Mesothelioma in an Integrated Health System

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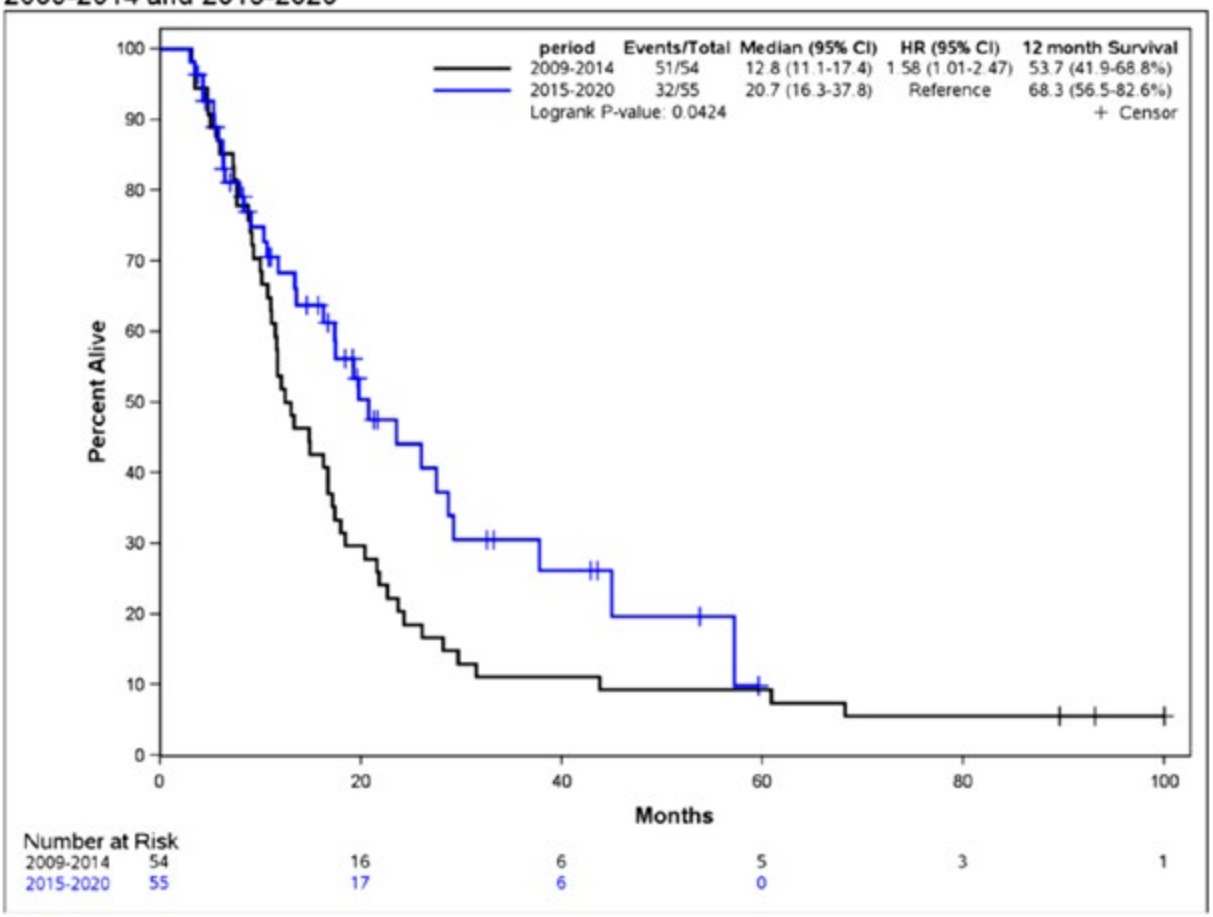
Introduction: Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor with an associated poor prognosis, median overall survival (OS) is 1 year, despite advances in treatment practices.1-4 NCCN guidelines recommend patients with MPM should be managed by a multidisciplinary team with experience in MPM management.5 Although there is no agreement on which surgical intervention is best,6-8 guidelines are consistent in recommending that surgeries be performed by skilled surgeons at high-volume centers.1 Improved outcomes due to regionalization of surgeries for patients with NSCLC has been demonstrated,9 but further evaluation of centralization of MPM surgeries has yet to be determined. **Methods:** Electronic medical records of 369 adult patients with MPM from 1/1/2009 to 12/31/2020 were reviewed and compared before (2009-2014) and after (2015-2020) MPM surgeries were regionalized to specialized surgeons and multidisciplinary review of MPM patient treatment options. We used the Kaplan-Meier method and log-rank tests to compare survival rates by period, by treatment type, and by stage. Patients were followed from cancer diagnosis date until they died or end of study follow-up, whichever occurred first. We also conducted Cox proportional hazards regression model to examine the overall survival with adjustments for age, gender, histology, stage, and Charlson Comorbidity Index (CCI). **Results:** Despite similar staging, more patients received any MPM directed treatment from 2015-2020 (n=127, 65%) compared with those patients from 2009-2014 (n=77, 45%) ($p<0.0001$). Specifically, there was an increase in patients who received pleurectomy/decortication (PD) from 2015-2020 (n=42, 21%) compared to those who received PD in 2009-2014 (n=6, 3.5%) (p=0.0001). Median survival in patients who received multi-modality treatment (surgery, systemic therapy, +/- radiation) during 2009-2014 was 16.7 months (95% confidence interval (CI), 10.8-34.8) compared to 5.7 months (95% CI, 4.0-9.2) in patients who received no treatment. From 2015-2020, median OS for patients who received multi-modality therapy was 23.5 months compared to median survival of 4.3 months in those who received no treatment. Landmark analysis showed a significant survival benefit in patients with early stage MPM from 2015-2020 compared to the 2009-2014 cohort with a median OS 20.7 months and 12.8 months, respectively (HR, 1.58; 95% CI, 1.01-2.47; p = 0.042) (Figure 1); while patients with advanced stage MPM showed no difference in survival between 2009-2014 and 2015-2020 cohorts (HR, 0.97; 95% CI, 0.71-1.32).

Figure 1. Survival of Patients with Early Stage (Stage I-II) Malignant Pleural Mesothelioma in 2009-2014 and 2015-2020



Conclusion: Consolidating mesothelioma surgery to specialized surgeons and regular multidisciplinary review of MPM cases to determine appropriate multimodality therapy improves OS in patients with MPM.

Keywords: Mesothelioma, Multi-modality treatment, regionalization

P37.03 The Epidemic of Malignant Mesothelioma in China: A Prediction of Incidence During 2016-2030

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Introduction: Since the increasing use of asbestos occurred in China and the long latency period after asbestos exposure, predicting the incidence of malignant mesothelioma are becoming more important for its prevention, diagnosis and treatment. A Bayesian age-period-cohort prediction model was fitted to predict the development trend from 2016 to 2030 based on the publicly available data of the national cancer registration network. **Methods:** The National Cancer Registration Network collects information on cancer cases from population-based cancer registries in China from the 1970s onwards. International Classification of Disease for oncology, version 10 (ICD10) was used to classify the cancer cases. Malignant mesothelioma incidence data were retrieved from the registration annual reports from 2005 to 2015. The Bayesian Age-Period-Cohort (APC) Modeling and Prediction package (Institute of Biomedical Engineering, Imperial College, London, UK) was used to describe the trend of malignant mesothelioma incidence and to predict the incidence rate and number of cases until the year of 2030. The classic APC model is often regarded as a log-linear Poisson model. The Bayesian hierarchical approach uses Gaussian random walk (RW) priors of different orders for the APC parameters. In our study, RW1 prior, which assumes a constant trend over the time scale, was used based on the assumption of a constant time trend, implying a stochastic restriction. Deviance information criterion (DIC value) was used to compare the fit degree of APC, AP and AC models. **Results:** The full three-factor model (age-period-cohort) was in turn significantly better than the two-factor AP and AC models. The DIC of the APC model was 74.01, indicating a good fit of the model, compared with other sub-models (79.13 for AC, 75.61 for AP, respectively). The crude incidence of malignant mesothelioma decreased from $0.22/10^5$ in 2005 to $0.16/10^5$ in 2015. After age standardization, the incidence remained stable over the 11-year period. The Bayesian APC model showed the total incidence increased from $0.14/10^5$ in 2016 to $0.19/10^5$ in 2030. The age-standardized incidence would remain steady. Considering the different distribution of malignant mesothelioma with respect to sex and age, we predicted the crude incidence rates stratified by the two factors. The incidence of male increased from $0.15/10^5$ in 2016 to $0.21/10^5$ in 2030, and those of female showed the same trend ($0.13/10^5$ in 2016 and $0.17/10^5$ in 2030). The details of incidence stratified by sex and age were showed in Table 1 and Figure 1. Furthermore, the estimated number of new incident cases was predicted to increase to 2775 in 2030 of which, 1554 would be male. **Conclusion:** The incidence of malignant mesothelioma would remain stable in the next ten years, but due to its high degree of malignancy, prediction of the incidence of malignant mesothelioma in this study will be of immediate value to call for clinicians' attention, so as to help in the prevention and control of the disease in high asbestos consumption area.

Keywords: malignant mesothelioma, prediction model, incidence

P38.01 p40 and p63 Immunohistochemistry in the Diagnostic Consideration of NUT Carcinoma in the Lung

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Introduction: NUT Carcinoma of the lung is an undifferentiated/poorly differentiated carcinoma characterized by a gene rearrangement in nuclear protein in testis (NUTM1); it has a monomorphic appearance, discrete nucleoli, infiltrating polymorphonuclear cells (PMN) and areas of abrupt keratinization. Immunohistochemical (IHC) staining shows the following profile: anti-NUT with a speckled pattern (>50% of the tumor cells), positive for cytokeratin, occasional staining for chromogranin/synaptophysin and most are p63/p40 positive due to presumed squamous lineage. Since NUT carcinoma usually presents at an advanced stage, it can be diagnostically challenging due to small sample size and/or biopsy related artifacts (crushing) that may raise a wide differential diagnosis and require an extensive IHC work up. Correct classification of NUT carcinoma is essential, since current chemotherapeutic agents are largely ineffective for NUT carcinomas.
Since p40 is superior to p63 in the discrimination of squamous from non squamous lung carcinomas, p40 immunohistochemistry has supplanted p63 in the work up of lung carcinoma. However, a previous study(1) and a case report(2) indicate that NUT carcinoma may be p40 negative while being p63 positive, suggesting that when NUT carcinoma is considered in the differential of a lung carcinoma, inclusion of p63 staining may be helpful. **Methods:** A series of three consecutive cases of NUT carcinoma of the lung were analyzed immunohistochemically for cytokeratin, p40, p63, chromogranin, synaptophysin, and TTF1. All three carcinomas underwent clinical testing for NUTM1 rearrangement by either fluorescent in situ hybridization or next generation sequencing. **Results:** The patients consisted of two men and one woman (age range 64-71). Two were never smokers and one was a former light smoker who quit three decades prior to diagnosis, and all had stage IV disease by PET scan. All patients had some neuroendocrine morphology that led to the consideration of either a large neuroendocrine carcinoma or small cell carcinoma, and all tumors were characterized by the presence of tumor infiltrating PMNs. All patients were negative for p40, two patients were p63 negative, two patients had neuroendocrine differentiation by synaptophysin, and two patients had scattered TTF1 positivity. All patients were NUT immunohistochemistry (3/3) and translocation positive. **Conclusion:** Here we report three consecutively diagnosed NUT carcinomas for which NUT carcinomas was initially excluded from the differential due to lack of squamous differentiation (negative p40 staining), but with additional work up NUT carcinoma was diagnosed. This series of three cases indicates that NUT carcinomas of the lung should not be excluded on the basis of negative p40 staining and that p63 staining may be helpful when considering the diagnosis of NUT carcinoma. Potential diagnostic indicators for a NUT carcinoma in a carcinoma with p40 negative/p63 positive or p40 negative/p63 negative phenotype may be the presence of infiltrating polymorphonuclear cells, scattered TTF1 positive cells, and no to light smoking status.

1) Tilson, M.P., Bishop, J.A.. Head Neck Pathol. 2014. 8:141-5.
2) Yatabe, Y., Kashima, J., Matsuda, K. Journal of Thoracic Oncology. 2020. 15(10)E176-178.

Keywords: NUT carcinoma, Immunohistochemical studies, Differential diagnoses

P38.02 The Prognostic Role of Neutrophil to Lymphocyte Ratio (NLR) In Lung Metastasectomy for Colorectal Cancer: A Meta-Analysis

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Introduction: Inflammation represents a hallmark of cancer. Neutrophil to lymphocyte ratio (NLR) is correlated to patients' inflammatory status and has been proposed as a promising biomarker in different types of cancer. In the same context, prognostic markers are still limited to define good candidates for lung metastasectomy for colorectal cancer (CRC). We reviewed the available literature on patients with CRC lung metastases undergoing surgery to evaluate the potential association between preoperative NLR and long-term prognosis. **Methods:** We identified original studies that compared the long-term outcomes between groups with elevated and lower levels of baseline NLR, from 1990 to 2021. The overall survival (OS) was the primary endpoint. The 3-,5-year survival and the 1-,3-year disease free survival (DFS) were the secondary endpoints. Both a fixed and a random effect model were used appropriately. The Q statistic and I^2statistic were used to assess the heterogeneity among studies. **Results:** Four articles met the inclusion criteria (kappa=0.906; 95% CI: 0.801, 1.000), incorporating 865 patients. The OS was significantly increased in the low NLR group (Weighted Mean Difference - WMD:-30.54 [95% Confidence Intervals - 95% CI:-41.50, -19.58]; p<0.001). Patients in the lower NLR group demonstrated a significantly higher survival at three years postoperatively (Odds Ratio - OR: 0.23 [95% CI:0.06, 0.96]; p=0.04). No significant difference was found regarding the 5-year survival and the 1-year DFS. Patients in the lower NLR group presented a significantly higher DFS at 3 years postoperatively (OR: 0.21 [95% CI: 0.07, 0.64]; p=0.007). **Conclusion:** Our outcomes indicate that NLR is a simple and feasible predictor of outcomes in patients undergoing lung metastasectomy for CRC. Future studies with greater study populations and longer follow-up are necessary to fully uncover the potential value of NLR implementation in clinical practice.

Keywords: lung metastasectomy, neutrophil-to-lymphocyte ratio, lung metastases

P39.01 Long-Term Outcomes and Characteristics of Unresectable Locally Advanced Thymic Malignancies

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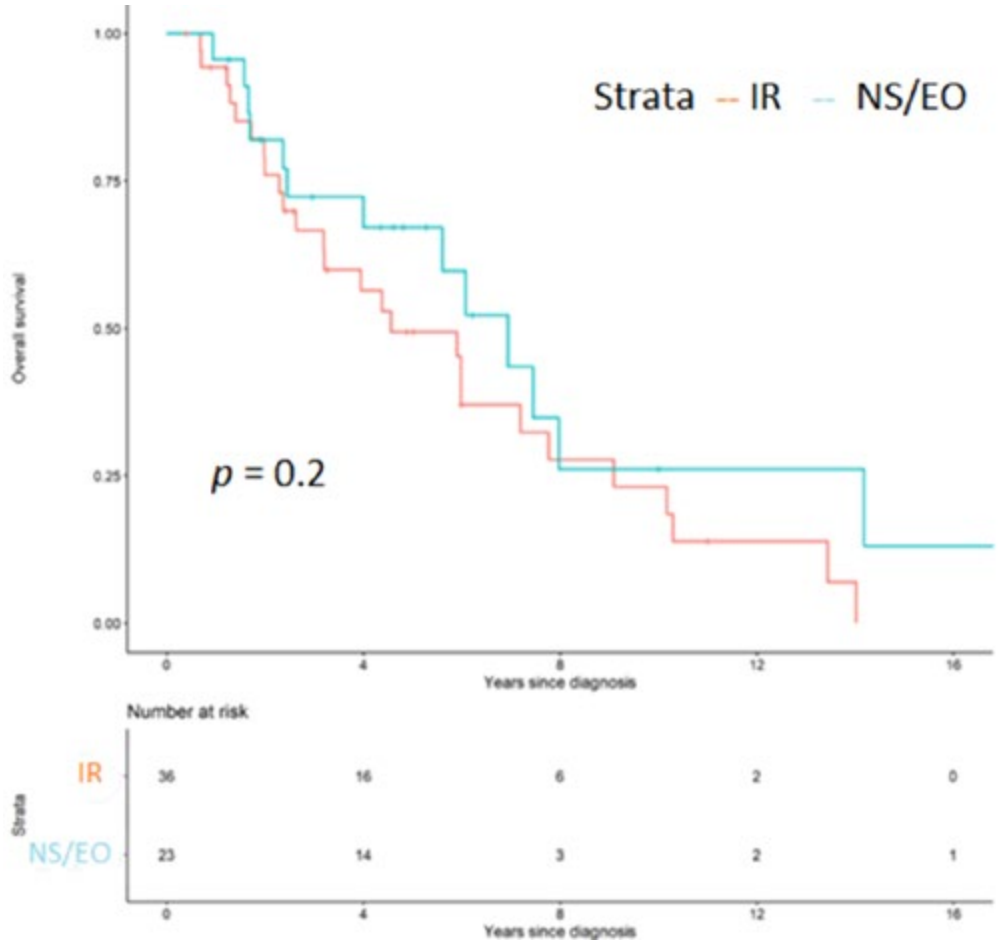
Introduction: Surgical resection of patients with thymic malignancies with extensive local invasion can be challenging, and the benefit resulting from an incomplete resection is unclear. We sought to define the characteristics, treatment approaches and reasons for unresectability in patients with localized, unresectable thymic tumors and analyze their long-term outcomes **Methods:** Retrospective review of patients with localized, unresectable thymic tumors treated at our institution between 1996-2019. Patients who had surgical exploration only without any resection, surgical exploration with incomplete (R2) resection, and patients who were deemed unresectable and treated non-operatively were included in the study cohort. We analyzed demographics, radiographic findings, pathology, treatment details, and patterns of progression and survival. Descriptive statistics and Kaplan-Meier survival analyses were performed **Results:** Fifty-nine patients were treated over the study period, 32 with thymoma (54%), 23 with thymic carcinoma (39%) and 4 with thymic carcinoid (7%). Almost all patients were TNM Stage III or IV. Nine patients (15%) were treated non-surgically (NS) and underwent definitive radiation therapy or chemoradiotherapy alone, 14 (24%) patients had surgical exploration only (EO) without resection, and 36 (61%) patients had surgical exploration with incomplete resection (IR). Among the patients who were explored (EO and IR), the most common intraoperative finding was invasion of great vessels or the myocardium (66%), disseminated pleural or lung metastases (14%), or both local invasion and intrathoracic dissemination (14%). Among the NS group, patients were deemed unsuitable for surgery due to the presence of unresectable metastases (22%), great artery involvement (56%), great vein involvement (11%), or severe comorbidities (11%). Forty-one patients (69%) developed progression (31 loco-regional; 10 distant) while 18 patients (31%) had stable disease during the observation period. Patients with unresectable thymoma had significantly longer overall survival (OS, p=0.02) compared to thymic carcinoma (median OS thymoma = 7.5 years; thymic carcinoma = 3.2 years). There was no significant difference in OS (p=0.2; Figure) or PFS (p=0.1) between IR and NS/EO patients. The median OS for IR patients was 4.6 years and 6.9 years for NS/EO patients. The median PFS was 0.8 years for patients in the IR group, and 1.6 years for those who had no resection (NS/EO)



Conclusion: Despite the presence of unresectable locally advanced disease, patients with advanced thymic malignancies exhibited long-term survival regardless of the primary treatment modality. In our series, patients who underwent incomplete surgical resections did not appear to fare any better than patients who underwent exploration only or non-operative treatment

Keywords: thymus, unresectable

P39.02 Does Neo-Adjuvant Chemotherapy Help in Locally Advanced Thymic Maliganancy?

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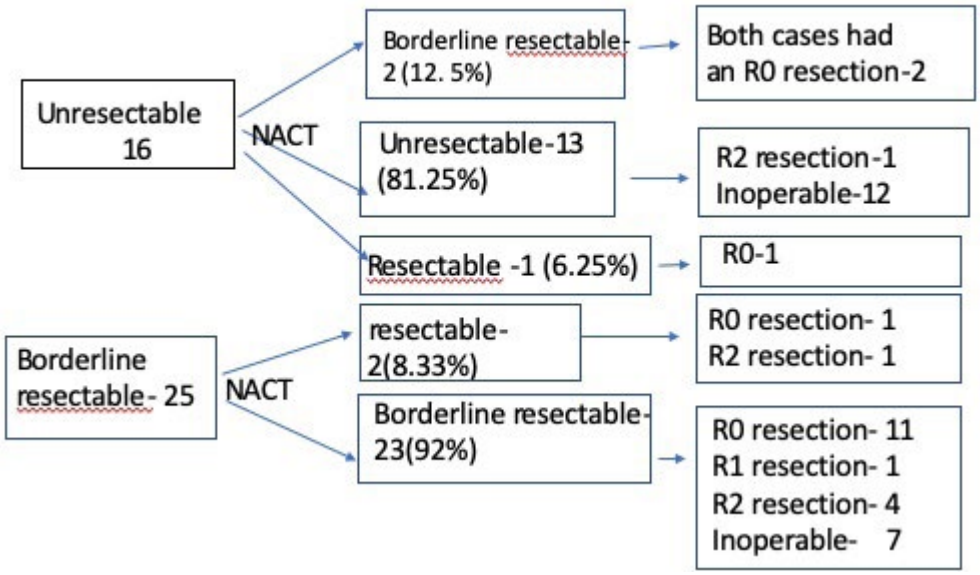
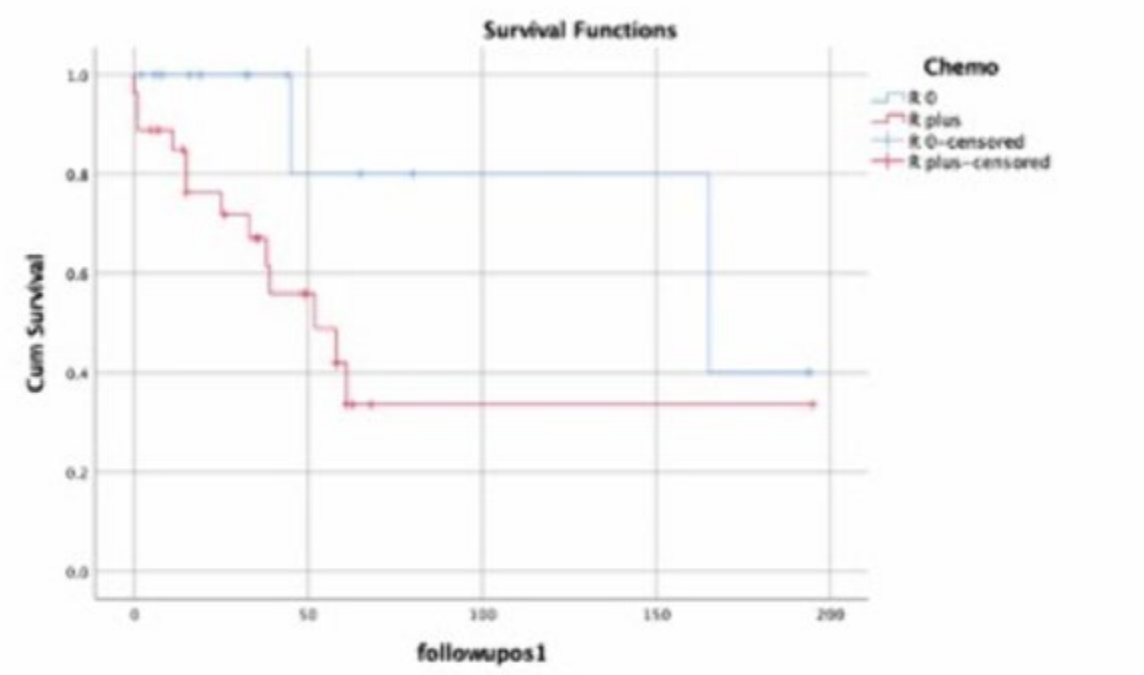
Introduction: Neoadjuvant chemotherapy is used to downsize thymic malignancies and improve R0 resection. However, there is no level I evidence for this. Here, we present our experience with neoadjuvant chemotherapy for locally advanced thymomas from a tertiary cancer center in India. **Methods:** This is a retrospective analysis of a prospective database. (Jan05 to Dec20) We included the following patients receiving neoadjuvant chemotherapy: Unresectable: Involving aortic arch / branches, main pulmonary trunk, heart Borderline Resectable: Involving SVC, brachiocephalic vein, main PA / branches, lung parenchyma Volumetric analysis was done using "ellipsoid" method for tumor volumes. Survival analysis was performed with Kaplan Meier method.

Results:



Forty-one patients received neoadjuvant chemotherapy. At presentation, 16(41.5%) were unresectable, 25(56.1%) were borderline resectable. Most common structures at risk were arch aorta and branches(31.7%), SVC(24.39%) and main Pulmonary Artery(19.51%). Average tumor volume was 655.75cm^3(90.45 – 4212.0) Good proportion of patients completed the planned chemotherapy(90.24%). However, only 56.1% came up for surgery. 4 progressed, 2 died due to chemotherapy related toxicity, 3 refused surgery and 9 remained unresectable. 12.5% of unresectable tumors and 44.0% of borderline tumors underwent R0 resection. 3/41 patients had complications Clavien-Dindo 3b and above with 1 mortality. The best volume reduction was seen in thymoma B2(54.84%) and thymic carcinomas(42.02%). At a median follow up of 34 months, 3 patients had local and 2 had systemic recurrences. Patients with R0 resection did significantly better than those with R+ resections or found unresectable. (p=0.03)



Median OS

R0- 165 months
R plus- 52 months

p-value -0.03 (significant)

Conclusion: R0 resectability remains the most important predictor of survival in thymic neoplasms. Neoadjuvant chemotherapy introduces the possibility of R0 reaction in unresectable tumors and should be strongly considered. In borderline resectable tumors, neoadjuvant chemotherapy affords a higher rate of R0 resection with less complex resections and minimal morbidity. This finding should be further evaluated in prospective multi centric studies

Keywords: thymoma, neo adjuvant chemotherapy, large mediastinal masses

P39.03 Primary Mediastinal Germ Cell Tumors: A 15-Years Experience Treatment in Rajavithi Hospital, Thailand

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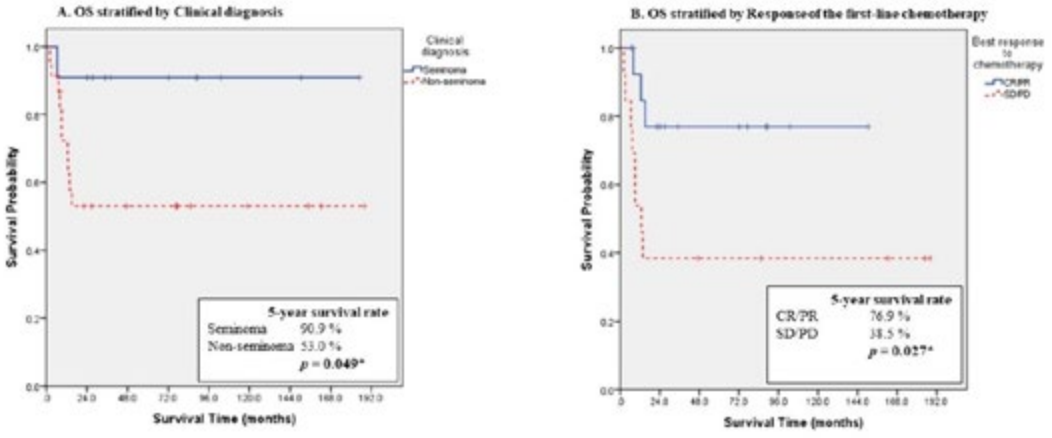
Introduction: Primary mediastinal germ cell tumors (PMGCT) are rare. They have a different behavior, and natural course compared to their gonadal counterparts. The objectives of this study were to characterize the clinical and biologic features of these tumors and to determine the overall outcomes with currently available treatment strategies. **Methods:** We retrospectively evaluated all patients who were diagnosed as primary mediastinal GCT between January 2004 and June 2019 in the Oncology Unit, Rajavithi hospital. Clinical characteristics, staging, treatment, and outcomes were collected and analyzed. **Results:** PMGCT were identified in 34 patients: 85.3% male with a median age 21 years (range, 15-44 years), 85.3% with ECOG performance status of 0 to 1. Thirty-two patients were diagnosed by histopathology included 10 seminoma, 14 non-seminoma, and 8 mixed GCT. Nine patients (26.5%) had distant metastases and the common metastatic sites were lung and liver. Treatment consisted of platinum-based chemotherapy in 30 patients (88.2%), surgery in 18 patients (52.9%), and radiation in 17 patients (50.0%). The combined treatment modalities were given in 22 patients (64.7%). The two most common first-line chemotherapy regimens were BEP (bleomycin, etoposide, and cisplatin) and VIP (etoposide, ifosfamide and cisplatin). The overall response rate to first-line chemotherapy was 53.6%, included a complete response rate of 7.2% and a partial response rate of 46.4%. After a median follow-up of 31.2 (2-188) months, 23 (67.6%) patients remain alive. Median overall survival (OS) was not reached with OS rate at 5-year being 66.1%. A significantly lower OS was found in non-seminoma compared with seminoma patients (5-year OS: 53.0% vs. 90.9%, p=0.049). Response to the first-line chemotherapy was the only significant (p = 0.0042) prognostic factor on multivariate analysis

Kaplan-Meier plot of overall survival in primary mediastinal germ cell tumor patients, stratified by

A. Clinical diagnosis

B. Response of the first-line chemotherapy



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Conclusion: The treatment results of our patients with PMGCT are comparable to those of Western countries. The platinum-based chemotherapy remains the standard of which systemic therapy is indicated and multimodality treatments are necessary. Prospective trials with multicenter, and new treatment approaches to improve outcome are required.

Keywords: mediastinal germ cell tumor, prognosis, survival

P39.04 Thymic Epithelial Tumors: The Importance of Invasive Investigation to Adequate Diagnosis

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Introduction: Thymic epithelial tumors (TET) are the most common neoplasms of the anterior mediastinum. The incidence of this disease is extremely low, and there is little data on the Brazilian context. This study aims to describe the experience from PUCRS's Sao Lucas Hospital Thoracic Surgery team on mediastinal tumor resections (MTR) during the investigation of TET. **Methods:** The Thoracic Surgery team from PUCRS's Sao Lucas Hospital maintains a prospective database with the Brazilian Thoracic Surgery Society. Data from patients who underwent investigation for TET within 2016 and 2020 were collected from medical records in March 2021. Descriptive analyses were performed on this data. We used the classification proposed by the World Health Organization (2004) to classify all cases found. **Results:** There were 90 MTR performed on a total of 87 patients between 2016 and 2020. Of these, 56 (64.36%) were female, and the average age was 54.28. Among performed MTR, 11 (12.22%) were due to TET, being 10 (11.11%) by thymoma and 1 (1.11%) by thymic carcinoma. From the 10 cases of thymoma, 7 (70%) were female, and the only patient diagnosed with thymic carcinoma was male. Of the 11 patients diagnosed with TET, the average age was 56. According to the TET classification used, 1 (9.09%) was type A, 5 (45.45%) was AB, 1 (9.09%) was B2, 1 (9.09%) was B3, 1 (9.09%) was C (thymic carcinoma was classified as type C), 1 (9.09%) classified as types B1 and B2, and another (9.09%) as types AB and B3. Among 10 cases of thymoma, 2 (20%) had myasthenia gravis (MG). Immediate postoperative mortality was zero. During yearly follow-up, only 1 (9.09%) patient had a recurrence of disease, and 1 (9.09%) died. It is important to highlight that from all 90 MTR performed, 80 (88.88%) occurred between 2016 to 2019 (18 in 2016, 16 in 2017, 21 in 2018, 25 in 2019), resulting in an average of 20 RTM per year. However, in 2020, only 10 (11.11%) RTM were performed, showing a significant reduction during the first year of the COVID-19 pandemic in Brazil. **Conclusion:** Our data converge to what is shown in the literature since a small portion of patients who underwent MTR had a thymoma diagnosis and only one had a diagnosis of thymic carcinoma. The most frequent type was AB. Studies demonstrate that 30-65% of patients with thymoma also have MG. On the other hand, our sample shows 20%. It is essential to emphasize the reduction in the number of procedures during the Sars-CoV-2 pandemic in 2020.

Keywords: thymic carcinoma, thoracic malignancies, thymoma

P39.05 Outcomes of Videothoracoscopic Thymectomy for Treatment Large-Sized Thymomas

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Introduction: Video-assisted thoracoscopy (VATS) is widely used in the treatment of mediastinal tumors. However, thymectomy (TE) performed through a median sternotomy remains the gold standard for treating large thymomas. The aim of this study is to improve the outcomes of treatment for large thymomas using VATS TE **Methods:** A retrospective analysis of 82 patients with early stages of thymomas who underwent surgical treatment in our department from 2002 to 2019 was carried out. The main group included 35 patients after VATS TE (group 1) for thymomas >5 cm. The control group (group 2) included 24 patients with large thymomas who underwent open thymectomy (OTE). Group 3 included 23 patients after VATS TE with thymomas <5 cm. A comparative analysis of immediate and long-term results between these groups was carried out. **Results:** Compared to OTE, VATS TE was characterized by a decrease in operative blood loss (258.6±149.2 versus 80.5±70.6 ml; p=0.001), postoperative complications (20% vs. 58%; p=0.005), reduced of the chest tube duration (3.1±2.2 vs. 1.6±1.1 days; p<0.001) and total time of hospital stay (12.7±5.5 vs. 7.6±4.1 days; p<0.001).The median duration of the follow-up was 59 months (8-202 months). There was no significant difference between these groups in terms of the overall survival (p=0.293) and recurrence-free survival (p=0.752). Masaoka stages, WHO histologic subtype but not thymoma size, were an independent prognostic factor for recurrence-free survival. **Conclusion:** Video-assisted thoracoscopic thymectomy is an effective and safe operation for large-sized thymomas, which, in comparison with open approach, is characterized by a decrease in blood loss, complications, duration of drainage and hospitalization with comparable results in overall and recurrence-free survival.

Keywords: video-assisted thoracoscopy, thymoma, thymectomy

P40.01 Maintenance Anlotinib After Induction Therapy With Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer: A Phase 2 Study

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Introduction: Patients (pts) with advanced non-squamous non-small-cell lung cancer (NSCLC) benefit from pemetrexed maintenance therapy after induction therapy with platinum-based chemotherapy. However, Pemetrexed needs to be given intravenously, and it has more serious and high incidence of side effects such as bone marrow suppression, rash and so on. This is the first trial to assess anlotinib as maintenance therapy after induction therapy with platinum-based chemotherapy in advanced NSCLC. **Methods:** Pts with stage IIIB or IV disease who had not progressed on four to six cycles of platinum-based chemotherapy, with at least one measurable lesion, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 participated. Eligible pts received maintenance therapy with anlotinib monotherapy (12 mg per day, per os; day 1–14; 21 days per cycle) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety profile. Clinical trial information: NCT03769805. **Results:** Between August 2019 and December 2020, 22 pts were enrolled from 7 centres. The median age was 63.5 years with 72.7% male. 50% pts were ECOG performance status (PS) 1. 18.2% had stage IIIB disease; 36% pts were non-squamous tumors. As of 19 Mar 2021, median follow-up was 16.1 months (range, 2.6-24.4), median PFS was 6.0 months (95%CI: 5.5-6.5). 1 pt achieved partial response ,19 had stable disease and 2 had disease progression. The ORR and DCR were 4.5% and 90.9%, respectively. Most common adverse events (AEs) were hypertension (50.0%), decreased platelet count (36.4%), hypercholesteremia (31.8%) and hypertriglyceridemia (22.7%). Grade≥3 AEs occurred in 22.7% pts (5/22 pts), such as hypertension (9.1%), gamma-glutamyltransferase elevation (4.5%). No grade 4/5 AEs were observed. **Conclusion:** Anlotinib appeared to have significant efficacy and favorable safety profile as maintenance therapy in pts with platinum-based chemotherapy for advanced NSCLC. Further study with larger sample size is warranted.

Keywords: maintenance therapy, Anlotinib

P40.02 Pemetrexed in Advanced-stage Lymphoepithelioma Carcinoma of Lung

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Introduction: Lymphoepithelioma Carcinoma of Lung former pulmonary lymphoepithelioma-like carcinoma) is a rare primary lung cancer, which was a subtype of large-cell lung cancer and other and unclassified carcinomas in third and 4th edition WHO classification of tumors, respectively. In the new 5th WHO classification, lymphoepithelioma carcinoma of lung is classified as a subtype of squamous cell carcinoma. As we all known, Pemetrexed isn't recommended for squamous cell carcinoma. However, little is known about the role of pemetrexed in treatment of advanced-stage lymphoepithelioma carcinoma of lung. **Methods:** From January 2008 to December 2020, we retrospectively analyzed patients who were diagnosed as stage C-lymphoepithelioma carcinoma of lung and received pemetrexed alone or combination with cisplatin/ carboplatin or checkpoint inhibitor in Guangdong Lung Cancer Institute. **Results:** A total of 23 patients were included in this study. The majority of patients were female (14/23,60.9%). The median age was 49 years (range 13 to 76 years old). All of patients were EGFR wild type. Among the 10 patients who received first-line pemetrexed alone (2) or combination with cisplatin/ carboplatin (3) or checkpoint inhibitor (5), the response and stable disease (SD) was observed in 2(20%) patients and 7(70%) patients, respectively. In second-line or more treatment, pemetrexed alone achieved stable disease and progress disease in 5 patients (42.7%), 7 patients (57.3%), respectively, except for one patient didn't received CT scan for assessing response. After median 19.3 months follow-up, PFS and MST in first line and second line or more line were6.8, 36.6, and 2.8, 18.9 months, respectively. **Conclusion:** Although lymphoepithelioma carcinoma of lung is classified as subtype of squamous cell carcinoma in 5th WHO classification of lung tumors, pemetrexed showed moderate response in advanced stage disease and warrant further study.

Keywords: Pemetrexed, Lymphoepithelioma Carcinoma of Lung, 5th WHO classification of tumors

P40.03 Palliative Radiotherapy Decreased Circulating White Blood Cells in Patients With Stage IV Lung Cancer

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Introduction: Radiotherapy plays an important role in the treatment of lung cancer, which kills cancer cells, but also damages normal structures including white blood cells in the circulation. The purpose of this study is to 1) exam whether circulating white blood cells change after radiotherapy, 2) study whether radiation dose is associated with reduction in circulating white blood cells, and 3) explore the relationship between the changes in circulating white blood cells and overall survival and quality of life (QOL). **Methods:** This is part of prospective pilot study. Patients with stage IV lung cancer treated with palliative radiotherapy were eligible. The variables of our interest included gender, age, stage, pathology, radiation dose, and complete white blood counts including lymphocyte, neutrophil, monocyte, and basophil. The differences of white blood cells before and after radiotherapy were calculated. Associations between radiation dose, QOL PROMIS-29 Profile v2.1, and survival were analyzed. Statistical significances were tested using paired t-test. Disparities in patient survival were analyzed by multivariate Cox regression models. Multivariate correlation analysis was performed using Pearson models. Ps less than 0.05 were significant. Data are presented as mean (95% confidence interval) unless otherwise specified. **Results:** A total of 80 patients enrolled, 43 patients (enrolled September 2019 to September 2020) with minimum follow-up of 6-months were included in this study. There were 30 males and 13 females, aged from 39 to 85 years. The 6-month survival rates were 77% (10/43) for patients. Paired t-test showed that total counts of lymphocyte, neutrophil, monocyte, and basophil all decreased significantly after radiation (data shown in table, All P<0.05). The radiation dose, ranged 20-60 Gy/3-30Fr, was significantly and linearly correlated with the reduction in absolute lymphocyte count , percentage lymphocyte reduction and percentage neutrophil increase during RT (r=0.53, P=0.001; r=0.41, P=0.01, r=-0.35, P=0.04, respectively). The percentage reduction in lymphocyte count from the baseline was significantly associated with the sociability (P=0.03) of QOL. The decreased lymphocyte absolute value was significantly associated with pain intensity (P=0.03) of QOL. Monocyte/lymphocytes ratio was significant for overall survival (HR=5.5, 95% confidence interval 0.91-33.40,P=0.04). **Table 1**

	Paired t-test			**Overall survival**		**QOL**	
	Before radiotherapy	**After radiotherapy**	**P**	**HR**	**P**	**Sociability**	**Pain intensity**
LYM	1.56±0.69	0.84±0.58	<0.001	1.25(0.23, 6.80)	0.9	0.26	0.03
LYM%	26.84±11.86	15.30±9.24	<0.001	-	-	0.03	0.20
NEUT%	61.64±14.33	74.18±12.83	<0.001	4.74(0.86, 25.99)	0.05	0.61	0.5
MON	0.59±0.31	0.44±0.23	0.02	3.60 (0.72, 18)	0.1	0.76	0.21
BASO	0.02±0.01	0.01±0.01	0.01	-	-	0.87	0.34
MON/LYM	0.43±0.31	0.65±0.45	0.01	5.50(0.91, 33.40)	0.04	-	-

Conclusion: This study demonstrated that palliative radiation can significantly decrease the counts of circulating white blood cells in patients with stage IV lung cancer. It is interesting to note that the ratio of monocytes to lymphocytes reduction after radiotherapy may predicted an unfavorable survival, and lymphocyte has significant impact on QOL, including measures in sociability and pain intensity.

Keywords: Palliative radiotherapy, stage IV lung cancer, Circulating white blood cells

P40.04 CNS Adverse Events and Survival in Patients with NSCLC Brain Metastases Treated With Concurrent Radiation and Immunotherapy

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Introduction: Immune checkpoint inhibitors (ICIs) are an essential component of metastatic non-small cell lung cancer (NSCLC) treatment. Metastatic NSCLC patients frequently develop brain metastases requiring treatment with CNS radiation therapy (CNS-RT). Prospective data on safety and outcomes with overlapping immunotherapy and CNS-RT is lacking. Retrospective studies have reported safety in this population with no increased risk of radiographic events of hemorrhage or radionecrosis. We completed a retrospective review to evaluate rates of clinically significant CNS adverse events (CNS-AEs) and OS in those receiving CNS-RT with and without concurrent ICI use. Our group previously presented data suggesting increased risk of AEs (ASCO 2018, abst# 2010). This analysis expands the sample size to evaluate impact on survival and uses statistical modeling methodology to account for patients with multiple RT events. **Methods:** We identified patients with NSCLC and brain metastases treated with CNS-RT at our institution from 2010-2017. Concurrent treatment with ICIs and CNS-RT was defined as ICI use within 3 months before or after CNS-RT. Clinically significant CNS-AEs were defined as new or worsening CNS edema without disease progression, new or worsening neurologic deficit, or need to start or increase corticosteroids. Cox proportional hazards models were used to implement time to CNS-AE and OS analyses, adjusting for concurrent use of ICIs as a time-varying covariate. A repeated events approach for modeling time to CNS-AE was used to account for correlated data among patients with multiple CNS-AEs. **Results:** We identified 158 patients with 242 cases of CNS-RT (72% GKRS, 28% other). Median RT treatments per patient was 1 (range 1-5). Patients were 54% female with median age 61 years at diagnosis, and ECOG 0-2 in 87% at time of CNS-RT. There were 16 cases of concurrent ICI exposure with CNS-RT, and 226 cases of CNS-RT without concurrent ICI exposure. Median follow-up from time of CNS-RT was 54.2 months. Twenty-two percent of patients experienced a CNS-AE at any time, and 16.5% of CNS-RT events (40 of 242) were followed by CNS-AE, including 4 (25%) in the concurrent exposure group and 36 (15%) in the non-concurrent exposure group. Median time to develop CNS-AEs was 2.5 months. When comparing the concurrent vs non-concurrent groups, there was no significant difference in CNS-AEs (HR 1.62, 95% CI 0.60-4.35, p=0.34). Model predicted median OS was 10.8 months for patients with concurrent ICI and 12.5 months without concurrent ICI (HR 0.87, 95% CI 0.48-1.58, p=0.64). **Conclusion:** Concurrent ICI use with CNS-RT was not associated with a significant difference in clinically significant CNS-AEs. OS was similar in those receiving ICIs within 3 months of CNS-RT and in those who did not, indicating there is no detriment or advantage to timing of ICI use in patients with brain metastases requiring radiation. However, a non-statistically significant trend is seen towards increased CNS AEs and worse OS in those receiving concurrent ICI with CNS-RT, raising the possibility that this study was not adequately powered to detect statistically significant differences.

Keywords: CNS radiation therapy, immunotherapy, brain metastasis

P40.05 Radiation-Related Platelet Reduction in Patients With Stage IV Lung Cancer

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Introduction: Platelet plays an important in multiple stages of cancer progression, cancer prognosis and treatment decisions. Many studies reported the prognostic significance of platelet or platelet/monocyte ratios at baseline in non-small cell lung cancer. The purpose of this study is to 1) exam whether radiotherapy reduces platelet, 2) study whether there is radiation dose associated with platelet decrease, and 3) explore the relationship between the reduction of platelet and overall survival and quality of life (QOL) in patients with metastatic lung cancer. **Methods:** This is part of a multicenter prospective study with close monitoring of quality of life and biomarkers. Patients with stage IV lung cancer patients treated with palliative radiotherapy were eligible. The variables of our interest included gender, age, stage, pathology, radiation dose, and platelet. The absolute differences of platelet, before and after radiotherapy were calculated. Associations between radiation dose, QOLPROMIS-29 Profile v2.1, and survival were analyzed. Data are presented as mean (95% confidence interval) unless otherwise specified. Statistical significances were tested using paired t-test. Disparities in patient survival were analyzed by multivariate Cox regression models. Multivariate correlation analysis was performed using Pearson models. Ps less than 0.05 were significant. **Results:** A total of 80 patients enrolled, 43 patients with a minimum follow-up of 6 months were included in this analysis. All have stage IV lung cancer, 39 non-small cell lung cancer. There were 29 males and 13 females, with median age of 63 years (range 39 to 85 years). Paired t-test showed that platelet decreased significantly after radiotherapy (233.49, 95%CI: 193.11-282.73; 185.31, 95%CI: 145.29-225.32, P=0.002), though the absolute number in reduction is limited. The total radiation dose, ranged 20-60 Gy/3-30 fxs, was significantly and linearly correlated with the reduction in platelet during RT (r=0.47, P=0.005). Interestingly, the decreased of platelet was significantly associated with the increased T-score of depression (r=0.38, P=0.04) and pain intensity (r=0.48, P=0.009) of QOL after radiation, but not significantly associated with overall survival at 6 months. **Conclusion:** This study demonstrated that palliative radiation can significantly decrease platelet. It is interesting to note that platelet reduction during radiotherapy also has significant impact on QOL, including measures in depression and pain intensity. In addition to validate these findings, future study shall take platelets into consideration.

Keywords: radiotherapy, stage IV lung cancer, platelet

P40.06 A Real-World Study: Efficacy and Safety of Anlotinib for Advanced Non-Small Cell Lung Cancer

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Introduction: Anlotinib is an oral novel receptor tyrosine kinase (RTK) inhibitor and targets multiple RTKs including VEGFR, PDGFR, FGFR, and c-kit, which has been approved as a third-line therapy for patients with advanced NSCLC by CFDA in May 2018 due to its high efficacy and low side effects in ALTER 0303 trail. Phased data from multiple studies of anlotinib report its clinical efficacy and safety, but its real-world data are scarce, and the efficacy of patients in real clinical practice is affected by many factors. This study aims to observe and explore the efficacy and safety of anlotinib in patients with advanced non-small cell lung cancer in the real world, and to summarize the treatment experience of a broad population. **Methods:** This study is a non-interventional, prospective, multi-center observational study of real world cases and all registered data are collected from real clinical practice cases. Adult patients diagnosed as advanced non-small cell lung cancer and treated with anlotinib were included. The primary endpoint was progression-free survival (PFS) and the secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. **Results:** As of March 15, 2021, a total of 186 patients were enrolled, of whom 174 were evaluable, with a median age of 62 years, including 112 males (64.4%) and 62 females (35.6%). There were 27 (15.5%) patients with brain metastasis, 39 (22.4%) patients with bone metastasis, and 11 (6.3%) patients with liver metastasis at baseline. 17 cases (9.8%) received anlotinib as firstline treatment and 35 cases (20.1%) as second-line treatment, whereas 122 cases (70.1%) as third-line or beyond treatment. Subgroup analysis showed that the PFS and OS of second-line treatment were 6.5 months and 16.9 months respectively, and for third-line or later treatment were 4.4 months and 12.2 months, respectively. In patients with third-line or beyond treatment, the PFS and OS were 4.6 months and 13.3 months in anlotinib monotherapy, whereas 4.3 months and 8.0 months in combination therapies. 42 patients (24.1%) had any grade of adverse events, of which 10 patients (5.7%) had grade 3 or above AEs, and 4 patients (2.3%) had serious AEs. The most common AEs were hypoalbuminemia (6.9%), hemoptysis (3.4%), alanine aminotransferase reduction (2.9%), anemia (2.9%), and hyponatremia (2.9%). **Conclusion:** This study suggests that in the real world, anlotinib has a prolonged trend in the treatment of second-line advanced NSCLC patients, showing a clinical advantage over previous treatment models. In patients with advanced NSCLC, anlotinib shows good efficacy and safety as a third line or beyond treatment, which are similar to the registration study.

Keywords: NSCLC, Targeted therapy, Real world study

P40.07 Immunotherapy Toxicity in Lung Cancer & the Impact of Thoracic Radiation Therapy

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Introduction: Immunotherapy is increasingly utilized either alone or in combination with chemotherapy and/or radiation therapy (RT) with improved survival. Immunotherapy related toxicity can appear similar to radiation induced toxicity. The contribution of concurrent or sequential thoracic radiation to immunotherapy related cardiopulmonary toxicity is not well understood. Current literature suggests that combination of immunotherapy and thoracic radiation does not result in an increase in high-grade toxicities, however clinicians continue to approach this combination with caution. **Methods:** All patients that received immunotherapy for non-small cell lung cancer (NSCLC) between 2011 and 2020 were included in the analysis. The electronic medical records were used to collect demographic, treatment, and toxicity data. RTOG toxicity scale was used to grade pneumonitis and CTCAE was used for all other toxicities. The first course of radiation therapy was used for analysis if patients received more than one course. The relationship between thoracic RT and the incidence of cardiopulmonary toxicities was evaluated through pairwise comparisons using Barnard's exact test of three groups including: patients who received thoracic RT ^{3} 45 Gy, thoracic RT < 45 Gy, and those who did not receive thoracic RT. To account for the three pairwise comparisons for each toxicity class, Bonferroni adjusted p-values were utilized. Additionally, the impact of RT type (thoracic vs. nonthoracic) and total dose (^{3} 45 Gy vs. < 45 Gy) over multiple courses of treatment was examined. The cause specific hazard ratios for toxicity outcomes were modeled using the Cox proportional hazards model, with time of treatment initiation designated as the time of origin. Candidate variables for inclusion included: receipt of any thoracic vs. non-thoracic RT, thoracic vs. nonthoracic RT received as most recent therapy relative to time of toxicity, total thoracic RT dose (^{3} 45 Gy or < 45 Gy), and total non-thoracic RT dose. The toxicity outcomes (all grade occurrences and grade 3-5 events) evaluated included cardiopulmonary toxicities of any type, pleural effusions, and pneumonitis events. **Results:** 251 patients met the inclusion criteria and were included in the analysis. The majority of patients were locally advanced or metastatic at presentation; 33.5% stage III & 56.6% stage IV. RT was given in 83.3% of patients and 63.7% of patients received thoracic RT. An elevated risk of grade 3-5 pleural effusions was found in patients who received thoracic RT and cumulative dose < 45 Gy, however, the group that received ^{3} 45 Gy did not reveal an increased risk of grade 3-5 pleural effusions. Overall, the remaining candidate variables were not found to significantly impact the evaluated toxicity outcomes ($p > 0.05$). **Conclusion:** An increased risk of pleural effusions was found in patients who received a prior cumulative RT dose of <45 Gy. However, overall, the results of this large single-institution retrospective review do not show an association with thoracic RT and increased risk of cardiopulmonary toxicity in patients receiving immunotherapy for NSCLC. Further dosimetric analysis will be conducted to better characterize cardiopulmonary toxicity outcomes relative to radiation dose to the heart and lung.

Keywords: thoracic radiation, immunotherapy, cardiopulmonary toxicity

P40.08 Bone-Targeted Agents Improve Survival in High Bone Tumor Burden Advanced Non-Small-Cell-Lung Cancer Patients Treated With PD-(L)1 Inhibitors

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Introduction: Bone-targeted agents (BTA) prevent skeletal-related events in cancer patients (pts) treated with chemotherapy (CT) with no significant impact on overall survival (OS). Among BTA, denosumab (DN) improved OS compared to zoledronic acid (ZA) in a subgroup analysis of advanced non-small-cell lung cancer (aNSCLC) pts with bone metastases (BM), while in the SPLENDOUR trial the addition of DN to 1st-line CT in aNSCLC did not improve survival. Currently, the impact of BTA in immune-checkpoint inhibitors (ICIs) treated aNSCLC with BM is unclear. **Methods:** Data from ICI treated aNSCLC pts with BM (03/2013-06/2020) in a single institution were retrospectively collected. BTA therapy was defined as treatment with DN or ZA administered -60/+30 days from ICI start and pursued concurrently. High bone tumor burden (HBTB) was defined as presence of ≥3 BM. Median OS (mOS) and progression free survival (mPFS) were estimated with Kaplan-Meier and multivariate analysis was performed by Cox proportional hazards regression model. Median follow-up was estimated by inverse Kaplan Meier. **Results:** Of 151 pts included, 68 (45%) received BTA. Among BTA treated pts, median age was 68 years old (range 30–87), males were 59% and 85% had a non-squamous histology; ECOG performance status (PS) was 0-1 in 82% and ≥2 in 18% pts. Programmed death-ligand 1 (PD-L1) expression was <1%, ≥1% and unknown in 20%, 60% and 20% of pts, respectively. ICI was the first line of treatment in 27 pts (40%), while 41 pts (60%) received it in second/further-line. BM radiotherapy was administered in thirty-one pts (46%). At a median follow-up of 34 months (m), BTA did not significantly prolong mOS [7.8 m (CI 95% 4.5-11.1) vs 6.8 m (95% CI 3.3-10.3), p= 0.71] or mPFS [1.7 m (95% CI 1.3-2.1) vs 1.2 m (95% CI 1-1.4), p=0.39] in the overall population. HBTB group included 78 pts: 16 (21%) received DN, 29 (37%) ZA, 33 (42%) did not receive any BTA. In HBTB pts, BTA significantly improve mOS [7.8 m (95% CI 3.4-12.2) vs 3.5m (95% CI 2.9-4), p= 0.01] and mPFS [2.6 m (95% CI 2.1-3.1) vs 1.8 m (95% CI 1.5-2.1), p= 0.002). BTA associated benefit in OS [HR 0.59 (95% CI 0.35-0.90), p=0.02] and PFS [HR: 0.53 (95% CI 0.32-0.83, p=0.006) was confirmed at multivariate analysis adjusting for PS, number of metastatic sites, therapy line, BM radiotherapy. In HBTB pts, ZA did not prolong mOS [3.8 m (95% CI 0.3-7.3) vs 3.5 m (95% CI 2.9-4.0), p=0.27], while DN significantly improve both mPFS [2.6 m (95% CI 0.6-4.6) vs 1.8 m (95% CI 1.5-2.1), p= 0.01] and mOS [15.1 m (95% CI 0.1-33.1) vs 3.5 (95% CI 2.9-4), p= 0.002] compared to no-BTA. **Conclusion:** In ICI treated aNSCLC with BM, BTA did not impact on survival. However, in HBTB subgroup BTA significantly improved OS and PFS, making these pts as the best candidates for BTA-ICI concurrent treatment. DN rather than ZA was associated with survival benefit, suggesting a synergy between ICIs and RANK ligand inhibition.

Keywords: Immune-checkpoint inhibitors, bone targeted agents, Advanced NSCLC

P40.09 Using Real World Data to Identify a Patient Cohort Who Require Prehabilitation to Improve Treatment Rates for Stage 3 NSCLC

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Introduction: Patients with stage 3 Non Small Cell lung Cancer (NSCLC) are a heterogeneous group. Recent National Lung Cancer Audit (NLCA) indicates a third of patients (36%) received no active treatment. We audited the treatment received by all stage III NSCLC patients treated between April 2014 and April 2017 at the Edinburgh Cancer Centre. Using this data, we hope to delineate patterns in our selection of treatment based on a patient's performance status and co-morbidities, to better understand which patient groups may be more likely to receive sub-optimal treatment. **Methods:** 374 patients were identified via local cancer registry. Patients were then categorised by treatment modality, ECOG performance status (PS) and Charlson morbidity score (CMS). Radical treatment was defined as chemoradiotherapy, radical radiotherapy or surgery. **Results:** 374 patients were identified: 190 males (50.8%) and 184 females (49.2%). 222 patients (59.36%) were aged ≥70yrs, with a median age of 71yrs (range 42-93yrs). Median follow-up period was 398 days (range: 0-2445 days). 105 patients (28.07%) had a CMS of ≥1. 118 patients (31.55%) had an adenocarcinoma tumour type, 117 patients (31.28%) had squamous histology, 35 patients (9.36%) had other NSCLC histology and 4 patients (1.07%) had non-lung cancer histology. Histology was unavailable for 100 patients (26.74%). Radical treatment was given to 200 patients - surgery (24 patients, 12%), chemoradiotherapy (99 patients, 49.5%) and radical radiotherapy (77 patients, 38.5%). Of those with a PS 0 (64 patients): 47 (73.44%) received radical treatment; 12 (18.75%) received non-radical treatment, and 5 (7.81%) did not receive any treatment. Of those with PS 1 (178 patients): 115 (64.61%) received radical treatment; 27 (15.17%) received non-radical treatment, and 36 (20.22%) did not receive any treatment. Of those with a PS 2 (112 patients): 37 (33.04%) received radical treatment; 29 (25.89%) received non-radical treatment, and 46 (41.07%) did not receive any treatment. 20 patients did not have a clear documentation of their PS – 18 of these did not receive any treatment. Of those with CMS 0 (269 patients): 152 (56.51%) received radical treatment; 56 (20.82%) received non-radical treatment, and 61 (22.68%) did not receive any treatment. Of those with CMS 1 (61 patients): 34 (55.74%) received radical treatment; 6 (9.84%) received non-radical treatment, and 21 (34.43%) did not receive any treatment. Of those with a CMS ≥2 (44 patients): 14 (31.82%) received radical treatment; 7 (15.91%) received non-radical treatment, and 23 (52.27%) did not receive any treatment. **Conclusion:** Those with a better PS and CMS were more likely to receive treatment with radical intent. Those with a higher CMS were far more likely to receive no treatment or non-radical treatment. These patients may benefit from prehabilitation prior to treatment, to allow provision of life prolonging therapy to a greater cohort.

Keywords: Prehabilitation, Audit, NSCLC

P40.10 Brain Metastases in Patients With Non-Small Cell Lung Cancer Treated With Immunotherapy. Real World Data From a Tertiary Hospital in Spain

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Introduction: The metastatic involvement of the central nervous system (CNS) has been traditionally related with an ominous prognosis in non-small cell lung cancer (NSCLC). Immunotherapy (IO) has (dramatically changed) revolutionized the treatment of non-oncogene addicted NSCLC but its tumour effectivity in the CNS has not been well established. The aim of this study is to identify if CNS metastases in lung cancer patients continue to be a major problem and a major cause of mortality in patients treated with IO. **Methods:** We performed a retrospective, observational and comparative study. We collected information regarding clinical factors, treatment, CNS involvement and outcomes from 185 patients with metastatic NSCLC treated with immunotherapy in Hospital Universitario Puerta de Hierro Majadahonda between March, 2014 and March, 2020. We performed a statistical analysis in order to exclude significant differences between both groups. We compared outcomes from patients with and without brain metastasis. **Results:** 22.2% of patients had brain metastasis (CNS involvement) at diagnosis or during the course of the disease. No significant differences were found between groups regarding sex, age, histology, PD-L1, IO line, type of IO and performance status (PS). No significant differences in survival (p = 0.437) nor in the presence of long-term survivors (p = 0.723 for 2 years or more) were found. Comparative data from both groups are shown in Table-1. Specific data from patients with CNS metastases are in Table-2.

Table-1. Comparative data

	Without CNS metastases (N=144)	With CNS metastases (N=41)	P
Sex	M: 45 (31.3%) F: 99 (68.8%)	M: 19 (46.3%) F: 22 (53.7%)	0.073
Age (median, years; range)	64.0 (40.0-82.0)	58.0 (44.0-78.0)	0.114
Histology	Adenocarcinoma: 87 (60.4%) Squamous cell carcinoma: 42 (29.2%) Carcinoma NOS: 15 (10.4%)	Adenocarcinoma: 31 (75.6%) Squamous cell carcinoma: 7 (17.1%) Carcinoma NOS: 3 (7.3%)	0.199
PD-L1 (median)	60.0	55.0	0.638
ECOG PS	0-1: 134 (93.1%) 2 or more: 6 (4.1%) Unknown: 4 (2.7%)	0-1: 37 (90.2%) 2 or more: 2 (4.9%) Unknown: 2 (4.9%)	0.170
IO line	1: 41 (28.5%) 2: 50 (34.7%) Subsequent: 53 (36.8%)	1: 9 (22.0%) 2: 16 (39.0%) Subsequent: 16 (9.0%)	0.553
Type of IO	Immunotherapy: 122 (84.7%) Chemoimmunotherapy: 15 (14.9%) IO + TKI: 7 (4.9%)	Immunotherapy: 35 (85.4%) Chemoimmunotherapy: 5 (12.2%) IO + TKI: 1 (2.4%)	0.768
Overall survival, months (median, CI 95%)	Global: 16.0 (7.7-24.3) 1 line: 18.0 (7.5-28.5) 2 line: 21.0 (7.0-35.0) Subsequent lines: 8.0 (4.3-11.7)	Global: 15.0 (10.3-19.7) 1 line: 19.0 (11.7-26.3) 2 line: 20.0 (0.0-43.7) Subsequent lines: 6.0 (0.1-11.9)	0.437 0.860 0.342 0.706
Long-term survivors	2 years or more: 28 (19.4%) 3 years or more: 8 (5.6%) 5 years or more: 4 (2.8%)	2 years or more: 9 (22.0%) 3 years or more: 4 (9.8%) 5 years or more: 2 (4.9%)	0.723 0.335 0.503

Table-2. Specific data from patients with brain metastases

Brain metastases before starting IO treatment	20 (50.0%)
Number of radiological metastases	1-2: 17 (41.5%) 3-10: 9 (22.0%) More than 10: 12 (29.3%) Unknown: 3 (7.30%)
Meningeal carcinomatosis	3 (7.5%)
Local treatments	Surgery: 3 (7.5%) Whole brain radiotherapy (WBRT): 24 (60.0%) Radiosurgery: 13 (32.5%)
Radiation necrosis	1 (2.5%)
Best CNS response	Progressive disease: 13 (31.7%) Stable disease: 5 (12.2%) Partial response: 16 (39.0%) Complete response: 2 (4.9%) Unknown: 5 (12.2%)

Conclusion: In our study, no significant differences were found in survival nor in the number of long-term survivors in the group of patients with brain metastases. The activity of immunotherapy on the central nervous system still needs to be defined and the impact on the outcomes of this subgroup of patients requires further investigation.

Keywords: NSCLC, brain metastases, immunotherapy

P40.11 Trimodality Therapy Protocol in 144 Superior Sulcus Patients: Good Results Even for Extended Resections and Indications

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Introduction: To define whether our extended indications for resection were justified, we assessed the results of a new protocol on staging and resection of sulcus superior tumors, treated in the years 2003 – 2017. All patients were uniformly staged using PET scanning and all received trimodality therapy. Because SST are seen as "local growers" with low metastatic potential, inclusion criteria were liberal, including vertebral involvement, clinical N2 disease and oligomestatic disease. The only contra-indication for resection, progression on induction treatment, did not occur. **Methods:** Our prospective database revealed 144 SST patients who were uniformly staged (with CT and PET scan) and treated (Chemo-radiotherapy and Surgery). They were divided in two groups: A) Standard cases, involvement of lung & chestwall only. B) Complex cases, with either vertebral invasion (14), encasement subclavian artery (5), involvement sternum (2), positive mediastinal nodal station (7), , supraclavicular or axillary lymphnodes (2) or (treated) oligometastasis (9) All patients also underwent mediastinal lymphnode dissection, with axillairy or Supraclavicular lymphnode dissection if needed Follow-up was complete (3 - 17 years) with no patient lost to follow-up. Clinical endpoint was overall survival. **Results: Data:** Numbers: Group A / B: 105 / 39 . Gender: M / F : 92 / 52 Age: 32 – 77 (med 57 yrs) Side: Left / Right: 39 / 105! Incision: Shaw/Paulson 127; Hemiclamshell 15; Both: 2 **Resection:** Lung: Lobectomy 134; Segmentectomy 1; Wedgeresection: 9 Vertebra (1-3): 4 Hemivertebra: 4 Vertebral wedge: 5 Pedicle 1 Subclavian artery: 5 (Anastomosis: 3 Graft: 2) Chest wall: No ribs: 5 1 rib: 6 2 ribs: 20 3 ribs: 45 4 ribs: 58 5 ribs: 10 Sternum (partial): 2 Clavicle: 1 **Pathology**: R0 resection: 123 R1 resection: 21 (14.5%) R2 resection: 0 **Survival:** Group A: 5-yr survival 67% 10 yr survival 61,7% Group B: 5-yr survival 41.8% 10-yr survival 41.8% **Mortality:** In hospital mortality: 2 Ninety-days mortality: 7 **Conclusion:** Complete staging, including PET, and trimodality therapy, give adequate results in SST patients, even in a group that is not always considered for resection (Group B). But more research on subcategories in this last group is wanted. . We have no explanation for the Left - Right distribution, but it is in according with our national database. The role of immunotherapy in the inductiontreatment is presently investigated

Keywords: superior sulcus therapy, trimodality therapy, extended procedures, extended procedures

P40.12 Cardiotoxicity in Lung Cancer Patients Treated With Immune-Checkpoints Inhibitors

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Introduction: Immunotherapy represents currently one of the most promising therapeutic approaches in systemic cancer treatment. Nevertheless, its broad clinical application revealed a number of important cardiovascular side effects (effects such as myocarditis, heart failure, cardiomyopathy, or pericarditis) of immunotherapeutics, which limit treatment options and decrease patients' prognosis and quality of life. The aim of this study was to assess the prevalence of cardiovascular risk factors (CVRF) in lung cancer patients treated with immunotherapy, and the incidence of cardiovascular events. **Methods:** We conducted an observational retrospective study selecting lung cancer patients treated with immunotherapy in our institution between 2014 and 2020, and analyzed their CVRF. **Results:** A total of 247 patients were analyzed. Data regarding demographic characteristics, cardiovascular risk factors and oncological information are shown in Table-1. Data regarding cardiac events are shown in Table-2.

Table-1. Clinical characteristics

Sex	M: 85 (34.4%) F: 162 (65.6%)
Age (median, range)	64.0 (36.0-82.0)
Hypertension	105 (42.5%)
Systolic arterial (median, range)	128.0 (87.0-194.0)
Dyslipidemia	81 (32.8%)
LDL (median, range)	102.0 (7.0-210.0)
Triglycerides (median, range)	120.0 (51.0-439.0)
Diabetes	32 (13.0%)
Smoking habit	Never smoker: 7 (2.8%) Current smoker: 103 (41.3%) Former smoker: 133 (53.8%) Unknown: 5 (2.0%)
IPA (packs-year, median, range)	44.0 (4.0-180.0)
History of coronary syndrome	14 (5.7%)
History of congestive heart failure	1 (0.4%)
Tumour stage when IO was started	I: 0 (0%) II: 0 (0%) III: 29 (11.7%) IV: 218 (88.3%)
Line of treatment	1: 125 (50.6%) 2: 97 (39.3%) 3 or more: 24 (9.7%) Unknown: 1 (0.4%)
Treatment	Atezolizumab: 13 (5.3%) Atezolizumab + bevacizumab: 5 (2.0%) Atezolizumab + platinum-based doublet: 2 (0.8%) Durvalumab: 11 (4.5%) Durvalumab + tremelimumab: 1 (0.4%) Nivolumab: 100 (40.5%) Nivolumab + daratumumab: 1 (0.4%) Nivolumab + platinum-based doublet: 21 (8.5%) Nivolumab + ipilimumab: 24 (9.7%) Pembrolizumab: 54 (21.9%) Pembrolizumab + platinum-based doublet: 15 (6.1%)
Best response to IO	Complete response: 17 (6.9%) Partial response: 86 (34.8%) Stable disease: 33 (13.4%) Progressive disease: 107 (43.3%) Unknown: 4 (1.6%)
Follow-up since IO start (months, median, range)	10.0 (0.0-70.0)

Table-2. Cardiac events

Patients who experienced a cardiac event (any kind)	45 (18.2%)
Myocarditis	1 (0.4%)
Pericarditis	1 (0.4%)
Congestive heart failure	9 (3.6%)
Arrhythmias	31 (12.6%)
Type of electrocardiographic alteration	QT elongation: 3 (1.2%) Right bundle branch block: 4 (1.6%) Left bundle branch block: 4 (1.6%) Supraventricular extrasystole: 6 (2.4%) Ventricular extrasystole: 2 (0.8%) Atrial fibrillation: 14 (5.7%)
Acute coronary syndrome	3 (1.2%)
Pulmonary thromboembolism	7 (2.8%)
Valvular disease (new diagnosis)	1 (0.4%)
Admissions due to cardiac disease	7 (2.8%)
Cardiac death	2 (0.8%)

Conclusion: Almost one fifth of the patients in our study experienced some kind of cardiac event but its association with IO remains unclear. Prospective studies with cardiovascular comprehensive follow-up protocols are needed in order to assess if there is a real casuistic relationship between the cardiac events in this population and IO treatment.

Keywords: Lung cancer, immunotherapy, cardiotoxicity.

P40.13 Lung Cancer 5-Year Survival in Croatia - Our Experience

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Introduction: Lung cancer is one of the most common cancer type[JM1] s in both genders, resulting in most of cancer-related deaths every year Since there are no data on the five-year survival of patients in Croatia, the aim of our research was to present real-life data for the first time. **Methods:** We analysed data from medical records of 1344 patients who were diagnosed with lung cancer in 2012 and 2013 and who were treated at the Department for respiratory diseases "Jordanovac", UMC Zagreb. **Results:** The predominant histology type was adenocarcinoma (45.9%), followed by squamous-cell lung cancer (27.4%) and small-cell lung cancer (13%). Metastatic disease was diagnosed at the presentation in half of our patients, while locally advanced disease in one third of them. Only 10% of our patients were diagnosed at a limited stage and curative surgical treatment was performed in 58.2%, while about 23% were treated with radiotherapy in combination or without chemotherapy. About one-ffith (280, 20.8%) of the cohort was diagnosed with stage IIIa disease, from whom 57 (20.4%) patients were surgically treated, with addition of neoadiuvant or adiuvant chemotherapy in 48 (84.2%) of them. Radiotherapy was performed in 108 (38.6%) of them, with chemotherapy addition in almost all of the cases (104, 96.2%). The majoritiy was treated with chemotherapy only (106, 37.8%) and a smaller proportion (22, 7.85%) was left untreated. Just over two-thirds of the cohort was diagnosed with advanced uresectable or metastatic disease, i.e stages IIIb or IV Median overall-survival (mOS) for the entire cohort was 8 (95% CI: 7.33-8.66) months. There was a significant gender difference in overall survival. Male patients had mOS of 8 (95% CU: 7.20-8.79) months, while female had 9 (95% CI: 7.46-10.53), p=0.001. Female 1-year and 5-year survival rate was higher than male (41.4% and 10.1% vs 32.7% and 5.8[JM1] %). There was no significant difference in survival rates regarding histological subtypes (adenocarcinoma vs squamous cell carcinoma -moS 7 vs 10 months, 95% CI 6.19-7.81 vs 8.82-11.17 respectively; p=0.411[JM2]). Non-smokers had longer survival compared to ex-smokers and current smokers (mOS 13 vs 8 vs 8 months, 95% CI: 10.62-15.37 vs 7-8.99 vs 7.04-8.95, respectively, p=0.064). Also, initial performance status had a significant impact on overall survival, with mOS for ECOG 0 patients of 11 months compared to mOS of 2 months for ECOG 2 and 3 patients (95% CI: 9.99-12.01 vs 1.40-2.59; p<0.001). Patients who were admitted through the emergency room had shorther survival from those who were referred (6 months vs 9 months; 95%CI 4.93-7.06 vs 8.23-9.76 respectively; p<0.001). **Conclusion:** These data from the largest lung cancer centre in Croatia show for the first time comprehensive 5-year survival data for lung cancer patients in Croatia. Our results do not deviate from the hitherto known data on lung cancer from 7-8 years ago in countries of equal development. Given the significant advances regarding availability of new diagnostic and therapeutic options during the last few years, these data represent a significant baseline for further investigation and comparison.

Keywords: 5 year survival, lung cancer

P40.14 Efficacy and Safety of Endostar Combined With Camrelizumab and Chemotherapy in Treatment of Advanced NSCLC: A Multi-Center Retrospective Study

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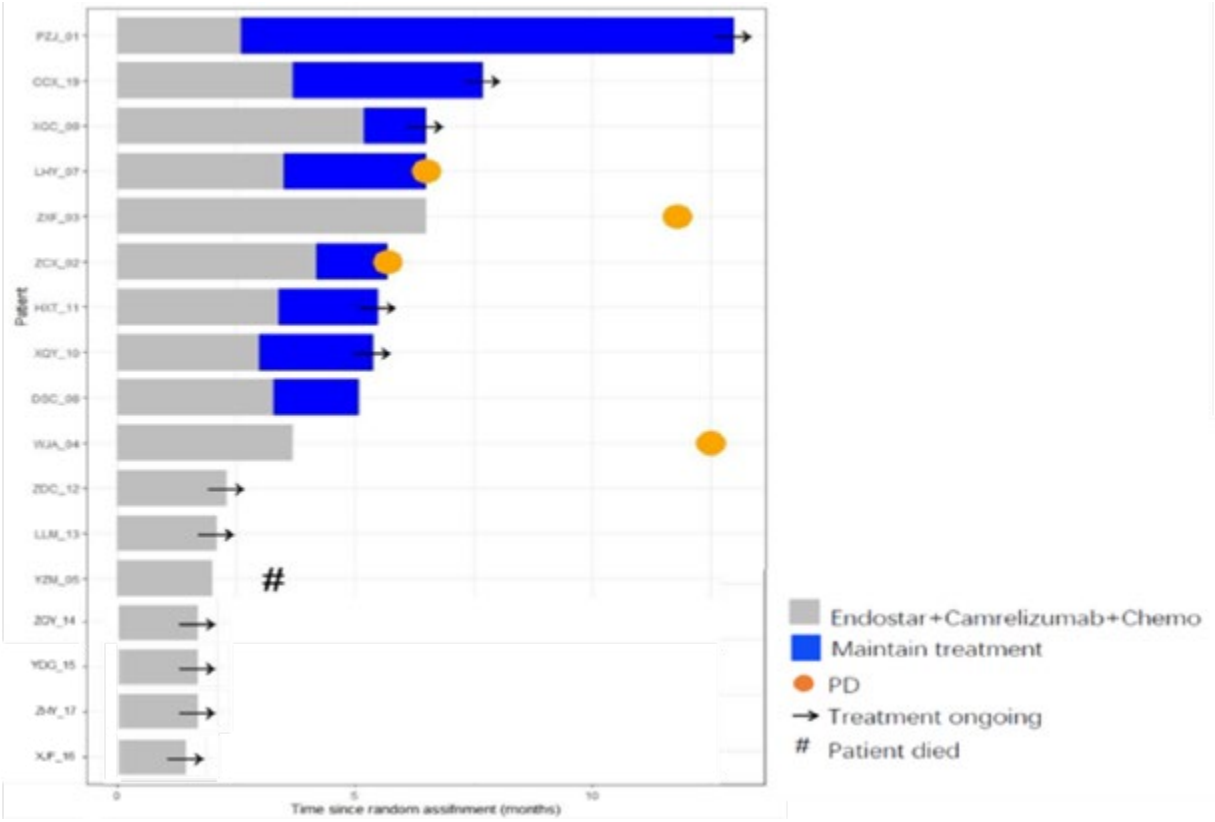
Introduction: Both Recombinant human endostatin (Endostar) and Camrelizumab have been approved in combination with chemotherapy in treatment of NSCLC in China. This study aims to observe the efficacy and safety of endostar plus Camrelizumab and chemotherapy in treatment of advanced NSCLC. This is periodic result. **Methods:** This is a multi-center, retrospective study. Advanced NSCLC patients (pts) who received endostar plus Camrelizumab and chemotherapy at least 2 courses were collected from December 2019. After two courses, the follow-up therapy will be decided by investigators. Baseline characteristics, efficacy evaluation and safety data were analyzed. Tumor response was evaluated according to RECIST 1.1. Adverse events (AEs) were graded according to NCI-CTC AE 4.0. The primary endpoint was progress-free survival (PFS), overall response rate (ORR), duration of response (DOR), overall survival (OS) and safety were included among secondary endpoint. **Results:** Untill Mar. 2021, 21 pts were enrolled, and 17 pts were analyzed. The median age of pts was 55 years. 71% was male, 90% was diagnosed at stage IV. 76% was adenocarcinoma and 19% was squamous cell carcinoma. 67% received endostar combined with Camrelizumab and chemotherapy as first-line. The ORR and DCR is 71% and 100% respectively, with one CR patient. The treatment of 52% (11) pts is ongoing and the median PFS was not reach. In the safety-evaluable population, the most common AEs is thrombocytopenia(24% >3 grade 10%), nausea and vomiting(24% >3 grade 5%) and liver damage (19%). One pt was considered as immune-related hepatitis. Reactive cutaneous capillary endothelial proliferation (RCCEP) caused by Camrelizumab is 10% and none in >3 grade AEs.



	All Grade AE [N (%)]	Grade 3 or higher AE [N (%)]
Hematological events		
Neutropenia	3 (14)	1 (5)
Leukopenia	3 (14)	0 (0)
Thrombocytopenia	5 (24)	2 (10)
Anemia	4 (19)	0 (0)
Non-hematological events		
Myocardial Enzymes Change	1 (5)	0 (0)
Nausea and Vomiting	5 (24)	1 (5)
Immune-related events		
Reactive cutaneous capillary endothelial proliferation (RCCEP)	2 (10)	0 (0)
Liver Damage*	4 (19)	1 (5)
Renal Damage	1 (5)	0 (0)
Hypothyroidism	0 (0)	0 (0)
Diarrhea and colitis	0 (0)	0 (0)
Pancreatitis	0 (0)	0 (0)
Pancreatitis	0 (0)	0 (0)

* One pt was considered as immune-related hepatitis

Conclusion: This retrospective study showed a promising efficacy and a good tolerance in advanced NSCLC pts with Endostar plus Camrelizumab and chemotherapy. This combined treatment maybe a new choice and we look forward to prospective study in furture.

Keywords: Camrelizumab, Endostar, NSCLC

P40.15 Proton Pump Inhibitors, Prior Therapy and Survival in Patients Treated With Immune Checkpoint Inhibitors for Advanced NSCLC

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Introduction: Emerging data suggest that concomitant medications (CM) influence response to immune checkpoint inhibitor (ICI). CM impact the host microbiome which may mitigate tumor-immune responsiveness. Proton pump inhibitor (PPI) use in patients treated with ICI has been associated with worse survival. Few data exist regarding the effect of PPI use in terms of the type of ICI or in the combination of ICI and chemotherapy. **Methods:** This retrospective study of patients with advanced cancer treated with ICI between 2011 and 2020 was conducted at The Ohio State University. Patients who received ICI as either single agent or in combination with chemotherapy were included. Clinical data was abstracted from chart review, including CM, toxicity, and survival. Overall survival (OS) was evaluated to date of death or last contact. Associations between OS and proton pump inhibitor (PPI) use were studied using log-rank tests and Cox regression analyses overall and by the groups of PD/L1 alone, PD/L1+CTLA4, and PD/L1 + chemotherapy. **Results:** We identified 415 patients with NSCLC treated with ICI, of whom 149 (36%) received PPI at time of ICI. The most common therapy was PD-1/L1; patient demographics were similar (Table 1). PPI use was not associated with OS across the entire cohort (p = 0.105). However, PPI use was associated with shorter OS in patients treated as PD-1/L1 alone (HR = 1.43, 95% CI = [1.06, 1.92], p = 0.019). No such association was observed for either the PD/L1+CTLA-4 (HR = 0.577, 95% CI = [0.229, 1.453], p = 0.24) or PD-1/L1+chemotherapy (HR = 0.940, 95% CI = [0.545, 1.621], p = 0.823) groups. The use of PPI was not associated with occurrence of irAE overall (p=0.27) or colitis in particular (p=0.83).

Table 1

Patient Characteristics	**No PPI**	**PPI**	**p value**
n= 415	266	149	
Immunotherapy (%)			
PD1/L1	149 (56.0)	100 (67.1)	
PD1/L1 + CTLA4	24 (9.0)	9 (6.0)	
PD1/L1 + chemotherapy	85 (32.0)	36 (242.2)	
OS	Hazard Ratio	95% Confidence Interval	
PD1/L1	1.43	1.06, 1.92	0.019
PD1/L1 + CTLA4	0.577	0.229, 1.453	0.243
PD1/L1 + chemotherapy	0.940	0.545, 1.621	0.823
irAE			0.265
irAE-colitis			0.830

Conclusion: PPI use was associated with shorter survival in patients with NSCLC treated with PD-1/L1 ICI monotherapy but not combination therapies. In patients also receiving CTLA-4 or chemotherapy, PPI use was not associated with survival. This may be due to the disruption of the microbiome by PPI use, particularly those organisms that promote PD-1/L1 response, and by chemotherapy. Further study is needed to determine the impact of CM, including PPI, on outcomes of patients treated with ICI.

Keywords: PPI, immunotherapy, NSCLC

P40.16 Real-World Data and Racial Outcomes for NSCLC in The Chemo-Immunotherapy Era

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Introduction: Lung cancer remains the leading cause of cancer death among both men and women. Recent pivotal trials established combination chemo-immunotherapy (IO) as the standard of care for advanced non-small cell lung cancer (NSCLC) without any targetable mutations. Unfortunately, minorities continue to make up less than 10% of patients enrolled in clinical trials. This means that the survival data reported in trials may or may not accurately reflect outcomes in a racially heterogenous population such as the state of Louisiana. **Methods:** We retrospectively collected data from patients with advanced NSCLC treated with chemo-IO between January 2014 and January 2020 through our healthcare system Ochsner Health. Primary objectives were overall survival (OS) and progression free survival (PFS). Progression was defined per RECIST v1.1. Kaplan-Meier survival analysis was utilized to estimate PFS and OS. Survival curves were compared between the race strata using the log-rank test. **Results:** We identified 264 patients with stage IV NSCLC who received chemo-IO. Median age was 65. 70% were white and 27% were black. 77% had adenocarcinoma and 20% had squamous cell carcinoma. 20% had brain metastases at diagnosis. 35%, 28% and 22% had a tumor proportion score of <1%, 1-49% and >50%, respectively. Probability of PFS at 12 and at 24 months was 0.61 (0.54-0.67) and 0.40 (0.32-0.48) respectively. Median PFS was 15.3 (13.2-18.9) months. Probability of OS at 12 and at 24 months was 0.61 (0.55-0.67) and 0.37 (0.29-0.44) with a median OS of 16.8 months (14.7-20.2). Median PFS among black and white patients was 21.9 (12.3-not estimable (NE)) and 15 (12.4-17.5) months, respectively (p= 0.135). Median OS among black and white patients was 20.2 (13.4-NE) and 16.2 (12.2-19.9) months, respectively (p= 0.114). Only 45 patients (17%) were able to receive 2nd line therapy. **Conclusion:** PFS and OS data for patients with stage IV NSCLC treated with chemo-IO reported in this study were not widely different from that data reported in prospective clinical trials. In the real world, delta between PFS and OS was much closer than in the clinical trials for stage IV NSCLC, with minority of patients going on to second line. Both PFS and OS were numerically superior in black patients compared to white patients, although the difference was not statistically significant. Further prospective studies with increased minority enrollment should be conducted to further evaluate any potential racial differences for patients with NSCLC on a larger scale.

Keywords: Non small cell lung cancer, chemo-immunotherapy

P40.17 Palliative Radiotherapy Decreased K^+ and $Ca^{2+}$of the Blood in Patients With Stage IV Lung Cancer

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Introduction: Ions play an important role in maintaining the stability of cell environment and the functional state of tissues and organs. Most of the published studies have been focused on the changes of blood cells after radiotherapy and chemotherapy, mainly circulating immune cells and circulating tumor cells. The purpose of this study is to explore the ions change in the blood of patients, the homeostasis of related organ function and physical function before and after radiotherapy. **Methods:** This is part of a multicenter prospective study on imaging blood biomarkers and quality of life (QOL). Patients with stage IV lung cancer scheduled to have palliative radiotherapy. The variables of our interest in this study included gender, age, stage, pathology, renal function test, liver function test and blood electrolytes with inclusion of K+, Na+, Mg2+ and Ca2+. The differences of renal function test, liver function test and blood ions test before and after radiotherapy were calculated. Physical function measures of the QOL PROMIS-29 Profile v2.1 were analyzed for survival were analyzed. Data are presented as mean (95% confidence interval) unless otherwise specified. Statistical significances were tested using T-pair test and P less than 0.05 were considered to be significant. Disparities in patient survival were analyzed by multivariate Cox regression models. Multivariate correlation analysis was performed using Pearson models. **Results:** A total of 80 patients enrolled since September 2019, 43 patients with minimum follow-up of 6 months were included in this study. This cohort contains 30 males and 13 females, aged from 39 to 85 years. The levels of K+ and Ca2+ in the blood decreased significantly after radiotherapy (4.14±0.45 vs. 3.98±0.43, P=0.007; 2.27±0.15 vs. 2.17±0.1, P=0.002, respectively). However, no significant changes was found in liver and renal function of stage IV lung cancer patients after radiotherapy (All P>0.05). There was no significant correlation between total radiation dose and K+ and Ca2+ levels (P>0.05). There was no significant associations between reduction of K+ and Ca2+ and overall survival (P0.05). But low levels of Ca2+ after radiotherapy was associated with a decline of physical function (r=0.01, P=0.004). **Conclusion:** This study demonstrated that palliative radiotherapy a significant reduction in blood levels of K+ and Ca2+ which predicted an unfavorable physical function, though not significant for overall survival in patients with stage IV non-small cell lung cancer. Should this results be validated by an external validation study, electrolytes shall be tested and corrected timely after palliative radiation.

Keywords: stage IV lung cancer, radiotherapy, Blood Ions

P40.18 Second Line Immunotherapy After Progression on a Different First Line Immunotherapy in Advanced Non-Small Cell Lung Cancer With Focus On Elderly

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Introduction: Background: Immune check point inhibitors (ICI) have become the standard of care in treatment of patients with advanced non-small cell lung cancer (NSCLC). After progression on first line ICI, 2nd line treatment with chemotherapy poses a challenge especially in elderly (age ≥70) or borderline performance status (ECOG ≥2) patients, as potential adverse effects could negatively impact quality of life. Current guidelines do not recommend switching to another immunotherapy after progression of disease (POD); however, there are some case series showing effectiveness of this strategy in select patients. We report here our experience in patients treated with a second line ICI after POD on first line ICI at Mayo Clinic, Florida, between 2016-2020, with focus on elderly and borderline performance status patients. **Methods:** A list of 153 NSCLC patients undergoing ICI therapy for advanced NSCLC was obtained from Mayo Clinic Florida database. A comprehensive chart review was conducted to identify patients who received a subsequent ICI therapy after progression on initial PD1-PDL1 inhibitor. Data collection included demographics, performance status, PDL1 status, overall survival (OS) ,progression free survival (PFS) and adverse events. **Results:** 27 out of 153 patients were treated with a second ICI after the first ICI was stopped due to progression (25 pts) or due to adverse effects (2 pts). Among the 27 pts, 14 were elderly (≥70) and 11 had ECOG ≥2. All patients had advanced NSCLC with 22 of 27 patients having metastatic NSCLC. 15 patients were positive for PDL1 expression (>1%) while 9 patients had no PDL1 expression (<1%). Of the 27 patients, 22 were initially treated with a PD1 inhibitor (17 with pembrolizumab and 5 with nivolumab) and 5 were treated with a PDL1 inhibitor (durvalumab). After progression, therapy was switched as following: • 18 patients were switched from a PD1 inhibitor (pembrolizumab or nivolumab), to a PDL1 inhibitor (atezolizumab, durvalumab and tremelimumab, or avelumab) • 3 patients were switched from a PDL1 inhibitor (Durvalumab) to PD1 inhibitor (pembrolizumab). • 6 patients were switched to a different agent of the same class. The median overall survival in our population was 27.4 months. The median PFS on a second ICI was 4.3 months. Median PFS on a second ICI in elderly patients and those with ECOG ≥ 2 was 4.8 months and 3.6 months, respectively. Grade ≥3 adverse events were reported in 7 patients (26%) including one patient who had the drug discontinued due to grade 3 hepatitis. Specifically, in the elderly patients, grade ≥3 adverse events were reported in 21% of patients (3/14) while the same was reported in 27% of patients (3/11) with ECOG ≥2. **Conclusion:** In patients with advanced NSCLC and borderline performance status or age ≥70, treatment with 2nd line immunotherapy after progression on a different 1st line immunotherapy was well tolerated and led to a PFS that is comparable to standard 2nd line chemotherapy.

Keywords: immunotherapy, non-small cell lung cancer (NSCLC), elderly

P40.19 Efficacy and Toxicity of Third-Line Chemotherapy in Advanced Non-Small Cell Lung Cancer

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Introduction: The main goal of chemotherapy in advanced non-small cell lung cancer (aNSCLC) is to improve survival and quality of life. While the absolute benefit of first- and second-line chemotherapy in this setting is well established, the role third-line chemotherapy (3LCT) is still controversial. Moreover, with the introduction of new agents such as immunotherapy (IO) and targeted therapies (TT), patients (pts) receive 3LCT in even more advanced settings. **Methods:** We retrospectively retrieved all cases of aNSCLC treated with systemic chemotherapy between January 2009 and September 2020. Pts who received at least three lines of chemotherapy and had evaluable response to 3LCT were considered eligible for this study, irrespective from other kind of treatments. Clinical and pathological data were extracted from Institutional database. Descriptive statistics were used for categorical variables. Median OS (mOS) and progression free survival (mPFS) were estimated through Kaplan-Meier method and compared by log-rank test. **Results:** Out of 435 cases treated with chemotherapy, 56 pts 3LCT were identified. Median age was 64 years (range 30–77). ECOG PS was 0 in 23.8% pts, 1 in 57.1% pts, ≥2 in 19.0% pts. Nineteen pts (34.5%) had ≥3 sites of distant disease (bone, liver and brain metastases in 38.2%, 21.8% and 23.6% of cases, respectively). As regards 3LCT regimen, 8.9% of pts received doublets, 16.1% docetaxel and 75.0% other single agent chemotherapy (mainly vinorelbine or gemcitabine). Disease control rate (DCR) with 3LCT was 31.0%. The median duration of disease control was 2.53 months (95%CI 1.91–4.05). After a median follow-up of 37.0 months, mPFS was 3.26 months (95% CI 1.97–3.75); mOS was 8.95 months (95%CI 5.49–16.91). A significant association was identified between ECOG PS and outcomes (HR 0.330, 95%CI 0.129-0.840, p 0.003 for mPFS; HR 0.352, 95%CI 0.145-0.853, p 0.0003 for mOS), and between number of metastatic sites (cut off ≥3) and OS (HR 0.501, 95%CI 0.262-.957, p 0.033). Thirty pts (56.4%) received further lines of treatment. Among pts treated with IO (91.1%), those who received IO after 3LCT (42.9%) had a significantly better PFS (4.2 vs 2.0, p 0.0093) and OS (19.2 vs 4.9, p <.0001) compared to those who received IO before 3LCT (48.2%). Nineteen pts (33.9%) experienced a grade ≥2 toxicity, mainly asthenia, anemia, neutropenia, nausea and vomiting. **Conclusion:** In our case series, 3LCT showed modest survival benefit while it was burdened by a high rate of toxicity. Pts who benefitted most from 3LCT were those with good ECOG PS and low disease burden, not pretreated with IO. The latter group nowadays represents a very small proportion of pts candidate to 3LCT. In conclusion, with the limitations of this retrospective analysis, 3LCT should be considered only in carefully selected pts and drugs with alternative mechanism of action or clinical trials should be preferred whenever possible.

Keywords: Chemotherapy, Advanced non-small cell lung cancer, survival

P40.20 Real-Life Analysis of Immunotherapy as the Second or Later Lines Treatment in Patients With Metastatic Non-Small Cell Lung Cancer

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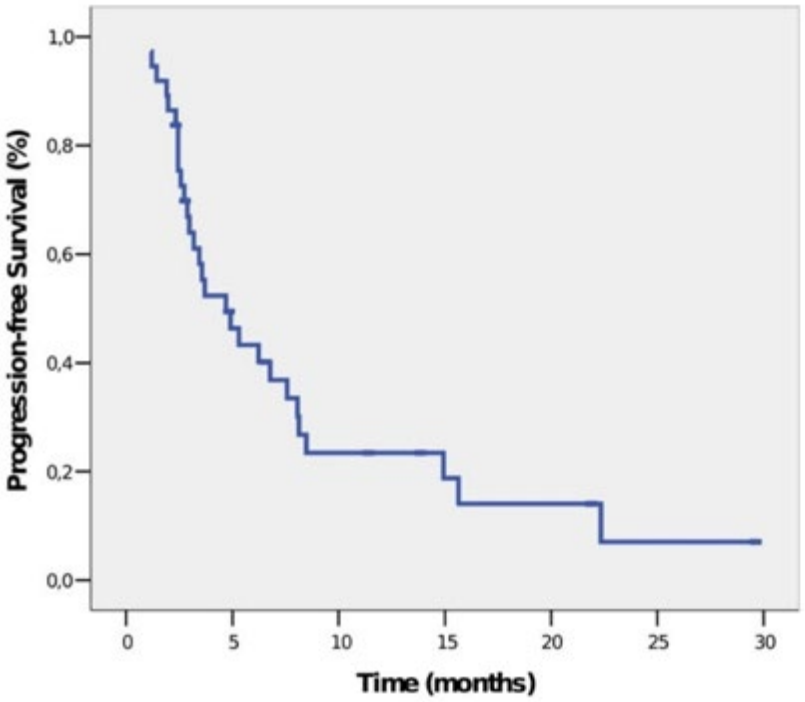
Introduction: Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer and in the absence of driver mutation preferred treatment is incorporation of immunotherapy.But for patients treated with chemotherapy alone,in second line setting atezolizumab or nivolumab are appropriate option regardless of PD -L1 expression.Herein we aimed to evaluate the efficacy and safety of immunotherapy for the second and later line settings in metastatic NSCLC. **Methods:** Totally,37 patients with metastatic NSCLC who received atezolizumab or nivolumab in the second or later lines were included.Clinicopathological features of patients and survival outcomes were analyzed.The safety profile and the factors that may predict survival were also evaluated. **Results:**

Figure 1: Median progression-free survival was 4.7 months in aptients with metastatic NSCLC who treated with immunotherapy



Twenty-nine(78.4%) of patients were men and 8 of patients(21.6%) were woman with median age of 61 years(range:42-80).At the initial diagnosis the majority of patients(64.9%) were advanced stage.Brain metastasis were detected in 15 patients(40.5%) at the initial diagnosis or during treatment.Histopathologically, the majority of patients had adenocarcinoma(n=23,62,2%). PD-L1 expression status were classified as <1% in 21 (63.6%), 1-49% in 8(24.2%) and >50% in 4(12.1%) patients.While 25(67.6%) patients received immunotherapy in the second line setting, 12 patients(32.2%) received in the third and subsequent lines. Atezolizumab was preferred in 22(59.5%) of these patients and nivolumab in 15 (40.5%) of them.The median cycle and duration were 5(range:2-24) and 3.7 months(range:1.7-29.6) for immunotherapy treatment.Objective response rate(ORR) was %35.1. At a median follow up 22.5 months,median progression-free survival (PFS) time was 4.7 months,while median overall survival (OS) time was 24.1 months.Univariate analysis for PFS revealed that gender(p=0.03), age(p=0.005), the presence of brain metastasis(p=0.02), PDL status >%1(p=0.035), ECOG PS(p=0.04) and the good response to frontline treatment(p=0.015) were found to be significant prognostic indicators.It also showed that the presence of brain metastasis(p=0.03), PDL status >%1(p=0.027), good response to frontline treatment(p=0.022) and atezolizumab preference(p=0.018) were prognostic factors for OS.Multivariate analysis indicated that good response to immunotherapy(HR:5.02,p=0.038) and good response to front line treatment(HR:0.48,p=0.13), atezolizumab preference(HR:3.23,p=0.034) were significantly independent prognostic factors for OS.Moreover,gender(HR:5.18,p=0.0018), age(HR: 0.18,p=0.003),ECOG PS (HR:11.3,p=0.002),PDL status >%1 (HR:0.32, p=0.006) and good response to immonotherapy (HR: 0.26, p = 0.002) were found to be significant independent prognostic indicators for PFS by multivariate analysis.The most common grade 3 or 4 adverse events seen in immunotherapy were pneumonitis in 3 patients, colitis in 1 patient.Moreover, rash and hypothyroidism were common immune-related grade 1-2 adverse events. **Conclusion:** Our real-life analysis indicated that atezolizumab and nivolumab improved survivals with good safety profile in second and later lines treatment of metastatic NSLC patients.

Keywords: Non-small cell lung cancer, immunotherapy, second and later line treatment

P41.01 Abscopal Response Induced by Thermal Ablation in Advanced NSCLC Patients Failed From Immunotherapy: Preliminary Result From a Phase 2 Trial

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Introduction: Previous study showed that abscopal response induced by radiotherapy plus immunotherapy occurred in 27% of patients with advanced solid tumors. In recent years, thermal ablation have shown immune-regulatory effect and prolonged survival of metastatic lung cancer patients. Hereby, we postulated that thermal ablation combined with immunotherapy might also result in abscopal response in patients of lung cancer who had local progression after the anti-PD-(L)1 immunotherapy. **Methods:** In this single-arm study, advanced NSCLC patients who had local progression from previous anti-PD-(L)1 inhibitor treatment were enrolled. All patients underwent combined immunotherapy and local ablative therapy and had at least 1 untreated lesion to evaluate the abscopal response (≥ 30% reduction of the largest diameter indicating response). The primary endpoint was the incidence of abscopal response. The secondary endpoints include the association of abscopal responses with survival outcomes and safety. **Results:** From January, 2020 to April, 2021, a total of 9 patients were enrolled. Among them, two patients had abscopal responses with an ongoing durable response time of 7.1 and 5.8 months respectively. All the 9 patients had efficacy evaluation of the ablative lesions, 3 (33.3%) of them had partial responses, 4 (44.4%) stable diseases, 1 (11.1%) progressive disease and 1 (11.1%) not evaluable. The ORR was 33.3% (3/9) and DCR was 77.7% (7/9). The median PFS and OS were not reached. The most common adverse events were pneumothorax (44.4%) pleural effusion (11.1%) and hemorrhage (11.1%). No ablation-related grade 3/4 adverse events were observed. Table 1. Baseline patient characteristics

Enrolled patients (n=9)	
Median age	63.5
Sex Male Female	8 (88.8%) 1(11.1%)
Smoking history Smoker Non-smoker	2 (22.2%) 7 (77.7%)
Histological type Adenocarcinoma Squamous cell cancer Others	5 (55.5%) 3 (33.3%) 1 (11.1%)
Number of patients with lesions 2 lesions 3 lesions ≥4 lesions	3 (33.3%) 2 (22.2%) 4 (44.4%)
PD-L1 expression Positive Negative	3 (33.3%) 6 (66.6%)

Figure 1. Scans from a patient with advanced NSCLC who received microwave ablation to the primary lesion in the right lower lobe of the lung. At 1.5 months after treatment, the ablation-treated lesion had been absorbed, the 4R/7 lymph node metastatic lesions also regressed significantly, indicating an abscopal effect. **Conclusion:** Local thermal ablation showed abscopal responses in metastatic NSCLC patients who failed from previous immunotherapy, which provides a promising approach for treatment of advanced NSCLC. Looking forward for the updated data of this phase 2 clinical trial.

Keywords: non-small cell lung cancer, abscopal response, ablative therapies

P41.02 Surgery for Small Pulmonary NUT Carcinoma: Case Report

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Introduction: NUT midline carcinoma is a rare and extremely aggressive cancer defined by rearrangement of the NUTM1 gene. In 2019, Chau et al. reported that the median overall survival (OS) was 6.5 months (95% confidence interval = 5.8 to 9.1 months), and thoracic primary had a poorest prognosis (OS = 4.4 months, 95% CI = 3.5 to 5.6 months). Here, we report one case living over 1 year after surgical treatment. **Methods:** A 82-year old former smoker Asian male had gone to the urology department after two times surgical treatments for bilateral renal cell carcinoma (first operation was left nephrectomy 14 years ago, and second one was right partial nephrectomy 5 years ago). Histopathology presented clear cell carcinoma of the kidney in both tumors. Regular computed tomography (CT) revealed small pulmonary nodule of 14 mm tumor size in the right upper lobe without any mediastinal and hilar lymph adenopathy. Positron emission tomography-computed tomography demonstrated abnormal accumulation within pulmonary nodule. He presented no symptom, and laboratory examinations showed slightly elevated values of ProGRP (115; 0-70.9 pg/mL), SCC (2.7; 0-2.5 ng/mL) and IL-2 receptor (992; 122-496 U/mL). Since metastatic pulmonary tumor was suspected, so wedge resection was performed for diagnostic and treatment purposes. **Results:** A gross examination showed a white cut surface of a solid tumor with an irregular border, measuring 25*12 mm in size. Microscopic examination revealed monotonous proliferation of small round cells with necrosis, which was not consistent with typical clear cell carcinoma. Lymphatic invasion and intrapulmonary metastases were found, but there was no pleural invasion, pleural dissemination, and venous invasion. The surgical margin was negative. Tumor cells were positive for epithelial membrane antigen (EMA) and vimentin, however those were negative for AE1/AE3, cytokeratin 7, cytokeratin 20, cytokeratin 5/6, CAM 5.2, thyroid transcription factor 1, calretinin, s-100, CD117, Meran A, HMB-45, Wilm's tumor suppressor gene 1 (WT-1), and D2-40. Subsequently, NUT immunohistochemistry (rabit monoclonal, C52B1, Cell Sgnaling) was performed to result in diffusely positivity in tumor nuclei with a speckled pattern. FISH and RNA sequencing revealed the presence of the BRD4-NUT fusion gene. There was no positivity of driver mutation (EGFR, ALK, ROS1), and PD-L1 expression showed 0%. Those results led to the final diagnosis of primary pulmonary NUT carcinoma with the BRD4-NUT fusion (pT3NxM0). After 3 months later from surgery, CT detected enlargement of mediastinal lymph nodes. The diagnosis was local recurrence, which was treated with radiotherapy. However, enlargement of right supraclavicular lymph node was found on 9 months after surgery. The lymph node was reduced by second radiotherapy, and the patient has been alive over 1 year after surgery. **Conclusion:** This study showed small pulmonary NUT carcinoma, which has been under control over 1 year by multiple local therapies. Since NUT is rare but highly malignant carcinoma, so it should not be forgotten for early diagnosis, and quick and certain treatment.

Keywords: lung cancer, NUT carcinoma, BRD4-NUT

P42.01 Tumor Size is an Independent Prognostic Factor after Pulmonary Metastasectomy

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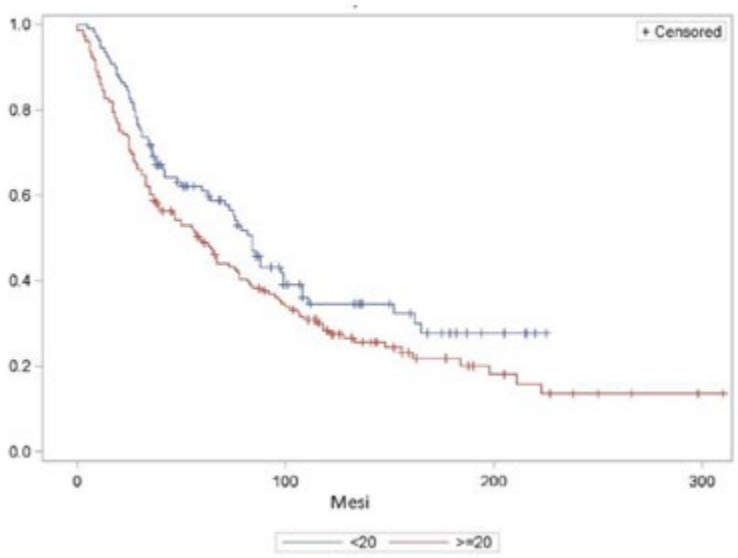
Introduction: Patients selection for lung metastasectomy is mainly based on several prognostic factors such as disease-free interval (DFI), number of nodules, nodal involvement and radicality of the resection. The dimension of resected metastases is an indirect indicator of tumour burden and probably increases the risk of local recurrence but its impact on survival remains to be confirmed. The aim of this study was to test the hypothesis that larger metastases have a worse long-term outcome. **Methods:** Data from a cohort of patients who underwent pulmonary metastasectomy in the period 1998-2018 was analysed to test the impact on survival of the number and size (diameter of the largest resected metastases < vs > 2 cm) of resected lesions, nodal involvement and R0 resection. Patients with a follow-up time inferior to 3 years were excluded. Overall survival was measured according to Kaplan Meier method and groups were compared by the log-rank test. Clinical relevance of prognostic factors was tested by univariate analysis and significant variables ($p<0.05$) were inserted into a Cox multivariate model. **Results:** The study group was composed of 314 patients (median age 58 years, males 44%) with different histology (epithelial 80%, sarcoma 13.7%, melanoma 4.5%, germ-cell tumors 1.9%) and a median disease-free interval of 50 months. A single metastasis was present in 289 cases (62.1%) and nodal involvement in 21 (6.7%). The largest resected lesion had a diameter less than 2 cm in 110 patients (41.4%). A radical resection was obtained in the majority of cases (293, 93.3%). Median survival in patients who had smaller metastases (<2 cm) was 63 months as compared to 55 months in those with larger lesions (figure 1, p 0.05). Multivariate analysis pointed out a more favourable outcome for patients having smaller (OR 0.54, CI 0.39-0.74) and single lesion (OR 0.58, CI 0.42-0.79), no nodal involvement (OR 0.5, CI 0.31-0.82) and who had an R0 resection (0.31, CI 0.16-0.58).



Conclusion: Size of resected lesions is an independent prognostic factor after pulmonary metastasectomy. Whether this effect is due to a higher rate of local recurrence or the expression of a biologically more aggressive disease remains unclear. In any case, a very accurate evaluation of resection margins should be performed when large (> 2cm) metastases are removed.

Keywords: Tumor size, prognostic factor, Pulmonary Metastasectomy

P42.02 Prognostic Indicators for Conventional Chemotherapy Response in Advanced Non-Small Cell Lung Cancer Patients in Resource-Limited Country

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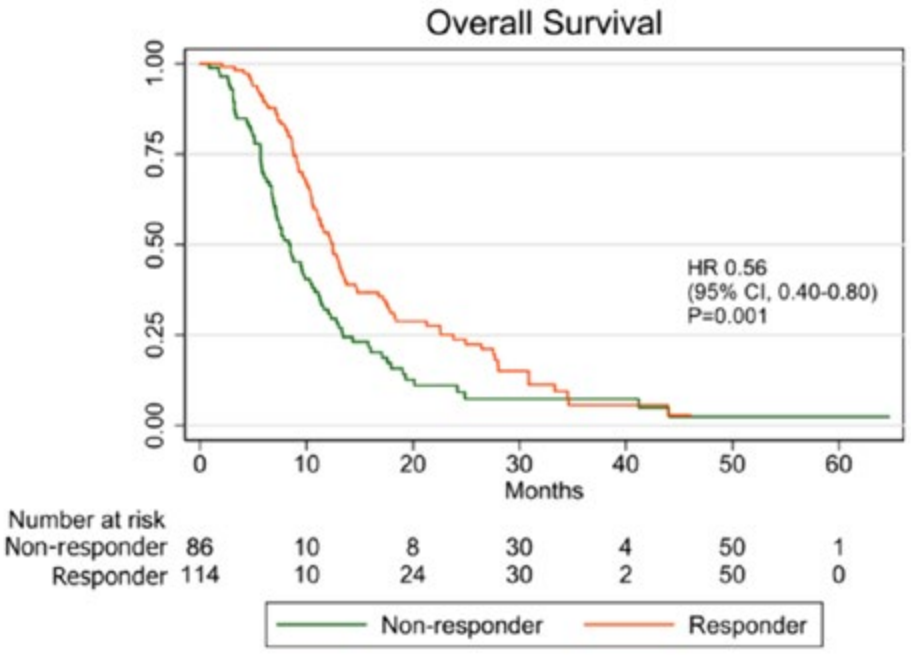
Introduction: Patients with advanced non-small cell lung cancer (NSCLC) are now surviving longer with targeted therapies and immunotherapies. Most of patients cannot access to these therapies due to cost of treatment and health-reimbursement system. Conventional chemotherapy is still mainly used in first line setting. Unlike novel therapies, no predictive biomarkers for patient selection. The aim of study is to explore factors influencing chemotherapy response. **Methods:** A retrospective cohort study was conducted between July 2014 and December 2018 in Surin Hospital Cancer Center, Thailand. All medical records of advanced NSCLC patients treated with platinum doublets in first line were reviewed for demographic data, smoking history, ECOG performance status, staging, histological subtypes, treatment, response rate (RR) and overall survival (OS). Kaplan-Meier model was used for survival time analysis. Prognostic factors for chemotherapy response were performed by multivariate logistic regression. **Results:** Two hundred patients were included for analysis. The mean age was 62.4(±9.6) years and no predominant in gender (49.5% female). Most patients were non-smoker (62.5%) and ECOG 0-1 (83%). Histological subtypes were non-squamous cell carcinoma (65.5%), squamous cell carcinoma (25.5%) and others (9%). Response rate (RR), stable disease (SD), progressive disease (PD) were 57%, 30% and 13%, respectively. Median OS of patients with response (Responder) was 12.5 months (95%CI,11.0-13.6) and patients with SD or PD (Non-responder) was 8.3 months (95%CI,7.0-10.3), HR 0.56, p=0.001 by log-rank test. Female (odd ratio, OR 3.72, p=0.003), squamous cell carcinoma (OR 2.69, p=0.013) and serum albumin ≥3.5 g/dL (OR 2.04, p=0.039) were prognostic factors for chemotherapy response according to multivariate analysis. **Conclusion:**



Female, squamous cell carcinoma subtypes and serum albumin ≥3.5 g/dL may be factors for predicting response to chemotherapy in first line advanced NSCLC patients who cannot access novel therapies. Responders have good prognosis for survival.

Table 1 Multivariate Logistic Regression Analysis for Predicting Response to Systemic Chemotherapy

Factor	OR (95% CI)	*P* value
Female	3.72 (1.57-8.80)	0.003
Age (year)	1.02 (0.99-1.06)	0.175
BMI	1.05 (0.95-1.15)	0.333
Smoker/Ex-smoker	1.85 (0.76-4.53)	0.176
ECOG: 0-1 *vs.* 2	1.24 (0.45-3.43)	0.676
Histology: SQ *vs.* NSQ	2.69 (1.23-5.88)	0.013
Albumin ≥3.5 g/dL: yes *vs.* no	2.04 (1.04-4.02)	0.039
Brain metastasis: yes *vs.* no	0.88 (0.34-2.23)	0.768

Keywords: prognostic factors, response, Chemotherapy

P42.03 Predictive Factors of Response to PD-(L)1 Inhibitors in Patients With Advanced Non-Small Cell Lung and High PD-L1 Expression

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Introduction: Tumor PD-L1 expression is the only validated predictive biomarker in advanced NSCLC patients (pts) treated with PD-(L)1 inhibitors. Analysis of PD-L1 expression by immunohistochemistry has been validated in histological samples. Smoking and overweight have been described as predictive factors of better outcome, whereas bone metastases, antibiotics, corticosteroids and proton pump inhibitors as possible negative predictive factors. The aim of our study was to analyze different potential predictive factors to PD-(L)1 inhibitors in pts with advanced NSCLC and high PD-L1 expression. **Methods:** This retrospective study was carried out in pts with advanced NSCLC and high PD-L1 expression treated with PD-(L)1 inhibitors with median follow-up of 12.8 months [3.6-73.9]. Clinical and histological variables of interest were registered. Kaplan-Meier estimations were used to calculate survival, while the log-rank test was implemented to make comparisons. The impact of variables on survival was assessed through univariate and bivariate analysis. **Results:** We included 86 pts, the mean age was 66 y [36-84], 24.4% were females, 73.3% were former smokers and 22.1% current smokers, 38,4% presented normal Body Mass Index, 79% pts had non-squamous NSCLC, and 12% pts had cytological sample for PD-L1 determination. 72 (83.7%) pts received monotherapy with PD-(L)1 inhibitor, 4 (4.7%) pts chemotherapy plus PD-(L)1 inhibitor and 10 (11.6%) pts received PD-(L)1 inhibitors with other immunotherapy drug. The median OS and PFS were 23.0 months (95% CI, 13.7 to 32.4) and 9.5 months (95% CI, 2.3 to 16.7), respectively. ORR and DCR in overall patients were 55.6% and 71.5%, respectively. The median OS in complete/partial response vs. stable disease vs. progression disease was not reached vs. 14.0 months (95% CI, 8.1 to 19.8) vs. 4.2 months (95% CI, 2.6 to 8.0), respectively (P<0,001). The median OS in patients receiving treatment beyond progression was not reached vs. 10.4 months (95% CI, 8.2 to 12.6) in patients that stopped treatment (P<0,001). A trend to better results were observed in patients with overweight or smokers, and a trend to worse OS was observed in pts with bone metastasis. No differences in OS were observed according to the tumor sample (cytological vs histological samples). **Conclusion:** Response to immunotherapy and treatment beyond progression were predictive of better outcome in pts with advanced NSCLC and high PD-L1 expression. No significant differences in survival were observed according to the type of tumor sample or clinical characteristics.

Keywords: Non Small Cell Lung Cancer, high PD-L1 expression, immunotherapy

P42.04 Prognosis Factors in Advanced Lung Cancer Patients Treated With Checkpoint Inhibitor-Based Immunotherapy

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Introduction: This study aims to analyze the efficacy of checkpoint inhibitor-based immunotherapy in advanced lung cancer patients, and explore the prognosis factors. **Methods:** Lung cancer patients treated with checkpoint inhibitor-based immunotherapy at a single institution from May 2017 to May 2020 were reviewed retrospectively. Tumor response was assessed according to immune response evaluation criteria in solid tumors (iRECIST). Survival estimates were evaluated as overall survival (OS) and progression free survival (PFS) by Kaplan-Meier survival curves. Prognosis factors were assessed by univariate and multivariate Cox-regression analyses. **Results:** Checkpoint inhibitor-based immunotherapy was administered in 84 lung cancer patients. Among these patients, only one was complete response, 25 were partial response, 34 were stable diseases and 24 were progressive disease. The median OS and median PFS were 25.93months and 6.90months, respectively. Cox multivariate analysis showed that, application of large dose corticosteroids (HR = 2.518 P = 0.004), late-line treatment (HR = 2.394 P = 0.003) and higher neutrophil to lymphocyte ratio (NLR) (HR = 2.682 P = 0.001) were related with poorer PFS. Application of large dose corticosteroids (HR = 3.216 P = 0.002) and higher NLR (HR = 4.125 P < 0.001) were associated with poorer OS. **Conclusion:** Checkpoint inhibitor-based immunotherapy is an effective strategy for advanced lung cancer patients. Patients who get first line immunotherapy may get more survival benefits, NLR level at the first best response might be a prognosis factor, and application of high dose corticosteroids was associated with poor prognosis.

Keywords: Checkpoint inhibitor-based immunotherapy, Neutrophil to lymphocyte ratio, lung cancer

P43.01 Three-Dimensional Virtual Planning for Nodule Resection in Solid Organs: A Systematic Review and Meta-Analysis

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Introduction: The use of preoperative information support is an asset to assist surgeons during challenging procedures. Studies on image-guided surgery (IGS) must be encouraged to guarantee proper usage of these post-processing technologies, which are the manipulation of radiographic images to achieve further qualitative or quantitative data. IGS systems could improve intraoperative orientation, identification, and location of anatomical structures and their variations, decreasing surgeon's workload and contribute to performance enhancement. This study aimed to assess the effects of three-dimensional (3D)-imaging virtual planning (3DVP) for nodule resection in the following solid organs: lung, liver, and kidney. **Methods:** Databases (MEDLINE, EMBASE, and Cochrane Library) were searched through 31st December 2020 to include randomized and non-randomized controlled studies that compared outcomes of surgical resection of lung, liver, or kidney nodule resection with and without 3D virtual planning with computed tomography. From each article, mean operation time (OT), mean estimated blood loss (EBL), mean postoperative hospital stay (POHS), and the number of postoperative events (POE) were extracted. The effect size (ES) of 3D virtual planning vs. non-3D planning was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS), being also calculated a general ES from all studies for OT, EBL, and POHS. Data were pooled using a random-effects model. Heterogeneity between studies was tested with the Q-test, and the quantity of its extent with I^2 index. All P-values less than 0.005 were considered statistically significant. **Results:** The literature search yielded 2397 studies, from which 86 were reviewed, and 10 met the inclusion criteria. From these ten articles, the main site of operation was the lungs in two, the liver in three, and the kidney in five. Were included 897 patients, from which 469 (52.3%) had undergone 3DVP, and 428 (47.7%) were non-3DPV controls. There was a significant difference in OT between groups with a moderate ES favoring the 3D group (ES: -0.42; 95%CI: -0.56, -0.29; I^2= 83.1%; p<0.001). Regarding EBL, there was a significant difference between 3D and non-3D with a small ES favoring IGS (ES: -0.15; 95%CI: -0.28 - 0.02; I^2=22.5%; p=0.0236). There was no difference between the 3D and non-3D groups for both POHS (ES: -0.01; 95%CI: -0.19,0.17; I^2=0.0%; p=0.925) and POE (odds ratio (OR): 0.80; 95%CI: 0.54,1.19; I^2=0.0%; p=0.267). **Conclusion:** 3D-imaging planning for surgical resection of lung, liver, and kidney nodules could significantly reduce OT and EBL with no effects on immediate POHS and POE. Although immediate perioperative results (POHS and POE) had not shown a significant difference between groups, any improvements in OT and EBL could positively influence medium and long-term postoperative clinical outcomes, lowering rates of surgical site infections, for instance, due to reduced OT.

Keywords: Three-dimensional, image-guided surgery, solid organs

P43.02 Inconsistencies Within Biomarker Test Reports Provide Opportunities for Future Patient Education

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Introduction: Targeted therapy and associated biomarker testing for somatic (acquired) alterations and other types of non-genomic biomarkers are becoming more common for the treatment of patients with lung cancer. Yet, the reports of test findings for providers to use in discussion with patients are not always written with the patient in mind. To support shared decision making, increased patient education may be needed to explain test results and how patients can communicate with providers about results and next steps for treatment. The purpose of this study was to identify differences and commonalities within biomarker test reports to inform future patient educational interventions. **Methods:** An audit process was conducted for 12 biomarker reports from commercial and governmental entities received from December 2020 to January 2021. Qualitative coding conducted by a minimum of 2 researchers was used to structure and categorize the information in the reports. Up to 4 academic hospital reports are still being collected and will be added to the study results for the final conference presentation. **Results:** The report audit included 3 FDA companion diagnostic (CDx) reports and 9 laboratory-developed tests (LDTs). Only 4 of the 9 LDT reports included a disclaimer that the tests were not all approved by the FDA. Overall, reports had a range of 6-37 pages in length; 3 of the 12 included a cover page including patient characteristics. Seven reports did not specify whether they were final and only 4 indicated the physician as the intended target audience. Reports varied on what and how much patient information was included. All reports indicated the disease type, 11/12 indicated the patient gender and age, and 9/12 included the cancer stage and patient address. Reports were inconsistent on including lab contact information and certification of results. Further, reports were inconsistent on the information used to describe the sample collected. Ten reports included a results summary, but the information contained in the summaries varied widely. Reports used different terminology when describing therapeutic options; 7/12 referenced FDA approval. Terms for biomarker are not standardized: the terms “variant”, “mutation”, “biomarker”, “alteration”, and “gene” were used interchangeably. Only 4 reports included a glossary of terms, and 11/12 reports contained clinical trial information, but there was variation in the placement and amount of trial information. **Conclusion:** Biomarker testing results reports are inconsistent in the type of information they provide, raising the possibility of confusing patients and/or driving uncertainty about next steps. Developing education on interpreting biomarker test reports and communicating with providers about the significance of the results on a patient’s treatment decision is challenging, particularly for a patient audience that may not have sufficient health literacy. Specific recommendations for education will include consistent use of plain language terminology for biomarkers and treatment options, interpreting results, and engaging in next steps for clinical trials.

Keywords: Biomarker test results reports, Patient education, Inconsistent terms

P43.03 LUPA-01: An Observational Study to Monitor Lung Cancer Patients' Activity and Assess Performance Status through a Wearable Device in Spain

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Introduction: Although standard measurement instruments of patients' Performance Status (PS) are simple and useful, they are subject to bias and limitations. PS assessment is key for the therapeutical decision making in cancer; however, the literature reports conflicting data about the reliability of PS measurements. Electronic Activity Monitoring (EAM) wearable devices that are able to objectively monitor daily life physical activity (PA) has recently started to be used in clinical and research oncology fields. According to the latest evidence, PA in terms of daily steps and awake time spent immobile are associated with PS. It is less clear whether other parameters might also be associated with PS. Interestingly, beyond PA, EAMs in form of wrist actigraphy have also been used in oncology to measure sleep quality (SQ), which is known to be highly related to PA. However, the use of these technologies is only emerging in these fields and further clinical research incorporating them is imperative to analyze PS. The objective of this study is to assess if it is possible to collect wearable-based PA measures and if they could correlate with ECOG-PS assessments. Also to evaluate if changes in patient-reported outcomes measures, SQ, and symptoms correlate with PS changes. **Methods:** LUPA-01 is an observational study that aims to objectively measure PS in Lung Cancer patients (NCT04751162). This is a 2-phase study and first patient in (FPI) was in February 2021. Participants are being asked to wear an actigraphy device and to install a mobile app on their smartphones for tracking PA, SQ and symptoms for 3 weeks. The ECOG-PS is being assessed by clinician at both baseline and subsequent visit after the 3 weeks. Correlations between ECOG-PS and wearable plus app-based data will be examined. Phase 1 is a feasibility study with a limited sample (N=10) of patients enrolled in 2 clinical sites to assess perceived utility. In Phase 2, 81 patients will be enrolled in 9 clinical sites equipped with both devices for 9 weeks. Scheduled visits will be made according to local standard practice. Data collected will be blinded to participants and clinical investigators. After the completion of the study, correlation analyses between ECOG-PS assessment by clinician and data collected through the wearable and app will be performed.

Keywords: wearable device, PS, Activity

P44.01 Clinical Predictive Markers of Response to Immunotherapy in Advanced Non-Small Cell Lung Cancer (NSCLC).

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Introduction: Overweight and obesity are associated with improved overall survival (OS) and progression-free survival (PFS) in patients treated with immune checkpoint inhibitors (ICI). EPSILoN score (EPSILoN), comprised of five clinical variables (smoking, Eastern Cooperative Oncology Group (ECOG) performance status, liver metastases, lactate dehydrogenase, and neutrophil-lymphocyte ratio), is a known predictive marker of response to immune checkpoint inhibitors (ICI). This study aims to validate body mass index (BMI) and EPSILoN as predictive markers of response in frontline ICI treatment of advanced NSCLC with or without concomitant chemotherapy. Clinical trials often underrepresent minority patients and do not stratify Hispanic patients. To our knowledge, this is the first study to assess these parameters among different race and ethnic groups. **Methods:** Patients with advanced NSCLC who received frontline ICI were identified using the electronic medical record. PFS and OS were retrospectively evaluated and stratified based on baseline BMI and EPSILoN. Due to lack of routine LDH testing, a modified EPSILoN (mEPSILoN) was used. Log-rank tests were used to compare PFS and OS between groups, and Kaplan-Meier curves were used to report PFS and OS. Subgroup analyses were performed for race and ethnicity and corresponding BMI and mEPSILoN were recorded. Patients in each group were quantified using descriptive statistics. **Results:** Thirty-six normal weight (NW) and 25 overweight and obese (OWO) patients were studied. Median PFS (mPFS) for OWO vs NW patients was 8.90 months vs 5.53 months (HR 0.54; 95% CI, 0.30-0.96; p=0.04). mPFS at 12 months was 45% for OWO patients and 23% for NW patients. Of patients with PD-L1 ≥50%, 14 patients were NW and 11 patients were OWO. Among patients with PD-L1 ≥50%, mPFS for OWO was not reached (NR) vs 6.73 months in NW patients (HR 0.23; 95% CI, 0.09-0.60; p=0.003), and the percent of patients that were PF at 12 months was 71% vs 15%. Of 56 patients with a calculable mEPSILoN, 29 patients had mEPSILoN 1 and 27 patients had mEPSILoN 2-3. Median OS for patients with mEPSILoN 1 vs 2-3 was NR vs 11.13 months (HR 0.32; 95% CI, 0.14-0.76; p=0.01) and 78% vs 49% survived at 12 months. Subgroup analyses showed that 67% vs 41% of Black Non-Hispanic patients (BNHP) vs White Non-Hispanic patients (WNHP) had mEPSILoN 2-3 while 60% vs 43% of all Black vs White patients had mEPSILoN 2-3. Twenty-two percent vs 48% of BNHP vs WNHP were OWO. **Conclusion:** OWO and lower mEPSILoN were associated with longer PFS and OS, respectively, in patients with advanced NSCLC who were treated with frontline ICI with or without concomitant chemotherapy, regardless of PD-L1 expression. These findings are consistent with studies that reported these parameters as predictive markers of response. This is the first study, to our knowledge, to evaluate these markers in frontline ICI treatment with or without chemotherapy. BNHP began ICI treatment with more advanced disease compared to WNHP. This finding is consistent when comparing all Black and White patients. Fewer BNHP were OWO vs WNHP, indicating possible poorer response to ICI. Further studies are needed to confirm these findings.

Keywords: immunotherapy, Predictive markers, non-small cell lung cancer

P44.02 Prevalence, Onset, and Severity of Renal Impairment With Pemetrexed/Carboplatin +/- Pembrolizumab in Metastatic Non-Squamous NSCLC

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Introduction: The combination of pembrolizumab, pemetrexed and carboplatin (p/p/c) is a NCCN category 1 recommendation for frontline treatment of metastatic non-squamous NSCLC, regardless of PD-L1 status. The purpose of this study is to retrospectively evaluate the real-world prevalence, onset, and severity of renal impairment in non-squamous NSCLC patients who received p/p/c compared to those who received pemetrexed and carboplatin (p/c). **Methods:** This retrospective review included patients with metastatic non-squamous NSCLC who received p/p/c or p/c as frontline treatment for metastatic disease. The primary outcome was difference in prevalence of renal impairment between the 2 groups, defined as grade 2 or greater increase in SCr per CTCAE v4.03. Secondary outcomes included difference in median time to onset of renal impairment between groups and difference in severity of renal impairment between groups. **Results:** A total of 100 patients met criteria and were included in this review. The majority of patients were male, former smokers and had an ECOG performance status of 1. The average age of patients in the p/p/c group was 73.6 years of age and in the p/c group was 63 years of age. The p/c group had a higher baseline CrCl versus the p/p/c group (88.9 versus 76.1 mL/min). For the primary outcome, 14 patients (29.2%) in the p/p/c group developed a grade 2 or higher increase in SCr, while 9 patients (17.3%) developed a grade 2 or higher increase in SCr in the p/c group. The median time to renal impairment was 118.5 days in the p/p/c group versus 63 days in the p/c group. Of the 14 patients receiving p/p/c who had a defined grade 2 or higher increase in SCr, 11 patients had a grade 2 increase, 2 patients had a grade 3 increase, and 1 patient had a grade 4 increase. Of the 9 patients receiving p/c who met the primary endpoint, all developed a grade 2 impairment. **Conclusion:** The prevalence of renal impairment in those who received p/p/c compared to those who received p/c was numerically higher. Also, the median time to renal impairment trended to occur later in the p/p/c group. Larger, prospective studies are needed to determine the true prevalence and mechanism of renal impairment in those receiving combination pembrolizumab, pemetrexed, and carboplatin.

Keywords: Real-world data

P45.01 Therapeutic effectiveness of Lorlatinib After Alectinib in Japanese Patients With ALK-Positive NSCLC in Real-World

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Introduction: Three anaplastic lymphoma kinase (ALK)-TKIs (crizotinib, alectinib and ceritinib) are available as 1st line setting in clinical practice in Japan. In the 2020 clinical practice guideline for lung cancer in Japan, lorlatinib is recommended as a subsequent therapy option for the patients with ALK-positive (ALK+) NSCLC whose disease has progressed after any ALK-TKI treatment. Alectinib, brigatinib and ceritinib are also recommended in the guideline. In addition, chemotherapy may be used after alectinib. However, there are no data to demonstrate the ALK TKI sequence treatment of loratinib as 2nd/3rd line after alectinib in clinical practice in Japan. Therefore, it is important to understand the post-marketing use of lorlatinib in Japanese patients with ALK+ NSCLC in real-world clinical practice to evaluate clinical effectiveness of lorlatinib. Main objective for this study was to reveal the real-world clinical effectiveness of lorlatinib in second /later line setting as ALK TKI sequence treatment after failure of alectinib in Japanese ALK+ NSCLC patients. **Methods:** The claims data from diagnosis procedure combination (DPC) hospitals provided by Medical Data Vision Co., Ltd. (MDV) were used for this study. Patients in this MDV had been identified from the following criteria; (1) ICD10 diagnosis of lung cancer (C34) and (2) patients who received alectinib and with prescription order for lorlatinib directly after alectinib therapy. In this review, patients with loraltinib in 2nd line or 3rd + line were defined based on the absence or presence of prescription of other drugs before the start of alectinib prescription. Baseline characteristics were summarized as descriptive analysis. The median DOT was estimated using the Kaplan–Meier (KM) method and individual DOT and treatment patterns were visualized as swimmer's plot for DOT including lorlatinib. **Results:** From the MDV data, 319 patients were identified as who received alectinib and with prescription order for an ALK-TKI (lorlatinib or ceritinib) or chemotherapy (pemetrexed(PEM) or PEM+ cisplatin(CDDP) or bevacizumab(BEV)+PEM+CDDP) directly after alectinib treatment. The gender (female; 59.9 %) was similar to that in clinical trials, however, the mean age of patients prescribed with alectinb was 61years and higher than that of previous report in clinical trials. 174 patients were prescribed lorlatinib after alectinib. Of the 174 patients who were prescribed lorlatinib after alectinib, median DOT estimated from KM was 149 days (95% CI; 109-200). 136 and 38 patients were prescribed lorlatinib in 2nd line and 3rd + line setting, respectively. **Conclusion:** ALK-TKIs including lorlatinib and chemotherapy treatment sequences after alectinib were observed nationwide in Japan. About half of the patients who were prescribed alectinib were prescribed lorlatinib as the next treatment following alectinib. The median duration of lorlatinib treatment in patients with ALK+NSCLC as the next treatment for alectinib was around 5 months.

Keywords: Lung cancer, Real world data, ALK+NSCLC, Lorlatinib

P45.02 Molecular Profile of Resistance Mutations Post Multiple Lines of Tyrosine Kinase Inhibitors in ALK-Positive Non-Small-Cell Lung Cancer

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Introduction: A large majority of ALK rearranged lung cancer patients show significant clinical response to various generations of ALK tyrosine kinase inhibitors (TKI). Despite long lasting remissions resistance eventually develops to these therapies. Most resistance mechanisms are targeted including mutations in ALK kinase domain and ALK gene amplifications and others are off target involving other gene pathways. These mechanisms may cause conformational changes that alter drug binding or develop other escape mechanisms. We share our experience of detecting molecular resistance mechanisms using next generation sequencing (NGS) post multiple lines of ALK inhibitor therapies. **Methods:** From October 2018 to March 2021, ALK-positive NSCLC patients who developed primary or secondary resistance after multiple lines of ALK TKIs and underwent NGS on secondary biopsy were analyzed for various mechanisms of resistance using thermofischer Ion Torrent™ Oncomine™ Focus 52 gene Assay . These cases were previously diagnosed as ALK translocated by ALK Ventana immunohistochemistry (IHC). **Results:** There were 21 cases which included 16 females and 5 males. The age ranged from 32 to 82 years (median 54 years). 23.8 %(5/21) patients had no molecular abnormality. 17/21(81%) had EML4-ALK.E13A20 variant, 2/21(1 %) had EML4-ALK. E20A20 variant and one case (0.5%) was KLC1 (9) - ALK (20) variant. ALK gene amplification was found in 2 cases and FGFR1 amplification in 1 case. Compound ALK gene mutations (p.Gly1269Ala, p.Asp1203Asn & p.Leu1196Met, p.Asp1203Asn) were seen in 2 cases and ALK p.Asp1203Asn and ALK p.(Q1188_L1190del) were seen in one case each. The variant allele frequency for ALK tyrosine kinase domain mutations ranged from 15 to 35%. 2 cases had additional MET skipping mutation, 1 case had KRAS G12C mutation and 1 had BRAF V600E mutation. **Conclusion:** NGS provides a great tool to view the insights of molecular mechanisms after multiple lines of TKIs in ALK rearranged lung cancers. These molecular abrasions also help strategize the future development of newer therapies.

Keywords: NSCLC, resistance, ALK rearranged

P45.03 Tepotinib in Patients with MET exon 14 (METex14) Skipping NSCLC as Identified by Liquid (LBx) or Tissue (TBx) biopsy

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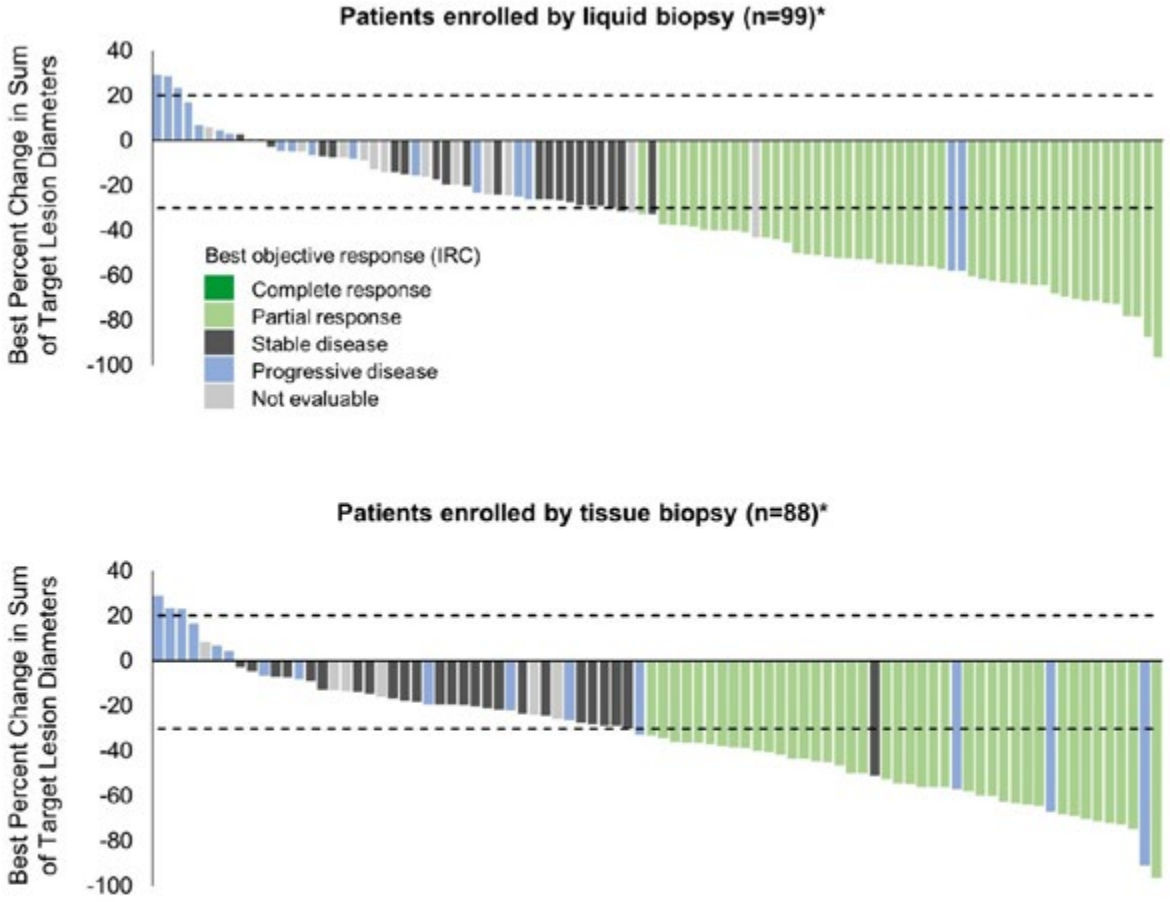
Introduction: METex14 skipping, an oncogenic driver occurring in 3–4% of NSCLC, can be detected by DNA- (NGS, Sanger sequencing) and RNA- (NGS, quantitative PCR assays) based methods using LBx or TBx samples. We investigated patient demographics and tepotinib efficacy according to the method of METex14 skipping detection. **Methods:** In the Phase II VISION study, patients with METex14 skipping advanced NSCLC, detected by LBx and/or TBx, received 500 mg (450 mg active moiety) tepotinib once daily. Primary endpoint was objective response by independent review committee using RECIST 1.1. Secondary endpoints included duration of response (DOR), and progression-free survival (PFS). Analysis in patients enrolled by LBx (L+) or TBx (T+) biopsy was predefined. **Results:** As of July 1, 2020, 7,673 patients had been pre-screened; 264/6,798 were positive by LBx, and 223/2,184 by TBx, for METex14 skipping (1.0% of LBx and 31.5% of TBx samples were not evaluable/analyzed). Subsequently, 99 L+ and 88 T+ patients were enrolled in Cohort A (**Table**; 36 patients were L+/ T+). LBx may have been used in patients with higher tumor burden, and those not suitable for TBx. Median treatment duration (range) was 6.9 months (0.7–43.3) in L+ patients (n=18 with treatment ongoing), and 7.0 (<0.1–43.3) in T+ patients (n=16 ongoing). Objective response rate (ORR) in L+ patients was 47.5% (95% CI: 37.3, 57.8), median (m) DOR was 10.8 months (7.6, 18.5), and mPFS was 8.5 months (6.7, 10.9). In T+ patients, ORR was 45.5% (34.8, 56.4), mDOR was 12.4 months (9.9, not estimable), and mPFS was 11.0 months (8.2, 13.7). Tumor shrinkage was observed in 87.9% of L+, and 89.8% of T+ patients (**Figure**).

		Patients enrolled by liquid biopsy* (n=99)	Patients enrolled by tissue biopsy† (n=88)
Negative tissue biopsy result, n (%)		5 (5.1)	-
Negative liquid biopsy result, n (%)		-	44 (50.0)
Median age, years (range)		72.4 (49–88)	73.1 (41–94)
Sex, n (%)	Male	52 (52.5)	49 (55.7)
	Female	47 (47.5)	39 (44.3)
Region	North America	28 (28.3)	24 (27.3)
	Europe	51 (51.5)	41 (46.6)
	Asia	20 (20.2)	23 (26.1)

History of smoking, n (%)	Yes	51 (51.5)	44 (50.0)
	No	44 (44.4)	36 (40.9)
	Missing	4 (4.0)	8 (9.1)
ECOG performance status, n (%)	0	23 (23.2)	28 (31.8)
	1	76 (76.8)	60 (68.2)
Histological subtype, n (%)	Adenocarcinoma	84 (84.8)	80 (90.9)
	Squamous	10 (10.1)	7 (8.0)
	Sarcomatoid	3 (3.0)	0
	Other	2 (2.0)	1 (1.1)
Line of therapy	Treatment-naïve	44 (44.4)	42 (47.7)
	Previously treated	55 (55.6)	46 (52.3)
≥3 lesions, n (%)	Target	28 (28.3)	14 (15.9)
	Non-target	50 (50.5)	30 (34.1)
Median tumor load of target lesions, mm (range)		64.5 (14.3–224.2)	53.4 (10.2–180.2)
Median time since initial cancer diagnosis, years (range)		0.4 (<0.1–4.4)	0.7 (<0.1–25.3)

*DNA-based Guardant Health 360 assay; †RNA-based Oncomine Focus assay. ECOG, Eastern Cooperative Oncology Group.



*Three patients (one L+ and two T+) are not shown due to baseline or on-treatment measurement not being available. IRC, independent review committee.

Conclusion: Tepotinib demonstrated durable clinical activity in patients with METex14 skipping NSCLC, as detected by LBx or TBx. These complementary testing methods led to similar efficacy with tepotinib in the VISION study.

Keywords: MET inhibitor

P45.04 Phase II Study of Brigatinib in ROS1 Positive Non-Small Cell Lung Cancer (NSCLC) Patients Previously Treated with Crizotinib: Barossa Cohort 2

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Introduction: Brigatinib is a next-generation tyrosine kinase inhibitor targeting ALK and ROS1. Crizotinib is the first drug approved for the treatment of ROS1 fusion-positive NSCLC. Standard treatment for crizotinib-resistant ROS1 positive NSCLC is not established. Barossa is a multicenter, phase II basket study of brigatinib in patients with ROS1 positive solid tumors. This study is composed of three cohorts. ROS1 inhibitor-naïve ROS1 positive NSCLC patients were enrolled in the cohort 1, and ROS1 positive NSCLC patients previously treated with crizotinib were enrolled in the cohort 2. Patients with ROS 1 positive solid tumors other than NSCLC were enrolled in the cohort 3. This time we report the cohort 2 results. **Methods:** Patients with advanced, previously treated with crizotinib, ROS1 positive NSCLC received brigatinib at a dose of 180 mg once daily with a 7-day lead-in period at 90 mg. The primary end point was objective response rate (ORR; RECIST 1.1) by independent review. Key secondary endpoint was PFS, OS, intracranial ORR (iORR), and safety. The sample size was set at 19 patients, with a one-sided alpha of 0.05, beta of 0.2, and threshold and expected values for primary endpoint of 20% and 50%, respectively. **Results:** From July 2019 and Jan 2020, 19 patients were enrolled from 9 institutions. Baseline characteristics as follows: median age (range): 60 (31-75) years; women, n=10 (53%); ECOG PS of 0 to 1, n=18 (95%); never smoker, n=11 (58%); tumor histopathological type: adenocarcinoma, n=18 (95%). Five and 6 patients achieved confirmed PR and SD assessed by independent review, respectively at data cutoff date of 30 Oct 2020. The ORR was 26.3% (90%CI, 11.0-47.6), and the disease control rate was 57.9% (95%CI, 33.5-79.7). The median duration of follow-up for PFS was 12.0 months. The median PFS was 7.3 months (95% CI, 1.3-9.3), and the 1-year PFS rate was 26.9% (95%CI, 9.2-48.6). Six patients had measurable brain metastases. The iORR was 50.0% (95%CI, 11.8-88.2), and the intracranial disease control rate was 83.3% (95%CI, 35.9-99.6). Grade ≥3 TRAEs were CPK increased (21.1%), infection (5.3%), AST and/or ALT increased (5.3%), hypercalcemia (5.3%), anorexia (5.3%), hypoxia (5.3%), erythema (5.3%), hypertension (5.3%). Pneumonitis was observed in one patient (5.3%, Grade 2). No treatment-related death was observed. **Conclusion:** Brigatinib has modest activity for ROS1 positive NSCLC patients previously treated with crizotinib, and marked intracranial efficacy. The safety profile of brigatinib was consistent with previous studies. Enrollment of the cohort 1 for ROS1 inhibitor-naïve NSCLC patients is ongoing, and the data will be presented at a future congress. Clinical trial information: JapicCTI-194851.

Keywords: Crizotinib-resistant, Brigatinib, ROS1

P45.05 Sequencing of PD-1 Inhibitors and TKIs in Metastatic NSCLC with MET Exon 14 Skipping Mutation May Influence Survival

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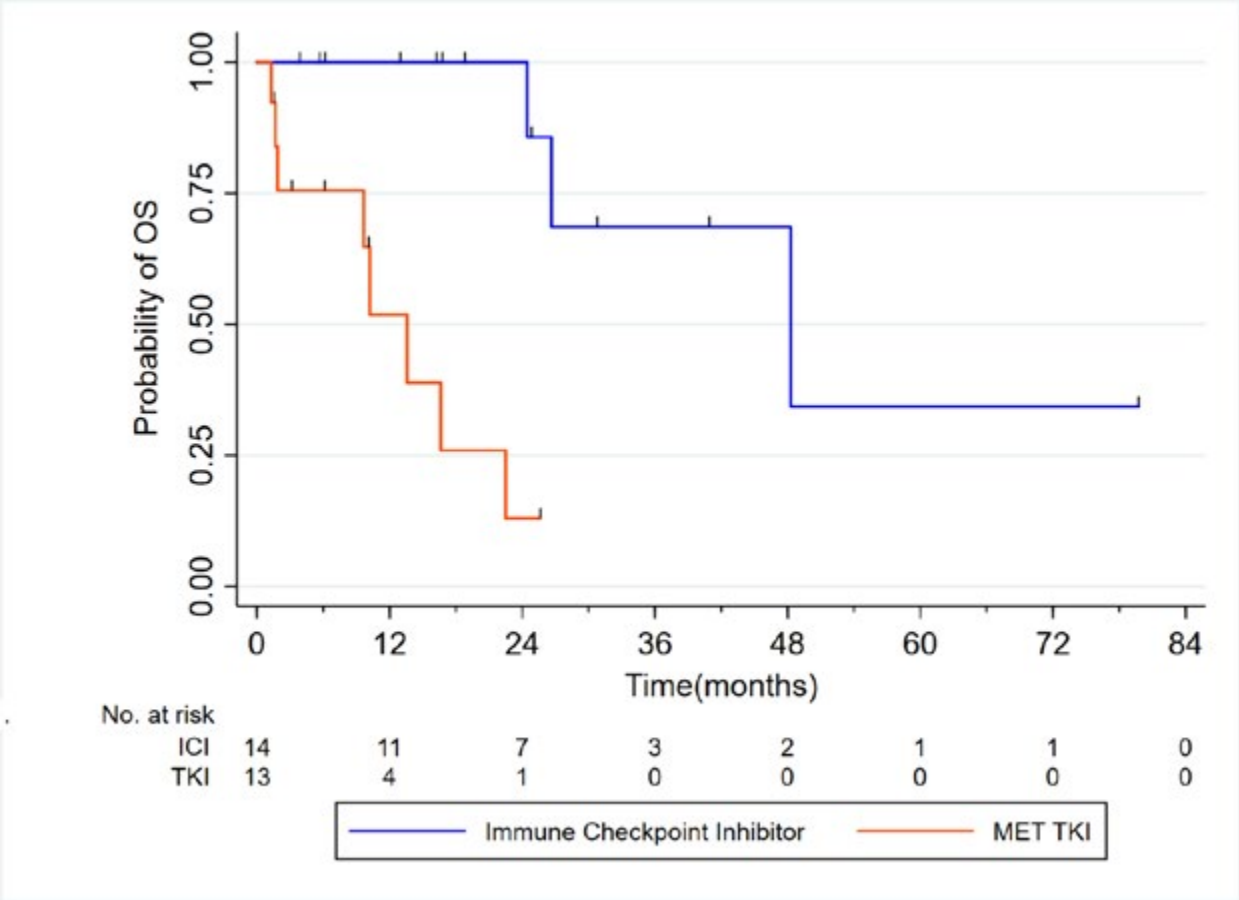
Introduction: The treatment landscape for patients with metastatic non-small cell lung cancer with a MET exon 14 skipping mutation (MET ex14) is rapidly changing, with recent approvals of MET selective tyrosine kinase inhibitors (TKIs) and reports of durable response to immune checkpoint inhibitors (ICI). Currently there are no published data that inform the sequencing of TKIs and ICI regimens. We sought to characterize treatment patterns and sequencing outcomes at 3 Ontario cancer centres. **Methods:** We reviewed all mNSCLC patients with MET ex14 identified by tissue or plasma NGS in the last 4 years. Patients with EGFR co-mutation or MET amplification alone were excluded. All systemic therapies and outcomes of ORR, PFS, OS, and adverse events (AEs) were captured. **Results:** We identified 46 patients with MET alterations, of whom 32 had MET ex14: median age 73 years (54-92), 63% female, 75% non-smokers, 21% ≥ECOG 2, 19% sacrcomatoid/pleomorphic histology, 69% PD-L1 ≥50%. Among 16 patients who received ICI, ORR was 50% with ICI monotherapy 60% with ICI plus chemotherapy. Responses were seen in 50% of non-smokers (n=12). The median PFS with ICI was 6.0 months (1.9-24.9). MET TKIs were received by 21 patients (17 crizotinib, 3 capmatinib, 1 cabozantinib), with an ORR of 29%. The median PFS with TKIs was 2.6 months (1.2-8.4). Median OS for the entire cohort was 24.4 months (10.2-48.3). Patients who received initial TKI (n=13) compared to those who received initial ICI (n=14) had significantly shorter OS (13.6 vs 48.3 months), even after adjusting for ECOG (HR 17.0; p=0.009) (Figure). All patients who progressed after ICI (9/13) received further treatment while only 50% of patients who progressed after TKI (8/11) received subsequent therapy. 8 patients received TKI therapy after ICI with a median time to TKI of 34 days (16-181). 6 patients (85.7%) experienced an early grade ≥3 AE (4 transaminitis, 2 pneumonitis) resulting in permanent discontinuation of TKI in half of patients. There were no treatment-related deaths.



Conclusion: Patients with MET ex14 NSCLC benefit from ICI irrespective of PD-L1 expression and smoking history. ORR and PFS with earlier generation TKIs (crizotinib) were poor. Patients who received ICIs as initial appears to have better OS. However, increased toxicity is seen when a TKI is used after ICI and careful monitoring is necessary. Future studies focusing on the optimal sequencing of TKIs and ICI-containing therapy should be prioritized, as well as broader access to newer generation MET TKIs with greater activity.

Keywords: MET exon14, MET TKI, Immune checkpoint inhibitors

P45.06 Overall Survival From a Phase 2 Study of Crizotinib in East Asian Patients With ROS1+ Advanced Non-Small-Cell Lung Cancer

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Introduction: Crizotinib provided a meaningful clinical benefit (objective response rate [ORR] of 71.7% and median progression-free survival of 15.9 months) in the primary analysis of a phase 2 study in East Asian patients with advanced ROS1+ NSCLC (NCT01945021; Wu, JCO. 2018;36:1405-11). Median overall survival (OS) was 32.5 months, but was not mature at the time of the primary analysis, with a median duration of follow-up of 21.4 months. Here we present updated OS and safety after an additional 3 years of follow-up. **Methods:** In this phase 2, open-label, single-arm trial, East Asian patients with ROS1+ NSCLC who had received ≤3 prior systemic therapies were treated with crizotinib 250 mg BID on a continuous daily dosing schedule in 28-day cycles. The primary endpoint was ORR by independent radiology review (previously reported); OS and safety were secondary endpoints. **Results:** The median age at baseline (N=127) was 51.5 y; 57.5% of patients were female, 97.6% had adenocarcinoma, 100% had ECOG PS 0/1, and 18.9%, 41.7%, 24.4%, and 15.0% had 0, 1, 2, or 3 prior chemotherapy regimens; and 39% of patients received subsequent anticancer therapy. As of July 1, 2020, median duration of follow-up for OS was 56.1 months. Median OS was 44.2 months (95% CI: 32.0, not reached [NR]) for the total population, 31.2 months (95% CI: 14.8, NR) for Japanese patients (n=26), 48.5 months (95% CI: 32.8, NR) for Chinese patients (n=74), and 43.7 months (95% CI: 21.7, NR) for other patients (n=27). Median OS was 51.5 months (95% CI: 23.3, NR) for patients with 0 prior regimens (n=24), 33.5 months (95% CI: 20.6, NR) for those with 1 prior regimen (n=53), 44.4 months (95% CI: 21.7, NR) for those with 2 prior regimens (n=31), and 48.0 months (95% CI: 19.5, NR) for those with 3 prior regimens (n=19). Median duration of crizotinib treatment was 101.7 weeks (range: 0.6-291.9 weeks). A total of 97.6% of patients had AEs considered related to crizotinib (TRAE), and 8.7% had treatment-related serious AEs. The 6 most common TRAEs of any grade were elevated transaminases (66.9%; 5.5% grade 3, 1.6% grade 4, 0 grade 5), vision disorder (48.0%; 0 grades 3-5), diarrhea (41.7%; 0.8% grade 3, 0 grades 4-5), nausea (41.7%; 1.6% grade 3, 0 grades 4-5), neutropenia (33.9%; 9.4% grade 3, 2.4% grade 4, 0 grade 5), and vomiting (33.9%; 0 grades 3-5). TRAEs led to crizotinib dose reductions in 17.3% of patients and permanent treatment discontinuations in 2.4% of patients. One death due to an AE (respiratory failure), which occurred after the primary analysis date, was considered treatment-related because the investigator relationship was reported as unknown. **Conclusion:** These results represent the largest phase 2 trial of an ALK inhibitor to treat patients with ROS1+ advanced NSCLC and provide a new benchmark for OS in East Asian patients. The safety profile with long-term follow-up was consistent with the known safety profile of crizotinib and supports the continued use of crizotinib in the treatment of patients with ROS1+ advanced NSCLC.

Keywords: crizotinib, Clinical trial, NSCLC

P45.07 Real-World Clinically-Relevant Toxicities of ALK TKIs in a Cohort of Patients With Advanced/Metastatic ALK+ NSCLC

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Introduction: Treatment with ALK-TKIs significantly prolongs overall survival (OS) in patients with ALK+ non-small cell lung cancer (NSCLC). Approximately 20-40% of patients experience adverse events (AEs) leading to dose reductions/temporary discontinuation in the published phase III trials and permanent treatment discontinuation due to toxicity in approximately 5-15%. Toxicity profiles of the different inhibitors overlap but some are also distinct. We describe rates of clinically-significant AEs and specific toxicity profiles in a real-world cohort of patients with ALK+ NSCLC. **Methods:** Patients with ALK+ advanced NSCLC at Princess Margaret Cancer Centre were included in this analysis; date of data cut-off was March 18, 2021. All AEs leading to treatment modifications were abstracted retrospectively along with clinico-demographic, treatment and survival data. Treatment modifications included dose reduction and temporary/ permanent discontinuation due to toxicity. **Results:** Of 147 patients with advanced ALK+ NSCLC, 138/94% received at least one ALK-TKI: alectinib (103/75%), crizotinib (75/54%), ceritinib (31/22%), lorlatinib (27/20%) and brigatinib (22/16%). In total, 258 individual ALK TKI lines (138 first-line, 72 second-line, 30 third-line, 20 fourth-to-seventh lines) of TKI-treatment were given. Median follow-up time was 26.4 months; 79 patients in active follow-up had ongoing ALK-TKI treatment at data cut-off. Summing all treatment durations, median (IQR) duration of receiving any ALK-TKI therapy/patient was 19.1 (29.0) months. While on ALK-TKI, 170 adverse events (AE) leading to treatment modifications occurred. In 112/66% cases these were related to a single AE: 59/53% were attributed to symptomatic toxicities; 53/47% were attributed to asymptomatic laboratory abnormalities. In contrast, 58/34% treatment modifications were attributed to a combination of AEs. Combined AEs were mostly symptom-related (23/40%) and symptom and lab-related (30/52%) and only rarely driven by multiple asymptomatic laboratory abnormalities alone (5/8%). Overall, 74/54% patients had at least one ALK-TKI treatment modification due to toxicity. Older aged patients (median age 62 vs 53 years, p=0.007) and never-smokers (84% vs 68%, p=0.04) were significantly associated with increased risk of AEs leading to treatment modification. Counting only one treatment modification per patient per ALK-TKI, treatment modifications occurred in 102/40% treatment lines: 28/37% patients on crizotinib, 19/61% with ceritinib, 33/32% with alectinib, 9/41% with brigatinib, and 8/30% with lorlatinib. Permanent discontinuation was observed in 63/24% treatment lines overall and in a much higher rate with crizotinib and ceritinib (45/43%) compared to the new generation-TKIs (alectinib, brigatinib and lorlatinib; 18/12%). As expected, AEs leading to treatment modifications were mainly gastrointestinal (26%) and liver toxicity (16%) with crizotinib and ceritinib, whereas the spectrum of AEs with the new-generation TKIs (alectinib, brigatinib, lorlatinib) leading to treatment modifications was broader, with less gastrointestinal (7%) and liver toxicity (10%) but more myalgia/CK elevation (6%) and slightly more neurotoxicity (5%). Median overall survival (OS) in patients with at least one treatment modification trended, but was not significantly different from patients without any treatment modification (47.0 vs 57.8 months, p=0.09). **Conclusion:** In a real-world cohort, treatment modifications on ALK-TKI were needed frequently, even with the newer generation of ALK-TKIs, highlighting the importance of availability of different ALK-TKIs for patients experiencing AEs to ensure tolerable targeted treatment.

Keywords: toxicity, ALK TKI, real-world

P45.08 Lorlatinib for Previously Treated ALK-Positive Advanced NSCLC: Primary Efficacy and Safety Data from a Phase 2 Study in China

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Introduction: Lorlatinib, a third-generation inhibitor of anaplastic lymphoma kinase (ALK), was shown in a global Phase 2 study to have potent overall and intracranial (IC) anti-tumor activity in patients with ALK-positive advanced non-small cell lung cancer (NSCLC) after progression on first- and/or second-generation ALK inhibitors (NCT01970865). Here we report primary data from a multicenter Phase 2 study conducted in China that investigated lorlatinib in ALK inhibitor-treated patients with ALK-positive NSCLC (NCT03909971). **Methods:** This ongoing, open-label, Phase 2 study enrolled patients in China with ALK-positive locally advanced/metastatic NSCLC and disease progression after crizotinib as the only ALK-inhibitor (Cohort 1), or after one ALK-inhibitor other than crizotinib, with or without prior crizotinib (Cohort 2). Patients with CNS metastases were eligible to enroll; one prior line of chemotherapy was permitted. All patients received lorlatinib 100 mg QD in a continuous 3-week cycle. The primary endpoint was objective response rate (ORR) by independent central review (ICR) per RECIST v1.1 in Cohort 1. Secondary endpoints included ORR in Cohort 2, IC-ORR, PFS, overall survival (OS), and safety. **Results:** In total, 109 patients were enrolled: 67 to Cohort 1 and 42 to Cohort 2. Among these, 36 patients in Cohort 1 and 21 patients in Cohort 2 had ≥1 intracranial lesion at baseline per ICR assessment. At data cutoff (August 10, 2020), ORR (95% CI) by ICR in Cohort 1 was 70.1% (57.7–80.7) and in Cohort 2 was 47.6% (32.0–63.6). IC-ORR was 80.6% in Cohort 1 and 47.6% in Cohort 2. See **Table** for additional response data. Median DOR by ICR was not reached in Cohort 1, and was 11.2 months in Cohort 2. Median PFS by ICR was not reached in Cohort 1, and was 5.6 months in Cohort 2. OS data were immature and median OS was not estimatable in either cohort. Median treatment duration was 11.4 months in Cohort 1 and 8.4 months in Cohort 2. Grades 3–4 treatment-related adverse events (TRAEs) occurred in 36 (53.7%) patients in Cohort 1 and 17 (40.5%) patients in Cohort 2; serious TRAEs occurred in 4 (6.0%) and 5 (11.6 %) patients in each cohort, respectively. No Grade 5 TRAE were reported in either cohort. The most commonly-reported any-grade AEs overall were hypercholesterolemia (92.7%) and hypertriglyceridemia (91.7%). **Table 1.** Summary of response data

	Cohort 1	Cohort 2	Total
Best overall response by ICR			
Patients in analysis	N=67	N=42	N=109
ORR, n (%)	47 (70.1)	20 (47.6)	67 (61.5)
95% CI	57.7–80.7	32.0–63.6	51.7–70.6
CR	8 (11.9)	2 (4.8)	10 (9.2)
PR	39 (58.2)	18 (42.9)	57 (52.3)
SD	8 (11.9)	6 (14.3)	14 (12.8)
Best overall intracranial response in patients with any intracranial lesions			
Patients in analysis	N=36	N=21	N=57
IC-ORR, n (%)	29 (80.6)	10 (47.6)	39 (68.4)
95% CI	64.0–91.8	25.7–70.2	54.8–80.1
CR	19 (52.8)	6 (28.6)	25 (43.9)
PR	10 (27.8)	4 (19.0)	14 (24.6)
SD	0	2 (9.5)	2 (3.5)

CI, confidence interval; CR, complete response; IC, intracranial; ICR, independent central review; ORR, objective response rate; PR, partial response; SD, stable disease

Conclusion: Lorlatinib showed robust clinical activity in Chinese patients with previously treated ALK-positive NSCLC, including those with CNS metastases. Safety data were consistent with previous findings.

Keywords: CNS metastases, Lorlatinib, ALK-positive NSCLC

P45.09 Real-World Sequencing of ALK-TKIs in Advanced Stage ALK-positive NSCLC patients in Canada

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Introduction: Overall survival (OS) of patients with ALK+ Non-Small Cell Lung Cancer (NSCLC) has been prolonged with the introduction of ALK-tyrosine kinase inhibitors (TKI) over the last decade. The aim of this analysis was to study treatment patterns, sequencing of ALK-TKIs and outcomes in a real-world cohort of ALK+ NSCLC patients. **Methods:** Data were analyzed for all patients with advanced/metastatic ALK+ NSCLC seen at Princess Margaret Cancer Centre (data cut-off date March 18, 2021), regardless of whether they were initially diagnosed with early stage (relapsed) or de novo advanced/metastatic NSCLC. Clinico-demographic, treatment and survival data were collected retrospectively. **Results:** Of 147 patients with advanced/metastatic ALK+ NSCLC, 32 were initially early-stage, while 115 were de novo advanced/metastatic. The median age was 59 years (range: 31 – 93); 84 (57%) were female; 111 (76%) were never-smokers; 32 (22%) had an ECOG performance status (PS) of 0, while 78 (55%) were PS1, and 33 (23%) were PS2+; 54 (47%) were Asian; 40 (35%) were Caucasian. Median follow-up time was 26.9 months from diagnosis of advanced/metastatic disease. Among the 147 patients, 138 (94%) received ALK-TKIs: 66 (48%) received only one ALK-TKI, while 42 (30%) had received two; 30 (22%) had received at least three. Overall, 75 (54%) had received crizotinib; 103 (75%) alectinib; 31 (22%) ceritinib; 22 (16%) brigatinib and 27 (20%) lorlatinib. Crizotinib (74; 54%) and alectinib (59; 43%) were given as first ALK-TKI in the majority of cases, whereas ceritinib, brigatinib and lorlatinib mainly were administered after failure of previous ALK-TKI and/or other systemic therapy in 26 (31%) in second-line, 25 (30%) in third-line, 12 (15%) in fourth-line, and 17 (21%) in fifth-line or beyond. Median progression-free survival irrespective of treatment line given was 9 months for crizotinib, 41.6 months for alectinib, 3.1 months for ceritinib, 3.7 months for brigatinib and 2.8 months for lorlatinib. Unlike clinical trials, brigatinib and lorlatinib were given often in PS 2+ patients near end-of-life or as fourth or fifth-line treatment. After removing such patients, median PFS was 7.1 (95%CI 1.8-NA) for brigatinib and 7.2 (95%CI 1.4-NA) for lorlatinib. Median overall survival (OS) from advanced/metastatic disease was 56.7 months, but is likely to increase as the first-line alectinib cohort matures. Median OS for patients treated first-line with crizotinib was 46.1 months, and not yet reached in patients treated with first-line alectinib. A total of 31 (21%) patients died within two years of diagnosis of advanced/metastatic disease. These patients did not significantly differ in age, sex or PS from patients with prolonged survival. Of these patients, 6 (19%) never received an ALK-TKI, but the majority received two lines (21; 68%) of ALK-TKI treatment. **Conclusion:** Sequencing of multiple ALK-TKIs has improved outcomes, but there is no single sequencing standard. Use of next generation ALK-TKIs in earlier lines of treatment may lead to more effective outcomes. Despite substantial progress, approximately 20% of patients still do poorly; identification of novel drug resistance mechanisms may further improve outcomes.

Keywords: ALK+ Non-Small Cell Lung Cancer, Treatment Sequencing, Survival Outcomes

P45.10 Effects of ALK Tyrosine Kinase Inhibitors in the Treatment of Metastatic NSCLC: A Systematic Review and Meta-Analysis

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Introduction: Somatic gene rearrangements of anaplastic lymphoma kinase (ALK) are seen in approximately three to five percent of NSCLC with inhibition of ALK leading to suppression of growth and survival signaling pathways. Several ALK tyrosine kinase inhibitors (TKIs) are now available with the question of whether next-generation ALK TKIs are best prioritized to the first-line metastatic setting. **Objective**: To assess the effects of oral next-generation ALK TKI therapy in the first line systemic treatment of adult patients diagnosed with metastatic ALK positive non-small cell lung cancer (NSCLC) compared to the first generation ALK TKI Crizotinib with a particular focus on blood brain barrier penetration. **Methods: Search methods**: A literature search for manuscripts was conducted using MEDLINE (1946 to January 28, 2021), EMBASE (1974 to January 28, 2021), and CENTRAL (January 28, 2021). Ongoing trials were identified using ClinicalTrials.gov. Abstract listings from major relevant medical oncology conferences between June 2020 and January 2021 were also searched. **Selection criteria**: All randomized or quasi-randomized controlled trials comparing next generation ALK TKI with the first generation ALK TKI Crizotinib were selected. **Data collection and analysis**: Two review authors independently assessed risk of bias and extracted the data. Time to event outcomes were pooled using the generic inverse variance method, while dichotomous outcomes were pooled using the random effect Mantel-Haenszel method. Data were pooled using fixed-effect or random-effect models as deemed appropriated. **Results:** This review included six randomised studies involving 1,558 adult participants with a median follow-up time of 15 months. Most studies were overall at low risk of bias for both efficacy and safety endpoints. Pooling data from six studies found high certainty evidence for a large increase in progression-free survival (hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.34-0.48); the absolute effect 32 more (95% CI 25 more to 38 more) per 100 participants without an event of progression or death at 12 months. In addition, there is moderate certainty evidence for no difference in overall survival (HR 0.72, 95% CI 0.56-0.94); the absolute effect 5 more (95% CI 1 more to 8 more) per 100 participants without an event of death at 12 months. Pooling data from five studies found moderate certainty of evidence for a moderate increase in CNS objective response (relative risk [RR] 2.96, 95% CI 2.20-3.98); the absolute effect 41 more participants (from 25 to 62 more) per 100 having a CNS objective response. In addition, there was low certainty evidence for moderate increase in time to central nervous system (CNS) progression (HR 0.18, 95% CI 0.10-0.35); the absolute effect 31 more (95% CI 18 more to 35 more) per 100 participants without an event of CNS progression or death at 12 months. Next-generation ALK TKIs likely result in no difference in adverse events. **Conclusion:** Overall, in the first line treatment of ALK positive NSCLC, treatment with next-generation ALK TKI improves clinical efficacy in terms of PFS, objective response, CNS objective response, time to CNS progression without compromising safety.

Keywords: ALK, NSCLC, Meta-analysis

P45 NOVEL THERAPEUTICS AND TARGETED THERAPIES - ALK/ROS1/MET

P45.11 Co-occurring CDKN2A/B Alteration Is Associated With Worse Survival Outcomes in Advanced ALK-Positive Non-Small Cell Lung Cancer

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Introduction: Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have demonstrated promising activity in ALK-positive (ALK+) non-small cell lung cancer (NSCLC). However, co-occurring genetic alterations, especially those occurring downstream of tumor initiation oncogenes, may influence the efficacy of target therapies. This study analyzed whether co-occurring alterations influence survival outcomes to second-generation anti-ALK therapy in metastatic ALK+ NSCLC patients. **Methods:** From March 2018 to February 2020, in a single center, we analyzed prospectively 44 tumor specimens of patients with metastatic ALK+ NSCLC. Those tumor samples with positive immunohistochemistry, assessed by D5F3 assay, underwent genotyping using the Next-Generation Sequencing platform (Foundation One CDx). Progression-free survival (PFS) and overall survival (OS) were estimated for the total cohort and main commutations. **Results:** Forty-two patients were analyzed, mean age was 52.5±10.7 years, females in 59.5%, never smokers in 73.8%, and ECOG PS (0-1) in 90.5%. The lung adenocarcinoma subtype was observed in 97.5% of tumor samples, and the predominant solid pattern was the most frequently reported in 23.8%. All patients received a second-generation ALK-TKI in the first or second-line, 82.5% and 17.5%, respectively. Alectinib, brigatinib, and ceritinib were administered in 79%, 13.1%, and 7.9% of the cases. EML4-ALK 3a/b variant was the most common (47.6%), followed by variant 1 in 38.1%. The median PFS in the overall cohort was 22.3 months. No significant differences were observed in the progression-free intervals according to the distinct variants, neither when the variable was dichotomized (3a/b variant vs. others). The most frequent co-occurrent alterations were TP53 (23.8%) and CDKN2A/B (14.3%). Loss of the CDKN2A/B gene was the most common genetic aberration (83.3%) within this subgroup. Among patients with co-current CDKN2A/B alterations, median PFS was significantly shorter than CDKN2A/B wild-type patients (9.3 vs. 28.2 months), p=0.047. The median PFS was shorter in patients harboring a commutation in TP53; however, this difference was not significant (10.7 vs. 22.8 months), p=0.147. The presence of CDKN2A/B co-occurring alteration was correlated significantly with higher baseline serum carcinoembryonic antigen (CEA) levels (p=0.008), and other EML4-ALK fusion variants rather than 3a/b (p=0.02). After adjusting for confounding variables, CDKN2A/B co-occurring alterations remained strongly associated with poorer PFS outcomes. **Conclusion:** Co-occurring genetic alterations in CKN2A/B confers a poor prognosis in patients treated with a second-generation ALK-TKI in metastatic ALK+ NSCLC patients. The loss of the CDKN2A/B gene was the most frequent alteration seen in this subgroup of patients.

Keywords: cyclin-dependent kinase inhibitor 2, ALK fusion positive NSCLC, lung cancer

P45.12 Renal Function Change During Alectinib in ALK Rearranged Non-Small Cell Lung Cancer: A Retrospective Multicentre Analysis

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Introduction: The therapeutic landscape of ALK rearranged non-small cell lung cancer (NSCLC) has dramatically changed in the last few years. Several studies reported a significative reduction of creatinine-based estimated glomerular filtration rate (eGFR) during crizotinib, suggesting a direct effect on creatinine tubular secretion due to the reversibility after discontinuation, the scarce cumulative effect and the discrepancy between different methods of renal function estimation. In clinical trials serum creatinine increased in 7.2% of patients with alectinib, but it could be higher in real life population. We hypothesized a class effect of ALK inhibitors (ALK-I) on creatinine secretion. **Methods:** We conducted a retrospective multicentre analysis to describe Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine based eGFR during alectinib in first line and further lines in patients with NSCLC. We collected clinical data and CKD-EPI creatinine based eGFR at baseline, 15 days, 30 days and 3, 6, 12 months after starting alectinib. **Results:** Thirty-nine patients with ALK rearranged NSCLC treated with alectinib were included in the analysis. Twenty-eight (71%) and ten (26%) patients received alectinib in first line and further lines respectively. Normal renal function, with eGFR $\geq$90 mL/min/1.73 m^2, was observed in 23 patients (58.9%) at baseline, while 36 patients (92.3%) had an eGFR grade $\leq$3a, corresponding to eGFR$\geq$45 mL/min/1.73 m2. Median serum creatinine increased from 0.85 mg/dL (baseline) to 0.95 and 0.98 mg/dL at days 15 and 30, and remained substantially stable in subsequent measurements (0.99, 1.00 and 0.99 at 3, 6 and 12 months respectively). Ten patients (25.6%) had an increase > 0.2 mg/dL of serum creatinine at day 30 compared to baseline. Median eGFR decreased from 86.6 mL/min/1.73 m^2 (baseline) to 79.2 and 78.3 mL/min/1.73 m^2 at days 15 and 30, and remained relatively stable at 3, 6 and 12 months (77.7, 75.7 and 76.8 mL/min/1.73 m^2). Eight patients (20.5%) had a reduction > 20 mL/min/1.73 m^2 in eGFR at day 30 compared to baseline. During alectinib, worsening in chronic kidney disease (CKD) stage was found in 18 patients (46%) and 4 patients (10.2%) shifted in stage 3b-5 CKD at days 30. In the 25 patients (64%) that reached 12 months of alectinib, worsening in CKD stage was noticed in 13 patients (52%) and shifting to stage 3b-5 CKD was observed in 2 patients (8%) at 12 months. No significant correlations were found between eGFR worsening and comorbidity, drugs, previous chemotherapy or crizotinib. **Conclusion:** We reported a non-negligible incidence of renal impairment during alectinib, irrespective of concomitant drugs, previous chemotherapy or significant comorbidity. There was a stabilization of renal function over time, suggesting a minimal cumulative effect and supporting the hypothesis that the eGFR reduction may be related to a possible effect on tubular creatinine secretion rather than to a real nephrotoxicity. Renal function impairment may lead to treatment discontinuation, thus in patients treated with ALK-I is essential to use methods for assessing renal function other than creatinine-based eGFR.

Keywords: renal function, toxicity alk-inhibitors, Alectinib

P45.13 Efficacy and Safety of Crizotinib in Real-World ROS1-rearranged NSCLC: A Retrospective Canadian Cohort

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Introduction: ROS1-rearranged non-small cell lung cancer (NSCLC), present in 1-2% of diagnoses, is a genetically distinct type of NSCLC which can be successfully managed through the use of targeted therapy, specifically the first-generation ALK-inhibitor, crizotinib, which doubles as highly effective inhibitor of aberrant ROS1 activity. Clinical trials have shown crizotinib to be safe and effective; however, the use of crizotinib and its safety and efficacy in real-world ROS1-rearranged populations requires further exploration. Consequently, this study initiated a retrospective, observational, population-based investigation into the safety and efficacy of crizotinib in ROS1-rearranged NSCLC patients diagnosed and treated in Alberta, Canada. **Methods:** Alberta patients with advanced or metastatic ROS1-rearranged NSCLC, receiving crizotinib as their first targeted ROS1-inhibitor between January 2014 and June 2020 were identified. Demographic, clinical, treatment and outcome data were extracted from the institutional Glans-Look Lung Cancer Research Database. **Results:** 21 ROS1-rearranged crizotinib-treated patients were identified: median age was 51.6 years, 67% female, 86% never-smokers. 96% had metastatic disease at crizotinib initiation (38% M1c stage), 67% ECOG < 2, and 57% of patients had previous exposure to systemic chemotherapy (including platin-pemetrexed) and/or immunotherapy. 38% of patients were alive, 29% with crizotinib therapy ongoing, at the time of analysis. One-year survival was 47% following crizotinib initiation; median OS and PFS were 33.3 and 10.6 months, respectively. Disease control rate was 62%, while 14% showed primary resistance to crizotinib. ECOG was not significantly associated with outcome or clinical response. Adverse events (AE) were reported in 52% of patients, most common were gastrointestinal (29%) or investigational disorders (14%), and primarily grade 1 or 2. 19% of patients experienced grade 3+ AE and subsequently terminated crizotinib. Treatment breaks +/- dose modifications occurred in 16%. Patients remained on crizotinib for a median 6.9 cycles before discontinuation. Progressive disease was the most common reason for crizotinib termination (40% of crizotinib discontinuations); upon termination 24% received additional systemic treatment (range 1-3), all receiving additional ROS1-inhibitors. 33% of crizotinib terminations were due to death. 29% of patients had brain metastases at crizotinib initiation and 14% developed brain metastases while on crizotinib, predominantly managed with radiotherapy (67%). Presence/absence of brain metastasis did not significantly impact outcome, but baseline brain metastases resulted in a shorter duration of use and lower rate of clinical response to crizotinib. 48% had high PD-L1 expression (>50%) and 29% received immunotherapy (all prior to crizotinib initiation), with mPFS of 10.1 weeks and DCR of 33%. PD-L1 expression nor immunotherapy use had a significant impact on survival. **Conclusion:** This real-world study suggests crizotinib therapy for ROS1-rearranged NSCLC in a Canadian clinical setting is an effective, safe and tolerable therapy; however, this real-world cohort was unable to completely meet the outcomes found in crizotinib-treated ROS1-rearranged clinical trial cohorts. As a real-world population, lack of ROS1 testing, delayed access to crizotinib and heavy pre-treatment resulted in high disease burden and early failures on crizotinib, likely impacting crizotinib efficacy. This reinforces the need for real-world data alongside clinical trial data and highlights the need for expeditious access to appropriate targeted therapies in this population.

Keywords: targeted therapy, real world outcomes, ROS1

P45.14 Real-World Experience on Treatment of crizotinib in ALK/ROS1/MET Alterated Non-Small-Cell Lung Cancer Patients in China

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Introduction: Although multiple clinical trials have demonstrated the efficacy of crizotinib in the treatment of anaplastic lymphoma kinase (ALK) / c-ros oncogene 1 (ROS1) fusion advanced non-small-cell lung cancer (NSCLC), the under-represented populations, as well as the complexities and diversity of day-to-day cancer care are still to be complemented. **Methods:** This retrospective analysis used the electronic health record-derived database of patients with ALK/ROS1 fusion or METalteration NSCLC who treated with crizotinib from Jan 2013 to Feb 2021. Baseline demographics, objective response rate(ORR), median progression free survival (PFS), overall survival (OS), and toxicity of crizotinib were collected and analyzed. **Results:** A total of 55 patients were included in the study, of which 36 with ALK fusion, and 13 with ROS1 fusion. The baseline of clinical characteristics of those patients were similar with that previously reported on crizotinib. Most patients were diagnosed young (with median age of 51 years), non-smokers and with good performance status. Fifty-two percent of the patients had prior chemotherapy, and 23 patients had brain metastases(BM), with 20 of them received intracranial radiotherapy. Besides, the ORR of crizotinib was 53% with a median PFS of 12 months (range: 1–102 months), whereas the median OS among patients was not reached. [L1] Finally, the drug toxicity was manageable with 16.4% showed grade 3 or more toxicity. Noticeably, one patient developed toxic epidermal necrolysis after 56 days of crizotinib treatment, and demised due to this dermatological adverse event. **Conclusion:** This retrospective analysis of a real-world experience confirmed the therapeutic benefit of crizotinib in ALK/ROS-1fusion-positive advanced NSCLC, and also in NSCLC with MET ex14 mutation. Our data showed crizotinib is tolerable and effective, which is comparable with literature report. Nevertheless, the occasional occurrence of serious cutaneous toxicity requires further attention.

Keywords: non–small cell lung cancer, anaplastic lymphoma kinase, crizotinib

P45.15 Clinical Outcomes, Long-Term Survival and Toleration With Sequential Therapy of First-Line Crizotinib Followed by Alectinib in ALK+ NSCLC

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Introduction: There has been limited data in clinical outcomes, long-term survival and toleration with sequential therapy of first-line Crizotinib(CRZ) followed by Alectinib(ALEC) in clinical practice for Chinese patients with advanced ALK+ NSCLC **Methods:** Medical records of patients with advanced ALK+ NSCLC treated with sequential therapy of first-line CRZ followed by ALEC(no intermittent systemic therapy was allowed between these two ALK-TKIs) from 4 hospitals in China were collected. Combined Treatment to failure(C-TTF) was defined as the period from the start of CRZ to the completely discontinuation of ALEC due to any cause. Overall survival(OS) was calculated as the period from the start of CRZ to the date of death due to any cause. **Results:** 56 patients were included in this analysis. Median Progression free survival(PFS) during the treatment of CRZ for overall population and CRZ-resistant patients were both 15.3 months. 47 patients switched to ALEC due to disease progression(pattern: CNS only, n=21; extracranial only, n=18; both CNS/extracranial, n=8, besides 9 patients continued the treatment of CRZ after the local or gradual progression), 7 due to toxicity(5 patients with grade 3-4 events of aminotransferase increased, 2 patients with grade 3 events of diarrhea), 2 due to patients' preference. Median PFS during the period of ALEC treatment for overall cohort and CRZ-resistant patients was 15.3 months and 13.4 months respectively. 8 patients continued the treatment of ALEC after experiencing the local or gradual progression while 2 patients completely discontinued ALEC due to toxicity(1 patient with grade 4 events of total bilirubin increased, the other with grade 5 events of interstitial pneumonia). Wtih the median follow-up of 32.3 months, median C-TTF was 39.2 months and estimated 5-year OS was 64.2% for overall cohort; moreover, median C-TTF was 37.5 months and estimated 5-year OS was 62.8% for CRZ-resistant patients with the median follow-up of 33.5 months. **Conclusion:** Sequential therapy of first-line CRZ followed by ALEC yielded survival benefits for patients resistant to or intolerant of CRZ. However, liver damage caused by ALK-TKIs should be closely paid heeds to.

	Overall cohort n=56	CRZ-resistant patients n=47
2-year no treatment failure rate	69.9%(95%CI: 55.6%-80.4%)	69.7%(95%CI: 54.2%-80.8%)
3-year no treatment failure rate	56.6%(95%CI: 41.7%-69.1%)	52.5%(95%CI: 36.7%-66.1%)
4-year no treatment failure rate	41.5%(95%CI: 26.2%-56.2%)	40.2%(95%CI: 24.8%-55.2%)
3-year overall survival rate	87.1%(95%CI: 73.0%-94.1%)	85.4%(95%CI: 69.8%-93.3%)
4-year overall survival rate	73.3%(95%CI: 52.2%-86.2%)	71.2%(95%CI: 50.5%-85.1%)
5-year overall survival rate	64.2%(95%CI: 37.8%-81.7%)	62.8%(95%CI: 36.7%-80.5%)

Keywords: ALK+ NSCLC, crizotinib, Alectinib

P45.16 Adverse Event Burden of Oral Tyrosine Kinase Inhibitors in EGFR and ALK Metastatic Non-Small Cell Lung Cancer

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Introduction: Tyrosine kinase inhibitors (TKIs) are widely used in the treatment of metastatic non-small cell lung cancer (NSCLC) with a driver mutation. These oral therapies offer increased efficacy and convenience for patients when compared to intravenous chemotherapy. However, reduced direct provider supervision with oral therapy makes the detection of treatment-related adverse events (trAEs) challenging. Though clinical trials investigating TKI use in NSCLC document highest-grade trAE frequency, data regarding the frequency and duration of these trAEs in the real-world setting is lacking. We completed a retrospective review of EGFR-mutated and ALK-rearranged NSCLC patients receiving TKIs to investigate the real-world trAE burden of these therapies. **Methods:** We identified patients with EGFR-mutated or ALK-rearranged NSCLC treated with TKI therapy at our institution between 2016 and 2019. Medical charts were reviewed for documentation of trAEs occurring over the course of each unique TKI regimen. Data gathered included trAE type, trAE start date and resolution date, and whether the trAE lead to TKI dose reduction, significant interruption of TKI therapy (defined as therapy hold for ≥2 weeks), and/or permanent discontinuation of the TKI. **Results:** We identified 66 patients with EGFR-mutated or ALK-rearranged NSCLC (56 EGFR, 10 ALK) exposed to a total of 142 TKI regimens. Patients were 64% female with a median age of 66 years (range 30-85 years) and ECOG 0-2 in 96% at time of treatment initiation. The most commonly used TKIs were osimertinib (57%), erlotinib (18%), and alectinib (10%). The median time to development of the first trAE after starting therapy was 21 days (interquartile range 13-56 days). Eighty-two percent of TKI regimens resulted in at least one trAE on therapy. The most common trAEs were rash/acne (occurring in 37% of regimens), diarrhea (35%), thrombocytopenia (14%), and dry skin (12%). Among those who developed these most common trAEs, the median percent time spent symptomatic from that trAE while on that TKI regimen was 54% for rash/acne (median duration 99 days), 49% for diarrhea (median duration 66 days), 66% for thrombocytopenia (median duration 91 days), and 39% for dry skin (median duration 28 days). For each TKI regimen, a trAE ultimately resulted in dose reduction, significant interruption of therapy, and/or permanent discontinuation of that TKI in 25% of cases. **Conclusion:** The most common trAEs among NSCLC patients receiving TKIs were rash/acne, diarrhea, thrombocytopenia, and dry skin. Most trAEs occurred at lower frequencies than reported in clinical trials. However, the most common trAEs persisted for a significant portion of time on that TKI regimen. Additionally, trAEs lead to therapy interruption, dose adjustment, and/or discontinuation in one quarter of regimens. This study is limited by its retrospective nature and dependence on chart review for trAE documentation, which may underestimate trAEs. Future prospective studies are needed to obtain accurate, real-time monitoring of trAEs and assess the impact of these chronic trAEs on quality of life and other patient-reported outcomes.

Keywords: Tyrosine kinase inhibitor, treatment-related adverse events, targeted therapy

P45.17 Outcomes of Patients on ALK Inhibitor Therapy in NHS Tayside Scotland UK

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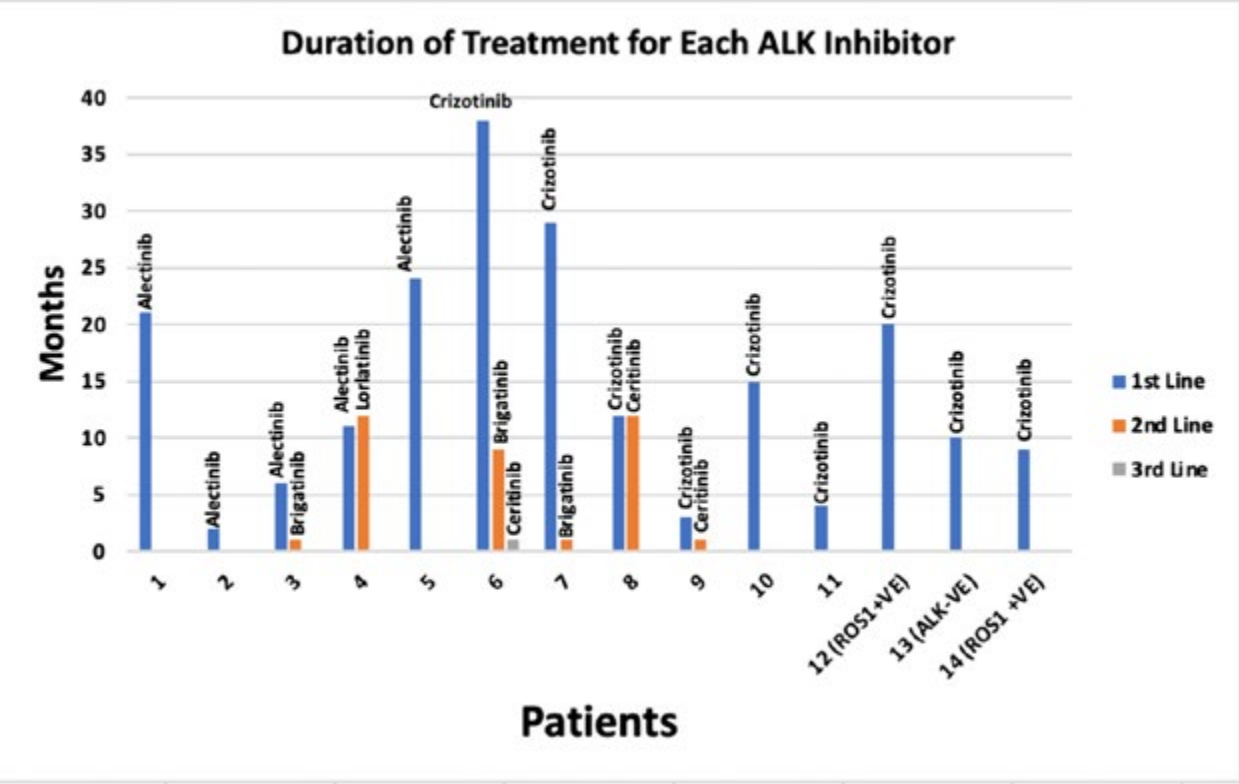
Introduction: Lung cancer is the most frequently diagnosed cancer in Scotland, but ALK and ROS 1 mutated lung cancer is rare. Targeted ALK therapy can provide durable responses with good tolerability. The outcomes of these patients in NHST are currently unknown and an audit was performed to clarify. Aim: To study the use and outcomes of ALK inhibitors in ALK mutated and Ros 1 mutated NSCLCa in NHST. **Methods:** Data from Dec 2016- Jan 2021 was extracted from Departmental databases and anonymised. 14 patients identified on ALK inhibitor treatment **Results:**



480 patients received systemic anti-cancer therapy (SACT) for NSCLC from 2016-2020. 14 (3%) received ALK inhibitor treatment 6 female and 8 male. Median age 61 years, range 53 - 66. 11 were ALK mutation positive, 2 ROS1 positive and 1 ALK negative Seven received chemotherapy as 1st line treatment before being treated with an ALK inhibitor. Six started on chemotherapy before mutation status known. 1st line ALK inhibitor received was Crizotinib for 9, and Alectinib for 5 Six went on to 2nd line treatment: 2 Ceritinib, 1 Lorlatinib and 3 Brigatinib. One patient went on to 3rd line treatment using Ceritinib. 13 out of 14 patients did not need dose changes. One patient on Lorlatinib required a dose reduction due to ECG changes. There were no Grade 3 or 4 toxicities in 13 of 14 patients. 1 patient started Ceritinib as 3rd line therapy and died 5 days later from acute renal failure, possibly related. 1st line treatment had the longest duration of disease control-38 months maximum recorded 2nd line treatment varied in efficacy with 3 patients achieving only 1 month benefit and 3 receiving 9-12 months of disease control. 8 patients have died due to progressive disease. 6 are alive; 5 on 1st line treatment and 1 on 2nd line.

Conclusion: Incidence of ALK mutated lung cancer in NHST is comparable to that reported in the European population of 2-8% (1). ALK inhibitors are well tolerated with few dose reductions required and only 1 postulated greater than grade 3 toxicity. In our limited cohort, greatest duration of benefit is achieved on first line therapy. We are meeting expected safety and efficacy standards in a Scottish population even during a global pandemic.

Keywords: ALK inhibitors; non small cell lung cancer;

P45.18 NSCLC Patients With ALK Gene Rearrangement – Croatian Experience

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Introduction: Anaplastic lymphoma kinase (ALK) gene rearrangements are present in a small subset of non-small-cell lung cancers (approximately 5%) what gives patients better survival outcomes. **Methods:** We analyzed the data of the patients diagnosed with advanced stage ALK positive NSCLC in University hospital center Zagreb, Department for pulmonary diseases from January 2018 until December 2020. **Results:** In observed period of time 64 patients were treated with ALK TKIs. 29 patients were treated with crizotinib in the first line and 27 of them progressed at the time of data cut off and 25 received alectinib in the second line, while one patient was treated with brigatinib. 35 patients were treated with alectinib in the first line. In the third line setting 10 patients were treated with brigatinib or lorlatinib. ALK TKIs were administered in the first line setting in 44 patients, in the second line setting in 14 patients and some patients were treated in the third, fourth and even fifth line (2, 3 and 1, respectively). There were 35 (55%) females with median age of 65 years (36-82). Almost half of them (43%) were current or ex-smokers with median pack/years 26.9 (2-75). Diagnosis was established by cytology specimens in 18 (27%) and by histology specimens in 46 (73%) patients. We observed median overall survival for all treated patients (mOS) of 47 months (95%CI 21.6-72.3), while mOS for patients treated with alectinib in the first line was not reached. Median progression-free survival (mPFS) was 12 months (95%CI 6,2 -14,7), but divided by TKIs - for crizotinib was 8 months (95% CI 5,1 – 10,8) and for alectinib it was not reached. mPFS2 for alectinib is 12 months (95%CI 2,3 – 21,6). **Conclusion:** We present real-life data of survival outcomes associated with sequencing of different ALK TKIs. Our data suggest that treatment with alectinib in the first line gives better survival benefit than earlier generation ALK TKIs.

Keywords: NSCLC, ALK TKI

P46.01 Progression After Targeted-therapy – An EGFR Case Report

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Introduction: Stage IV non-small cell lung cancer with epidermal growth factor receptor (EGFR) mutation is a challenging disease after gaining resistance to 3rd generation tyrosine kinase inhibitors. In its progression it may present other identifiable mutations or even histological transformation, although most cases are only eligible to chemotherapy treatment or clinical trials. **Methods:** We present a clinical case about a patient who has been followed in our hospital since 2014. **Results:** Female, 54 years, former light smoker, without relevant personal or family medical history. In april 2014 she was diagnosed with lung adenocarcinoma cT2aN0M0 and submitted to right upper lobectomy plus adjuvant chemotherapy. The patient remained clinically stable until february 2016 when she had pain in the right sacroiliac joint with functional impotence. PET-CT detected a metabolic activity lesion (SUV 8.98) in the sacral and sacroiliac region plus multiple bilateral lung nodules without metabolic expression. Bone lesion biopsy revealed metastasis of lung adenocarcinoma, with an EGFR exon 21 mutation. Palliative bone radiotherapy was performed and gefitinib was started. Twelve months later, the patient presented constitutional symptoms, and CT-scan showed an increase in the number and size of the already known pulmonary micronodules. Liquid biopsy detected EGFR T790M mutation, and osimertinib was started. Despite the good clinical response, pulmonary nodules showed an indolent increase, with clinical and imaging progression two years later. Pulmonary nodule was biopsied, finding no mutation T790M or any other mutation, except EGFR exon 21 mutation. Three years after the stage IV diagnosis, she started chemotherapy with carboplatin+pemetrexed followed by maintenance with pemetrexed. After a new progression, pembrolizumab was started. She did only 3 months of immunotherapy due to intolerance and clinical and imaging progression in bone level and new lung lesions (all the biopsies showed PD-L1 expression between 70%-80%). In december 2020 she started docetaxel + nintedanib, showing no signs of progression so far. **Conclusion:** This is a case report of a long survivor, even after the tumor showed Osimertinib resistance. We also demonstrate that in this EGFR mutation-positive tumor PDL1 expression was not an useful predictor to immunotherapy response, which is supported by recent literature. New clinical trials are needed for this subgroup of patients.

Keywords: EGFR, TKI, NSCLC

P46.02 Impact of Real-World DNA- and RNA-Based Rebiopsy Testing in EGFR-Mutated NSCLC Progressing on Osimertinib.

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Introduction: Unavoidable progression of EGFR-mutated NSCLC on EGFR-TKI treatment forces us to seek solutions for further therapies. Based on a specific clinical case we discuss the necessity of comprehensive molecular characterization of the progressive disease in real-word practice. Rebiopsies are strongly needed to provide information regarding the mechanisms of acquired resistance to EGFR-TKIs. The necessary data, however, may be reliably obtained only by deep targeted next generation sequencing (NGS) of both DNA and RNA. . **Methods:** Ten nanograms of genomic DNA were purified from each formalin-fixed paraffin-embedded biopsy using a crude DNA extraction method. Subsequent DNA-NGS analysis of SNVs, indels and CNVs across 161 unique cancer-associated genes was carried out using Oncomine Comprehensive Assay v3 sequencing on the Ion Torrent™ S5+system (ThermoFisher Scientific) according to the manufacturer's instructions. Additionally, cfDNA from plasma was analyzed for relevant DNA-mutations by the Oncomine Lung cfDNA NGS-assay, as indicated by the manufacturer (ThermoFisher Scientific). RNA-NGS was performed on total RNA extracted from a hepatic metastasis to detect gene fusions by using Archer FusionPlex® Lung kit in consonance with the manufacturer's instructions (ArcherDX, Inc.). **Results:** A 62-year-old woman, never-smoker, was diagnosed with EGFR-mutated (p.E746_A750delELREA ex19del) pulmonary adenocarcinoma in the left upper lobe and metastases to pituitary gland, cerebral frontal lobe, and several extracranial sites, corresponding to T3N2M1c disease. The patient received stereotactic radiosurgery (SRS) against two intracranial processes followed by Erlotinib and achieved intra- and extracranial partial response (PR). Fifteen months later, biopsy-verified intrathoracic progression harbored the original EGFR ex19del and an acquired EGFR p.T790M mutation was observed. Second line Osimertinib 80 mg QD was initiated. Plasma cfDNA sampled at 4, 7, and 13 months on this treatment revealed no presence of circulating EGFR-mutated clones. However, new progression with liver metastases was observed after 15 months. A tumor rebiopsy examined by DNA-NGS showed persistent EGFR ex19del and p.T790M mutation accompanied by MDM2-amplification and missense PTEN p.C124S substitution. The EGFR ex19del and p.T790M mutations reappeared in concomitantly sampled plasma cfDNA. Based on these results no additional targeted treatment options were possible, and chemotherapy with Carboplatin/Pemetrexed was initiated while continuing Osimertinib, achieving only short-term stabilization of the disease. However, additional NGS analysis of RNA isolated from the hepatic metastasis showed ANK3-RET fusion on chromosome 10q (breakpoint chr10: 61994446, chr10: 43612032), and RET-TKI was initiated (Pralsetinib). This finding may further explain the progression on Osimertinib, as other types of RET-fusions have been reported as mechanisms of acquired resistance to first line Osimertinib. **Conclusion:** 1. In this case, RNA-NGS revealed acquisition of the ANK3-RET fusion, which had not been previously reported on second line Osimertinib. The finding allowed the patient to receive further targeted treatment by combining Osimertinib with the RET-TKI, Pralsetinib, which is ongoing. The outcome will be discussed at The IASLC 2021 WCLC. 2. Complementary RNA-based testing is important to implement as a standard diagnostic strategy to better uncover the molecular evolution in advanced EGFR-mutated NSCLC and contribute to identification of further targeted treatment possibilities when progression during Osimertinib occur.

Keywords: acquired RET-fusion, RNA-based rebiopsy testing, Osimertinib progression, EGFR-mutated NSCLC

P46.03 Targeting ROS1 Gene Rearrangement by Crizotinib as Neoadjuvant Treatment Before Definitive Radiotherapy in Locally Advanced NSCLC

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Introduction: The ROS1 tyrosine kinase oncogene is located on chromosome 6q22.1 and it can undergo fusion with different partners in 1-2% of NSCLC cases, resulting in constitutive ROS1 kinase activation. ROS1-fusions occur most frequently in younger patients, females, and never/ light-smokers. The Tyrosine Kinase Inhibitor (TKI) Crizotinib has high activity in ROS1-rearranged advanced NSCLC, comparable to that observed in the more common ALK-positive NSCLCs.. The recommended treatment in locally advanced NSCLC is chemo-radiotherapy, preferably administered concomitantly if possible, while TKI treatments are currently not recommended even in case of tumors with druggable genomic targets like ROS1, ALK, or EGFR. We report a case in an elderly patient with locally advanced ROS1-rearranged NSCLC, in whom Crizotinib was used as neoadjuvant before radiotherapy with curative intent. **Methods:** The patient was staged according to the IASLC 8th Staging Classification. Testing for ALK- and ROS1-fusions was performed by immunohistochemistry (IHC), Fluorescence in situ hybridization (FISH), and Next Generation Sequencing (NGS) analysis of RNA extracted from formalin-fixed paraffin-embedded diagnostic biopsy. RNA-NGS was performed by Archer FusionPlex® Lung kit (ArcherDX, Inc.).. Possible mutations in EGFR and other 21 relevant genes were assessed by DNA-NGS using Ampliseq colon-lung cancer panel v2 (ThermoFisher Scientific). **Results:** The patient was an 81-year-old female, never-smoker, having a tumor in left upper lobe and spread to mediastinal lymph nodal station 4R and 7, i.e. stage T1cN3M0. MR scan showed no brain metastases. Only comorbidity was arterial hypertension. Performance Status was 1, no weight loss, both pulmonary FEV1 and diffusion capacity were favorably 90% of expected . Biopsies from primary tumor and mediastinal lymph nodes showed lung adenocarcinoma (LAC), IHC-positive for TTF-1 and CK7, negative for P40. IHC was negative for ALK and positive for ROS1, and FISH confirmed the ROS1-rearrangement. No mutations in EGFR or other genes were detected by DNA-NGS, while RNA-NGS showed the fusion of ROS1 with CD74 (break-point chr5:149784243, chr6:117645578). Thus, the patient had locally advanced LAC and was in a condition allowing sequential chemo-radiotherapy with curative intent, though not concomitant treatment due to advanced age. However, the patient did not accept chemotherapy, but wished targeted treatment for the ROS1-rearrangement . Accordingly, the patient was treated with Crizotinib 250 mg BID with good tolerance and symptoms improvement. PET/CT scan after 5 weeks revealed a partial response both in primary tumor and mediastinal lymph nodes. Crizotinib treatment was ceased and Radiotherapy 2 Gy x 33F, 5F/W for a total dose of 66Gy was initiated and will be followed by one year of adjuvant Crizotinib. Update will be presented at the 2021 WCLC. **Conclusion:** Although ROS1- fusions are more frequent in younger NSCLC patients, this case highlights that all ages should be screened for this gene rearrangement. The rapidly achieved partial remission points towards a potential future for ROS1-TKIs used as neoadjuvant treatment in locally advanced ROS1-rearranged NSCLC before definitive, curatively intended radiotherapy or surgery. However, this needs to be further substantiated in randomized trials.

Keywords: crizotinib, ROS1-rearrangement, Targeted neoadjuvant treatment

P46.04 Different Effects of Crizotinib Treatment in Three Lung Adenocarcinoma Patients With Various ROS1 Fusion Variants

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Introduction: Ros proto-oncogene 1 (ROS1) which is minor driver genes (1-2% of NSCLC) encodes receptor tyrosine kinase (RTK). ROS1 drives cell transformation by gene rearrangement. ROS1 rearrangement constitutively activate ROS1 kinase domain. ROS1 rearrangement is caused by the chromosome translocation. Although several fusion partners have been reported, correlation between ROS1 fusion pattern and clinical outcome is still unclear. The present study aimed to clear the relationship between ROS1 fusion partners and clinical courses. **Methods:** We investigated three ROS1-rearranged lung adenocarcinoma cases who were diagnosed and administered crizotinib treatment at Nihon University Itabashi Hospital in Tokyo, Japan. Three cases were positive for TTF-1 immunohistochemical expression and negative for p40. Epidermal growth factor receptor (EGFR) gene mutation and anaplastic lymphoma kinase (ALK) fusion transcripts were not detected in all three cases. To investigate ROS1 fusion sequences, total RNA was extracted from two FFPE tissues and a pleural effusion sample. After cDNA synthesis, reverse transcription(RT)-PCR products were analyzed by sanger sequencing. Immunohistochemical analysis was performed using anti-ROS1 antibody(clone SP384). **Results:** Case1: 70s, non-smoking female patient who has been controlled by crizotinib (250mg, 2times/day to 250mg/day) for total 32 months. Her clinical stage was IVB(T3N2M1c) with brain and bone metastasis. ROS1 fusion variant was CD74 exon5-ROS1 exon34. Case2: 50s, non-smoking female patient who has been well controlled by crizotinib (250mg, 2times/day) for over 3 years. Clinical stage was IIIB(T3N3M0) and fusion variant of SDC4 exon2-ROS1 exon 32(exon33 deleted) was confirmed. Case3: 60s, smoking male patient (Stage cIVB, TXN3M1c) who were administered crizotinib treatment (250mg, 2times/day). However, after one year, renal dysfunction and metastasis to the abdominal cavity and skin, and the patient died. His tumor had mixed fusion variant SDC4 exon2-ROS1 exon 34 and also SDC4 exon2-ROS1 exon35. ROS1 IHC expression was higher in case3 than others. **Conclusion:** The relationship between the different ROS1 fusion variant and the clinical courses including crizotinib sensitivity is still unclear. It was suggested, however, that the differences of ROS1 fusion variants may correlate with the activity level of ROS1 signal transduction ,depending on ROS1 overexpression status, and aggressive tumor behavior.

P46.05 Durable Response to Double Dose Osimertinib 160mg in EGFR-Mutated Non-Small Cell Lung Cancer With Brain Metastases

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Introduction: In non-small cell lung cancer (NSCLC) patients, metastasis to the brain harbors a poor prognosis and it occurs more commonly in EGFR-mutated patients. Osimertinib has better CNS penetration compared to previous generations of EGFR-TKIs. However, progression of disease is commonly observed in a median of 10-14 months after the initiation of EGFR-TKI treatment. Although not endorsed by any guidelines, the use of double dose osimertinib has been reported anecdotally in clinical settings of CNS progression with limited durability. Herein, we present an EGFR-mutated NSCLC patient with brain metastases currently demonstrating exceptional durability in response to double dose osimertinib after CNS progression was observed with a standard dose. **Methods:** Case presentation **Results:** A 47-year-old male was diagnosed with stage IV(cT2aN3M1) lung adenocarcinoma with multiple osseous and three subcentimeter brain metastases. Upon confirmation of EGFR exon 19 deletion mutation, the patient was started on afatinib. The patient demonstrated excellent overall response including a decrease of all three brain metastases until CNS progression occurred 12 months later. Subsequently, afatinib was discontinued and changed to standard dose osimertinib(80mg daily). The patient tolerated the treatment well with stable disease on MRI brain and CT chest until CNS progression of two lesions(right parietal lobe 6mm->10mm, left parietal lobe 1mm->3mm) was observed 9 months later. For better control of brain metastases, the dose of osimertinib was increased from 80mg to 160mg. The patient tolerated the double dose osimertinib(160mg daily) well with a decrease in size of the two largest, CNS progressive lesions(right parietal lobe 10mm->4mm, left parietal lobe 3mm->1mm) and resolution of smaller brain metastases. Thereafter, stable disease was observed on MRI brain and CT chest until CNS progression occurred 8 months later. Continuation of double dose osimertinib combined with stereotactic radiosurgery on the progressive lesions led to complete resolution of brain metastases. Recent follow-up imaging studies revealed no evidence of active metastases on MRI brain and stable disease on CT chest. The patient is demonstrating a durable response of over 24 months to double dose osimertinib and tolerating the treatment very well with grade 1-2 facial/scalp rash controlled with topical treatment. **Conclusion:** According to recent studies, the median PFS of double dose osimertinib after CNS progression from brain metastasis is less than 12 months. Our case demonstrated superior durability of double dose osimertinib for over 24 months. The case suggests that double dose osimertinib of 160mg can be well tolerated with minimal adverse events and demonstrate prolonged efficacy in treating EGFR-mutated NSCLC with brain metastasis after CNS progression from a standard dose of 80mg.

Keywords: EGFR-mutated NSCLC, Double dose osimertinib 160mg, NSCLC with brain metastasis and CNS progression

P46.06 Response of an Advanced Lung Cancer Mass to Targeted Therapy

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Introduction: Evaluating a young patient with suspected advanced lung cancer is dramatic. Speed of investigation can impact treatment and survival. This report shows the management chosen that diminished a large EGFR+ lung tumor and the importance of a multidisciplinary assessment. **Methods:** The patient medical record was reviewed in March 2021 and then reported in this study. **Results:** A 37-year-old man was referred to the Thoracic Oncology outpatient clinic with back pain, dry cough, important weight loss in 6 months, and use of cannabis and cocaine (ECOG 1). A chest CT showed a hollow lesion in the right upper lobe (RUL) (5.2 x 4.2cm), compressing the right main bronchus and upper and middle lobes; several small lesions with cavitated center distributed over the lung parenchyma, and mediastinal (upper and lower) and hilar lymph nodes prominent ipsilaterally. In one month, a new CT showed an increase in the lung tumor (6.7 x 5.7 x 5.5 cm) with areas of central necrosis and spiculated edges; osteoblastic lesions distributed in bones; and multiple nodules on the liver, spleen, right kidney, and adrenals. The patient's performance was evaluated in a multidisciplinary meeting to ensure the best approach and the quickest way to obtain the material for analysis. A percutaneous lung biopsy was performed, confirming pulmonary adenocarcinoma. With a clinical stage of IVB (cT3N2M1c), it was instituted a plan with 2 cycles of 21 days of carboplatin, paclitaxel, and pemetrexed. Skull MRI showed multiple lesions in the central nervous system (CNS), opting for WBRT as treatment. In parallel, the molecular analysis demonstrated a mutation in EGFR (deletion of exon 19). At follow-up, patient reported pain control, weight gain, and overall clinical improvement. On control CTs, lung tumor showed significant regression, presenting only a cystoid lesion with slightly thickened walls and predominantly air content (4.7 x 3.7cm); notable reduction in the number of nodules in lungs, abdominal and pelvic organs. The multidisciplinary team chose to start gefitinib 250mg, 1x/day, due to the existing mutation. In new CTs, 10 months after diagnosis, the patient had no evidence of disease in the CNS, liver, and kidney. He had the same RUL image, but persistent bone and adrenal metastases. Early restaging: cT2bN2M1c. After 2 months, patient reported inappetence, weight loss of 7 kg, and prostration. In control CTs, chest images remained like previous ones; abdominal, pelvic, and CNS scans showed disease progression. A new plan was instituted: maintenance of gefitinib, evaluation for SBRT, and search for T790M mutation in EGFR, which came out positive. Patient continues treatment in a multidisciplinary outpatient clinic. **Conclusion:** We demonstrate the importance of a joint assessment, mainly because this patient could have been considered unfit for systemic treatment due to his fragility and volume of the disease. Age, quickness for obtaining the sample, an association of mutation with aggressive neoplasia, and correct treatment ensured an excellent response. The median survival for stage IV is 7-12 months; this patient already has 15 months of survival.

Keywords: Advanced lung cancer, targeted therapy, Multidisciplinary assessment

P46.07 Afatinib-Related Pneumonitis in Metastatic EGFR-Positive NSCLC

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Introduction: Lung cancer is the third commonest cancer in Indonesia, and the first case of death in all cancer in both gender. EGFR mutation frequency in cytological sample in Indonesia was 44.4%. Afatinib is second generation epidermal growth factor receptor tyrosine kinase inhibiot, which inhibits epidermal growth factor receptor (EGFR), human epidermal factor receptor-2 (HER2) and HER4. Afatinib first introduced in Indonesia in 2016, and get approval for national health insurance program in 2018. The side effect of afatinib are skin rash, diarrhea, paronichia and pneumonitis. Here were reported a 69 yo female with diagnosis of lung adenocarcinoma T3N3M1 brain, lung EGFR mutation exon 19 deletion. She was treated with afatinib 40mg. Her condition was improved, but after 2 months of treatment, she complained of cough and shortness of breath. On chest HRCT showed bilateral pneumonitis. After inclusion of infection and heart failure, she was treated with pulse-dose steroid, but her condition deterioriated, and she passed away with respiratory failure. **Methods:** This is a case report, written informed consent has been obtained from her family member. **Results:** HRCT of lung showed bilateral pneumonitis. **Conclusion:** Pneumonitis is a very rare adverse event of EGFR TKI, however can be devastating. We reported acute pneumonitis related to afatinib in metastatic adenocarcinoma, although already been diagnosed and treated early, but difficult to manage.

Keywords: EGFR TKI, afatinib, pneumonitis

P47.01 SGNTUC-019: Phase 2 Study of Tucatinib and Trastuzumab in Solid Tumors: Lung Cancer Cohorts (Clinical Trial in Progress)

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Introduction: Tucatinib, a highly selective human epidermal growth factor receptor 2 (HER2)-directed tyrosine kinase inhibitor recently approved in multiple regions for overexpressed/amplified (HER2+) metastatic breast cancer, is also being developed as a novel therapy for patients with metastatic colorectal, gastric, and gastroesophageal cancers. In xenograft models of HER2 overexpression and HER2-mutated tumors, dual targeting of HER2 with tucatinib and trastuzumab showed superior activity to either agent alone. Interim results from the MOUNTAINEER study have shown promising activity for tucatinib and trastuzumab in HER2+ metastatic colorectal cancer. In 23 response-evaluable subjects, an objective response rate of 52% was observed with a median progression-free survival of 8.1 months (95% confidence interval [CI]: 3.8 months to not evaluable) and a median overall survival of 18.7 months (95% CI: 12.3 months to not evaluable). HER2 amplifications and mutations have been identified as critical drivers in 1% to 3% and 2% to 4% of lung cancers, respectively. There currently exists no standard of care for lung cancer patients with HER2 alterations. HER2+ and HER2-mutated lung cancers are proposed to be clinically distinct and may further subdivide lung cancer patients for targeted therapies. The SGNTUC-019 basket study (NCT04579380) is evaluating tucatinib in combination with trastuzumab in patients with previously treated, locally advanced, unresectable or metastatic solid tumors that display HER2 overexpression/amplification or activating mutations. We describe the design of the lung cancer cohorts. **Methods:** SGNTUC-019 is a multi-cohort, open-label, international Phase 2 study. Patients must be ≥18 years old; have an ECOG PS of ≤1; have adequate hepatic, hematological, renal, and cardiac functions and coagulation; and have no previous exposure to HER2-directed therapy. The primary objective is antitumor activity with confirmed objective response rate as the primary endpoint. Secondary endpoints include disease control rate, duration of response, progression-free survival, and overall survival. The HER2+ non-squamous non-small cell lung cancer (NSCLC) cohort and the HER2-mutated NSCLC cohort each will enroll 12 response-evaluable patients. If ≥2 responses are observed in either one or the other of the cohorts, the cohort will be expanded to a total of 30 patients. For eligibility, HER2 alterations in tumor tissue can be demonstrated as HER2+ by previous immunohistochemistry (IHC)/in situ hybridization (IHC 3+/signal ratio ≥2.0 or gene copy number >6) or as HER2 amplification/mutation by a previous next-generation sequencing (NGS) assay (tissue or blood) or an on-study NGS assay (blood only). Patients with brain metastases may be eligible; patients in the HER2+ or HER2-mutated NSCLC cohorts will be required to undergo a baseline brain MRI. Patients will receive tucatinib 300 mg orally twice a day and trastuzumab 8 mg/kg intravenously on Cycle 1 Day 1 then 6 mg/kg every 21 days from Cycle 2 Day 1. Disease assessments per RECIST 1.1 are every 6 weeks for the first 24 weeks, then every 12 weeks. Quality of life will be evaluated every 2 cycles using EQ-5D-5L. Enrollment at US sites began in December 2020, and site initiation is in progress in Asia and the EU.

Keywords: tucatinib, basket study, HER2-targeted therapy

P47.02 EV-202: Phase 2 Study of Enfortumab Vedotin for Previously Treated Advanced Solid Tumors Including Non-Small Cell Lung Cancer

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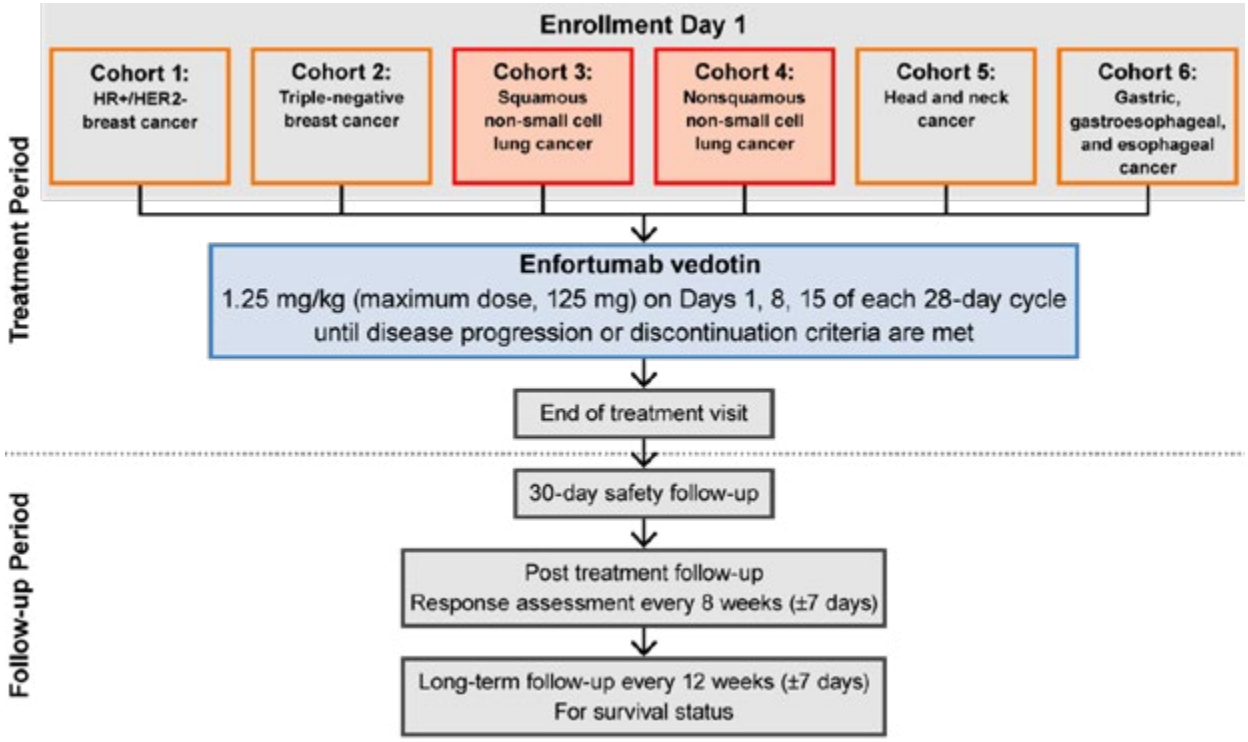
Introduction: Despite therapeutic advances, lung cancer remains a leading cause of cancer death worldwide. Nectin-4, a cell adhesion molecule, is highly expressed in several epithelial tumor types, including non-small cell lung cancer (NSCLC). Targeting Nectin-4 in NSCLC provides a novel treatment approach. Enfortumab vedotin (EV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody directed against Nectin-4, and monomethyl auristatin E (MMAE), a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. MMAE release within the cell disrupts the microtubule network, inducing cell cycle arrest and apoptosis. In 2019, EV received accelerated approval by the US FDA for the treatment of adults with locally advanced/metastatic urothelial carcinoma (la/mUC) who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. In EV-301, a phase 3, randomized clinical trial of patients with previously treated la/mUC, EV significantly prolonged overall survival compared with chemotherapy (docetaxel, paclitaxel, or vinflunine). This trial-in-progress describing general methodology for all cohorts was presented at the 2020 ASCO Annual Meeting. **Methods:** This multicohort, open-label phase 2 study (NCT04225117) evaluates efficacy and safety/tolerability of EV in patients with previously treated locally advanced/metastatic solid tumors. Approximately 240 patients (~40 patients/cohort) with histologically/cytologically confirmed disease and ECOG performance status of ≤1 are enrolling into six tumor-specific cohorts (**Figure**). Within the NSCLC cohorts, patients must have previously received mutation-targeted therapy (if eligible) and progressed, relapsed, or discontinued treatment due to toxicity after one platinum-based therapy for locally advanced/metastatic disease, but received ≤2 lines of cytotoxic therapy, or have progressed or relapsed within 6 months of a platinum-based neoadjuvant, adjuvant, concomitant chemoradiation regimen for early stage or locally advanced disease. Patients must have previously received therapy with a PD-1/L1 inhibitor, unless therapy is contraindicated. Nectin-4 expression is not required for eligibility and is being tested for exploratory outcomes. Patients with active CNS metastases, grade ≥2 sensory/motor neuropathy, ongoing grade ≥3 immunotherapy-related hypothyroidism or panhypopituitarism, ongoing immunotherapy-related adverse events requiring high-dose steroids, or a history of uncontrolled diabetes mellitus are excluded. Patients will receive 1.25-mg/kg EV intravenously on Days 1, 8, and 15 of each 28-day cycle. The primary endpoint is investigator-assessed confirmed objective response rate (RECIST v1.1); secondary endpoints include duration of response, disease control rate, progression-free and overall survival, and safety/tolerability. An interim analysis is planned based upon prespecified response criteria. Recruitment is ongoing at ~50 sites in North America and Japan.



Abbreviations: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Keywords: Novel Therapeutics, Targeted Therapies

P47.03 Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met+ Advanced Non-Small Cell Lung Cancer: Stage 2

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Introduction: Telisotuzumab vedotin (Teliso-V) is an anti-c-Met antibody conjugated with a tubulin inhibitor, monomethylauristatin E. The c-Met receptor tyrosine kinase is the cell surface receptor for hepatocyte growth factor (HGF) encoded for by the MET proto-oncogene. c-Met overexpression occurs in various solid tumors, including non-small cell lung cancer (NSCLC), and the aberrant activation of the c-Met/HGF axis contributes to tumor progression, angiogenesis, invasive growth, metastasis, and resistance to therapies. Following encouraging evidence of anti-tumor activity in a Phase 1 study (Strickler et al. J Clin Oncol 2018;36:3298–3306), a Phase 2 study was initiated to explore the safety and efficacy of Teliso-V monotherapy in 3 cohorts (based on histopathology and epidermal growth factor receptor [EGFR] mutation) and 5 subgroups (based on c-Met expression) of patients with c-Met$^+$ advanced NSCLC (study Stage 1), followed by expansion into an appropriately selected population based on study Stage 1 results for further evaluation of safety and efficacy (study Stage 2). **Methods:** This Phase 2, non-randomized, single-arm, adaptive study (NCT03539536) is enrolling patients aged ≥18 years with Eastern Cooperative Oncology Group performance status ≤1 and locally advanced or metastatic c-Met$^+$ NSCLC who have received 1–2 prior lines of therapy (including systemic chemotherapy, immunotherapy, and targeted therapy, if eligible). Based on data from study Stage 1 (Camidge et al. AACR 2021), the cohort of patients with non-squamous EGFR wild type c-Met$^+$ NSCLC met prespecified criteria to transition to the study Stage 2 single-arm expansion cohort. Study Stage 2 enrollment commenced in February 2021 and is ongoing; up to approximately 160 patients will be enrolled in study Stage 2. c-Met status is determined centrally by immunohistochemistry. The primary endpoint is overall response rate per independent central review (based on Response Evaluation Criteria in Solid Tumors version 1.1). Secondary endpoints are duration of response, disease control rate, progression-free survival, and overall survival. Quality of life will be evaluated as an exploratory efficacy endpoint and safety and tolerability will be assessed. Pharmacokinetic and biomarker samples will also be collected for analysis. Teliso-V is administered as a 30±10 min intravenous infusion at a dose of 1.9 mg/kg every 2 weeks until disease progression or study discontinuation criteria are met.

Keywords: Advanced non-small cell lung cancer, Developmental Therapeutics-Molecularly Targeted Agents, Tumor Biology – Immunoconjugates (Non-IO)

P47.04 TROPION-Lung02: Datopotamab Deruxtecan (Dato-DXd) Plus Pembrolizumab and Platinum-Based Chemotherapy in Advanced NSCLC

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Introduction: First-line treatment with immunotherapy plus platinum-based chemotherapy has significantly improved survival in patients with advanced/metastatic NSCLC; however, many patients progress within 1 year. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. Preclinical studies suggest that combining Dato-DXd with platinum-based chemotherapy and an anti–PD-1/PD-L1 inhibitor may result in enhanced antitumor activity and improved clinical outcomes. Results from the TROPION-PanTumor01 study demonstrated an overall response rate of 21%, a disease control rate of 67%, and a preliminary median progression free survival of 8.2 months (all by blinded independent central review) in patients with NSCLC treated with Dato-DXd 6 mg/kg. Here we describe the phase 1b TROPION-Lung02 trial (NCT04526691) evaluating Dato-DXd combined with pembrolizumab ± platinum-based chemotherapy in previously treated or treatment-naive patients with advanced/metastatic NSCLC without actionable genomic alterations. **Methods:** TROPION-Lung02 is a multicenter, 2-part, open-label, phase 1b study of Dato-DXd in combination with pembrolizumab ± platinum-based chemotherapy in patients with advanced/metastatic NSCLC without actionable genomic alterations (ie, in ALK, EGFR, or other genes with approved therapies). Two dose levels of Dato-DXd (4 mg/kg [cohorts (C) 1, 3, and 5] and 6 mg/kg [C 2, 4, and 6] Q3W) will be studied in combination with pembrolizumab 200 mg Q3W (all C), and 4 cycles of carboplatin AUC 5 Q3W (C 3 and 4) or cisplatin 75 mg/m^2 Q3W (C 5 and 6). Patients aged ≥18 y (≥20 y in Japan), must have an ECOG PS of 0 or 1, have measurable disease per RECIST version 1.1, and be willing to undergo tumor biopsies for exploratory assessment of TROP2 and other biomarkers. Patients with asymptomatic or stable/treated brain metastases may be included. For part 1 (dose escalation; C 1-6), patients could have received ≤2 prior lines of anticancer therapy for metastatic disease. For part 2 (dose expansion) C 1 and 2, prior anti–PD-1/L1/L2 or anti–CTLA-4 immunotherapy is not permitted; patients could have received treatment with 1 line of platinum-based chemotherapy. In C 3-6, prior systemic anticancer therapy for metastatic NSCLC is not permitted. The primary objective is to assess the safety and tolerability, including but not limited to dose-limiting toxicities (part 1), and treatment-emergent adverse events and adverse events of special interest (parts 1 and 2). Secondary objectives (parts 1 and 2) include overall response rate, duration of response, and progression free survival (all investigator-assessed per RECIST 1.1), overall survival, pharmacokinetics, and incidence of antidrug antibodies. Study sites (≈15) are planned in the US, Japan, Taiwan, Spain, and Italy. Clinical results will be presented.

Keywords: antibody drug conjugate, pembrolizumab, NSCLC

P47.05 A Phase 2 Study of Datopotamab Deruxtecan (Dato-DXd) in Advanced NSCLC With Actionable Genomic Alterations (TROPION-Lung05)

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Introduction: Treatment options and outcomes for patients with advanced/metastatic NSCLC with actionable genomic alterations that progresses after approved targeted therapies are poorly characterized. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. Results from the ongoing phase 1 study (TROPION-PanTumor01) in advanced/metastatic NSCLC support further evaluation of Dato-DXd in this population. Among patients with NSCLC (with or without actionable mutations) who received the 6 mg/kg dose, the overall response rate by blinded independent central review (BICR) was 21%, disease control rate was 67%, and preliminary median progression-free survival was 8.2 months; Dato-DXd 6 mg/kg had a manageable safety profile. Here we present a phase 2 trial (TROPION-Lung05; NCT04484142) that will evaluate the efficacy, pharmacokinetics, and safety of Dato-DXd in patients with advanced or metastatic NSCLC with actionable genomic alterations. **Methods:** TROPION-Lung05 is an open-label, single-arm, phase 2 study that will evaluate Dato-DXd in patients with advanced/metastatic NSCLC with actionable genomic alterations, such as EGFR, ALK, ROS1, RET, MET, NTRK, and BRAF, and radiographic disease progression on or after ≥1 kinase inhibitor and ≥1 line of platinum-based chemotherapy. Patients with asymptomatic or stable/treated brain metastases are eligible. A tumor specimen is required for biomarker analyses. Approximately 75 study sites in North America, Europe, and the Asia Pacific region are or will be included. Patients will receive Dato-DXd 6 mg/kg as an intravenous infusion once every 3 weeks. The primary endpoint is overall response rate by BICR per RECIST version 1.1. The primary analysis is planned once all patients have been followed up for at least 9 months after start of treatment or have discontinued from the study. Secondary outcome measures include duration of response and progression free survival (both as assessed by BICR and investigator per RECIST 1.1), overall survival, pharmacokinetics, safety, and the proportion of patients who develop antidrug antibodies. Biomarkers will be evaluated for potential associations with efficacy.

Keywords: antibody drug conjugate, NSCLC , genomic alterations

P47.06 TROPION-Lung04: Datopotamab Deruxtecan (Dato-DXd) Plus Durvalumab and Platinum-Based Chemotherapy in Advanced NSCLC

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Introduction: Few treatment options are available for patients with advanced/metastatic NSCLC without actionable genomic alterations that has progressed on standard therapies. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. Results from a phase 1 study (TROPION-PanTumor01) in advanced/metastatic NSCLC support evaluation of Dato-DXd as a potential treatment option for these patients. Among patients with NSCLC who received the 6 mg/kg dose, the disease control rate was 67%, the overall response rate by blinded independent central review was 21%, and the preliminary median progression free survival was 8.2 months. Results from preclinical studies suggest that the addition of Dato-DXd to first-line platinum-based chemotherapy + anti–PD-1/PD-L1 therapy may enhance antitumor responses in patients with advanced/metastatic disease. Here we describe the phase 1b TROPION-Lung04 trial (NCT04612751) evaluating Dato-DXd in combination with durvalumab ± platinum-based chemotherapy in patients with advanced or metastatic NSCLC without actionable genomic alterations. **Methods:** TROPION-Lung04 is a multicenter, 2-part, open-label, phase 1b study of Dato-DXd in combination with durvalumab ± platinum-based chemotherapy in patients with advanced/metastatic NSCLC without actionable genomic alterations (ie, in ALK, EGFR, or other genes with approved therapies). Two dose levels of Dato-DXd (4 mg/kg [cohorts (C) 1, 3, and 5] and 6 mg/kg [C 2, 4, and 6] Q3W) will be evaluated in combination with durvalumab 1120 mg Q3W (all C), and 4 cycles of either carboplatin AUC 5 Q3W (C 3 and 4) or cisplatin 75 mg/m^2 Q3W (C 5 and 6). Patients must be ≥18 y (≥20 y in Japan), have an ECOG PS of 0 or 1, have measurable disease per RECIST version 1.1, and be willing to undergo tumor biopsies for assessment of TROP2 and other biomarkers. Patients with asymptomatic or stable/treated brain metastases may be included. For part 1 (dose escalation; C 1-6), ≤2 prior lines of anticancer therapy for metastatic disease are allowed. In part 2 (dose expansion) C 1 and 2, prior PD-1/L1/L2 or CTLA-4 immunotherapy is not permitted; treatment with 1 line of platinum-based systemic chemotherapy is acceptable. In part 2 (dose expansion) C 3-6, prior systemic anticancer therapy for metastatic NSCLC is not permitted. The primary objective is to assess the safety and tolerability, including but not limited to dose-limiting toxicities (part 1) and treatment-emergent adverse events and adverse events of special interest (parts 1 and 2). Secondary objectives (parts 1 and 2) include overall response rate, duration of response, and progression free survival assessed by investigator, as well as overall survival, pharmacokinetics, and incidence of antidrug antibodies. Global study sites (≈20) are planned, including sites in the US, Japan, Australia, South Korea, France, and Canada. Clinical results will be presented.

Keywords: antibody drug conjugate, durvalumab, NSCLC

P47.07 KEAPSAKE Study of Telaglenastat vs Placebo Plus Standard-of-Care in 1L KEAP1/NRF2-Mutated Non-Squamous Metastatic NSCLC

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Introduction: The KEAP1/NRF2 pathway is mutationally activated in approximately 20-25% of NSCLC patients. NRF2 activation protects against oxidative stress and promotes tumor growth and survival. KEAP1/NRF2 mutations in advanced NSCLC are associated w/ dramatically shorter survival and poor outcomes following standard-of-care therapy. These tumors have heightened dependency on glutaminase-mediated conversion of glutamine to glutamate due to upregulation of NRF2 target genes involved in glutamine metabolism, which support a massive increase in glutathione synthesis. Telaglenastat (CB-839) is an investigational, first-in-class, potent, oral glutaminase inhibitor which has demonstrated activity in KEAP1/NRF2-mutated NSCLC cell lines and xenograft models. This study will evaluate the safety and efficacy of telaglenastat + standard-of-care pembrolizumab (pembro) and chemotherapy as 1L therapy in patients with KEAP1/NRF2-mutated non-squamous metastatic NSCLC (NCT04265534; Skoulidis et al. ASCO 2020). **Methods:** This phase 2, randomized, multicenter, double-blind study will enroll ~120 patients with histologically or cytologically documented stage IV non-squamous NSCLC with KEAP1 or NRF2 mutations, no prior systemic therapy for metastatic NSCLC, measurable disease (RECIST v1.1), ECOG PS 0-1, and no EGFR, ALK, ROS, or other actionable mutation w/ available approved therapy in the1L setting. KEAP1 or NRF2 mutations will be determined by next-generation sequencing (NGS); and study-provided liquid biopsy NGS will be available. Patients will be randomized 1:1 to receive telaglenastat (800 mg BID PO) or placebo, plus pembro, carboplatin, and pemetrexed at standard doses on day 1 of each 21-day cycle. Patients will be stratified by STK11/LKB1 mutational status and M stage of cancer (M1a-b vs M1c). The study includes an initial safety run-in period (1 cycle). The co-primary endpoints are safety and investigator-assessed progression-free survival (RECIST v1.1). Secondary endpoints include overall response rate, duration of response, and overall survival, as well as performing efficacy analyses in the subgroup of patients w/ biochemical confirmation of KEAP1/NRF2 pathway activation. Findings of this novel biomarker-selected study will inform the efficacy and safety profile of telaglenastat + standard-of-care chemoimmunotherapy in previously untreated patients with KEAP1/NRF2-mutated, non-squamous metastatic NSCLC. A separate screening protocol (NCT04698681) is also available to assess KEAP1or NRF2 mutational status based on liquid biopsy NGS, which may be used to determine KEAPSAKE trial eligibility of patients whose mutational status is unknown. https://clinicaltrials.gov/ct2/show/NCT04265534.

Keywords: glutaminase, KEAPSAKE, telaglenastat

P47.08 A Phase II, Single-arm, Multicenter, Efficacy of 80 mg Osimertinib in Patients With Leptomeningeal Metastases Associated With EGFR Mutated NSCLC

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Introduction: Leptomeningeal metastases (LM) are severe, an aggressive complication of cancer, characterized by tumor cell spread to the cerebrospinal fluid (CSF) and leptomeninges. The higher incidence of LM in EGFR mutated non-small cell lung cancer (NSCLC) has been observed, especially after treated with 1st or 2nd generation EGFR TKI. The Osimertinib, the third generation irreversible EGFR TKI, has been developed to target T790M mutation. Unlike other EGFR TKIs, Osimertinib showed homogenous distribution to the brain suggesting high penetration of blood-brain barrier, and clinical efficacy in intracranial lesions has been demonstrated from the retrospective analyses. In addition, from prospective study, double dosage (160mg) of osimertinib demonstrated meaningful clinical efficacy in LM by extending progression-free (PFS) and overall survivals (OS). However, despite the approval of Osimertinib as 1st line treatment option by the FDA in EGFR mutated NSCLC, many other countries are still in use of Osimertinib as a subsequent treatment option in selected patients. This study is designed to evaluate the clinical efficacy and safety of Osimertinib in patients with LM who failed from the previous first- or second-generation EGFR TKI. **Methods:** This study (BLOSSOM) is a Phase II, open-label, single-arm, multicenter study to evaluate the clinical efficacy of 80mg Osimertinib in patients with LM in EGFR mutated, either exon 19 deletion or L858R, NSCLC. From the 5 sites across South Korea and first or second-generation EGFR TKI pre-treated patients will be recruited. A total of 80 patients, 40 patients with T790M positive and 40 patients with T790M negative, will be recruited and treated with 80mg of Osimertinib until disease progression or intolerable adverse event. All the patients will be required to have at least one site of LM as identified by the radiologists from the central site that can be assessed by MRI which is suitable for repeat assessment. If the patient has no T790M mutation, the extracranial lesion must be stable following previous EGFR TKI treatment. The primary endpoint is OS. The secondary endpoints are blind independent committee review assessed RANO-LM criteria to evaluate the LM-objective response rate, LM-duration of response, LM-disease control rate, LM- PFS and this will be assessed based on the T790M mutation status. The RECIST 1.1 response assessed by investigator, CSF cytology clearance rates, disease-related symptom, and pharmacokinetics in plasma and CSF will be evaluated. The first patient received treatment in Dec. 2020, and the expected timeline for the final analyses is Q3, 2023. This study is conducted under an applicable regulatory requirement and supervision of the institutional review board (NCT04563871).

Keywords: leptomeningeal metastases, EGFR, osimertinib

P47.09 Tepotinib + Osimertinib for EGFR-Mutant NSCLC with Resistance to First-Line Osimertinib Due to MET amplification: INSIGHT 2

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Introduction: MET amplification (METamp) is a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), including osimertinib. METamp, as measured using fluorescence in situ hybridization (FISH), occurs in ~30% of patients who progress on EGFR TKIs. There is an unmet need for targeted treatment options for these patients. Combination treatment with an EGFR TKI and a MET TKI may overcome MET-related osimertinib resistance. Tepotinib is an oral, once daily (QD), highly selective, potent MET TKI. In the INSIGHT study (NCT01982955), the combination of tepotinib and the EGFR TKI gefitinib (n=12) improved outcomes compared to chemotherapy (n=7) in patients with EGFR-mutant METamp NSCLC and EGFR TKI resistance (n=19). Median progression-free survival (PFS) was 16.6 vs 4.2 months (hazard ratio [HR]=0.13; 90% confidence interval [CI]: 0.04, 0.43) and median overall survival (OS) was 37.3 vs 13.1 months (HR=0.08; 90% CI: 0.01, 0.51). Objective response rate was 66.7% vs 42.9% and median duration of response was 19.9 vs 2.8 months. The current study design was previously presented at ESMO 2020, as well as other local congresses (JSMO and CSCO). **Methods:** INSIGHT 2 is a global, open-label, Phase II trial of tepotinib + osimertinib in patients with advanced EGFR-mutant NSCLC. Following a protocol amendment in April 2020, the study is enrolling patients with acquired resistance (radiological documentation of disease progression following previous objective clinical benefit) to first-line osimertinib and have METamp by FISH (GCN ≥5 or MET/CEP7 ratio ≥2). Patients must be ≥18 years old, have an Eastern Cooperative Oncology Group performance status of 0/1, and normal organ function. Both tissue and liquid biopsy, obtained at the time of progression to osimertinib, will be sent for central confirmation of METamp. Liquid biopsy samples will also be used for exploratory biomarker evaluation. Enrollment is allowed based on local FISH testing while awaiting central confirmation of METamp. Patients will receive 500 mg QD (450 mg active moiety) tepotinib + 80 mg QD osimertinib until disease progression, unacceptable toxicity, or consent withdrawal. The safety of this dose regimen has been confirmed in a safety-run in period. The study is anticipated to enroll 120 patients. Primary endpoint is objective response by independent review (RECIST v1.1) in patients with METamp; centrally confirmed by FISH. Secondary endpoints include objective response by investigator assessment, duration of response, disease control, PFS, OS, pharmacokinetics, health-related quality of life, tolerability, and safety. An exploratory tepotinib monotherapy arm will enroll 12 patients to assess the contribution of tepotinib to the activity of the combination. At progression (determined by independent review committee), monotherapy patients can switch to combination treatment. These patients will be analyzed separately. Recruitment is ongoing, with >600 patients prescreened. Approximately 125 sites in 17 countries are expected to participate in Europe: Belgium (3 sites), France (8), Germany (13), Italy (8), Netherlands (3), Russia (7) and Spain (11); Asia: China (19), Hong Kong (2), Japan (10), Korea (4), Malaysia (7), Singapore (3), Taiwan (6), Thailand (3) and Vietnam (4); and North America (US [14]). As of March 2021, 95 sites are active.

Keywords: MET amplification, NSCLC, tepotinib

P47.10 Neoadjuvant Osimertinib in EGFR-Mutant Stage IIIA/B NSCLC - A Phase 2 Open-Label Pilot Study

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Introduction: Definitive chemoradiation followed by durvalumab is the standard of care in Stage III NSCLC. EGFR-mutant NSCLC is treated by EGFR-TKIs in stage IV disease with a higher ORR compared to chemotherapy. This study tested the feasibility and efficacy of osimertinib as systemic induction therapy before definitive radiation therapy in EGFR-mutant stage III NSCLC patients. Growth tumor volume (GTV) and ORR were the primary outcomes, while toxicity and DFS were secondary outcomes. **Methods:** This phase 2, open-label pilot study, which enrolled NSCLC stage IIIA/B patients harboring an EGFR-mutation. Osimertinib (80 mg) was given daily for 12 weeks as induction treatment before definitive radiotherapy and/or surgery. 13 out of 20 planned patients have been enrolled. A positron emission tomography-computed tomography (PET-CT) was performed at baseline and weeks 3, 6, and 12. Response was assessed by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. In cases of response, the patient underwent definitive radiotherapy at the 12th week and then was re-evaluated for surgery. In cases of disease stabilization or progression at 3 or 6 weeks, the study was discontinued, and patients were planned for standard chemo-radiotherapy. GTV, planned target volume (PTV), and V20% were calculated for all patients prior to osimertinib initiation and 12 weeks after initiation. Circulating ctDNA and protein biomarkers were collected for future analysis at baseline, 6 weeks, and 12 weeks. All the patients will be followed for 2 years. **Results:** Here we present the preliminary analysis of our data. So far, 13 patients have been enrolled. 11 females and 2 males; all non-smokers. The median age is 73.0 ± 5.4 years, and all having adenocarcinoma. Exon 19 deletion was found in 9 patients, exon 21-point mutation in 3 patients, and 1 patient had a rare activating mutation. T1, T2, T3, and T4 were in 2, 9, 1, and 1 patients, respectively. N2 and N3 were in 10 and 3 patients respectively. Thus, stage IIIA, B, and C were in 5, 5, and 3 patients, respectively. 9 patients have completed 12 weeks of osimertinib, while 1 patient discontinued the study due to unrelated adverse events. 6 patients have safely completed definitive radiation, 1 underwent an operation and 3 are still on osimertinib therapy. Out of 9 pts, 2 had CR and 7 had PR (RECIST). Pre-osimertinib GTV & PTV were 20.2 ± 42.9 cm^3 and 196.4 ± 241.5 cm^3. Both were reduced to 12.8 ± 21.8 (-36.7%) and 181.9 ± 113.0 (-7.4%) cm^3, respectively. No safety issues were noticed in association with osimertinib during osimertinib therapy nor during the radiation period. **Conclusion:** Osimertinib therapy is feasible in stage III EGFR-mutant NSCLC with an ORR of 90%. No specific adverse events were reported and there were no drug-associated serious adverse events during the radiation period. Osimertinb therapy decreases the GTV by 36% while PTV was reduced by 8%. In conclusion, even though the DFS is immature, it seems that induction systemic therapy with osimertinib for stage III patients is feasible and should be considered as an alternative to chemotherapy in this setting.

Keywords: EGFR-mutant, NSCLC stage III, osimertinib

P47.11 COMPEL: Chemotherapy With/Without Osimertinib in Patients With EGFRm Advanced NSCLC and Progression on First-Line Osimertinib

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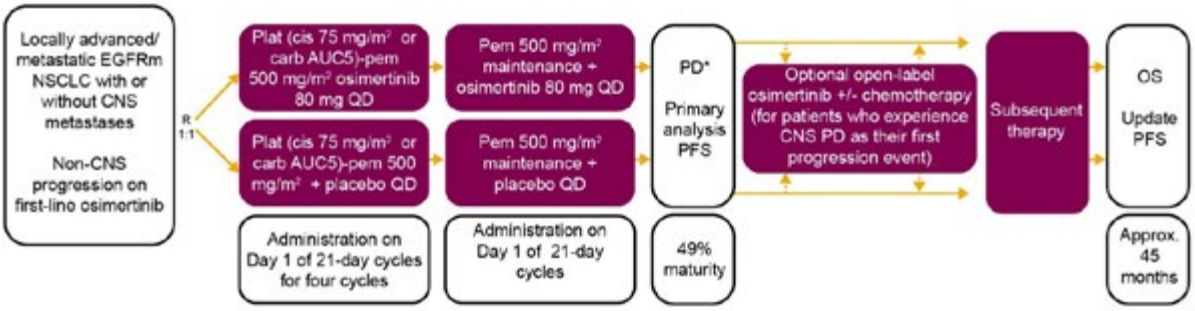
Introduction: Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits EGFR TKI-sensitizing and EGFR T790M resistance mutations with demonstrated efficacy in EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC), including central nervous system (CNS) metastases. Osimertinib is the preferred first-line treatment in EGFRm advanced NSCLC; however, progression eventually occurs. Guidelines recommend that upon systemic progression, osimertinib be discontinued and platinum-based doublet chemotherapy be initiated. Tumor heterogeneity means that while some tumor cells become osimertinib-resistant, others may remain sensitive. Continued osimertinib treatment during chemotherapy may be beneficial compared with chemotherapy alone, particularly in patients with CNS metastases given osimertinib has demonstrated superior CNS efficacy compared with chemotherapy. In addition, continuing osimertinib may prevent rebound phenomenon. COMPEL (NCT04765059) will evaluate efficacy and safety of chemotherapy and osimertinib versus chemotherapy and placebo in patients with EGFRm advanced NSCLC who experienced non-CNS progression following first-line osimertinib therapy. **Methods:** COMPEL is a phase III, randomized, double-blind, placebo-controlled study (Figure). Eligible patients: adults (age, ≥18 years); WHO PS of 0–1; life expectancy of >12 weeks; non-squamous EGFRm (Ex19del/L858R) locally advanced, metastatic or recurrent NSCLC. Patients must have radiological evidence of non-CNS progression following initial response to first-line osimertinib; patients with clinical or radiological evidence of CNS progression on first-line osimertinib are ineligible. Approximately 204 patients will be randomized (1:1) across treatment arms, stratified per presence or absence of stable CNS metastases. Patients in Arm A will receive pemetrexed plus cisplatin or carboplatin (plat-pem; investigator's choice; cisplatin 75 mg/m^2, carboplatin AUC5, pemetrexed 500 mg/m^2) plus osimertinib 80 mg, followed by pemetrexed maintenance 500 mg/m^2 and osimertinib 80 mg. Patients in Arm B will receive plat-pem plus placebo, followed by pemetrexed maintenance and placebo. Patients will receive first treatment dose within four weeks of their last first-line osimertinib dose. Serial imaging of the chest, abdomen and brain are required. Treatment will continue until RECIST 1.1- or CNS RECIST 1.1-defined progression, or until another discontinuation criterion is met. Patients may continue treatment post-progression provided they benefit. Cross-over from placebo to osimertinib is allowed if progression is confined to the CNS. The primary objective is to compare efficacy in Arm A versus Arm B per progression-free survival (PFS). CNS PFS and non-CNS PFS will be individually evaluated as secondary endpoints, as will overall survival. Safety will also be reported. First patient enrolled expected April 2021; results expected September 2024.

Figure



*Chest and abdominal imaging will continue until RECIST 1.1-defined non-CNS progression; brain imaging will continue until CNS RECIST 1.1-defined CNS progression. Modified "CNS" RECIST 1.1 guidelines are based on the neuroimaging criteria of Response Assessment in Neuro-Oncology Brain Metastases. Frequency of imaging: every six (± one) weeks for the first 13 cycles and then every 12 (± one) weeks thereafter (all relative to randomization).
AUC, target area under the curve; carb, carboplatin; cis, cisplatin; CNS, central nervous system; OS, overall survival; pem, pemetrexed; PD, progressive disease; QD, once daily; R, randomization

Keywords: non-small cell lung cancer, EGFR mutation, progression

P47.12 ALKternate: A Proof of Concept Study in ALK-Rearranged NSCLC Alternating Lorlatinib With Crizotinib After Disease Progression

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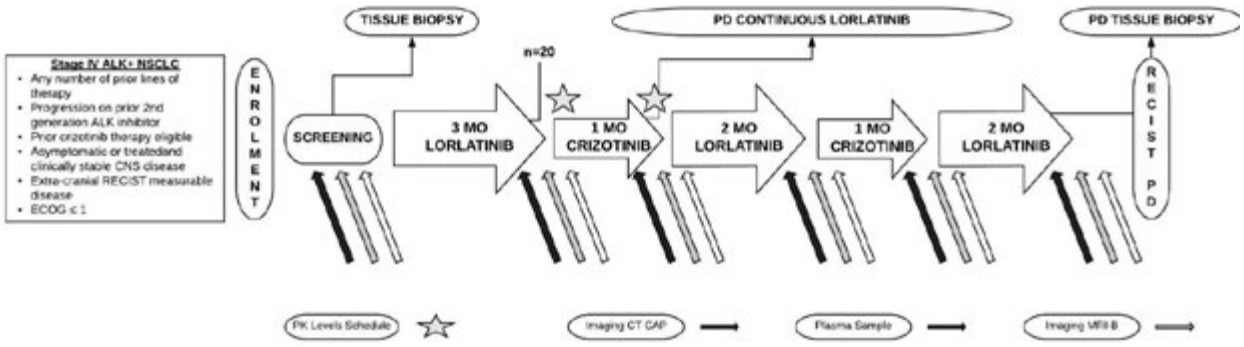
Introduction: Standard frontline therapy for patients with advanced ALK-NSCLC has rapidly evolved to 2nd generation ALK TKIs based on superior survival. Regardless, resistance to treatment is inevitable. Most will receive multiple lines of TKIs +/- chemotherapy before eventually dying from the disease. Lorlatinib is a 3rd generation ALK TKI active against a broad range of acquired ALK kinase domain (KD) resistance mutations. A recent report demonstrated re-sensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. Increased knowledge of the resistance mechanisms is key to overcoming its emergence. Recent reports have detailed diverse compound ALK mutations and frequent ALK independent mechanisms, including MET activation. Based on knowledge of the varying patterns of resistance to different ALK TKIs, ALKternate is testing the hypothesis that treatment with alternating TKIs will re-equilibrate the selection pressure for enrichment of resistant clones. **Methods:** ALKternate is a proof of concept open label multi-centre translational study alternating lorlatinib (100mg OD) with crizotinib (250mg BD) (Figure 1. including eligibility). The aim is to identify whether this fixed alternating schedule of ALK TKI is: safe; feasible and active, resulting in prolonged systemic and intracranial disease control via delaying the emergence of ALK TKI resistance. A secondary aim is to investigate whether plasma ALK-dependent and independent resistance profiles can be used to monitor therapy effectiveness. The primary outcome measure is time to treatment failure (TTTF) with alternating therapy. Secondary end points include best OR, PK analysis, PFS, DCR (systemic and CNS) after lorlatinib induction and the first cycle of alternating therapy, OS, toxicity, PROs and QOL measures. Plasma ctDNA and proteomic biomarkers will be analysed. See preliminary results in accompanying abstract #418. Enrolled patients must demonstrate disease control after induction lorlatinib to continue alternating therapy. Imaging occurs more frequently initially (Figure 1.), before 12- weekly after two alternating cycles in those with disease control. Enrollment began Q3 2019. In 2020 the trial saw delays and halted recruitment due to the COVID-19 pandemic. In 2021 it is open and recruiting. Trial registration number: ACTRN12619000844145. RECIST PD- Radiological Response Evaluation Criteria in Solid Tumors, Version 1.1, defined progressive disease Figure 1. ALKternate trial schema



Keywords: Drug resistance, ALK, Clinical trial

P47.13 First-in-Human, Dose Escalation and Expansion Study of MT-6402 in Patients With PD-L1 Expressing Advanced Solid Tumors

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Introduction: MT-6402 is a de-immunized engineered toxin body (ETB) targeting PD-L1 for solid tumors that carries a Shiga-like Toxin-A (SLT-A) payload with the addition of cytomegalovirus (CMV) antigen seeding technology (AST). MT-6402 is capable of efficiently forcing internalization of the PD-L1 receptor bound to MT-6402 and works through two distinct and novel mechanisms of action: (i) direct cell-kill via enzymatic and permanent ribosome inactivation by SLT-A, and (ii) targeted cell-kill by directing endogenous CMV-specific T-cells to the tumor. As a result, MT-6402 kills PD-L1 expressing cells at low (nmol) IC50 and is capable of significantly reducing tumor volume in PDX tumor models. The second mechanism of action, AST, involves MT-6402 mediated delivery of the CMV antigen payload (pp65 antigen) inside the tumor to be processed and presented on the target cell surface in context with MHC-I. By fundamentally altering the immunophenotype of the PD-L1 expressing tumor cells to appear infected by CMV, MT-6402 is able to redirect a potent and natural CMV-specific T-cell response. CMV-specific T-cells, which are known to circulate in tumor environments, can be less prone to exhaustion and may represent a significant portion of a CMV-infected person's T-cell repertoire. Here we report the initiation of a phase 1, first-in-human, open-label, dose escalation, and dose expansion study of MT-6402. **Methods:** The study will be conducted in 2 parts (NCT04795713). Primary objectives of Part A are to evaluate the safety/tolerability of MT-6402 and estimate the maximum tolerated dose (MTD) using the modified toxicity probability interval design-2. Primary objectives of Part B are to confirm the recommended phase 2 dose and evaluate efficacy using objective response rate (RECIST 1.1 criteria). Secondary objectives include pharmacokinetics, duration of response, progression-free survival, overall survival, and immunogenicity. Patients must be 18 years or older; ECOG PS of 0-1; with PD-L1 positive advanced solid tumors (of any degree and assessed by one of the FDA-approved immunohistochemical assays in Part A and by SP263 in Part B) not amenable to standard, life-prolonging treatment, and have received prior treatment with a checkpoint inhibitor if one is approved for the specific cancer type. In total, approximately 138 patients will be enrolled including 24-30 patients in Part A and 108 in Part B in 3 expansion cohorts (NSCLC, SCCHN, and PD-L1 positive tumor agnostic) (n = 36 per arm). MT-6402 will be administered over 30 minutes via intravenous infusion in 28-day cycles. The starting schedule is weekly dosing on Days 1, 8, 15, and 22; this may be modified to a less frequent schedule based on tolerability. In Part A, the starting dose will be 16 g/kg based upon the highest non-severely toxic dose in non-human primates; in Part B, the starting dose will be the MTD determined in Part A. Treatment will continue until disease progression, unacceptable toxicity, death, withdrawal of consent, or another reason. Enrollment is estimated to begin at several US centers in the first half of 2021.

P47.14 Study Design of SCORPION: Multi-Center, Phase II Study Following Platinum-Based Chemotherapy Plus ICIs in Patients with NSCLC

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Introduction: Docetaxel (DTX) plus ramucirumab (RAM) is one of the standard treatment for patients with non-small-cell lung cancer (NSCLC) in second line setting, which shows survival superiority to DTX in REVEL study. Recently, platinum-based chemotherapy plus immune check point inhibitors (ICIs) have become one of the front line standard treatment for NSCLC, but prospective data of DTX plus RAM following front line platinum-based chemotherapy plus ICIs are not reported. Previous translational research revealed that residual ICIs efficacy was observed beyond 20 weeks after termination of those, which possibly enhanced the activity of second-line treatment. Further, VEGF-R2 blockade by RAM could enhance not only DTX activity but also antitumor immunity by improving T-cell function. Based on the background, we conducted the SCORPION, multi-center, phase II study evaluating the efficacy and safety of DTX plus RAM following platinum-based chemotherapy plus ICIs. The study started from November 2018, and is now ongoing with patient recruitment, and here we present the study design of SCORPION. **Methods:** The SCORPION is an open-label, multicenter, single-arm phase II trial to evaluate the efficacy and safety of DTX plus RAM following platinum-based chemotherapy plus ICIs. The primary endpoint of this study is objective response rate according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. Secondary endpoints include overall survival, progression-free survival, and safety. Patients receive 60 mg/m2 of DTX 10 mg/kg of RAM on day 1 with strong recommendation of primary prophylactic pegfilgrastim use on day 2. DTX plus RAM is planned to repeat every 3 weeks until disease progression or the appearance of unacceptable toxicity. Tumor assessment is specified to perform every 6 weeks. Major eligibility criteria are as follows, (1) histologically or cytologically confirmed NSCLC, (2) stage III/IV or recurrence, (3) confirmed progression after first-line treatment with platinum-based chemotherapy plus ICIs, (4) age ≥ 20 years, (5) Eastern Cooperative Oncology Group performance status 0 or 1, (6) at least one measurable disease as defined by RECIST version 1.1, (7) adequate hematological and organ functions. **Results:** The results of the SCORPION study are expected to provide new findings regarding the clinical benefit of DTX plus RAM in new era of platinum-based chemotherapy plus ICIs.

P47.15 A Phase IA Study of Ceritinib + Trametinib in Patients With Advanced ALK- or ROS1- Rearranged NSCLC: Preliminary Results

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Introduction: In patients with non-small cell lung cancer (NSCLC) harboring oncogenic ALK or ROS1 alterations, monotherapy with tyrosine kinase inhibitors (TKIs) has yielded high response rates. However, responses are not durable and patients eventually succumb to drug-resistant disease. In preclinical models of EML4-ALK NSCLC, ALK and MEK co-inhibition resulted in increased depth and duration of response compared to monotherapy. **Methods:** We are conducting a multi-institution phase Ia trial of ceritinib + trametinib in patients with ALK- or ROS1-rearranged NSCLC who have progressed on prior oncogene-targeted therapy (NCT03087448). The primary endpoint of this study is to determine the safety and tolerability of the combination and determine the recommended phase 2 dose (RP2D). Secondary endpoints include measures of efficacy and pharmacokinetics. We are using a 3 + 3 dose escalation scheme starting at dose level 1: ceritinib 300 mg* + trametinib 1.5 mg orally daily, with dose escalation to level 2: ceritinib 450 mg* + trametinib 1.5 mg orally daily and level 3: ceritinib 450 mg* + trametinib 2.0 mg orally daily. Cycle length is 28 days. Dose limiting toxicity (DLT) is defined as any treatment-related grade 3 or 4 clinically evident non-hematologic toxicity; grade 4 neutropenia or thrombocytopenia lasting > 7 days, or febrile neutropenia. * Given with a low-fat meal. **Results:** As of April 2021, nine patients (8 ALK- and 1 ROS1-rearranged) have enrolled in the study and completed at least 1 cycle of therapy. Six ALK+ patients enrolled at dose level 1, two ALK+ and one ROS1+ patients enrolled at dose level 2. The median number of prior lines of therapy was five. The most common adverse events (AE, all grades) were rash (67%), diarrhea (55%), and elevated AST/ALT (44%). The most common attributable grade 3 or higher AE was elevated AST/ALT (33%), which occurred after cycle 1 in all patients. One DLT (grade 3 rash) was observed at dose level 1 (rash), no DLTs were observed at dose level 2. Of nine patients evaluated for best response, two (22%) had partial response (PR) (both in dose level 1), three (33%) had stable disease (SD) (all in dose level 1), and four (44%) had progressive disease (PD) (1 in dose level 1 and 3 in dose level 2). The single ROS1+ patient had PD. Preliminary overall response rate (ORR) was 22% while disease control rate was 56%. One ALK+ responder with four prior lines of therapy experienced an 88% reduction in tumor size by RECIST 1.1 criteria. **Conclusion:** Preliminary data from this trial suggests that the combination of ceritinib and trametinib is safe and tolerable with no unexpected toxicities. The ORR of 22% in a heavily pre-treated patient population suggests that the approach of targeting both ALK and MEK may be an effective therapeutic strategy in a subset of patients who have progressed on prior ALK-targeted monotherapies. Further evaluation of biomarkers of response and resistance are planned as is enrollment at dose level 3, in order to determine the RP2D.

Keywords: ROS1, MEK, ALK

P47.16 Preliminary Efficacy and Safety Results About a Phase II Trial of Afatinib and Bevacizumab in Untreated NSCLC Harboring EGFR Sensitive Mutations

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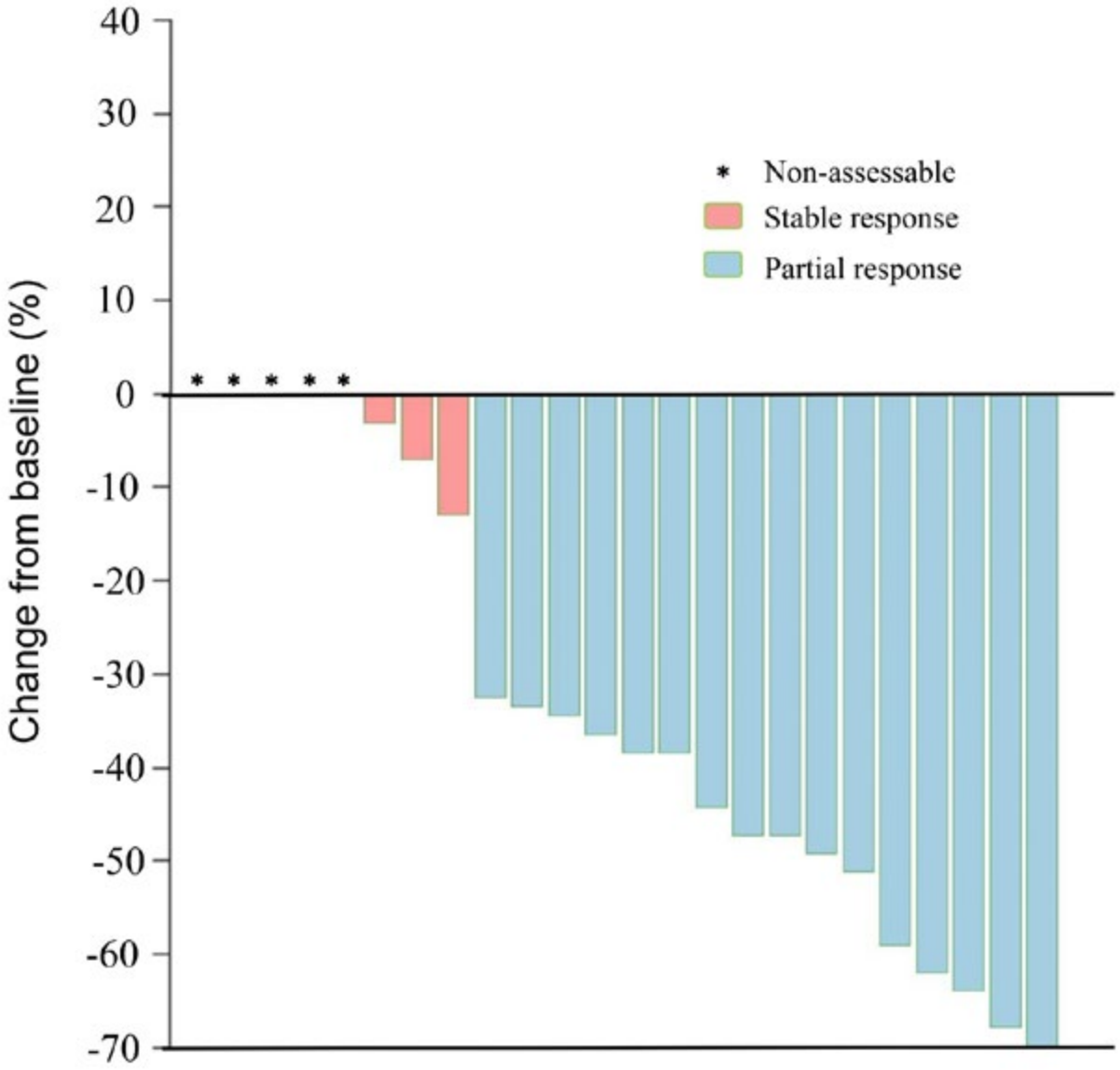
Introduction: To report the efficacy and safety results of afatinib and bevacizumab in untreated NSCLC patients with EGFR sensitive mutations (ChiCTR2000034451). **Methods:** In this open-label, single-arm, non-randomized, multi-center, phase II study, patients aged ≥18 years with EGFR sensitive mutated locally advanced or metastatic NSCLC from 9 centers in China received afatinib 30mg doses once daily and bevacizumab 7.5mg/Kg every three weeks until disease progression or unacceptable toxicity. The preliminary efficacy analysis was conducted in patients with ≥1 measurable lesion (RECIST 1.1) at baseline imaging and with ≥2 available tumor assessment (evaluable-for-response set, EFR), which was evaluated in terms of objective response rate (ORR), disease control rate (DCR), and remission depth (the best percentage change from baseline in the sum of longest tumor diameters). The safety analysis was conducted in full analysis set (FAS) of patients who received at least one dose of study drug. **Results:** At data cut-off (7 Apr 2021), 24 patients were enrolled and the median follow-up time was 4.5 months (range, 0.5-9.9), of which 19 patients (79.2%) were included in EFR and 24 patients (100%) were included in FAS. Nineteen patients (79.2%) hold the classical mutations of EGFR L858R or 19del, five patients (20.8%) hold the non-calssical sensitive mutations. Confirmed ORR was 84.2% (16/19) while DCR was 100% (19/19) in EFR, with a median remission depth of 45% (range, 3-70%). The most common adverse events in FAS were diarrhea (20/24, 83.3%), skin rashes (17/24, 70.8%), oral ulcer (14/24, 58.3%) and paronychia (10/24, 41.7%). One patient (1/24, 4.2%) was observed grade 3 adverse event of diarrhea, no other grade 3 or higher adverse events occurred.



Conclusion: The combined use of afatinib and bevacizumab is efficacious in treating NSCLC patients harboring EGFR sensitive mutations, with acceptable toxic effects.

Keywords: non-small cell lung cancer, afatinib, bevacizumab

P47.17 Capmatinib vs Docetaxel in Pretreated Patients With MET Exon 14 Skipping–mutated Stage IIIB/IIIC or IV NSCLC (GeoMETry-III)

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Introduction: MET exon 14 skipping (METex14) mutations occur in 34% of patients with non–small cell lung cancer (NSCLC). Capmatinib is a MET inhibitor (METi) approved in the USA and Japan for the treatment of adult patients with metastatic METex14-mutated NSCLC. The approval was based on the results from the phase 2 GEOMETRY mono-1 study (NCT02414139), in which capmatinib 400 mg oral twice daily (bid) showed substantial antitumor activity and manageable safety in patients with advanced METex14-mutated NSCLC. In this study, an overall response rate (ORR) of 68% in treatment-naive patients (N=28) and 41% in patients who had received 1 or 2 prior lines of therapy (N=69) was observed. In the GeoMETry-III clinical trial (NCT04427072), we aim to evaluate the efficacy and safety of capmatinib vs docetaxel as second-line or third-line therapy in patients with METex14-mutated locally advanced or metastatic NSCLC. Single-agent docetaxel is an established standard of care in this pretreated setting, irrespective of tumor histology. **Methods:** This multicenter, open-label, randomized, global, phase 3 trial began enrollment in September 2020 and is currently recruiting adult patients with EGFR wild-type, ALK-rearrangement negative, stage IIIB/IIIC or IV METex14-mutated NSCLC who have progressed on 1 or 2 prior lines of systemic therapy and are candidates for single-agent docetaxel. Other key eligibility criteria include ≥1 measurable lesion per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), an Eastern Cooperative Oncology Group performance status of 0 or 1, and no prior treatment with METi or hepatocyte growth factor–targeting therapies. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within 2 weeks prior to study entry to manage CNS symptoms are excluded. Eligible patients (~N=90) are randomized 2:1 to receive oral capmatinib 400 mg tablets bid with or without food or docetaxel 75 mg/m^2 intravenously every 21 days. Randomization is stratified by number of prior lines (1 or 2) of systemic therapy. Patients randomized to the docetaxel arm are eligible for crossover to the capmatinib arm after blinded independent review committee (BIRC)–confirmed progressive disease and if they meet the eligibility criteria prior to crossover. The primary endpoint is BIRC-assessed progression-free survival (PFS) per RECIST v1.1. The key secondary endpoint is BIRC-assessed ORR per RECIST v1.1. Other secondary endpoints include investigator-assessed ORR and PFS; BIRC- and investigator-assessed duration of response, time to response, and disease control rate; overall survival; safety; pharmacokinetics; patient-reported outcomes; and BIRC-assessment of intracranial antitumor activity per the Response Assessment in Neuro-Oncology Brain Metastases criteria in patients with baseline CNS lesions. **Results:** Not applicable **Conclusion:** Not applicable

Keywords: Capmatinib, non-small cell lung cancer, MET exon 14 skipping mutation

P47.18 Almonertinib With Radiotherapy vs Concurrent Chemoradiotherapy in Unresectable Stage III EGFR-mutant NSCLC (ADVANCE Trial)

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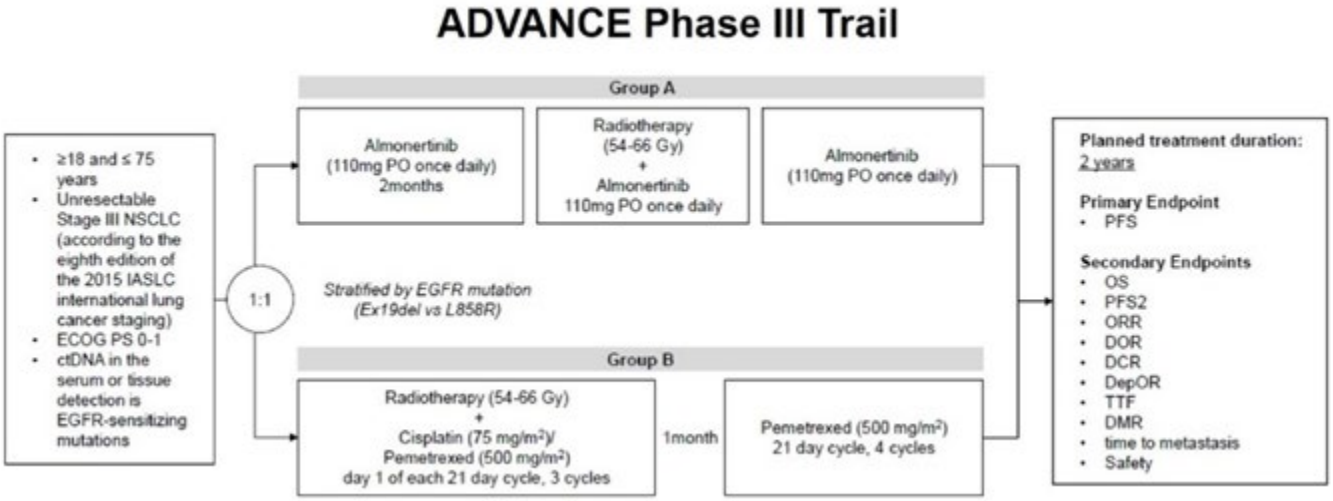
Introduction: For patients with unresectable stage III non-small cell lung cancer (NSCLC), the standard of care is concurrent chemoradiotherapy (CRT), and the PACIFIC trail demonstrated significant progression-free survival (PFS) and overall survival (OS) benefit with the consolidation durvalumab for those without progression. However, the number of patients with EGFR-positive mutation in the PACIFIC trial is small (6%, 43/713), and the subset analyses assessing PFS (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.40-1.75) and OS (HR 0.97, 95% CI 0.40-2.33) between durvalumab and placebo were inconclusive. Therefore, a more effective therapeutic strategy for this population needs to be further investigated. Almonertinib (HS-10296) is a novel, third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) approved in China to treat EGFR-mutant NSCLC. Based on this information, we conducted a phase III trial to assess the efficacy and safety of almonertinib with radiotherapy as a potential chemotherapy-free option in the treatment of unresectable stage III EGFR-mutant NSCLC (ChiCTR2000040590). This is the first trail to explore almonertinib and radiotherapy combination with induction EGFR-TKI in the unresectable setting. **Methods:** This is a multicenter, randomized, open-label, phase III trial. In total this trial aims to enroll approximately 254 patients with unresectable stage III EGFR-mutant NSCLC who have not received systemic or local antineoplastic therapy. Patients will be randomized (1:1) to receive almonertinib with radiotherapy (group A) or concurrent CRT (group B), stratified by EGFR mutation (Ex19del vs L858R). In group A, almonertinib induction therapy (110mg PO once daily) will be given for 2 months firstly, followed by almonertinib (110mg PO once daily) combined with radiotherapy (total dose 54-66 Gy, once daily, 5 times a week). In group B, radiotherapy (total dose 54-66 Gy, once daily, 5 times a week) in combination with cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2) on day 1 of 21-day cycles (every 3 weeks) will be given for 3 cycles, followed by pemetrexed maintenance (500 mg/m2) every 3 weeks for 4 cycles. Patients in group B will be eligible to cross over to receive almonertinib therapy if all protocol-specified criteria are met. The primary endpoint is PFS. Secondary endpoints included OS, time to second objective disease progression (PFS2), objective response rate (ORR), duration of response (DOR), disease control rate (DCR), depth of response (DepOR), time to treatment failure (TTF), distant metastasis rate (DMR), time to metastasis and safety. Planned total treatment duration is 24 months. The first patient had been enrolled in March 2021.



Keywords: almonertinib, radiotherapy, NSCLC

P48.01 Anlotinib Plus Docetaxel vs Docetaxel for 2nd-Line Treatment of EGFR negative NSCLC (ALTER-L018): A Randomized Phase II Trial

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Introduction: Anlotinib, a novel oral small molecule multi-target TKI for potently targeting VEGFR, FGFR, PDGFR and c-Kit, has dual effects of anti-tumor angiogenesis and inhibition of tumor growth. The positive phase III trial (ALTER0303) showed anlotinib improved both progression-free survival (PFS) and overall survival (OS) survival as a single agent in third-line treatment of advanced non-small cell lung cancer (NSCLC). Here, ALTER-L018 is aimed to assess efficacy and safety of anlotinib plus docetaxel in patients with refractory advanced NSCLC whose disease had progressed during or after first-line platinum-based chemotherapy with or without Immune checkpoint inhibitors treatment. **Methods:** In this multi-institutional, randomized, controlled comparative, phase II trial, patients from 10 sites in China, with EGFR wild-type NSCLC progressing after first-line platinum-based chemotherapy (combined with or without Immune checkpoint inhibitors), were randomly allocated (1:1) to receive anlotinib (12mg QD from day 1 to 14 of a 21-day cycle) plus docetaxel (75mg/m^2 Q3W) (group A+D) or docetaxel (75mg/m^2 Q3W) only (group D). Primary end point was PFS, and secondary end points included OS, ORR, DCR and safety. This trial is registered with ClinicalTrials.gov, number NCT03624309. **Results:** Between Jan 14, 2019, and Apr 5, 2021, 74 patients (pts) were randomly allocated, while 8 pts were excluded due to inclusion violations (demographics are shown in Table 1). At data cutoff (Apr 5, 2021), 66 pts. were available for efficacy and safety analysis. The median PFS in group A+D was significantly improved compared with group D [4.03m(95%CI:2.98-5.08) vs 1.7m(95%CI: 0.45-2.95); HR 0.40 (95%CI:0.21-0.77), p=0.004)]. The median OS has not reached. For tumor response, ORR were 35.71% vs 7.89% (p=0.01) and DCR were 82.14% vs 55.26%(p=0.03) in group A+D and group D, respectively We noted treatment-emergent adverse events in 26 (92.86%) of 28 patients in group A+D safety population and 33 (86.84%) of 38 patients in group D safety population. The most common grade≥3 TRAE were leukopenia (3, 11%), neutropenia (3, 11%) and thrombocytopenia (2, 7%) in group A+D and leukopenia (3, 8%), neutropenia (2, 5%) and thrombocytopenia (1, 3%) in group D The toxicities in group A+D and group D were manageable with appropriate dose reductions and supportive care

Table 1: Demographics		
	Anlotinib plus Docetaxel (n=28)	Docetaxel (n=38)
Median age, years	54 (51-57)	57 (54-60)
Age group, years		
< 60	22 (79%)	23 (61%)
≥ 60	6 (21%)	15 (39%)
Sex		
Men	23 (82%)	30 (79%)
Women	5 (18%)	8 (21%)
Disease stage		
III	6 (21%)	6 (16%)
IV	22 (79%)	32 (84%)
ECOG PS		
0	7 (25%)	8 (21%)
1	21 (75%)	30 (79%)
Histologic subtype		
ADC	21 (75%)	24 (63%)
Non-ADC	7 (25%)	14 (37%)
Smoking history		
Never smoker	6 (21%)	12 (32%)
Former smoker	15 (54%)	18 (47%)
Current smoker	7 (25%)	8 (21%)
Front line treatment		
platinum-based chemotherapy with ICIs	5 (18%)	9 (24%)
platinum-based chemotherapy	23 (82%)	29 76%)
* Data Cut-off: Apr 5, 2021		

Conclusion: The combination of anlotinib plus docetaxel improves survival as second-line treatment of EGFR negative NSCLC patients in terms of PFS, ORR, DCR, and has a manageable safety profile. It has been proved to be an effective regimen for EGFR negative NSCLC patients progressing after first-line platinum-based chemotherapy combined with Immune checkpoint inhibitors.

Keywords: Anlotinib EGFR wild-type NSCLC Second-line therapy

P48.02 Real-World Data of Dacomitinib in EGFR TKI-Naïve Patients With Advanced Epidermal Growth Factor Receptor-positive Non-small Cell Lung Cancer

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Introduction: Dacomitinib is a second-generation epidermal growth factor receptor (EGFR) Tyrosine Kinase Inhibitor targeted for EGFR sensitizing mutations in patients with non-small cell lung cancer (NSCLC). The efficacy of dacomitinib in patients with advanced NSCLC harboring EGFR mutation was shown in ARCHER 1050. However, data on efficacy of dacomitinib in real-world remain rare. **Methods:** Ninety-nine patients with advanced NSCLC who received dacomitinib (30mg daily or 45 mg daily) after initial diagnosis or 1-4 cycle of chemotherapy treatment were included in this ambispective (both retrospective and prospective) multicentric study. Treatment outcomes of these patients were analyzed. **Results:** Ninety-nine patients managed in seven centers were enrolled, the median age was 44 years (range, 32-76), 61.6% were female and 93.9% were adenocarcinoma. Patients received dacomitinib with 30mg daily in 82.8% of cases. A total of 17.2% of patients received 1-4 cycles of chemotherapy before dacomitinib treatment. 31.3% (31/99) of patients had central nervous system (CNS) metastases at baseline. In patients evaluable for response analysis (n=69), objective response rate (ORR) was 75.4%, and disease control rate (DCR) was 100%. The median time to tumor response (TTR) in responding patients was one month (range, 0.7-13.4 months). For subgroup analysis, ORR and DCR were 75.4% (43/57) and 100% (57/57) in untreated patients. Among 31 patients with CNS metastases, 21 cases were evaluated for intracranial efficacy, of whom ORR was 76.2%, DCR was 100%. The median progression-free survival (PFS) was 14.1 months, and overall survival (OS) was not reached (median follow-up time: 14.8 months). Dacomitinib dosage was modified in 16.2% of patients. Safety profile was acceptable, no adverse events (AEs) related deaths was observed. **Conclusion:** Dacomitinib showed significantly active in EGFR TKI-naïve patients with advance EGFR-positive NSCLC, and was well tolerated.

Keywords: dacomitinib, NSCLC, EGFR TKI

P48.03 Spectrum of Resistance Mechanisms to First, Second and Third Generation Tyrosine Kinase Inhibitors in EGFR Mutant NSCLC Patients

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Introduction: Resistance to first(1st), second(2nd) and third (3rd) generation of tyrosine kinase inhibitors(TKIs) in EGFR mutant NSCLC targeted therapies can be classified as either primary (i.e., intrinsic) or secondary (i.e., acquired). Primary resistance implies a de novo lack of response whereas secondary resistance refers to disease progression after a period of initial clinical benefit.Next generation sequencing(NGS) offers a comprehensive method of detecting these mechanisms to decide the next line of treatment. **Methods:** We retrospectively analyzed 453 samples of NSCLC for primary and secondary resistance to 1st , 2nd and 3rd TKIs . NGS was performed using thermofischer Ion Torrent™ Oncomine™ Focus 52 gene Assay . These cases were divided into 4 groups.1)Primary resistance to first and second generation TKIs 2)Primary resistance to 3rd generation TKI 3)Secondary resistance to 1st and 2nd generation TKI 4) Secondary resistance to 3rd generation TKI.Last group was further subgrouped into A when 3rd generation TKI was offered as second line after 1st or 2nd generation TKIs on detection of T790M and subgroup B when it was given as first line. **Results:** Group1 had 13 cases. There were 2 cases of complex EGFR exon 19 mutation p.Glu746_Leu747delinsValPro, 4 cases of EGFR exon 20 insertion, 1 case of dual EGFR L833V & H835L mutation , 2 cases with EGFR amplification with EGFR exon 19 del and PIK3CA C420_P421del along with EGFR exon 19 del . Four cases had no additional abnormality. Group 2 had 5 cases:1 case had L858R and E709A dual mutation, 2 cases had KRAS G13C and KRAS G12V along with EGFR exon 19 del. One case had EGFR amplification and one case had MET amplification along with EGFR exon 19 del respectively.Group 3 had 36 cases including 10 cases of EGFR L858R and 26 cases of exon 19 deletion.T790M mutation was detected in 8 patients, MET amplification in 7 cases,one case had both T790M and MET amplification. One case lost the primary EGFR exon 19 del. Other mutations detected were KRAS G13C, PIK3CA H1047R, TP53 R213Q and TP53 C242fs. Group3 had 16 cases with 7 cases in subgroup A and 9 cases in subgroup B. In subgroup A T790M mutation was lost in 6 out of 7 cases.One case which lost T790M developed ALK translocation.One case of EGFR exon 19 del retained EGFR T790M with EGFR C797S in cis allele. Other mutations detected were PIK3CA E542K and KRAS G12C. In subgroup B one case showed EGFR C 797S(both cis and trans) besides the primary EGFR exon 19 del. One case showed BRAF G469A along with EGFR exon 19 del. Other mutations detected were CTNNB1 D32N, KRAS G12V, and PIK3CA E542K **Conclusion:** Resistance development is unavoidable in EGFR mutant advanced NSCLC on any generation of TKIs. NGS offers an advantage in diagnosing mechanism of resistance for further choice of therapy.

Keywords: resistance, NSCLC, EGFR mutation

P48.04 EGFR Germline Mutations in Chinese Lung Cancer Patients: A Single Institutional, Retrospective Study

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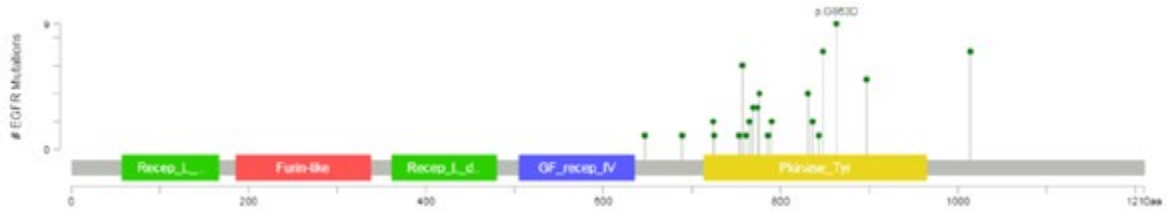
Introduction: Germline EGFR-T790M mutation has been proved to be associated with hereditary lung cancer (LC) in multiple studies. However, the role of other EGFR variants in genetic susceptibility to LC has not been well investigated. **Methods:** This study retrospectively reviewed a cohort of 31,906 Chinese LC patients with their white blood cells or para-carcinoma tissue samples sequenced. All nonsynonymous variants in the coding regions of EGFR gene were analyzed, and variants with a frequency higher than 0.01 in the population database were filtered out. Variants that have been previously reported in literatures were included in the final analysis cohort, including variants related to the sensitivity or resistance of tyrosine kinase inhibitors (TKIs), previously reported germline variants, and variants with functional studies. **Results:** A total of 22 different heterozygous germline variants from 64 patients with LC were identified (Figure). The top five common germline variants included G863D (14.1%), P848L (10.9%), D1014N (10.9%), K757R (9.4%), V897A (7.8%). The median age at diagnosis was 61.5 years (range: 44-88 years; 8 unknown); 60.9% (39/64) patients were male (1 unknown); 53.1% (34/64) patients were ever-smokers (8 unknown). The majority of patients were adenocarcinoma (75%, 48/64), followed by unclear diagnoses (15.6%), multiple primary carcinomas (6.3%) and squamous carcinoma (3.1%). Cancer family history was reported in 17 patients, including 11 patients with their family members diagnosed as LC, and 6 patients with history of other cancers. Concomitant somatic mutations were detected in 36 patients, including L858R or 19 exon deletions (concurrent with resistant mutations or not) (35.9%, 23/64) and other activating mutations (concurrent with resistant mutations or not) (20.3%, 13/64). Among 23 patients harboring L858R or 19 exon deletions, 14 patients received EGFR-TKIs treatment and the median duration of treatment (DOT) was 9.5 months (range: 2-17 months). Among 13 patients harboring other activating mutations, 9 patients received EGFR-TKIs treatment and the survival data was not available for 4 patients. One patient harboring germline T790M mutation and somatic L861Q and G719A mutations received icotinib and the DOT was 15 months. For the remaining four patients, the DOT was shorter than 6 months. One patient with germline P848L mutation did not respond to either ecotinib or afatinib. Another patient with germline R831H mutation received gefitinib treatment and the progression-free survival was 14 months.



Conclusion: This study identified more EGFR germline variants other than the previously reported T790M mutation. Patients with EGFR germline variants may benefit from TKIs treatment.

Keywords: EGFR germline mutation, EGFR-TKI, lung cancer

P48.05 Is Relapse-Free Survival at 2-Years an Appropriate Surrogate for Overall Survival at 5-Years in EGFR-mutated Resected NSCLC?

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Introduction: The phase 3 ADAURA trial identified a highly significant hazard ratio (HR) of 0.17 for disease-free (i.e., relapse-free) survival (RFS) favoring adjuvant osimertinib, but a non-significant immature overall survival (OS) HR of 0.40. However, is RFS an appropriate surrogate for OS in this setting? OS is still the gold standard in health technology assessments, but it will take years for ADAURA's OS data to mature. In the ADAURA-eligible setting, we compared HRs for clinico-demographic-treatment variables between RFS censored at 2 years (RFS-2YRS) with OS censored at 5 years (OS-5YRS), and explored reasons why such a relationship may exist. **Methods:** A retrospective analysis from Princess Margaret Cancer Centre of all patients with EGFR-mutated resected NSCLC (diagnosed 2012-2018) utilized Kaplan-Meier curves and Cox regression to compare RFS-2YRS and OS-5YRS for common clinico-demographic-treatment variables. We explored how these patients were managed after relapse, and compared their OS outcomes to patients with de novo advanced/metastatic EGFR-mutated disease. **Results:** Among 104 patients with EGFR-mutated resected NSCLC, female=66%; median age=67 years; never-smokers=73%; Stage IB=41%; Stage II=34%; Stage IIIA=25%. Univariable Cox regression results comparing RFS-2YRS and OS-5YRS are presented in the table. Overall, HRs were either similar or slightly attenuated at OS-5YRs when compared to RFS-2YRS. Among the n=63 (61%) patients who relapsed, 81% were due to distant metastases. Only 8% were treated with curative surgery or chemoradiation at the time of relapse (an additional 3% were offered but declined curative treatment). The remaining patients (92%) were managed as advanced/incurable cancer. Of those treated at Princess Margaret, 75% received first-line EGFR-TKI therapy, while 4% received other systemic therapies; 8% had developed multifocal disease that was monitored rather than treated systemically; and 8% died before systemic therapy could be started or had concurrent comorbid conditions. Starting with diagnosis of advanced/metastatic disease, there were no differences in the OS of this relapsed cohort (n=63) versus 252 de novo advanced/metastatic NSCLC (log-rank p=0.29). The adjusted HR for OS was 0.82 (95% CI: 0.55-1.24).

All Resected EGFR-mutated Stage I-III NSCLC	Unadjusted HR (95% CI)	Global p-value	Unadjusted HR (95%CI)	Global p-value
Clinical Variables	**RFS-2YRS**		**OS-5YRS**	
Age (per 10-year increase)	0.88 (0.64-1.23)	0.46	0.90 (0.57-1.41)	0.64
Male *versus* Female	1.46 (0.81-2.64)	0.21	1.28 (0.57-2.84)	0.55
Never- *versus* Ever-Smoker	1.01 (0.52-1.95)	0.97	1.39 (0.52-3.17)	0.51
Disease Stage II *versus* IB Disease Stage III *versus* IB	1.87 (0.89-3.91) 3.15 (1.50-6.62)	0.01	3.97 (1.26-12.47) 5.44 (1.70-17.43)	0.02
Adjuvant *versus* No Adjuvant therapy	1.11 (0.62-1.98)	0.72	2.17 (0.94-5.05)	0.07
All Resected EGFR-mutated Stage I-III NSCLC	**Adjusted HR* (95% CI)**	**Global p-value**	**Adjusted HR* (95%CI)**	**Global p-value**
Age (per 10-year increase)	0.99 (0.70-1.41)	0.97	1.08 (0.66-1.77)	0.77
Male *versus* Female	1.60 (0.88-2.91)	0.12	1.29 (0.57-2.91)	0.54
Never- *versus* Ever-Smoker	1.08 (0.56-2.10)	0.81	1.54 (0.58-4.13)	0.39
Adjuvant *versus* No Adjuvant therapy	0.55 (0.27-1.10)	0.09	0.89 (0.33-2.39)	0.82
*Hazard ratios adjusted for stage (IB vs II vs III)				

Conclusion: Among early-stage patients with EGFR-mutated resected NSCLC, 92% were treated as advanced/metastatic disease at the time of relapse. Their survival (from the time of relapse) was similar to those diagnosed initially with EGFR-mutated advanced/metastatic cancer. This information helps explain why relapse-free survival censored at 2-years represents an acceptable surrogate endpoint for overall survival at 5-years.

Keywords: EGFR, NSCLC

P48.06 A Network Meta-Analysis (MA) of First-Line Lung Cancer Treatment With Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs)

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Introduction: Over the last two decades, the treatment options for non-small cell lung cancer harbouring EGFR mutations have expanded rapidly from chemotherapy to encompass first, second and third generation TKIs alone or as part of combination therapy. While chemotherapy, gefinitib and erlotinib have often been used as comparator arms in clinical trials, newer standard options like osimertinib, afatinib, dacomitinib and combination therapies have rarely been compared directly for efficacy or toxicity outcomes. In this study, we conduct a systematic review and network MA to allow the direct and indirect comparison of the various first-line treatment options for EGFR-mutant NSCLC. **Methods:** A comprehensive literature search was performed on MEDLINE/PubMed, Embase, the Cochrane Library and China National Knowledge Infrastructure with a cutoff date of 31 December 2019, using the search terms “non-small cell lung carcinoma”, “epidermal growth factor receptor” and “tyrosine kinase inhibitors”. Randomised controlled trials (RCTs) evaluating the effectiveness and safety of treatments for patients with EGFR-mutant NSCLC were selected. The main outcome measures that were extracted and analysed were progression free survival (PFS), overall survival (OS) and adverse events (AEs). A network geometry of the treatments was constructed, and the effectiveness and safety of the treatments compared using a multivariate meta-regression model with random-effects that adopted a frequentist approach. To rank the prognosis of all the geometric patterns, we used surface under the cumulative ranking (SUCRA) values. Both node-splitting and inconsistency modeling were used to test the consistency assumption. **Results:** A total of 14 RCTs including 4221 patients, undergoing 9 different interventions, were included in the final analysis. For PFS, single agent osimertinib, followed by combination gefitinib- chemotherapy, followed by erlotinib-ramucirumab were the top 3 ranked treatments in relation to gefitinib alone based on the SUCRA score, with hazard ratios (HRs) of 0.43 (95% CI 0.36-0.52), 0.53 (95% CI 0.46-0.62) and 0.52 (95% CI 0.38-0.72) respectively. For overall survival, gefitinib- chemotherapy, then osimertinib, then erlotinib ramucirumab were the top 3 ranked treatments with HRs compared to gefitinib alone of 0.57 (95% CI 0.46-0.73), 0.76 (95% CI 0.58-1.00) and 0.75 (0.42-1.34) respectively. We performed subgroup analyses based on age (>/<65 years old), smoking status, mutation type (Exon 19 deletion/Exon 21 L858R) and the presence or absence of brain metastases; the same survival trends were seen across the subgroups. Osimertinib had the lowest risk ratio of AEs at 0.36 (95% CI 0.21-0.62) in relation to afatinib-cetuxumab, which had the highest risk of AEs. **Conclusion:** Osimertinib, gefitinib-chemotherapy, and erlotinib-ramucirumab give the best survival outcomes in the first-line treatment of EGFR mutant NSCLC. Of these, osimertinib also has the best toxicity profile. These results, in line with the FLAURA study, show that osimertinib is highly effective and tolerable and should be the standard in these patients.

Keywords: Tyrosine kinase inhibitor, Network meta-analysis, Epidermal growth factor receptor

P48.07 Real-World Impact of Upfront Osimertinib in Reducing Health Resource Utilization by Preventing Brain Metastases

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Introduction: Up to 70% of non-small cell lung cancer (NSCLC) patients develop central nervous system (CNS) metastases during the course of their disease, which are associated with poor quality of life and high medical costs. This study aims to evaluate the real-world impact of osimertinib in preventing CNS metastases in advanced EGFR-mutant NSCLC and reducing healthcare resource utilization for their management. **Methods:** All consecutive EGFR-mutant advanced NSCLC patients treated in our hospital with third-generation EGFR-TKI osimertinib after the drug registration in Italy (January 2019 to December 2020) were considered. We evaluated CNS Progression-Free Survival (PFS), cumulative incidence of symptomatic CNS metastases upon treatment failure, hospitalization rate, locoregional treatments and treatment-related side effects in patients treated with osimertinib with those reported in patients treated with first or second-generation TKIs in the same time frame the previous 2 years (January 2017 to Decembre 2018). Log-rank test and Pearson's chi-squared test were used to analyze the results. **Results:** Data from 47 patients were retrieved. Twenty-six patients received first or second-generation EGFR-TKIs and 21 received osimertinib. Five patients had synchronous CNS metastases in each group. 11/26 (42.3%) patients treated with first or second-generation TKIs experienced CNS progression during TKI treatment compared to no one in the osimertinib group (p = 0.007 chi-square) with median CNS PFS of 42.5 months versus Not Reached, respectively (p = 0.021). Among patients treated with first or second-generation TKIs experiencing CNS progression, 10 patients had symptomatic CNS progression that required hospitalization in 6 cases, with a median length of stay of 23 days (range 9-54). Six patients received CNS radiotherapy (4 WBRT and 2 stereotaxis), while 3 patients underwent neurosurgery. 8 / 26 (30.8%) patients died due to progressive brain metastases. Overall, patients treated with osimertinib had a better safety profile than patients treated with first/second-generation TKIs (Grade ≥2 adverse events in 16 / 26 (61.5%) versus 2 / 21 (9.5%), p = 0.005). **Conclusion:** CNS metastases are associated with substantial symptomatic burden, poor survival and health resource utilization in EGFR-mutant NSCLC patients. Compared to historical controls treated with first or second-generation TKIs, the prolonged CNS disease control by upfront use of osimertinib translated into lower resource utilization and better clinical outcomes.

Keywords: health resource utilization, osimertinib, brain metastasis

P48.08 The Efficacy and Clinical Survival Outcome of Different First-Line Treatments in EGFR Mutant Non-Small Cell Lung Cancer With Brain Metastases

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Introduction: Brain metastasis is one of the most important factors for poor prognosis of lung cancer, and the incidence of brain metastasis in EGFR mutant(m+) advanced NSCLC is more common. The purpose of this study is to explore the best method for EGFRm+ NSCLC with brain lesions, and to find out correlative factors influencing survival outcome. **Methods:** The clinical data of NSCLC with brain metastases was retrospectively analyzed. Most patients had received 1st generation EGFR TKI, and patients were divided into 4 group, group A: EGFR-TKI monotherapy, group B: EGFR-TKI plus Chemotherapy (CT), group C: EGFR-TKI plus bevacizumab, group D : EGFR-TKI plus CT and bevacizumab. The efficacy of intracranial and extracranial lesions and survival outcome were analyzed. **Results:** A total of 1159 EGFRm+ advanced NSCLC patients from December 2017 to May 2020 were screened, and 228 (19.7%) had brain metastasis at baseline in the treatment-naive. Among them, 194 patients had complete medical record and follow-up data. At the follow-up date (January 1, 2021), 147 patients had disease progressed and 78 patients had died. The intracranial PFS of group A ,B ,C ,D were 11.1m(n=97),11.3m(n=59),21.2m(n=19),and14.5m(n=19),respectively. No difference was found between groups A and B (P=0.745), so as C and D groups (P=0.684). But the intracranial PFS of group C+D(with bevacizumab) was significantly longer than group A+B(11.3m vs 21.0m, P=0.007).The extracranial PFS of groups A, B, C, and D were 11.0m, 14.3m, 21.7m, and 18.9m, and the P value were 0.006, 0.002, and 0.011 respectively, when compared with group A. The mOS of groups A ,B were 27.8m and 24.2m,respectively, but group C and D had not yet reached. The intracranial ORR of group A, B, C, and D were 17.9% (14/78), 37.3% (19/51), 60.0% (9/15), and 66.7% (10/15), respectively. The extracranial ORR were 48.5% (47/97), 81.1% (43/53), 73.7% (14/19), and 73.7% (14/19),respectively. **Conclusion:** For EGFRm+ NSCLC with brain metastases, the first-generation EGFR-TKI plus bevacizumab can significantly improve the efficacy of intracranial lesions, delay the progression of intracranial lesions, and prolong suvival time. Although the first-generation EGFR-TKI plus CT could improve extracranial ORR when compared with ERGF-TKI monotherapy, it has limited efficacy on intracranial lesions and could not increase survival time. EGFR-TKIs plus CT and bevacizumab did not achieve the expected effect of the powerful combination, but increased the incidence of toxicity and adverse reactions to a certain extent.

Keywords: targeted therapy, driver gene, brain metastases

P48.09 Body Mass Index Predicts Benefit From Adding Metformin to EGFR-TKIs in Patients With Lung Adenocarcinoma: Subanalysis From an RCT

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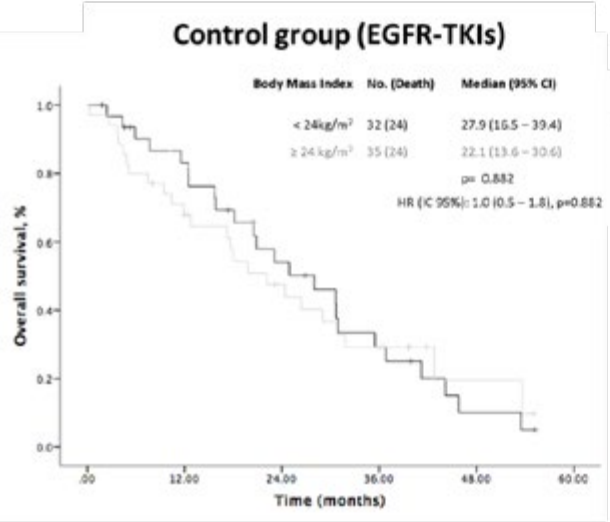
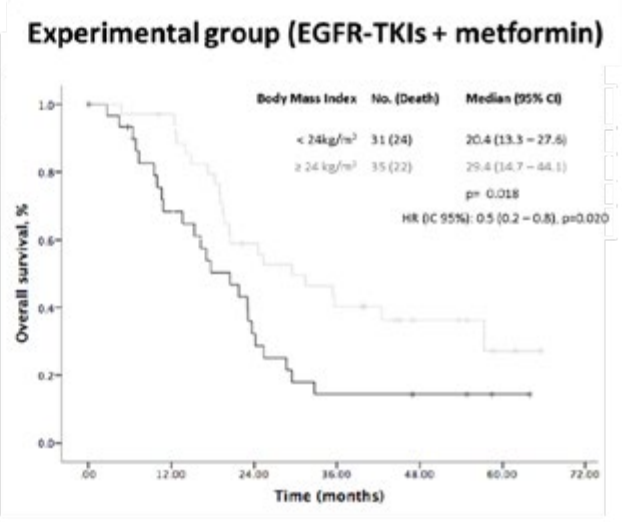
Introduction: Evidence regarding the synergistic association between EGFR-TKIs and metformin has been controversial, with conflicting results from phase II clinical trials performed in different populations. The reasons for the discrepancies could be related to differences in the populations studied in each single-country trial. Interestingly, one factor which was not evaluated in either trial was whether the benefit from metformin was dependent on body mass index (BMI) or baseline glucose uptake by the tumor through PET-CT-FDG. In this study, we performed a post-hoc analysis to estimate survival outcomes according to baseline BMI in patients included in a randomized phase II clinical trial. **Methods:** Post-hoc subanalysis performed using the database from a randomized phase II clinical trial performed in Mexico (NCT03071705). In this study, a total of 139 patients were included and randomly assigned to receive EGFR-TKIs (erlotinib, afatinib or gefitinib) or EGFR-TKIs plus metformin (500 mg BID). Among the study participants, a total of 133 patients had complete information regarding anthropometric variables and were included in this subanalysis. Patients were stratified according to BMI (<24 vs. ≥24) and median tumor glucose uptake (SUV ≤8.6 vs. >8.6) to analyze progression-free survival (PFS) and overall survival (OS) according to these subgroups in each study arm. **Results:**





A total of 133 patients met criteria and were included in this subanalysis, among which n=67 were randomized to the control arm of the study, while n=66 were randomized to the experimental arm. Mean age for the entire population was 59.3 (± 13.0), while 64.7% (86/133) were female. PFS for patients in the control group had no differences when stratifying patients according to BMI (27.9 vs. 22.1 months; p=0.882), while PFS was significantly longer in patients in the experimental group who had a BMI ≥24 (12.8 vs. 8.2 months; p=0.011). OS was also significantly longer for patients included in the experimental arm who had a BMI ≥24 vs. BMI <24 (29.4 vs. 20.4 months; p=0.018). BMI was independently associated with a prolonged PFS (HR: 0.4 [0.2-0.8]; p=0.008) and OS (0.5 [0.2-1.0]; p=0.05) in the experimental group. In terms of glucose uptake, having an SUV >8.6 was independently associated with a shorter PFS in the entire study population (HR 1.7 [95%CI 1.1-2.4]; p=0.005). No differences in terms of survival were observed when stratifying by study arm and SUV. **Conclusion:** In patients with BMI ≥24 treated with EGFR-TKIs, addition of metformin significantly correlates with improved PFS and OS.

Keywords: Metformin, EGFR, Body Mass Index

P48.10 Efficacy of EGFR-TKIs vs TKIs Plus Chemotherapy as First-Line Treatment in EGFR-Mutation Lung Adenocarcinoma With Liver Metastases

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Introduction: Liver metastasis is the main cause for the poor prognosis of patients with advanced non-small cell lung cancer (NSCLC). Exploring effective treatment measures is an urgent problem for these patients. At present, the standard first-line treatment of advanced NSCLC with EGFR mutation is EGFR-TKIs monotherapy. However, the efficacy remains poor in those patients with liver metastases. The objective of this study is to evaluate the efficacy of EGFR-TKIs plus chemotherapy in EGFR-mutation NSCLC patients with liver metastases. **Methods:** Total of 1973 advanced NSCLC patients with EGFR mutation enrolled in Henan Cancer Hospital/Affiliated Tumor Hospital of Zhengzhou University from April 2016 to June 2020 were retrospectively analyzed. EGFR mutation was detected using polymerase chain reaction (PCR) analysis or "Next-generation" sequencing technology (NGS) of DNA from peripheral blood cells or tumor samples. There were 145 patients with liver metastases among them. Patients were divided into two groups, and received EGFR-TKIs monotherapy or EGFR-TKIs plus chemotherapy, Clinical responses were evaluated according to RECIST 1.1. Evaluation indicators included short-term efficacy (ORR and DCR) of the primary lesions and liver metastases, and long-term efficacy (PFS). The factors related to PFS were also analyzed. **Results:** In this study,113 patients were finally screened. There were 72 patients in the EGFR-TKIs monotherapy group and 41 patients in the EGFR-TKIs plus chemotherapy group. The median follow-up time was 21.3 months. At the follow-up deadline(2021-01-01), 88 patients were disease-progressedprogression and 54 patients died. The Mean age was 60 years old. 42 (37.2%) were men and 71 (62.8%) were women. Former or current smokers were 22 (19.5%) and never smokers were 91 (80.5%). Eastern Cooperative Oncology Group performance status 0 (ECOG PS) were 64 (56.6%), ECOG PS 1 were 38 (33.6%) and ECOG PS 2 were 11 (9.7.0%). 51 (45.1%) had brain metastases. 58 (51.3%) harbored EGFR 19 deletion and 47 (41.5%) were EGFR 21 L858R, and 8(7.1%) were rare-mutations. Clinical characteristics were matched in two groups. Compared with EGFR-TKIs monotherapy, the PFS in combination group was longer, and the median PFS was 12.23 months vs 8.6 months (P=0.017). Median OS had an improved trend in combination group than in EGFR-TKIs alone although without statistical significance (25.2 vs 29.6 m; P = 0.274). The ORR of primary lung lesions had no significant difference between two groups 64.1% vs 45.6%, P=0.065). The ORR of liver lesions in combination group was significantly higher than EGFR-TKIs monotherapy group (64.1% vs 43.1%, P=0.038). **Conclusion:** In conclusion, our studied showed that EGFR-TKIs plus chemotherapy as first-line treatment achieved longer PFS and better efficacy of liver lesions in EGFR mutation NSCLC patients with liver metastases than EGFR-TKIs monotherapy.

Keywords: liver Metastases, targeted therapy, driver gene

P48.11 ctDNA Dynamic Detection Reveals the Advantages of EGFR Tyrosine Kinase Inhibitors Combined With Chemotherapy in NSCLC Patients

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Introduction: EGFR is a major oncogene which frequently occurred in about 10-30% of non-small cell lung cancer (NSCLC) patients. EGFR T790M mutation is the main mechanism of acquired resistance to the first generation EGFR tyrosine kinase inhibitors (TKIs). Chemotherapy is widely used in lung cancer patients and is considered as a subsequent therapy when TKI-resistance occurred. In this study, we aimed to evaluate the effect of pemetrexed by dynamic detection of EGFR T790M in patients with TKI treatment. **Methods:** Targeted next-generation sequencing of 18 cancer-related genes was performed in a College of American Pathologists (CAP) accredited and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory of Shanghai OrigiMed Co., Ltd, for genomic alteration identification. **Results:** A total of 100 advanced NSCLC patients harboring EGFR sensitive mutations, including 19_Del and L858R were finally selected for further study. These samples consisted of 66 (66%) male and 34 (34%) female, with a median age of 65 years. In this cohort, 47 patients received TKI (icotinib or gefitinib) treatment and 53 patients received TKI combined with pemetrexed treatment. Molecular dynamic detection was performed on the 4th month (first monitoring stage), the 8th month (second monitoring stage), and 12th month (third monitoring stage), respectively. In TKI treatment group, the proportion of T790M mutation emerged in the first monitoring stage was high, and gradually decreased in the second and the third monitoring stage. While in TKI combined pemetrexed treatment group, the proportion of T790M mutation emerged was relatively consistent in three stages. Tumor cell abundance could be estimated by EGFR mutation abundance. Our results showed that EGFR mutation abundance significantly decreased in patients with TKI treatment or TKI plus pemetrexed treatment. Then the EGFR mutation abundances of TKI treated patients began to increase in the second stage, and reached the highest in the third stage. While in patients with TKI combined with pemetrexed, EGFR mutation abundance still decreased in the second stage, and began to rise in the third stage, and only rose to the level equivalent to that in the first stage. **Conclusion:** Our study indicated that combined chemotherapy can effectively alleviate the TKI resistance, and supported that NGS-based ctDNA detection can be effectively used in the precise treatment of lung cancer.

Keywords: EGFR tyrosine kinase inhibitors, dynamic detection, non-small cell lung cancer

P48.12 Concurrent Chemotherapy and First-Generation EGFR-TKI as First-Line Treatment in Advanced Lung Adenocarcinoma Harboring EGFR Mutation

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Introduction: Previous studies have demonstrated that combination of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) and other anti-tumor agents may delay drug resistance. However, the efficacy and safety of this combination still remains controversial. In this study, we retrospectively reviewed the efficacy and safety profile of concurrent use of EGFR-TKI and platinum-based doublet chemotherapy as first-line treatment for advanced lung adenocarinoma patients in real world. **Methods:** A total of thirty evaluable patients with advanced lung adenocarcinoma and activated EGFR mutation have concurrently received EGFR-TKI and platinum-based doublet chemotherapy with or without anti-angiogentic agent bevacizumab. Safety profile and efficacy were retrospectively reviewed. **Results:** At the time of a median follow-up period of 22.1 months, 18 patients experienced disease progression and 6 patients died because of disease after concurrent chemotherapy and EGFR-TKI with or without bevacizumab. The median progression-free survival (mPFS) was 21.2 months (95%CI 12.631-29.798). Of 28 patients who had measurable lesions, the objective response rate (ORR) and the disease control rate (DCR) were 71.4% and 96.4% respectively (1 complete remission, 19 partial response and 7 stable disease). Patients harboring EGFR exon19 deletion mutation had relatively longer PFS than those with EGFR exon21 L858R mutation, though no significant difference was observed (21.4 vs 15.6 months, P=0.343). The most frequently seen grade 3/4 AE was hematologic toxicities including neutropenia and leukopenia, seen in 3 cases (10%). Three patients ceased bevacizumab due to vascular events including hypertension (grade 2, 2/30, 6.7%) and venous thrombosis (grade2, 1/30, 3.3%), and continued EGFR-TKI and platinum-based doublet chemotherapy. **Conclusion:** The combination therapy of first-generation EGFR-TKI combining with platinum-based chemotherapy is promising as first-line treatment for advanced lung adenocarcinoma patients harboring activated EGFR mutations, and is well-tolerated. Patients harboring EGFR exon19 deletion mutation may benefit more from this combination strategy compared to those harboring EGFR exon 21 L858R mutation.

Keywords: epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), platinum-based doublet chemotherapy, advanced lung adenocarinoma

P48.13 Clinical Factors Associated With Treatment Outcomes in EGFR Mutant Non-Small Cell Lung Cancer Patients. Real Life Experience in Argentina

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Introduction: Tyrosine kinase inhibitors (TKI) are the standard of care in patients with Non Small cell lung cancer (NSCLC) harbouring EGFR mutations (EGFRm). Although nowadays the treatment of choice are the 3rd generation inhibitors, in developing countries there is still a low accessibility. It has not been resolved if there is any particular subgroup of patients that could benefit with sequential treatment, looking for prognostic factors and mechanisms underlying resistance is crucial to improve the choice of treatment. The aim of this study is analyze the prevalence, characteristics, and clinical outcomes of metastatic NSCLC EGFRm treated with TKI. **Methods:** Retrospective observational study was conducted in Hospital Italiano from Buenos Aires, consecutive NSCLC EGFRm patients diagnosed between April 2011 and December 2020 were included. We analyze factors that were associated with the first/second or third TKI prescription. **Results:** 138 patients were included, the median age 70 years (IQR 60-79), 67% (92) non-smokers, 95% adenocarcinomas. 78% (108) were diagnosed in stage IV, 11% (16) Locally advanced non-surgical stage, 11% (16) early stages. Most frequently detected mutations were exon 19 and 21, prevalence of uncommon mutations 13% (18). 6% had a the novo T790M mutation. 25% (36) had brain metastasis at diagnosis, and 29% (40) >3 metastatic sites. 85% (118) patients recibe TKI. 18% (22) started with third generation TKI, while 92% started with 1st or 2nd generation inhibitors, some of them because of the time that the treatment was prescribed, the 3er generation TKI wasn't approved, and others because of lack of accessibility.

Table 1	1st or 2nd Gen n = 96	3rd Gen n = 22	
Age Mean	69	66	p=0.3
PS 0-1	74%	77%	p=0.7
Female	65%	59%	p=0.6
Smoking	37%	18%	p=0.08
Uncommon	14%	7%	p=0.2
Brain Metastasis	19%	45%	p=0.08

The ORR with TKI was 75% (89), 13% (15) stable disease,12% (14) progression. ORR with 3rd generation ITK was 91% (20). The median progression free survival (mpfs) in first and second ITK generation was 12 months, with a median follow up of 18 months in the 3er generation ITK the mpfs was not reached, 36% of patients with 3rd generation TKI progressed against 83% with 1st or 2nd generation inhibitors. HR 0.44 (IC95 0.21- 0.92) LongRank p= 0.029. Median overall survival (OS) was 20 months, with no significant difference according to the TKI used HR 0.6 (95 CI 0.28 - 1.33) LongRank p = 0.22. **Conclusion:** The main factor associated with prescription of a 3rd generation ITK was CNS involvement. Although ORR and PFS were higher in the 3rd generation ITK, we did not observe significant differences in OS. The main barrier in the use of 3rd generation TKIs in our country is access.

Keywords: EGFR, lung cancer, TKI

P48.14 Metastatic NSCLC -Re-Challenging With Fist Generation TKI After a Drug Free Holiday After Resistance to 3rd Generation TKI

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Introduction: Lung cancer is the most common cancer worldwide in males & a good number of patients present with metastatic disease. Though EGFR mutated patients respond to EGFR TKIs, resistance develops ultimately. Overcoming 3rd generation EGFR TKI resistance is a big challenge. **Methods:** 20 patients of metastatic adenocarcinoma, confirmed with core biopsy & IHC (EGFR positive) were offered Erlotinib initially. Osimertinib was offered to those who developed EGFR TKI resistance due to T790M mutation (10 cases). All 10 patients eventually developed resistance to Osimertinib. All patients were given 3 months drug free holiday & then re-challenged with Erlotinib. **Results:** 4 out of 10 (40%) patients responded to the therapy. 6 patients had progression & were managed by systemic chemotherapy & radiation. **Conclusion:** Literature shows up to 50% metastatic adenocarcinoma, EGFR positive patients who had developed EGFR TKI resistance to 1st & 3rd generation TKIs, responds to re-challenge with first generation TKI after a drug free holiday. In this series 40% patients responded. This approach should be tried & non-responders can be offered systemic chemotherapy & radiation.

Keywords: Metastatic adenocarcinoma, EGFR TKI resistance

P48.15 EGFR Mutated Non-Small Cell Lung Cancer Treatment Pathway – What Is the Best Way?

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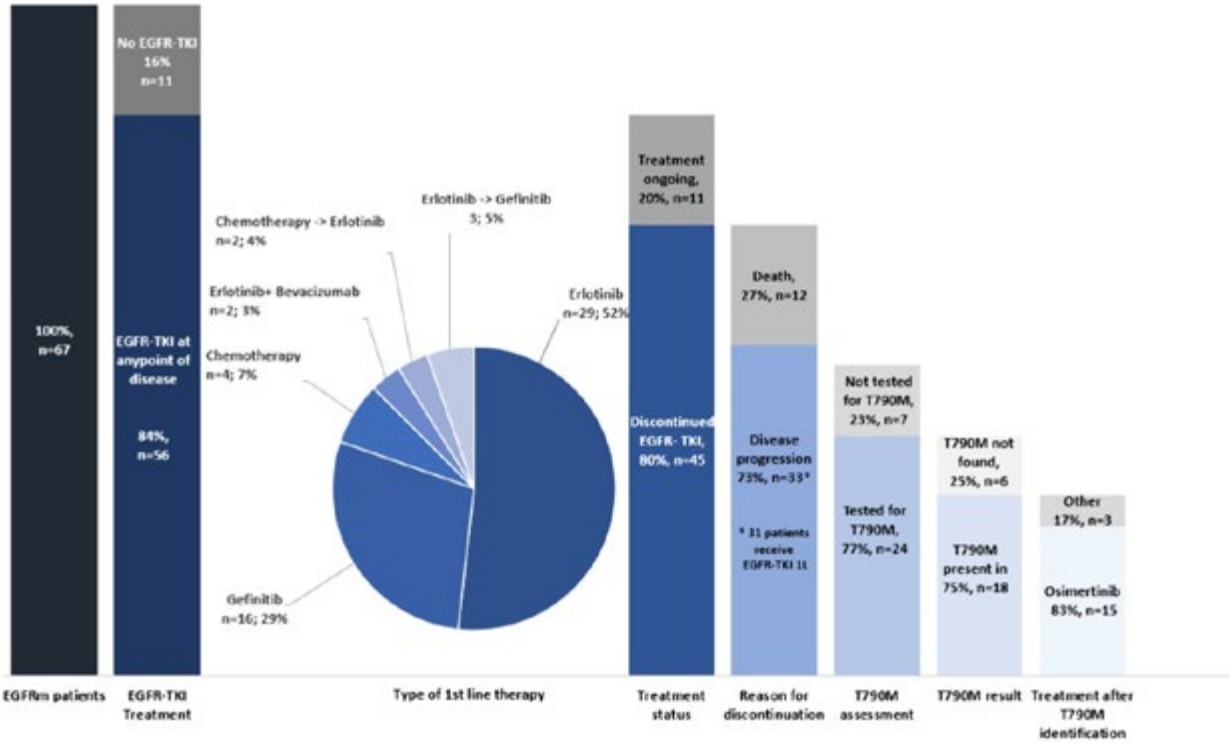
Introduction: EGFR tyrosine kinase inhibitors (EGFR-TKIs) are considered the standard first-line (1L) treatment for advanced EGFR-mutated (EGFRm) NSCLC. However, patients acquire resistance to 1st- or 2nd-generation EGFR-TKIs through various mechanisms, T790M mutation is the most common one. 2L treatment and beyond is less well-defined. We aimed to characterize a Portuguese cohort of EGFRm NSCLC regarding treatment patterns, clinical outcomes and molecular testing practices. **Methods:** Real-world retrospective cohort study, including patients diagnosed, with EGFRm, locally advanced or metastatic NSCLC, between January 1st, 2016 and December 31st, 2017 in a Portuguese Comprehensive Cancer Center (PCCC). The follow-up period ended on December 31st 2018, except for overall survival which was considered until December 31st 2019. Data collected from medical/administrative records, covered demographics, tumor histology, disease stage, EGFR mutation. Treatment outcomes such as progression free-survival (PFS), overall survival (OS) and treatment duration (TD) were evaluated. Descriptive statistics were conducted for demographic, clinical and resource utilization data. Kaplan-Meier method was used for survival analysis. **Results:** 67 patients were included. Of these, 56 received a EGFR-TKI treatment at any point of their disease. At diagnosis, the most common EGFR mutations were exon 19 deletion (55.4%; n=31) and exon 21 point mutation (L858R) (33.9%; n=19). The most common 1L treatments for EGFRm NSCLC patients were 1st generation EGFR-TKIs, namely erlotinib (51.8%; n=29) and gefitinib (28.6%; n=16). Median TD was 9.9 (95% CI: 6.6-12.5) months, median PFS was 8.1 (95% CI: 6.6-10.6) months and median OS was 21.3 (95% CI: 12.6-37.3) months for those who received EGFR-TKI treatment (n=56). 45 patients interrupted 1L treatment due to death (n=12, 26.7%) or disease progression (n=33, 73.3%). Of those, 24 patients were tested for T790M that was found in 18 (75%) patients. 83.3% (n=15) of T790M patients received osimertinib as 2L (Figure 1).

Figure 1 - Summary of EGFRm patient journey



Conclusion: First-generation EGFR-TKIs were the preferential 1L treatment for the EGFRm NSCLC. Osimertinib is currently indicated as standard of care (SoC) 1L EGFR-TKI but was not approved for 1L treatment at the time of the study. Nevertheless, this study demonstrates that there is a limited number of patients receiving Osimertinib after a 1L EGFR-TKI. In this disease, a long-term plan to increase patient survival is crucial and further research is needed.

Keywords: NSCLC, EGFRm, EGFR-TKIs

P48.16 The Effect and Safety of Anlotinib as a Third Line or Further Therapy in Non-Small Cell Lung Cancer Patients With Liver Metastasis

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Introduction: Anlotinib has been proven to prolong the progression-free survival (PFS) and overall survival (OS) as a third line or further therapy compared with placebo for non-small cell lung cancer (NSCLC). Herein we evaluate the effects and prognosis in patients with liver metastasis (LM) treated with anlotinib/placebo. **Methods:** The post-hoc analysis was based on the ALTER 0303 phase 3 randomized clinical trial (ClinicalTrials.gov identifier: NCT02388919). Clinicopathological characteristics, driven genes' status (EGFR, ALK, and ROS1) and survival time were extracted, PFS and OS were evaluated with clinical profile data, together with treatment-associated adverse events (AEs). **Results:** A total of 78 cases with liver metastasis were enrolled from 439 randomly assigned patients. The anlotinib was associated with longer PFS (median, 3.0 months; 95% CI, 2.0-3.9) compared with placebo (median, 0.9 months; 95% CI, 0.7-1.1), with a hazard ratio (HR) of 0.23 (95%CI, 0.12-0.42;P<0.0001). Furthermore, OS was also better in anlotinib group (median 6.6 months; 95% CI, 5.3-7.9), compared with placebo (median 4.0 months; 95% CI, 2.2-5.8), HR 0.61 (95%CI, 0.36-1.02; P = 0.055). The lower baseline ECOG score (0 vs 1 vs 2), normal serum LDH/AST and albumin level appeared a longer OS (all P<0.005), besides, normal serum LDH/γ-GT/amylase/alkaline phosphatase level showed a better PFS (all P<0.05). Anlotinib was more associated with hand-foot syndrome (7.7% vs 0) and serum TSH level rise (7.7% vs 3.8%), all AEs were no more than grade 3. **Conclusion:** Anlotinib could lead to a better overall survival and progression-free survival in pretreated NSCLC patients with LM, the AEs were manageable, which suggested anlotinib is a potential third line or further therapy in this group.

Keywords: NSCLC; liver metastasis;Anlotinib

P48.17 Real-World Study of Patients With EGFR Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer Treated With First-Line Osimertinib

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Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the recommended treatment for patients with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (EGFRm). Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFRm and EGFR T790M, with demonstrated efficacy in NSCLC CNS metastases. Interim analysis of this real-world (rw) study reports the demographic and clinical characteristics, rw time to next treatment or death (rwTTNTD) and rw time to treatment discontinuation (rwTTD) of patients receiving osimertinib at first-line (1L) in the US. **Methods:** A multi-country prospective cohort study is in progress, analyzing patients with locally advanced or metastatic EGFRm NSCLC treated with 1L osimertinib monotherapy in the US, Europe, and Asia. The US analysis includes data from the nationwide Flatiron Health electronic health record-derived de-identified database, curated via technology-enabled abstraction. Adult patients initiating 1L osimertinib from 1 April 2018 until 30 March 2020 were selected and followed until 30 June 2020 for this interim analysis. Further follow-up is planned until 2023. The index date was the date of 1L osimertinib monotherapy initiation. rwTTNTD is defined as time from index date to start of next systemic therapy or death in the absence of next systemic therapy. rwTTD is defined as time from index date until last episode of 1L osimertinib monotherapy or death. Median rwTTNTD and rwTTD (with 95% confidence interval [CI]) was estimated using the Kaplan Meier product-limit method. **Results:** Among 548 patients, 82% presented with stage IV and 1% stage IIIB at initial diagnosis; 16% initially presented at stage I-IIIA and progressed prior to index date. Non-squamous cell carcinoma represented 97% on histologic analysis. At index, median age was 70 years (interquartile range: 61-78), the majority were female (69%) and White (54%). 57% had no documented smoking history and, of patients with recorded ECOG, 79% had a performance score of 0/1 at index. For EGFRm profile: 85% had a common mutation (51% Ex19del and 34% L858R); 8% had uncommon mutations; 3% had de novo T790M; 3% had co-mutations; and 1% had unknown mutations. Of 427 patients with a baseline brain scan, 43% had brain metastasis. Median follow up was 9.6 months. Median rwTTNTD was 17.9 months (95% CI: 16.2 – 23.6 months) and median rwTTD was 17.2 months (95% CI: 13.8 – 19.8 months). At the end of follow-up, 58% of patients remained on 1L therapy, 19% received second-line treatment, 18% died on treatment, and 5% of patients discontinued treatment. **Conclusion:** This study provides insight into the use of osimertinib in the 1L setting for EGFRm NSCLC. rwTTNTD and rwTTD reinforce effectiveness in this rw population. Further analyses are planned to determine longer-term outcomes.

P49.01 Drug Holiday Based on Minimal Residual Disease Status After Local Therapy Following EGFR-TKI Treatment for Patients With Advanced NSCLC

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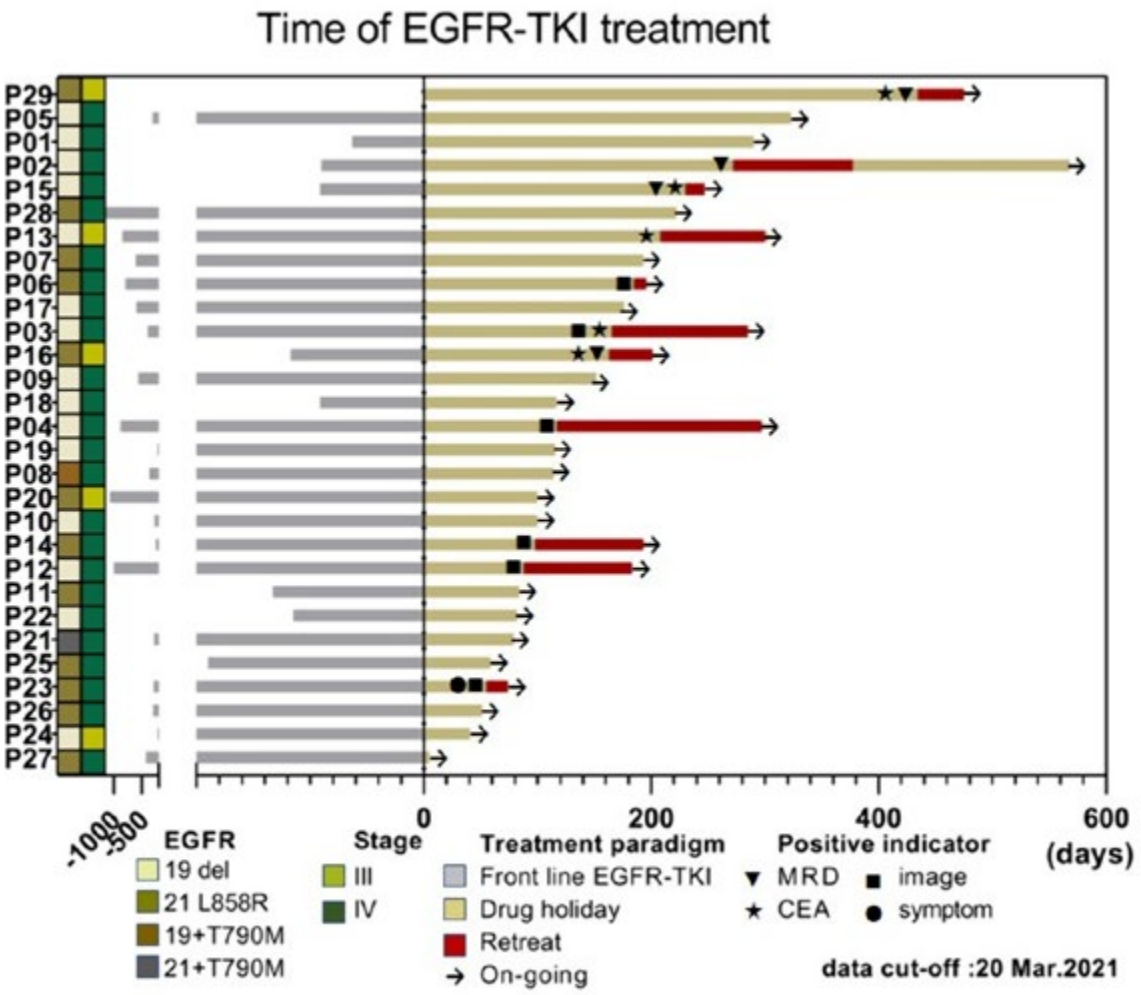
Introduction: Local consolidative therapy (LCT)has been confirmed to improve the overall survival of patients with non-small cell lung cancer (NSCLC) receiving targeted therapy and continuation of target therapy is currently recommended. it is unknown whether patients could benefit from targeted therapy holiday if no visible lesions and negative minimal residual disease (MRD) after LCT. **Methods:** Detection of ctDNA in periphery blood was performed to identify MRD in patients with EGFR mutant oligo-residual disease after LCT. EGFR-TKIs were ceased for patients who met criteria: (1) no imagery lesions after surgery; (2) negative MRD; (3) normal serum carcinoembryonic antigen (CEA); (4) asymptomatic. Negative MRD was defined as no driver genes or a maximum of one cancer-related gene was detected. Follow-up would be done every three months and EGFR-TKIs would be retreated If any of the above drug holiday criteria were missed. This study was exploring part of CTONG 1602 (NCT03046316), which was approved by Research Ethics Committee of Guangdong General Hospital&Guangdong Academy of Medical Sciences. **Results:** 38 patients with stage IIIB or IV NSCLC were screened for MRD after LCT following targeted therapy between June 2019 to February 2021. Except for 2 patients with positive MRD, 36 patients met drug holiday criteria. 7 patients refused participation. For 29 patients enrolled the median duration of front-line treatment with EGFR-TIKs was 298 days (0-1699 days). The median drug holiday was 117 days (5-434 days). Eleven (37.9%) patients met at least one issue of drug holiday criteria during follow-up with median drug holiday 165 days (55-434 days), and six of them presented with imagery lesions, five relapsed in previous sites of disease (2 in lung, 3 in brain), one patient relapsed in new site (brain). all these six patients (100%) were responsive to EGFR-TKI retreatment. The other five patients with positive MRD (EGFR mutation) and/or increased levels of CEA met drug holiday criteria again after 3 months of EGFR-TKI retreatment, and two of them(P02 and P13) therefore gained second drug holiday(Fig 1).



Conclusion: Drug holiday based on MRD status was feasible for patients treated with EGFR-TKI on the basis of LCT. Brain metastases were higher risk of recurrence after drug holiday.

Keywords: Drug holiday, minimal residual disease, Local consolidative therapy

P50.01 RELAY, Erlotinib Plus Ramucirumab in Untreated, EGFR-Mutated, Metastatic NSCLC: Outcomes by EGFR Exon 19-del Variants

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Introduction: EGFR Exon 19-del mutations consist of distinct molecular variants and represent a heterogeneous disease entity. Distinct Exon 19 variants confer a differential sensitivity to EGFR-TKIs as well as different patterns of resistance. This exploratory analysis aimed to determine the impact of Exon 19-del variants on clinical outcomes in the RELAY trial. **Methods:** Patients with untreated metastatic NSCLC, with an EGFR Exon 19-del or 21_L858R mutation and no CNS metastasis, were randomized (1:1) to receive erlotinib (150 mg/day) with either ramucirumab (10 mg/day) (RAM+ERL) or placebo (PBO+ERL), Q2W, until progression or unacceptable toxicity. The primary endpoint was progression free survival (PFS). Secondary and exploratory endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS), safety, and biomarker analysis. This post-hoc analysis assessed the association of Exon 19-del variants detected at baseline by Guardant 360 next-generation sequencing (NGS), which were classified as common vs. uncommon (ΔE746_A750del vs. other), with clinical outcomes and treatment emergent (TE) gene alterations at disease progression were examined. Statistical analyses included Cox regression models and Kaplan-Meier estimation. **Results:** Of the 134 patients with an EGFR Exon 19-del mutation, 67% had the common variant. Clinicopathological characteristics and co-occurring gene alterations at baseline were comparable between common and uncommon variants, with the exception of never smokers (52% vs. 75%, respectively). RAM+ERL showed a meaningful improvement in PFS in both variant subgroups (Table 1). While ORR and DCR were comparable between RAM+ERL and PBO+ERL arms in patients with common and uncommon variants, median DOR was favorable for RAM+ERL in all Exon 19-del variants. Regardless of treatment arm, upon disease progression, TE-T790M (38% vs. 17%) and TE-TP53 (16% vs. 0%) mutations were more frequent in Exon 19-del common variant compared with uncommon variants. OS data are immature with a high overall censoring rate (81%).

Table 1: Clinical outcomes in common and uncommon Exon 19-del variants

	Common (ΔE746_A750del) Exon 19-del variants		**Uncommon (other) Exon 19-del variants**	
	RAM+ERL n=39	**PBO+ERL n=51**	**RAM+ERL n=23**	**PBO+ERL n=21**
PFS				
Median, months	15.2	9.9	19.4	13.9
HR (95% CI)	0.56 (0.34-0.93)		0.65 (0.28-1.52)	
1 year PFS rate, %	71	38	69	65
ORR - % (95% CIs)	87.2 (73.3, 94.4)	88.2 (76.6, 94.5)	87.0 (67.9, 95.5)	90.5 (71.1, 97.4)
DCR - % (95% CIs)	100 (91.0, 100)	96.1 (86.8, 98.9)	91.3 (73.2, 97.6)	95.2 (77.3, 99.2)
DOR	**n=34**	**n=45**	**n=20**	**n=19**
Median, months	14.1	8.4	13.8	11.3
HR (95% CI)	0.62 (0.37-1.04)		0.69 (0.31-1.57)	

RAM– ramucirumab; ERL - erlotinib; PBO – placebo; 95% CI – 95% Confidence Intervals; PFS – progression free survival; ORR – objective response rate; DCR – disease control rate; DOR – duration of response

Conclusion: In RELAY, RAM+ERL showed consistent improvements in PFS in all Exon 19-del variants examined. The higher proportion of TE-T790M and TE-TP53 mutations in patients with the common variant underscore potentially different resistance mechanisms between Exon 19-del variants. These results support RAM+ERL as a suitable first-line treatment option for patients, irrespective of Exon 19-del mutation variant.

P50.03 A Real-World Cohort Study of EGFR TKIs in Patients with NSCLC with Uncommon EGFR mutations (UpSwinG)

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Introduction: EGFR TKIs are an established treatment option for patients with EGFR mutation-positive NSCLC harboring common mutations (Del19 or L858R), but are less established in the 7–23% of NSCLC tumors harboring uncommon EGFR mutations. These mutations are highly heterogeneous, and increased use of sensitive sequencing-based detection methods and liquid biopsy will increase detection frequency in real-world clinical practice. **Methods:** In this non-interventional, global, multicenter, retrospective study (NCT04179890), existing medical or electronic health records were searched for consecutive patients with uncommon EGFR mutations (T790M, ex20ins, major uncommon [G719X, L861Q or S768I], 'other', or compound mutations) who were EGFR TKI-naïve at diagnosis, treated with erlotinib, gefitinib, afatinib, osimertinib, or other systemic therapy. Endpoints were time to treatment failure (TTF), ORR, OS, and duration of response (DoR). **Results:** Overall, 246 patients (median age: 69.5 years; Asian: 83.7%; brain metastases: 6.9%; ECOG PS ≥2: 12.6%) were recruited from nine countries. EGFR TKIs were received as first-line treatment in a majority of patients (n=226; 91.9%); 132 (53.7%), 105 (42.7%), and 7 (2.8%) received afatinib, first-generation EGFR TKIs, and osimertinib. Most patients (n=140; 56.9%) received >1 line of therapy. Patient mutation categories included: major uncommon (n=179; 72.8%), compound (n=82; 33.3%), other (n=21; 8.5%), and ex20ins (n=29; 11.8%). Mutations at first-line treatment start were detected using PCR (60%) or sequencing (23%), predominantly based on tissue biopsy (84%). The quality of pathology reports varied, often lacking in-depth information on mutations e.g. 21% of ex18 and 72% of ex20ins were undefined. Overall, median TTF, OS, and DoR with EGFR TKIs was 9.9, 24.4 and 10.0 months, and ORR was 43.4%. In patients treated with first-line chemotherapy (n=20), median TTF and DoR was 6.6 and 4.0 months, and ORR was 41.2%. Patients with major uncommon and compound mutations appeared to have the most favorable outcomes overall (**Table**). Patients treated with afatinib had longer median TTF and DoR, vs those treated with first-generation EGFR TKIs. Among patients receiving the approved 40 mg starting dose of afatinib (n=93), median TTF and OS were 12.8 and 24.8 months. **Conclusion:** EGFR TKIs were the preferred treatment option in patients with uncommon EGFR mutations in a real-world setting, and should largely be considered the standard of care. Patients with major uncommon and compound mutations had the most encouraging outcomes. Optimal treatment requires improvements in pathology reports, with more emphasis on implementation of NGS methodology and precise definition of mutations.

Patients treated with afatinib	Median TTF, months	Median OS, months	ORR, %	Median DoR, months
All (n=132) Major uncommon (n=94) Compound (n=46) Other (n=9) Ex20ins (n=18)	11.3 14.3 12.6 10.8 8.3	24.5 24.5 23.4 20.2 22.5	43.8 50.6 52.5 28.6 18.8	12.0 12.0 10.0 10.5 5.5
Patients treated with first-generation EGFR TKI				
All (n=106) Major uncommon (n=80) Compound (n=32) Other (n=12) Ex20ins (n=10)	8.8 9.8 12.4 7.3 5.2	24.2 28.5 31.3 12.8 21.0	44.1 47.3 43.8 55.6 16.7	6.0 6.5 6.0 4.5 3.0

Keywords: uncommon EGFR mutations, EGFR TKI, EGFR mutation-positive NSCLC

P50.04 Amivantamab in Combination With Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: No targeted therapies are available for metastatic epidermal growth factor receptor mutant (EGFRm) NSCLC after progression on osimertinib or for tyrosine kinase inhibitor (TKI)-resistant mutations such as EGFR exon 20 insertions (Exon20ins); for these patients, chemotherapy remains the standard of care (SOC). Amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity, has demonstrated monotherapy activity in patients with diverse EGFRm NSCLC, including Exon20ins and osimertinib-relapsed disease. Combining amivantamab with chemotherapy in metastatic EGFRm NSCLC may improve outcomes due to the antibody's dual-targeting nature and immune cell-directing activity. We present the preliminary experience with amivantamab in combination with chemotherapy from the ongoing CHRYSALIS study (NCT02609776). **Methods:** Patients had advanced NSCLC and were eligible for platinum-based chemotherapy in accordance with SOC. Amivantamab was dosed weekly at 1400 mg (1750 mg ≥80 kg) for the first 4 doses, then at 1750 mg (2100 mg ≥80 kg) every 3 weeks (Q3W) + pemetrexed (500 mg/m^2) and carboplatin (AUC 5; up to cycle 4) in a 21-day cycle. Response was assessed by investigator per RECIST v1.1. Tolerability was assessed using a 3+3 dose de-escalation design. **Results:** Of the 5 patients who were initially dosed, 3 were evaluable for dose-limiting toxicity (DLT); no DLTs were observed, and dose expansion up to 20 patients has been initiated. As of 20 Oct 2020, 16 patients (3 with bodyweight ≥80 kg) had received the combination; 13 were treated beyond cycle 1 and 5 beyond cycle 3. Median age was 63 years, 15 had EGFR mutation, 2 had baseline brain metastases, and 13 had ≥1 prior lines of therapy (LOT), with 8 heavily-pretreated (2–7 prior LOT). Most common treatment-emergent adverse events (TEAEs) were infusion-related reaction (69%) and rash (44% dermatitis acneiform + 31% rash). Seven patients (44%) had grade ≥3 TEAEs; most frequent events collectively reflected anticipated cytopenias (19% neutropenia, 6% anemia, 6% thrombocytopenia) – one patient discontinued carboplatin due to anemia. Preliminary cycle 1 pharmacokinetic (PK) data (n=9) suggest no impact of chemotherapy on amivantamab exposure. Preliminary trough concentration comparisons suggest that higher doses of amivantamab given Q3W (21-day cycle), are similar to the recommended dose for monotherapy given every 2 weeks (28-day cycle). Six patients had disease assessments by the 20 Oct 2020 data cut: 2 partial responses (PRs, including 1 patient with treatment-naïve EGFR Exon20ins), 3 stable disease, and 1 progressive disease. Since the clinical cut off, 2 other patients with treatment-naïve EGFR Exon20ins reported PRs, for a total of 3/3 responses in this subpopulation. **Conclusion:** Amivantamab combined with chemotherapy was tolerable, with toxicity profiles consistent with that observed with each therapy alone. Amivantamab exposure was not impacted by chemotherapy, and preliminary PK results support Q3W dosing. This regimen is being evaluated in the frontline treatment of EGFR Exon20ins NSCLC in the phase 3 PAPILLON study (NCT04538664).

Keywords: Chemotherapy, Amivantamab, EGFR Exon 20 Insertion

P50.05 Natural History and Real-World Treatment Outcomes for NSCLC Patients with EGFR Exon 20 Insertion Mutation: An IASLC- ASCO CancerLinQ Study

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Introduction: Epidermal Growth Factor Receptor (EGFR) exon 20 insertion (ex20ins) mutations account for 2-3% all non-small cell lung cancer (NSCLC) patients. Patients with ex20 ins do not respond to standard EGFR TKI therapy. In this work, we have analyzed the characteristics, treatment patterns and outcomes in this subgroup of NSCLC patients. **Methods:** The ASCO CancerLinQ Discovery dataset was queried to identify patients diagnosed with NSCLC between the years 1995-2018 and with EGFR ex20ins mutations. Data were extracted on patient demographics, tumor characteristics, treatments and outcomes, and compared with Chi-square and ANOVA tests. Kaplan-Meier (KM) curves were generated for comparing overall survival with log-rank tests. All analyses were performed using Python 3.6. **Results:** A total of 357 patients were eligible. Patient characteristics: median age 68 years, female 53.5%, white race 63% and black race 9%. Approximately 62% had stage 4 disease, and 30% had brain metastasis. 54% of the patients were treated with chemotherapy and 15% with immune check point inhibitors (ICI). In patients with brain metastasis, 16% were treated with ICI, 18% targeted therapy and 59% with chemotherapy. The median survival of the entire group is 23.8 months. Among patients with stage 4 disease: 51% were females, 64% white race, 37% had brain metastasis, 18% were treated with ICI, 14% targeted therapy and 60% treated with chemotherapy. In the analysis of stage 4 patients, the median survival of the group was 16.8 months. Stage 4 patients that received ICI had better survival vs. those who did not (29.1 vs. 14.7 months; p=0.01). Stage 4 patients treated with ICI and chemotherapy had better survival compared to those treated with chemotherapy alone (29.1 vs. 16.5 months, p=0.01). Stage 4 patients treated with targeted therapy had better survival compared to those that did not receive targeted therapy (20.6 vs. 16.1 months; p=0.03). **Conclusion:** Stage 4 NSCLC patients with EGFR ex20ins mutation had favorable real-world survival when treated with ICI and targeted therapy.

Keywords: targeted therapy, EGFR, exon20 insertion

P50.06 First-Line Therapy in NSCLC harbouring EGFR or HER2 Exon 20 Insertion Mutation. Hunting for the Best Candidate

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Introduction: Treatment of first-line NSCLC harboring EGFR and HER2 exon 20 insertion mutation (ex20-ins) remains an unmet clinical need. Poziotinib (POZ), a new generation tyrosine kinase inhibitor (TKI), is under investigation in first and further-line setting as a potential targeted therapy. Data from the ZENITH20 ongoing trial (Cohort 3) demonstrated a median Progression-Free Survival (mPFS), an ORR and a DCR of 7.8 months (m), 28% and 86%, respectively, in patients (pts) with treatment naïve EGFR-ex20-ins NSCLC; however, chemotherapy (CT) with or without immunotherapy (IO) still remains the standard first-line in this subset. Here we present results on first line treatment in EGFR or HER2 ex20-ins NSCLC pts. **Methods:** Data from 31 consecutive aNSCLC pts with EGFR or HER2 ex20-ins treated from May 2018 to April 2021 with POZ 16mg once daily or less within Expanded Access Program at our institution were retrospectively collected. Clinical and pathological data were extracted from Institutional database. Descriptive statistics were used for categorical variables. Median OS (mOS) and mPFS were estimated through Kaplan-Meier method and compared by log-rank test. Median follow-up was estimated by inverse Kaplan Meier. **Results:** Among 31 patients, the median age was 59 years old (range, 25 – 80 years), most patients were younger than 70 years (73%) and females 23 (77%); ECOG performance status (PS) was 0, 1 and 2 in 9, 16 and 5 pts, respectively. Twenty-three pts had EGFR ex20-ins while 8 had HER2 ex20-ins. Five pts received poziotinib as first line treatment and 26 as second or further-line therapy. Objective response rate (ORR) and disease control rate (DCR) for POZ were 31 and 79%, respectively. At data cut-off all pts progressed on POZ and only 4/31 were alive. After a median follow-up of 19.8 months mPFS and mOS for POZ were 5.7 m (95%CI 0.6 – 6.9), and 7.6 m (95% CI 5.2 – 9.9 m), respectively, in the overall population. Out of 31 5 pts received POZ, 22 CT/CT-IO and 4 other TKIs (afatinib/osimerinib) as first line treatment. Median PFS was 5.4 m 5.5 m and 3.8 m for pts treated with CT/CT-IO, POZ and other TKIs, as first line therapy respectively. ORR and DCR for pts treated with a first line therapy other than POZ were 40% and 69% respectively. **Conclusion:** POZ showed a clinical activity in EGFR or HER2 ex20-ins NSCLC pts irrespective of the treatment line. In our analysis first-line mPFS seems to be comparable among all treatments, however due to the small sample of pts treated with first-line POZ it is difficult to drown conclusion. Indirect comparation between our pts treated with first line CT/CT-IO or other TKIs versus pts receiving first-line POZ in ZENITH20 Trial-Cohort 3 (EGFR therapy-naïve), the mPFS and DCR seems to favor POZ as best first line treatment in aNSCLC. Further data are needed.

Keywords: poziotinib, EGFRexon20, NSCLC

P50.07 Afatinib Treatment Response in Advanced Lung Adenocarcinomas Harboring Uncommon Mutations in Chinese Population

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Introduction: Epidermal growth factor receptor(EGFR) tyrosine receptor inhibitors(TKIs) have improved the prognosis of mutant lung cancer, but the clinical application value of TKIs for non-classical EGFR mutation is not clear, especially for patients with rare uncommon mutations. **Methods:** This was a single-center, single-arm, retrospective study in China. A study based on electronic medical records was performed to collect data from afatinib effectiveness of patients with stage IIIB/IV lung adenocarcinoma bearing uncommon mutations. **Results:** 42 patients with uncommon mutation treated by afatinib were enrolled. Objective response rate(ORR) was 50.0% (10 of 20 patient). Median time to treatment failure(TTF) was 11.7 months(95% CI: 8.5–18.3). Of those, median TTF was 15.0, 11.7, and 16.6 months in patients with G719X, S768I, and L861Q mutations, respectively. In patients with the rare uncommon mutation, median TTF was 10.0 months and the ORR was 50.0%. Afatinib demonstrated clinical activity across a set type of specific rare mutations, including EGFR L747P, A767_V769dup, and L833V/H835L, with a case of TTF > 1 year. Molecular profiling reports of 16 afatinib-resistant biopsy samples were available, and the secondary T790M mutation was detected in one patient with L833V/H835L mutation and one harboring S768I/L858R mutation. **Conclusion:** Our findings suggested that afatinib led to a promising effectiveness in patients harboring uncommon mutations. Mechanisms of afatinib resistance vary and need further investigation.

Keywords: non-small cell lung cancer, uncommon mutation, afatinib

P50.08 Targeting HER2 or EGFR Exon 20 Insertion Mutation in Lung Cancer - A Case Series from India

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Introduction: BACKGROUND Around 4% of EGFR mutated Non Small Cell Lung Cancers (NSCLC) harbour exon 20 in-frame insertions. 2-4% of patients with NSCLC also have HER2 mutations, out of which 90% are exon 20 insertions. Insertion mutations at EGFR and HER2 both occur at analogous positions in exon 20. These mutations confer intrinsic resistance to most of the Tyrosine Kinase inhibitors(TKI's). Clinical trials are underway to estimate treatment benefits for novel molecules to target EGFR or HER2 exon 20 mutations. In this study, we provide the data of four patients with NSCLC associated with EGFR or HER2 exon 20 mutations. We also report the clinical benefit in an Indian setting. **Methods: METHODS** We collected Next Generation Sequencing-based Comprehensive Genomic Profile (CGP) testing data from medical oncologists across India. We collated data from the test reports along with clinical information. Here, we describe the results of EGFR or HER2 exon 20 targeting in our retrospective cohort. **Results: RESULTS** We collated 297 CGP test reports from 12 medical oncologists. Four patients had EGFR or HER2 exon 20 insertion mutation. Three had HER2 mutation and one person had EGFR mutation. One mutation was detected through liquid biopsy and the remaining ones were identified through tissue biopsy. Two patients were on Poziotinib outside of a clinical trial, one was on Osimertinib and the fourth person was on Trastuzumab emtansine. Two patients are having ongoing treatment responses at 6 months. One person on Poziotinib was on the medicine for 2 months. One person on Trastuzumab emtansine took the drug for 7 months. **Conclusion: DISCUSSION** EGFR or HER2 exon 20 insertion mutation in NSCLC provides a promising target for novel molecules. Even in an Indian setting, clinically meaningful responses are observed.

Keywords: EGFR HER2 Exon 20 mutation, poziotinib

P50.09 Characteristics and Clinical Outcomes of HER2 Mutated Non-small Cell Lung Cancer Patients Detected by NGS in Routine Clinical Practice

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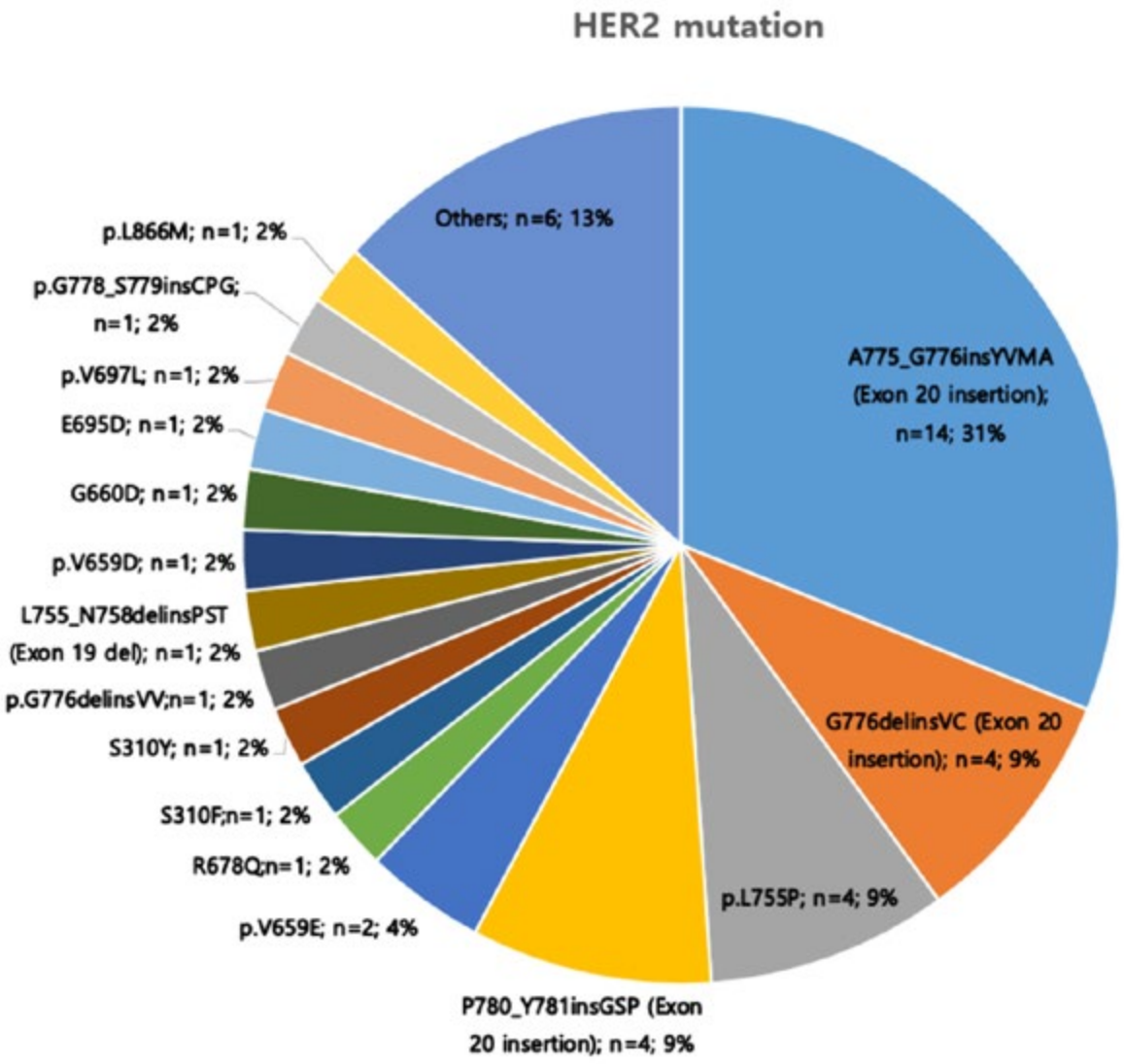
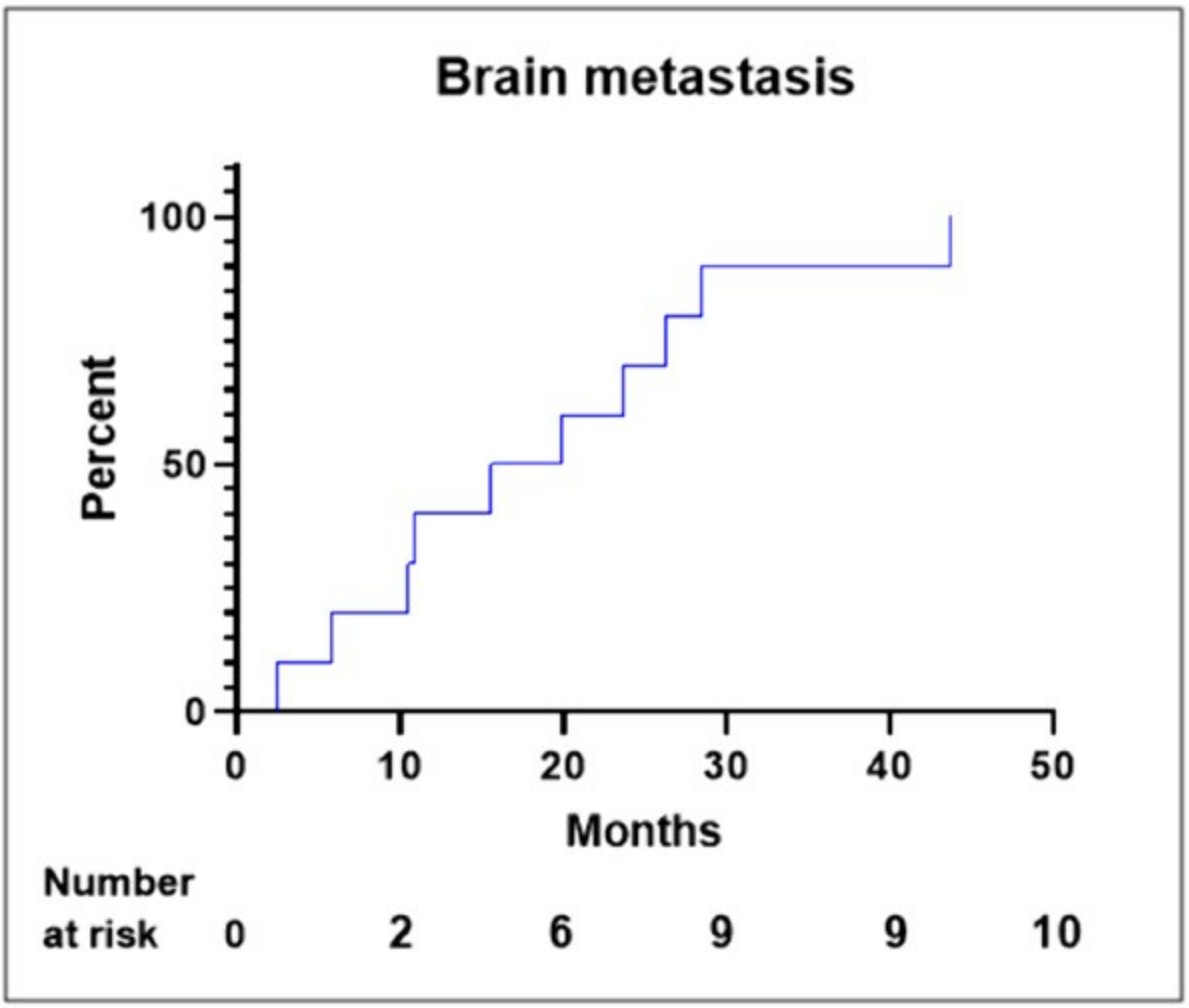
Introduction: Mutations in HER2 have been identified as an oncogenic driver gene for NSCLC(Non-small cell lung cancer), but not much is known in routine practice. This retrospective study was conducted to better understand the clinical characteristics of advanced NSCLC patients harboring HER2 mutations treated with chemotherapies and HER2-targeted agents in real world. **Methods:** We identified 44 patients with NSCLC with HER2 gene rearrangement who were treated at Severance Hospital between December 2016 and February 2021, by tissue and/or blood next generation sequencing(NGS). Clinical data including patient characteristics, mutation status, incidence of metastasis for distant lesions, and response to each chemotherapy were retrospectively analyzed. **Results:** The median patient age was 58.1 years, and 61.4% of the patients were female. Most of the patients (63.6%) were never-smokers. Adenocarcinoma was predominant (97.7%). Sixty-six percent of patients had an extrathoracic metastatic lesion, and 31.8% had an intracranial lesion at the initial presentation. Median time to development of brain metastases was 15.6 months (range 2.4–43.7 months). The most common type of HER2 mutation was 14 base pair in-frame insertion in exon 20, A775_G776insYVMA. Two of the 44 patients had concomitant driver mutation, one with EGFR mutation(V769M) and other with BRAF mutation(V600E). The median overall survival time for total patients was 14.8 months (95% confidence interval [CI]: 7.8–21.8). Patients who were treated with pemetrexed-based chemotherapy, the overall response rate and progression-free survival time were 30.3% and 7.6 months (95% CI: 3.8–11.6), respectively. The overall response rate and progression-free survival time were 0.0% and 2.3 months (95% CI: 0.0–5.3), respectively, for the with HER2 targeted therapy


HER2 mutation
A775_G776insYVMA (Exon 20 insertion); n=14; 31%
G776delinsVC (Exon 20 insertion); n=4; 9%
p.L755P; n=4; 9%
P780_Y781insGSP (Exon 20 insertion); n=4; 9%
p.V659E; n=2; 4%
R678Q;n=1; 2%
S310F;n=1; 2%
S310Y; n=1; 2%
p.G776delinsVV;n=1; 2%
L755_N758delinsPST (Exon 19 del); n=1; 2%
p.V659D; n=1; 2%
G660D; n=1; 2%
E695D; n=1; 2%
p.V697L; n=1; 2%
p.G778_S779insCPG; n=1; 2%
p.L866M; n=1; 2%
Others; n=6; 13%



Conclusion: Our study interrogated clinical characteristics of real world HER2-positive NSCLC patients in single ethnicity confirmed by NGS. Given its novel characteristics and distinct clinical responses the treatment strategy for HER2-positive NSCLC remains to be further developed with conventional chemotherapies and targeted therapies.

Keywords: HER2 mutation, Next generation sequencing, Lung cancer, brain metastasis

P51.01 Tepotinib plus an EGFR TKI in patients with EGFR-mutant NSCLC and resistance to EGFR TKIs due to MET amplification (METamp)

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Introduction: METamp is a mechanism of acquired resistance to tyrosine kinase inhibitors (TKIs) and is reported to occur in ~30% of patients treated with EGFR TKIs; there is a high unmet need for effective treatment options in these patients. Combination treatment with a MET TKI plus an EGFR TKI may overcome MET-related EGFR TKI resistance. We report clinical activity of tepotinib plus an EGFR TKI in this population. **Methods:** Tepotinib plus an EGFR TKI has been investigated in the Phase (P) Ib/II INSIGHT study (NCT01982955). In PIb, patients received oral tepotinib (300 mg or 500 mg) plus 250 mg gefitinib once daily. In PII, patients received tepotinib 500 mg plus gefitinib or chemotherapy. METamp was determined using FISH (gene copy number ≥5 and/or MET/CEP7 ratio ≥2). The combination of tepotinib plus an EGFR TKI has also been explored in clinical practice, including compassionate use. **Results:** In the INSIGHT study, 18 patients with METamp received tepotinib plus gefitinib (PIb, n=6; PII, n=12). Median (range) treatment duration for the combination was 6.9 (1.7–13.8) months in PIb and 11.3 (1.4–22.7) months in PII; three patients are still ongoing treatment (≥4 years). A total of 12/18 (67%) patients had a response; 4/6 in PIb with a duration of response (DOR) of 5.5, 5.6, 11.7, and 12.5 months, respectively, and 8/12 patients in PII with a median (m) DOR of 19.9 months (90% CI: 7.0, NE). In PII, mPFS was 16.6 months (8.3, NE) and mOS was 37.3 months (NE, NE); both greatly improved versus chemotherapy (PFS HR 0.13 [0.04, 0.43], OS HR 0.08 [0.01, 0.51]). The table shows information on patients with duration of treatment >12 months (8/18 patients). Outside clinical trials, several patients have received tepotinib plus an EGFR TKI in clinical practice; information on two patients receiving this combination >6 months is shown (Table). A 62-year-old female is currently benefitting from tepotinib plus osimertinib after receiving chemotherapy, afatinib, osimertinib, and immunotherapy. A 79-year-old male, who received prior gefitinib and osimertinib, is currently benefitting from tepotinib plus osimertinib.

Source		Age*	Gender	Prior treatment	Time on most recent prior EGFR TKI, months	METamp, **GCN	EGFR TKI***	Time on treatment,**** months	Treatment ongoing****
INSIGHT	PII	42	F	Afatinib	5.7	13.9	Gefitinib 250 mg	53.1	Yes
	PII	66	M	Erlotinib	9.8	13.3	Gefitinib 250 mg	50.3	Yes
	PII	68	F	Erlotinib	15.8	6.7	Gefitinib 250 mg	48.3	Yes
	PII	52	F	Gefitinib	26.8	12.4	Gefitinib 250 mg	22.1	No
	PII	53	F	Gefitinib	46.3	7.7	Gefitinib 250 mg	21.1	No
	PII	67	M	Gefitinib	6.6	5.2	Gefitinib 250 mg	14.2	No
	PIb	60	M	Gefitinib, chemo, erlotinib	6.0	5.4	Gefitinib 250 mg	13.8	No
	PIb	63	M	Gefitinib	11.5	7.3	Gefitinib 250 mg	13.1	No
Clinical practice	US	62	F	Chemo, afatinib, osimertinib, immunotherapy	12.0	N/A (NGS] , Archer)	Osimertinib 80 mg	6.7	Yes
	HK	79	M	Gefitinib, osimertinib	11.5	10 (NGS; Foundation Medicine)	Osimertinib 80 mg	6.3	Yes

*At the beginning of combination treatment; **In the INSIGHT study, METamp was determined using FISH, in clinical practice one patient was tested by liquid biopsy using the Archer NGS assay, and one patient was tested by tissue biopsy using the Foundation Medicine NGS assay; ***EGFR TKI given in combination tepotinib 500mg (450 mg active moiety) treatment; ****As of March 2021. EGFR; epidermal growth factor receptor; GCN, gene copy number; METamp; MET amplification; N/A, not available; NGS, next generation sequencing; TKI, tyrosine kinase inhibitor.

Conclusion: The combination of tepotinib with an EGFR TKI, including osimertinib, shows clinical activity in the treatment of patients with EGFR TKI-resistant NSCLC due to METamp. Tepotinib plus osimertinib is currently being investigated in the INSIGHT 2 study (NCT03940703) in patients with METamp EGFR-mutant NSCLC with acquired resistance to first-line osimertinib. Enrollment is ongoing in 125 sites in 17 countries; encouraging preliminary activity has been observed.

Keywords: MET inhibitor, MET amplification, tepotinib

P51.02 Stacking on the Targets: Secondary Resistant, Potential Targetable Genetic Alterations in Patients With Epidermal Growth Factor Receptor NSCLC

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Introduction: With multiple tyrosine kinase inhibitors (TKI) approved for EGFR mutated NSCLC over the last decade, patients with this disease have superior outcomes compared to other NSCLC subsets. However, resistance to these agents is inevitable. With first and second generation TKI, the most common resistant mechanism is development of EGFR T790M mutation. However, now that osimertinib has emerged as the most favorable first-line EGFR TKI, we are now seeing a plethora of new resistance pathways. Retesting for actionable mutations at progression is important since secondary genetic alterations may sometimes be discovered which may be exploited for therapeutic benefit. **Methods:** We conducted a single institution, retrospective study of EGFR mutated lung cancer patients at our institution between January 2018 and January 2021 for who complete records were available. Patients who developed potentially- actionable mutations (specifically MET amplification, BRAF V600E mutation, FGFR 1/2/3 alterations, RET/ALK/ROS fusions) at progression were selected for analysis. Descriptive statistics was used to characterize this cohort. **Results:** A total of 234 patients with EGFR mutation positive NSCLC were treated at our institution during the time period specified: 127 had EGFR exon 19 deletion mutations and 107 had L858R mutation. 14 patients were found to have potentially secondary potentially- actionable mutations at the time of progression on osimertinib. Seven of these were detected on tissue-based NGS and 7 on liquid biopsy. Median age of these patients was 64.5 years (range, 56 to 85). Ten patients had received osimertinib as first line treatment and 4 as second line after first or second generation TKI. Median time on EGFR TKI to detection of these mutations was 17.5 months (range, 2-72). Eight (57.1%) had FGFR 1/2/3 alterations, 1 patient has just been started on FGFR inhibitors in addition to continuing osimertinib. They have not been assessed for response as yet. Two have been initiated on chemotherapy in addition to osimertinib and have had disease stability. Others have been managed with palliative radiation to progressive lesions. Four (28.6%) had MET amplification but three had rapid progression before any therapeutic intervention was performed and one was added on chemotherapy. One patient had BRAF V600E mutation and received BRAF+MEK inhibitors in addition to continuing osimertinib with excellent clinical response, and 1 had HER2 mutation who received carboplatin/pemetrexed/pembrolizumab. No RET/ROS/ALK fusions were found in our cohort. **Conclusion:** Repeating tissue-based or blood-based NGS at progression on EGFR TKI can be very useful. Novel resistance pathways are being discovered in patients who progress on osimertinib and actionable secondary mutations are sometimes found on repeat testing. Ongoing trials such as the ORCHARD trial are looking at biomarker-driven therapies for patients who progress on osimertinib but do not account for rarer or newer actionable mutations. Real world data on specifics of resistance mutations to osimertinib could lay the foundation for more robust multi-arm clinical trials.

Keywords: resistance, osimertinib, EGFR

P51.03 Oritinib (SH-1028), a Third-generation EGFR-TKI in Advanced NSCLC Patients with Positive EGFR T790M: Results of a Single-arm Phase Ib Trial

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Introduction: Oritinib (SH-1028) is an oral, high-selective irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) selectively targeting both sensitizing EGFR and EGFR T790M mutations. Herein, we report the preliminary efficacy and safety of oritinib in EGFR T790M-positive advanced non-small-cell lung cancer (NSCLC) patients previously treated with EGFR TKIs from dose-extension cohort of phase Ib study (NCT03823807). **Methods:** Eligible patients were advanced NSCLC patients aged ≥ 18 years, with centrally confirmed EGFR T790M-positive mutation and prior EGFR-TKI treatment. Patients with asymptomatic, stable CNS metastases were eligible into the study. Oritinib 200 mg was given orally once daily until disease progression or unacceptable toxicity. Primary efficacy endpoint was objective response rate (ORR) per RECIST v1.1. Secondary efficacy endpoints included disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), depth of response (DepOR), overall survival (OS). **Results:** From March 2019 to December 2019, 60 patients from 9 centers of China were enrolled in dose-extension cohort and 59 patients received at least one dose of oritinib and had at least one tumor assessment. Median age was 59 years old, 64.4% of patients were female and 49.2% received ≥ 2 prior systemic anticancer therapies. At the time of data cutoff (Mar 17, 2021), 36 of 59 patients achieved confirmed partial responses with ORR of 61.0% (95% CI:48.2%, 73.8%) per investigator. mPFS was 9.7 months (95% CI: 7.2, 13.8). The most common treatment-emergent adverse events included diarrhea (47.5%), increased blood creatine phosphokinase (27.1%) and decreased platelet count (13.6%). Grade 3 or 4 AEs occurred in 15 of 59 patients (23.7%) with increased blood creatin phosphokinase being the most common grade 3 or 4 AE (3.4%). No interstitial lung disease or prolonged QT interval were reported. **Conclusion:** Oritinib demonstrated potential clinical benefit in advanced NSCLC patients with EGFR T790M mutation following prior therapy with EGFR TKIs. The phase II study (n=220 patients) is ongoing to confirm these findings.

Keywords: NSCLC, EGFR T790M, Target therapy

P51.04 Pattern of Disease Progression on Osimertinib and Subsequent Treatment in Patients with EGFR- Mutated Non-Small Cell Lung Cancer

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Introduction: Osimertinib is the standard of care for patients with non-small cell lung cancer (NSCLC) who progressed with acquiring T790M mutation during first or second-generation EGFR tyrosine kinase inhibitors (TKI). Little is known about dynamics of treatment failure on osimertinib and subsequent treatment patterns following progression with osimertinib in the real world. **Methods:** We identified patients who began treatment with osimertinib after previous EGFR-TKI from June 2014 to November 2018 from electronic records. Patients' tumor characteristics, efficacy outcomes, affected organs from imaging studies and treatment modalities before and after osimertinib were analyzed. **Results:** In total, 98 patients were included. When starting osimertinib treatment, bone (46.9%) and brain (44.9%) were the most common single metastatic organ, while disease progression during osimertinib was more frequent in thorax (77.3%) than bone (29.5%) or brain (20.5%). Extracranial disease progression was confirmed in 70 of 89 patients (78.7%), whereas patients with intracranial failure only and both intracranial and extracranial failure were 6 (6.7%) and 13 (14.6%), totaling 19 (21.3%) patients. Among patients who showed PD in brain, patients who newly developed brain metastasis was 15.8% (3/19). Progressive disease (PD) preferentially involved preexisting metastatic organ; bone PD in bone metastasis (odds ratio 15.3, 4.1-56.9, <.01), brain PD in brain metastasis (odds ratio 11.6, 3.1-44.1, <.01), and liver PD in liver metastasis (odds ratio 10.4, 2.5-43.2, <.01). Osimertinib had yielded objective response rate of 61.2% (60/98), and disease control rate of 76.5% (75/98). After PD during osimertinib, 70 out of 98 patients were treated with subsequent treatment. The types of post PD treatments included (1) cytotoxic chemotherapy (51.4%), (2) osimertinib continuation (27.1%), and (3) radiation (14.3%). Remaining patients were treated with another EGFR TKI (4.3%) and checkpoint inhibitor (2.9%). **Conclusion:** Osimertinib showed enhanced activity in brain metastasis and PD occurred preferentially in preexisting metastasis. In spite of different PD patterns, subsequent treatments were systemic treatment in most cases. Further investigation for control of metastasis such as local ablative treatment during osimertinig is awaited for EGFR mutant NSCLC patients.

Keywords: osimertinib, EGFR mutation, non-small cell lung cancer

P51.05 Sequential Afatinib and Osimertinib in Patients With Advanced EGFRm+ NSCLC and Acquired T790M: The Real-World UpSwinG study

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Introduction: The ErbB family blockers, afatinib and dacomitinib, and the third-generation EGFR TKI, osimertinib, confer significant clinical benefit versus first-generation EGFR TKIs (erlotinib and gefitinib) in patients with EGFR mutation-positive (EGFRm+) NSCLC. However, no prospective data exist directly comparing afatinib, dacomitinib and osimertinib. In terms of overall survival (OS), outcomes are highly dependent on the availability and implementation of subsequent therapy following acquired resistance to first-line therapy. As emergence of T790M is the predominant mechanism of resistance to afatinib, occurring in up to 50–70% of cases, there is an argument for reserving osimertinib for second-line use. Given the current paucity of approved targeted treatment options post osimertinib, such an approach could provide a net survival benefit versus first-line osimertinib. A previous retrospective study (GioTag) demonstrated encouraging OS (>3 years) in patients with acquired T790M treated with sequential afatinib and osimertinib. **Methods:** In this non-interventional, global, multi-center study (NCT04179890), existing medical or electronic health records were identified for consecutive EGFR TKI-naïve patients with EGFRm+ NSCLC (Del19 or L858R) treated in regular clinical practice with first-line afatinib and, following the detection of T790M, second-line osimertinib. The primary objective was time to treatment failure (TTF). Secondary objectives included OS, overall response rate (ORR) and description of methodology used for detection of T790M. Data were analyzed descriptively. **Results:** Overall, 207 patients were enrolled and 191 analyzed. At the start of afatinib treatment, median age (range): 62 years (34–88); female: 55%; Asian 67%; ECOG PS (0/1/≥2): 31%/57%/12%; brain metastases: 14%; mutation status (Del19/L858R): 71%/29%. At the start of osimertinib treatment: ECOG PS (0/1/≥2): 25%/61%/14%; brain metastases: 14% (end of osimertinib: 29%). Mutations were predominantly detected by PCR-based methods (81%/86% at start of afatinib/osimertinib). Overall, median TTF and OS were 27.7 and 36.5 months, respectively. ORR with afatinib and osimertinib was 74% and 45%. TTF, OS and ORR were generally consistent across subgroups (Table). **Conclusion:** These real-world data substantiate the previous GioTag study and support the possible use of sequential afatinib and osimertinib in patients with EGFRm+ NSCLC and acquired T790M. Outcomes were particularly encouraging in Del19+ patients and Asians, but noteworthy activity was also observed across all subgroups including those with poor ECOG PS or brain metastases. The proportion of patients with poor ECOG PS (12%, 14%) or brain metastases (14%, 14%) remained stable prior to, and after, afatinib treatment (before osimertinib). Optimal sequence of EGFR TKIs requires further evaluation in clinical trials. **Table**

	Median TTF, months (95% CI)	Median OS, months (95% CI)	ORR, % Afatinib	ORR, % Osimertinib
Overall	27.7 (24.0–30.2)	36.5 (32.9–41.8)	73.6	45.2
Del19	28.6 (24.5–31.2)	38.0 (33.1–44.4)	74.0	47.1
L858R	22.1 (19.8–30.4)	33.1 (24.9–41.8)	72.7	40.4
Asian	28.8 (22.4–31.2)	42.3 (33.2–63.5)	79.3	48.0
Non-Asian	25.5 (22.1–28.6)	31.3 (27.2–38.0)	67.3	36.0
No brain metastases	28.4 (24.3–30.8)	37.6 (33.1–42.3)	71.2	45.8
Brain metastases	21.4 (19.2–30.9)	29.6 (22.4–NR)	91.3	41.7
ECOG PS <2	28.5 (24.0–30.9)	39.8 (32.9–45.2)	77.9	47.9
ECOG PS ≥2	29.6 (20.5–32.3)	33.1 (21.8–37.6)	70.6	40.0
Asian + Del19	29.7 (23.0–33.0)	43.8 (33.2–71.1)	-	-

Keywords: afatinib, osimertinib, EGFR mutation-positive NSCLC

P51.06 Outcomes of First-Line TKI Treated Advanced NSCLC with Distinct Types of EGFR Mutations: Brain Metastasis and de Novo T790M

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Introduction: The clinical features, survival outcomes and patterns of treatment failure of advanced non-small cell lung cancer (NSCLC) patients harboring distinct subtypes of EGFR mutations and receiving first-line EGFR tyrosine kinases inhibitor (TKIs) are not fully understood. **Methods:** Consecutive metastatic EGFR-mutant NSCLC patients receiving first-line EGFR-TKIs were enrolled and classified into two groups based on the EGFR mutation subtypes: common mutation (L858R or exon 19 deletion), uncommon mutation (other EGFR mutations). **Results:** Of the 1081 patients included, 74 (6.8%) harbored uncommon mutations. The baseline characteristics were generally balanced between the two groups, except that bone metastasis developed less frequently in patients with uncommon mutations (p=0.02). No significant difference of survival outcomes was found between the two groups, except that among patients with baseline brain metastasis, the intracranial time to progression was significantly shorter in patients with uncommon mutations. Nine of the 17 patients with de novo T790M mutation received Osimertinib, whose overall survival tended to be longer than the remaining 8 patients without Osimertinib treatment (p=0.08), and those harboring common mutations and receiving second-line Osimertinib after developing acquired T790M mutation (n=116) (p=0.10). The patterns of treatment failure were generally consistent between the two groups, except that patients with uncommon mutations had higher risk developing progressive disease in the brain. **Conclusion:** First-line EGFR-TKIs seems to be less effective in controlling and preventing brain metastasis in patients with uncommon EGFR mutations and Osimertinib is associated with promising efficacy in patients with de novo T790M mutation, which warranted further validation

Keywords: uncommon EGFR mutations, brain metastasis, de novo T790M

P51.07 Small Cell Transformation of Non Small Cell Lung Carcinoma: Tissue Biopsy Is Here to Stay!

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Introduction: The present study investigated the occurrence of small cell transformation of non small cell lung carcinoma as a mechanism of resistance to EGFR TKIs, along with its associated clinicopathologic features, mechanisms and clinical implications in the Indian population. **Methods:** This was a retrospective study which studied 1350 lung carcinoma patients between 2014-2019, of which 7 patients showed a small cell transformation at progression. The clinical characteristics, treatment outcomes and pathologic features were reviewed. **Results:** Among the 1350 lung cancer patients, 470 patients were EGFR mutant, of which 390 recived EGFR TKI during their course of treatment. Of these, 260 progressed, and 7 of them showed smll cell transformation. Six out these seven cases showed a del19 mutation and one case had an uncommon p.L861Q mutation in the EGFR gene. Two cases underwent NGS testing and revealed additional alterations in the PI3KCA gene. All seven cases had received EGFR TKI, and the median time to small cell change was 9.53 months, with a median progression free survival of 4.5 months. **Conclusion:** This study reviews the mechanisms of small cell transformation, along with clinical and treatment outcomes. It also highlights that re biopsy at the time of progression is imperative, as emerging liquid biopsy tools although highly sensitive in the detection of resistance mutations like T790M, cannot detect small cell change. The predominance of its incidence with a del19 mutation in this Indian population is hypothesis generating and requires confirmation.

Keywords: EGFR mutant NSCLC, Small cell transformation, EGFR TKI resistance mechanisms

P52.01 Understanding Treatment Preferences of Patients With KRAS p.G12C[LC1] [MK2] – Mutated Advanced Non-Small Cell Lung Cancer

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Introduction: Sotorasib, a novel, first-in-class, oral targeted therapy is in development for the treatment of KRAS p.G12C–mutated non-small cell lung cancer (NSCLC). The primary endpoint of sotorasib clinical studies reported to date has been objective response rate. Longer-term outcomes (e.g., overall survival) for sotorasib and patient preferences for treatment of KRAS p.G12C-mutated NSCLC are not currently available. Therefore, qualitative interviews were conducted with treatment-experienced patients with advanced KRAS p.G12C–mutated NSCLC to gain insight into: (a) patient experiences with treatment, (b) preferences for treatment attributes and benefit-risk profiles, and (c) willingness to accept uncertainty in longer-term treatment efficacy for a less toxic oral therapy in the second-line setting. **Methods:** Qualitative interviews were conducted with patients with locally advanced or metastatic KRAS p.G12C–mutated NSCLC who have undergone systemic therapy for NSCLC in the first-line setting. Twenty-four treatment-experienced, adult patients were recruited from the Ohio State University James Cancer Hospital. Of these, 17 participated in a single, 60-minute individual telephone interview using a semi-structured interview guide. Participants were asked to describe their experiences with NSCLC treatment, including benefits and side effects and their impact and importance, as well as to select their preference between two scenarios describing different combinations of treatment outcomes and toxicity profiles. **Results:** Among participants, mean (standard deviation) age was 63.6 (7.1) years, 12/17 (71%) were female, and 13/17 (76%) identified as white. All participants had received chemotherapy, and 8 (47%) had also received immunotherapy for advanced NSCLC. Ten participants (59%) reported experiencing multiple and/or severe toxicities from chemotherapy that significantly impacted their daily lives. Treatment toxicities associated with chemotherapy were fatigue (n = 16), hair loss (n = 12), nausea/vomiting (n = 10), weight change (n = 7), neuropathy (n = 7), change in appetite/taste of food (n = 7), gastrointestinal complications (n = 6), depression (n = 4), and mouth sores (n = 3). When asked to choose between an intravenous treatment with a benefit-risk profile similar to taxane-based chemotherapy and an oral treatment with a benefit-risk profile similar to sotorasib, the majority of participants (88.2%) chose an oral treatment with a hypothetical benefit-risk profile similar to that of sotorasib and indicated that they perceived a hypothetical 25% to 35% response rate to be meaningful despite an unknown survival benefit. **Conclusion:** This was the first study to provide insight into the perspectives of patients with advanced KRAS p.G12C–mutated NSCLC. A range of experiences with NSCLC treatment was reported, and treatment-related preferences appeared to be somewhat dependent on previous treatment experience. Even without mature survival data, previously treated patients perceived a hypothetical 25% to 35% response rate of the oral therapy with a benefit-risk profile similar to sotorasib to be a meaningful benefit and favorable compared with the well-established survival expectations with taxane-based chemotherapy.

Keywords: Patient Experiences, KRAS p.G12C-mutated NSCLC, Qualitative interviews

P52.02 High SHP2 Expression Determines the Efficacy of PD-1/PD-L1 Inhibitors in Advanced KRAS Mutant Non-Small Cell Lung Cancer

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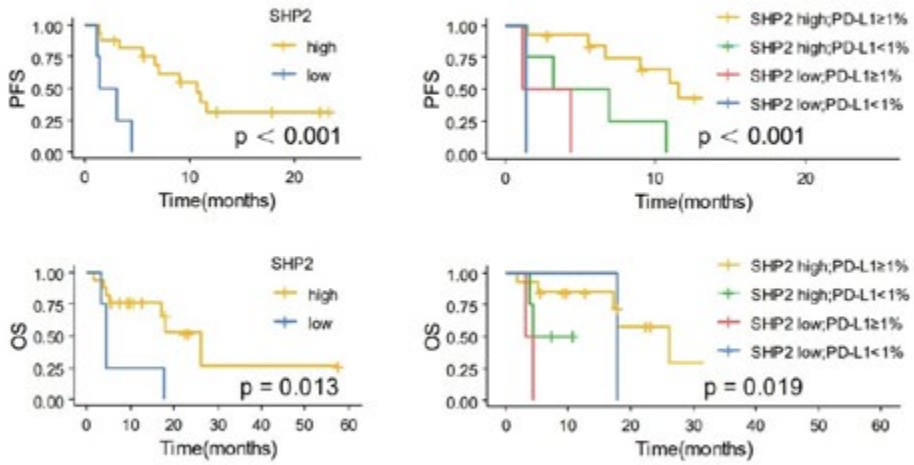

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Conclusion: High expression of SHP2 could predict the efficacy of ICI and better survival in advanced KRAS mutant NSCLC patients.

Keywords: SHP2, KRAS, immunotherapy

P52.03 Efficacy of Sotorasib in KRAS p.G12C-Mutated NSCLC with Stable Brain Metastases: A Post-Hoc Analysis of CodeBreaK 100

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Introduction: Sotorasib is a first-in-class small molecule that specifically and irreversibly inhibits $KRAS^{G12C}$. The phase 1/2 CodeBreaK 100 trial evaluated sotorasib in patients with pretreated advanced non-small cell lung cancer (NSCLC) harboring KRAS p.G12C. In the registrational phase 2 part, sotorasib showed an objective response rate (ORR) of 37.1% and a median progression-free survival (PFS) of 6.8 months. Here, we report on the activity of sotorasib in patients with treated brain metastases (BM). **Methods:** Patients from the phase 1/2 CodeBreaK 100 trial receiving 960mg dose were included. Patients with active untreated BM were excluded. Patients who had BM resected or had received radiation therapy ending ≥4 weeks prior to the trial were eligible. Systemic response was assessed by independent central review per RECIST 1.1. The presence of neurologically stable/asymptomatic BM at baseline was determined by investigators. CNS response was retrospectively evaluated by central neuroradiologic review, using the response assessment in neuro-oncology BM (RANO-BM) criteria, in patients with ≥1 target CNS lesions (≥ 10mm) and/or non-target CNS lesions. For non-target lesions, stable disease (SD) refers to response that is neither complete response (CR) nor progressive disease (PD). **Results:** 174 patients were included: 40 had stable BM (23.0%) while 134 (77.0%) had no BM at baseline. In the BM group, 65% had received prior radiotherapy, and 20% had received prior brain surgery. Systemic efficacy of sotorasib per RECIST 1.1 is shown in the **Table**. Per central RANO-BM review, 16 patients had baseline and ≥1 on-treatment evaluable scans: 3 had target and 13 had non-target CNS lesions. 9 patients had 1 lesion, 2 had 4 lesions, and 5 had ≥5 lesions. Of 13 patients with non-target CNS lesions, 2 had CR, 11 had SD. Of 3 patients with target lesions, 1 had SD, and 2 had PD. Overall, intracranial disease control was achieved in 14 of 16 patients (87.5%) with evaluable BM. Safety in the BM group was consistent with previous reports.

Systemic response	BM N = 40, evaluable	Non-BM N = 132, evaluable
ORR – % (95% CI)	25.0 (12.7, 41.2)	41.7 (33.2, 50.6)
Median duration of response – months (95% CI)	11.1 (3.5, NE)	10.0 (6.8, NE)
Disease control rate – % (95% CI)	77.5 (61.6, 89.2)	84.1 (76.7, 89.9)
Median PFS – months (95% CI)	5.3 (2.7, 7.3)	6.7 (5.3, 8.2)
Median overall survival (OS) – months (95% CI)	8.3 (7.3, 12.5)	13.6 (10.0, NE)

Conclusion: Sotorasib demonstrated systemic durable anticancer activity, with a median PFS and OS of 5.3 and 8.3 months in NSCLC patients with stable BM previously treated with radiation or surgery. Intracranial complete responses were observed, with continued intracranial stabilization observed in the majority of patients with evaluable BM. Additional studies are ongoing to evaluate sotorasib in patients with active untreated BM (NCT04185883).

Keywords: brain metastases, KRAS p.G12C, sotorasib (AMG 510)

P52.04 Histone Deacetylase 6 Inhibition Reveals Metabolic Vulnerabilities in KRAS Non-Small Cell Lung Cancer

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Introduction: Lung tumors are characterised has having high glucose and lactate use, and high heterogeneity in their metabolic pathways. Decades of research provides comprehensive knowledge of the rewired metabolic programs driven by oncogenic KRAS, including glucose metabolism, fatty acid synthesis, glutamine metabolism, autophagy signaling and redox homeostasis. KRAS mutations in non- small cell lung cancer (NSCLC) often occur with co-mutations in other genes such as TP53 and LKB1, and these co-existing genetic mutations can determine clinical response. Currently, there are clinical trials ongoing assessing the efficacy of histone deacetylase 6 (HDAC6) inhibitors in combination treatments in many cancers. However, the exact mechanism of action employed by these inhibitors remains elusive. Recently, it was discovered that HDAC6 plays a role in the regulation of cancer cell glycolysis. Here, we sought to explore the specific metabolic vulnerabilities protruded by HDAC6 inhibitors in NSCLC, and hence, help identify novel combination regimens for the treatment of specific genotypes of NSCLC. **Methods:** Using both seahorse technology and a series of mass spectrometry approaches we examined the metabolic changes in response to HDAC6 inhibitors in KRAS/LKB1 (KL) and KRAS/TP53 (KP) NSCLC both in vitro and in vivo. We also performed RNA sequencing experiments to decipher the differences between these specific genotypes of NSCLC when treated with HDAC6 inhibitors. Based on the metabolic rewiring observed, we performed efficacy experiments in $KRAS^{+/LSL\text{-}G12D}$;$LKB1^{fl/fl}$ (KL) genetically engineered mouse models (GEM) using HDAC6 inhibitors in combination with a specific metabolic inhibitor. Immunoprofiling experiments were conducted on KL GEMs to explore any distinct changes in the immune populations as a result of this combination regimen. **Results:** We observed, in cell lines and murine tumors, that HDAC6 inhibition reduces glycolysis in KL NSCLC but not in KP NSCLC. Using environmentally relevant conditions, we discovered a dependency on the nicotinamide adenine dinucleotide (NAD+) salvage pathway in the KL tumors. Moreover, upon treatment of KL tumors with a HDAC6 inhibitor we observe further enhancement of this pathway. Combining HDAC6 inhibitors with inhibitors of the NAD+ salvage pathway offers increased efficacy in KL NSCLC models, providing a rationale for new combination regimens for this specific genotype of NSCLC. **Conclusion:** HDAC6 has not previously been implicated as a metabolic regulator in NSCLC. Here, using HDAC6 inhibitors we have revealed distinct metabolic vulnerabilities in specific genotypes of NSCLC. More specifically, when treated with HDAC6 inhibitors, KL tumors rely on the NAD+ salvage pathway as a compensatory mechanism for survival and combination regimens targeting both these pathways offers promising clinical utility.

Keywords: Metabolism, HDAC6i, LKB1

P52.05 Dual RAF/MEK Inhibitor VS-6766 for Treatment of KRAS Mutant NSCLC: Novel Combinations Targeting G12C or G12V Variants

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Introduction: KRAS is mutated in 25% of non-small cell lung cancer (NSCLC) adenocarcinoma, with KRAS G12C and G12V mutations occurring in ~13% and ~7% of patients, respectively. Whereas G12C inhibitors (G12Ci) sotorasib (AMG 510) and adagrasib (MRTX849) have demonstrated promising antitumor activity in patients with KRAS G12C mutant (mt) NSCLC, KRAS G12V mt NSCLC remains an unmet need. VS-6766 is a unique dual RAF/MEK inhibitor which has shown single agent activity against KRAS G12V mt NSCLC (Guo Lancet Oncology 2020). **Methods:** We assessed synergistic antitumor effects of VS-6766 with G12C or focal adhesion kinase (FAK) inhibitors in KRAS G12C or G12V NSCLC preclinical models, respectively. **Results:** In KRAS G12C mt NSCLC, emerging data suggest that G12Ci monotherapy may be insufficient for maximal depth or duration of response, and combinations with agents that target additional nodes in the RAS pathway (vertical blockade) may be necessary. In 3D proliferation assays, VS-6766 was synergistic with both sotorasib and adagrasib in reducing viability of a panel of KRAS G12C mt NSCLC cell lines. Accordingly, VS-6766 effectively suppressed pERK across KRAS G12C mt NSCLC cell lines as a single agent, and the combination of VS-6766 + G12Ci showed improved depth and duration of inhibition relative to G12Ci alone. In KRAS G12C mt NSCLC xenograft models (H2122, H358), combination with VS-6766 (0.3 mg/kg QD) augmented tumor growth inhibition by sotorasib, whereas trametinib (0.3 mg/kg QD) was much less effective in augmenting sotorasib efficacy. Strikingly, triple combination of VS-6766, sotorasib and FAK inhibitor conferred tumor reductions of ≥35% in all mice in both models. In KRAS G12V mt NSCLC, CRAF signaling was essential for tumor progression in a genetically engineered mouse tumor model (Sanclemente Cancer Cell 2018), providing rationale for testing the RAF/MEK inhibitor VS-6766 in KRAS G12V mt NSCLC. As RAF and MEK inhibition have been reported to activate FAK as a potential resistance mechanism, the combination of VS-6766 with the FAK inhibitor defactinib has been studied. In 3D proliferation assays in vitro, VS-6766 was synergistic with defactinib in reducing viability of KRAS mt cell lines with the broadest synergy observed in KRAS G12V mt cell lines, as compared with G12C and G12D cell lines. In a KRAS G12V mt/TP53 null NSCLC model, which has previously been shown to be CRAF dependent, VS-6766 monotherapy induced statistically significant tumor regression, while trametinib at the same dose did not. FAK inhibition further augmented the tumor regression induced by VS-6766. These preclinical data correlate well with the clinical observation of partial responses in patients with KRAS G12V mt NSCLC treated with VS-6766 monotherapy (Guo Lancet Oncology 2020) or in combination with defactinib. Furthermore, this combination regimen of VS-6766 with defactinib exhibited a manageable safety profile with no patients discontinuing for adverse events (Krebs AACR 2021). **Conclusion:** These results support the ongoing registration-directed study evaluating VS-6766 ± defactinib for treatment of recurrent KRAS G12V mt NSCLC (NCT04620330) and provide rationale for the clinical evaluation of VS-6766 in combination with a G12C inhibitor for treatment of KRAS G12C mt NSCLC.

Keywords: NSCLC, KRAS, VS-6766

P53.01 Clinical Application of NGS Technology. Therapeutic Possibilities and Future Perspectives

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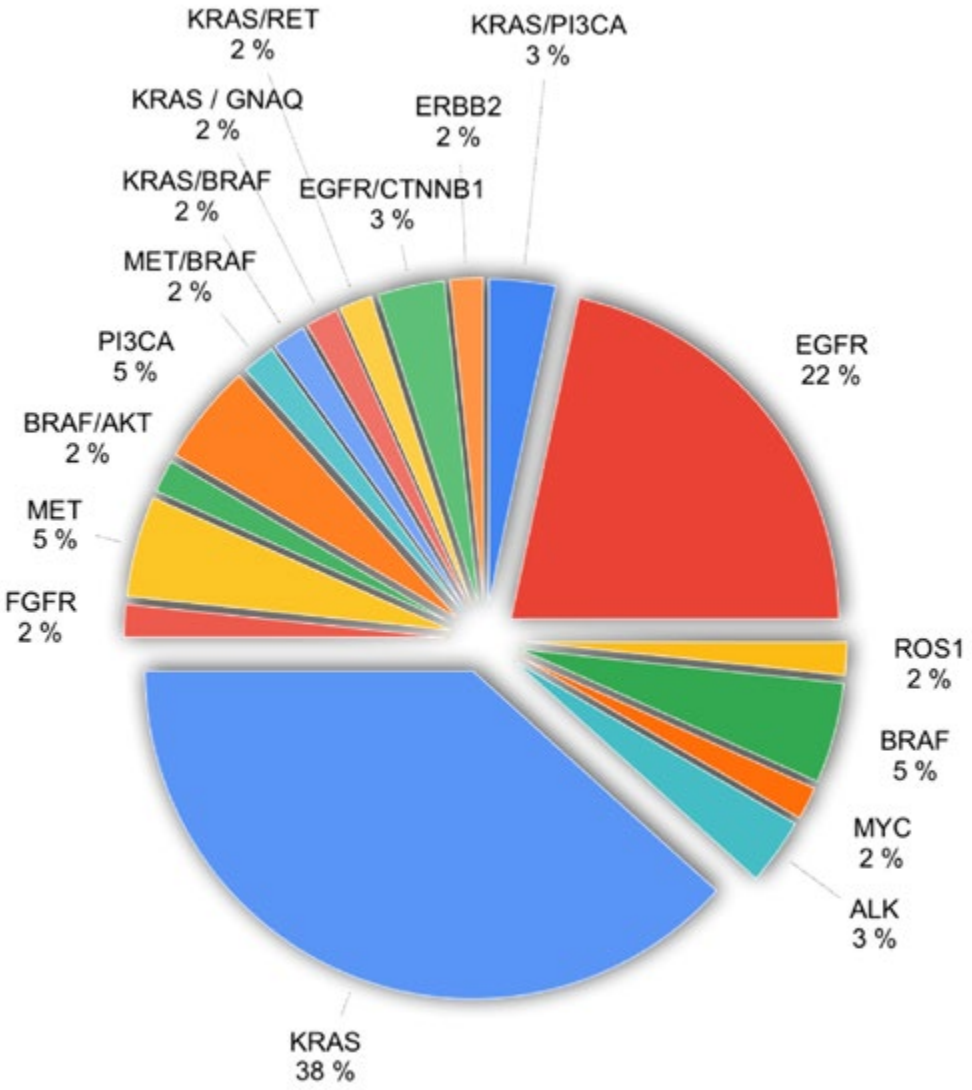
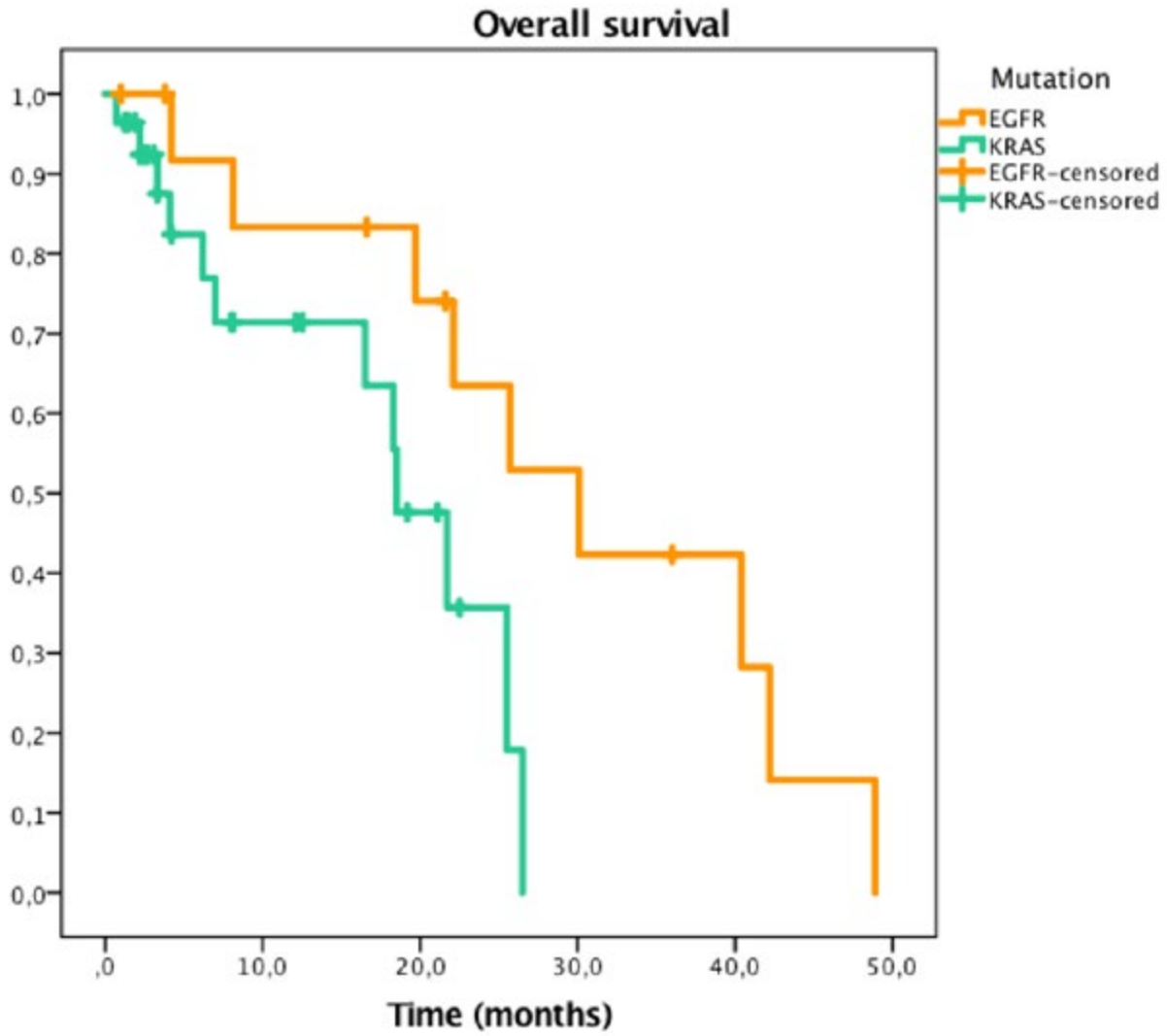
Introduction: Next Generation Sequencing (NGS) has been a breakthrough in the field of oncology. The genetic alterations discovered have enabled the development of target therapies, thus extending the life expectancy of lung cancer patients **Methods:** For this work we have applied Ion Torrent NGS and Oncomine Focus technologies to lung cancer samples from patients in our center detecting genetic alterations in 60 of them. **Results:**





Most of the cases (90%) corresponded to adenocarcinoma. The results (Fig.1) reveal that single nucleotide variants were the most common mutation (62%) with special emphasis on KRAS EXON 2 Codon 12 p.Gly12 Cys, followed by EGFR EXON 19 deletion (12%). With a similar incidence we can also highlight a mix of combined genetic disorders including EGFR/CTNNB1, KRAS/BRAF, KRAS/GNAQ, KRAS/PI3CA, KRAS/RET and BRAF/AKT alterations. It was also found fusions in 5% of total cases (SLC34A2-ROS1, EML4-ALK, RET, MET); point genetic variations in 2% (ERBB2 p.Gly1015Glu); ALK translocation in 2% and BRAF p.Val600Glu hotspots in 2%. The PDL-1 expression was greater than 50% in 38,3% of the patients. The 90% of patients received oncologic treatment including: 1) Chemotherapy (41,6%), adding immunotherapy in 28% of them; 2) Immunotherapy-based treatment using monotherapy (16,6%); and 3) Targeted therapy (21,6%).

Kaplan-Meier survival curves have been calculated for KRAS and EGFR genetic alterations (Fig.2). The median Overall Survival (mOS) for EGFR-mutated population was equal to 30,1 months (95% IC: 18,5-41,7 months) whereas mOS from KRAS-mutation group was 18,5 months (95% IC: 14,1-22,9 months). Log-Rank test was statistically significant with a pvalue equal to 0,027. **Conclusion:** Current genetic sequencing is providing us a huge amount of information about cancer driver mutations and opens up the door to the development of better treatments based on targeted therapy.

Keywords: Next Generation Sequencing, targeted therapy, Clinical application of NGS technology. Therapeutic possibilities and future perspectives.

P53.02 Efficacy and Safety of Larotrectinib in Patients With Tropomyosin Receptor Kinase (TRK) Fusion-Positive Lung Cancer

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Introduction: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers that have been identified in various adult and pediatric tumor types. While NTRK gene fusions are highly enriched in certain rare cancers, they are also found at lower frequencies in more common tumors, including non-small cell lung cancer (NSCLC). Larotrectinib is a first-in-class, central nervous system (CNS)-active, highly selective TRK inhibitor approved for patients with TRK fusion-positive cancer, demonstrating a 78% objective response rate (ORR) across 175 adult and pediatric patients (McDermott et al. ESMO 2020). We report updated data for patients with TRK fusion-positive lung cancer. **Methods:** Patients with TRK fusion-positive lung cancer treated with larotrectinib enrolled in two clinical trials (NCT02122913 and NCT02576431) were included in this analysis. Larotrectinib 100 mg BID was administered. The primary endpoint was ORR, assessed by independent review committee (IRC) and investigators (INV) per RECIST v1.1. **Results:** As of July 20, 2020, 20 patients were enrolled: 19 NSCLC (all adenocarcinomas) and 1 small cell lung cancer (SCLC). Ten patients had baseline CNS metastases. Median age was 49 years (range 25–76 years). Patients received a median of 3 prior lines of systemic therapies with 13 (65%) receiving ≥2. Among 15 evaluable patients, ORR was 87% (95% confidence interval [CI] 60–98) per IRC and 73% (95% CI 45–92) per INV. In patients with baseline CNS metastases, ORR was 88% (95% CI 47–100) per IRC and 63% (95% CI 25–91) per INV (Table). In all IRC-evaluable patients, the median for duration of response (DOR) was not reached (95% CI 5.5–not estimable [NE]). The median PFS and OS were 33.0 months (95% CI 7.6–NE) and 40.7 months (95% CI 17.2–NE), respectively. The 12-month rates for DOR, PFS and OS were 64%, 62% and 86%, respectively. Duration of treatment ranged from 0.03+ to 51.5+ months. At data cut-off, 7 patients had progressed, with 5 continuing treatment post-progression. Treatment-related adverse events (TRAEs) were mostly Grade 1–2 with Grade 3–4 TRAEs reported in 10% of patients. **Conclusion:** Larotrectinib achieved rapid and durable responses with extended survival benefits and a favorable safety profile. These data support testing for NTRK gene fusions in patients with lung cancer.

	All patients (N=20)		Patients with CNS metastases at baseline (n=10)	
	INV	IRC	INV	IRC
Evaluable patients	15	15	8	8
ORR, % (95% CI)	73 (45–92)	87 (60–98)	63 (25–91)	88 (47–100)
CR, n (%)	1 (7)	2 (13)	0	0
PR, n (%)	10 (67)	11 (73)	5 (63)	7 (88)
SD, n (%)	3 (20)	2 (13)	2 (25)	1 (13)
PD, n (%)	1 (7)	0	1 (13)	0

CI, confidence interval; CNS, central nervous system; CR, complete response; INV, investigator assessment; IRC, independent review committee assessment; PD, progressive disease; PR, partial response; SD, stable disease.

Keywords: Larotrectinib, NTRK gene fusions, lung cancer

P53.03 The Characteristics of FGFR Genetic Aberrations in Chinese Lung Cancer Patients

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Introduction: There are more than a dozen fibroblast growth factor receptor (FGFR) inhibitors in a variety of cancer types in development, including lung cancer .The frequency and types of FGFR aberrations in Chinese NSCLC patients may have great value for clinical therapeutic application. **Methods:** A total of 8399 lung cancer patients (pts) whose tumor tissue sample underwent hybridization capture-based next-generation sequencing were reviewed. All patients were also analyzed for mutations in EGFR, ALK, RET, MET, ROS1, as well as other oncogenes. **Results:** FGFR 1-4 aberrations, including mutations, fusions, gene amplifications and gene deletion, were detected in 7.6% (636/8399) of lung cancer pts, the incidence of FGFR alteration were more frequently observed in lung squamous cell carcinomas (19.4%,162/837) than lung adenocarcinomas (5.5%, 303/5495). FGFR gene mutation (65%) was highest identified, followed by amplification (38%) , fusion (6%, table) and deletion (1%). FGFR1, mostly amplification, was detected in 50% (316/636), FGFR2 in 19%, FGFR3 in 21%, and FGFR4 in 20%. The frequency and types of FGFR aberrations were different in lung adenocarcinomas with mostly FGFR1 fusion (1.1%) and amplification(7.4%) and lung squamous cell carcinomas with mostly FGFR1 amplification (14.62%) and FGFR3 fusion(1.1%). Furthermore, lung cancer pts with FGFR gene fusion and amplification are mainly stage I and II, but a small number of patients are also detected in stage II pts 7%, 7/101. FGFR fusions retaining the intact kinase domain were identified in 10 patients (0.12%), including 9 FGFR3-TACC3 and 1 novel fusion FGFR2-FAM184B, which may have caused FGFR2 overexpression. Concomitant EGFR mutations or amplification (15 pts), ALK fusion (3 pts), ROS1 fusion (1 pts) and MET mutation or amplification (4 pts) were observed in different pts, in whom FGFR fusions may have mediated resistance to anti-EGFR/ALK/ROS1/MET therapies.

Table. Frequency of FGFR fusions

Fusions	Fusion region	N (%)
FGFR3-TACC3	EX18E:EX11	3(7.14%)
	EX17:EX8	3(7.14%)
	EX17:EX10	2(4.76%)
	EX18E:EX13	1(2.38%)
	EX8:EX9	1(2.38%)
FGFR3-LETM1	EX8:Promoter	1(2.38%)
FGFR3-SZT2	EX7:EX61	1(2.38%)
FGFR3-PCDH7(intergenic)	EX8:intergenic	1(2.38%)
FAM53A(intergenic)-FGFR3	intergenic:EX18E,intergenic:EX8	2(4.76%)
FGFR3-chr20 55284041	EX18E:chr20 55284041	1(2.38%)
FGFR2-FAM184B	EX17:EX8	1(2.38%)
FGFR2-GRK5	EX17:EX1	1(2.38%)
FGFR2-SORBS1	EX17:EX24	1(2.38%)
FGFR2-PROM1	EX18:EX11	1(2.38%)
FGFR2-chr10 122732846	EX17:chr10 122732846	1(2.38%)
FGFR2-NPVF(intergenic)	EX14:intergenic	1(2.38%)
OPALIN-FGFR2	EX6E:EX2	1(2.38%)
ATE1-FGFR2	EX11:EX2,EX5:EX17	2(4.76%)
chr10 123156582-FGFR2	chr10 123156582:EX18	1(2.38%)
DEC1(intergenic)-FGFR2	intergenic:EX6	1(2.38%)
FGFR1-TACC1	EX1:EX2	1(2.38%)
FGFR1-STAU1	EX1:EX7	1(2.38%)
FGFR1-LETM2	EX12:EX8	1(2.38%)
FGFR1-KCNU1(intergenic)	EX3:intergenic	1(2.38%)
FGFR1-SLC22A23	EX13:EX10	1(2.38%)
FGFR1-ISL1(intergenic)	EX8:intergenic,EX4:intergenic	2(4.76%)
DDHD2-FGFR1	EX5:EX2	1(2.38%)
ZMAT4-FGFR1	EX2:EX2	1(2.38%)
HELZ-FGFR1	EX33E:EX6	1(2.38%)
chr8 76149982-FGFR1	EX0:EX2	1(2.38%)
chr8 138590655-FGFR1	EX0:EX2	1(2.38%)
UNC5D(intergenic)-FGFR1	intergenic:EX2	1(2.38%)
LOC100996508-FGFR1	EX1:EX2	1(2.38%)
TACC1(intergenic)-FGFR1	intergenic:EX2	1(2.38%)
Total		**42(100%)**

Conclusion: We report the prevalence of FGFR aberrations in a large lung cancer pts, including mutations, gene amplifications, gene deletion and one novel FGFR fusion. Our results revealed the potential therapeutic strategies with FGFR inhibitors for Chinese patients with lung cancer.

Keywords: FGFR, genetic aberrations, lung cancer

P53.04 Local Therapies vs. Specific TKIs as the Initial Treatment for Oligo-Recurrent Lung Adenocarcinoma With Driver Mutations

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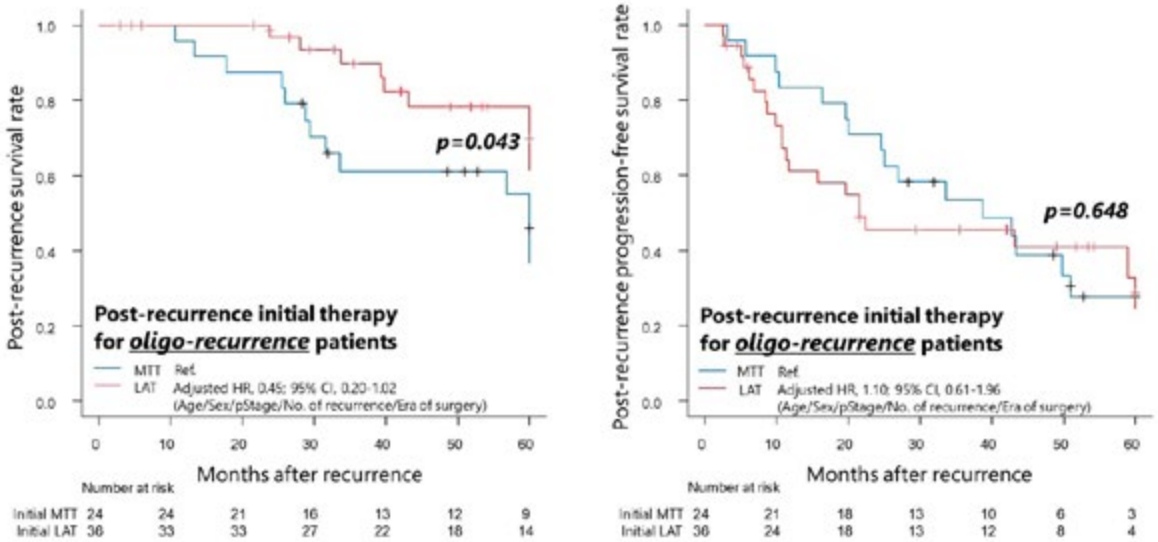
Introduction: Several studies have reported the efficacy of local therapies for lung cancer patients with postoperative oligo-recurrence. However, the preference for local ablative therapies over specific tyrosine-kinase inhibitors for oligo-recurrence patients with driver mutations remains controversial. We aimed to investigate the optimal initial treatment strategy in oligo-recurrence lung cancer patients with driver mutations. **Methods:** Among 2,159 lung adenocarcinoma patients who underwent surgical resection at our institute between 2008 and 2017, we retrospectively evaluated 272 patients with postoperative recurrence. Oligo-recurrence was defined as 1-3 recurrent lesions. We investigated oligo-recurrence patients with driver mutations focusing on post-recurrence therapies and prognoses. **Results:** The median follow-up period was 52 months. In total, 155 (57%) patients had driver mutations, and as initial post-recurrence therapies, local ablative therapies and specific tyrosine-kinase inhibitors were administered to 37 and 100 patients, respectively. Of them, 70 (45%) met the criteria for oligo-recurrence, and as initial post-recurrence therapies, local ablative therapies and specific tyrosine-kinase inhibitors were administered to 36 and 24 patients, respectively. Compared with specific tyrosine-kinase inhibitors, local ablative therapies significantly improved post-recurrence survival (p=0.043) but not post-recurrence progression-free survival (p=0.648) in oligo-recurrence patients. In also the multivariable analyses adjusted for number of recurrence, the results were similar for both post-recurrence survival (local ablative therapies: hazard ratio, 0.45; 95% confidence interval, 0.20-1.02) and post-recurrence progression-free survival (local ablative therapies: hazard ratio, 1.10; 95% confidence interval, 0.61-1.96). Patients who received local ablative therapies, even if they were not the initial treatment, had superior post-recurrence survival than those treated with specific tyrosine-kinase inhibitors alone (p=0.027).



Conclusion: Although specific tyrosine-kinase inhibitors have a profound therapeutic benefit in lung cancer patients with driver mutations, local ablative therapies should be considered the first treatment choice for patients with oligo-recurrent lung cancer. Furthermore, the combination of local ablative therapies and specific tyrosine-kinase inhibitors may be a promising treatment strategy.

Keywords: oligo-recurrence, driver mutation, local ablative therapy

P53.05 Inhibition of Tumor Cell Intrinsic Complement Regulatory Proteins Leads to Decreased Tumor Growth in a Mouse Model of NSCLC

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Introduction: The complement system is part of the innate immune system that interfaces with adaptive immunity. Complement activation triggers a series of proteolytic cascades that converge on C3, leading to the formation of the membrane attack complex (MAC) that causes cell lysis of target cells. Within the complement system, there are multiple regulatory proteins that act to inhibit or decrease complement activation; these proteins include Factor H (fH), CD55, and CD59. Complement activation can mediate tumor progression through production of anaphylatoxins (C3a/C5a) that act to block anti-tumor immunity. However, complement activation can also inhibit tumor growth through the formation of the MAC complex leading to cancer cell killing. Previous studies by our lab showed that complement inhibition, either with use of a global genetic $C3^{-/-}$ mouse or with pharmacologic agents targeting the C3a and C5a receptors, inhibited tumor growth and metastasis by acting as immunomodulators in a tumor cell-extrinsic manner. Here we hypothesize that tumor cell-intrinsic upregulation of complement regulatory proteins, such as fH and CD55, leads to increased tumor growth by inhibiting formation of the MAC complex and thereby preventing tumor cell lysis and death. **Methods:** We used an orthotopic syngeneic mouse model where murine cancer cells are implanted into the left lungs of syngeneic mice. These studies used CMT167 and LLC cells, which have KRas mutations, and EA1 and EA2 cells, which express the fusion kinase Eml4-Alk. Using RNAseq, we compared the transcriptome of cancer cells recovered from tumors to the transcriptome of their respective cell lines grown in vitro. To study the role of complement regulatory proteins in tumor cells, we silenced fH in murine cell lines using both shRNA constructs as well as a CRISPR knockout. These cells were implanted into the lungs of mice and tumor volume was measured after 2-3 weeks. Knockdown was validated by qPCR. We treated mice with a novel tumor-targeting fH antibody and monitored tumor growth by CT imaging. **Results:** RNAseq analysis indicates an increase in complement regulatory proteins in vivo versus in vitro in our cell lines, specifically fH in EA1, LLC, and CMT167 cells and CD55 in CMT167 cells. We observed a decreased volume of fH knockdown tumors compared to control tumors in EA1 cells orthotopically injected into the left lung of WT C57Bl/6 mice. CMT167 fH knockdown cells did not show a difference in tumor growth. However, CMT167 CD55 knockdown cells formed smaller tumors in vivo compared to the control tumors. Furthermore, the use of a tumor cell-targeting fH antibody led to decreased tumor growth in EA1 tumors compared to control. **Conclusion:** Taken together, our data indicate that tumor cell-intrinsic complement regulatory proteins play a role in tumor progression. Inhibition of these proteins leads to decreased tumor growth in a mouse model of NSCLC indicating that targeting these pathways has a therapeutic potential to treat NSCLC patients.

Keywords: complement, NSCLC, Factor H

P53.06 A Multi-Phase Quality Initiative to Improve Processes of Care for Non-small Cell Lung Cancer (NSCLC) in US Community Cancer Centers

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Introduction: Accurate staging, biomarker identification, and high-fidelity processes of care are critical for evidence-based treatment of NSCLC. To this end, the Association of Community Cancer Centers (ACCC) conducted a national, multi-phase effort to identify and provide guidance on key issues related to optimal care for patients with stage III/IV NSCLC. **Methods:** The quality improvement (QI) initiative, guided by an expert steering committee, included 5 phases: 1: Site Selection; 2: Topic Identification, Quality Measure Development & Education; 3: Data Collection & Analysis; 4: Implementation of Educational Intervention; 5: Analyze & Repeat. After site selection, baseline data were collected to assess key areas (demographics and clinical features, biomarker testing, process of care) across all sites using standardized data collection instruments. Baseline data were reviewed with each project team and a QI topic was selected via planning tele-conferences. An onsite (or virtual) full-day workshop was conducted with multidisciplinary cancer team members, including invited expert faculty, to define goals and develop site-specific QI projects. The main objects were to implement process-level improvements and develop quantitative benchmarks. Follow-up data collection (quantitative, qualitative, and process-level) was specific to each project and site (some were modified due to COVID-19) and all sites provided follow-up data on biomarker testing. Statistical analyses included summary statistics, frequency tables, and chi-square tests. **Results:** In pre-implementation (baseline) data collected at the six sites from 2018-2019, median patient ages were 65-72 years; 50% Stage III and 50% Stage IV. The race distribution of patients and proportions insured under Medicare, Medicaid, or commercial varied substantially across sites. Biomarker testing also varied in 2018-2019, with clinicians having requested testing for 48-94% of Stage IV patients (with four sites >80%). When biomarkers were evaluated, EGFR and ALK were included in 70-100% of tests, BRAF and ROS1 in 14-87% of tests, and NTRK testing was rare. PDL1 was evaluated in 40-97% of patients. Important process-level improvements were achieved with the QI projects in 2020. Two sites focused on immune-related adverse events (irAEs), conducting a clinician survey to assess gaps in knowledge and care around identification and management of irAEs and developing a patient questionnaire to identify early signs of irAEs. A site focused on clinical trial enrollment and education and established a referral partnership with an NCI-designed cancer center. Two sites focused on biomarker testing, making progress towards standardization. Interventions included creation of a process map for ordering, optimizing workflow by standardizing key elements and template order-sets, increasing liquid biopsy use, and implementing pathology-driven reflex testing at diagnosis. Three sites improved testing rates of Stage IV patients from baseline to follow-up (48% to 81%; 67% to 100%; 80% to 100%). When biomarkers were tested in 2020, the use of panel testing was 87% overall (>70% for every site). Liquid biopsy was used regularly at three sites, testing 23%, 25%, and 40% of patients. **Conclusion:** This initiative aided six cancer programs in improving processes of care for patients with stage III/IV NSCLC. Despite some COVID-19 disruption, participating sites remained committed to implementing changes around biomarker testing, well-coordinated care delivery, and symptom management.

Keywords: biomarker testing, immune-related adverse events, Quality of Care

P53.07 Clinical and Genomic Insights Into of Chinese Lung Cancer Patients with HER2 Amplification

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Introduction: Background:HER2 alterations was one of subsets of patients with specific genetic alterations of NSCLC patients. Despite that HER2 alterations in NSCLC have been studied for years, there is still no consensus about subgroup definitions, especially for HER2 amplification. In this study, we analyzed the genomic and clinical characteristics of HER2-amplified Chinese lung cancer patients, in order to find the appropriate treatment modalities for these patients. **Methods:** We reviewed 7643 Chinese lung cancer patients with paired tumor-normal samples sequenced by a 1021 gene panel. Tumor mutational burden (TMB) was defined as the number of somatic non-synonymous mutations per megabase of the panel region. **Results:** 2.8% patients (214/7643) had HER2 amplification, and 95 of them carried only HER2 amplification. The copy number ranged from 3 to 265, and median was 10. Based on the median, the patients were divided into higher and lower groups. RTK-RAS and PI3K signal pathway were common in these patients. TP53 was the most common concomitant mutation in both higher group (80%) and lower group (80%) patients. The lower group showed higher proportion patients with genetic mutation in RTK-RAS pathway than higher group (84.6% vs 58.2%, p=0.00626). The main reason was that lower group had higher proportion NF1 gene mutation (25% vs 0). Then, TMB was compared in two groups, and lower group showed higher TMB than higher group (16 vs 11, p=0.0069). 15 of 95 patients had the data of survival in multiple-lines, including 4 of treated with immunotherapy, 4 of treated with afatinib, and 11 of treated with chemotherapy. The progression free survival(PFS) of two groups was no difference (4 vs 4, p=0.27). However, the patients treated with immunotherapy showed longer PFS than patients treated with chemotherapy (5.5 vs 2, p=0.0078). Patients treated with afatinib also had longer PFS than those treated with chemotherapy, although there was no significant difference (4 vs 2, p=0.079). **Conclusion:** In conclusion, the patients with lower copy numbers of HER2 had more mutation in RTK-RAS pathway that may be a potential target to combination treatment for this patients. Meanwhile, our study showed immunotherapy and target therapy were better than chemotherapy for patients with HER2 amplification.

Keywords: NSCLC, HER2 amplification, TMB

P53.08 Concomitant Fibrates and Immunotherapy in Non-Small Cell Lung Cancer Patients in the Veterans Health Administration

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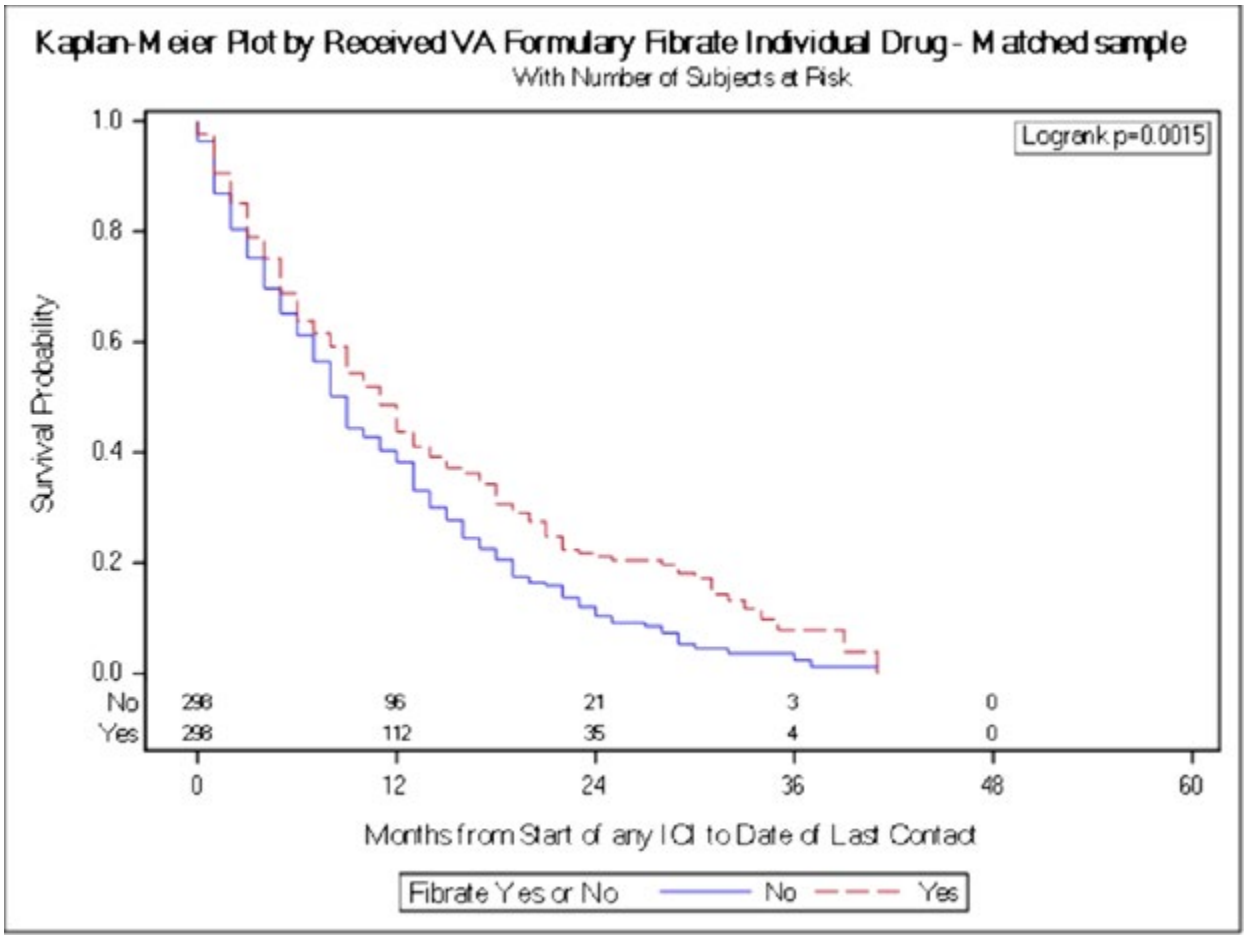
Introduction: Preclinical studies indicate peroxisome proliferator-activated receptor (PPAR) agonists such as fibrates induce metabolic switching and activate mitochondria, thereby upregulating cytotoxic T-lymphocyte activity and enhancing response to immune checkpoint inhibitors (ICI). However, there is currently no evidence in human populations on the clinical impact of fibrates as an adjunctive strategy with ICI. We evaluated real-world evidence to explore the association of fibrates with survival in patients with non-small cell lung cancer (NSCLC) treated with ICI within the Veterans Health Administration. **Methods:** We conducted a nested cohort study of Veterans diagnosed with NSCLC between 2010 and 2018 who were treated with ICI by utilizing the national VA database. Exposure to fibrates was defined by a filled prescription within 90 days of an ICI infusion. χ^2 tests were used to compare characteristics of Veterans who were exposed versus unexposed to fibrates. Overall survival (OS) rates, measured from start of ICI, were compared. Cox proportional hazard multivariate analysis (MVA) was used to identify factors associated with OS. A sensitivity analysis of Veterans with stage IV NSCLC who received docetaxel without ICI was similarly performed. **Results:** The study cohort included 3,593 Veterans who received ICI with non-exclusive exposures to nivolumab (59.5%), pembrolizumab (35.0%), durvalumab (6.8%), and atezolizumab (3.3%). Their median age was 69, and a plurality had male gender (97.0%), white race (72.8%), Elixhauser comorbidity index 0-4 (28.3%), adenocarcinoma (47.6%), and stage IV disease at diagnosis (40.9%). In this nested cohort, 301 (8.4%) were exposed to fibrate, predominantly gemfibrozil (288 or 95.7% of fibrate group). Veterans receiving fibrates were more likely to be ≥66 years of age, white, male, and married, and to have greater comorbidity burden, and less likely to receive chemotherapy (all p≤0.012). Fibrate exposure was associated with improved OS both on MVA (HR 0.86, 95%CI 0.75-0.99, p=0.042) and in a matched subset (HR 0.75, 95%CI 0.63-0.90, p=0.001) (**see figure**). In contrast, among 968 Veterans with stage IV disease receiving docetaxel, fibrates were not associated with OS on MVA (HR 0.99, 95%CI 0.79-1.25, p=0.962) or in a matched subset (HR 1.02, 95%CI CI 0.75-1.39, p=0.885)



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Conclusion: Fibrates are associated with improved OS among NSCLC patients receiving ICI but not among those receiving cytotoxic chemotherapy. This is the first study to date evaluating PPAR agonists in patients receiving ICI for NSCLC and supports a potential role for fibrates as an adjunct to enhance ICI response.

Keywords: fibrates, Immune checkpoint inhibitors, PPAR agonists

P54.01 Analysis of the Support Needs of Lung Cancer Patients

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Introduction: While survival for most groups of lung cancer patients has been extended through the use of novel agents, patients still experience substantial unmet needs. These needs span many domains, including physical, emotional, financial and others. Supportive care is fundamental for all lung cancer patients, but their unmet needs may differ depending on many factors. CareAcross is a digital multilingual platform which provides personalized, evidence-based support to cancer patients, complementary to their oncology teams. The online patient engagement had demonstrated many needs, which were deemed important to be analyzed further. **Methods:** The ability of the CareAcross platform towards patient-reported outcomes collection was utilized to collect information about patients' needs, their sources of support, and their degree of satisfaction, among others. More specifically, a survey was conducted among the platform's members who are patients with lung, breast, colorectal or prostate cancer; these were predominantly from the in UK, France, Germany, Italy and Spain. The March 2019 survey included questions regarding the areas, sources and perceived effectiveness of support; this data was combined for analysis with other data previously collected from the same patients. **Results:** Among all patients, 95 lung cancer patients responded; almost half (49%) were still on active treatment at the time of data collection. The most common needs expressed included: nutrition (65% vs 68% of those on active treatment), side-effects (50% vs 60%), emotions (34% vs 32%), anxiety for scans and follow-up appointments and tests (30% vs 23%). Those who did not seek nutritional support expressed reduced need to address side-effects (45%) but an increased emotional deficit (42%). Among their sources of support, most patients cited their family and friends (72% vs 72% of those on active treatment); their medical team (42% vs 43%), online support groups (24% vs 33%), other support groups (12% vs 13%), and charities (10% vs 13%). Regarding their satisfaction with the support they received, only 25% reported receiving the full support they were looking for; the needs of 61% were partially met, while 15% felt they were not getting any support. Higher overall satisfaction with support received was reported by those who included family and friends as a source (26%, 63% and 11% for full, partial and none, respectively), and slightly higher by those who included their medical team as a source (28%, 69%, and 3%). **Conclusion:** Supportive care is an important part of integrative lung cancer treatment. Although the number of patients in this analysis is not large, the findings indicate that, regardless of treatment status, most patients require support for nutrition, side-effect management, and emotional wellbeing. Most patients seek support from family and friends, and less than half pursue such support through their medical teams. Compared to online groups, support groups and charities were less sought after, although certain selection bias is expected given the data collection medium. These needs present a substantial opportunity for targeted improvements in supportive care of lung cancer patients, during treatment and beyond.

Keywords: side effects, nutrition, support

P54.02 Palliative Treatment of Tumor Stenoses of the Trachea and Bronchi

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Introduction: Many methods of treatment of tumor stenoses of the trachea and bronchi are known: laser destruction, argonoplasmic coagulation, radiofrequency ablation (RFA) and others. The most effective method is endobronchial RFA, but it also does not prevent restenosis of the trachea and bronchi. When using the RFA method, tumor restenosis occurs in approximately 30% of patients. We have proposed a new combined method of treatment of tumor stenoses in patients with squamous cell lung cancer. The aim of the study was to prevent the occurrence of restenosis in patients, and the task was to improve the quality and life expectancy of patients with IIIB and IV stages of central lung cancer. **Methods:** The proposed method was performed in 15 patients with IIIB stage (11 patients) and IV stage (4 patients) with central squamous cell lung cancer complicated by tumor stenosis . Age of patients from 62 to 78 years. From them: women-4, men-11. Initially, we performed endobronchial RFA of tumor using a fibrobronchoscope, rigid bronchoscope, electrodes and Fotek-150 apparatus. After recanalization of the bronchi in the next step after 2 weeks, we injected 30 mg of cisplatin into the tumor under general anesthesia using a rigid Friedel bronchoscope, fibrobronchoscope, and endobronchial injection sludge. **Results:** We observed our patients for 5 months. None of them developed tumor bronchial restenosis during this period. **Conclusion:** 1) The proposed method is effective in the treatment of tumor stenoses of trachea and bronchi; 2) This method requires further observation and study;

Keywords: lung cancer, radiofrequency ablation, endobronchial treatment, lung cancer,, lung cancer, tumor stenosis bronchi, radiofrequency ablation

P54.03 Bilateral Indwelling Pleural Catheters

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Introduction: Indwelling pleural catheters (IPCs) are established in pleural effusion management. They are evidence based, easy to insert and patient-centred. A PubMed, Medline, Cinahl and Google Scholar search for 'bilateral indwelling pleural catheters' revealed only 2 case reports of bilateral IPCs, all in non-malignant disease. **Methods:** With local Caldicott approval, all patients with bilateral IPCs in Northumbria HealthCare NHS Trust from January 2015 to march 2021 were identified. Basic demographics, clinical presentation, histological diagnoses and outcomes were collected. Quality of life data was collected at the time using the Palliative Care Outcome Scale score. Descriptive statistical methodology was applied. **Results:** 5 patients were identified. 4 (80%) were male and 1 was female. Diagnoses were pancreatic (2), gastric (1), unknown primary (1) and breast cancers (1). All had bilateral therapeutic aspirations, and none had non-expandable lung. All chose IPC for fluid management. All IPCs were sequentially inserted. No complications arose, and 3 patients with GI cancers died with the IPCs in situ (mean time to death after 1st IPC 3.2 months), and did not auto-pleurodese. The patient with breast cancer auto-pleurodesed, and had one drain removed, but the other stayed in until death (length to death from 1st IPC 12.6 months). The patient with the cancer of unknown primary is still alive at the time of wrting. Breathlessness and fatigue all improved significantly at 30 days. All patients had chemotherapy and managed activities of daily living. **Conclusion:** This is a small cohort of patients: bilateral IPCs are tolerated and acceptable. Our centre does not pursue aggressive drainage or talc insertion via the IPC due to local economic and staffing constraints. We encourage other centres to get in touch to share data.

Keywords: indwelling pleural catheter, malignant pleural effusion, lung cancer

P54.04 Detecting Elevated Risk of Diminished Quality of Life Among Lung Cancer Patients by Using Wearable Devices

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Introduction: Survival and outcomes of lung cancer patients have dramatically improved in recent years due to early diagnoses and personalized treatments. Nevertheless, lung cancer patients suffer from long-term health problems that can lead to a reduced quality of life that can negatively impact their prognosis and survival. The aim of this study is to identify patients with elevated risk of diminished quality of life by using objective data obtained from a wearable device. **Methods:** A watch-like wearable device ("Kronowise 3.0", Kronohealth SL, Spain) was placed in the patient´s wrist for a whole week, registering 24h a day, temperature, physical activity, and light exposure. Eligible participants were patients aged >18 years old, diagnosed with non-small cell lung cancer at the Medical Oncology Department at Puerta de Hierro University Hospital in Madrid, with ECOG 0-1. Written informed consent was obtained from all patients prior to initiation of the study. **Results:** A total of 112 patients were included; 28 were diagnosed with localized disease (IA-IIIB), and 84 with advanced stage IIIC/IV receiving different treatments (radiotherapy, chemotherapy, immunotherapy, chemotherapy plus immunotherapy, tyrosine kinase inhibitors) (Table 1). From every monitoring, more than 1.000.000 data records are being analyzed, and more than 130 indicators are obtained by using expert knowledge. Preliminary results suggest that the device detects sleep disorders, inactivity, and other factors that could influence the quality of life. Table 1. Number of patients classified by stage

STAGE	N (112)
LOCALIZED IA/IB IIA/IIB IIIA/IIIB	2 9 17
ADVANCED IIIC IV	7 77

Table 2. Number of patients classified by treatment

STAGE	TREATMENT	N (112)
LOCALIZED	chemotherapy	8
	immunotherapy	4
	chemo-immunotherapy	1
	Follow-up	15
ADVANCED	radiotherapy	1
	chemotherapy	22
	immunotherapy	31
	chemo-immunotherapy	5
	tyrosine-kinase inhibitors	17
	Follow-up	7

Conclusion: Kronowise device may serve as a useful tool to detect elevated risk of diminished quality of life among lung cancer patients. Physical, emotional, and clinical interventions to improve quality of life in this subgroup of patients will be designed according to the results obtained, in order to improve quality of life during and after cancer treatment, increasing patient´s reassessment support care.

Keywords: wearable device, long survivors, quality of life

P54.05 Stereotactic Radiotherapy for Brain Metastases in Patients With Lung Cancer: Cyberknife Experience

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Introduction: It was aimed to evaluate the efficacy, local control and survival in patients with non-small cell lung cancer with brain metastases who underwent stereotactic radiotherapy (SRT) using the Cyberknife-M6 system. **Materials and Methods:** Ethics committee (no 2018-7/6) and scientific research project [OUAP (T) 2019/1] approval were obtained for the study. Patients were fixed with a non-invasive cranial mask. Cranial MRI and CT simulation images were transferred to the planning system and fused. Risky organs were contoured automatically. Resection cavity or gross target volume (GTV) was contoured in contrast-enhanced T1-weighted MRI sections. Planning target volume (PTV) was created with a margin of 2 mm to the cavity and 0-1 mm to the other lesions. For healthy brain tissue (whole brain minus GTV), the cut-off values of V10Gy (<12 cc), V12Gy (<10 cc) for SRS, and V18Gy (<30 cc) for SRT were used. A treatment plan was established to cover 95% of PTV at the prescribed dose. After treatment patients were followed up with cranial MRI every 3 months. **Results:** Between 1 October 2018 and 1 August 2020, 20 cases and 40 metastases were treated. The median age was 61 (46-80). The median number of metastases was 2 (1-5). Surgery was performed in 8 cases. Median tumor/cavity diameter was 10 mm (2-45). A median of 18 Gy / 1 fx (18-20) SRS was applied to 19 lesions, and a median of 25 Gy (24-30) / 5 fx (3-6) SRT was applied to 21 lesions. Planning MRI-SRT interval was median 4 days (1-19). Treatment was completed in a median of 5 days (2-8) for those who underwent fractionated SRT. Median GTV and PTV was found 0.76 cc (0.01-17.9) and 1.16 cc (0.05-26.76), respectively. Median conformity index (CI), near CI and homogeneity index was found 1.09 (1.01-3.14), 1.13 (1.01-3.31) and 1.16 (1.08-11.25), respectively. Prescription isodose covering 95% of PTV was found to be 85.9% (80-92.7%). Risky organ tolerance was not exceeded in any case. For healthy brain tissue, median V10Gy, V12 Gy and V18 Gy values were 3.37 cc (0.44-16.28), 2.36 (0.3- 12.26) and 7.16 cc (2.2-31.78), respectively. The cases were evaluated on March 1, 2021. The median follow-up period was 9 months (1-15), 9 cases died and 11 cases were alive. The median overall survival (OS) after SRT was 13 months (1-25). The objective / stable response rate of 17 cases evaluated in the median 2 months (2-3) was 88% (15/17) and 84% (27/32) for 32 metastases. During the follow-up period, local control was 76% (13/17). Asymptomatic radionecrosis was observed in 4 cases (23%) in a median of 8 months (6-12). **Conclusion:** For limited brain metastasis, upfront SRT applications are standard today instead of WBRT in order to reduce neurocognitive side effects. SRT is an alternative treatment method for patients who are not suitable for surgery and also for postoperative cavity irradiation. In our study, local control was found to be 76% with a median OS of 13 months after SRT. Cyberknife-M6 system was found to be effective and safe.

Keywords: Brain metastases, Stereotactic radiotherapy, efficacy

P54.06 The FITNESS Study: Geriatric Assessment, Treatment Toxicity, and Biospecimen Collection Among Older Adults With Lung Cancer

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Introduction: Older adults with chronic disease prioritize remaining functionally independent. Our primary objective is to describe functional disability and treatment toxicity among older adults with lung cancer. **Methods:** This prospective cohort study included adults aged ≥60 years with any-stage, newly diagnosed non-small cell lung cancer (NSCLC). Study assessments include the Cancer and Aging Research Group cancer-specific Comprehensive Geriatric Assessment (CARG CGA), monthly functional status assessments, a short physical performance battery (SPPB), treatment toxicity, and longitudinal biospecimen collection including blood and gut microbiome (stool). **Results:** 50 patients were enrolled. At baseline, the average age was 71.7 years. 92% were Caucasian, and all were of non-Hispanic ethnicity. Clinical characteristics were stage III/IV (n=45, 90%) and stage I/II (n=5, 10%); 68% had adenocarcinoma subtype, and 24% squamous. First-line treatments were chemotherapy (44 %), immunotherapy (22%), or a combination of chemo-IO (30%); 2 patients received targeted treatments. The median baseline CARG toxicity score was 8 (range 2-12). Among patients with treatment toxicity (n = 49), 39 (79.6%) experienced grade 1-2, while 10 (20.4%) had ≥ grade 3 toxicity. For those with CARG scores ≤7 (lower risk), 13.6% had ≥grade 3 treatment toxicity versus 28.0% with CARG scores ≥8 (higher risk). The median functional disability score was 1 (range 1-13) at baseline indicating no ADL impairment. At 6-months, 23 patients completed assessments. Patients' "no fall" risk decreased/worsened from 55% at baseline to 47% at 6-months. The median SPPB score at baseline was 10 (range 0-12), and was 9 (range 5-12) at 6-months. Lastly, CARG CGA scores, including CARG toxicity, were found to be correlated with microbial biomarkers before the start of treatment, including the relative abundance of Streptococcus (p-value = 0.003, associated with higher CARG scores) and Clostridia (p-value = 0.02, associated with lower CARG scores).

		Carg Score n (%)	
Toxicity Grade		<= 7	8+
	1-2	19 (86.36)	18 (72)
	3-5	3 (13.64)	7 (28)
Correlation with CARG score (gut mWGS relative abundances)		Effect Size	p-value (Negative binomial Wald test)
	Streptococcus salivarus	3.53	0.003
	Clostridia	-0.09	0.01
	Alistipes finegoldii	-2.05	0.03
	Ruminococcus	-0.25	0.04

Conclusion: The CARG toxicity calculator is a potentially valid assessment to predict treatment toxicity among older adults with NSCLC receiving newer treatments and correlates with molecular biomarkers including the gut microbiome. Future research will test for causality in these associations and whether these biomarkers can be modified to alter treatment outcomes.

Keywords: functional status, biomarkers, lung cancer

P55.01 Standard of Care Disparity in a Global Cancer Support Group: Examining an Advocate Survey to Inspire Change.

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Introduction:

Advocates from patient support groups offer valuable insights into perceived standard of care around the world. We investigated the disparities that ALK Positive cancer patients face in 22 countries around the world. **Methods:** We presented patient advocates with a 10 question survey, asking them to provide answers around the quality of care they receive. Advocates were volunteers from the largest patient support group for ALK Positive cancer globally. 51 surveys were analysed and results were arranged by country to show differences in patient care globally and inconsistencies within a country. **Results:** While over half (26) of responders rated their care “Very good” or “Excellent”, twenty answered “OK”, four “Very bad” and 1 “Unacceptable”, highlighting the need for improvements in a mainly European and North American patient group. Nine of the eleven countries with more than one representative had two or more different answers; eight of which contained a rating of “OK” or lower. Advocates deemed the three most important areas for improvement as access to clinical trials, access to targeted therapies and research. Access to Trials and Medication each featured in ten different countries answers. Six advocates from different countries stated they do not believe ALK patients have appropriate access to targeted therapies; three of which were from countries that also gave positive answers. When asked what prevents patients accessing medication, the three largest number of responses were for government funding, drug approval and patient cost. Government funding featured in eleven countries responses, followed by four and five for drug approval and patient cost respectively. Over 85% (41/47) of advocates stated they receive routine scans (CT/MRI/PET) in line with their expectations, but some stated MRI’s were only performed if patients had prior metastases or were symptomatic. The same percentage, 85%, of advocates answered that they do receive NGS testing, in the form of either tissue or liquid biopsy. Nearly 90% of advocates believe their country's oncologists are experienced with ALK Positive cancer. The negative responses for this question were all from different countries, three of which also had positive responses. Conclusion: By exploring our advocates' responses, we discovered areas where standard of care differs both by, and within, countries. Using this information, our advocates know where to focus their efforts to improve care for themselves and others.

Keywords: advocacy, global, patient

P55.02 Robotic Surgery in Canada: Are Patients Willing to Pay Out-of-Pocket?

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Introduction: Robotic-assisted thoracic surgery has been demonstrated to be safe and effective but is associated with high capital and operating costs which are not reimbursed by the Canadian government, limiting patient access to this platform. We hypothesized that Canadian patients who had experienced robotic surgery on research or philanthropic funds would have been willing to contribute payments out-of-pocket to gain access to this technology. **Methods:** This is a retrospective, cross-sectional, observational study within the robotic thoracic surgery population at the highest volume institution for robotic surgery in Canada. All patients who had underwent robotic thoracic surgery from January 2014 to July 2020 were invited to participate by telephone and asked to complete a survey about demographics, degree of satisfaction with robotic thoracic surgery, and willingness to contribute to the cost of their robotic operation in the absence of research funds. Associations were examined by the chi-square test ($p < .05$). **Results:** Of the 547 patients who had underwent robotic-assisted thoracic surgery in this period, 83.19% (459/547) were eligible and 89.54% (411/459) completed the survey. The mean (SD) age at surgery was 65.44 (10.27) years, and 58.64% (241/411) were female. On a scale of 1 (Poor) to 10 (Excellent), 85.89% (353/411) stated that their overall experience with robotic thoracic surgery was 8 or higher. With regards to postoperative experience, 88.81% (365/411) were either satisfied or very satisfied during their hospital admission, while 86.13% (354/411) were either satisfied or very satisfied with their recovery after discharge. Of all the respondents, 70.56% (290/411) stated that, in the absence of research funds, they would have paid the $2,000 supplement to government healthcare coverage in order to have access to robotic thoracic surgery. Factors found to be significantly associated with participants' willingness to pay this supplement were postsecondary education ($p < .001$), an annual income of $60,000 or more at the time of surgery ($p = .034$), private insurance coverage ($p = .011$), an overall experience with robotic thoracic surgery rated as 8 or higher ($p < .001$), and an overall postoperative experience after discharge from the hospital rated as satisfying or very satisfying ($p = .004$). **Conclusion:** The majority of patients at a high-volume center for robotic surgery would have been willing to pay a supplement out-of-pocket to have access to this technology. At a time where patients are being recognized as important stakeholders in healthcare policy, this study provides important insights into the conversation of robotic surgery funding.

Keywords: Robotic-assisted thoracic surgery, willingness to pay, Canada

P55.03 Results of The First Survey Using EORTC QLQ INFO25 on Information Acquisition and Satisfaction of Lung Cancer Patients in Japan

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Introduction: The Japanese Lung Cancer Society published its Lung Cancer Guidebook for Patients (the "Guidebook") in November 2019. Although the provision of information related to diagnosis and treatment by society is considered necessary for patients, no previous reports have scientifically examined the guidebook's usefulness. Although there is a lot of medical information provided by professionals for patients, we thought it was essential from an academic perspective to evaluate whether patients are delighted with this information in a quantified form. Since quantified data would help future revisions of the guidebook, we conducted the first questionnaire survey on satisfaction with medical information in Japan. **Methods:** We conducted a web-based questionnaire to clarify the guidebook's role in obtaining information for lung cancer patients using the EORTC QLQ-INFO 25, an international evaluation method. We calculated EORTC QLQ C30 and INFO25 scores to analyze the satisfaction level with the information patients received about their disease. Readers and non-readers of the guidebook were stratified in the analysis. Patients were asked to participate in this survey through patient associations and the Lung Cancer Society. **Results:** Of 332 patients (110 males and 222 females), 284 (86%) completed the questionnaire. One hundred seventy patients participated in the patient group, and 96 (29%) used the guidebook. The most common age group among the questionnaire respondents was 55-59 years old, which is considered a relatively young population among Japan's lung cancer patients. We asked the source of medical information. The most significant number of patients received notification from the Internet, followed by their doctor, and then from patient groups. The EORTC QLQ C30 scores for readers and non-readers were not statistically different, indicating no bias in the patient background regarding the quality of life between the two groups. This survey results suggested that patients who belonged to patient groups were inclined to get more information about things other than treatment. The OVERHELP score, a measure of satisfaction with medical information, was calculated and compared. We found no statistically significant difference in OVERHELP scores between the two groups of readers and non-readers. Patients who used both the Patient's Association and the Guidebook tended to rate the information as applicable (p=0.04) than those who did not use either the Patient's Association or the Guidebook. While the guidebook we published this time was in paper form, the questionnaire survey was conducted via the Internet. Therefore, a relatively large number of respondents obtained medical information from the Internet. To verify the paper-based guidebook's usefulness, we should include the patients who were not familiar with the Internet in the future. **Conclusion:** This study is the first survey using scientific methods to evaluate information provision and patient satisfaction with an academic society-led initiative. The results show that the use of patient associations and guidebooks helps obtain information and provides a basis for discussing information provision to patients with lung cancer in the future.

Keywords: EORTC QLQ-INFO 25, Patient guidebook, Information with information

P56.01 Semiquantitative Assessment of Tumor Spread Through Air Spaces in a Historic Cohort of Lung Adenocarcinomas Following Open Surgical Resection

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Introduction: “Aerogenous” spread of lung cancer has been noted since 1980. The equivalent "spread through air spaces (STAS)" was introduced in the 2015 World Health Organization (WHO) Classification of Lung Tumors as a new concept of invasion. Previous studies have shown that STAS occurred in 34-51.4% of resected lung tumors (across all stages) and is associated with poor outcomes. However, some evidence suggests that STAS represents ex vivo artifact. For example, retrieval of the specimen through a small port during video-assisted thoracic surgery (VATS) could detach tumor cell clusters via mechanical force. This study examines the STAS status of lung cancer before VATS was widely used. **Methods:** Invasive lung adenocarcinomas surgically resected via thoracotomy at our institution between 1990 and 1992 were analyzed semi-quantitatively as "no STAS", "low STAS" (1–4 single cells or clusters), or "high STAS" (≥5 single cells or clusters) on hematoxylin and eosin stained slides. The distance between the farthest STAS focus lying within the alveolar space and the edge of the main tumor (Maximal Spread Distance, MSD) was measured. We excluded cases with multiple foci of tumor, preoperative radiation and/or chemotherapy, positive surgical margins, or distant metastasis from the study population. Stage-matched invasive lung adenocarcinomas resected by VATS in 2020 were retrieved with the same criteria and compared. A chi-squared test or Fisher's exact test was performed on Prism 5 (GraphPad) to determine the impact of clinicopathologic parameters on STAS. P values were considered statistically significant at less than 0.05. **Results:** Between 1990 and 1992, 56 lung resections met criteria for inclusion. The mean age of the study cohort was 64.4 years (range 37–83), and 51.8% were male. Thirty-two cases (57.1%) underwent lobectomy, 21 cases (37.5%) sublobar resection, 3 cases (5.4%) pneumonectomy. The mean size of tumor was 3.0 cm (range 0.8 - 10 cm). Among the histologic subtypes, 23 cases (41.1%) were acinar predominant, followed by solid (26.8%), papillary (21.4%), micropapillary (8.9%) and lepidic (1.8%) subtypes. Of these, we found STAS present in 42/56 cases (75%) and no STAS in the remaining 14 cases (25%). In the group with STAS, 10 cases (17.9%) had low STAS and 32 cases (57.1%) had high STAS. The MSD was greater than 0.5 cm in 35 cases (83.3% of STAS cases). There were no statistically significant associations between STAS and gender, age, operation, predominant subtypes of adenocarcinoma, tumor size, pleural invasion, lymphovascular invasion, or tumor stage. In comparison, STAS was identified in 54 of 88 cases resected in 2020 (61.4%). The incidence of STAS was higher in 1990-92 than in 2020 (P= 0.045). **Conclusion:** The lower rates of STAS in contemporary cohorts may reflect shifts in lung cancer biology and disease management over the last 30 years. These findings suggest that VATS does not contribute significantly to generation of artifactual tumor STAS.

Keywords: spread through air spaces, thoracotomy, video-assisted thoracic surgery

P56.02 Novel Low Malignant Potential/Vascular Invasive (LMPVI) Grade is Superior to WHO 2015 and IASLC 2020 Adenocarcinoma Grade

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Introduction: Approximately 15% of stage I lung adenocarcinomas will recur despite adequate surgical therapy. There is currently no agreed upon prognostic marker of recurrence to predict who might benefit from post-surgical adjuvant therapy. **Methods:** Tumor slides from AJCC 8th edition stage I/0 lung adenocarcinomas from two hospitals were reviewed and divided into training (safety-net hospital, n=227) and validation (suburban hospital, n=290) cohorts. Based upon published criteria, low malignant potential adenocarcinoma (LMP), WHO-2015 and IASLC-2020 grades were assigned. Univariate/multivariate analysis was performed to determine pathologic features associated with recurrence free (RFS), disease specific (DSS), and overall survival (OS) in the training cohort and outcomes were compared with the validation cohort. **Results:** Excluding AIS/MIA/LMP from the training cohort, univariate followed by multivariate analysis revealed vascular invasion (VI) alone was significant in all three measured outcomes (RFS: HR=3.77, p=0.001; DSS: HR=5.62, p=0.003; OS: HR=1.80, p=0.014). A grading system was devised (LMPVI) combining AIS/MIA/LMP as G1, VI as G3, and non-AIS/MIA/LMP/VI as G2. Outcomes at 7-years were similar in both the training and validation cohorts (Figure 1A/B) with 100% DSS and 83-85% OS for G1; 90-96% RFS/DSS and 70-71% OS for G2; and 62-65% RFS, 72-76% DSS, and 48-53% OS for G3. LMPVI-G3 predicted the highest rate of recurrence and maximal separation from G2 compared to either the WHO-2015 (Figure 1C) or IASLC-2020 (Figure 1D) grade. 7-year RFS estimates for LMPVI-G3 stratified by invasive tumor size (Figure 2) were 80% if ≤1 cm, 67% if >1 but ≤2 cm, and 43% if >2 cm (p=0.049). LMPVI-G3 >1 cm and >2 cm invasive size adenocarcinoma comprised 23% and 7% of the combined cohorts, respectively. **Conclusion:** LMPVI was superior to WHO-2015 and IASLC-2020 grades at predicting recurrence. Prospective adjuvant therapy trials should be considered for patients with stage I LMPVI-G3 adenocarcinoma >1 cm invasive size.

Keywords: adenocarcinoma, Pathology, grade

P56.03 Prognostic Value of Tumor Spread Through Air Spaces in Patients With Lung Adenocarcinoma after Radical Surgery

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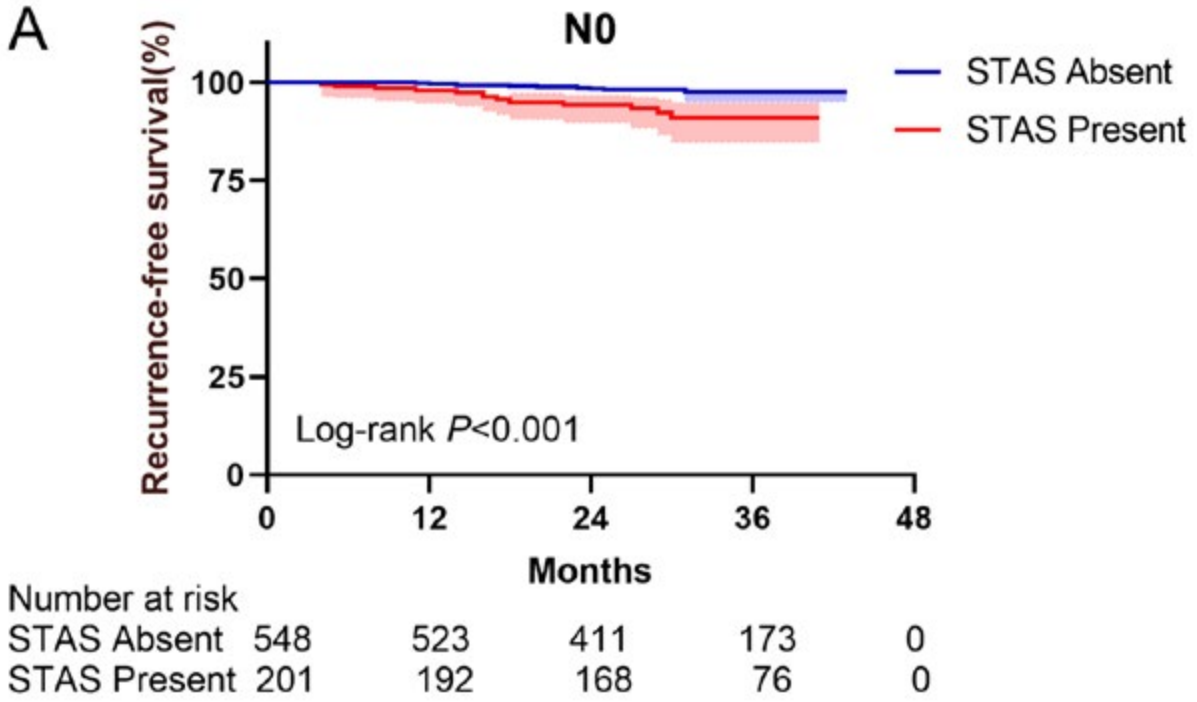
Introduction: Tumor spread through air spaces (STAS) has been identified as an invasive pattern in lung adenocarcinoma (ADC), but the correlations between clinicopathologic features and STAS and the prognostic value of STAS have not been well studied in all stages of ADC with a lager sample size. The purpose of this study was to investigate these correlations and evaluate the prognostic value of STAS in patients with ADC after radical surgery. **Methods:** 988 patients with completely resected lung adenocarcinomas were reviewed. Recurrence-free survival (RFS) was defined as the time between the date of surgery to the date of disease recurrence or the last follow-up. Pearson's chi-square test or Fisher exact test was used for comparing the relationship between STAS and clinicopathological features. The log-rank test was used to identify potential prognostic factors and multivariate Cox regression models were used to explore independent prognostic factors. **Results:** Of the 988 patients, STAS was found in 328 (33.2%) patients. STAS was significantly frequent in patients with ever smoking (P=0.049), micropapillary-predominant (MPA) and solid-predominant adenocarcinoma (SPA) (P<0.001), N1-3 diseases (P<0.001), stage II-III (P<0.001), the presence of VPI (P<0.001), the presence of LVI (P<0.001) and the presence of NI (P<0.001). Univariate analysis revealed that patients with the presence of STAS had a significantly worse RFS in patients with stage I(P=0.002), N0 diseases (P<0.001) and intermediate grade lung adenocarcinoma (Acinar-Predominant Adenocarcinoma; APA/ Papillary-Predominant Adenocarcinoma; PPA/Invasive Mucinous Adenocarcinoma; IMA) (P<0.001), but not in patients with stage II-III(P=0.96), N1-3 disease (P=0.90) and high grade lung adenocarcinoma (MPA/SPA) (P=0.35). Multivariate analysis demonstrated that STAS was an independent prognostic factor for RFS in patients with stage I(P=0.018) and N0 diseases (P=0.011). Specially, STAS had independent prognostic significance for RFS in patients with intermediate grade lung adenocarcinoma (APA/PPA/IMA) of N0 diseases (P=0.009). Moreover, STAS status was a significantly prognostic factor for RFS in patients of N0 diseases after lobectomy (P=0.004) and sublobar resection (P=0.03) in univariate analysis. Multivariate analysis found that STAS status remained an independent predictor for RFS in patients of N0 diseases after lobectomy (P=0.008), but not in patients after sublobar resection (P=0.062).



Conclusion: The presence of STAS is a significant risk factor for recurrence in N0 and stage IADC patients. Moreover, it will significantly increase the risk of recurrence for patients with intermediate grade lung adenocarcinoma of N0 diseases. The presence of STAS is a high risk factor for recurrence in N0 patients after lobectomy or sublobar resection.

Keywords: prognostic factors, Lung adenocarcinoma, tumor spread through air spaces

P56.04 Pathological Features & Prognosis of NSCLC Patients With Enteric Adenocarcinomas Without Expression of TTF-1 and Napsin A

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Introduction: Enteric differentiation can occur in lung adenocarcinoma, and when this component exceeds 50%, the tumor is classified as pulmonary adenocarcinoma with enteric differentiation (PAED). The enteric pattern of enteric lung adenocarcinoma shares morphologic and immunohistochemical features with colorectal adenocarcinoma and it consists of glandular and/or papillary structures sometimes with a cribriform pattern, lined by tumor cells that are mostly tall-columnar with nuclear pseudostratification, luminal necrosis, and prominent nuclear debris. Poorly differentiated tumors may have a more solid pattern. These tumors show at least one immunohistologic marker of enteric differentiation (CDX-2, CK20 or MUC2). Enteric adenocarcinoma is a rare histologic type of primary lung adenocarcinoma. Detailed clinical, pathological and molecular features about these subgroup of patients is lacking, particularly if TTF-1 and Napsin A aren´t expressed. **Methods:** NSCLC patients who were diagnosed from January 2018 until March 2021 were identified by review of the patient records. Only lung adenocarcinoma patients whose tumors didn`t express either TTF-1 or Napsin A, but were positive for either CDX-2, CK20 or MUC2 were included in the data analysis. Primary tumor of the gastrointestinal tract was excluded either by PET-CT and/or CT and endoscopy (gastroscopy, colonoscopy, and rectoscopy). **Results:** A total of fourteen (eight male (57,1%) and six female (42,9%) patients were identified in the patients` records. On average, the patients were 67 years old, the median age was 68. The youngest patient was 54 and the oldest one was 83 years old. Three patients were diagnosed at local stages (I-III), eleven patients had metastatic disease (stage IV). Four of these eleven patients had a mutation of the KRAS gene, which corresponds to 37%. This percentage is higher than the average frequency of mutations in the KRAS gene in pulmonary adenocarcinomas (25%). Half of the patients had a tumors with protein expression of PD-L1 (50%). Four patients of the complete cohort underwent surgical resection of the primary tumor and five patients received radiotherapy. Every patient, who got radiotherapy, suffered from stage IV. Three patients received irradiation of brain metastasis and two of bone metastasis. A systemic therapy was administered to nine patients. Seven patients had a combined chemo-/ immuntherapy as firstline treatment (either cisplatin, pemetrexed, and pembrolizumab or carboplatin, nab-paclitaxel, and atezolizumab) and one got only a combination chemotherapy (carboplatin and nab-paclitaxel). Median disease-free survival was eight, median progression-free survival was four months. Median overall survival could not be calculated. However, six and twelve months survival rates were 35.8 and 25.0 %, respectively. **Conclusion:** This is the far largest reported series of PAED patients without any expression of TTF1- or Napsin A. It seems that this subgroup of pulmonary adenocarcinoma patients has a poorer prognosis compared to other patients with lung adenocarcinomas.

Keywords: "non-small-cell lung cancer", "enteric adenocarcinoma", "TTF-1/Napsin-A negativity"

P56.05 Detection Rate and Prognosis of Nodal-Micro Metastasis by IHC in pN0 Resectable Non-Small Cell Lung Cancer

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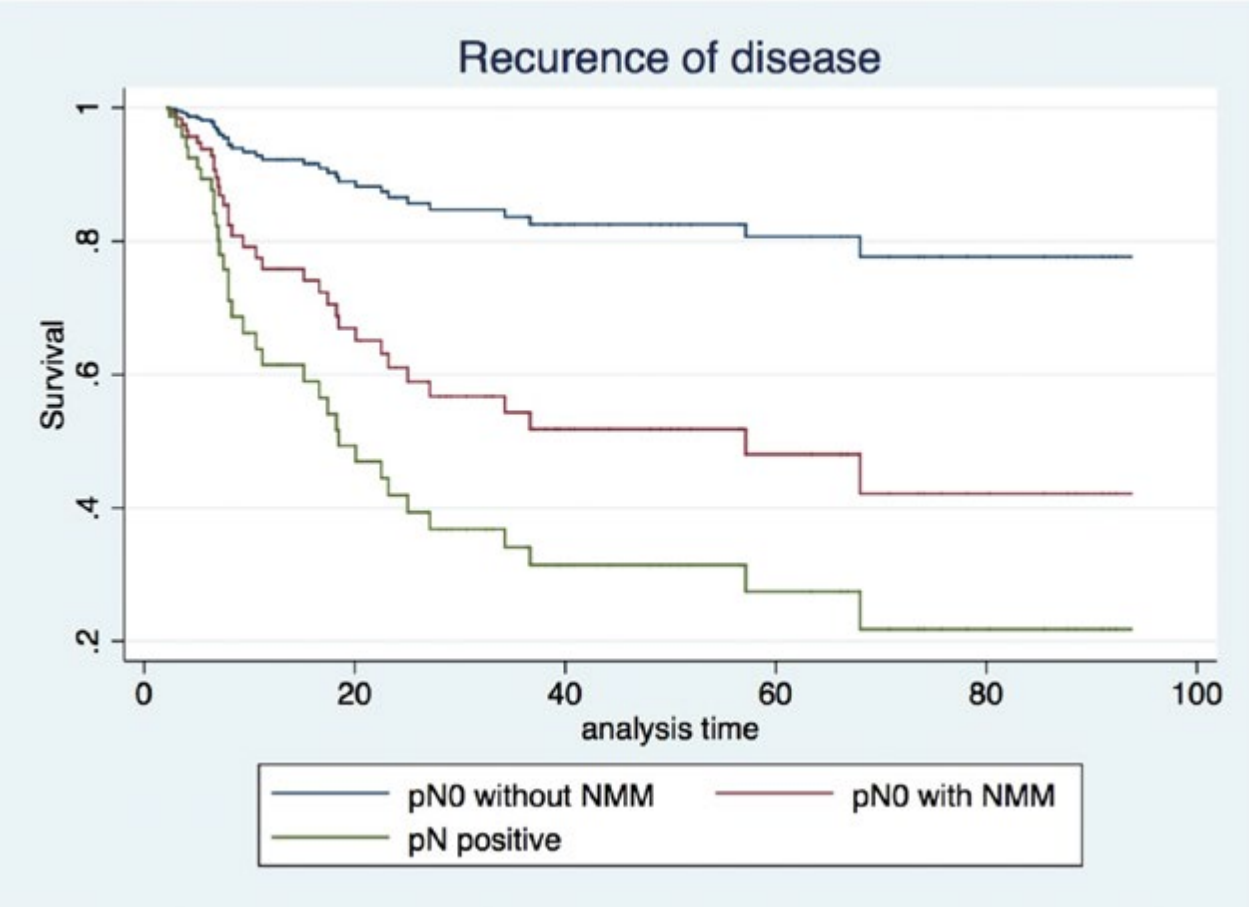
Introduction: The aim of this study is to evaluate impact of detection of nodal-micro metastasis (NMM) by special IHC on pathological nodal upstaging and prognosis in pathological N0 resectable NSCLC. **Methods:** NSCLC patients who underwent curative pulmonary resection without any induction therapy in Maharaj Nakorn Chiangmai Hospital between January 2012 to December 2018 were retrospectively reviewed. In pathological N0 patients, IHC cytokeratin AE1/AE3, p53 and BerEp4 were used to stain LN slide to detect NMM. After IHC staining, patients were divided into three groups, pN0 group, pN0 with NMM group and pN positive group. Primary endpoint was the percentage of nodal upstaging among pN0 patients and secondary endpoint was disease-free survival and overall survival. **Results:** There were 225 patients included in this study; 98 patients with pN0 and 127 patients with pN positive. Among pN0 patients, NMM was found in 20 of 98 patients (20.41%); 3(3.06%) in hilar and interlobar regions, 15 (15.30%) in mediastinal region and 2(2.04%) in both hilar and mediastinal regions. In multivariable analysis, tumor size more than 4 centimeters only one factor reached statistically significant difference (risk ratio = 11.87, 95% CI=2.75-51.15, p=0.001). Tumor recurrence was found in 21 patients (26.92 %) in non-NMM group, 10 patients (50%) in MNM group and 89 patients (70.08%) in N positive group (p< 0.001).In multivariable analysis, the hazard ratio (HR) of tumor recurrence in NMM group was 3.42 (95 %CI = 1.10-10.64, p=0.034) and in N positive group was 6.03 (95 %CI = 1.73-20.97, p=0.005). However, overall survival in NMM group was not different from pN0 without NMM (HR =1.12 (95%CI=0.09-13.90)

Table: Number of patient and % of pathological upstaging

	Conventional H&E stain		Special IHC staining		% of Pathological upstaging
	LN Negative	LN Positive	LN Negative	LN Positive	
N1	98	0	93	5	5.1
N2	98	0	81	17	17.35
N1+N2	98	0	78	20	20.41



Conclusion: Nodal-micro metastasis was identified in 20.41% of pN0 resectable NSCLC patients. Tumor size was associated with NMM. Patients with NMM have more tumor recurrence than those without NMM.

Keywords: Nodal-micro metastasis, BerEP4, AE1/AE3,p53, resectable NSCLC

P56.06 Clinical Significance and Potential Function of S100A10 in Lung Adenocarcinoma

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Introduction: To investigate the clinical significance and potential function of S100A10 in lung adenocarcinoma. **Methods:** The RNA-seq data of lung adenocarcinoma tissues and normal lung tissues in The Cancer Genome Atlas (TCGA) database and Genotype-Tissue Expression (GTEx) project were obtained from the UCSC Xena. The correlation between S100A10 expression and clinicopathological features in patients with lung adenocarcinoma was analyzed. The Metascape database was used for Gene Ontology (GO) enrichment analysis of S100A10-related genes. Another 32 pairs of lung adenocarcinoma and matched lung tissues were selected to verify the expression of S100A10 protein by immunohistochemistry. **Results:** The expression of S100A10 in lung adenocarcinoma tissues was significantly higher than that in normal lung tissues on RNA ($P<0.001$) and protein ($P=0.009$) levels, and the RNA expression level in lung adenocarcinoma tissues was significantly correlated with tumor stage ($P=0.004$), lymph node metastasis ($P=0.0002$), overall survival ($P=0.002$) and disease-free survival ($P=0.011$). GO enrichment analysis showed that S100A10 related genes were significantly enriched in terms of cell adhesion, suggesting that S100A10 may be mainly involved in the process of cell adhesion in lung adenocarcinoma. **Conclusion:** S100A10 is highly expressed in lung adenocarcinoma and is significantly correlated with some clinicopathological features, overall survival (OS) and disease-free survival (DFS) by Kaplan–Meier (KM) analysis, indicating a potential biomarker for diagnosis and prognosis for lung adenocarcinoma.

Keywords: Lung adenocarcinoma, S100A10, TCGA

P57.01 Immunotherapy Fits Everyone? Prognostic Markers for Immune-checkpoint-Inhibitor (ICI) in Non-small Cell Lung Cancer (NSCLC)

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Introduction: Treatment with ICIs has revolutionized cancer treatment over the past few years. ICIs, namely antibodies directed against PD-1 or PD-L1, were approved for the 2nd or subsequent line treatment of metastatic NSCLC without treatable driver mutations and for the 1st line setting, either alone or in combination with chemotherapy. Not all patients will experience favorable response to treatment with ICI. Thereby, prognostic and predictive markers, are of utmost importance for the physician to really know whether the ICI will be beneficial for the patient or not. The purpose of this analysis is to present real world data of prognostic and predictive markers for ICIs therapy in a population of NSCLC patients treated in a Community Hospital. **Methods:** A descriptive retrospective analysis of 89 consecutive patients with advanced NSCLC treated between February 2016 and December 2020 with anti-PD-1 checkpoint inhibitors, was performed. Survival outcomes (Overall survival and Progression free survival – OS and PFS) were determined, as well as the impact on survival of the following factors: male gender, ECOG PS, use of steroids or antibiotics, body mass index (BMI) and weight change, liver and pleural metastases, lactate dehydrogenase (LDH) levels, KRAS mutation and expression of PD-L1. **Results:** A total of 89 patients were studied. The median age was 72 (range 43-87), 71,9% were male (n=64). At diagnosis, 76 (85,4%) had stage IV disease, 31 (34,8%) had pleural metastases and 11 (12,4%) had liver metastases. More than half of the patients had a non-squamous carcinoma (66,3%). Sixteen, 37 and 36 patients received ICI in first, second, and third or later lines, respectively. Median OS was 27 months (C.I. 95% 17.2-36.8). This outcome was significantly inferior in pts with: high LDH levels (log-rank p=0,03; 17.0 months C.I. 95% 11.5-22.5 vs 32.0 months C.I. 95% 13.8-50.2); liver metastases (log-rank p=0.003; 14 months CI. 95% 7.5-20.5 vs 32 months CI. 95% 24.3-39.7); and pleural metastases (log-rank p=0.021; 20 months CI. 95% 13.6-26.4 vs 38 months CI. 95% 17.8-58.2). No relationship was found between male gender, ECOG PS, BMI and weight change, use of steroids or antibiotics, KRAS mutation and expression of PD-L1 with OS. Median PFS was 4 months (C.I. 95% 1.0-6.9). In patients with high LDH levels (log-rank p=0,019; 2.0 months C.I. 95% 1.1-2.9 vs 8.0 months C.I. 95% 2.8-13.2); and weight loss of more than 5% (log-rank p=0.006; 1 months C.I. 95% 0.0-2.2 vs 8 months C.I. 95% 3.1-12.9) PFS was significantly inferior; No relationship was found between KRAS mutation and PD-L1 expression with PFS. **Conclusion:** The data we present shows an heterogeneous population in real world settings and demonstrates the importance of high LDH levels, liver or pleural metastases as prognostic features associated with poor OS. In our population no relationship was found between PD-L1 expression and OS or PFS. It is important to mention, however, that not all patients with PD-L1>= 50% underwent ICI treatment in first line. Despite this, we can conclude that ICI was effective, even in later lines.

Keywords: immune-checkpoint-inhibitor, prognostic markers, non-small cell lung cancer

P57.02 Integration of Systemic / Tumor PD-L1 as a Predictive Biomarker of Clinical Outcome in Advanced NSCLC Patients Treated With Anti-PD-(L)1 Agents

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Introduction: Tumor PD-L1 expression is a predictive biomarker for NSCLC patients (pts) receiving anti-PD-(L)1 agents. However, clinical benefit has been observed regardless of tumor PD-L1 expression, suggesting the existence of other PD-L1 sources. The aim of our study was to analyze whether integrating systemic and tumor PD-L1 is more predictive of outcome in advanced NSCLC pts receiving PD-(L)1 blockade agents. **Methods:** Pretreatment blood samples were collected to evaluate PD-L1 levels on circulating immune cells, platelets (PLTs), platelet microparticles (PMPs) and plasmatic concentrations of soluble PD-L1 (sPD-L1). Tumor PD-L1 status was assessed by immunohistochemistry. The percentages of circulating PD-L1+ leukocytes, PLTs, sPD-L1 levels and tumor PD-L1 expression were correlated with clinical outcome. **Results:** 29 healthy donors and 119 advanced NSCLC pts treated with anti-PD-(L)1 were prospectively included. Median follow-up: 10.97 months [IQR: 6.06-21.87]. Median age of NSCLC patients was 65 (36-84), 78.1% were male and the most common histology was non-squamous (61.3%). Tumor PD-L1 expression (IHC 22C3 pharmDx) : <1% 30 pts (25.2%), 1-49% 35 (29.4%), ≥50% 37 (31.1%), not evaluable 17 (14.3%). PD-(L)1 inhibitors were given in 1st line in 37 pts (31.1%) and in ≥2nd line in 82 (68.9%), and given as monotherapy in 104 pts (87.4%), combination with chemotherapy in 11 pts (9.2%), or with other immunotherapy in 4 pts (3.4%) pts. Significantly longer progression free survival was observed in pts with higher percentage of PD-L1+ CD14+, PD-L1+ neutrophils, PD-L1+ PLTs and PD-L1+ PMPs and significantly longer overall survival was observed in pts with higher percentages of PD-L1+ CD14+ and high tumor PD-L1 expression (Table 1). Higher levels of integrated PD-L1 data of circulating and tumor PD-L1 results significantly stratified patients according to efficacy of PD-(L1) blockade agents (PFS: HR 0.29; 95% CI: 0.16-0.54, p<0.0001; OS: HR 0.28; 95% CI: 0.14-0.54, p=0.0002), even when tumor PD-L1 expression was excluded. Table 1

	PFS			**OS**		
Variables	HR	95% CI	P	HR	95% CI	P
% PD-L1+ CD4+	0.76	0.44-1.32	0.33	0.79	0.45-1.39	0.42
% PD-L1+ CD8+	0.69	0.41-1.16	0.16	0.81	0.47 – 1.39	0.45
% PD-L1+ NK	1.17	0.69-1.99	0.55	1.1	0.63 – 1.9	0.72
% PD-L1+ CD14+	0.36	0.22-0.58	<0.001	0.58	0.37- 0.93	0.02
% PD-L1+ Neutrophils	0.51	0.32-0.8	<0.01	0.68	0.43–1.07	0.09
% PD-L1+ PLTs	0.48	0.26-0.88	0.02	0.97	0.51-1.96	0.93
% PD-L1+ PMPs	0.49	0.28-0.87	0.02	0.57	0.29-1.1	0.09
pg/ml sPD-L1	1.26	0.81-1.97	0.29	1.24	0.78-1.97	0.34
% TPS ≥50% vs <1% ≥50% vs 1-49%	0.65 0.61	0.36-1.18 0.32 - 1.15	0.23 0.23	0.47 0.59	0.24-0.91 0.31-1.12	0.02 0.02

Conclusion: Our results suggest that the integration of circulating PD-L1+ leukocytes, PLT, PMPs and sPD-L1 and tumor PD-L1 expression could be helpful to decide the best treatment strategy in advanced NSCLC pts candidates for anti-PD-(L)1 agents.

Keywords: immunotherapy, Biomarker, NSCLC

P57.03 Cellular Engagement and Interaction in the Tumor Microenvironment (TME) Predicts Response to ICI in Metastatic NSCLC

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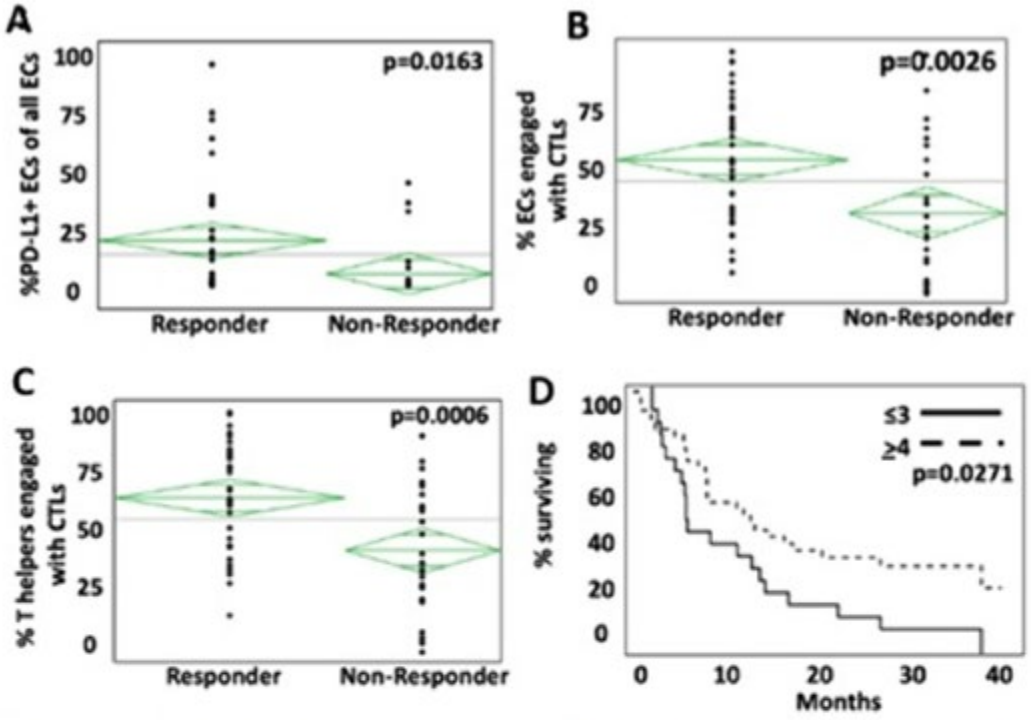
Introduction: Immune checkpoint inhibitors (ICI), monoclonal antibodies against PD-1/PD-L1, have improved the survival of patients with metastatic non-small cell lung cancer (mNSCLC). Tumor expression of PD-L1 is currently the only approved biomarker for ICI selection. It does not describe the complex interaction between immune cells and tumor cells in the tumor microenvironment (TME) and is an imperfect biomarker. We used multiplex fluorescent immunohistochemistry (mfIHC) to mathematically model the TME to determine the impact of cellular distribution and engagement on response to ICI in mNSCLC. **Methods:** Pretreatment whole tissue from patients with mNSCLC who received ICI were subjected to mfIHC. Primary antibodies against CD3, CD8, CD163, PD-L1, pancytokeratin, and FOXP3 were used and simple and complex phenotyping as well as spatial analyses was performed using InForm software. Helper T lymphocytes (HTL) were identified as $CD3^+CD8^-$, cytotoxic T lymphocytes (CTL) as $CD3^+CD8^+$, antigen presenting cells (APC) as $CD163^+$, and tumor cells (EC) as pancytokeratin positive. PD-L1 was measured on both ECs and APCs. The nearest neighbor distance and cell-to-cell engagement was also calculated. Statistical analyses were performed using JMP 14 software. **Results:** 68 samples from 65 patients with mNSCLC were used. Patients were 39-79 years old (median 67); 42% were male and 77% had adenocarcinoma histology. Biopsies were obtained from the primary site (64%), metastatic LN (20%), and a distant metastatic site (16%). The most common ICI was atezolizumab (47%) which was primarily given in the 2^{nd} line setting (38%). 43% of patients were non-responders (progression of disease (PD) as the best response) while 57% were responders (no PD) to ICI. The percentage of PDL1+ EC was significantly higher in responders compared to non-responders (p=0.0163, Figure A). CTL engagement with EC and CTL engagement with HTL was significantly higher in responders versus non-responders (p=0.0026 and p=0.0006, respectively, Figures B and C). The combination of these 3 characteristics yielded the best sensitivity and specificity to predict lack of response to ICI and was associated with OS (p=0.0271, Figure D).



Figures A, B, C: The percentage of PD-L1⁺ EC, ECs engaged with CTLs, and HTLs engaged with CTLs was significantly higher in responders compared to non-responders (A, B, C, respectively).

Figure D: The three characteristics (PD-L1⁺ EC, EC engagement with CTL, and HTL engagement with CTL) were treated as a continuum and were divided into quartiles and assigned points (0-3). The score 0 was defined as the lowest quartile (ie, lowest PD-L1 expression or cellular engagement). Patients with scores ≤3 had a significantly lower OS compared to patients with scores ≥4.

Conclusion: The combination of CTL engagement with EC and HTL along with increased expression of EC PD-L1, which represents enhanced endogenous immune reactivity, more accurately differentiated non-responders to ICI compared to EC PD-L1 alone (AUC 0.72 versus 0.55) and captures the importance of cellular interactions in the TME. We will plan to validate our prognostic score in patients treated with frontline ICI and chemo-ICI.

Keywords: multiplex fluorescent immunohistochemistry, immunotherapy, tumor microenvironment

P57.04 Predicting Treatment Response to 1st- line Pembrolizumab in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients with High PDL1 Expression

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Introduction: Combination of pembrolizumab and chemotherapy has shown improved survival in advanced NSCLC compared to chemotherapy alone. However, the overall response rate has only increased from 45% to 60% by adding chemotherapy to pembrolizumab alone for patients with high PDL1 expression (PD-L1 ≥50%). Currently no biomarker or clinicopathological features can be used to identify the subgroup with tumors PD-L1 ≥ 50% who would respond well to pembrolizumab alone in the 1st-line setting. We hypothesize a machine learning model trained on pre-treatment CT image radiomic features can be used as a digital biomarker to select the aforementioned subgroup, thereby reducing chemotherapy related toxicity and mitigating health care expenditure. **Methods:** We retrospectively identified stage III/IV NSCLC patients who received 1st-line single pembrolizumab at British Columbia Cancer (Vancouver, Canada), with PDL1 ≥50% and all had baseline staging CT within 6 weeks prior to starting immunotherapy and the 1st follow-up (FU) CT within 12 weeks after treatment initiation. The baseline and 1st follow-up CTs were reviewed by two oncological radiologists to identified the lung tumors on the baseline CT images and assess tumor response (i.e., partial response, PR vs progressive disease, PD) using RECIST 1.1 criteria. Utilizing an in-house CT Otsu based thresholding segmentation program and radiomic feature extraction pipeline, we identified potentially discriminating features from CT lung tumor images. We performed sequential forward feature selection to identify the 10 most highly classifying features from discrete shape, texture, and intensity radiomic features generated for 3 distinct tumor segmentation masks (lesion core, core with perimeter transition pixels, and the ring of parenchymal tissue surrounding the lesion). In this study, we leveraged an 8-Xfold validation Linear Discriminate Analysis (LDA), a simple machine learning method trained on these 10 features, to discriminate tumor response to 1st-line pembrolizumab as evaluated at FU CT scans. **Results:** Sixty-eight patients were included (44% male, 73±6 yrs, 52ES/12CS/4NS; pack years: 43±18; ECOG range: 0-3). Twenty-eight showed response to the 1st-line pembrolizumab and forty had progressive disease. We identified eighty-four lung tumors in these patients which we extracted radiomic features from the five central slices, providing us with a pseudo-volumetric CT image training and test set (N=380). ROC analysis of the LDA model resulted in an accuracy of 79.4% [SN: 0.882, SP: 0.684] (AUC: 0.79) for our patient dataset. Given our class label imbalance, we performed precision-recall (PPV vs Sensitivity) analysis to identify sources of class bias (AUC vs No-skill AUC: 0.80 vs 0.59). **Conclusion:** Our data showed that a rudimentary and interpretable machine learning method can lead to appropriate treatment paths for advanced stage lung cancers. A combination of all mask features performed well on this task with a majority of the features selected being texture and intensity features from the core plus edge transitionary boundary pixels. Future analysis will be conducted using other machine learning methods to validate these findings, while keeping the LDA as the primary analysis method.

Keywords: immunotherapy, radiomics, CT

P57.05 Low Variant Allele Frequency of TP53 as a Biomarker for PD-1/PD-L1 Inhibitors in Lung Adenocarcinoma

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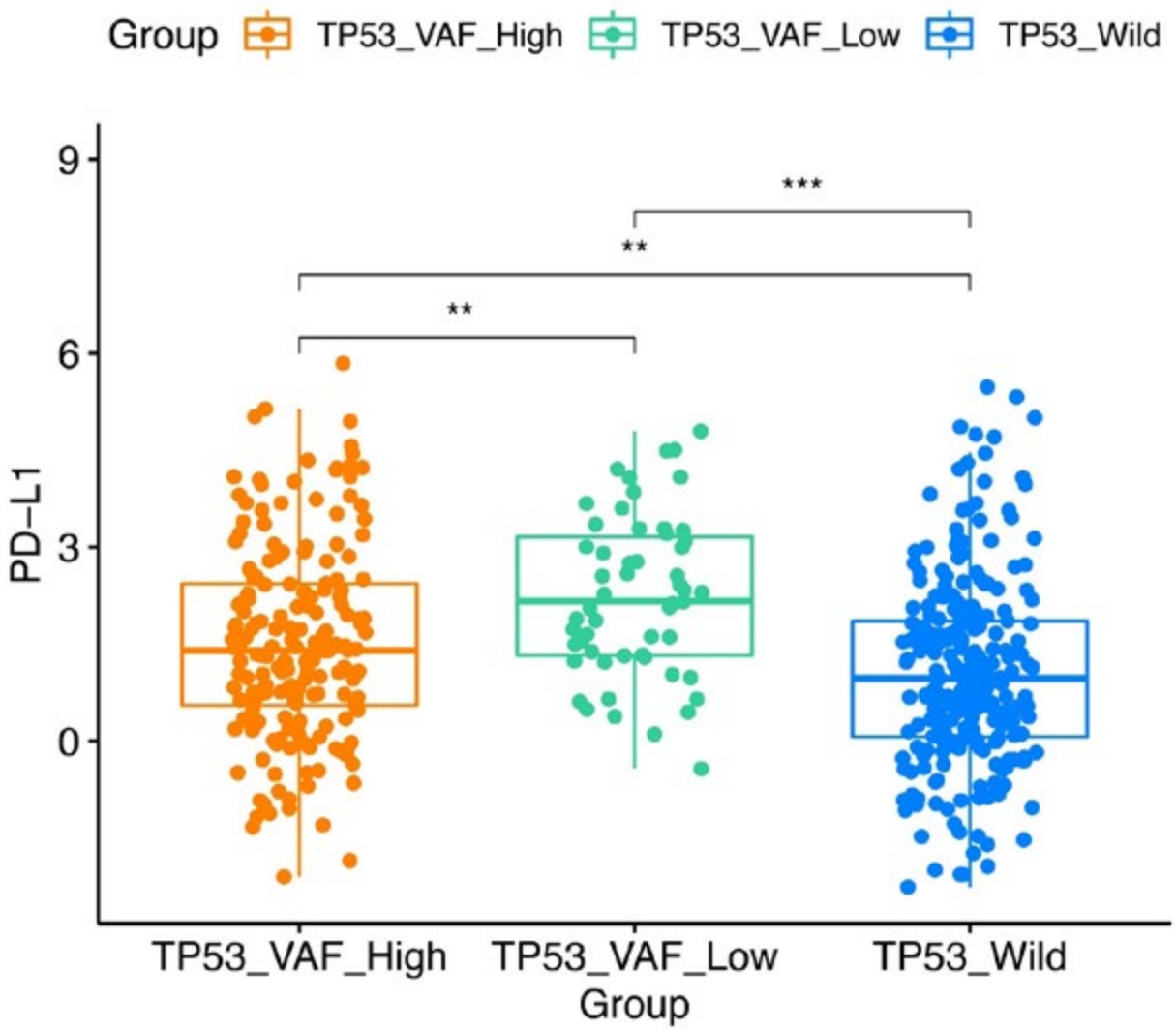
Introduction: Genomic alterations in TP53 have been proven to be correlated with the efficacy of immune checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC). NSCLC patients with TP53 mutations experienced higher objective response rate (ORR) and longer overall survival (OS) when receiving programmed death-1 (PD-1) inhibitors. However, the relationship between variant allele frequency (VAF) of TP53 and ICI efficacy is still unknown. **Methods:** An integrated analysis of clinical, genomic and transcriptomic data of lung adenocarcinoma (LUAD) patients from public database was conducted to explore the influence of TP53 VAF in tumor immune microenvironment and clinical outcomes of LUAD patients treated with ICIs. Single-sample GSEA (GSVA) was used to calculate the score for enrichment of gene sets relating to immune microenvironment. Association between TP53 VAF and progression-free survival (PFS) of PD-1/PD-L1 treatment were analyzed by Kaplan-Meier analysis and univariate Cox proportional hazards regression analysis. **Results:** A total of 469 LUAD patients from TCGA database were included as discovery cohort and 159 LUAD patients from MSK cohort were included as validation cohort. When using 25% as the cut-off of TP53 VAF, among 469 patients, 236 were wild-type TP53, 55 were low TP53 VAF and the other 178 were high TP53 VAF. The median PD-L1 (CD274) expression of patients with low TP53 VAF was significantly higher than that of patients with high TP53 VAF (FPKM: 4.46 vs 2.64, p = 0.0018) and wild-type TP53 (FPKM: 4.46 vs 1.96, p <0.0001). Low TP53 VAF group demonstrated enriched CD8+ T cell and Treg cell, comparing with high TP53 VAF group and wild-type group. There's no significant difference in enrichment of CD8+ T cell and Treg cell between high TP53 VAF group and wild-type group. Among 159 patients treated with PD-1/PD-L1 monotherapy, 73 were wild-type TP53, 36 were low TP53 VAF and the other 50 were high TP53 VAF. The median PFS of patients with low TP53 VAF was significantly longer than that of patients with high TP53 VAF (5.43m vs 3.30m; HR, 0.53; 95%CI, 0.32-0.89; p = 0.0158) and wild-type TP53 (5.43m vs 2.47m; HR, 0.51; 95%CI, 0.32-0.81; p =0.0045). However, there is no significant difference in PFS between high TP53 VAF and wild-type (3.30m vs 2.47m; HR, 0.94; 95%CI, 0.64-1.38; p = 0.764).



Conclusion: Not all TP53 mutations are associated with superior efficacy of PD-1/PD-L1 inhibitors. Low TP53 VAF can be used as a predictive biomarker for PD-1/PD-L1 inhibitor treatment.

Keywords: Biomarker, immunotherapy, Lung adenocarcinoma

P57.06 EGFR Mutational Status and PD-L1 in Early-Stage Brazilian Non-Small-Cell Lung Cancer

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Introduction: Targeted therapies and immunotherapy have revolutionized the clinical management of non-small cell lung cancer (NSCLC) patients. However, most tailored therapies are focused on non-resectable cases. The ADAURA trial reported an anti-EGFR as a potential adjuvant therapy for EGFR-mutated NSCLC resected patients. The frequency of EGFR mutations varies according to ethnicity, sex, and disease stage. Aim: To describe the frequency of EGFR mutations and PD-L1 expression in early-stage (Ib-IIIa) non-squamous NSCLC patients from Brazil. **Methods:** We evaluated a retrospective series of NSCLC patients (n=302) with disease IB to IIIA (AJCC 7th edition) diagnosed between 2005 and 2020 at a nonprofit cancer center (Barretos Cancer Hospital). All tumor tissues were histologically confirmed as non-squamous NSCLC. EGFR mutational status was assessed in DNA isolated from FFPE tissues by available local tests, including Next Generation Sequencing (NGS; TruSight Tumor 15, Illumina), Cobas v2 EGFR Mutation Test, and Sanger sequencing method. PD-L1 expression was assessed by immunohistochemistry (IHC; antibody clone 22C3 PharmaDx) and reported as Tumor Proportion Score (TPS), categorized in < 1%, 1-49%, and ≥ 50%. **Results:** Enrolled non-squamous NSCLC patients were diagnosed at disease stage IB (n=75), IIA (n=43), IIB (n=45) and IIIA (n=139) and 19.2% (n=58) of them were never smokers. EGFR mutational status was assessed in 98% of the cases (n=297) with a failure rate of 6.4% (n=19) and PD-L1 expression was assessed only in suitable samples (n=188). EGFR mutations were detected in 17.3% (n=48) tumors. EGFR mutations were associated with female sex (p=0.01) and never smokers (p<0.0001). EGFR mutated patients presented a higher overall survival compared with wild-type patients (p=0.002). PD-L1 positivity was detected in 36.7% of the cases [TPS 1-49% n=44(23.4%); TPS >50% n=25(13.3%)]. High PD-L1 expression (TPS>50%) was associated with lower progression-free survival compared with low and negative PD-L1 expression (p=0.01). PD-L1 positivity was associated with smoking (quitter p=0.03; current p=0.05), weight loss (p=0.001) and increased disease staging (IIB p=0.01; IIIA p=0.03). Adjusted Cox Regression model showed EGFR mutational status (EGFRm HR=0.53, p=0.022), race (non-white HR=0.455, p=0.005) and performance status (PS2 HR=4.4 and PS3/4 HR=6.1, p<0.0001) were independently associated with worse. **Conclusion:** The frequency of EGFR mutations was 17.3% and PD-L1 positivity was 36.7 in early-stage non-squamous NSCLC patients from Brazil. These resectable patients EGFRm or PD-L1-positive could be eligible for adjuvant tailored treatment.

Keywords: EGFR, PD-L1, adjuvant therapy

P57.07 The Scottish Immunotherapy Prognostic Score (SIPS) Predicts Response to First-Line Pembrolizumab for Metastatic Non-Small Cell Lung Cancer

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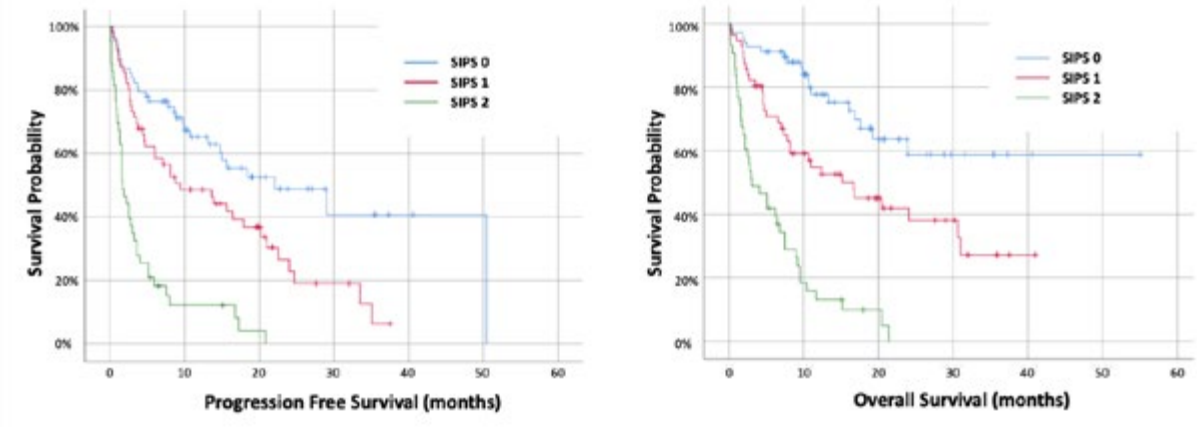
Introduction: The anti-PD1 immune checkpoint inhibitor pembrolizumab is an established first-line treatment option for patients with metastatic non-small cell lung cancer (NSCLC) with PDL1 expression ≥50%. Durable responses may be seen in a subset of patients; however, many derive little clinical benefit from treatment. Biomarkers that predict response are an unmet clinical need. Biomarkers of the systemic inflammatory response predict survival in NSCLC. We evaluated the prognostic significance of these biomarkers in first-line pembrolizumab for metastatic NSCLC. **Methods:** All patients treated with pembrolizumab monotherapy for metastatic NSCLC with PDL1 expression ≥50% at a regional cancer centre in Scotland were identified from the electronic patient record. Key inflammatory biomarkers (white cell count, neutrophil count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albumin, prognostic nutritional index) within 14 days of starting treatment were recorded. The relationship between these and progression-free survival (PFS) and overall survival (OS) were examined using Cox-regression and Kaplan-Meier methods. **Results:** Data were available for 167 patients with median age 69 and 89 (53%) female. Median PFS was 8.7 months and median OS was 15.2 months. On multivariate analysis albumin and neutrophil count were each independently associated with PFS (both p<0.001) and OS (both p<0.001). Given the consistent, highly significant relationship between albumin and neutrophil count with both PFS and OS a simple cumulative score combining these biomarkers was explored. The Scottish Immunotherapy Prognostic Score (SIPS) assigned 1 point each for albumin <35g/L and neutrophil >7.5X10^9/L to give a 3-tier score: 0 (low-risk), 1 (moderate-risk), 2 (high-risk). SIPS was predictive of PFS (HR2.45 95%CI 1.89-3.18 (p<0.001)) and OS (HR2.82 (95%CI 2.12-3.75 (p<0.001)). It stratified PFS from 1.7 months (SIPS:2), 9.4 months (SIPS:1) to 22.1months (SIPS:0) (p<0.001) and OS from 3.1 months (SIPS:2), 16.7 months (SIPS:1) to “not reached” (SIPS:0) (p<0.001) (Figure 1). The relative risk of death before 6 months was 2.65 (95% CI 1.78-3.80) in patients with SIPS 2 compared to those with SIPS 0-1 (p<0.001).



Conclusion: SIPS, a cumulative score of albumin and neutrophil count, predicts survival in patients with NSCLC receiving first-line pembrolizumab monotherapy. Unlike many proposed prognostic scores in this setting, SIPS uses only routinely collected pre-treatment test results and provides a 3-teir categorical score. This simple score stratifies survival across a clinically meaningful time period and may assist treatment decision making. Additional work is needed to define the risks and benefits of this approach. We advocate evaluation of the prognostic utility of this biomarker of systemic inflammation in other immunotherapy treatment settings.

Keywords: First-line Pembrolizumab, Scottish Immunotherapy Prognostic Score, Biomarkers of systemic inflammation

P57.08 High Performance Radiomic Classifier to Predict the Response to Immunotherapy in Advanced NSCLC

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Introduction: The groundbreaking results of immune checkpoint inhibitors (ICIs) in NSCLC still leave uncovered the identification of prognostic and predictive biomarkers. Radiomics is a non-invasive approach endowed with the potential to unveil clinically relevant clues by decoding tumor characteristics. Thus, we aimed to develop a CT-based radiomic classifier to predict the response to ICIs in advanced NSCLC. **Methods:** A cohort of 117 consecutive NSCLC patients undergoing ICIs was investigated. Overall, 851 radiomic features (RFs) were extracted from pretreatment CT scans through a dedicated software (SlicerRadiomics). Primary endpoint was the response to ICIs per RECIST. Patients with complete/partial response and stable disease lasting at least 6 months were defined as responders (R) and those with stable disease lasting less than 6 months or progression as non-responders (NR). The workflow depicted in Figure 1A was developed to build a radiomic classifier. First, a Monte Carlo cross-validation which exploits hierarchical clustering and correlation analysis to select RFs, and a logistic regression model to predict the response to ICIs, were used to identify informative RFs. Then, an ad-hoc genetic algorithm was implemented to select a subset of top informative RFs which maximize the classifier accuracy. Kaplan Meier and log-rank tests were performed to assess the discriminative ability of RFs. **Results:** From March 2017 to July 2019, we enrolled 117 advanced NSCLC treated with ICIs (11% as Ist line, 89% as IInd or more line). Median OS and PFS were 7.8 (95%CI, 5.4-12.8) and 2.5 months (95% CI, 1.1-3.9), respectively. According to RECIST criteria, 76 patients (65%) belonged to NR, while the remaining 41 (35%) were R. A CT-based radiomic classifier including 20 RFs was generated. Using a leave-one-out cross-validation approach we demonstrated that our classifier was associated with clinical response, reaching high performances chiefly in terms of AUC (AUC = 0.88, Figure 1B). Importantly, NSCLC patients classified as non-responders according to radiomic predictor displayed a significantly worse OS (median OS 4.5 months, 95% CI, 3.8-6.7) compared to responders (median OS not reached) (Figure 1C).

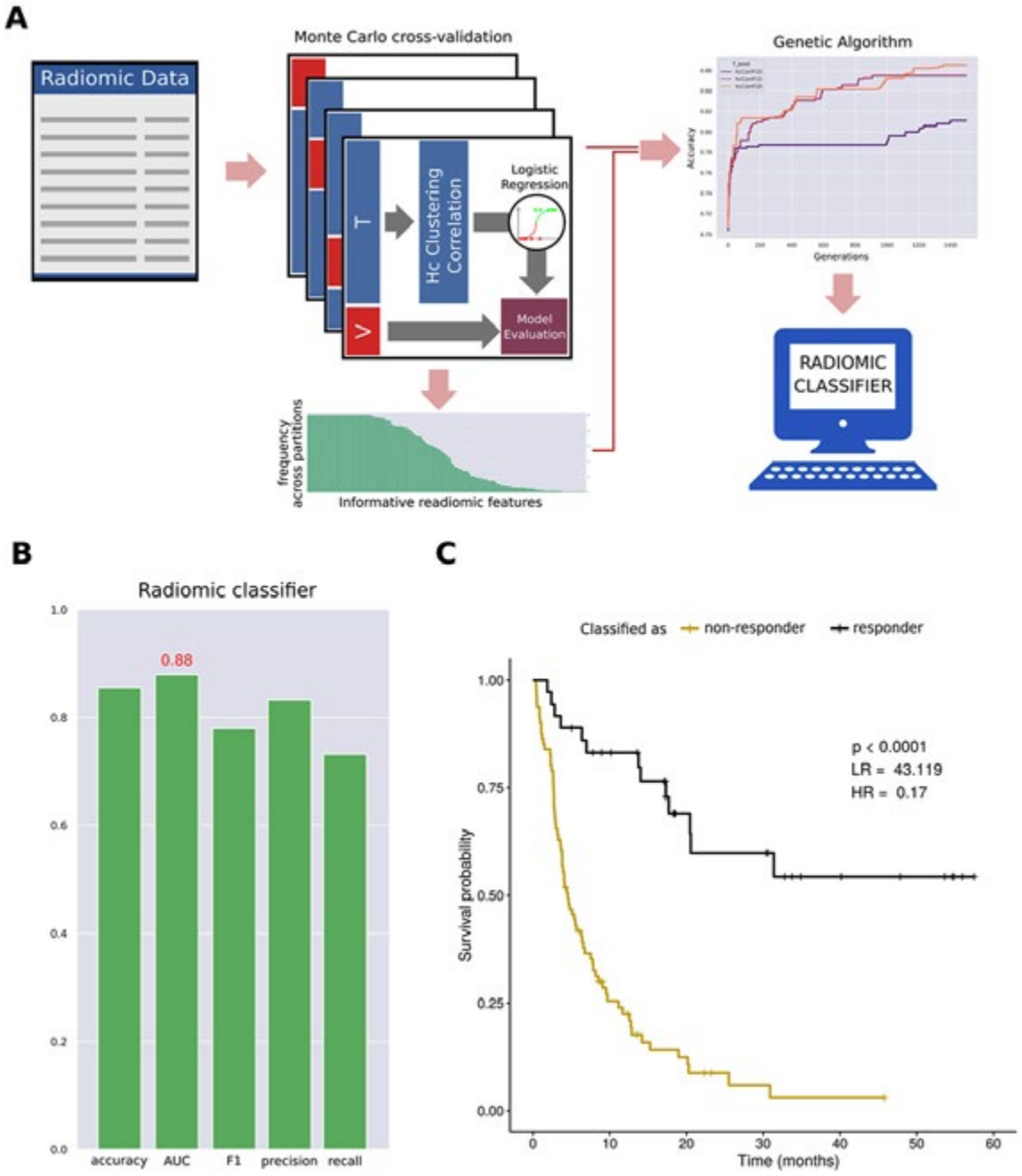

Figure 1: **A)** Schematic representation of the computational workflow used to build the radiomic classifier. **B)** Radiomic classifier performances. **C)** Overall survival of patients (N=117) classified as non-responders and responders based on our radiomics classifier.

Conclusion: Our CT-based radiomic classifier was able to identify NSCLC patients who might benefit from ICIs. Once validated in a large external cohort, the approach followed here could represent a step toward the achievement of individualized decision support for patients with advanced NSCLC.

Keywords: Immune checkpoint inhibitors, predictive biomarkers, radiomics

P57.09 Common Oncogenic Driver Mutations and PD-L1 Expression in Non-Small Cell Lung Cancer of Smokers and Never Smokers

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Introduction: Recent studies have shown an inverse relationship between programmed death-ligand 1 (PD-L1) expression and EGFR mutations and a correlation between high PD-L1 expression and smoking history. **Methods:** This is a single-centre retrospective study to examine the relationship between common driver mutations (EGFR mutation and ALK rearrangement) and PD-L1 expression in NSCLC in ever smokers and never smokers. Tumour PD-L1 expression was assessed using Ventana SP263 monoclonal antibody. Light, moderate and heavy smokers were patients who had smoked < 20, 20 to 39, and ≥ 40 pack-years, respectively. Results

Figure 1 Distribution of levels of PD-L1 expression according to driver mutation status, smoking status and histological subtype of NSCLC

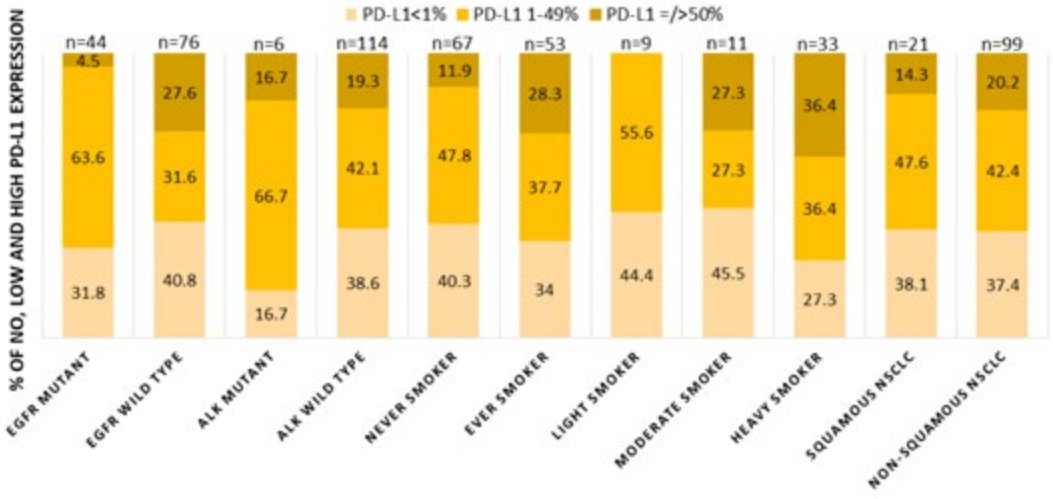

Table 1 shows the common driver mutations and PD-L1 expression in NSCLC according to patients' smoking status. Sensitising EGFR mutations were more common in never smokers than in smokers (P<0.001). A higher proportion of smokers had high PD-L1 expression (TPS ≥50%) [15 (28.3%) of 53] compared to never smokers [8 (11.9%) of 67] (P=0.024). Figure 1 shows the distribution of the levels of PD-L1 expression according to the various clinical characteristics. High PD-L1 expression was seen in 21 of 76 (27.6%) patients with EGFR wild-type tumours but only in 2 of 44 (4.6%) patients with tumours harbouring sensitising EGFR mutations [OR, 6.1 (95% CI, 1.5 – 24.7), P=0.002]. 5 out of 6 tumours with ALK rearrangement expressed no or low PD-L1 expression (P=1.000). Among the 53 smokers, a higher proportion of heavy smokers [12 (36.4%) of 33] than non-heavy smokers [3 (15.0%) of 20] had high PD-L1 expression [OR, 2.2 (95% CI, 0.8 6.5), P = 0.123]. There was no association between the level of PD-L1 expression and the histological subtype of NSCLC.

Table 1 Sensitising EGFR mutation, ALK rearrangement and PD-L1 expression in NSCLC according to smoking status of the patients

Characteristic	**No. of patients (%)**		**OR (95% CI)**	**P value**
Smoking status	Never smoker	Ever smoker		
	67 (55.8%)	53 (44.2%)		
Sensitising EGFR mutation				
Positive	38 (56.7%)	6 (11.3%)	4.5 (2.1 - 9.7)	<0.001
Exon 18 mutation 1				
Exon 19 deletion 16				
Exon 21 L858R mutation 27				
Negative	29 (43.3%)	47 (88.7%)		
ALK rearrangement				
Positive	4 (6.0%)	2 (3.8%)	1.3 (0.4 - 4.2)	0.693
Negative	63 (94.0%)	51 (96.2%)		
PD-L1 expression				
TPS ≥50% (High)	8 (11.9%)	15 (28.3%)	2.9 (1.1 - 7.5)*	0.024*
TPS 1-49% (Low)	32 (47.8%)	20 (37.7%)		
TPS <1% (None)	27 (40.3%)	18 (34.0%)		
OR = Odds ratio, CI = confidence interval, TPS = tumour proportion score * Comparison between high PD-L1 expression (TPS ≥50%) versus no or low PD-L1 expression (TPS <50%) and ever smoker versus never smoker				

Conclusion: High PD-L1 expression in NSCLC is more common in smokers than in never smokers and in EGFR wild-type than EGFR-mutant NSCLC. There was a trend to a positive correlation between the level of PD-L1 expression and smoking intensity.

Keywords: EGFR mutations, PD-L1 expression, smoking status

P57.10 Clinicopathological Analysis of Anti-Tumor Immunology-Related Factors After Chemoradiotherapy for Lung Cancer

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Introduction: Recently, involvement of immune cells such as T cells, activation of immune effector cells, and reduction of immunosuppressive cells have been shown to be a part of mechanisms of antitumor effect of chemotherapy. Some chemotherapy and radiotherapy induce immunogenic cell death (ICD), leading to immune response against cancer cells. However, the expression of ICD related factors in clinical specimens are still unknown. We investigated the expression of ICD related factors before and after chemoradiotherapy in non-small cell lung cancer (NSCLC) and analyzed its relationships with other clinicopathological characteristics of lung cancer. **Methods:** First, 41 patients of NSCLC resections after induction chemoradiotherapy and 29 patients of salvage surgery after standard treatment for unresectable advanced NSCLC performed at our institute between 2002 and 2017 were included. Of these patients, 19 with EF3 and EF2 having few residual tumors were then excluded, results in 51 patients being reviewed. We performed immunohistochemical staining of several ICD related factors such as calreticulin, $CD8^+$ T cells, $FOXP3^+$ T cells and PD-L1. Various clinical and pathological data were reviewed retrospectively to analyze prognostic factors for disease free survival (DFS) after surgery. **Results:** Thirty-five male and sixteen female patients were included. Their median age was 61 years (range: 32 to 73 years). The majority of patients received pre-operatively chemoradiotherapy (90.2%, 46/51). Vascular invasion was observed in 14 patients (27.5%). Lymphatic invasion was observed in 12 patients (23.5%). The comparison of before and after chemotherapy revealed an increase of calreticulin, $CD8^+$ T cells, and PD-L1expression. Tertiary lymphoid structures (TLS) associated with tumor were observed in 25 patients (49.0%). Univariate analysis revealed that chemotherapy alone, vascular invasion, lymphatic invasion, low intra-tumoral $CD8^+$ T cells and tertiary lymphoid structures were significantly associated with poorer DFS. Multivariate analysis showed that low intra-tumoral $CD8^+$ T cells and TLS were significantly associated with poorer DFS. In addition, the number of FOXP3+ T cells within the TLS correlates with intra-tumoral / peri-tumoral PD-L1 expression. **Conclusion:** We found that the expression of calreticulin, $CD8^+$ T cells, and PD-L1 were increased after chemoradiotherapy. Moreover, low intra-tumoral $CD8^+$ T cells and tertiary lymphoid structures were associated with poorer prognosis.

Keywords: chemoradiotherapy, immunogenic cell death, tertiary lymphoid structures

P57.11 The Role of Serum Proteomic Signature in Predicting Survival by PD-L1 Status in Patients With Non-Small Cell Lung Cancer Receiving Immunotherapy

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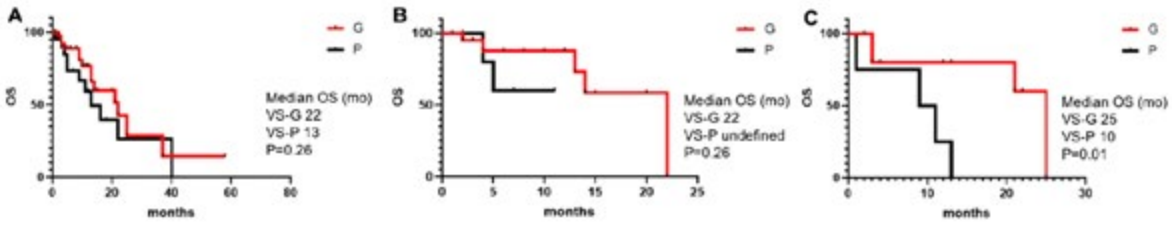
Introduction: The VeriStrat test is a blood-based proteomic test derived from machine learning which uses a mass spectrometry (MS) - based signature. Results from this test can indicate a more aggressive disease state and have shown prognostic utility in different stages, histologies, and treatment types for patients with non-small-cell lung cancer (NSCLC). Recently, the VeriStrat test has also shown prognostic and potentially predictive utility in patients receiving immunotherapy. **Methods:** This is a retrospective study that includes 68 patients with advanced stage NSCLC who received immunotherapy alone or in combination with cytotoxic chemotherapy. Patients underwent VeriStrat testing from 2016 to 2020. Spectra from blood samples were evaluated to assign patients into the VeriStrat 'Good' (VS-G) or VeriStrat 'Poor' (VS-P) group. **Results:** Better overall survival (OS) was observed in the VS-G group compared to the VS-P group (median OS of 22 vs. 13 months, P=0.26). There was no significant difference in progression free survival (PFS) between VS-G and VS-P groups (median PFS 5 vs. 4 months, P=0.40). Among patients with PD-L1 expression level < 1%, the VS-G group demonstrated significantly increased OS in comparison to VS-P group (median OS 25 vs. 10 months, P=0.01). PFS was not significantly different between the groups (median PFS 5 vs. 3 months, P=0.35). Among patients with PD-L1 expression level ≥1% there was no significant difference in PFS (P=0.55) and OS (P=0.26) between VS-G and VS-P groups.



(A) OS of patients who received ICI alone + combination (B) OS of patients who received ICI alone + combination and PD-L1 ≥1
(C) OS of patients who received ICI alone + combination and PD-L1<1

Conclusion: Blood-based proteomic testing has the potential as a predictive biomarker for survival outcomes in NSCLC patients receiving an ICI-based regimen. Its predictive role may defer according to PD-L1 status, thus requiring further studies.

Keywords: immunotherapy, VeriStrat, NSCLC

P57.12 Clinical and Molecular Features of Chinese Lung Cancer Patients With Germline Mismatch Repair Gene Mutations

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Introduction: Lynch syndrome is caused by germline mutations of DNA mismatch repair (MMR) genes, which increases risk of specific cancer types, especially colorectal and/or endometrial carcinoma. With the wide spread of Next generation sequencing (NGS), certain lung cancer patients were found to have Lynch syndrome. The clinical and genomic features of these patients in Asian are largely unknown. **Methods:** NGS data from a targeted panel of 73 or 1,021 known cancer genes from paired cancer and germline DNA of 30,963 Chinese lung cancer patients was analyzed to identify pathogenic or likely pathogenic (P/LP) germline variants in MMR genes based on American College of Medical Genetics and Genomics(ACMG) 2015 guideline. MSI was determined using MSIsensor0.5, MSI score >10% was defined as MSI-H. **Results:** Totally, 47(0.15%) patients were found to harbor germline variants in MMR genes, 4 were MLH1, 2 were MSH2, 21 were MSH6 and 21 were PMS2, with 40 lung adenocarcinoma, 6 lung squamous cancer and 1 small cell lung cancer . The median age at diagnosis of lung cancer was 58 years (ranger 32-84), 22 (46.8%) patients were female. Only 2 of 47 patients were MSI-H, the other were MSS. The most common gene mutations were TP53 (48.9.5%), EGFR (36.2%), ERBB2 (10.6%), LRP1B (10.6%), NF1 (10.6%). The mutation frequencies of ERBB2 and NF1 were significantly higher in the 47 patients were higher than those of the entire cohort (P = 0.016 and P = 0.030, respectively, fisher's exact test). 4 patients detected ALK rearrangement mutations. One patient carried EGFR L858R mutation benefited from ecotinib for 2 years, and one patients with the same EGFR mutation received gefitinib for 15 months. **Conclusion:** Most lung cancer with germline MMR mutations are MSS, and the mutation landscape of these patients are similar to the entire cohort. ERBB2 and NF1 mutations are enriched in the setting of lynch syndrome. Patients with EGFR mutations response to EGFR tyrosine kinase inhibitors (TKI). Additional investigation is need to determine the efficacy of EGFR TKIs in these patients.

Keywords: Germline mutation, Asian lung cancer, mismatch repair gene

P57.13 Correlation of TP53/KMT2C co-mutation and Tumor Microenvironment in Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of non-small cell lung cancer (NSCLC). KMT2C/TP53 co-mutations have been reported as a potential biomarker to predict responses to ICIs therapy in NSCLC. In the meantime, the tumor microenvironment (TME) also plays a central role in the efficacy and development of resistance to ICIs. But the correlation of KMT2C/TP53 co-mutations with immune signatures remains unclear. **Methods:** The whole-exome sequencing with corresponding whole transcriptome sequencing data of 971 NSCLCs was obtained from TCGA. The proportion of various types of immune cells in the tumor microenvironment was analyzed by Xcell. Survival analysis was performed using Cox proportional hazards model, with a p value determined by a log-rank test. **Results:** In total, the data of 971 patients (505 LUAD and 466 LUSC) was analyzed including 382 females and 553 males with a median age of 67 (range 38-90). About 12% (113/971) patients had TP53/KMT2C co-mutations. In comparison to TP53/KMT2C co-mut-, the co-mut+ subgroup contained significantly higher naive $CD8^+$ T cells (mean, 0.399% vs 0.271%, $p<0.01$), Type 1 T helper cells (Th1) (mean, 0.37% vs 0.149%, $p<0.01$), type 2 T helper cells (Th2) (mean, 7.99% vs 4.89%, $p<0.01$) and gd T cells (mean, 34% vs 31.9%, $p<0.05$). We also found that in the LUAD cohort, the overall survival (OS) showed a significant negative correlation with the proportion of Th2 cells ($p<0.01$). Meanwhile, we observed that there was no significant difference in OS between the co-mut+ and co-mut- subgroups in the NSCLC cohort. **Conclusion:** The previous report indicated that oncogenic driver genes could modulate TME. We identified that the TP53/KMT2C co-mutations had a significant correlation with naive $CD8^+$ T cells, Th1, Th2 and gd T cells. The interaction of the TP53/KMT2C co-mutations with the different cells in the TME is not clear. So deeper validation is in need, in order to better understanding of the mechanism and monitoring the response and resistance to ICIs therapy in clinical practice. Another notable result is that there is no significant difference in OS between the TP53/KMT2C co-mut- and co-mut+ subgroups, suggesting that TP53/KMT2C co-mutations would be a predictor of the clinical benefit of ICIs, but not of a prognostic marker.

Keywords: KMT2C/TP53 co-mutations, the tumor microenvironment, NSCLC

P57.14 LRMP Associates With Immune Infiltrates and Acts as a Prognostic Biomarker in Lung Adenocarcinoma

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Introduction: Lymphoid-restricted membrane protein (LRMP), also known as Jaw1, is an endoplasmic reticulum-associated protein that is expressed in a developmentally regulated fashion in both the B and T cell lineages. However, the relationship between LRMP and prognosis of lung adenocarcinoma (LUAD) and tumor-infiltrating lymphocytes remains unclear. **Methods:** The expression levels of LRMP mRNA in tumor and normal tissues were analyzed via Tumor Immune Estimation Resource2.0 (TIMER2.0) and Gene Expression Profiling Interactive Analysis2 (GEPIA2). LRMP protein expression was examined in The Human Protein Atlas (HPA). The association between LRMP expression and clinicopathological variables was analyzed using Pearson chi-squared test. GEPIA2 and Kaplan–Meier plotter databases were used to analyzed the clinical prognostic significance of LRMP. To further confirm the underlying function of LRMP, the data were analyzed by gene set enrichment analysis. In addition, Tumor Immune single-cell Hub (TISCH) was used to investigate the distribution of LRMP in the LUAD immune microenvironment; TIMER and CIBERSORT were used to investigate the relationships among LRMP, LRMP co-expressed genes and tumor-infiltrating immune cells; Finally, the correlations between LRMP and immune checkpoints were analyzed with TIMER 2.0. **Results:** The expression of LRMP was significantly low in LUAD, and correlated with vital status, age, gender, TNM stage, new tumor event type of LUAD patients. High LRMP expression was related to a better prognosis in patients with LUAD. GSEA results showed that immuno-related and cell adhesion pathways were enriched in samples with high LRMP expression. In LUAD tumor immune microenvironment, LRMP was mainly distributed in tumor infiltrating immune cells. TIMER and CIBERSORT results showed that LRMP and its co-expressed genes were positively correlated with various tumor infiltrating immune cells and their markers. In addition, LRMP was positively correlated with immune checkpoints. **Conclusion:** In conclusion, LRMP expression was significantly reduced in LUAD patients, which indicated a poor prognosis. The expression of LRMP was significantly associated to the levels of immune cell infiltration and immune checkpoints expression. Therefore, LRMP may be used as a prognostic biomarker and as an indicator of immunotherapy response. Further studies need to validate our findings.

Keywords: LRMP, immune infiltration, Lung adenocarcinoma

P57.15 Safety and Efficacy of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Patients With Low Creatinine Clearance Rate

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Introduction: The safety and efficacy of immunotherapy among non-small cell lung cancer (NSCLC) patients with creatinine clearance rate (Ccr) < 45mL/min remains unclear as this population has traditionally been excluded from clinical trials with immune checkpoint inhibitors (ICIs). **Methods:** We retrospectively analyzed the therapeutic toxicity and clinical outcomes of NSCLC patients with Ccr< 45 mL/min before treatment who received at least one dose of ICIs between January 2017 and August 2020 at Guangdong Provincial People's Hospital. Propensity score matching was used to select matching patients with Ccr≥ 45 mL/min before treatment according to the ratio of 1:2. Progression-Free Survival (PFS) were estimated with the Kaplan-Meier method between these two groups. Creatinine clearance rate was calculated by Cockcroft Gault formula. **Results:** 18 patients with Ccr < 45 mL/min at baseline were include into analysis. The ORR was 30.77% and the median PFS was 12.37 months (95% confidence interval [CI] :10.32-14.42). Grade1-2 immune-related adverse events (irAEs) occurred in 22.22% of patients. The most commonly occurring grade 1-2 irAEs was erythra (11.11%). Grade≥3 irAEs was reported in 1 patient who required ICI discontinuation for grade 3 interstitial pneumonia. After ICI initiation, decreased in creatinine clearance rate from baseline were infrequent and mild (Figure A), and no patients experienced grade 3 or 4 renal irAEs or required ICI discontinuation or corticosteroid administration for management of renal toxicity. After propensity score matching, 12 patients with low Ccr and 24 patients with high Ccr were matched for survival analysis, whose clinical characteristics (including median age, sex, staging, ECOG PS, smoking history, treatment line, EGFR/ALK mutant, brain metastatic and liver metastatic)were comparable. There was no significant difference in median PFS between the low Ccr group (median PFS:11.8 months, 95% CI:9.07-14.53) and high Ccr group (median PFS:7.70 months, 95% CI:1.56-13.84) (P=0.3521, Figure B). **Conclusion:** In this retrospective analysis, treatment with immunotherapy in NSCLC patients with low creatinine clearance rate appears to be safe, and responses to ICIs can be durable in this population. Additional studies are needed in larger cohorts of patients to determine the safety of immunotherapy in patients with low creatinine clearance rate.

Keywords: renal toxicity, non-small cell lung cancer, immunotherapy

P57.16 Inflammatory Markers as Predictors of Treatment Response and Survival in Patients With Non-Small Cell Lung Cancer Treated with PD-1 Inhibitors

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Introduction: A variety of serum biomarkers have been previously correlated with clinical outcomes in patients with advanced-stage non-small cell lung cancer (NSCLC) treated with PD-1 inhibitors, with widely variable results. The primary aim of our study was to evaluate the prognostic and predictive value of peripheral blood-based inflammatory biomarkers, both at baseline (pre-treatment) and post-treatment, in the above patient population. **Methods:** A retrospective study of the clinicopathological features and treatment data of 117 patients with advanced-stage NSCLC, treated with nivolumab or pembrolizumab at the Oncology Unit of Sotiria Athens General Hospital, was performed. Baseline and post-treatment absolute counts of neutrophils (ANC), lymphocytes (ALC), monocytes (AMC), eosinophils (AEC) and platelets (PLT), LDH as well as the ratio of neutrophils to lymphocytes (NLR), platelets to lymphocytes (PLR) and myeloid to lymphoid cells (M:L) were correlated with treatment response, durable clinical benefit (DCB), defined as absence of disease progression at 6 months, progression-free survival (PFS) and overall survival (OS). **Results:** 58,1% of patients had no immune-related adverse events (IrAEs), while rash and hyperthyroidism were observed in 17.9% and 12.8% of patients, respectively. PD-L1 status and treatment with nivolumab (versus pembrolizumab) were both independently associated with DCB (OR=1.38; 95% CI: 1.13 – 1.68; p=0.002 and OR=5.06; 95% CI: 1.50 – 17.07; p=0.009, respectively).In multivariate analysis, increased pretreatment PLR [HR (95% CI): 0,79 (0,63 — 0,99); p=0,040] was correlated with worse PFS, while age, PS, and nivolumab treatment were the only parameters found to be independently associated with OS. **Conclusion:** Pre-treatment PLR and PD-L1 status may independently predict PFS and OS, respectively, in advanced-stage NSCLC patients treated with PD-1 inhibitors. The prognostic and predictive implications of serum inflammatory markers in this challenging clinical setting should be investigated in further large-scale prospective studies.

Keywords: PD-1 inhibitors, Advanced non-small cell lung cancer, biomarkers

P58.01 Dysbiosis of Fecal Microbiome in Advanced Non-Small-Cell Lung Cancer

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Introduction: Emerging evidence has demonstrated that fecal microbiome is significantly associated with non-small-cell lung cancer (NSCLC) tumorigenesis and immunotherapy efficacy. In addition, fecal microbiota transplant has shown its potential augmenting the efficacy of PD1/PD-L1 blockers in preclinical and early phase clinical studies. However, few studies have focused on fecal microbiome in patients with advanced NSCLC. In this study, we aimed to characterize the fecal microbiome in advanced NSCLC patients and healthy population, and to investigate the differences of fecal microbiome before and after anti-tumor therapy. **Methods:** Fecal samples from a total of 91 NSCLC patients and 39 healthy volunteers were collected from August 2018 to January 2020, including 10 patients with paired samples collected before and after chemotherapy or immunotherapy, respectively. The hypervariable V3-V4 regions of the 16S rRNA in fecal samples were sequenced. **Results:** All patients were diagnosed with advanced NSCLC, including stage III (n=11) and stage IV (n=80). Of the 91 patients, 57 were diagnosed with adenocarcinoma, 30 were squamous cell carcinoma and 4 were others. 11 patients didn't receive any therapy before samples collection. Alpha diversity of the fecal microbiome in lung cancer patients was significantly lower than that of healthy population (Chao1 P=0.038, faith_pd P=0.027). Beta diversity, described by unweighted principal coordinate analysis (PCoA), revealed that the composition significantly differed between patients and healthy controls at species and genus levels. Advanced NSCLC patients had higher levels of Parabacteroides, Lactobacillus, Veillonella but lower abundance of Prevotella, Faecalibacterium, Lachnospira, Phascolarctobacterium, Roseburia, and Subdoligranulum (P<0.05). Higher levels of Butyricicoccus (P=0.0625) and Dialister (P=0.0625), along with a lower abundance of Hungatella (P=0.125),were found after chemotherapy compared to baseline. After immunotherapy, the levels of Anaerostipes, Blautia, Butyricicoccus, and Hungatella tended to increase(P=0.125), while the level of Lactobacillus tended to decrease(P=0.125). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis showed that altered microbiota observed between lung cancer group and healthy control group was enriched in pathways including valine, leucine and isoleucine biosynthesis, peptidoglycan biosynthesis, thiamine metabolism and etc. **Conclusion:** Advanced NSCLC patients have lower diversity and characteristic bacterial community in comparison with healthy volunteers. Identified microbiota might serve as new biomarkers for advanced NSCLC patients and predict the efficacy of chemotherapy or immunotherapy. However, further studies are warranted to confirm. Targeting on the enriched microbiome-related pathways might be a potential research direction to improve patients' survival.

Keywords: lung cancer, fecal microbiome, 16S rRNA gene sequencing

P59.01 Clinical Characteristics of Patients With MET Amplification-Positive NSCLC After EGFR-TKI Therapy

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Introduction: Patients with epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) ultimately acquire resistance to EGFR tyrosine kinase inhibitors (TKIs) during treatment. In 5–22% of these patients, resistance is mediated by aberrant mesenchymal epithelial transition factor (MET) gene amplification. Here, we evaluated the emergence of MET amplification after EGFR-TKI treatment failure based on clinical parameters. **Methods:** We retrospectively analyzed 186 patients with advanced EGFR-mutant NSCLC for MET amplification status by in situ hybridization (ISH) assay after EGFR-TKI failure. We collected information including baseline patient characteristics, metastatic locations and generation, line, and progression free survival (PFS) of EGFR-TKI used before MET evaluation. Multivariate logistic regression analysis was conducted to evaluate associations between MET amplification status and clinical variables. **Results:**

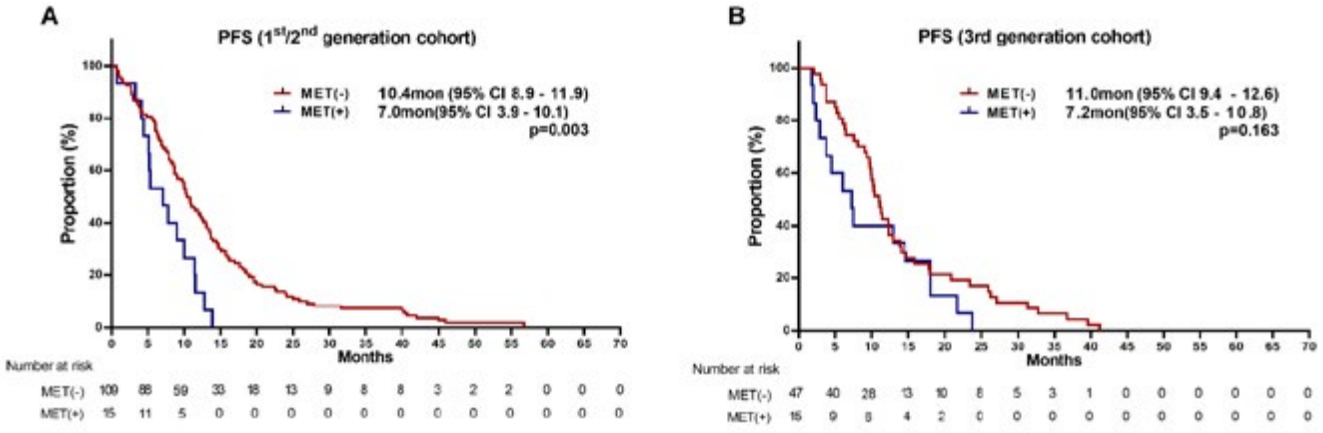

Table 1. Logistic regression analysis of clinical factors predicting MET amplified status

Category	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.983	0.948–1.020	0.360	-	-	-
Sex (male versus female)	0.753	0.341–1.663	0.483	-	-	-
Smoking status (never versus ex- or current smoker)	2.819	1.271–6.252	0.011	3.457	1.326–8.440	0.011
TKI generation (first/second versus third)	2.319	1.049–5.126	0.038	2.727	0.636–11.684	0.177
TKI line (first line versus ≥ second line)	2.550	1.136–5.723	0.023	0.950	0.225–4.002	0.944
Baseline *EGFR* mutation site						
Exon 19	1					
Exon 21	0.735	0.320–1.688	0.735	-	-	-
Other MT	0.926	0.102–8.390	0.946	-	-	-
PFS of most recent TKI	0.930	0.875–0.988	0.019	0.898	0.833–0.967	0.004
Liver metastases (no PD versus PD)	1.800	0.749–4.325	0.189	-	-	-
Brain metastases (no PD versus PD)	0.162	0.065–0.402	< 0.001	0.138	0.051–0.347	< 0.001

HR, hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; MT, mutation; PFS, progression-free survival; PD, progression of diseas

Regarding baseline EGFR mutations, exon 19 deletion was predominant (57.5%), followed by exon 21 mutation (39.2%). The proportions of MET ISH assays performed after first/second-generation and third-generation TKI failure were 66.7% and 33.1%, respectively. The median PFS for the most recent EGFR-TKI treatment was shorter in MET amplification-positive patients than in MET amplification-negative patients (mPFS of 1st/2nd generation TKI cohort, 7.0 vs. 10.4 months, p = 0.003, PFS of 3rd generation TKI cohort, 7.2 vs. 11.0 months, p=0.163). Multivariate logistic regression demonstrated that a history of smoking, short PFS on the most recent TKI, and less intracranial progression were associated with a high probability of MET amplification (all p < 0.05). **Conclusion:** Our results demonstrated the distinct clinical characteristics of patients with MET amplification-positive NSCLC after EGFR-TKI therapy. Our clinical prediction can aid physicians in selecting patients eligible for MET amplification screening and therapeutic targeting.

Keywords: non-small cell lung cancer, Epidermal growth factor receptor, MET amplification

P59.02 Profile of Next-Generation Sequencing (NGS) on MET exon 14 Skipping Mutation and MET Amplification in Lung Cancer: A Calibration Project in China

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Introduction: MET is an oncogenic driver and becomes a significant therapeutic target in lung cancer. Detection of MET alterations is essential for clinical treatment decision-making. With the advancement of diagnostic technology, next-generation sequencing (NGS) becomes an option. However, it has limited probe design and coverage of specific regions of introns, and the quality of testing varies widely among different laboratories. Moreover, clinically defined cut-off values for MET amplification vary considerably and lack uniform criteria. Hence, we initiated a calibration project to understand the NGS landscape of MET detection in China, providing evidence for testing standardization and clinical therapy guidance. **Methods:** The NGS-based calibration project was conducted by The Primary Health Care Foundation of China from May to November 2020. A questionnaire was used to collect laboratory information, MET detection information, and NGS assay parameters from respondents. An external quality assessment (EQA) was designed to evaluate the capability to detect MET alterations, and it includes two rounds of testing. The first adopted five standard samples with or without MET exon14 (METex14) skipping mutation and different MET copy number gain. The second round used five clinical samples with different skipping mutations. Respondents' results were evaluated that whether they matched the expected results and scored based on predefined criteria. **Results:** Thirty-two independent laboratories participated in and completed the project. Twenty institutions adopted Illumina, followed by Thermo Fisher (n=8) and BGI (n=3). 23 of 32 laboratories (71.8%) reported MET mutations at DNA level. Detection of METex14 skipping often requires exon 14 with adjacent upstream and downstream intron regions effectively covered. While six only covered exon 14, 19 laboratories used panels covering a wider range of MET exons. Nearly 60% (n=19/32) of laboratories validated MET amplification results, and FISH (n=12/19) was the primary validation approach. In 24 laboratories that adopted hybridization capture-based approach, sequencing depth of plasma ranged from >1000 ->4000X, which was higher than tissue (500X-1000X). Sequencing panels used for tissue sample varied from small panels within 50 genes to large up to 500 genes, and for plasma were mainly small panels (<50 genes). Sixteen laboratories stated that LoDs for SNVs and Indels were 1% in tissue and some defined it as 0.1% in plasma samples. The reported LoDs and cut-off values for CNVs were mainly 3-4 copies in tissue samples. In EQA, pass rate was 81.25% (n=26/32). It showed that false-negative results mainly from MET amplification, partially due to cut-offs variation across companies. Notably, only 5 laboratories reported MET polysomy. Ten laboratories with full scores were selected for clinical samples testing. One misinterpreted a 1.6% allele frequency mutation as a false-positive METex14 skipping mutation. **Conclusion:** MET testing performance varies depending on the panel selection, technical strength, experimental capability, quality control, etc. Moreover, the detection of MET amplification remains a challenge compared to METex14 skipping. Our data indicate that the Chinese sequencing market and services are considerable and have a large room for advancement. Further data is needed to support standardization and clinical interpretation.

Keywords: MET alterations, Next generation sequencing assay, External quality assessment

P59.03 Comparison of Two RNA-Based Platforms for Detection of Fusions and Met Splicing Variant in Non Small Cell Lung Cancer Samples

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Introduction: ALK, ROS1, RET, NTRK fusions and MET exon 14 skipping variant (METex14) are present in 5-15% of advanced non-small cell lung cancer (NSCLC), and their identification is mandatory for selection of targeted therapies. Although FISH is considered the gold standard to determine gene fusions, their limitations are well known and it cannot be multiplexed. GeneReader Next Generation Sequencing (NGS) (Qiagen) and nCounter (Nanostring) allow multiple detection of fusion and splicing transcripts. The aim of the present work was to compare the two platforms in NSCLC samples. **Methods:** First, a validation study was performed using six cell lines harboring gene fusions. Next, tumor samples from 77 NSCLC patients visited in our Oncology Department were prospectively collected and tumor RNA was purified using High Pure FFPET RNA Isolation Kit (Hoffman-La Roche) and analyzed using GeneReader and nCounter custom panels. The GeneReader panel contains specific junction probes for the detection of METex14 and fusion transcripts involving ALK, ROS1, RET, FGFR1- 3, NRG1, NTRK1- 3, EGFR and BRAF genes. GeneReader analysis and interpretation were performed with the QCI-Analyze and QCI-Interpret software's (Qiagen). The nCounter custom panel targets ALK, ROS1, RET, NTRK1-3 and NRG1, together with METex14. It is based on a dual strategy; detection of specific fusions and imbalances between the 3' and 5' mRNA regions, which enable the recognition of fusions not identified with the specific primers. nCounter counts were analyzed with the nSolver Analysis software (Nanostring) followed by an "in house" algorithm **Results:** In the validation study, nCounter and Genereader showed 100% concordance with the known genotype of cell lines for ALK, ROS1, RET fusions and METex14. In the prospective study, valid results were obtained for 76/77 (98.7%) of samples tested. Paired analysis showed a 94.7% concordance (72/76) between the results obtained by nCounter and GeneReader NGS, corresponding to a Cohen's kappa of 0.825 [CI=0.659-0.991]. Overall, 12 samples tested positive by both techniques, namely EML4-ALK (n=4), ALK-CLTC (n=1), CCDC6-RET (n=1), KIF5B-RET (n=1) and EZR-ROS1 (n=2) and METex14 (n=3). Four discordant cases were observed. Two of them corresponded to a SLC34A2-ROS1_S13del2046: R32 fusion and a METex14 variant detected only by nCounter, while two cases corresponded to HLA-DRB1-MET and RAD51-HLA-C fusions detected by Genereader but not included in the nCounter panel. Finally, the remaining 60 patients were pan-negative. **Conclusion:** NGS and nCounter can be used as routine diagnostic techniques for the detection of fusions and splicing variants in NSCLC. The combination of both platforms allows a more comprehensive characterization of these two types of molecular alterations

Keywords: nCounter, Fusions, NGS

P59.04 Molecular Characterization of Unactionable EGFR Mutation in Non-Small Cell Lung Cancer

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Introduction: Actionable mutations in epidermal growth factor receptor (EGFR), including exon 19 deletions, exon 21 L858R and other uncommon sensitizing EGFR mutations, are associated with positive responses to anti-EGFR-targeted therapy. However, a few patients(pts) with non-small cell lung cancer harbor unactionable EGFR mutation. The molecular characterization of unactionable EGFR mutation in non-small cell lung cancer and whether patients with NSCLC harboring unactionable EGFR mutation have targeted and immunotherapy opportunities remains unclear. **Methods:** The study retrospectively analyzed pts with NSCLC whose tissues were send to perform parallel hybridization-based next-generation sequencing with the pan-cancer panel, Pair-wise comparison of TMB was analyzed in unactionable EGFR mutation cohort, actionable EGFR mutation cohort and non-EGFR mutation cohort, Fisher's exact test was performed on different cohort to analysis the differentiated mutated genes (DMGs). **Results:** Among 3992 pts with NSCLC, 1794 pts were fall into actionable EGFR mutation cohort where exon 21 L858R, exon 19 deletions, exon 20 variation and other uncommon sensitizing EGFR mutations accounted for 45%, 42%, 7% and 6% respectively. 83 pts and 2115 pts were fall into unactionable EGFR mutation cohort and non-EGFR mutation cohort respectively. The result of pair-wise comparison of TMB between three cohorts indicated unactionable EGFR mutation cohort had the highest proportion of TMB-H patients (56%, median TMB:12 muts/Mb), while the proportion of TMB-H in actionable EGFR mutation cohort and non-EGFR mutation cohort was 7% (median TMB: 3.84 muts/Mb) and 37% (median TMB: 3.84 muts/Mb). The prevalence rate of DNA damage repair (DDR) genes was significantly higher in unactionable EGFR mutation cohort compared with the other two cohorts and it indicated that DDR genes may contribute to the higher-proportion of TMB-H in unactionable EGFR mutation cohort. Fisher's exact test indicated DMGs, including TP53, LRP1B, CDKN2A, KEAP1, were inclined to mutate in unactionable EGFR mutation cohort compared with other cohorts. **Conclusion:** Mutations in DNA damage repair and TMB-H which serve as predictive marker for immunotherapy accounted for the highest proportion in unactionable EGFR mutation cohort. But at the same time, CDKM2A and KEAP1 which serve as a negative predictive marker for immunotherapy occurred significantly in unactionable EGFR mutation cohort.

Keywords: EGFR,TMB,DDR

P59.05 Integration of Molecular Cancer Classification and NGS to Identify Metastatic Cancer Patients Eligible For Lung Cancer Directed Therapy

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Introduction: For patients with metastatic disease, identification of both the primary tumor type and molecular alterations increases eligibility for targeted therapies. The 92-gene assay (CancerTYPE ID) is a validated gene expression classifier of 50 tumor types and subtypes for metastatic patients with unknown or uncertain diagnoses. Multimodal biomarker testing identifies actionable alterations to guide therapy selection. Here, a database of metastatic cases integrating molecular cancer classification with secondary biomarker analysis was analyzed to assess clinical utility in patients with lung cancer with known histology but unknown primary site of origin. **Methods:** MOSAIC (Molecular Synergy to Advance Individualized Cancer Care) is an IRB-approved, de-identified database of metastatic cases with unknown or uncertain diagnoses submitted for CancerTYPE ID testing and tissue type-guided multimodal biomarker testing (NeoTYPE profiles, Neogenomics). Metastatic cancers classified as adenocarcinoma, squamous cell carcinoma (SqCC), carcinoid and small/large cell carcinoma were evaluated by next-generation sequencing (NGS), fluorescent in situ hybridization (FISH) and immunohistochemical (IHC) analyses to identify primary site of tumor. **Results:** Molecular diagnoses by CancerTYPE ID of 2151 patients included 271 (12.6%) with non-small cell lung carcinoma features [NSCLC; 157 lung adenocarcinomas (7.3%), 114 SqCCs (5.3%)], 10 (0.5%) lung carcinoid tumors and 71 (3.3%) with small/large cell carcinoma features. Gene fusion analysis by FISH identified 5 ALK (5.9%), 5 MET (6.0%), 1 RET (1.2%), and 1 ROS1 (1.2%) alterations in adenocarcinoma, as well as 2 MET alterations (3.4%) in SqCC. The mutational frequency of the 10 most commonly mutated genes for each lung cancer subtype are shown in Table 1. Mutations identified included genes for which targeted therapies are available, including capmatinib for MET exon 14 skipping mutations and dabrafenib for BRAF V600E mutations. Multimodal biomarker testing for pan-TRK identified 1 (1.5%) lung adenocarcinoma, 7 (15.2%) SqCC and 6 (24.0%) small/large cell carcinoma cases, which were eligible for larotrectinib and entrectinib. PD-L1 expression was seen in 95 (83.3%) lung adenocarcinoma, 58 (74.4%) SqCC, 5 (62.5%) lung carcinoid and 32 (62.8%) small/large cell carcinoma cases. Table 1. Top 10 gene mutations frequency by NGS

Main Type (Subtype)		Top 10 Gene Mutations Detected by NGS									
NSCLC	Lung Adenocarcinoma	TP53	KRAS	KEAP1	KMT2D	STK11	ARID2	BRCA2	CHD2	EPHA5	KMT2C
		65.6%	41.9%	26.7%	20.0%	15.6%	14.3%	14.3%	14.3%	14.3%	14.3%
	Squamous Cell Carcinoma (Lung)	TP53	KMT2D	ARID1A	SMARCA4	FAT1	PIK3CA	KEAP1	LRP1B	MTOR	NTRK3
		71.0%	32.4%	23.5%	23.5%	22.2%	20.0%	17.7%	16.7%	16.7%	16.7%
	Neuroendocrine (lung carcinoid)*	-	-	-	-	-	-	-	-	-	-
Other	Neuroendocrine Small/large cell lung carcinoma	TP53	CTNNB1	APC	DICER1	RANBP2	RB1	RUNX1	SETD2	SMARCA4	TSC2
		67.4%	27.3%	18.2%	18.2%	18.2%	18.2%	18.2%	18.2%	18.2%	18.2%

*low case number, unable to analyze; % indicated cases with detected gene abnormalities out of all cases with available test results.

Conclusion: Analysis of the MOSAIC database identified a subset of patients with metastatic cancers eligible for lung cancer directed targeted therapy and immunotherapy based on tumor type, genetic alterations, and PD-L1 expression. Molecular profiling combined with cancer classification may lead to improved therapy options for patients with advanced disease of unknown primary and may provide further evidence for subsequent combination trials of targeted therapies or immunotherapies to improve patient outcomes.

Keywords: advanced metastatic cancer, Gene Expression, molecular profiling

P59.06 Prognostic Nutritional Index in Real-World Patients Receiving Systemic Therapy for Driver Mutation-Positive Metastatic NSCLC

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Introduction: The Prognostic Nutritional Index (PNI) is an indicator of nutritional and immune status. Initially a prognostic index to evaluate the risk of recurrence and predict survival in patients following surgical procedures, recent studies have indicated the PNI may also have prognostic ability in non-resected lung cancer. The PNI has been shown to be independently predictive of outcome in patients with advanced/metastatic NSCLC (mNSCLC) treated with platinum-based chemotherapy (CTx). In response, this study explored the prognostic value of the PNI among real-world driver mutation-positive patients with mNSCLC receiving palliative intent systemic therapies, including (CTx), tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICI). **Methods:** Alberta patients diagnosed with driver mutation-positive (KRAS, ROS1, EGFR or ALK) mNSCLC receiving a first-line palliative-intent systemic therapy were identified. Demographic, clinical, treatment and outcome data were extracted from the institutional Glans-Look Lung Cancer Research Database. PNI was calculated as: [serum albumin (g/L) + 5 × peripheral blood lymphocytes ($\times 10^9$/L)] using blood component values taken ≤30 days prior to systemic therapy initiation. Receiver operator characteristic (ROC) curves were constructed to identify optimal cut-off points for PNI, and patients were stratified by this factor. Kaplan-Meier analysis and Cox Proportional Hazards models were used to investigate the association between PNI and outcome. **Results:** 200 patients were identified (Table 1):

	Driver Mutation				
	ALK (n=46) N (%)	**EGFR (n=93) N (%)**	**KRAS (n=51) N (%)**	**ROS1 (n=10) N (%)**	**Pooled Cohort (n=200) N (%)**
PNI Value					
'Low' (Below cut-point)	24 (52)	50 (54)	33 (65)	4 (40)	111 (56)
'High' (Above cut-point)	22 (48)	43 (46)	18 (35)	6 (60)	89 (44)
Sex					
Male	22 (48)	41 (44)	19 (37)	4 (40)	86 (43)
Female	24 (52)	52 (56)	32 (63)	6 (60)	114 (57)
Age at Diagnosis					
Median (IQR)	58.1 (50.2–68.4)	65 (55 –75)	67.3 (61.3–73.8)	52.8 (49.5-61.7)	63.2 (55.9-73)
< 70 years	36 (88)	58 (62)	34 (67)	9 (90)	137 (69)
≥ 70 years	10 (22)	35 (38)	17 (33)	1 (10)	63 (31)
Smoking History					
Ever	22 (48)	43 (46)	49 (96)	1 (10)	115 (58)
Never	24 (52)	45 (49)	2 (4)	9 (90)	80 (40)
Unknown	0 (0)	5 (5)	0 (0)	0 (0)	5 (2)
ECOG					
Good (ECOG 0 or 1)	36 (78)	44 (47)	39 (76)	9 (90)	128 (64)
Poor (ECOG >1)	9 (22)	16 (17)	12 (24)	1 (10)	38 (19)
Unknown	0 (0)	33 (36)	0 (0)	0 (0)	33 (17)
1L Treatment Type					
CTx	6 (13)	0 (0)	18 (35)	2 (20)	26 (13)
ICI	0 (0)	0 (0)	22 (43)	2 (20)	24 (12)
Concurrent CTx/ICI	0 (0)	0 (0)	11 (22)	1 (10)	12 (6)
TKI	40 (87)	93 (100)	0 (0)	5 (50)	138 (69)
Median PFS (months) [95% CI]	9.9 [7.1 – 17.5]	13.5 [10.3 – 15.9]	7.0 [4.6 – 14.2]	9.8 [2.6 – NYR]	11.7 [9.5 – 13.9]
Median OS (months) [95% CI]	50.0 [25.3 – NYR]	20.6 [17.5-25.5]	20.4 [16.0 – 39.5]	33.3 [2.5 – NYR]	24.5 [20.0 – 27.6]

NYR: not yet reached

Kaplan-Meier survival analysis revealed that mOS was significantly different by driver mutation-type, where generally ALK-rearranged NSCLC showed superior survival times to the other driver-mutation types (Table 1; log-rank p=0.04). mPFS was greatest in those receiving TKI in the first-line setting, in comparison to CTx (13.5 vs. 6.7 months, log-rank p=0.01) Stratified by optimal cut-point, 'high', compared to 'low' PNI had significantly longer mOS (27.6 vs. 20.4 months, log-rank p=0.03), but PFS was not significantly different between high/low PNI (13.5 vs. 10.3 months, log-rank p=0.23) A Cox Proportional Hazards model, constructed for the pooled cohort and controlling for known confounders revealed that PNI failed to retain prognostic value for OS; 'good' ECOG (<2) and never-smoking history emerged as independently prognostic of prolonged OS (HR: 0.47, p=0.002 and HR: 0.53, p=0.008, respectively). Similarly, PNI was not prognostic of PFS, but rather good ECOG was prognostic of prolonged PFS (HR: 0.55, p=0.03) and CTx prognostic of reduced PFS in relation to TKI (HR: 3.4, p=0.02) **Conclusion:** Among real-world driver-mutation positive mNSCLC, ECOG serves as a more robust prognosticator of outcome than PNI. Utility of PNI as a prognostic tool appears limited in this population.

Keywords: prognostic nutritional index, real-world outcomes, driver-mutation

P59.07 Mutation Profile of BRAF in Chinese Non-Small Cell Lung Cancer Patients

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Introduction: BRAF mutation is one of the most common driver gene mutations in non-small cell lung cancer (NSCLC) patients, especially in adenocarcinoma. BRAF alterations have been identified with the clinical application of next generation sequencing (NGS),however, mutation profile and co-occurring genomic alterations of BRAF have not been fully understood in Chinese non-small cell lung cancer patients. **Methods:** We enrolled 14703 Chinese NSCLC patients with confirmed histology subtype of adenocarcinoma, squamous carcinoma and large cell carcinoma. FFPE samples and matched peripheral blood or plasma were sequenced for NGS based 1021 cancer genes panel assay. **Results:** Comprehensive genomic profiling including single nucleotide variants (SNV), short and long insertion and deletion (Indel), copy number variations (CNV) and gene arrangement/ fusion were analyzed. 1.78% (261/14703) of Chinese NSCLC patients harbored at least one BRAF genomic alteration, which was mainly composed of patient with SNVs and Indels (97.3%, 254 patients), copy number variations (16.1%, 42 patients), and gene rearrangements (5.0%, 13 patients). None BRAF CNV was detected. Of the 42 patients carried CNV, 38 of them carried both CNV and BRAF SNV/Indel, whereas two of them carried both CNV and gene arrangement/fusion and two of patients carried aforementioned three types of alteration. BRAF V600E were the most common BRAF mutations, which accounted for 36% of all BRAF mutation, respectively. The most common resistant alteration G469A accounted for 11%. A total of nine types of BRAF rearrangement were detected from eight patients. AGK-BRAF were the most common BRAF rearrangement, which accounted for 36% of all BRAF rearrangement. Further analysis of co-occurring BRAF mutations revealed that of BRAF mutated Chinese NSCLC patients harbored both BRAF mutations and other driver gene mutation, such as EGFR, KRAS, PI3KCA. **Conclusion:** This study revealed BRAF variation in approximately 1.78% of Chinese NSCLC patients. BRAF V600E were the most common BRAF mutations, which accounted for 36% of all BRAF mutation. BRAF mutated Chinese NSCLC patients harbored both BRAF mutations and other driver gene mutation, such as EGFR, KRAS, PI3KCA.

Keywords: BRAF, mutation profile, non-small cell lung cancer

P59.08 Identifying the Origin of Lung-Specific Cancer of Unknown Primary Based on Comprehensive Genomic Profiling Optimized With DNA Methylation

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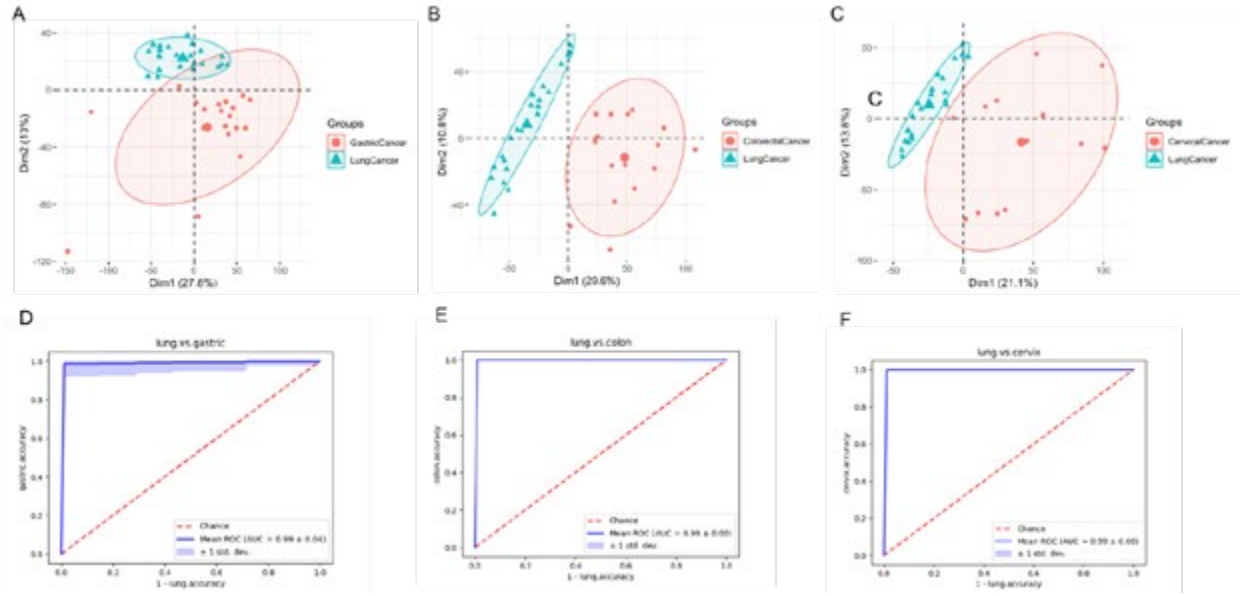
Introduction: Precise diagnosis of the tissue origin for metastatic carcinoma is essential to decide the treatment scheme and improve outcome. The purpose of this study is to predict the primary site for lung-specific cancer of unknown primary (CUP) through genomic and DNA methylation profiles. **Methods:** Comprehensive genomic profiling (CGP) was performed to determine the genomic status within individual paired samples, and targeted bisulfite sequencing was exploited to interrogate their methylation status. Model training subjects were consisted of lung cancer and another type of cancer to compute the prediction signature weights for each DMR feature. **Results:** A total of 300 patients with multi-site malignancies including lung and other organ lesions were screened retrospectively. Excluding individuals clearly diagnosed with imaging modalities and IHC staining, 40 patients needed further differential diagnosis. Among them, 26 cases were identified with novel molecular events like EGFR or ALK alterations; the remaining 14 lung-specific CUPs were located with another type of caners in stomach (n=5), intestine (n=5) and cervix (n=4). Of the 14 CUP cases, mutation spectrum analyses could distinguish metastatic disease from multiple primary tumors, while it was hard to determine the origin of metastatic cancers. However, methylation profiles not only predicted the consistent results with mutation spectrum, but also identified the origin of tumors through our train classification models (AUC>0.98), which can be confirmed with patients' clinical efficacy who received treatments guided by prediction signature. Collectively, compared with genomic profiles, DNA methylation demonstrated better tumor traceability to determine the primary site of CUPs. **Conclusion:** The signature based on within-sample CGP testing optimized with DNA methylation could exactly identify the origin of lung-specific CUPs.



Keywords: cancer of unknown primary, comprehensive genomic profiling, DNA Methylation

P59.09 Landscape of Targetable Genomic Alterations in Hispanic/Latinx Patients With Non-Small Cell Lung Cancers

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Introduction: Despite significant advances in lung cancer therapeutics, real-world data describing the genomic landscape of non-small cell lung cancer among diverse populations remains limited. We aim to describe the landscape of targetable genomic alterations in Hispanic/Latinx patients with non-small cell lung cancers in an international database. **Methods:** Patient-specific targetable genomic alterations were analyzed using the open-source international genomic data-sharing consortium American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (GENIE). Using cBioPortal as a query database, we analyzed 656 samples from 595 Hispanic/Latinx patients with lung adenocarcinoma for the prevalence of targetable genomic alterations among this ethnic group, divided by sex and age group: =<45 years-old, 46-65 years-old, or >65 years-old. **Results:** Among 656 samples from 595 unique Hispanic/Latinx patients with lung adenocarcinoma, 59.5% (n=354) of samples were from females, and 40.5% (n=241) from males. The most common targetable genomic alterations were mutations in the EGFR gene in 27.9% (n=183) of samples, KRAS in 20.1% (n=132), ERBB2 in 6.4% (n=42), and BRAF in 5.8% (n=38). Fusions involving ALK (3.5%, n=23), ROS1 (2.6%, n=13), and RET (1.5%, n=10) involved a minority of samples. Among age groups, females represented a statistically significantly larger prevalence of the samples in younger adults, with 63% among those =<45 years old, 67% 46-65 years old, and 58% on those >65 years old. The prevalence of genomic alterations by age group and sex are presented in Table 1. Table 1:

Genomic Alterations	Females % (n)	Males % (n)	p-value	=<45 years-old % (n)	46-65 years-old % (n)	>65 years-old % (n)	p-value
EGFR mutations	32.0 (127)	21.6 (56)	<0.001	26.7 (16)	26.4 (79)	29.9 (88)	0.617
KRAS mutations	20.9 (83)	18.9 (49)	0.302	11.7 (7)	20.7 (62)	21.1 (62)	0.233
BRAF mutations	4.0 (16)	8.5 (22)	0.014	1.7 (1)	5.4 (16)	7.1 (21)	0.229
ERBB2 mutations	6.8 (27)	5.8 (15)	0.369	3.3 (2)	7.7 (23)	5.9 (17)	0.389
ALK fusions	5.1 (20)	1.2 (3)	0.005	16.7 (10)	3.0 (9)	1.4 (4)	<0.001
ROS1 fusions	3.1 (10)	1.7 (3)	0.277	9.1 (4)	3.8 (9)	0	<0.001
RET fusions	1.5 (6)	1.5 (4)	0.606	3.3 (2)	1.3 (4)	1.4 (4)	0.491

Conclusion: Among an international sample of Hispanic/Latinx with lung adenocarcinoma women and younger adults with lung cancer displayed a larger prevalence of targetable genomic alterations. As therapeutics advances continue to develop in lung cancer care, understanding the genomic landscape of diverse populations with lung cancer will help ensure equitable delivery across diverse racial/ethnic groups.

Keywords: lung cancer, latinx, genomic

P59.10 A Sneak Peak in the Future World of EGFR Mutations: ML Based PFS Differences Between Del 19 and L858R

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Introduction: Exon del 19 and L858R mutations account for 90% of EGFR mutant NSCLC. LUX lung 3/6 initially reported a survival difference between these two. However other studies did not demonstrate the same. By using ML, it is possible to discover novel patterns between data and predict cancer susceptibility, recurrence, prognostication, and therapy. This is a real-world study which aims to evaluate effect of these two molecular subtypes on OS/PFS. **Methods:** 413 patients of stage IV EGFR mutant NSCLC were analysed for clinicopathologic features, treatment details and survival outcomes .Statistical analysis was done using R (version 3.5.1). The PFS prediction models were built using ensemble decision trees, and random forest. Ensemble decision trees were built and validation was performed using survival analysis. Clustering regression techniques were then applied to train and test prediction of 1st PFS of patients. The metrics used for assessing model results were sensitivity, specificity, accuracy, precision. **Results:** The median age of the cohort was 59 years comprising 53% males and 47% females. 275 (66.5%) patients showed a del19 mutation and 138 (33.5%) harbored L858R. After clustering, the important variables were age ($p<0.05$), ECOG PS ($p<0.04$), PDL1 ($p<0.09$), smoking status ($p<0.01$) and number of ETM sites (median 1.2, $p<0.06$), brain metastasis ($p<0.06$) and gender ($p<0.08$). At data lock in, 405 patients were included for survival analysis of which 266 patients received 1st line TKI. Median PFS for each drug according to mutation is depicted in Table 1.

Table 1: OS and PFS differences in del19 vs L858R groups . PFS: progression free survival , OS: Overall survival

Therapy	**PFS (months)**				**OS (months)**			
	Overall	Del19	L858R	P value	Overall	Del19	L858R	P value
								value
1st Line								
Gefitinib	9.9	11.9	7.3	0.0005*	21.03	23.4	16.6	0.04*
Erlotinib	8.2	9.1	7.9	0.3	20.1	22.1	16.5	0.02*
Afatinib	15.5	15.4	11.9	0.6	26.6	28.8	21.3	0.004*
Osimertinib	16.5	16.9	13.5	0.2	NR	NR	NR	--

The prediction for 1st PFS for del19 showed mean absolute error of 2.6 months and 4.72 months for L858R. The accuracy was 79.8% with 82% sensitivity , 79% specificity and AUC: 0.72. The precision was 92% with a Mathews correlation coefficient of 0.59. **Conclusion:** Del19 and L858R mutations differ with respect to prognosis and therapeutics. In our population, del19 cases were more commonly male, and depicted a better PFS on 1st line TKI when compared to L858R positive cases (commonly female). This study is unique in that it utilises machine learning modeling with a fair accuracy to demonstrate that ECOG PS, age at diagnosis, and smoking status are the three main predictive factors of PFS in these patients

Keywords: Epidermal growth factor receptor (EGFR), prediction, del19

P59.11 Real-World Data of NGS Diagnostic Biomarker Testing for Lung Cancer Patients in Japan

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Introduction: Oncomine Dx Target Test Multi CDx system (ODxTT) was reimbursed in Japan in 2019, and the second half of 2019 was a transitional period for clinical introduction. There was a concern that time from test to treatment introduction (TTT) might be longer than that of simultaneous single tests in clinical practice at the time of initial phase of introducing . However, TTT of ODxTT was revealed to be comparable with that of simultaneous single companion diagnostics (CDx) tests (JSMO2021). In this report, we updated the current status of lung cancer CDx in Japanese clinical practice. **Methods:** The Medical Data Vision (MDV) dataset includes claims data for reimbursement between 1st Jun 2019 and 31st Mar 2020 was reviewed in this study. Main objective was to investigate the proportion of testing pattern and TTT after approval of ODxTT. **Results:** MDV dataset included 13,772,678 pts and around 1,053,981 diagnostic procedures by Nov 2020. 6049 lung cancer pts (ICD10 C34) was identified by the criteria for this analysis from Jun 2019 to Mar 2020 because the receipt code was changed and unable to be tracked due to the revision of drug price compensation in April 2020. Overall biomarker testing proportion (at least one test) was 74.6% for EGFR, 53.3% for ALK, 39.4% for ROS1, 81.1% for PD-L1, 5.5% for BRAF V600E and 7.7% for ODxTT. The change of testing proportion and median TTT (range) for ODxTT and simultaneous tests were shown in Table 1 and 2 respectively.

Table 1. Change in Testing proportion

	Jun-Dec 2019	Jan-Mar 2020
ODxTT	5.0 % (223/4416*)	10.8 % (177/1633*)
Simultaneous tests (EGFR, ALK, ROS1, PDL1)	24.1 % (1063/4416*)	21.7 % (355/1633*)

* Total number of ODxTT + 4 simultaneous tests (EGFR, ALK, ROS1, and PDL1) + 5 simultaneous tests (EGFR, ALK, ROS1, PDL1, and BRAF) in each period

Table 2. Changes in median TTT (days, range) of each Testing pattern

	Jun-Dec 2019		Jan-Mar 2020	
	N	median TTT (range)	N	median TTT (range)
ODxTT	223	23 days (2-432)	177	22 days (2-205)
Simultaneous tests (EGFR, ALK, ROS1, PDL1)	1063	23 days (2-496)	355	21 days (2-224)

Conclusion: Compared to the data from the last reporting period, ODxTT has become more widely used in clinical practice. As in the previous report, and after transition phase, TTT of ODxTT was comparable with that of simultaneous biomarker testing (EGFR, ALK, ROS1, and PD-L1) which contributed to a shorten TTT.

Keywords: Real World Data, NGS, companion diagnosis

P59.12 KRAS Mutation Subtypes in Non-Small Cell Lung Cancer and Clinical Outcomes: A Single Centre Experience

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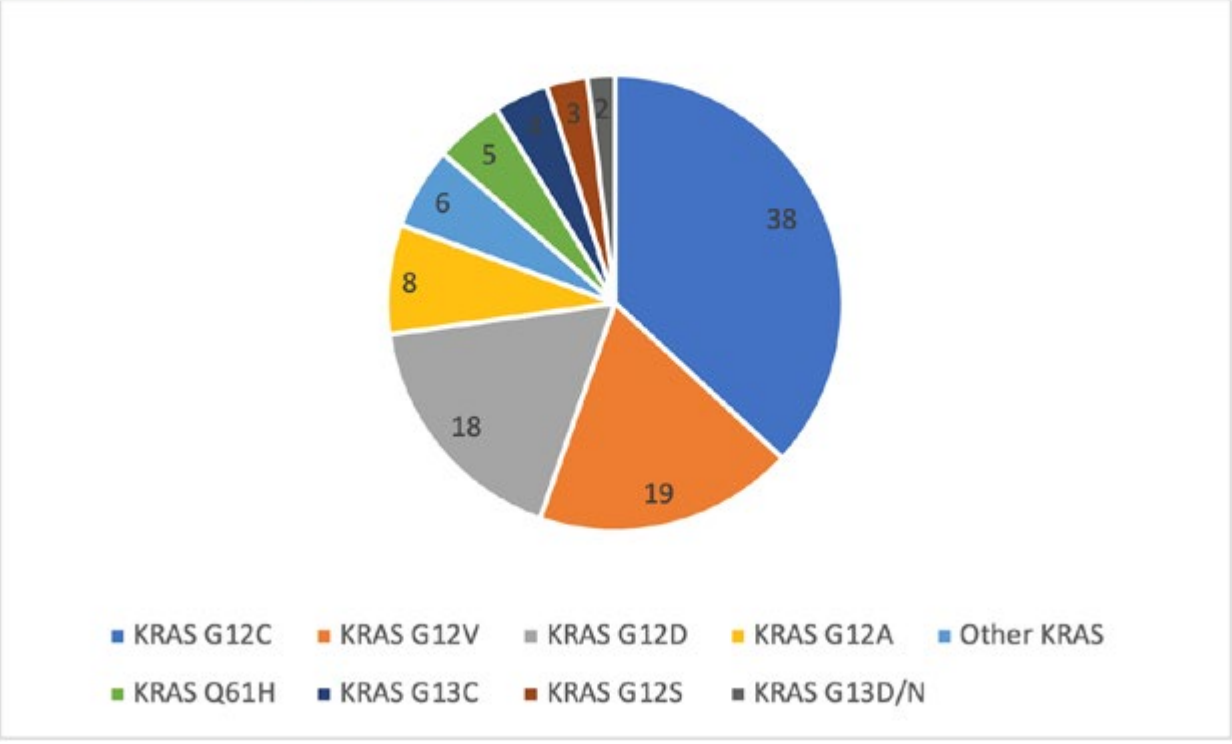
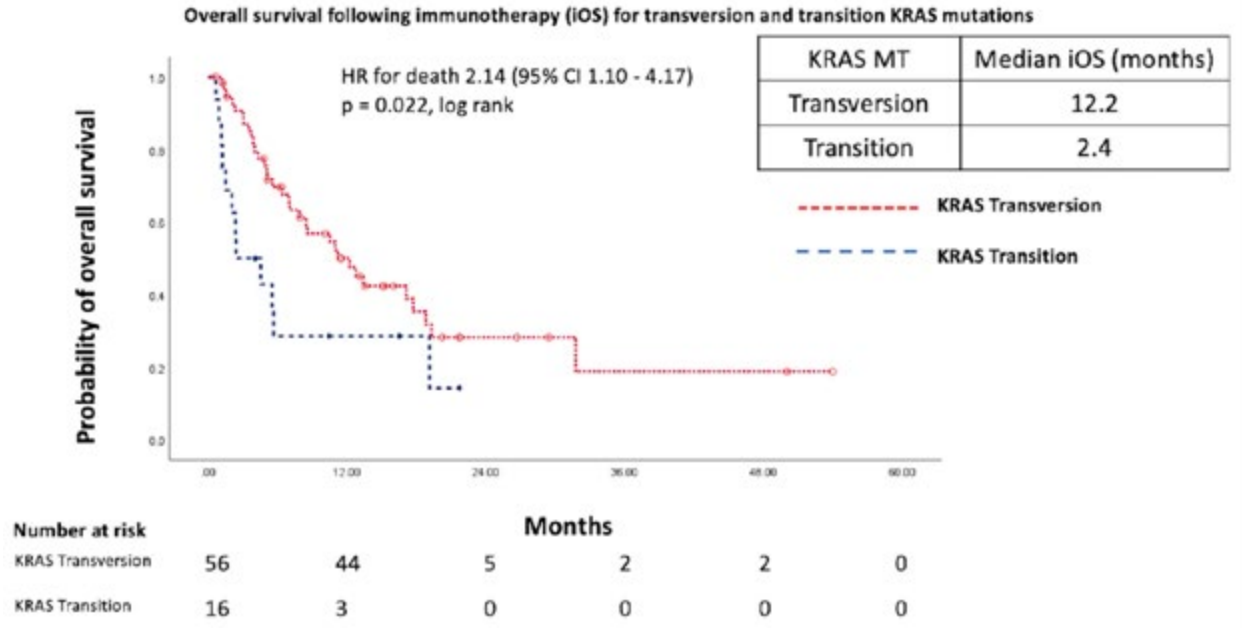
Introduction: KRAS is a common molecular driver in lung adenocarcinoma. KRAS subtypes can be grouped into transversion mutations (exchange of a purine for a pyrimidine bases or vice versa) such as KRAS G12C/G12V and transition mutations (interchange of a purine for another purine or interchange of a pyrimidine for another pyrimidine) such as KRAS G12D. This study assessed the efficacy of treatment and CNS prevalence across different subtypes of KRAS mutant NSCLC. **Methods:** Retrospective review of routine, clinical, molecular testing in NSCLC at a single centre over an 8-year period was performed. Clinicopathological information was obtained from medical records in patients with a KRAS mutation. Overall survival (OS) and Progression free survival (PFS) from diagnosis and OS following immunotherapy (iOS; in any line of treatment) were assessed using the Kaplan-Meier method and differences in survival were assessed by log-rank test. The difference between light/non-smokers and heavy smokers was assessed by Pearsons chi squared test. The presence of CNS disease was assessed by multivariate, nominal, logistic regression. **Results:** From 1054 assessed 272 (25.8%) were found to be KRAS mutant with 72 patients receiving immunotherapy for stage III/IV disease. Immunotherapy included any PD(L)1, CTLA4 or investigational immunotherapy. KRAS G12C was found in 103 patients (38%), KRAS G12D in 48 patients (18%) and KRAS G12V in 53 patients (19%) (Figure 1). There was no difference in the presence of CNS disease across KRAS subtypes (p = 0.149). Non/light smokers were more likely to have a transition KRAS mutation than transversion mutation (p < 0.001).

Figure 1: Distribution of KRAS mutation (%) subtypes in all patients (N = 272). Please note that due to rounding this does not add to 100.



There was no difference across specific KRAS mutation subtype for PFS, OS or iOS. Transversion KRAS mutations had better iOS than transition KRAS mutations (Figure 2).



Conclusion: Transversion KRAS mutations may predict for improved OS following immunotherapy but requires validation in a larger prospective cohort. Retrospective analysis of this cohort by PDL1 is underway.

Keywords: KRAS, immunotherapy

P59.13 The Prediction Performance of TP53 / RB1 Co-Mutation on Small-Cell Lung Cancer Transformation in Patients With Non-Small Cell Lung Cancer

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Introduction: It has been proven that patients with EGFR mutant non-small cell lung cancer (NSCLC) who harbored loss-of-function mutation in both TP53 and RB1 are more prone to small-cell lung cancer transformation (SCLC-T). This study aims to investigate the prediction performance of TP53 / RB1 mutations on SCLC-T in patients with NSCLC. **Methods:** Patients with pathologically confirmed SCLC-T who performed hybridization capture based next-generation sequencing of 1021 cancer-related genes using tumor tissue and / or malignant effusion samples were retrospectively enrolled in this study. Their clinicopathological characteristics, genetic profiles and treatment were reviewed. **Results:** From 2016 to 2021, a total of nine patients were enrolled. The median age at diagnosis was 53 years (range 44-65 years); 55.6% (5/9) patients were male and 33.3% (3/9) patients were ever-smokers. All patients except for one with NSCLC (P5, details not known) were initially diagnosed with adenocarcinoma. One patient had pleural effusion sample sequenced at initial diagnosis and tumor tissue samples at the time of transformation (P1), and the remaining cases had only tissue and / or effusion samples at the time of transformation or after that time. Mutation in EGFR, TP53 and RB1 was detected in 100%, 88.9% and 55.6% of patients, respectively (Figure). All patients with RB1 mutations had TP53 mutations detected. All patients were previously treated with EGFR tyrosine kinase inhibitors before transformation. For P1, RB1 mutation was detected at initial diagnosis. After SCLC-T, 2 mutations disappeared and 14 mutations emerged, which may be caused by tumor heterogeneity or evolutional pressure, or related to phenotypic transformation. Copy number variants were more frequently identified in patients with RB1 mutation (100%, 5/5) than in patients without RB1 mutation (50%, 2/4). RB1 mutation was not detected in the tumor sample for P8 at the time of transformation, but was subsequently found in the cerebrospinal fluid collected after 6 months. **Conclusion:** TP53 / RB1 co-mutation was identified in about half of patients with SCLC-T and may be presented after transformation. Inferring phenotypic transformation only through the presence of TP53 / RB1 co-mutation may result in missed diagnosis of SCLC-T, which should be combined with other techniques such as serum tumor marker neuron specific enolase or pathological exanimations of re-biopsy samples.

Keywords: TP53 / RB1 co-mutation, non-small cell lung cancer, Small-cell lung cancer transformation

P59.14 Concordance and Performance of ddPCR Compared to NGS for The Detection of KRAS G12C Mutation

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Introduction: KRAS G12C mutation detection is possible with multiple molecular techniques that differ from its performance and costs of implementation. Although next-generation sequencing (NGS) is considered ideal for its detection capabilities, equipment and sample costs make it a limited option in some settings. Polymerase chain reaction assays (PCR), on the other hand, offer both qualitative and quantitative evaluations at a lower cost. **Methods:** In a retrospective cohort study, digital droplet PCR (ddPCR) was compared in terms of diagnostic performance with NGS to detect KRAS G12C mutations in EGFR-, ALK- samples of patients with NSCLC. Employed kits were PrimePCR™ ddPCR™ Mutation Detection Assay (Bio-Rad Laboratories, Inc, Hercules, CA, U.S.A.) and Oncomine™ Focus Assay (Thermo Fisher Scientific Inc.,Waltham, MA, U.S.A). **Results:** A total of 60 samples were obtained. KRAS G12C mutations were detected in 11 samples yielding a positivity of 18.3% (95%CI 8.54-28.1%). In the case of ddPCR, by utilizing a threshold of 2000, 9 samples were marked as positive. This technique detected mutations in 15% of samples (95%CI 5.96 – 24.03%). Considering NGS as the gold standard sensitivity of ddPCR reached 81.8% and specificity of 100%. With regards to positive predictive value, it reached 100% and a negative predictive value of 96%. Agreement between the two tests is estimated at 96.6% with a concordance of k = 0.88. **Conclusion:** Regarding diagnostic accuracy, ddPCR is reliable and accordant for the diagnosis of KRAS G12C mutations among NSCLC patients. Although a reduced sensitivity is expected, its negative predictive value is high, offering good diagnostic capabilities in the clinical setting.

Keywords: diagnosis, NGS, KRAS G12C

P59.15 Is CD73 Expression a Druggable Mechanism of Resistance in EGFR-TKI-Treated EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)?

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Introduction: EGFR-inhibitors are effective in EGFR-mutant NSCLC, but resistance invariably develops. Various mechanisms of resistance are described, including upregulation of immune-related factors. CD73 is an immunoinhibitory protein promoting tumor growth and metastasizing, and has been proposed to be modulated by EGFR-TKI treatment. We aimed at evaluating CD73 and related immune marker expression at various time points during sequenced EGFR-TKI treatment, including osimertinib, to identify potential biomarker combinations / signatures for CD73-based therapeutic opportunities in EGFR-resistant tumors. **Methods:** Tissue samples from patients included in a clinical trial (NCT02504346) executed in Northern Europe evaluating osimertinib in EGFR-mutated EGFR-TKI pretreated NSCLC patients were analyzed. Tumor tissue was sampled at diagnosis, before starting osimertinib as next-line EGFR-therapy, and at progression on osimertinib. Expression of CD73, CD39, HLA-E and NKp46 were profiled by IHC, and correlated to treatment status, response and other clinical data. Separation of tumor epithelium from tumor non-epithelium using deep learning models was employed. **Results:** A total of 122 samples were evaluable from 72 patients (18 males, 54 females, median age 68 years (range 33-86)). Tumors from 39 patients harbored a deletion in exon 19, whereas 20 had a L858R point mutation, and one L861Q. In tumors from 23 patients, a T790M-mutation was detected after 1st line of EGFR-TKI treatment, whereas 38 were negative and 11 had an unknown T790M-status. Overall, CD73 and HLA-E showed significantly higher expression in epithelium, while CD39 and NKp46 showed higher expression in the stroma. When comparing expression levels at baseline vs pre-osimertinib there was no significant change in expression patterns for any marker. Of four tumors where post-osimertinib staining could be compared to pre-osimertinib levels, three cases showed increased expression of HLA-E and NKp46, while 2 cases had an increase in CD73 expression. There was also a trend for higher CD73-expression in samples from T790M-negative vs T790M-positive cases after first-line EGFR-therapy. Detailed analyses of staining pattern correlated to mutational status will be presented. **Conclusion:** There were differences in expression pattern among immune markers in EGFR-mutated NSCLC. There were examples of increased expression of HLA-E, NKp46 and CD73 in tumor tissue sampled at progression on osimertinib as second or later line EGFR-TKI therapy, however the numbers are small. This study indicates the relevance of immune-related factors for resistance development in EGFR-treated lung cancer patients.

Keywords: resistance, EGFR, CD73

P59.16 Characterizing the Tumour-Immune Microenvironment in EGFR Mutant NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) comprises around 80% of lung cancers, with mutations in epidermal growth factor receptor (EGFR) effecting approximately 26%. These constitutive activating mutations promote tumour cell proliferation and survival, and are inevitably refractory to tyrosine kinase inhibitors (TKIs) as well as current classes of immune checkpoint immunotherapy (ICI). Third generation TKI Osimertinib offers prolonged disease-free survival, however the reasons for the lack of efficacy of ICI in EGFR mutant tumours remain unclear. The cellular immune composition of the tumour microenvironment is increasingly being recognised as a major factor in host-tumour responses. **Methods:** The use of multispectral immunohistochemistry (IHC) is a valuable tool to investigate the cellular composition of these tumours. Here we compare a cohort of EGFR exon 19 deletion (LREA) tumours to stage matched EGFR wild type (WT) tumours by multispectral IHC. Automated staining was performed for CD8, FoxP3, PD-1, CD68, PD-L1 and cytokeratin markers using MOTiF™ PD-1/PD-L1 lung cancer kit, and slides imaged by Vectra®Polaris™. Image analysis was performed using QuPath, and marker counts were obtained within tumour and adjacent microenvironment compartments **Results:** Immune cells marked by CD8, FoxP3, PD-1, CD68 composed 5%-30% of total cells in the WT tumours, while LREA tumours contained 5% to 15% of total cells (t-test p = 0.17). While these immune cells trended to be lower in LREA tumours, further investigation into their distribution in a larger cohort of patients is required. The LREA cohort displayed poorer progression free survival (PFS) following resection and platinum therapy than the WT cohort (468 days vs 622 days, p=0.2). Neighbourhood mapping suggested cellular populations within the tumour microenvironment which associated with the different tumour profiles. **Conclusion:** Our data suggests that tumour intrinsic mechanisms may result in poorer host-tumour responses. One such mechanism is the immunosuppression of the local microenvironment, and we aim to expand this work to encompass a wider cohort of patient tumours and cellular markers.

Keywords: NSCLC, tumour microenvironment, spatial

P59.17 EGFR Mutation Status, Liver Metastasis, and Overall Survival in Advanced Lung Adenocarcinoma Patients

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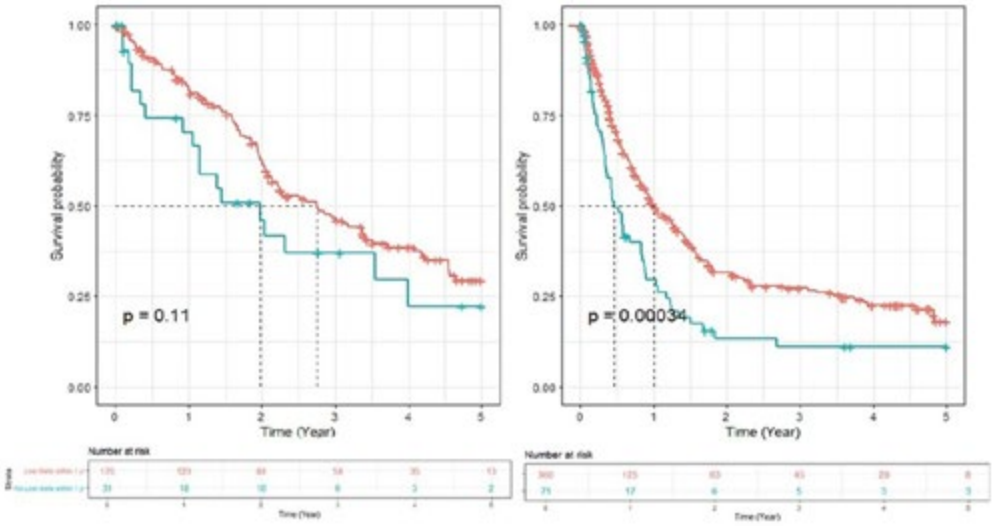
Introduction: Liver metastases are associated with poor prognosis in non-small cell lung cancer patients. In this study, we explored the relationship between EGFR mutation status, incidence of liver metastases within one year of stage IV diagnosis, and overall survival in an unselected lung adenocarcinoma real-world population. **Methods:** Stage IV lung adenocarcinoma patients routinely tested for EGFR and ALK molecular alterations between 2014-2016 were included in this retrospective cohort analysis. Patients with ALK-rearrangements were excluded in this analysis. Clinico-demographic and pathologic data was abstracted from electronic patient records. Continuous variables were evaluated using the Mann-Whitney's U test and categorical variables with the chi-squared test. Multivariable analyses were performed to obtain adjusted hazard ratios (aHR) for overall survival. **Results:**

Figures 1 (left) and 2 (right) Kaplan-Meier plots of overall survival (in years) after diagnosis of stage IV lung adenocarcinoma in EGFR-mutated (Figure 1, left) and EGFR/ALK-wildtype patients (Figure 2, right). Log-rank test p-values are presented. Red line represents patients without liver metastases within one year of diagnosis. Blue line represents patients with liver metastases within one year of diagnosis.



Of 642 stage IV patients, 207 (30.4%) had EGFR-mutated tumors and 435 (64%) had wild-type (EGFR/ALK-negative) tumors. 31/207 (15%) patients with EGFR-mutated tumors and 72/435 (17%) patients with wildtype tumors developed one or more liver metastases within one year of stage IV diagnosis. Liver metastases were associated with statistically significant reduction in overall survival in the wildtype group (p<0.001; Figure 1); there was a trend of reduced overall survival in patients with EGFR-mutated tumors and liver metastases (p=0.11; Figure 2). The aHR for overall survival in the wildtype group was 1.77 (95%CI:1.31-2.41) while in the EGFR-positive group, the aHR was 1.63 (95%CI:0.96-2.77). Among the 103 patients with liver metastases, overall survival was non-significantly better in patients with EGFR mutations (aHR 0.63; 95%CI:0.28-1.40; p=0.257). **Conclusion:** In stage IV patients with tumors carrying EGFR mutations, as with patients with EGFR/ALK wildtype tumors, developing liver metastases at diagnosis or within one-year of diagnosis of stage IV disease was associated with poorer survival.

Keywords: EGFR, liver Metastases, Overall survival

P59.18 Evaluation of ROS1 Expression in a Large Cohort of Early Stage Lung Cancer

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Introduction: ROS1 rearrangements is an infrequent, but attractive target for therapy. In this study we investigate the feasability of ROS1 immunohistochemical analysis (IHC) and correlate the findings with FISH and NGS (Next generation sequencing) in a large population of lung cancer resections, and their histopathological and clinical characteristics. **Methods:** We analyzed tissue from a biobank at Oslo University Hospital, containing samples from resected lung cancer specimens that were made into tissue micro array (TMA) blocks. ROS1 IHC analyses were performed with the use of two different ROS1-directed antibody clones: D4D6 from Cell Signaling and the SP384 from Roche Diagnostics. The IHC positivity was grouped into one of six groups: negative, weak and patchy, weak and diffusely, strong and patchy, strong and diffusely and no viable tumor cells. H-score was also measured. ROS1 FISH and NGS (Ion Torrent, Oncomine Comprehensive Assay v3) was performed on fresh tissue and/or formalin fixed paraffin embedded tissue for all positive cases (more than weak and patchy staining) and also some negative cases. **Results:** 992 cases were analyzed, and we found 28 (D4D6) and 40 (SP384) positive cases with IHC. Of these 3 (D4D6) and 4 (SP384) showed ROS1 rearrangement with FISH, and with 3 (D4D6 and SP384) cases we also found a ROS1-CD74 fusion with sequencing. Of the positive IHC samples 25 (D4D6) and 34 (SP384) were sequenced. For three cases, ROS1 fusion was detected with sequencing and these were also positive with FISH, and had a H-score of 200-300 in both the IHC-clones. These were two women and one male, two smokers/former smoker and one never smoker, in stage IIa or IIb, and they were from 62-75 years old. The histology were adenocarcinomas (solid and two mucinous/mixed mucinous non mucinous.). They all had the same fusion partner (CD74). The frequency of ROS1 positivity in the whole study population based on our algorithm was 0,3% (3/992). The frequency within cases with adenocarcinomas was 0,5% (3/543). In addition, three FISH positive cases were NGS-negative. Two of the cases were negative for both D4D6 and SP384, and one was negative for D4D6 and showed diffusely and weak positivity for SP384.

	Negative	**Patchy, weak**	**Patchy, moderate/ strong**	**Diffusely, weak**	**Diffusely, moderate, strong**	**No viable tumorcells**
D4D6	907	24	1	18	9	33
Mean H-score	0	17	35	76	211	
Range H-score	0	5-40	35	60-120	130-300	
FISH Positive/	3/54	0/2	0/1	0/14	3 /4	
NGS	0/72	0/3	0/1	0/15	3/9	
SP384	898	31	1	24	15	23
Mean H-score	0	25	40	100	204	
Range H-score	0	5-40	40	60-140	120-300	
FISH	2/52	0/2	0/1	1/16	3/9	
NGS	0/66	0/3	0/1	0/19	3/14	
Absolute numbers if not otherwise specified.						

Conclusion: Both IHC-clones showed a strong and homogenous staining with H-score above 200 in the three cases were both FISH and NGS confirmed the presence of ROS1 fusion. The ROS1 frequency in adenocarcinomas was 0.5%, which is somewhat lower than what has been found in studies including mostly stage IV (1-3 %).

Keywords: molecular pathology, ROS-1

P59.19 MET Alterations and Co-Drivers With Poor Prognosis in Patients With Metastatic Non-Small Cell Lung Cancer

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Introduction: Mesenchymal-epithelial transition factor (MET) is found in less than 5% of patients with NSCLC, it is associated with a worse outcome and as a resistance mechanism. For which promising molecular drivers are recently emerging as new therapeutic targets. Up to 15% patients with EGFR mutation-positive or ALK fusion-positive appears to be one of the resistance mechanisms, in our country these targets represented around 40%, so this study analyzed the incidence and characteristics for patients with MET mutation in our institution. **Methods:** From March 2018 to February 2019 in a single-center, we evaluated 256 formalin-fixed paraffin-embedded (FFPE) samples of NSCLC using next generation sequencing (NGS) platform. **Results:** Genomic alterations in MET gen were found in 10.6% (26) of patients. Median age was 61.9-years old. Gene mutation was higher in women 80.8%, and adenocarcinoma (100%) with intermediate grade of differentiation (44%). Most of patients present advance disease (80.8%) with metastases in contralateral lung (42.2%) and node disease (34.6%). PDL-1>1% was present in 30.8% of patients while 36.8% had CEA>10 pg/ml and no correlation with TMB were found. MET co-occurrent with TP53 (57.7%) and PDGFRA (42.3%) genes. In terms of survival, MET was negative impacted in PFS (2.2 vs. 9.1 months; p<0.001) and OS (11.1 vs. 39.0 months; p=0.026). MET plus PDGFRA was a poor prognosis to PFS (2.1 vs 7.3 months; p= 0.010) while MET plus TP53 present worse overall survival (6.0 vs 39.9 months; p= 0.078). **Conclusion:** In our population, the incidence of MET alteration was higher than the reported in the literature. NSCLC patients with MET gene alterations have a poor prognosis and exist co-drivers that decrease survival. It is important to know the incidence of alterations that when concurrent with the MET mutation confer a worse prognosis, since it leads us to look for therapeutic targets that could benefit these patients.

Keywords: NGS, MET, CO-DRIVER

P59.20 Natural History of Kras Mutant Non-Small-Cell Lung Cancer in the Immunotherapy Era: A Single-Centre Retrospective Study

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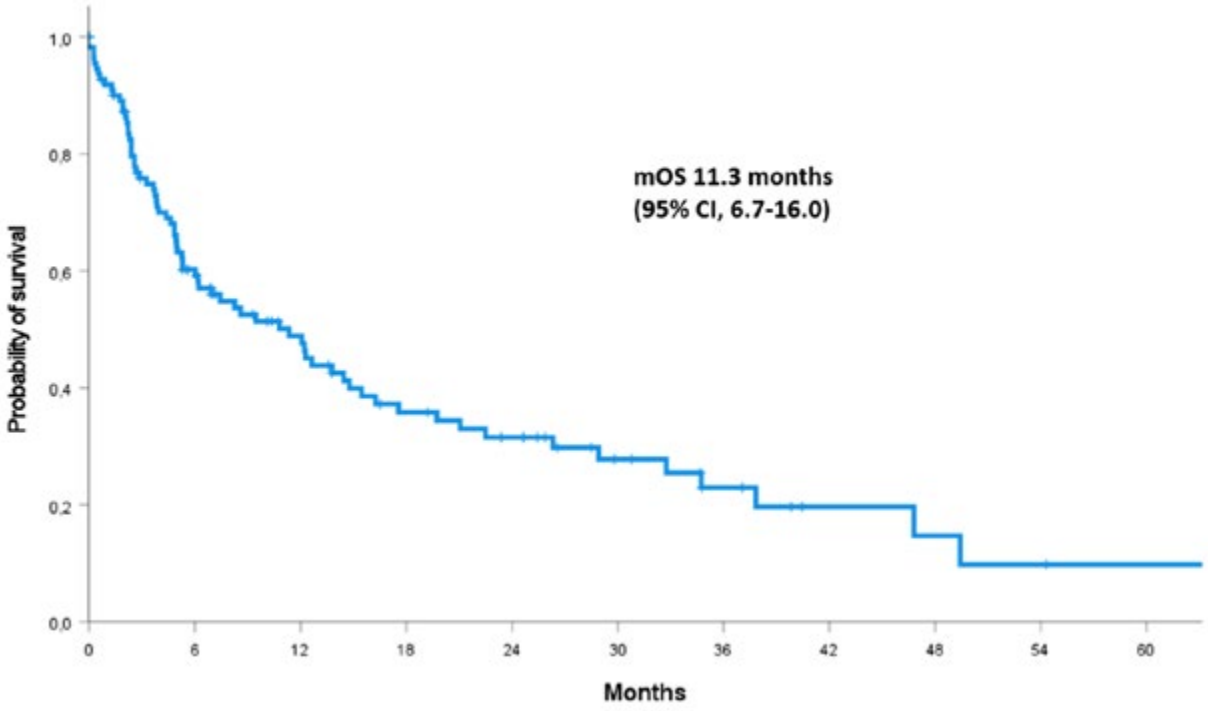
Introduction: KRAS mutated NSCLC represents the main subgroup of oncogene-addicted tumors. Relevantly the clinical behaviour of patient with different types of KRAS mutations may differ. In this retrospective real-world cohort, we report about clinical characteristics and survival data of patients with KRAS-mutation positive advanced NSCLC diagnosed at our Institution. **Methods:** Using electronic medical records, we retrospectively evaluated the natural history of patients with KRAS mutant advanced NSCLC. Diagnostic specimens underwent next-generation targeted sequencing (Ion Torrent) with a 22 genes panel. Programmed death ligand-1 expression was determined by immunohistochemistry using the 22C3 clone and assessed according to tumour proportion score. **Results:** 177 patients were identified (median age 68.8 years, all caucasian, male 66.7%, current/former smokers 89.9%). Most patients had adenocarcinoma histology (85.3%), of whom 7.3% of mucinous and 4% of acinar subtype. Diagnostic techniques included lung biopsy (40.7%), bronchoscopy (29.4%), lung resection (10.2%), and others (19.7%). Distribution of KRAS mutations was: G12C 38.5%, G12D 13.6%, G12V 16.4%, G12A 9.0%, others 22.5%. PD-L1 expression levels were: ≥50%, 1-49%, <1% and unknown in 22.6%, 28.2%, 43.5%, and 5.6%, respectively. 112 (63.3%) patients were treated with first-line therapy (median age 67.9 years, male 68.8%, current/former smokers 93.8, adenocarcinoma 87.5%). The distribution of KRAS mutations was as follows: G12C 36.6%, G12D 17%, G12V 11.6%, G12A 11.6%, others 23.2%. PD-L1 expression levels were: ≥50%, 1-49% and <1% in 24.1%, 31.3%, and 44.6%, respectively. First-line systemic treatment was chemotherapy (50.9%), anti-PD1/PD-L1 single agent therapy (24.1%), chemo-immunotherapy (11.6%), others (13.4%). At a median follow-up of 24.3 months (range 16.0-32.6), median overall survival (mOS) of the entire series was 9.4 months (95% CI, 6.4-12.0). mOS in patients with G12C, G12D, G12V, G12A was 10.2, 6.1, 9.2, and 3.9 months, respectively. After a median follow of 26.6 months (range 21.5-31.7), mOS of patients treated with first-line treatment was 11.3 months (95% CI 6.7-16.0). mOS by mutation type in treated patients was 12.3 (G12C), 6.2 (G12D), 15.5 (G12V) 3.9 (G12A) months, respectively. No statistically significant OS differences were found by comparing one mutation subtype with all the others.



Conclusion: We report about the natural history of a real-life cohort of advanced KRAS-mutated NSCLC patients. The prevalence of different KRAS mutation subtypes was the same as previously reported. No differences in OS by mutational status were observed. However, treatment heterogeneity may have hampered these results. Further analysis including co-mutational status evaluation and progression-free survival by type of treatment are ongoing.

Keywords: Real-world data, KRAS, NSCLC

P59.21 Impact of Reflex Testing on Pathology Based Molecular Testing in Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Comprehensive molecular testing is essential to provide personalized and effective care for patients with metastatic non-squamous (non-Sq) NSCLC. Ordering of next-generation gene sequencing (NGS) is often delayed until the first medical oncology visit. To improve rates of timely comprehensive molecular profiling among newly diagnosed patients with advanced non-Sq NSCLC, we implemented a reflex, molecular testing pathway (NGS and RNA fusion panel) on tumor, nodal or metastatic specimens, initiated at the time of initial pathology review, that obviated the need for a separate specimen-specific order. Samples insufficient for the full NGS panel (156 genes) were automatically assessed by a more limited Penn Precision Panel (PPP) with 20 genes that include all NCCN recommended biomarkers. We analyzed the clinical impact of this reflex molecular ordering pathway on comprehensive pathology based molecular testing amongst patients with newly diagnosed advanced non-Sq NSCLC. **Methods:** A retrospective cohort study of newly diagnosed stage IV non-Sq NSCLC patients treated at our institution was performed. Proportion of patients tested (reflexed vs. ordered by physician), sample types used for NGS, adequacy and completeness of testing were compared between those who underwent testing prior to (2015-2016) and after implementation of reflex testing (2017-2019). We reviewed the downstream effects of reflex testing on detection of actionable alterations amongst newly diagnosed patients in 2019. The Z test was used to compare proportions (alpha = 0.05). **Results:** Between 01/2015, and 12/2019, 1161 patients with newly diagnosed non-Sq NSCLC underwent 778 molecular tests. Proportion of patients with comprehensive molecular testing increased with implementation of reflex testing, 39.2% (183/466) pre-2017 vs. 45.8% (318/695) post-2017, p= 0.03. After implementation of reflex testing in 2017, a total of 549 molecular tests were performed with 96% initiated through the reflex pathway. Cytology specimens (liquid molecular vials) were utilized with similar frequency to formalin-fixed paraffin embedded (FFPE) tissue specimens (cytology n= 286, 52%; FFPE tissue n=263, 48%, p=0.35), since cytology is utilized as the preferential testing specimen when adequate at our institution. Due to insufficient material, 120 samples were reflexed to PPP. Of these, 32.5% (39/120) were cytology specimens, 67.5% (81/120) were FFPE (p=<0.001). Among the 134 newly diagnosed patients in 2019, 46 patients (34.3%) had an actionable mutation detected by pathology based molecular testing: 38/46 (82.6%) were detected on reflex molecular testing, 26/38 (68.4%) were detected on full NGS/RNA Fusion panels, 9/38 (23.7%) were detected on the PPP panel, and 3/38 (7.9%) on a single gene molecular test. **Conclusion:** At a single institution, implementation of a reflex molecular testing pathway increased the proportion of patients who underwent comprehensive tissue-based molecular testing upon initial diagnosis of non-Sq NSCLC. Cytology specimens were used as commonly as FFPE for molecular testing, and were the preferentially used specimen at our institution. These results support the use of reflex testing pathways and cytology specimens to increase rates of comprehensive molecular testing.

Keywords: biomarker testing, Tissue testing, NGS

P59.22 Biomarker Testing for Advanced Lung Cancer by Next-Generation Sequencing in Real World Practice

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Introduction: Next-generation sequencing (NGS) -based assays for the detection of actionable drivers in non-small-cell lung cancer (NSCLC) is not widely used for clinical practices in our region in the developing countries in clinical practice. With an increasing list of actionable targets, limited tissue, and arduous single gene assays, NGS for broad trials in clinical practice is an attractive approach. We present here our experience with NGS for biomarker testing in 135 patients with advanced lung cancer **Methods:** A retrospective observational study was conducted. Consecutive stage-III and stage-IV NSCLC patients with NGS predictive biomarker testing were included. Predictive biomarker testing was performed in each patient/case using either Foundation Liquid biopsy™ Solid Tumor DNA or Oncomine Focus Assay™ on Ion-Torrent sequencing platforms. Molecular testing was carried out in the setting of the Hospital Italiano de Buenos Aires, Argentina in patients with unresectable/advanced NSCLC. **Results:** The total number of consecutive patients analyzed in the study was 135, 57% men (n=77), median age 67 years (r36-90). Within the analyzed cohort, 21.5% were non-smokers. Most patients showed adenocarcinoma histologic subtype/ histology. At least one clinically relevant actionable molecular target was detected in 48% of the patients, 27% of them with approved drugs in Argentina. Adding the possibility of entering a clinical trial, compassionate use or expanded access program, to the prevalence of patients with targetable drivers rises to 48% taking into account only actionable molecular drivers and leaving aside immunotherapy or chemo immunotherapy trials. In our cohort there were no findings for drug agnostic treatments. There were 15% of patients who, even carrying a molecular driver, could not access the drug for different reasons (clinical deterioration, issues related to bureaucracy, among others). **Conclusion:** This is a relevant study from South America that analyzes the challenge of implementing NGS in clinical practice and describes the mutational landscape of lung cancer patients to study the impact of NGS in understanding cancer biology and therapy decision-making result of treatment. Our study demonstrates the clinical utility of NGS tests to identify actionable variants and help to make treatment decisions in advanced lung cancer.

Keywords: Target therapy, Biomarker, NGS

P59.23 Biomarker Testing for Non-Small Cell Lung Cancer at a Tertiary Referral Hospital in Ireland: Challenges and Opportunitie

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Introduction: Patient selection for systemic therapy in non-small cell lung cancer (NSCLC) is based on immunologic (PD-L1) and genomic biomarkers. Availability of suitable tumour biospecimens can limit biomarker testing. Plasma genotyping is an emerging technology for biomarker testing in NSCLC. Completion of all recommended testing of NSCLC is challenging in our real world population and the rate of incomplete testing is not known. In order to assess this problem we aimed to evaluate 1. the rate of biomarker testing in NSCLC patients; 2. the proportion of patients with an identified biomarker, and 3. the rate of insufficient sample yield and number of invasive diagnostic procedures per patient, to inform a potential role for plasma genotyping. **Methods:** We retrospectively identified patients with histologically-proven NSCLC from a large tertiary referral centre in Dublin from 01/2015-12/2019. Patients with small cell lung cancer (SCLC), mesothelioma, no tissue diagnosis, and/or incomplete staging were excluded. Clinical, radiologic, and pathologic data, including PD-L1 and genomic biomarkers (EGFR, ALK, ROS1) at baseline, were collected. The number of diagnostic procedures required to obtain adequate histopathologic samples, as well as outcomes of sampling were also recorded. Ethical approval was obtained from the RCSI Hospitals Group. **Results:** A total of 1222 patients with NSCLC were identified, of which 876 were analysable (346 excluded: small cell lung cancer [N = 153], mesothelioma [N = 13], clinical diagnosis only [N = 179], and incomplete staging [N = 1]). The majority were male: 53%. The median age was 71 years. Performance status of 0 -1 was present in 68%. Tumour histology was most commonly adenocarcinoma: 55.6%. The majority of patients had advanced disease: stage III = 21%; stage IV = 36%. Biomarker results are outlined in Table 1. Most patients (63%) required more than one diagnostic procedure to procure evaluable tumour material for histologic diagnosis or biomarker testing.

Table 1: Results of biomarker tests in advanced stages of NSCLC 2015 to 2019

	EGFR Mutation (Stage IV non-squamous)	ALK Rearrangement (Stage IV non-squamous)	ROS1 Rearrangement (Stage IV non-squamous)	PD-L1 (Stage III)	PD-L1 (Stage IV, Since Approval in March 2018)
Requested	208 (86% of 243)	182 (75% of 243)	141 (58% of 243)	64 (35% of 185)	92 (81% of 113)
Present	21 (9%)	3 (2%)	4 (3%)	n/a	n/a
Absent	159 (65%)	153 (84%)	119 (84%)	n/a	n/a
≥ 50 %	n/a	n/a	n/a	20 (31%)	31 (36%)
1 – 49 %	n/a	n/a	n/a	20 (31%)	22 (24%)
< 1 %	n/a	n/a	n/a	18 (28%)	37 (40%)
Insufficient sample	28 (12%)	23 (13%)	13 (9%)	6 (9%)	2 (2%)
Assay failure	0	3 (2%)	5 (4%)	0	0

Conclusion: The proportion of PD-L1 positivity in the local population is similar to published data however identification of oncogenic driver mutations was low relative to findings in other populations. Testing for genomic biomarkers may be incomplete due to tissue sample limitations in approximately one sixth of patients. In a real-world setting, the majority of patients with NSCLC undergo multiple invasive procedures for histologic assessment/biomarker testing, a finding of important clinical implications. These findings suggest a role for plasma genotyping as a reliable and non-invasive method of biomarker testing. PD-L1 still requires a core biopsy and this remains an unmet need.

Keywords: biomarkers, non-small cell lung cancer, Plasma genotyping

P59.24 Genomic Abnormalities in Malignant Pleural Effusion of Lung Cancer Patients Detected by Multiplex Ligation-Dependent Probe Amplification

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Introduction: Malignant pleural effusion related to lung cancer (MPE-LC) is a common occurrence in medical practice and its diagnosis is a challenge for clinical laboratories. It is known that most of metastatic tumors to the pleura present chromosomal gains and losses, which can be detected by cytogenomic techniques such as the Multiplex Ligation-dependent Probe Amplification (MLPA). The aim of this study is to evaluate genomic abnormalities in tumor cells from pleural fluid (PF) of patients with lung cancer (LC) by MLPA technique. **Methods:** We evaluated 23 samples of PF: 16 samples from MPE of LC patients (13 with positive cytology, 2 negative and one suspicious) and 7 samples from patients with benign PE (cardiac transudate, parapneumonic and tuberculosis). DNA was extracted using the QIAMP DNA Blood kit (QIAGEN, Valencia, California) and the cytogenomic analysis was performed using the MLPA P175-B1 Tumor Gain kit (MRC-Holland®, Amsterdam, Netherlands), in search of pathogenic CNVs and specific point of BRAF mutations. The results were analyzed with the GeneMarker® software (SoftGenetics, LLC, State Collage, PA). **Results:** From the 16 cases of MPE-LC, MLPA identified genomic changes in 7 cases with cancer cells in the PF: 1 case with point mutation BRAF (7q34) p.V600E (c.1799T>A) and MDM2 (12q15) duplication; 1 with CDK4 (12q14), MDM2 (12q15) and CCND1 (11q12) duplications (fig 1); 1 with AURKB (17p13) deletion; 1 with AURKB (17p13) deletion and AURKA (20q13), MDM4 (1q32) duplications; 1 with EGFR (7p11), ERBB2 (17q12) and TOP2A (8p12) duplications; 1 with MDM2 (12q15) duplication and 1 case with FGFR1 (8p12) deletion, MDM2 (12q15), CCND2 (12p13) duplications and point mutation BRAF (7q34) p.V600E (c.1799T>A). MLPA analysis of control group showed normal results (fig2). **Conclusion:** The MLPA technique detected genomic abnormalities in seven MPE-LC samples, when at least 30% of tumor cells were present in the cytological examination. The findings of pathogenic variants in MPE-LC can be valuable to explore new targets for the treatment of lung cancer patients.

Keywords: MLPA, lung cancer, malignant pleural effusion

P59.25 Prognostic and Treatment Characteristics of Metastatic KRAS G12C Mutant NSCLC

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Introduction: To describe pattern of treatment and prognostic factors of survival in stage IV KRAS G12C mutant NSCLC (KRASG12C+) in Alberta, Canada **Methods:** Patient's data were retrieved from the institutional Glans-Look Lung Cancer Research database. KRASG12C+ (AJCC TNM 8th edition) in Southern Alberta, Canada during 2018-2020 periods were included. Differences in overall survival (OS) were compared using Kaplan-Meier survival Log-Rank tests. Predictors of OS were estimated using multivariate Cox Proportional Hazard statistics. A priori statistical significance was $p < 0.05$. Analyses were performed using SPSS statistical software (version 25). **Results:** 102 KRASG12C+ patients were identified. The median follow-up time was 22 months, median age was 69 years and 67% were women. 33% had brain metastasis at diagnosis. ECOG performance status was 0-1 in 38%, ≥2 in 36% or unknown in 26%. 45% (46/102) of cases expressed high PD-L1 (≥50%). Almost all were non-squamous histology (98%) with 96% being adenocarcinoma. 47% (48/102) received first-line systemic anti-cancer treatment (SACT) as pembrolizumab (26%), platinum-based chemotherapy (12%), pembrolizumab plus chemotherapy (8%), other chemotherapy (2%, includes trial and single agents). KRASG12C+ who expressed PD-L1 (≥1%) were more likely than PD-L1 negative group to receive SACT (p=0.04). Of PD-L1 high, 43% (20/46) compared to 60% (15/25) within PD-L1 negative group did not received SACT. The most common reason for no SACT was poor performance status (35%) overall and among PDL-1 high group (45%). Overall 15% (15/102) of KRASG12C+ had second-line SACT for progressive disease: 7% were ICI, 7% chemotherapy and 1% targeted therapy (EGFR TKIs). The number of treatment line ranged from 1-2. Among the SACT group, the median OS was 19.7 months. Median OS was lower in men (4.5 months) and if brain metastasis was present (4 months) Table 1. Within the pembrolizumab group, median OS was 3.5 months in male while not yet reached in female KRASG12C+ (p= 0.06). Men had higher distant disease burden with significantly higher rate of brain metastasis at diagnosis [brain metastasis (men vs women) = 46 vs 16%, p=0.04]. In multivariate analysis, male sex correlated with poorer OS [HR (male)= 1.97, p=0.02].

Table 1: Prognostic Factors Of Survival In Stage IV KRAS G12C Mutant NSCLC

Variables	Median OS, months **All patients n= 102**	Median OS, months **SACT group n= 48**	Reference variable	Hazard Ratio (95% CI) **All patients n=102**	P value for HR
Treatment category	**P <0.01**		chemotherapy		
Pembrolizumab	32.2	-		0.37 (0.12-1.16)	0.09
Platinum doublet chemotherapy	7.8	-		-	-
Pembro + platinum chemotherapy	**	-		<0.01	0.97
No SACT	2.7	-		2.11 (0.78-5.7)	0.14
Had RT (all sites)	5.7	18.9	No RT	0.91 (0.49-1.69)	0.76
Had 2L	19.7	19.7	No 2L	0.85 (0.32-2.28)	0.75
PD-L1 status	**P= 0.04**	P=0.73	PD-L1 negative		
High (≥50%)	11.8	32.2		1.33 (0.63-2.81)	0.46
Low (1-49%)	5.4	24.3		1.35 (0.61-3)	0.46
Negative	4.6	13.2		-	-
ECOG status	**P=0.02**	P=0.77	ECOG 0-1		
0-1	12.5	19.7		-	-
2-3	3.3	NR		1.8 (0.97-3.35)	0.06
Brain metastasis	**P=0.02**	**P <0.01**	No brain met.		
Yes	4.3	4		0.9 (0.5-1.6)	0.71
No	13.2	20		-	-
Median Age, yr.	69.0	68.5	-	1.0 (0.97-1)	0.88
Gender	**P <0.01**	**P <0.01**	Female		
Male	3.2	4.5		1.97 (1.12-3.5)	**0.02**
Female	12.5	24.3		-	-

***Note**: P values next to variable headings represent the Log Rank (Kaplan-Meier) values*
*** value not available for pembrolizumab plus chemotherapy group, all patients (n=8) still alive*
2L= second-line, CI= confidence interval, NR= not reached, OS= overall survival, RT= radiotherapy, SACT= systemic anti-cancer treatment

Conclusion: About half KRASG12C+ received SACT. PD-L1 positive more likely than the negative patients to be treated (p0.04). Pembrolizumab was the most common regimen (25.5%) with median OS of 32 months similar to the Keynote 024 trial finding (~30 months). Male KRASG12C+ more likely to present with brain metastasis at diagnosis and had poorer survival.

Keywords: Brain metastasis, Gender, KRAS mutant NSCLC survival

P59.26 Comparison of RT-PCR, NGS and FISH/IHC Methods in Detection of Gene Fusions

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Introduction: To establish an ALK gene fusion detection protocol from the RNA level based on quantitative reverse transcription PCR (RT-qPCR) technique and compare the consistency of the protocol with NGS and FISH/IHC methods on clinical lung cancer FFPE tissue samples. **Methods:** We applied the RT-qPCR-based ALK gene fusion detection protocol to 17 lung cancer FFPE tissue samples and compared its consistency with the NGS method. In addition, for the other 9 lung cancer FFPE tissue samples, we compared the concordance of the detection results among three methods, i.e., RT-qPCR, NGS, and FISH/IHC. **Results:** This RT-qPCR-based protocol can detect nine common EML4-ALK fusion types, which were divided into four experiment systems: ALK-1 (E13;A20), ALK-2 (E20;A20), ALK-3 (E6a;A20, E6b;A20) and ALK-4 (E2;A20, E2;ins117A20, E14; ins11del49A20, E15del60;del71A20, E18;A20). Among the 17 clinical FFPE samples, RT-qPCR detected a total of 16 positive cases and 1 negative case, which showed 100% consistency with the NGS testing results. In addition, among the 9 clinical FFPE samples tested by three methods, 6 (66.7%) were tested positive by FISH/IHC, 5 positive (55.6%) by RT-qPCR, and 5 positive (55.6%) by NGS. Seven samples had concordant results for all three methods, including 4 positive and 3 negative samples, with a consistency of 77.8%. For the two samples with inconsistent detection results, one of them was positive by FISH/IHC and RT-qPCR, and negative by NGS, and the other was positive by FISH/IHC and NGS, and negative by RT-qPCR, which was due to that the fusion form of ALK gene in this sample was out of our detection range. Therefore, if this sample was excluded, the concordance rates of RT-qPCR with FISH/IHC and NGS were 100% (8/8) and 87.5% (7/8), respectively. **Conclusion:** We established an RT-qPCR-based protocol for rapid ALK gene fusion detection which has the advantage of low cost and easy operation. The good agreement between its testing results and NGS and FISH/IHC indicates that it may have great value in clinical application.

Keywords: ALK fusion, RT-qPCR, FFPE

P59.27 Complementary Utility of Combined ALK/ROS1 FISH with Immunohistochemistry for ALK/ROS1 Rearrangement Testing in Lung Cancer

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Introduction: Testing for EGFR mutations, ALK and ROS1 rearrangements and BRAF mutations are now recommended as the essential minimum predictive biomarkers to be tested in primary non-squamous NSCLC patients presenting with advanced disease. While the ALK D5F3 Ventana immunohistochemistry (IHC) Assay is approved for detection of ALK rearrangements and for targeted therapy, ROS1 IHC only serves as a screening tool for ROS1 rearrangements with demonstration of gene fusions by molecular methods required for confirmation and targeted treatment. Nevertheless, equivocal IHC results, although uncommon, still occur with the D5F3 ALK assay necessitating complementary methods for confirmation. The recent availability of combined ALK/ROS1 break-apart fluorescence in-situ hybridisation (FISH) probes offer the advantage of tissue conservation with ability to analyse both gene alterations in a single tissue section. The aim of the present study was to study the utility of the combined ALK/ROS1 FISH assay as a complement to ALK and ROS1 IHC in routine predictive biomarker testing algorithms. **Methods:** Over a 6-year study period, all EGFR wild type NSCLC samples were subject to automated ALK D5F3 Ventana IHC assay and ROS1 IHC using the D4D6 (Cell signalling technology) clone as a manual lab developed test. Diffuse strong granular staining in tumor cells for ALK and ROS1 protein was interpreted as positive. All cases of equivocal ALK staining and positive ROS1 staining was subject to combined ALK/ROS1 FISH using the FlexISH ALK/ROS1 DistinguISH Probe (Vysis) performed as per manufacturers' instructions. Presence of ALK/ROS1 break apart signals and/or isolated ALK/ROS1 3' signals in >15% of interpretable tumour nuclei was considered as positive for ALK or ROS1 rearrangement. **Results:** The ALK Ventana Assay was performed in 711 formalin fixed paraffin embedded EGFR wild type NSCLC samples including biopsies, lymph node excisions and cell blocks. Of these, 12% (85/711) were positive, 2% (13/711) were equivocal, 75% (539/711) were negative, while in the remaining 11% (76/711), result could not be evaluated due to exhaustion of tumor tissue. FISH analysis in four of the ALK IHC equivocal cases show absence of ALK translocations while no tissue remained for FISH analysis in the remaining equivocal cases. ROS1 IHC was performed in 434 cases of the above cohort of which 7% (30/434) were positive. ROS1 immunopositivity was enriched among ALK IHC positive cases with 43% (19/44) of ALK IHC positive cases also showing protein expression of ROS1. FISH analysis revealed ROS1 translocation in two cases (both showing diffuse strong ROS1 protein expression and negative ALK IHC) while all dual ALK/ROS IHC positive cases tested by FISH showed presence of only ALK rearrangements with non-rearranged ROS1 signals. **Conclusion:** Tissue adequacy remains the major limiting factor for predictive biomarker testing in lung cancer. The use of combined ALK-ROS FISH allows for excellent demonstration of ALK and ROS1 rearrangements in the same section using the same criteria validated in single gene break apart FISH probes. ROS1 protein is commonly overexpressed in ALK rearranged NSCLC and may represent cross reactivity with ALK or a related protein.

Keywords: ALK, ROS1, FISH

P59.28 Protocol Adaptation for gDNA Extraction of FFPE Samples of Lung Adenocarcinoma Tissue and Related Mediastinal Lymph Nodes

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Introduction: Lung adenocarcinoma, the most common subtype of non-small-cell lung carcinoma (NSCLC), is characterized by low response to treatment with 50% rate of metastases at diagnosis and low five-year survival. To associate the molecular evaluation of mediastinal lymph nodes (MLN) obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) to the histological examination could improve TNM staging and diagnosis. Our objective is to adapt and optimize the genomic DNA (gDNA) extraction protocol to be used in formalin-fixed paraffin-embedded (FFPE) samples from tumor tissue and mediastinal lymph nodes for molecular analysis. **Methods:** The gDNA from 28 paired samples of primary tumor (PT) obtained by transthoracic biopsy or tumor resection, and MLN obtained by EBUS-TBNA were extracted with GeneRead DNA FFPE kit (Qiagen). Fourteen paired samples were submitted to the manufacturer's protocol (MP- one 10 µm cut of FFPE samples incubated in deparafinization solution for 3 minutes at 56° C, followed by incubation in proteinase K, RNAse free water and FTB buffer for 1 hour at 56°C); eight paired FFPE samples were submitted to an adapted protocol (AP- no use of deparafinization solution, 3-4 10 µm cuts of directly incubated in a mix containing proteinase K, RNAse free water and FTB buffer for 3 hours at 56ºC), and 6 paired samples were submitted to both protocols (MP-AP). The gDNA quantification was performed in the Qubit 3.0 fluorometer (Thermo Fisher Scientific). Paired t test was applied, considering statistically significant $p \leq 0.05$. **Results:** The range of gDNA yield obtained in the MP was 0.121-8.51 ng/µL for tumor samples and 0.025-1.14 ng/µL for MLN samples, and 1.04-26.0 ng/µL and 0.065-3.11 ng/µL, respectively, in the AP. In the paired samples extracted using both protocols, the range of gDNA obtained was 0.121-2.65 ng/µL and 1.04-4.95 ng/µL for PT samples ($p=0.030$) and 0.043-0.054 ng/µL and 0.065-3.11 ng/µL for MLN samples ($p = 0.071$). **Conclusion:** To obtain purified gDNA from FFPE samples is a laborious process, especially in archived samples over 5 years old and in samples with scarce cellularity, as are the small fragments of lung tissue obtained by transthoracic biopsy, or MLN fragments obtained by EBUS/TBNA. We observed a significant improving in the gDNA extraction for tumor samples using the AP protocol and a trend in improving for MLN samples, probably due to the small sample size. Changes in commercial protocols are frequently required to ensure better molecular results in these types of samples.

Keywords: FFPE samples, Lung adenocarcinoma, gDNA extraction

P59.29 Frequency of PIK3CA Mutations and Therapeutic Outcomes in NSCLC

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Introduction: PIK3CA (phosphatidylinositol-3 kinase) mutations have been found in multiple tumor sites including NSCLC among others, in the latter the frequency range between 2-7%. It has been related to cell growth, metabolism and survival as part of the PI3K-AKT-mTOR pathway. As part of this pathway, it may be amenable to targeted therapies which target mTOR. **Methods:** We conducted a retrospective study using the institutional Glans Look Lung Cancer Research (GLR) database, which contains demographics, treatment and outcome data. A cohort was extracted from the GLR comprised of patients diagnosed with a non-small cell cancer, between 2011 and 2020, with a PIK3CA mutation, complete pathology and molecular analysis. They were stratified by demographics (sex, age, ECOG, etc.), tumor characteristics (PIK3CA mutation type, associated co-mutations, PD-L1 status) and treatment (initial and subsequent treatment, type of therapy, etc.). The endpoints were frequency and type PIK3CA mutations, association with co-mutations and impact on treatment efficacy. **Results:** 25 patients were identified, 56% were female, 70.84 was the median age at diagnosis, 52% were ECOG 1, 48% were Stage IV with 84% being Adenocarcinomas and 52% had confirmed smoking history. By data cut off 36% were still alive.

	E545K	E542K	H1047R	H1047L
PIK3CA (n:25)	11 (44%)	7 (28%)	6 (24%)	1 (4%)
EGFR (n:9)	3 (33.3%)	3 (33.3%)	3 (33.3%)	0
Sensitive (Del19, L858R)	2	1	3	
Resistance (Exon 20 Insertion)		1		
Intermediate (Exon18/Exon20)	1	1		
KRAS (n:1)		1 (100%)		
ALK (n:1)	1 (100%)			
ROS-1 (n:1)				1 (100%)
PD-L1 Expression (n:22)	10 (45.4%)	6 (27.2%)	5 (22.7%)	1 (4.5%)
High >50% (22.7%)	2	2	1	
Low 1-49% (22.7%)	3	1	1	
Negative <1% (54.5%)	5	3	3	1

48% of PIK3CA mutations had an associated co-mutation. KRAS and ROS1 were unspecific and not targeted. The median survival on EGFR inhibitors was 24.84m (22.48m including Poziotinib), 27.3m on Alectinib and 10.64m on Immunotherapy. These were affected by comorbidities, performance status and side effects.

	Stage I (n:2)	Stage II (n:2)	Stage IIIA (n:3)	Stage IIIB (n:5)	Stage IIIC (n:1)	Stage IVA (n:4)	Stage IVB (n:8)
Curative Intent	1	2	2	3			
Surgery/Adjuvant Chemotherapy +/- RT		1		1			
Radical RT	1	1	2				
Concurrent ChemoRT +/- Durvalumab				2			
Recurrence/Progression	No	Yes	Yes	Yes			
Total (n)		1	1	3			
Palliative Setting	1	1	2	2	1	4	8
Declined/No further Tx	1			1		2	1
Palliative RT (1st L)			1	1	1		2
Chemotherapy (1st L)						1	1
Chemo + Pembrolizumab (1st L)							1
TKI (1st L)		1	1	1		1	3
Gefitinib			1	1			1
Afatinib		1		1		1	1
Alectinib							1
Immunotherapy (1st L)				1			
Nivolumab				1			
Pembrolizumab							
Progression to 1st L		No	No	Yes	Yes	Yes	Yes
2nd Line Tx (n)				2	1	1	2
TKI (2nd L)				1			2
Immunotherapy (2nd L)				1			1
Chemotherapy (2nd L)					1	1	
Progression to 2nd L						Yes	
3rd Line Tx (n)						1	
Alive (n:9 - 36%)	1 (50%)	2 (100%)	2 (66%)	0	1 (100%)	0	3 (37.5%)

Conclusion: PIK3CA mutations did not follow a specific pattern and, despite being associated with other mutations in almost half the cases, they do not seem to influence treatment response or median survival either with TKI or checkpoint inhibitors. Infrequent mutations need to be further assessed to determine their impact while future research should focus on defining the subgroup where inhibitors of the AKT pathway may prove beneficial.

Keywords: Co-mutations, NSCLC, PIK3CA

P59.30 Genomic Landscape of Lung Cancer in the Young

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Introduction: Lung cancer in the young is a rare and poorly understood entity. Various studies have reported a high frequency of actionable mutations in young patients. In this study we explored the genomic landscape of non-small cell lung cancer (NSCLC) in younger and older patients from a predominantly non-smoker population. **Methods:** Comparative study of the genomic profile of NSCLC young (≤40 years old) vs older patients (>40 years old) from Instituto Nacional de Enfermedades Neoplásicas (INEN). Archival paraffin-embedded tumor samples were profiled with NGS using the FoundationOne CDx assay to identify short variants alterations (insertions and deletions), copy number variations (CNV), tumor mutational burden and microsatellite instability in 324 driver genes and rearrangements in 28 commonly rearranged genes. TMB was defined as the total number of all synonymous and non-synonymous variants present at >5% allele frequency and reported as mut/Mb. It is classified in low (≤5 mut/Mb), intermediate (6 to 19 Mut/Mb) and high TMB (≥20Mut/Mb). **Results:** Overall, 62 tumors were profiled, 32 from young and 30 from older patients. Clinicopathological features (smoking status, clinical stage, and histology) were similar between groups, except for gender (65.6% of females in the younger group vs 40% in the older group, p=0.043). At least one actionable mutation was found in 84.4% vs 83.3% in younger vs older patients, respectively. Alteration rates in main genes were: BRAF, 3.1% (n=1) vs 0%; EGFR, 46.9% (n=15) vs 43.3% (n=13); ERBB2, 12.5% (n=4) vs 16.7% (n=5); KRAS, 15.6% (n=5) vs 16.7% (n=5); ALK, 6.3% (n=2) vs 3.3% (n=1); RET, 0% vs 3.3% (n=1); ROS1, 3.1% (n=1) vs 3.3% (n=1); NTRK1, 0% vs 3.3% (n=1) and MET, 3.1% (n=1) vs 13.3% (n=4). Mean TMB was 4.04 Mut/Mb (SD±3.98) for young vs 8.06 Mut/Mb (SD±9.84) for older patients (p=0.016). There were not significant differences in CVN, frequency of gene rearrangements, or microsatellites instability. **Conclusion:** Both groups had a remarkably high frequency of actionable alterations and overall, there is a great opportunity of treatment with targeted therapy for our whole patients' population with NSCLC. Unlike previous reports, a similar distribution of clinicopathological variables between the age groups was found except for a female preponderance among the young and. In our context, where lung cancer is a disease occurring predominantly in non-smokers in both the young and in the older, no significant differences in the proportion of targetable mutations between younger and older patients were detected.

Keywords: non-small cell lung cancer, Genomic profiling, tumor mutational burden

P59.31 A High Number of Co-Current Genetic Alterations Is Associated With Poor Survival in EGFR Mutated Metastatic NSCLC Patients

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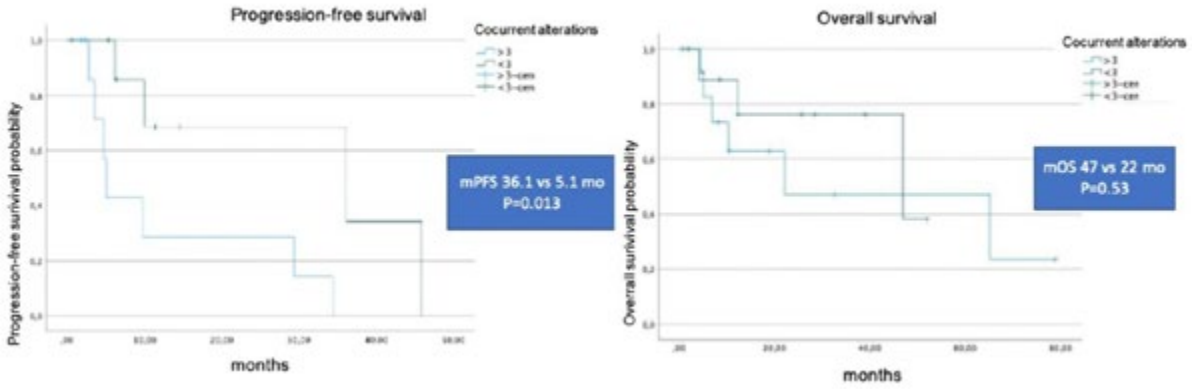
Introduction: Patients with NSCLC harboring EGFR mutations have good tumor responses with EGFR TKI, however approximately 10% of patients show no disease control. Survival in patients receiving EGFR-TKI is associated with the number of genomic alterations and TMB also been associated with worse clinical outcomes. The importance of co-current genomic alterations detected by foundation one remains to be determined. We decide to explore the importance of co-current alterations in our NSCLC patients with EGFR mutations. **Methods:** In a single center from March 2018 to February 2020 we analyzed prospectively 23 tumor tissue of NSCLC patients with EGFR mutations. Patients were diagnosed with RT PCR, and underwent genotyping using Next generation sequencing platform, Foundation One assay. Kaplan Meier curves were used to evaluate median progression-free survival (PFS) and Overall survival (OS). **Results:** Twenty three patients were evaluated in this cohort. Mean age was 57. 56.5% patients were never smoker. 13 (56.5%) patients had >3 co-current genomic alterations in the foundation one assay. Adenocarcinoma was the only histological type (100%) and solid pattern the most common subtype (34.8%). Exon 19 del and L858R were the most common mutations. 11 patients received EGFR- TKI as first-line treatment. The most common co- current alteration was TP53 mutation in 12 patients (48%). A ROC curve was done and 3 mutations was related with a difference in survival (AUC 0.67 sensitivity: 90.3 %, specificity: 71.2%). Median PFS was 36.1 vs 5.1 months in patients with <3 vs >3 mutations (p= 0.013). OS was higher in the <3 mutations group, with median OS of 47 months vs 22 months but this was not significant. (p=0.53) (Figure 1)



Conclusion: In NSCLC patients with EGFR mutations treated with EGFR-TKI the presence of three or more genomic alterations evaluated by the Foundation one assay was associated with worse survival.

Keywords: Foundation One, EGFR, co mutations

P59.32 Physician Attitudes Toward Genetic Testing and Targeted Therapy for Advanced NSCLC Patients in China: A Nationwide Survey

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Introduction: The purpose of this survey is to explore the situation of genetic testing and targeted therapy in advanced non-small cell lung cancer (NSCLC) patients in China. **Methods:** The survey was conducted in oncology, respiratory and thoracic surgery departments between May 2020 and September 2020 across 135 cities in China. The participating physicians had >5 years of clinical experience in NSCLC diagnosis and treatment. **Results:** Among 450 participating physicians, 361(80.2%) and 89 (19.8%) were from the tertiary and non-tertiary hospitals, respectively. For newly diagnosed patients, epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) rearrangement, and ROS proto-oncogene 1 (ROS1) fusion testing were recommended by 83.4%, 72.9% and 68.3% of physicians, respectively. For patients who had not received any tyrosine kinase inhibitor (TKI) therapy, who had received one line, and who had received ≥2 lines of TKI therapy, the recommended percentage of genetic testing by physicians declined gradually, which were 81%, 56% and 45%, respectively. Similarly, with the increasing number of TKIs treatment lines, the genetic testing rate of patients decreased gradually, which were 77.9%, 59.5% and 46.7%. Patients refused genetic testing either because their incomprehension or it was costly. The accessibilities of genetic testing of EGFR, ALK and ROS1 in respective pathology departments were 81.9%, 75.5% and 65.6%, respectively. Among the newly diagnosed patients with EGFR mutation, 77% received TKI therapy during first-line treatment, of which 49% were treated with Gefitinib. Furthermore, among patients with ALK rearrangement, 71% received TKI therapy during first-line treatment, of which 64% were treated with Crizotinib. Among patients with ROS1 fusion, 65% received TKI therapy during first-line treatment, of which 88% patients were treated with Crizotinib. The recommended percentage of physicians, the percentage of patients' genetic testing and the proportion of TKIs use were all higher numerically in tertiary hospitals. **Conclusion:** Although driver gene mutation is common in Asian NSCLC patients, some newly diagnosed Chinese patients failed to undergo timely testing and consequent targeted therapy, especially for ROS1 fusion. Compared to the tertiary hospitals, the physicians' awareness of genetic testing, accessibility of genetic testing of the hospital, and patients' genetic testing rate were lower in non-tertiary hospitals. Patients with EGFR mutation or ALK rearrangement received more targeted therapy than those with ROS1 fusion. Thus, imparting education on ALK and ROS1 to physicians and patients is imperative to increase the recommended percentage of genetic testing and the proportion of targeted drug therapy.

Keywords: genetic testing, targeted therapy, non-small cell lung cancer

P60.01 Investigation of Aurora Kinase A as a Potential Biomarker of Radiation in Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Aurora Kinases belong to a family of serine/threonine kinases with three known subtypes: AURKA, Aurora B (AURKB) and Aurora C (AURKC) (Tao et al., 2008). Their overexpression is linked to tumorigenesis, chemotherapy, and radiation resistance. AURKA inhibition leading to enhanced radiosensitivity has been demonstrated in our laboratory. There is interest in determining whether the increased expression of AURKA is linked to patient survival. The purpose of this study is to examine the correlation between increased AURKA expression in patient biopsies and survival in patients with NSCLC. **Methods:** One hundred and one patients were recruited to a prospective study where the patient was offered radical and high dose palliative radiation for NSCLC—65% of patients presented with stage III and IV advanced disease. Archived biopsy samples collected before radiotherapy were stained for AURKA expression using immunohistochemistry. The tumour cells on each slide were counted and categorised as negative, borderline, weak or definite staining. The percentage ratio of staining on each slide between each category was recorded. The combined percentage of weak and definite categories in each slide were added and classified as a "positive stain" with borderline and negative categories a "negative stain". The mean of the combinations of weak and definite stains in all slides was calculated (12.92%). Slides with a combined total percentage of weak and definite staining greater than 12.92% would be defined as AURKA positive. The mean staining of weak and definite slides was correlated with overall and progression-free survival. **Results:** The median overall survival for patients entering the study was 266 days (8.8 months), 95% Confidence Interval (CI), 203 - 374 days). Median progression-free survival was 171 days (5.7 months (95% CI 116 - 279 days). There was no statistical difference in overall and progression-free survival between AURKA positive and AURKA negative biopsies. (figure1).

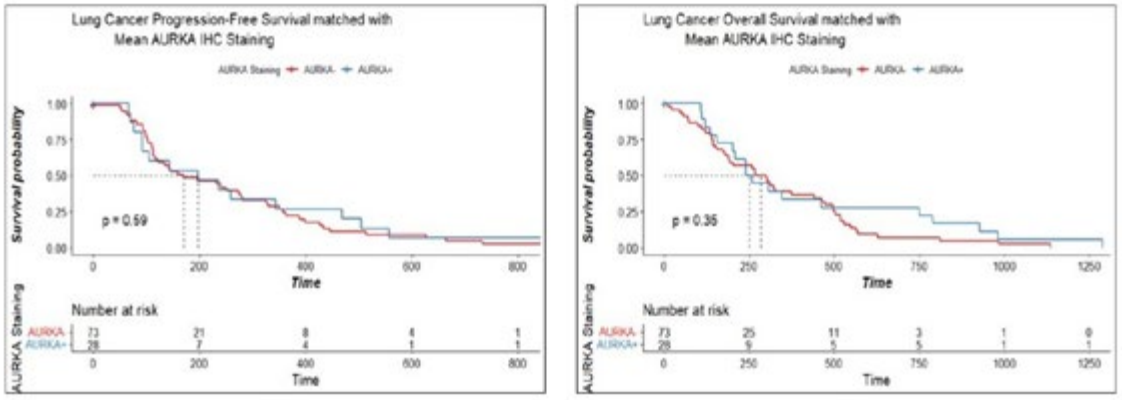

Figure1: Kaplan-Meir curves demonstrating the correlation between Aurora Kinase staining with overall and progression-free survival. Both survival curves demonstrate no statistically significant difference in survival. **Conclusion:** Conclusions: The expression of AURKA did not result in significant differences in overall or progression-free survival.

Keywords: Pathology, non-small cell lung cancer, Radiation Biomarker

P60.02 Polymorphisms of APE1(T444G), hOGG1(C977G), XRCC1(G839A), XPD(T2251G), XPG(G3310C), XPC(A2815C) Genes in Lung Cancer Patients

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Introduction: Lung cancer (LC) the leading cause of cancer deaths in males for decades, has recently become one of commonest causes for women too. The DNA repair system is the first barrier in the onset pathway of genomic instability and carcinogenesis under the effect of mutagens. As has been shown in some studies, genetic polymorphisms of the DNA repair system are associated with the risk of LC development (Cai et al.,2014; Liu et al., 2017; Zhou et al.,2015). **Methods:** We examined 273 newly diagnosed LC patients (female, mean age = 58.5 years) received medical treatment in the Kemerovo Regional Oncology Center (Kemerovo, Russian Federation), and 249 healthy donors from Kemerovo, Russian Federation, (female, mean age = 54.0 years) were investigated in this study. For this study, blood samples from LC patients were obtained prior to all diagnostic or therapeutic procedures. All healthy donors included in the control group did not have any chronic diseases, not take any drugs with knowning mutagenic effects. DNA was isolated from venous blood using a standard procedure. The polymorphic markers - APE1(T444G), hOGG1(C977G), XRCC1(G839A), XPD(T2251G), XPG(G3310C), XPC(A2815C), - were genotyped using an allele specific PCR (the single nucleotide polymorphism (SNP) express method and the reagent kit were designed by Lytech Research and Production Co., Moscow, Russia). Statistical analysis was carried out using the software SNPstats (http://bioinfo.iconcologia.net/SNPstats), «Statistica 10.0» (StatSoft Inc., USA). The expected frequency of control genotypes was checked by the Hardy-Weinberg equilibrium test through on-line testing software (http://ihg.gsf.de/cgi-bin/hw/ hwa1.pl). **Results:** In this study, we profiled SNPs located within DNA repair genes in 273 genomic DNA samples from LC patients and 249 genomic DNA samples from healthy donors. The distribution of genotypes and allele frequencies in each group were in accordance with Hardy–Weinberg equilibrium. A statistically significant association was found between the LC and the XPC gene polymorphism rs2228001. In LC patients, the frequency of the A allele was 57.0% compared with 68.0% in the control group (P=0.0002), which indicates that this allele is a marker of a low risk of LC. The association with LC was most significant (according to the minimum Akaike criterion) in the dominant model, for which the odds ratio [adjusted for age and smoking (ORadj)] was 0.56 (95%CI:0.39–0.81,Padj= 0.0018). In addition, APEX1, rs1130409 gene polymorphism had a protective effect (log-additive model: ORadj=0.71;95%CI=0.54–0.92;padj=0.0095) against the risk of LC in women. The frequency of the T allele was 53.0% in LC patients compared with 62.0% in the control group (P=0.0029). **Conclusion:** Our obtained results indicate that the presence of the major allele A of the XPC gene and the major allele T of the APEX1 gene is associated with a protective effect for LC. The obtained results indicate that a search would be justified of promising markers for a carcinogenic among genetic polymorphisms of the DNA repair enzymes. Funding.This work was carried out with the financial support of the state assignment No. 0352-2019-0011 and with the financial support grant of the RFBR and the Kemerovo region in the framework of the scientific project no. 20-44-420012 r_a.

Keywords: lung cancer, polymorphisms of the DNA repair system, genes

P60.03 Transcriptome and Genome Profiles of Metastatic Lung Cancers Highlighted Predictive Power of Infection-Related Model in Metastasis

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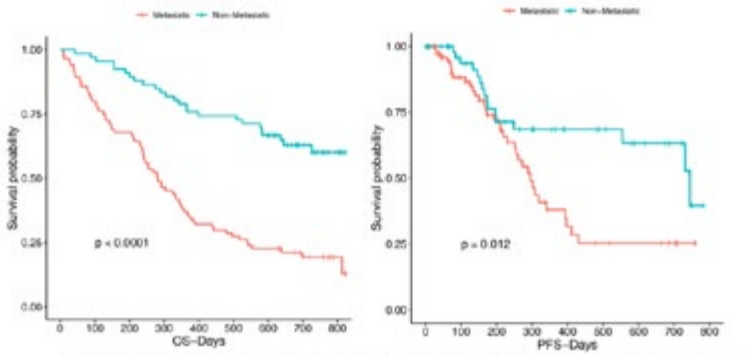
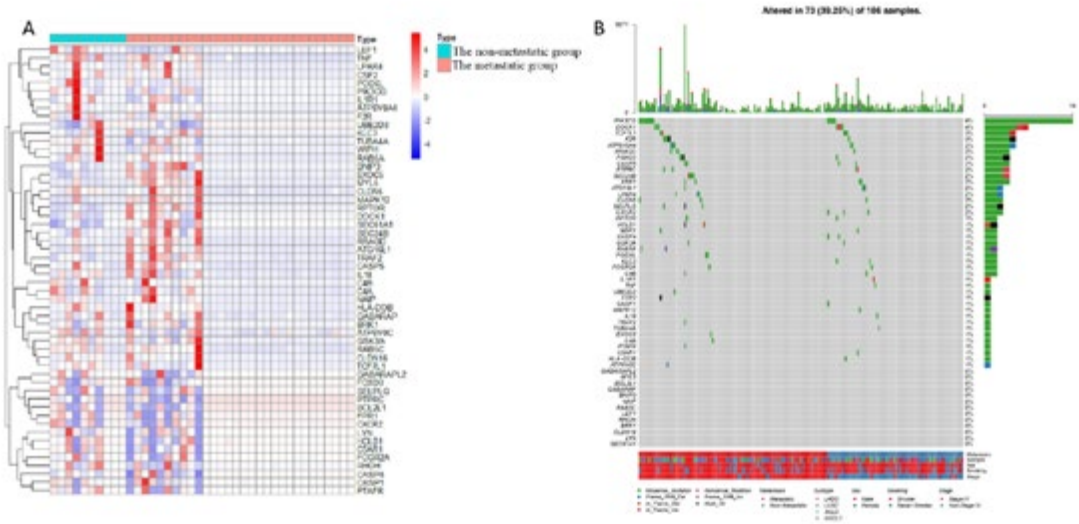
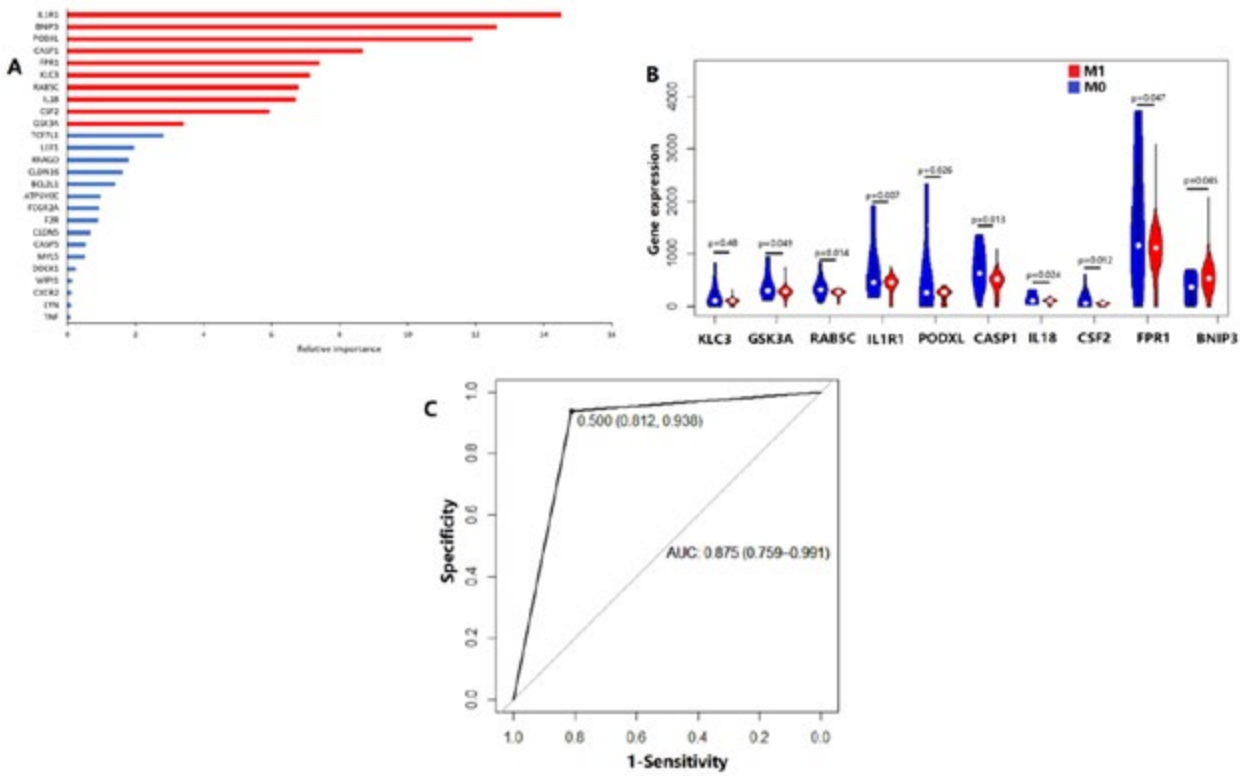
Introduction: Metastasis seriously affected the prognosis of lung cancer. The close relationship between microbes and lung cancer was found. However, the roles of infection-related pathways and genes in lung cancer metastasis remained unclear. **Methods:** We performed RNA sequencing and Whole-exome sequencing on a total of 197 lung cancer samples. We explored the complex correlation among metastasis, infection-related genes expression, genes mutation status, survival, tumor mutation burden, and therapeutic response. Then, we employed the public cohort with 865 lung cancer patients to validate our clinical findings and construct predictive models. After genes selection by machine learning method, infection-based models were built and their predictive performance in metastasis were evaluated. **Results:** The transcriptome and genome profiles of metastatic lung cancer patients were summarized. Between the metastatic and non-metastatic groups, our findings showed that a total of 2283 genes were differentially expressed, and 53 genes were differentially mutated. When compared with metastatic patients, non-metastatic patients showed longer overall survival (p<0.001) and progression free survival (p=0.012). We identified 7 metastasis-related infection pathways and corresponding top 10 genes, which were used for the construction of the final XGBoost model and the clinical nomogram. The AUCs of above two predictive models was 0.875 and 0.646, respectively.



A. Survival analysis by metastatic status in lung cancer



B. The expression profile and the mutation profile of 54 infection-related genes in lung cancer.



Conclusion: The study highlighted that combining infection-related genes presented good prediction performance in lung cancer metastasis. And these ten infection-related genes were potential to be clinical targets against metastasis of lung cancer. The nomogram helped clinicians identify patients at high risk of metastasis.

Keywords: lung cancer, metastasis, microbes

P60.04 TTF1 Expression in Advanced Lung Adenocarcinoma and Survival Outcome: An Observational Study

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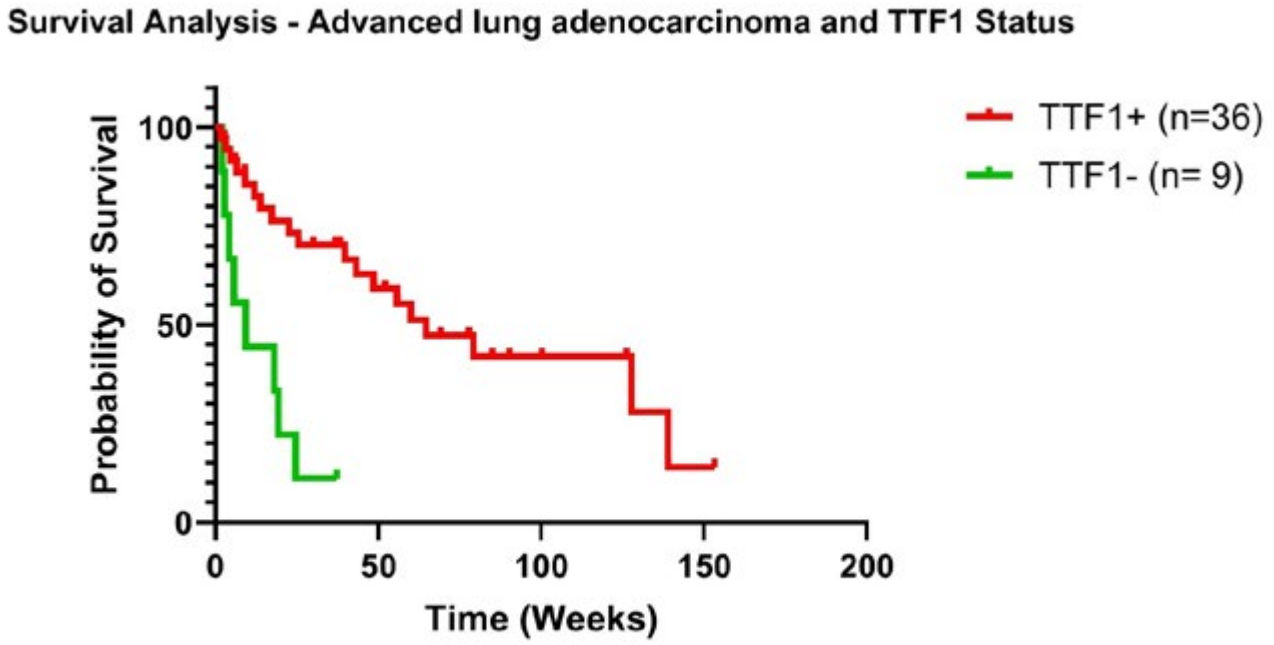
Introduction: Prognosis of advanced lung adenocarcinoma remains poor despite significant advances in treatment options. Current literature calls for independent prognostic biomarkers to better stratify patient risk. Thyroid transcription factor 1 (TTF1) is regulatory protein that is suggested to be a favourable prognostic indicator independent of stage at diagnosis. The mechanism for this remains unclear with loss of differentiation of tumour a possible explanation. Further research, however, is needed for clinical application. This study explores TTF1 expression in adenocarcinoma of the lung and its correlation to survival outcomes as well as explores patterns of incidence in relation to tumour grade, gain of function mutations and PD-L1 status. **Methods:** This is a retrospective, observational, single-centre study of lung adenocarcinoma diagnosed between July 2017 and July 2020 in a large regional cancer centre in Victoria, Australia. Immunohistochemical reports and patient specific data were collected from patient records and analysed with simple descriptive statistics, binomial testing and Kaplan-Meier survival curves. **Results:** A total of 86 adenocarcinoma of lung primary cases were identified (Age Range 49-89, Mean 69, ratio female to male 56%:44%). Of the total cases, 83% were TTF1 positive (n=71) and 13% negative (n=10). Gain of function mutations were present in 10.5% (n=9) of the cohort, with majority of these cases being TTF1 positive (78%, n=7). PD-L1 status analysis was completed in 44.7% of cases, with a majority being TTF1 positive (80% n=20). Overall, TTF1 negative tumours appeared more likely to be poorly differentiated (p=0.02), however TTF1 positive tumours did not have a significant association with well differentiated tumours (p=0.56). Overall, TTF1 positive tumours had a significantly longer survival compared to TTF1 negative tumours (median survival 64.7 weeks vs 9.4 weeks, on univariate analysis p<0.0004) . TTF1 positive tumours seem to have a longer overall survival regardless of their PD-L1 status, compared to the TTF1 negative group (p=0.04).



Conclusion: TTF-1 expression in lung adenocarcinoma appears to be a good prognostic indicator regardless of PD-L1 status. Whilst TTF-1 negative status appears to be correlated with poorly differentiated tumours, positive TTF1 status does not necessarily reflect a degree of differentiation. These findings, are hypothesis generating and being planned to be validated in a larger cohort in a prospective manner, to define the clinical utility of TTF1 as a predictive/prognostic biomarker.

Keywords: TTF1, prognosis, Lung adenocarcinoma

P60.05 Radiomic Signature to Predict Outcomes in EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: Lung cancer with a detectable EGFR mutation represents between 15% and 50% of cases depending on the geographic area. There are currently 5 approved tyrosine kinase inhibitors (TKI), including first, second, and third generations. Although osimertinib is currently the standard of care, cost-effectiveness could be improved by identifying a subset of patients who will present longer progression-free survival (PFS) with other more accessible treatments. We propose a non-invasive approach based on radiomics and machine learning to identify these patients' risk of progression. **Methods:** We included histologically proven cases of NSCLC with confirmed EGFR mutations (exon 18, 19, and 21), from patients who started TKI-therapy between January 2012 and January 2020 and had a 12-months follow-up. The primary endpoint was PFS after 12 months of treatment, obtained from RECIST assessment in CT or from death cause. We performed manual volumetric segmentation of lung lesions in CT scans acquired before EGFR-TKI administration and extracted 70 radiomic features using three filter types, obtaining a total of 182 features per patient. We evaluated eight machine learning algorithms with several hyperparameters configurations using leave-one-out cross-validation (LOOCV). The models were compared with the mean accuracy across folds. **Results:** A total of 44 patients with EGFR variant–positive NSCLC receiving EGFR-TKI therapy were included, of which 19 cases (44%) showed progression at 12 months (age at treatment start: 71 (14) years; 68% females; 16 on erlotinib, 2 on afatinib, 1 on osimertinib) and 25 (66%) presented PFS of more than 12 months (age at treatment start: 74 (9) years; 76% females; 16 on erlotinib, 4 on afatinib, 4 on osimertinib, 1 on gefitinib). The higher LOOCV accuracy was 0.71, obtained using a decision tree that showed a sensitivity of 88% in detecting PFS patients and a negative predictive value of 75% (22 true PFS, 9 true progressions). The selected decision tree used three radiomic features: median intensity in the unfiltered image, minimum intensity in the laplacian-filtered image (sigma=1) and difference entropy in the laplacian-filtered (sigma=3). Additionally, within the PFS group, a random forest classifier distinguished between patients with stable disease and cases of partial response with a mean accuracy of 0.84 on LOOCV. **Conclusion:** These preliminary results are a promising first step in adopting radiomic signatures as risk factors for treatment choice in NSCLC patients. A larger dataset is needed to increase the significance of results, and this will be achieved by following the methodology pipeline developed for this work: each new patient admitted to our institution for TKI therapy undergoes segmentation and radiomic extraction of the tumor in the baseline CT scan before starting treatment. Building a reliable dataset is a crucial step that opens the door for developing multiple predictive models. A multicenter study, guiding other health institutions to follow the proposed pipeline, would further increase predictive accuracy and robustness of results. This could enable a cost-effective, noninvasive preliminary identification of patients with advanced-stage variant-positive NSCLC who could benefit significantly from EGFR-TKI treatment.

Keywords: Artificial Intelligence, EGFR, lung cancer

P60.06 Systematic Variant Profiling Delineates the Radiogenomic Landscape of Cancer

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Introduction: The impact of common or rare gene mutations on the sensitivity of cancers to ionizing radiation remains largely unknown. We conducted a systematic, arrayed (single variant per well) profiling effort to identify gene mutations that alter cellular sensitivity to radiation and validated some of our findings using a clinical cohort of patients who received thoracic radiotherapy alone. **Methods:** Candidate mutations were prioritized on the basis of genotype-phenotype associations from our previously completed large-scale cancer cell line irradiation profiling study (doi: 10.1038/ncomms11428), location within conserved protein domains, and functional impact (MutationAssessor). We used site-directed mutagenesis to generate mutant clones (2 clones per variant) and transferred the ORFs into lentiviral vectors in SV40 lung primary immortalized cells (BEAS2B). For clinical validation, an IRB-approved study was used to identify patients treated with lung radiotherapy alone. 197 patients with primary (stage I–IV) or recurrent lung cancer and patients with other cancer types and solitary metastases or oligometastases to the lung were included. Death without evidence of local failure was treated as a competing event, and Fine and Gray regression modeling was used to examine potential predictors of local failure. **Results:** Over 600 cancer variants were tested in ~1200 experimental replicates, comprising 91 genes. We identified known and new radioresistant and radiosensitive variants involved in several cellular functional categories including cellular signaling, cytoskeleton, cell cycle, apoptosis, DNA methylation, and DNA repair. Variants that conferred resistance in BEAS2B cells were significantly more likely to confer resistance in TERT-HU1 and NCI-H520 cells, suggesting that most functional variants are cellular context indifferent. Variants under somatic oncogenic selection (hotspot mutants) were significantly more likely to confer resistance to radiation. Several infrequent cancer variants (< 1% prevalence in cancer), including those in ERBB3, SMAD4, TGFBR1, VHL, CTNNB1, and MAP2K1, conferred radiation resistance. Some genes (e.g. KEAP1) demonstrated significant intragenic allelic variation in the magnitude of conferred resistance and other genes (e.g. CTNNB1) displayed both resistance and sensitivity in a protein domain-dependent manner. KRAS (resistant; HR 2.23; P= 0.02) and CTNNB1 exon 3 (sensitive; HR 0.3; P = 0.04) mutants conferred resistance and sensitivity, respectively, to radiotherapy in our clinical cohort. **Conclusion:** We report on a large-scale profiling effort to identify mutant alleles that govern radiation survival. Our results reveal new insights into potentially actionable determinants of tumor sensitivity to radiotherapy and accelerate clinical validation of common and rare gene mutations that impact radiation sensitivity.

Keywords: radiotherapy, mutations, genetic

P60.07 Comprehensive Genomic Profiling of Microsatellite Instability-High Lung Cancer in China

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Introduction: Microsatellite instability-high (MSI-H) is the first indication biomarker for pan-cancer immunotherapy approved by FDA. However, it is rare in lung cancer, the understanding of the molecular characteristics of MSI-H lung cancer still limited, especially in Chinese patients. **Methods:** The next-generation sequencing and clinicopathological data of 8492 Chinese lung cancer patients in the Geneplus database were analyzed retrospectively, including 1021 genes, MSI loci and tumor mutational burden (TMB) analysis information. MSI was analyzed using MSIsensor (v0.2), and the threshold of MSI-H was 8. TMB analysis interrogated single nucleotide variants, small insertion and deletion, with VAF ≥ 3%. TMB-H patients were identified with ≥ 9 mut/MB (upper quartile of data from Geneplus). **Results:** MSI-H was identified in 38 patients (0.45%), including 19 cases of lung adenocarcinoma, 6 cases of lung squamous cell carcinoma, 6 cases of small cell lung cancer and 7 cases of lung cancer with unknown pathological results. The median age of diagnosis was 62 (range: 16-78), and male patients accounted for 63.16%, 68% of them were stage IV. TMB, POLD/POLE1 and common driver alterations were observed in 73.68%, 21.05% and 44.74% MSI-H patients respectively. The driver alterations included EGFR mutation/amplification (12 cases), ALK fusion (3 cases), HER2 amplification (1 case) and ROS1 fusion (1 case). The most recurrent mutant genes were TP53 (78.95%), LRP1B (50.00%), MLL2 (44.74%), EGFR (44.74%) and FAT1 (39.47%). MSI-H patients were further divided into MMR group and non-MMR group according to somatic mismatch repair (MMR) genes mutated or not. Twenty patients were included in MMR group, with MLH1 (50%), MSH3 (45%) MSH2(10%), MLH3(5%) and MSH6 (5%) mutations, respectively. MMR gene germline mutation was identified in only one patient (MSH2 p.R621*), who also had somatic mutations of PMS2 and MSH2, and his somatic mutation number reached 99. The prevalence of high TMB in MMR group was significantly higher than that in non-MMR group (100% vs 44.44%, Wilcoxon, p<0.001). Comparing recurrent gene mutations of two groups, we found that the prevalence of MLL2, FAT1 and POLE/POLD1 in MMR group was significantly higher than that in non-MMR group (65.00% vs 22.22%, p=0.0009; 65.00% vs 11.11%, p=0.011; 35.00% vs 5.56%, p= 0.045; Fisher). **Conclusion:** MSI-H is relatively rare in Chinese lung cancer patients, but it can be seen in various subtypes. It is usually accompanied by high TMB, and may coexist with both gene mutations positively associated with immunotherapy and driver alterations negatively associated with immunotherapy. Somatic MMR mutations tend to increase TMB. Adequate investigation should be made to determine immunotherapy efficacy in these patients.

Keywords: MMR, MSI-H, TMB-H

P60.08 Systemic Immune-Inflammatory Index (SII) as a Biomarker for Metastatic Non-Small Cell Lung Cancer

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Introduction: Inflammation contributes to tumor development and progression. Neutrophils promote tumor metastasis by increasing vascular permeability while platelets interact with tumor cells through TGFB and NF-KB pathways promoting growth. Lymphocytes on the other hand are thought to inhibit tumor-cell division. Systemic immune-inflammatory index (SII) has been developed as a simple biomarker in solid tumors to elucidate role of inflammation in malignancy. SII has not been studied in metastatic NSCLC. This study aimed to evaluate prognostic and predictive role of SII in metastatic NSCLC. **Methods:** Data was obtained retrospectively for 236 patients with metastatic NSCLC between 1/1/2015-12/31/2020, who received systemic therapy. SII was calculated at treatment initiation as Platelet count x Neutrophil count/ Lymphocyte count. Overall survival (OS) and Progression Free survival (PFS) were determined as time from start of first line treatment till death and progression or death respectively. Univariate and multivariate Cox regression and Chi-squared analyses were utilized to determine significance of the findings. **Results:** An optimal SII cut-off value of 1238.5 was determined using a receiver operator curve (ROC). Tobacco use was associated with higher SII (2028 vs 1399 p =0.01). Higher SII was noted for females (1952 vs 1789 p=0.49), age <70 years (1919 vs 1831 p=0.74), African-Americans vs Caucasians (2030 vs 1875 p=0.76), Chronic obstructive pulmonary disease (1987 vs 1807 p=0.49), steroid (2319 vs 1753 p=0.06) and antibiotic use (2310 vs 1791 p=0.14) within one month prior to treatment, and with coronary artery disease (2122 vs 1808 p=0.33); however these differences were not statistically significant. No statistically significant differences were noted based on histology: adenocarcinoma vs Squamous cell carcinoma vs large cell (1675.5 vs 1833.8 vs 1232.8 p=0.9). A low SII (<1238.5) was associated with improved PFS as compared to a high SII (median: 12.7 vs 7.2 months; HR 1.051, 95%CI 1.025-1.073, p<0.0001). Low SII however was not associated with improved OS (14.5 vs 12.7 months; HR 1.014; 95%CI 0.992-1.033), p=0.17). In low SII group, PFS was 11.3 vs 16.7 vs 5.9 months compared to a PFS of 6.9 vs 10.6 vs 5.9 months in high SII group for patients receiving chemotherapy vs targeted therapy vs immunotherapy respectively. **Conclusion:** SII may be a potential predictive marker for response to treatment. However, it does not appear to be a prognostic biomarker given lack of statistically significant difference in OS. SII is an easy and inexpensive tool to obtain, which makes it an appealing prediction biomarker. Future studies should evaluate the role of SII and its change following treatment, on response to immune checkpoint inhibitors.

Keywords: Biomarker, NSCLC, Systemic immune-inflammatory index

P60.09 Real-World Readiness of US Laboratories to Test Metastatic NSCLC Patients for Rare Actionable Genomic Variants by NGS

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Introduction: Various rare driver genomic variants have been investigated in metastatic non-squamous non-small cell lung cancer (mNSCLC). Individually they are considered rare (<3% prevalence), however, studies have shown collectively they represent up to 14.5% of the mNSCLC mutation profile. While multiple targeted therapies for rare variants such as NTRK fusions, MET exon14 skipping and RET fusions have been approved in the US for 1st line therapy in mNSCLC, other variants such as HER2 exon20ins, EGFR exon20ins, and FGFR-alterations are also gaining traction. This ever-growing number of actionable biomarkers is driving the need to use multi-gene testing such as NGS to ensure that actionable variants are tested prior to 1st line treatment. Here, we assessed US laboratory real-world NGS testing adoption and readiness that enables comprehensive genomic testing required to identify mNSCLC patients harboring any of these emerging actionable biomarkers. **Methods:** US NGS testing landscape in mNSCLC was assessed utilizing our Diagnostic Network for Precision Medicine (DXRX) data solution. Real-world data from 186,971 patients diagnosed with mNSCLC from Q12019 through Q32020 was used to calculate the NGS testing rate for these patients. NGS testing readiness and adoption for the top 25 US laboratories representing 70% of the overall US mNSCLC patient testing volume in 2019 was also assessed. **Results:** Overall, NGS testing rates in mNSCLC in the US dropped slightly from 58% in 2019, to an average of 53% in 2020 despite new targeted therapy approvals and changes in recommendations as described in ASCO/CAP and NCCN guidelines supporting NGS testing for mNSCLC patients. 84% of the top 25 labs offer in-house NGS testing for mNSCLC, accounting for 64% of the NSCLC testing volume. 55% offer NGS testing capable of identifying common and rare mutations such as HER2 ex20ins and EGFRex20ins. Additionally, 79% of these labs also offer RNA-based NGS panels, more suitable for detecting any fusions involving FGFR and NTRK genes. 24% of these NGS testing labs can test liquid biopsy samples, useful for tissue limited scenarios. **Conclusion:** Non-pharmaceutical interventions such as lockdowns to limit spread of COVID-19 infection are likely linked to the drop in testing rate observed in 2020 versus 2019. NGS is the desirable method that enables simultaneous, comprehensive testing to identify any actionable driver genomic variants present. However, adoption of NGS is still limited and highly centralized in the US. Today, only a small number of top labs can identify patients harboring any of this new wave of biomarkers for appropriate management. Barriers to NGS testing readiness and/or adoption include low demand due to lack of physician awareness and entrenched testing practices and conditions favoring sequential, single biomarker testing such as lab logistics, cost and reimbursement factors. Increasing awareness of clinical utility for broader genomic testing, which includes increasing involvement and effective use of tumor boards inclusive of pathologists to manage all mNSCLC patients will help establish the need and drive for use of NGS to ensure patients harboring common or rare actionable variants are identified.

Keywords: rare mutation, Next Generation Sequencing, precision medicine

P60.10 A 27-Gene IO Assay to Capture the Tumor Immune Microenvironment Is Associated With Response in Metastatic and Primary Tumors

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Introduction: Although ICIs have radically altered standard of care for NSCLC patients, response rates remain lacking which suggests a need for new biomarkers to aid in clinical decision making. Current biomarkers rely on primary tumor-specific phenotypes, but do not assess the surrounding microenvironment. New biomarkers capable of assessing either the primary or metastatic site would expand access and improve response rates to ICIs. The 27-gene IO algorithm and assay threshold values were designed using triple-negative breast cancer (TNBC) samples but have also shown a significant association with durable clinical response in NSCLC. We hypothesized that the translatability of the 27-gene IO assay between TNBC and NSCLC may be attributed to the IO-score's measurement of the tumor-immune microenvironment (TIME) which includes the immune response and stromal physiology rather than conventional tumor-only phenotypes. To better discern the ability of the 27-gene IO assay to measure TIME-specific signatures independent of tumor or tissue type, we sought to macro-dissect tumor and adjacent non-tumor tissue to measure their respective IO-scores as well as examine the association between IO-score from either the primary tumor or metastatic site and 1-year progression-free survival (PFS) with ICIs. **Methods:** The 27-gene IO assay was performed to generate IO-scores from macro-dissected tumor, adjacent non-tumor, or whole FFPE tissue section for each sample in a cohort of NSCLC biopsies (n=12). Spearman correlations were used to assess the relationship between IO-scores obtained from each site within the sample. In a separate cohort of 67 advanced-stage NSCLC patients, we calculated Cox proportional hazards with 95% CIs to assess the association between response to ICIs (1-year PFS) and IO-score from either primary (n=31) or metastatic tumor sites (n=36). **Results:** The IO-scores obtained individually from both the tumor and adjacent non-tumor tissues were significantly associated with the IO-score of the total specimen (ρ=0.73, p=0.01 and ρ=0.80, p=0.003, respectively), while the tumor and adjacent non-tumor tissue was not significantly correlated (ρ=0.56, p=0.06). The IO-scores from primary tumors and metastatic sites were significantly associated with 1-year PFS (HR:0.32 95%CI: 0.10 to 0.98, p=0.04; HR:0.22 95%CI: 0.059 to 0.81, p=0.01, respectively). **Conclusion:** Crosstalk between the tumor and the adjacent tissue is captured by the IO-score of either region demonstrating the 27-gene IO assay measures a comprehensive tumor microenvironment signature that includes more information than can be obtained from the tumor alone. Based on these data, we examined whether the association between IO-score and response to ICIs was consistent in either metastatic sites or primary tumors. Indeed, the IO-score was significantly associated with response to ICIs in both tumor types. We hypothesize that the correlative IO-scores between macro-dissected regions and the whole specimen, as well as the significant association between IO-score and response to ICIs in either the primary or metastatic sites are due to the uniqueness of the 27-gene IO assay's assessment of TIME. The IO-score may provide valuable data for clinical decision making when considering ICIs for primary and metastatic tumors.

Keywords: immunotherapy, Tumor immune microenvironment, Biomarker

P60.11 Trends in Molecular Testing for Metastatic Non-Small Cell Lung Cancer in The US Oncology Network Community Practices

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Introduction: The identification of multiple molecular drivers of lung cancer and development of targeted therapies has led to changes in biomarker testing for metastatic non-small cell lung cancer (mNSCLC). The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium pragmatic study evaluated real-world trends in molecular testing rates and assays used in patients with mNSCLC receiving care in US Oncology Network practices across the United States. **Methods:** A retrospective observational chart review study examined iKnowMed electronic health records among patients with mNSCLC receiving first-line (1L) systemic therapy in The US Oncology Network between 04/01/2018 and 03/31/2020. Baseline demographic/clinical characteristics and testing patterns for ALK, BRAF, EGFR, NTRK and ROS1 biomarkers were assessed. The type of assay used for molecular testing, including next-generation sequencing (NGS) and turnaround times (TAT) were examined over the observation period. Molecular testing rate trends were assessed using the Cochrane Armitage test. **Results:** A total of 3474 adults were identified; the majority were de novo stage IV (84%), median age was 69 years, 51% were female, 19% had squamous histology, 74% had adenocarcinoma histology, and 76% had a documented ECOG performance status of 0-1. As shown in the table, over the study period, testing rates were highest for ALK and EGFR at 70%, while testing for ROS1, BRAF and NTRK were lower (68%, 55%, and 17% respectively). Rates of tests that yielded BRAF results increased by 8% ($p=0.0050$) and NTRK results, 13% ($p<0.0001$), and stayed relatively stable in ALK, EGFR and ROS1. NGS testing increased ($p<0.0007$) during the observation period: from 18% to 32% for ALK, 47% to 60% for BRAF, 36% to 53% for EGFR, and 20% to 43% for ROS1. NTRK was predominantly tested using NGS throughout the study period. The median (interquartile range) TAT from mNSCLC diagnosis to NGS order was 6 (1, 19) days, and TAT from NGS order to results was 18 (13, 27) days across all biomarkers. Table. Biomarker-Molecular Assay Testing for mNSCLC

Variable	Overall	Apr 2018 to Sep 2018	Oct 2018 to Mar 2019	Apr 2019 to Sep 2020	Oct 2019 to Mar 2020	P-value
Total patient count, n	3474	1078	848	871	677	
ALK test, n (%)[a]	2446(70)	765(71)	607(72)	601(69)	473(70)	0.3914
FISH^	1429(58)	532(70)	378(62)	308(51)	211(45)	< 0.0001
IHC^	302(12)	53(7)	63(10)	109(18)	77(16)	< 0.0001
NGS^	572(23)	140(18)	127(21)	152(25)	153(32)	< 0.0001
Not documented^	143(6)	40(5)	39(6)	32(5)	32(7)	0.4242
BRAF test, n (%)[a]	1912(55)	548(51)	480(57)	485(56)	399(59)	0.0014
PCR^	360(19)	129(24)	94(20)	102(21)	35(9)	< 0.0001
Sanger^	196(10)	64(12)	51(11)	51(11)	30(8)	0.0537
NGS^	966(51)	255(47)	241(50)	231(48)	239(60)	0.0006
SNaPshot^	49(3)	9(2)	17(4)	10(2)	13(3)	0.2862
Pyrosequencing^	37(2)	18(3)	7(2)	5(1)	7(2)	0.0475
Not documented^	304(16)	73(13)	70(15)	86(18)	75(19)	0.0092
EGFR test, n (%)[a]	2443(70)	763(71)	596(70)	603(69)	481(71)	0.8777
PCR^	611(25)	194(25)	162(27)	180(30)	75(16)	0.0067
Sanger^	343(14)	114(15)	83(14)	77(13)	69(14)	0.5438
NGS^	1037(42)	274(36)	253(43)	256(43)	254(53)	< 0.0001
SNaPshot^	22(1)	7(1)	7(1)	4(1)	4(1)	0.8327
Pyrosequencing^	57(2)	27(4)	8(1)	10(2)	12(3)	0.1585
Not documented^	373(15)	147(19)	83(14)	76(13)	67(14)	0.0027
ROS1 test, n (%)[a]	2348(68)	739(69)	583(69)	572(66)	454(67)	0.2635
FISH^	1282(55)	483(65)	336(58)	280(49)	183(40)	< 0.0001
IHC^	215(9)	56(8)	57(10)	75(13)	27(6)	0.7400
NGS^	670(29)	149(20)	145(25)	180(32)	196(43)	< 0.0001
Not documented^	181(8)	51(7)	45(8)	37(7)	48(11)	0.0829
NTRK test, n (%)[a]	572(17)	114(11)	146(17)	152(18)	160(24)	< 0.0001
IHC^	26(5)	4(4)	5(3)	6(4)	11(7)	0.4780
NGS^	485(85)	103(90)	126(86)	130(86)	126(79)	0.0089
Not documented^	61(11)	7(6)	15(10)	16(11)	23(14)	0.0369

[a]Column percentage denominator: total patient count per time period ^Column percentage denominator: total patients with any test for the specified biomarker P-values from Trend Analysis by Cochrane Armitage test. P values are unadjusted. **Conclusion:** NGS testing increased consistently during the 2-year observation period in this community based study. Median TAT for NGS results was 18 days. Interventions to improve testing and TAT for results will be examined in the prospective phase of the MYLUNG study.

Keywords: molecular testing, molecular assays, biomarkers

P60.12 Prevalence of c-Met overexpression (c-Met+) and Impact of Prior Lines of Treatment on c-Met Protein Expression in NSCLC

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Introduction: Teliso-V, an anti–c-Met antibody conjugated with monomethyl auristatin E, is currently being investigated as monotherapy in c-Met+ 2nd/3rd-line metastatic NSCLC in a phase 2 study (NCT03539536). Here we present prevalence of c-Met+ NSCLC based on histopathology and EGFR mutation status. c-Met expression change from archival (diagnostic (Dx)/ post-Dx biopsy) vs fresh (tumor biopsy at time of study prescreening) is also presented for patient subsets. **Methods:** In this study, patients were prospectively selected for c-Met–positive expression by immunohistochemistry (central assay; SP44 antibody). Archival or fresh tumor tissue was eligible for c-Met expression testing and enrollment consideration. Per protocol, if archival tissue was c-Met negative, patients could provide fresh tumor tissue for reassessment of c-Met expression. **Results:** As of December 2020, 841 patients evaluable for c-Met expression have been prescreened (Table 1). c-Met+ rates were lower in EGFR wild-type (25%) vs mutant (37%) non-squamous cohorts. Squamous histology had a 39% positivity rate. c-Met+ rates were higher in fresh vs archival tumor tissue. Similar trends were observed when EGFR wild-type and mutant cohorts were separated based on c-Met–high or –intermediate groups (Table 2). Sixteen patients (non-squamous cohorts: EGFR mutant, N=8; EGFR wild-type, N=8) initially reported c-Met–negative status based on archived tissue and submitted fresh tissue for c-Met reassessment. Tumors from EGFR mutant (50%) and wild-type (12.5%) cohorts had changes in c-Met status from negative to positive, potentially due to prior anti-EGFR or immuno-oncology/chemotherapy treatments, degradation of the epitope over time in the sample, or heterogeneity within tumor lesions. Table 1

	Patients	**c-Met Positive, %[a] (n)**
NSQ EGFR MU	245	37 (90)
NSQ EGFR WT	446	25 (122)
Squamous	150	39 (58)

[a]The c-Met–positive cutoffs (by immunohistochemistry using SP44 antibody) were derived from retrospective receiver operating characteristic analysis of phase 1 (NCT02099058) Teliso-V monotherapy data. Cutoffs were established as membrane staining: non-squamous (≥25% 3+) and squamous (≥75% 1+) NSCLC. MU, mutant; NSQ, non-squamous; WT, wild-type.

Table 2

Evaluable Patients	NSQ EGFR MU c-Met High (n=53)	NSQ EGFR MU c-Met Intermediate (n=37)	NSQ EGFR MU c-Met+ (N=90)	NSQ EGFR WT c-Met High (n=54)	NSQ EGFR WT c-Met Intermediate (n=58)	NSQ EGFR WT c-Met+ (N=112)	Squamous (N=58)
Pos. Total, %	22	15	37	12	13	25	39
Pos. Fresh, %	30	20	50	18	20	38	54
Pos. Archival (Dx or post-Dx), %	16	12	28	10	11	21	33

NSQ c-Met high: ≥50% 3+; NSQ c-Met intermediate: ≥25% to <50% 3+.
Dx, diagnostic; MU, mutant; NSQ, non-squamous; Pos., positive; post-Dx, after diagnosis with intervening treatments before prescreening for the study; WT, wild-type.

Conclusion: Based on defined cutoffs, 25%–39% of NSCLC tumors were c-Met+. Consistent with prior observations, an increase in c-Met expression was observed in tumor tissue after anti-EGFR treatments. The increase in c-Met expression following immuno-oncology/chemotherapy treatments was a new observation. Additional data are needed to make conclusive remarks.

Keywords: c-Met, teliso-v, NSCLC

P60.13 MYLUNG Consortium: Molecularly Informed Lung Cancer Treatment in a Community Cancer Network. Pragmatic Prospective RWR Study

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Introduction: Recent improvements in lung cancer mortality can be ascribed to the discovery of molecular drivers, immunotherapy and utilization of drugs targeting these alterations. Despite national organizations endorsing comprehensive biomarker testing for patients with NSCLC, obstacles remain to routine testing and their use in driving therapeutic decisions. Engaging community practices within the US Oncology Network, we initiated a real world research program aimed to pragmatically identify and overcome barriers to timely and appropriate comprehensive biomarker testing in a large community-based diverse population of patients with lung cancer. Over the next 5 years, the MYLUNG program will evaluate biomarker testing workflows and algorithms, provider acceptance and use of biomarker results to inform treatment decisions, and appropriate adoption of new treatments as they become approved for use in patients with NSCLC. The program is comprised of three principal and integrated components: Protocol 1 was a retrospective cohort study (N=3474 patients) evaluating biomarker testing patterns, results, and initial treatment over a 2-year period that ended in March 31, 2020. Protocol 2 is a prospective, non-interventional cohort study (described below) studying the current testing practices of patients with newly diagnosed NSCLC who are candidates for systemic therapy. Protocol 3 is a platform of prospective interventional trials, engaging 20-30 resource and geographically diverse practices in The US Oncology Network, which will enroll approximately 7500 patients. Protocol 2 practices will serve as their own controls for subsequent interventional trials in Protocol 3. **Methods:** Protocol 2 is a prospective, non-interventional study that will enroll approximately 1000 patients with histologically or cytologically documented early stage, locally advanced, and advanced non-squamous NSCLC who are eligible for active systemic therapy across 10 community practices in The US Oncology Network. The primary objective is to examine the proportion of patients who receive biomarker testing results prior to initiating systemic therapy or death, as well as reasons for initiating systemic therapy without biomarker test results, in order to define the operational feasibility of comprehensive biomarker testing. Secondary objectives include determining the proportion of patients that receive appropriate biomarker-directed treatment, and reasons for not receiving appropriate treatment. We will also examine timelines for the patient journey from initial presentation to diagnosis, biomarker test order and results, first medical oncology visit, and treatment initiation. Additionally, we will examine single versus multi-gene biomarker testing, progression-free survival (PFS) and overall survival (OS) of patients with molecular targets who receive FDA-approved targeted therapy versus patients receiving systemic therapy without biomarker results. We will quantify differences in biomarker testing rates based on socioeconomic status, ethnic diversity, and practice resources. Enrollment began in January 2021 and is expected to enroll for 9-12 months. Information obtained from Protocol 2 will be used to identify an initial set of workflow and technology interventions to be tested in Protocol 3, which is targeted to begin enrollment in the fall of 2021.

Keywords: molecular testing, biomarkers, Targeted Therapies

P60.14 A United States Study Focused on Patients' Understanding of, Attitudes Towards, and Barriers to the Use of Biomarker Testing for NSCLC

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Introduction: As broad biomarker testing is included in clinical guidelines for patients with non-small-cell lung cancer (NSCLC), continued efforts are needed to understand the patient perspective to gauge barriers to access, patient awareness, and educational strategies to improve result comprehension and self-advocacy to ask for biomarker testing as part of a care plan. **Methods:** An online survey was distributed through two patient advocacy networks (LUNGevity Foundation and Patient Advocate Foundation) and a national research panel to identify patients with NSCLC. Survey intention was to understand patient awareness/prevalence of biomarker testing and key attitudes/barriers to access. Data were collected April-June 2020. Descriptive analyses characterize overall responses and sub-analyses categorize the differences between key subgroups. Six focus groups were conducted October-November 2020 to better understand the patient experience, confirm survey results, and explore solutions to identified barriers. **Results:** Our analysis included 248 patients with NSCLC: 161 from a general population comprised of patients from a national panel and Patient Advocate Foundation, and 87 from LUNGevity. Notable differences within the LUNGevity sample compared to the general patient population (GPP) were: the GPP included more racially diverse patients, lower income patients, and patients on Medicaid or with no health insurance. Patients who were aware of biomarker testing tend to learn about it before treatment begins; however, this is less likely for lower-income patients and those treated at smaller hospitals. Oncologists were the primary source of information for all patients – a minority also use their own Internet research, patient advocacy groups, or provided materials. Of those in the GPP (46%) needed to seek out testing by two or more doctors, compared to 22% of the LUNGevity group. Eleven percent of the LUNGevity group and 35% of the GPP did not discuss biomarker testing or targeted therapies with their care team. Additionally, 60% of those patients in the general group assumed the doctor would address testing with them if it was relevant. Compared to the LUNGevity group, the GPP was less confident asking their oncologist why biomarker testing was not performed. (100% very confident/somewhat confident vs. 56% very confident/somewhat confident). When asked about their testing results, 88% of the LUNGevity group knew their results or knew they were not tested, compared to 52% of the GPP. Of those from the GPP who knew they were tested, 27% were unaware of their results. When discussing results with their care team, 67% of the LUNGevity group and 44% of the GPP indicated they understood the terms being used. Overall, patients who have been tested were more likely to continue to have questions about how their results would impact treatment. Those in the GPP were more likely than those in the LUNGevity group to have additional questions about insurance coverage, ability to pay, frequency of testing, and risks. **Conclusion:** These results demonstrate that expanded and enhanced patient education and patient-provider communication on biomarker testing is needed. There is a significant divide between the general patient population and those connected to resources of patient advocacy organizations.

Keywords: biomarker testing, Underserved patients, Barriers

P61.01 Intelligence Assistant Million Early-Stage Lung Cancer Research Program in China

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Introduction: To improve the prognosis of the lung cancer population in China, smoking control and the proposal of lung cancer prevention and treatment are very urgent. However, in 2015, the lung cancer condition was still severe. The data published by He Jie et al. on CA Cancer demonstrated that there were 4.292 million new diagnosed cases and 2.814 million deaths in China. Lung cancer is the No. 1 incidence cancer in China and the top cause of cancer death. To change the current condition of high incidence, high mortality, and low 5-year overall survival rate in China, we established the Chinese Alliance Against Lung Cancer and organized and propagated the 'Chinese expert consensus of pulmonary nodules'. **Methods:** In this consensus, the screening criteria for lung cancer was: elder than 40 years old and exist one of the following risk factors: 1) smoking more than 400 cigarette year (or 20 package year); or ex-smoker more than 400 cigarette year (or 20 package year), quit smoking less than 15 years; 2) high risk on the exposure to professional toxic materials (such as asbestos, beryllium, uranium, and radon); 3) comorbidly of chronic obstructive pulmonary disease, diffused pulmonary fibrosis or history of tuberculosis; 4) history of a malignant tumor or family history of lung cancer. **Results:** The criteria on the age have significantly improved the early diagnosis of lung cancer. For example, in Zhongshan Hospital Fudan University (Table 1), from January 2014 to June 2019, 16,400 cases with pulmonary nodules received surgical treatment. The pathological diagnosis confirmed 9,980 cases (60.8%) were in the early stage of lung cancer. The average age of surgical patients decreased from 63 years old (2014) to 50 years old (2019). These cases could reach ten years of overall survival year by over 90%, significantly surpassing the current 20% on 5-year overall survival rate. Most significantly, the 9,800 patients cost 800 million RMB. Suppose we calculated the social contribution by working years. In that case, decreasing to 50-year-old when they received surgery could save 10 to 15 years on working, increase 1,000 million incomings and 100 million taxes for the county.

Table 1 Statistics on surgical cases in Zhongshan Hospital Fudan University among lung cancer screening program between 2014-2019

Year	2014	2015	2016	2017	2018	2019	Total
Surgical No. (cases/year)	1218	1766	2472	2998	3745	4218	16417
Malignant No. (cases/year)	1095	1579	2238	2733	3458	3894	14997
Early-stage of lung cancer No. (cases/year)	789	1045	1356	1766	2235	2789	9980
Everage age (year old)	63	61	57	55	53	50	54.8
Surgical cases age < 50yrs (cases/year)	-	-	269	340	673	693	1975

Conclusion: In our real-world clinical experience, if we start screening lung cancer at age 50, we will see misdiagnosis on 1975 cases of pulmonary nodule patients younger than 50 years old. By now, there are more than 50 hospitals have registered in this program, and we are waiting for more real-world study-based data.

Keywords: lung cancer, screening, LDCT

P61.02 The Use of PLCOm2012 vs PLCOm2012noRace Risk Prediction Models in a UK Lung Cancer Screening Programme

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Introduction: The PLCOm2012 lung cancer (LC) risk prediction model can be used to select participants most likely to benefit from low-dose CT (LDCT) screening. It was derived and validated in a North American population, including categories such as American Native & Native Hawaiian. Therefore a re-parametrised version of the model, $PLCOm2012_{noRace}$, which removes the ethnicity predictor, has been suggested as more globally applicable. We sought to evaluate the clinical impact of switching between these two models in a UK screening programme. Preliminary analysis of this data was presented at the British Thoracic Oncology Group meeting in April 2021. **Methods:** The Manchester Lung Health Checks (LHC) pilot used PLCOm2012 at a threshold of ³1.51% to select participants for LDCT screening. We retrospectively re-calculated $PLCOm2012_{noRace}$ scores for all participants and assessed the potential impact. The effect of changing the ethnicities of the whole cohort was also explored. **Results:** A total of 2,541 participants underwent a LHC of which 1,426 (56.1%) were eligible for LDCT screening. Median PLCOm2012 score was 1.76% (IQR 3.44%). The majority of participants were white (96.1%). Using $PLCOm2012_{noRace}$ at a threshold of ³1.5% would have selected 0.87% (n=22/2,541) more participants for LDCT with no significant change in the overall median risk (1.8%, IQR 3.5%). None of the individuals whose LDCT eligibility changed have subsequently been diagnosed with LC. CT eligibility changed more in non-white vs white individuals (11.5% vs 0.66%, $p<0.001$). $PLCOm2012_{noRace}$ reduced risk scores in black participants (6.7% dropped below screening threshold; 20% reduced individual scores by >0.5%) and increased risk scores in Asian participants (15.7% rose above screening threshold; 39% increased individual score by >0.5%). Had PLCOm2012 been applied with the whole cohort scoring for black ethnicity, 205 (14.4%) more participants would have been eligible for CT, and if all scored as Asian there would have been 388 (27.2%) fewer. **Conclusion:** Our data demonstrates similar overall performance between PLCOm2012 and $PLCOm2012_{noRace}$ in a real-world UK-based LC screening programme. There was no significant impact in terms of LDCT scans performed and no LCs were missed. However, $PLCOm2012_{noRace}$ did appear to disproportionately impact LC risk scores for non-white participants. As the majority of our participants were white further work is needed to assess impact within more ethnically diverse populations.

Keywords: Risk models, Epidemiology, lung cancer screening

P61.03 Comparison of the Sensitivity of Different Screening Algorithms to Select Lung Cancer Patients for Screening in a Cohort of German Patients

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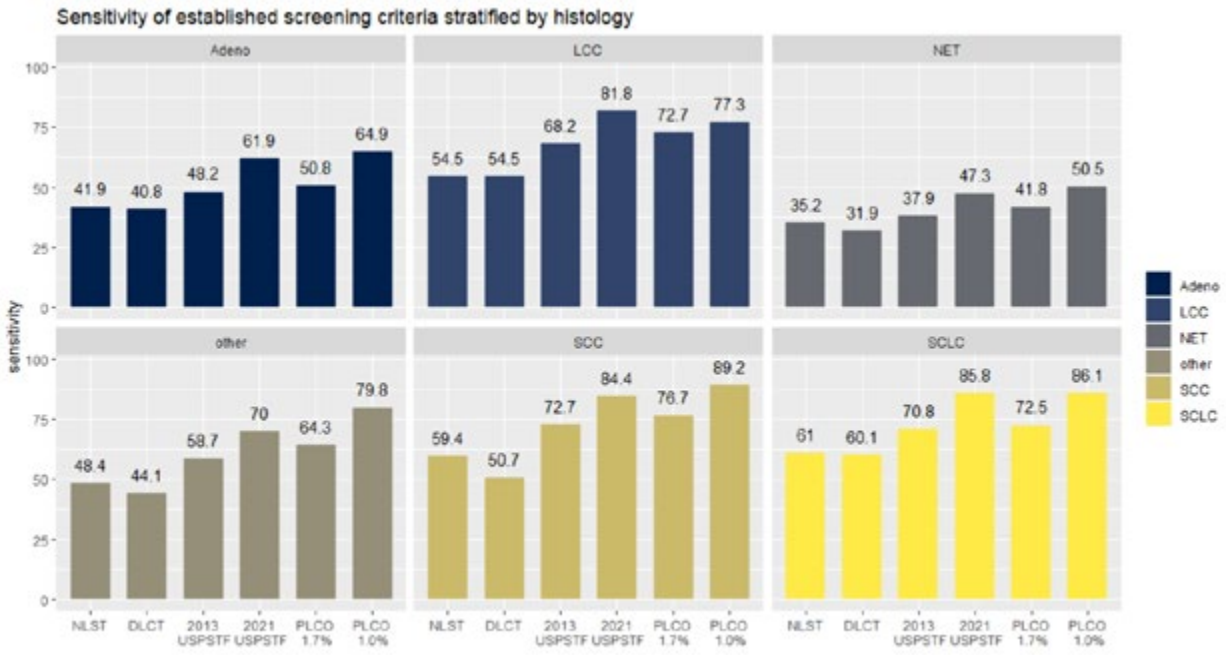
Introduction: Trials of computer tomography (CT) based screening for lung cancer have shown a mortality advantage for screening in North America and Europe. In contrast to other regions, Europe has not yet widely implemented CT screening. One important hurdle to the widespread implementation in Germany is the choice of inclusion criteria for screening. Due to biological and epidemiological differences, it is important to test screening criteria in a German population before using them as the foundation for broad public health measures in Germany. **Methods:** We used data from the data warehouse of the German Center for lung research (DZL), including around 9000 patients diagnosed with lung cancer in one of six lung cancer centers throughout Germany. Age and smoking history were available in 3623, who were used in the analysis. We compared the sensitivity to select lung cancer patients for lung cancer screening of the following screening criteria: the National Lung Screening Trial (NLST), the Danish Lung Cancer Screening Trial (DLCST), the 2013 and 2021 US Preventive Task Force (USPSTF), and the Prostate, Lung, Colorectal, and Ovarian no race model (PLCOm2012noRace) with risk thresholds of 1% and 1.7%. We compared the sensitivity in all patients as well as stratified by histology (adenocarcinoma, large-cell carcinoma (LCC), neuroendocrine tumors (NET), squamous-cell carcinoma (SCC), small-cell carcinoma (SCLC)). To calculate the PLCOm2012noRace 6-year risk we used pack years as cigarettes per day was not available, and the centered values of the PLCOm2012noRace model when values in variables used for the model were missing. **Results:** Overall, the PLCOm2012noRace model with a threshold of 1%, selected the highest proportion of lung cancer patients for screening (73.2%), followed by the 2021 USPSTF (69.7%), the PLCOm2012noRace 1.7% (59.8%), the 2013 USPTF (56.8%), NLST (48.3%) and the DLCST criteria (44.9%). The PLCOm2012noRace risk criteria with a threshold of 1% had the highest sensitivity over all histologies except for LCC, where the 2021 USPTF selected a higher proportion of patients.



Conclusion: All selection criteria performed better in histologies associated with a higher attributable risk for smoking like SCC, and SCLC. The risk model based PLCOm2012noRace with a threshold of 1% outperformed all other established criteria. Regarding the choice of inclusion criteria in a German setting, a comparison of the specificity of the different criteria in a large setting is warranted.

Keywords: histology, sensitivity, screening

P61.04 Disparities Related to Low-Dose Computed Tomography Screening Eligibility Criteria for Lung Cancer: A Single-Center Analysis

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Introduction: The United States Preventive Services Task Force (USPSTF) published guidelines in 2013 for lung cancer screening using low-dose computed tomography (LDCT) based on the National Lung Screening Trial results. Both the 2013 and expanded 2021 guidelines may perpetuate disparities as they do not take into account multiple risk factors. Risk-based models, such as the PLCOm2012, include criteria that impact diverse populations, particularly women and Black individuals, at high risk for lung cancer. The goal of this analysis was to compare the percentage of lung cancer cases who would have been eligible for LDCT screening according to the 2013 USPSTF guidelines versus the risk-based assessment. **Methods:** We identified Black and White patients greater than age 55 years with lung cancer between 2014 and 2018 using the Georgetown University Medical Center tumor registry. A medical chart review was conducted by resident physicians to collect: age at diagnosis, sex, race, education, body mass index, smoking history (current/former, cigarettes per day, duration smoked, and years quit), and clinical characteristics (i.e., lung disease). We then compared the 2013 USPSTF criteria (55-80 years, >30 pack-years, current smoker, or quit within 15 years) vs. the PLCOm2012 model using a 6-year risk threshold of >1.7% to determine the percentage of patients meeting each set of criteria (overall, and by race and gender). **Results:** The cases (N=447) were 36% Black and 52% female. The mean pack-years was 43.2 (SD=31.6). The majority (88%) had non-small cell lung cancer. Overall, the PLCOm2012 more effectively selected individuals vs. the 2013 USPSTF criteria (Table 1). The risk prediction model identified 71% of cases vs. 46% by the USPSTF criteria and this finding was consistent across race and sex sub-groups (p<0.0001). There was a significant sex disparity with 41% of females vs. 51% of males being identified by the 2013 USPSTF criteria (p=0.032). There was no sex disparity using the PLCOm2012 model (p=0.506). The 2013 USPSTF criteria had equally poor sensitivity in both Black and White individuals.

Table 1. Sensitivity of the USPSTF 2013 Criteria and the PLCOm2012 Risk Prediction Model Stratified by Race and Sex (N=447)

	USPSTF2013	PLCOm2012 risk ≥1.7%/6y	p-value	N
Overall	45.6% (41.0% - 50.4%) (A)	71.4% (66.9% - 75.5%) (B)	P<0.0001	447
Race*				
Whites	45.9% (39.9% - 51.9%) (C)	72.4% (66.8% - 77.6%) (D)	P<0.0001	279
Blacks	46.6% (38.7% - 54.6%) (E)	69.6% (61.8% - 76.6%) (F)	P<0.0001	161
Sex				
Females	41.3% (34.9% - 47.9%) (G)	69.8% (63.5% - 75.6%) (H)	P<0.0001	235
Males	51.4% (44.5% - 58.3%) (I)	72.6% (66.1% - 78.5%) (J)	P<0.0001	212

Caption: This table demonstrates the sensitivity of the USPSTF 2013 criteria compared to the PLCOm2012 risk prediction model greater than 1.7% risk over 6-year threshold stratified by race and sex. Sensitivity analyses are as follows: (C) vs. (E), p=0.886; (D) vs. (F), p=0.526; **(G) vs. (I), p=0.032;** (H) vs. (J), p=0.506.

*Seven individuals included in this analysis declined racial identification.

Conclusion: Our study demonstrated that the PLCOm2012 model selected a significantly larger percentage of lung cancer cases compared to the 2013 USPSTF guidelines. Further, the 2013 USPSTF criteria selected significantly fewer women indicating that it contributes to gender disparities in lung cancer early detection. While the new 2021 USPSTF guidelines may improve sensitivity, models like the PLCOm2012 are more inclusive of high-risk groups and may serve as a tool to ameliorate disparities.

Keywords: Disparities, low-dose computed tomography, Risk models

P61.05 Time to Loosen Up: Liberalizing Lung Cancer Screening Guidelines Might Save More Lives

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Introduction: The USPSTF recommended annual lung cancer (LC) screening with low-dose CT in current or former smoker adults, ages 55-80, with a 30 pack-year smoking history, that quit within 15 years. Other guidelines, such as NCCN, have similar criteria. In 2021, the USPSTF updated its screening guidelines, expanding the age group to adults ages 50-80 and lowering the smoking threshold to 20 or more pack-year history. We aimed to compare the screening eligibility with the new USPSTF proposed guidelines compared to the previous USPSTF LC screening guidelines in patients with LC prior to their diagnosis. **Methods:** We created an IRB-approved observational study. Patients who were current or former smokers diagnosed with LC between 2016 and 2019 were included in the analysis. Charts were reviewed for demographics and detailed smoking. Associations between eligibility with current and previous USPSTF screening guidelines were examined using the chi-square test. **Results:** We reviewed 530 subject charts, of which 428 were included in the analysis. Of those, 186 subjects met the previous USPSTF screening criteria for LC. There were 242 subjects that were ineligible for screening according to previous USPSTF guidelines, mainly due to age and smoking history. With the newly approved USPSTF guidelines, 242 (56.5%) of the subjects would have been eligible for screening compared to the 186 (43.5%) subjects that were eligible (chi-square = 14.65, p=0.00012). [Table 1] Furthermore, 32 (37%) out of the 186 ineligible subjects under the new USPSTF recommended guidelines would have met screening criteria if all former smokers were included in the eligibility criteria regardless of their quitting date (chi-square = 5.117, p=0.023).

	Screening Ineligible N (%)	Screening Eligible N (%)	P-value
Old USPSTF lung cancer screening guidelines	242 (56.5)	186 (43.5)	p=0.000129
New USPSTF lung cancer screening guidelines	186 (43.5)	242 (56.5)	

Table 1. Eligibility in old versus new USPSTF lung cancer screening guidelines **Conclusion:** In our study, ineligible subjects mainly fail the screening criteria due to age and pack-year history of smoking. Regardless of not meeting all criteria for screening, these individuals were eventually diagnosed with cancer. Our study correlated with available data that suggests that with the current screening guidelines, individuals at high risk for lung cancer can be missed. In our study, there was a statistical association between an eligibility in subjects that would have met the more lenient currently approved guidelines. Liberalizing guidelines is associated with more high-risk subjects undergoing screening, therefore potentially increasing the rates for early detection. To improve rates of screening and overall LC mortality, organizations should continue to re-evaluate their guidelines and aim to keep expanding LC screening guidelines in attempts to improve LC mortality.

Keywords: smoking, screening, Early detection

P61.06 Participants With Family History of Cancer Have a Higher Participation Rate of Low-Dose Computed Tomography for Lung Cancer Screening

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Introduction: Family history of cancer is an important risk factor for lung cancer. Studies have shown that it may also affect the willingness to lung cancer screening. To describe the low-dose computed tomography (LDCT) participation rate with a history of common cancers in a population-based screening program. **Methods:** The analysis was conducted in the context of the Cancer Screening Program in Urban China, which recruited 282,377 eligible participants aged 40-74 years from 8 cities in Henan province from 2013 to 2019. A total of 55,428 participants were evaluated to be high-risk for lung cancer by an established risk score system and were subsequently recommended for LDCT. In this study, we calculated the overall and group-specific participation rates by a family history of common cancers, as well as compared the differences in participation rates between different groups. Obtain odds ratios (ORs) and 95% CIs derived by multiple logistic regression model. **Results:** Of 55,428 with high-risk for lung cancer, 22,260 subjects undertook LDCT (participation rate of 40.16%). We found that a family history of lung cancer, esophageal cancer, stomach cancer, liver cancer, and colorectal cancer were associated with increased participation in LDCT screening. The odds of participants with a family history of one cancer, two cancers, three cancers, and four or more cancers undertaking LDCT screening were 0.9-fold, 1.7-fold, 1.8-fold, and 2.5-fold higher than participants with no family history of cancer (OR: 1.88, 95% CI: 1.80-1.96; OR: 2.65, 95% CI: 2.51-2.79; OR: 2.83, 95% CI: 2.64-3.04; OR: 3.46, 95% CI: 3.15-3.79), respectively. Compared with those without a history of cancer, as the number of cancer family history increases, compliance gradually increases (P<0.001). **Conclusion:** There was room for improvement regarding lung cancer screening yield given the relatively low participation rate. Lung cancer screening in populations with a family history of cancer may be a choice.

Keywords: Family history, screening, Adherence

P61.07 Advancing Health Equity in Cancer Care: The Lived Experiences of Poverty and Access to Lung Cancer Screening

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Introduction: Individuals living with low income are more likely to smoke, have a higher risk of lung cancer, and are less likely to participate in preventative healthcare (i.e., low-dose computed tomography (LDCT) for lung cancer screening), leading to equity concerns. To inform the delivery of an organized pilot lung cancer screening program in Ontario, we sought to contextualize the lived experiences of poverty and the choice to participate in lung cancer screening. **Methods:** At three Toronto academic primary-care clinics, high-risk screen-eligible patients who chose or declined LDCT screening were consented; sociodemographic data was collected. Qualitative interviews were conducted. Theoretical thematic analysis was used to organize, describe and interpret the data using the morphogenetic approach as a guiding theoretical lens. **Results:** Eight participants chose to undergo screening; ten did not. From interviews, we identified three themes: Pathways of disadvantage (social trajectories of events that influence lung-cancer risk and health-seeking behaviour), lung-cancer risk and early detection (upstream factors that shape smoking behaviour and lung-cancer screening choices), and safe spaces of care (care that is free of bias, conflict, criticism, or potentially threatening actions, ideas or conversations). We illuminate how 'choice' is contextual to the availability of material resources such as income and housing, and how 'choice' is influenced by having access to spaces of care that are free of judgement and personal bias. **Conclusion:** Underserved populations will require multiprong interventions that work at the individual, system and structural level to reduce inequities in lung-cancer risk and access to healthcare services such as cancer screening.

Keywords: lung-cancer screening, health equity, low income

P61.08 A Light Gradient Machine-Enabled Radiomics Model for Survival Prediction in Non-Small-Cell Lung Cancer-Not Otherwise Specified

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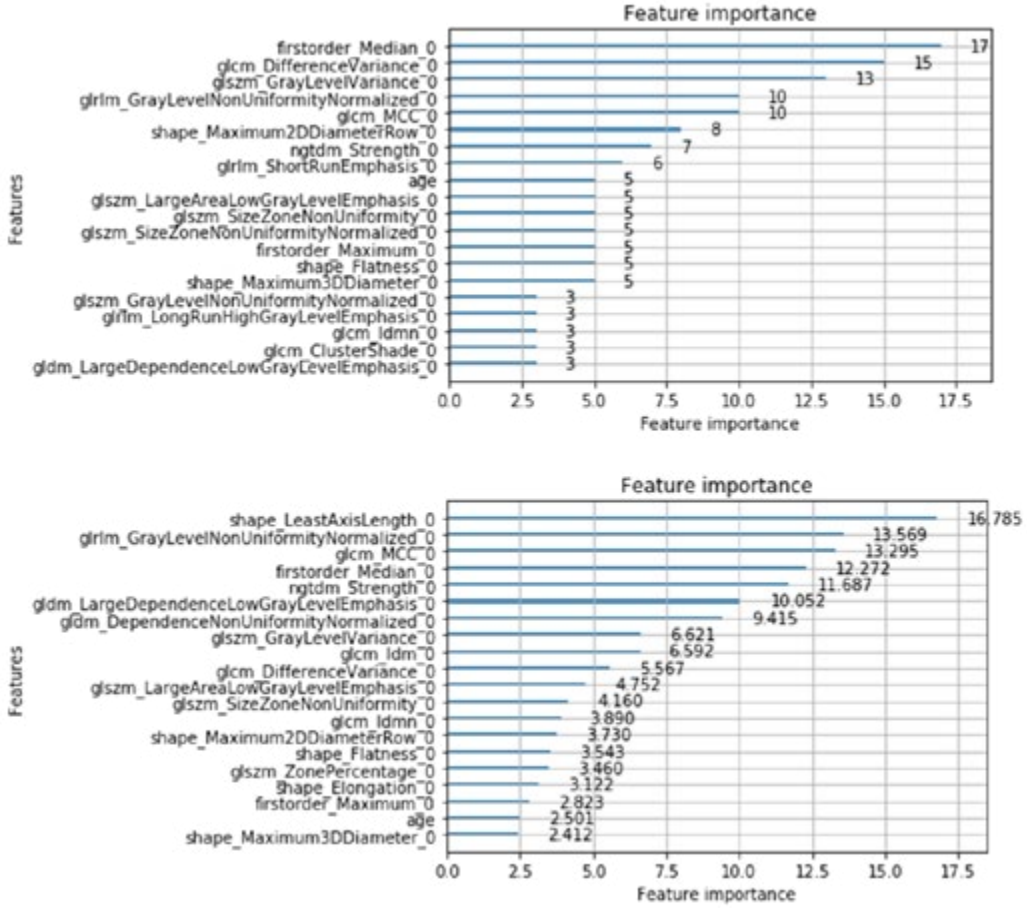
Introduction: Histology diagnosis of non-small-cell lung cancer (NSCLC) depends on the location and the size of the biopsies. Non-small-cell lung cancer-not otherwise specified (NSCLC-NOS) is a common histologic diagnosis due to uncertain histological subtype. Although NSCLC has been researched intensively, the number of studies on NSCLC-NOS is quite limited. Accurate survival prediction helps clinicians and patients in decision-making about cancer management and improves patient outcomes. We proposed to apply light gradient machine (LightGBM)-enabled radiomics model for survival prediction in NSCLC-NOS. **Methods:** Planning CT image sets, contour data sets and clinical data sets of 61 NSCLC-NOS patients from The Cancer Imaging Archive were included. Patients were labeled into three groups according to their survival times into less than 1 year, 1-3 years and more than 3 years. The patients were randomly partitioned for model training and validation. Demographic features and clinical features were extracted from the clinical data sets. Radiomic features were extracted from the CT image of the contoured planning tumor volume using PyRadiomics. LightGBM was trained to predict the survival outcome for individual patients. Feature importance was analyzed based on information gain from features in LightGBM model. Model performance was evaluated using F1 score and average area under the curve (AUC). **Results:** A total of 107 radiomic features, 2 demographic features and 11 clinical features were extracted. Among the top 20 features in feature importance analysis, age is the only non-radiomics feature (Figure 1). Results show significantly different performances in predicting survival with an AUC value of 0.97, 0.83 and 0.87, respectively, in the groups of less than 1 year, 1-3 years and more than 3 years.



Conclusion: The LightGBM-enabled radiomics model depicting the correlation of PTV and survival outcome could be used to accurately predict the individual patient's survival, which could potentially improve the utility of radiotherapy for NSCLC-NOS from a precision treatment perspective. The proposed model can facilitate the personalized treatment decisions, thus improving treatment outcome. To our knowledge, this is the first study on survival prediction of NSCLC-NOS using LightGBM-enabled radiomics model.

Keywords: non-small cell lung cancer, survival prediction, radiomics

P61.09 Feasibility of Lung Cancer Screening With Low-Dose Computed Tomography in a Rural Community Setting; An 8-Year Experience

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Introduction: Low-dose computed tomography (LDCT) screening guidelines per the United States Preventive Services Task Force (USPSTF) represent the most effective method to detect lung cancer at an early stage. Despite this, adoption of this practice has been mostly urban-centered and established protocols for screening in rural communities remains limited. To date, there is no published literature suggesting feasibility of an effective LDCT screening program at the rural level. Our data set contradicts this notion. **Methods:** We performed a retrospective analysis of prospectively collected data from our LDCT program database collected at a single instutition, 302 bed rural community hospital. Data was collected from 2013-2021. Referral patterns for LDCT screening follow the USPSTF guidelines. Results of imaging was in concordance with Lung-RADS guidelines. Patient entries were deidentified and included patient demographics, additional imaging, and diagnostic or therapeutic interventions that had occurred. **Results:** Data from 2013 to 2021 found a total of 7807 screening studies were completed in the LDCT program. 117 (1.55%) patients obtained an invasive diagnostic/therapeutic procedure following abnormal results on screening LDCT. Nondiagnostic intervention rate was 0.4% of all screened patients and 29.9% of patients who had a positive screening test. A total of 114 (1.4%) lung cancers were detected and stratified into early (65%) vs late disease (35%). Of the patients with positive lung cancer findings, 40 (35% of these patients were discovered during repeat annual screenings). These were comparable to other larger multicentral trials and showed no major differences in the outcomes followed.

Figure 3: Since inception, we have detected a total of 114 cancers, 91 (79.8%) of which have been lung cancers. The table below shows whether they were discovered because of an initial screening or were an interval development and whether they were early or late stage. As we have completed 7807 total screenings, our overall lung cancer detection rate among screeners is about 1.2%. That percentage does not include patients that have been diagnosed at another facility.

Surveillance Type	N	%
Initial Baseline	**51**	**56%**
Early or Limited	33	65%
Late or Extensive	18	35%
Interval Development	**40**	**44%**
Early or Limited	29	73%
Late or Extensive	11	28%
Grand Total	**91**	**100%**

Figure 4: Patient demographics

Patient Demographics Ascertained Through Data Pool
Age Mean 63
Gender Females: 3142 Males: 4665
Race >99% White, Nonhispanic
Pack Year Smoking History Average 42.4 Pack Year Smoking History

Conclusion: LDCT screening programs are feasible in the rural community setting. Our data suggests similar outcomes in terms of lung cancer discovery rate (1.4%) when compared to large urban multicenter trials. We found that the majority of patients with a lung cancer diagnosis obtained from CT screening were at a lower stage at time diagnosis. Our data suggests the effectiveness of the LDCT screening protocols, and our institution specific creation suggests feasibility in other rural community centers. This represents the first published outcomes data for LDCT in a rural hospital setting.

Keywords: lung cancer screening, Rural, feasibility

P61.10 Swiss Pilot Low-Dose Computed Tomography Lung Cancer Screening Study

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Introduction: Low-dose computed tomography (LDCT) lung cancer screening is endorsed by United States guidelines and has recently been shown effective in a large European randomized controlled trial. Nevertheless, the actual realization of a lung cancer screening program is challenging and depends on country-specific factors. This pilot study aimed to evaluate implementation, execution and performance of LDCT lung cancer screening in Switzerland. **Methods:** Starting from October 2018, asymptomatic participants aged 55-74 years with more than 30 pack-years smoking history were enrolled at a tertiary hospital in Switzerland. Participants with history of lung cancer, major (palliative) health problems or those that had a thorax CT scan 18 months prior to enrollment were excluded. First line we evaluated lung cancer risk according NLST guidelines. Secondly, we estimated lung cancer risk using the PLCOm2012 model risk calculater with a threshold of 5%. Lung nodules were assessed according Lung-RADS 1.1 {ACoR. Lung-Screening Reporting and Data System (LungRADS) Version 1.1. 2019}. Participants were predominantly recruited through flyers, a newspaper article and pulmonary specialists. Screening consisted of one LDCT-scan and follow-up was recommended for suspicious nodules only. LDCT assessment was performed by two radiologists, one of them a board certified chest radiologist. Enrollment and follow-up are currently ongoing. **Results:** To date, 75 participants with a median age of 62 years (interquartile range [IQR] 56-67 years) were included. The median number of pack years smoked was 49 (IQR 41-58 pack years) and 25 (33%) were female. The median PLCOm2012 6-year lung cancer probability was 2.7% (IQR 2.6-2.9%) and 19 (26%) participants had stopped smoking before enrollment. Of the 75 participants, 61 (81%) were found to have calcified or non-calcified lung nodules. 6 participants required follow up imaging of suspect nodules which resulted in a recall rate of 8%. At baseline, lung cancer was found in 2 (2.7%) participants. The lung cancers were one squamous cell carcinoma (stage IIIA) and one adenocarcinoma (stage IV). **Conclusion:** In this Swiss LDCT lung cancer screening pilot study using modified inclusion criteria, lung nodules were found in a significant number of participants of whom 2.7 % were diagnosed with lung cancer to date. To date, the recall rate for follow-up imaging is 8%.

Keywords: Early detection, lung-cancer screening, feasibility study

P62.01 PREVALUNG: Evaluation of Lung Cancer Prevalence in Patients With Smocking-associated Atherosclerotic Cardiovascular Diseases

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Introduction: Lung cancer is the leading cause of cancer related death in France and Worldwide. Lung cancer screening based on low dose thoracic computed tomography (low dose CT) in patients selected on age and lifelong tobacco consumption has proven to improve lung cancer related mortality. However, the definition and identification of patients eligible for lung cancer screening is a challenge that may limit lung cancer screening program implementation. Epidemiological data shows that 30 to 40% of patients with lung cancer present a history of cardiovascular disease, mainly atheromatous diseases such as peripheral arterial diseases and coronary artery stenoses. We hypothesized that patients with history of smoking who developed atheromatous disease could represent a population at high risk to develop lung cancer. Our main objective was to evaluate the prevalence of lung cancer among patients with atherosclerotic disease and history of tobacco consumption. Our second objective was to evaluate the lung cancer screening program implemented to measure the prevalence. **Methods:** We implemented a monocentric prospective epidemiological study to evaluate the prevalence of lung cancer among 500 patients with inclusion criteria i.e age 45-75 years old, history of at least 10 years of daily tobacco consumption preceding the onset of an atherosclerotic disease. Principal exclusion criteria were history of active carcinoma < 5 years, symptoms of lung cancer, follow-up for lung nodules and grade IV dyspnea. Patients with inclusion criteria are referred for an inclusion visit (V0) with a thoracic surgeon by adult cardiologists, vascular surgeons and adult cardiac surgeons in charge of the patient. After information and inclusion, a low dose CT scan is scheduled within 7 months and a smoking cessation visit is proposed in case of active smoking. Blood and gut microbiota samples are harvested the day of the low dose CT. Positive low-dose CT are discussed weekly at the multidisciplinary thoracic oncologic staff meeting and managed accordingly to the current European and national recommendations. A clinical follow-up is scheduled by phone at 3, 6 and 12 months after the low-dose CT to evaluate oncologic and cardiovascular events. **Results:** Between November 2019 and April 2021 we included 487 of the 500 patients scheduled, 330 low dose CT were completed, 7 localized primary lung cancer were resected by minimally invasive lobectomy, 1 patient was treated by radiation alone without pathological proof for a lung nodule, 1 patient was related with systemic therapy for a stage IV primary lung cancer and 2 patients are waiting for surgical resection for clinically localized lung cancers. **Conclusion:** The implementation of a lung cancer screening program dedicated to patients followed-up for tobacco related atherosclerotic diseases is feasible and will allow to evaluate both lung cancer prevalence and short-term benefits of lung cancer screening in this population.

Keywords: lung cancer, atherosclerosis, screening

P62.02 A Predictive Model to Guide Brain MRI Surveillance in Patients With Metastatic Lung Cancer: Impact on Real World Outcomes

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Introduction: Development of brain metastasis (BM) in lung cancer is common and treatment of BM can lead to significant morbidity. While early BM detection may lead to improved outcomes, there are currently no evidence-based consensus guidelines regarding the optimal frequency of brain MRI surveillance. In this study, we developed a predictive model for BM risk to help guide brain MRI surveillance in patients with metastatic lung cancer without BM at time of distant metastasis. **Methods:** Patients from Stanford Health Care diagnosed with de novo or recurrent metastatic lung cancer from January 2017 to June 2019 and had tumor next generation sequencing data available were included. The primary outcome was the time from the diagnosis of metastatic disease to the development of BM, with death as competing risks, followed through March 2021. We applied Fine and Gray competing risk regression to develop a prediction model for 3-year BM incidence from the time of metastatic disease diagnosis based on the following factors: demographics, tumor characteristics, smoking status, tumor mutations, and systemic therapy received. Features for the prediction model were selected using machine learning-based regularization methods: LASSO, adaptive-LASSO, MCP, and SCAD. We validated the proposed model using a bootstrap-cross validation method based on 1,000 resamples. Model performance was evaluated using calibration and discrimination that was assessed via time-varying AUC. In addition, we evaluated model performance by identifying patients predicted to be high risk for BM based on the proposed model (estimated 3-year BM risk > 50%) and comparing outcomes between those with more frequent brain MRI surveillance (<7.5 months between scans) versus less frequent within this subgroup (>7.5 months). **Results:** The study cohort included 493 patients with the following characteristics: mean (standard deviation) diagnosis age of 67.1 (12.2), 47.7% male, 47.5% non-Hispanic white, 70.4% adenocarcinoma, 50.9% de novo stage IV. In this cohort, 137 (27.8%) developed BM, 136 (27.7%) died without developing BM, and 220 patients (45%) were censored over 1002 person-years. The 3-year cumulative incidence of BM was 33.1% (95% confidence interval (CI) 27.9, 38.3%). The prediction model included 37 variables that were selected by at least one of the four regularization methods that we considered, which included: race, histology, stage, driver mutation status. The prediction model yielded good discrimination with AUC of 75.4 based on bootstrap-cross validation. Of 81 high-risk patients, 27 (33%) developed BM and 12 (15%) died prior to BM. Of the 27 patients with BM, 11 patients (41%) had a “missed” 6-month brain MRI surveillance opportunity (BM detected >7.5mo after last brain MRI or date of metastasis, whichever was later). Compared to those who had brain MRIs more frequently in this high-risk subgroup, patients with “missed” opportunities had larger BM (91% with BM > 5mm versus 56%; OR 7.78, CI 0.84-95) and were more likely to undergo surgery (18% v. 6%; OR 3.33, CI 0.33-51). **Conclusion:** The proposed model can accurately identify patients at high risk of BM. These patients may benefit from more intensive brain MRI surveillance to identify BM at earlier stages and reduce morbidity of subsequent BM treatment.

Keywords: MRI surveillance, predictive model, brain metastasis

P62.03 Survival After Distant Recurrent Versus De Novo Stage IV Metastatic Lung Cancer Under Low-Dose Computed Tomography Screening

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Introduction: Despite recent breakthroughs in early detection and therapies, advanced lung cancer (LC) still poses a therapeutic challenge. Nearly half of LC patients are diagnosed at an advanced stage, and one-third of patients diagnosed with early stage (I-III) LC would relapse and develop an advanced disease. While current clinical trials and treatments do not typically distinguish between recurrent versus de novo Stage IV metastatic patients, recent studies show that recurrent patients have better overall survival (OS) versus de novo patients. However, these findings were mainly driven by comparing regional recurrence and de novo metastasis, and a potential survival difference among distant recurrent versus de novo patients remains unknown. Patients with disease recurrence may have more indolent tumor biology and differential prior treatment compared to those with de novo metastasis. Furthermore, prognostic evaluation of these advanced metastatic disease types has been in the context of no screening, and the potential impact of primary LC detection mode through low-dose computed tomography (LDCT) screening on survival after metastatic disease has not be fully examined. In this study, we evaluate the prognostic impact of advanced disease type, i.e., recurrent (regional and distant) vs. de novo metastatic LC, utilizing data from the National Lung Screening Trial (NLST) that include participants who underwent LDCT screening. **Methods:** We used data from NLST that enrolled 53,452 participants in 2002-2004 and followed through 2009. Our study cohort included 972 participants who were either diagnosed with Stage IV de novo metastatic disease or developed disease recurrence (regional or distant) after Stage I-III LC diagnosis across two screening arms (LDCT or chest X-ray). The outcome was OS after metastatic or recurrent disease diagnosis. We applied Cox regression to evaluate the association between OS and metastatic disease type – i.e., de novo vs. recurrent, adjusting for age, sex, race, histology, smoking status, and screening arm. Subgroup analyses were conducted by excluding regional recurrent patients and by restricting to the LDCT-screening arm. **Results:** Of 972 patients, 34.6% had recurrence (14.0% regional and 86.0% distant) and 65.4% were de novo metastatic patients. The analysis showed that recurrent (regional and distant) patients have significantly better OS (3-year OS: 20.1% versus 8.5%) versus de novo patients, with an adjusted-hazard ratio (aHR) of 0.75 (p=0.0003). This significant survival gain among recurrent patients persisted when comparing distant recurrent versus de novo patients (3-year OS: 17.5% versus 8.5%; aHR 0.80, p=0.006). Notably, the survival benefit among distant recurrent compared to de novo patients was more pronounced when the analysis was restricted to the LDCT-screening arm (3-year OS: 19.9% vs 9.0%, aHR 0.73, p=0.009). **Conclusion:** Prognostication is the key element influencing treatment decision in patients with advanced disease. Our study shows that advanced disease type (regional, distant recurrence, and de novo metastasis) is a significant prognostic factor for metastatic LC, with its effect most pronounced among the population who underwent LDCT-screening. This finding can help inform clinicians to improve the patient selection for designing future clinical trials treating advanced LC in the LDCT screening era.

Keywords: National Lung Screening Trial (NLST), metastatic lung cancer, recurrence

P62.04 Neoteric Small Extracellular Vesicles Based Biomarker for Predicting Cancerous Sub-Solid Nodules of Lung

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Introduction: Sub-solid nodule (SSN) is a common radiographic finding, and due to the possibility of malignancy, further evaluation is urgently needed for the prevention and management of lung cancer (LC). The study aims to identify small extracellular vesicles (sEVs) based biomarker integrated into radiomics-clinical features through cross-scale to differentiate the suspicious SSN and predict the risk of LC. **Methods:** The study enrolled patients with SSN including LC and Benign nodules (BN) and Healthy persons as a control to discover sEVs differentials expressed miRNAs (DEMs) as biomarker by next-generation sequencing (NGS) (n=9) and validation (n=103) by RT-qPCR. Through cross-scale integration of small-molecule biomarker and macro-imaging, the prediction model was developed by Logit and Logistic algorithms and further interpreted into an easy-to-use nomogram by Cox-proportional hazards modeling. **Results:** Present study has discovered various sEVs DEMs, and sEVs-miR-424-5p was selected as a novel potential biomarker for validating cohort. The results depicted that sEVs-miR-424-5p represented higher efficacy by the area under the curve (AUC) ranged from (0.7991 to 0.9553, $p<0.01$) in between groups. Furthermore, the 10 radiomics signs and 4 clinical features of SSN were merged with sEVs-miR-424-5p and obtained the correlation matrix of each sign. Afterward, the significant features were proceeded in multivariate logistic regression analysis to develop the cross-scale integrated modeling, which yielded a significantly higher AUC of 0.931 ($p<0.0001$). **Conclusion:** sEVs-miR-424-5p could be a novel biomarker for distinguishing SSN of LC and BN populations, and its association with the cross-scale fusion of radiomics-clinical features will provide great potential to be an errorless prediction of malignant SSN.

Keywords: small-extracellular vesicles, Sub-solid pulmonary nodules, lung cancer screening

P62.05 Identifying Risk-Factors for Lung Cancer Diagnosis After Detection of Incidental Lung Nodules

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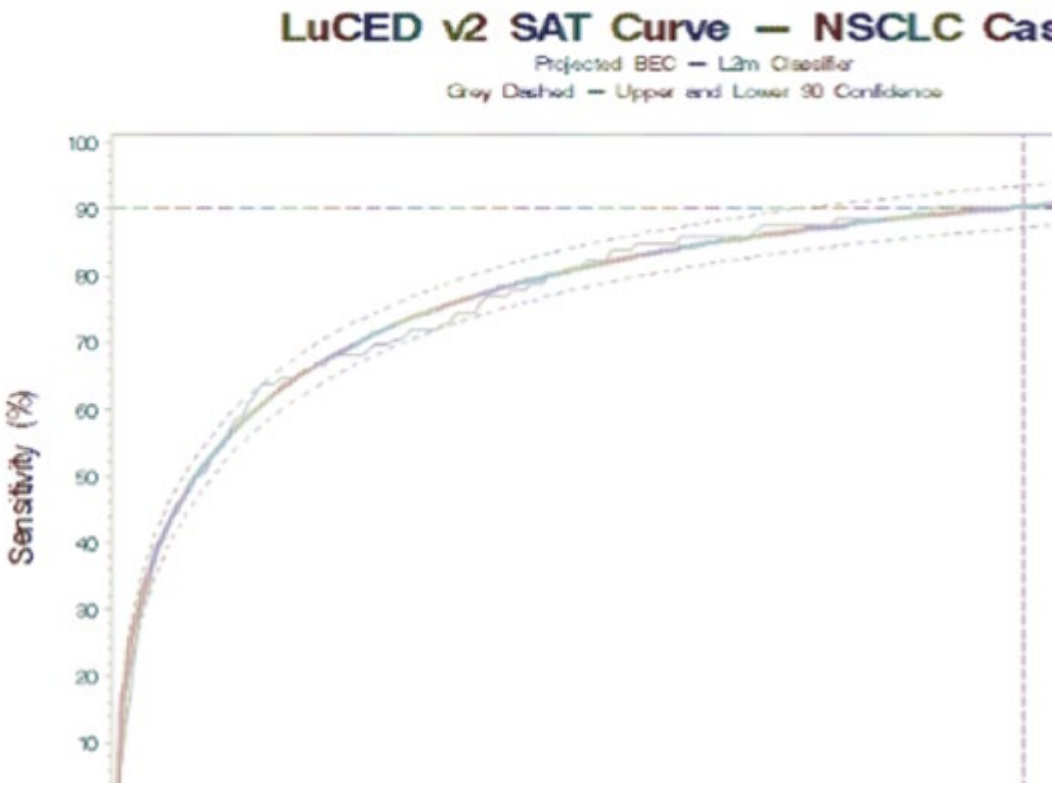
Introduction: Early detection of lung cancer is important for improving long-term survival. Systematic management of incidentally detected pulmonary nodules can improve early detection; however, most persons with a pulmonary nodule do not have lung cancer. We investigated clinical and demographic characteristics associated with diagnosis of cancer in the granuloma-endemic Mississippi Delta region of the US. **Methods:** Our incidental lung nodule program (ILNP) conducts multi-disciplinary reviews of pulmonary nodules identified as suspicious on routine radiologic studies (outside of the lung screening program) across a large healthcare system. We prospectively track demographic and clinical characteristics from the ILNP, and evaluated predictive ability of each characteristic for identifying lung cancer. We estimated odds ratios (OR) with 95% confidence intervals (CI) using logistic regression. Areas under the Receiver-Operator Curve (AUC) were estimated for predicting lung cancer with our models. **Results:** The ILNP evaluated 14,252 cases, 694 (4.86%) of which were diagnosed with lung cancer. The median age was 64 years, 58% were female, and 65% white / 29% black. The lung cancers diagnosed in this program had a stage distribution of 50% Stage I, 10% Stage II, 17% Stage III and 16% stage IV. Individual factors with significant predictive ability in univariate models included age OR[CI]: 1.04[1.03-1.05], BMI 0.95[0.94, 0.96], co-morbidities 1.2[1.2-1.3], prior cancer 1.6[1.4-1.9], family cancer history 2.1[1.8-2.5], COPD 2.8[2.4-3.3], Asbestos exposure 4.7[2.7-7.8], pack-years smoked 1.01[1.01-1.02], smoking status (active 5.8[4.6-7.4], former < 15 years 7.3[5.5-9.8], former > 15 years 7.3[5.5-9.6] vs. never), number of nodules 1.13[1.07-1.20], largest nodule size 1.06[1.05-1.06], nodule location (ORs varied 0.50 to 1.17 with upper lobes at highest risk). Nodule edge characteristics and nodule density were not predictive of a cancer diagnosis, but had a high percentage of missing information. Our full multi-variable model included age, BMI, co-morbidities, family cancer history, COPD, asbestos exposure, pack-years of smoking, smoking status, nodule number, nodule size, nodule location, and cavitation. This model had an AUC of 0.84 for predicting cancer diagnosis in patients with incidentally detected lung nodules (Figure 1). Using the optimal cut-off from this predictive model to identify lung cancer yielded a sensitivity of 73% and specificity of 79%.



Conclusion: Systematic management of incidental lung nodules is important for identifying persons with early stage lung cancer. Clinical characteristics, beyond those identified by radiology, are useful in identifying patients whose incidentally detected nodules are most likely to result in a lung cancer diagnosis in this real-world population.

Keywords: risk-factors, incidental nodule detection, Early detection

P62.06 A Radiomics Nomogram for Preoperative Prediction of Occult Lymph Node Metastasis in Early-Stage Solid Lung Adenocarcinoma

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Introduction: The aim of this study was to establish and validate a nomogram based on radiomics features for preoperative prediction of occult lymph node (OLN) in early-stage solid lung adenocarcinoma patients. **Methods:** A total of 244 patients with cT1-2N0M0 solid lung adenocarcinoma who underwent preoperative contrast-enhanced chest computed tomography (CT) were divided into a primary group (n=160) and an independent validation group (n=84). The records of 851 radiomics features of primary tumor were extracted. Lasso regression analysis was used to reduce data dimension and select features. Multivariable logistic regression was utilized to identify independent predictors of OLN and develop a prediction nomogram. The performance of prediction model was assessed with regard to its calibration and discrimination. Decision curve analysis (DCA) was performed to estimate the clinical usefulness of nomogram. **Results:** The prediction model was consisted of a clinical factor (CT-reported tumor size) and a radiomics feature (Rad-score). The nomogram presented good discrimination, with a C-index of 0.782 (95% CI, 0.768-0.796) in the primary cohort and 0.813 (95% CI, 0.787-0.839) in the validation cohort, and good calibration. DCA proved that the radiomic nomogram was clinically useful. **Conclusion:** This study developed and validated a nomogram that incorporates with clinical and radiomics factors, which can be tailor for the preoperative individualized prediction of OLN in early-stage solid lung adenocarcinoma patients.

Keywords: solid lung adenocarcinoma, occult lymph node, radiomics

P62.07 Pre-surgical Assessment of Mediastinal Lymph Node Metastases in Stage IA Non-small-cell Lung Cancers

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Introduction: CT and FDG-PET measurements of mediastinal lymph nodes (MLNs) of patients with non small cell lung cancers (NSCLCs) are recommended for pre-surgical prediction of MLN metastases. As the frequency of MLN metastases differs markedly by the cancer consistency on CT, and clinical staging determines the possible treatment choices, particularly surgery, we decided to assess the sensitivity and specificity of CT and FDG-PET for predicting MLN metastases in a prospectively collected cohort of clinical Stage IA NSCLC patients. **Methods:** We reviewed all patients enrolled in the Mount Sinai Health System, prospective cohort between 2016 and 2020, who had pre-surgical FDG-PET and underwent surgery with mediastinal lymph node resection and/or pre-operative endobronchial ultrasound (EBUS) for a fist primary clinical Stage IA NSCLC≤ 30 mm in maximum diameter on pre-surgical CT. For each patient, the maximum short-axis diameter cutoff values for MLNs on the pre-surgical CT images was classified as: ≤ 10.0 mm, 10.1-15.0 mm, 15.1-20.0 mm, and >20.0 mm. The highest SUVmax of any MLN for each patient were classified as: ≤ 2.5, 2.6-3.0, 3.1-4.0 or >4.0. **Results:** Of the 470 patients, 58.1% (n=273) were women (197 men) and the median age at time of surgery was 68 years (IQR: 63.0-74.0), 466 had MLN resections and 4 has EBUS alone. NSCLC consistency was solid in 81.7% (n=384), part-solid in 13.4% (n=63), and nonsolid in 4.9% (n=23). There was no significant difference by nodule consistency with respect to age, sex, smoking status or tumor location. Median maximum diameter of the tumor on CT of solid, part-solid, or nonsolid NSCLCs was not significantly different (16.7 mm vs. 19.0 mm vs. 17.0 mm, p=0.10). Histology was adenocarcinoma for all 63 part-solid and 23 nonsolid NSCLCs. Cell-type among the 384 solid NSCLCs was adenocarcinoma for 272 (70.8%), squamous-cell for 49 (12.8%), typical carcinoids for 48 (12.5%), and other NSCLC cell-types for 15 (3.9%). Among the 470 patients, none with part-solid (n=63) or nonsolid (n=23) NSCLCs had MLN metastases. Solid NSCLCs were identified in 384 patients, no NSCLC ≤ 10 mm (n=47) in maximum diameter or diagnosed as typical carcinoid (n=48) had MLN metastases. Among the remaining 297 patients with solid NSCLCs 11-30 mm, 7 (2.4%) had MLN metastases. Area-under-the curve (AUC) for predicting MLN metastases in solid NSCLCs, using the CT maximum short-axis MLN diameter was 0.62 (95% CI: 0.44-0.81, p=0.18) and using the highest SUVmax of any MLN, AUC was 0.58 (95% CI: 0.39-0.78, p=0.41). Neither AUCs were significantly different from chance alone. Optimal cutoff for prediction of MLN metastases was ≥ 18.9 mm for CT maximum short-axis diameter [sensitivity 14.3% (95% CI: 0.0% -57.9%); specificity 100.0% (95% CI:98.9%-100.0)] and for highest SUVmax was ≥ 11.7 [sensitivity 14.3% (95% CI: 0.0% -57.9%); specificity 99.7% (95% CI:98.3%-100.0)]. **Conclusion:** CT and SUVmax had low sensitivity but high specificity for predicting MLN metastases in solid NSCLCs 11-30 mm. Clinical Stage IA NSCLCs≤30 mm should be based on CT maximum tumor diameter and MLN maximum short-axis diameter≤20 mm.

Keywords: mediastinal lymph nodes, Computed Tomography Screening, Lung neoplasms

P62.08 The Non-Intrusive LuCED® Test for Detection of Early-Stage Lung Cancer: A Subgroup Analysis for Chronic Obstructive Pulmonary Disease (COPD)

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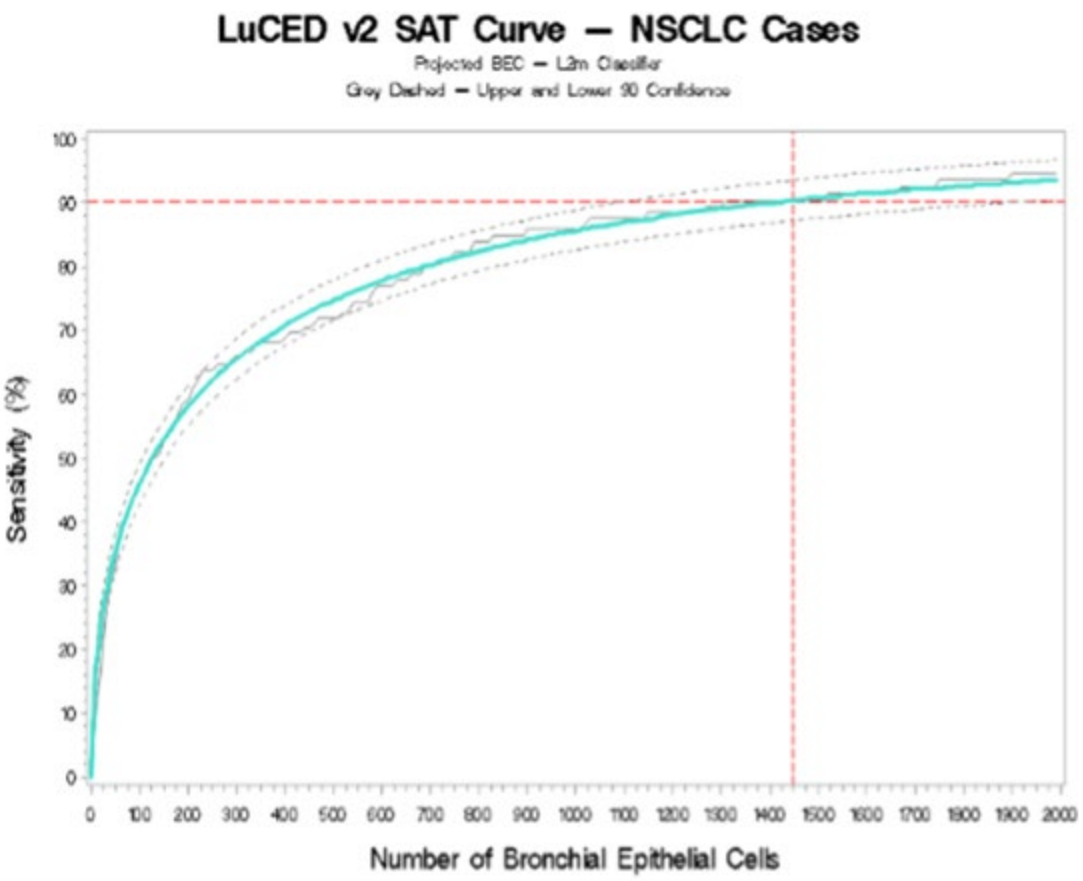
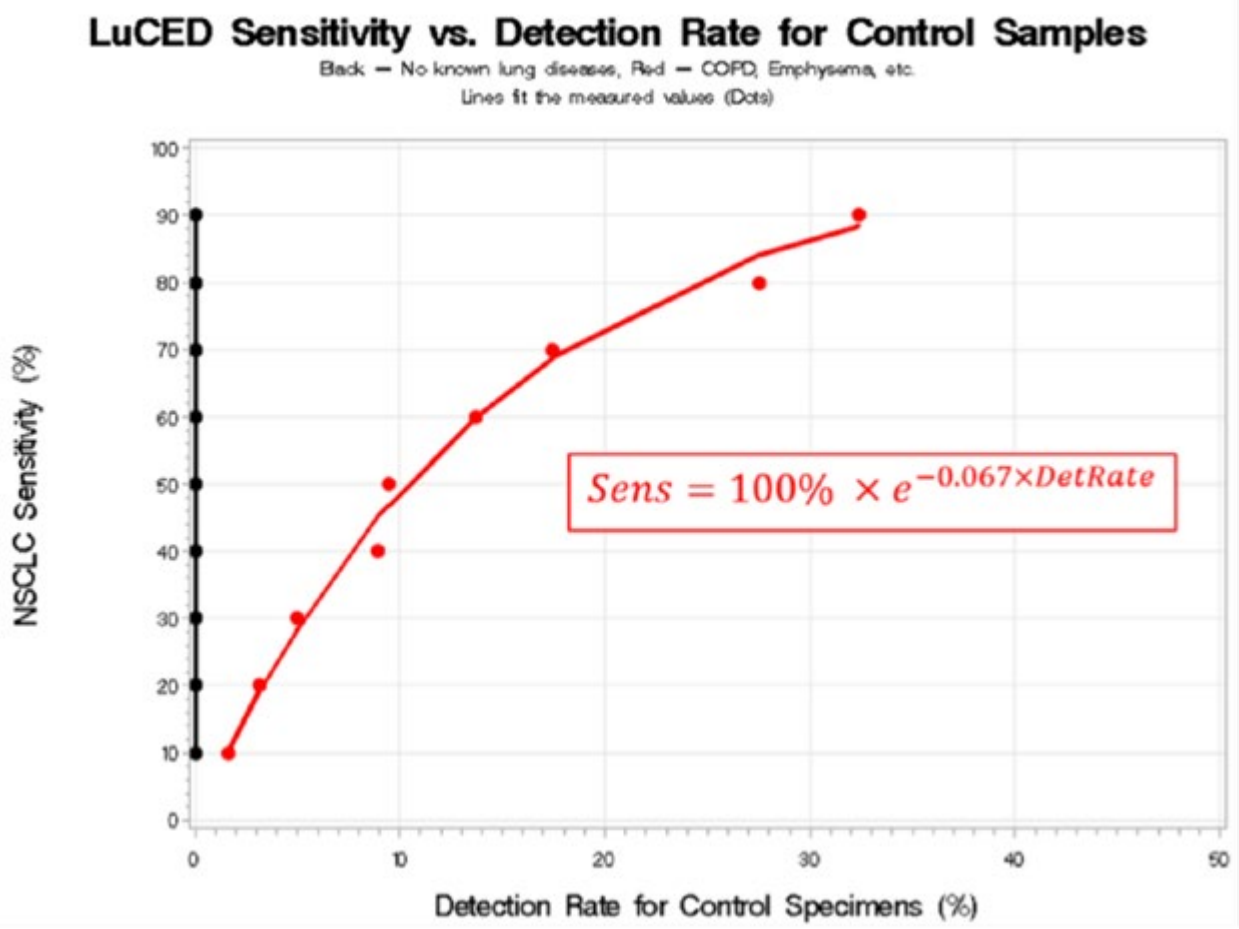
Introduction: VisionGate's LuCED® test for lung cancer measures 934 features in each cell imaged in 3D by the Cell-CT™. Sensitivity and specificity, both exceeding 90%, have been reported (Wilbur, et. al., Cancer Cytopathology, 123:9,548-556). The relationship between sensitivity and an enumeration of bronchial epithelial cells (BECs) is shown in the SAT curve – for example, 1450 BECs yields a sensitivity of 90%. A normal result is assigned for cases with sufficient BECs and no detected abnormal cells.



Methods: LuCED AI was trained to identify cells with a cytologic diagnosis of atypia+. Accordingly, specificity for LuCED is measured for patients who are free of lung disease. Here, we investigate the rate of LuCED abnormal case reports for patients who are free of lung cancer but with or without non-cancer disease such as COPD. Two case-level ROC curves were produced by setting the required BEC count for a desired sensitivity and then recording the rate of LuCED abnormal reports for two control populations: 1. Free of lung disease, 2. With COPD or other non-cancer disease. **Results:** The study used 62 cases with lung disease and 37 cases without lung disease. The resulting case level ROC curves are shown below:

Conclusion: ROC analysis shows, for a given sensitivity, that the rate of abnormal case reports for control specimens with COPD is elevated relative to cases without COPD. This is expected as COPD is associated with pre-cancer indicating that LuCED is sensitive to these conditions. A further implication is that LuCED specificity, measured on controls without lung disease, is nearly perfect. These results underscore prior claims of high sensitivity and specificity in detection of lung cancer with the added benefit of pre-cancer detection. A future area of focus would evaluate the LuCED test for primary triage of high-risk individuals to LDCT for detection of early-stage lung cancer.



Keywords: LuCED NSCLC Dysplasia

P62.09 A Prospective Cohort Evaluation of the Sensitivity and Specificity of the Chest X-Ray for the Detection of Lung Cancer in Symptomatic Adults

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Introduction: The chest radiograph (CXR) plays a pivotal role in the triage of symptomatic individuals with potential lung malignancy. In the United Kingdom the National Institute of Clinical Excellence recommends CXR as an initial investigation in those aged over 40 with specified symptoms or in the presence of one symptom and smoking history. Urgent specialist evaluation is advised if the CXR demonstrates an abnormality suggestive of malignancy. The evidence regarding the effectiveness of the CXR in this role is incomplete and based upon the retrospective evaluation of populations identified with lung cancer. The design of these studies prevents the evaluation of correctly excluded cases and an estimation of the test specificity. This prospective cohort study aimed to establish the accuracy of the CXR in the investigation of malignancy amongst symptomatic adults over the age of 50 for intrathoracic malignancies Secondary aims were to evaluate how a history of smoking alters the test characteristics, the role of CXR follow-up, and whether the reported presence of abnormalities for which no follow-up is advised predict the presence of malignancy. **Methods:** The study population was a cohort of consecutive "self-request" CXR studies prospectively collated between January 2011 and October 2016 as part of the National Awareness and Early Diagnosis Initiative. The initiative combined an early lung cancer diagnosis awareness campaign with a policy of open access to a CXR. Individuals were able to obtain a CXR providing they met eligibility criteria. The criteria were symptoms persisting for at least 3 weeks (cough, fatigue, shortness of breath, chest pain, loss of appetite or loss of weight) and age over 50. Patient's self-reported paper questionnaires collected during the study period formed the cohort for this study, with patient subsequently cross referenced with the regional cancer registry to identify intrathoracic malignancies. The CXR report was retrieved and coded using a novel definition of a positive test as a CXR resulting in investigation with CT. Studies were positive if the report documented an abnormality with a recommendation which directly (or indirectly after a CXR or clinical follow-up) led to investigation with CT. Studies which did not result in investigation with CT were considered negative. **Results:** 8,948 CXR outcomes were evaluated. 496 positive studies led to a diagnosis of 80 patients with Non-Small Cell Lung Cancer (NSCLC) amongst 101 primary intrathoracic malignancies. Within two-years, a cumulative total of 133 NSCLC amongst 168 primary intrathoracic malignancies were observed. The sensitivity and specificity for NSCLC were 76% (95%CI 68-84) and 95% (95%CI 95-96) within 1-year and 60% (95%CI 52-69) and 95% (95%CI 95-96) within 2-years. The 2-yr positive and negative likelihood ratios were 12.8 and 0.4. The results did not differ for NSCLC compared to all primary malignancies. **Conclusion:** A positive test strongly increases the probability of malignancy whereas a negative test moderately reduces the risk. A quarter of NSCLC will have a negative CXR in the year prior to diagnosis. The findings allow the risk of malignancy following a negative test to be estimated.

Keywords: Early detection, Chest-xray, Investigations

P62.10 AI-Based Three-Dimension Reconstruction for Pulmonary Nodules -New Auxiliary Exploration for Thoracic Surgery

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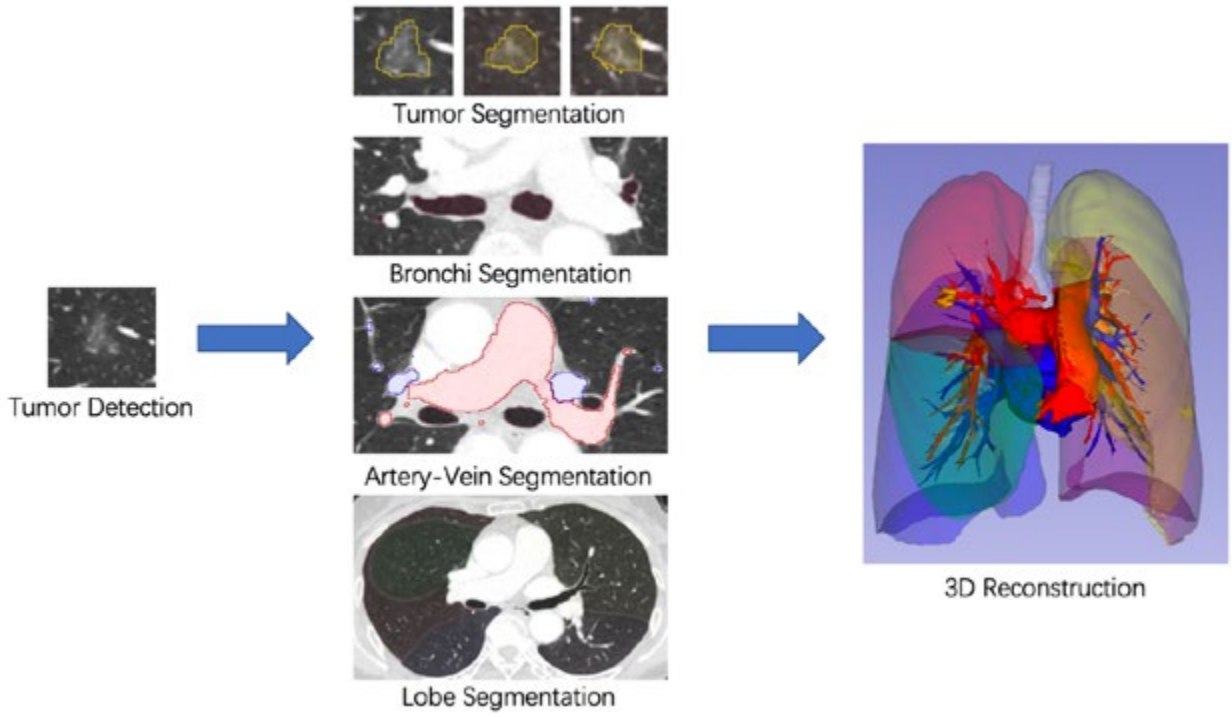
Introduction: More pulmonary nodules are discovered as computerized tomographic scan deeply applied in clinical practice, accurate exploration for small pulmonary nodes is still challengeable during the procedure of thoracic surgery. Artificial intelligence may promote the clinical detection for these nodes and revealing anatomic variation. Lots of software have been used in guiding in during VATS (video-assisted thoracic surgery) with 3D vision. **Methods:** AI-Based Semi-automatic and High-Precision Pulmonary Three-Dimensional Reconstruction mainly based on deep-learning technology. Relying on these targets with various features and technology proposals, we adapted different methods to segment and reconstruct tumors, lobes, bronchi and vessels separately. An automatic region-grow based method is used to segment the bronchi, while there have been 6,000 DICOMs learned by 3D Convolution Neural Network for detecting and identified pulmonary nodules, and 120 DICOMs was learned for lobes fractures segmentation and pulmonary artery-vein vessels segmentation with 3D-VNet. All the AI automatic results can be imported to 3DSlicer for manual operation to fix and confirm the final 3D reconstruction. 30 patients with information consent were included, whose DICOMs were used for reconstruction by AI-based reconstruction systemic and Mimics reconstruction (version 21.0), we calculated reconstruction steps for the comparison between these two tools, such procedure was separated with for models (airways, tumors, lobes and vessels).



Results: Such AI-based reconstruction system is explored for automatic identification in DICOMs, visual image can be showed in AI-based reconstruction, which highly lessened time of reconstruction ($p<0.00001$) when compared with conventional reconstruction tools, with all cases can be clearly identified the position in pulmonary segments. Tumors and airways can be automatically calculated in AI-based reconstruction systemic, with less manual intervention in lobes ($p<0.00001$) and vessels ($p<0.00001$), when comparing with Mimics reconstruction with similarly results. **Conclusion:** A new exploration for thoracic surgery was executed and such AI-based 3D reconstruction system was completed for small pulmonary nodules with high fficiency and accuracy.

Keywords: Artificial Intelligence, Three-dimension reconstruction, Pulmonary nodules

P62.11 Germline Genetic Testing in Patients with Lung Cancer in a Mexican Center

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Introduction: Germline variants explain a minority of Lung Cancer (LC) cases. Accumulating evidence have shown a role of genes of the Fanconi pathway, such as BRCA2, CHEK2 and PALB2, in LC. Suggested features of LC patients (pts) carrying germline mutations are young pts, pts with double primary tumor, and cancer family history (CFH). Nowadays, guidelines for genetic testing (GT) in LC have not been published. GT could provide benefits such as target therapy and cascade testing for relatives. Herein, we describe the result of germline GT with a Multigene (MPG) panel in LC pts. **Methods:** We reviewed medical records of LC pts from jan2018-dec2020. We gathered clinical, familial and demographic information. We evaluated if LC pts would be candidates for GT according to their age, multiple primary tumors and CFH. Also, we evaluated the age and the diagnosis of relatives with cancer in order to evaluate if they met NCCN criteria for GT. Therefore, we offered Genetic Counselling (GC) and GT to those selected LC pts. A panel for 84 genes associated with hereditary cancer was prescribed for pts who accepted to participate in the study. We used descriptive statistics and non-parametric tests. **Results:** 72 pts were included for this analysis. Mean age was 63y (SD 12). 41 pts (57%) were smokers. 33 (46%) were females. 36 pts (51%) met criteria for GT, but only 6 pts accepted GT (3M,3F). Those who had GT were younger (mean 49y vs 64y). There was no significant difference between smoke consummation between the 2 groups (p= 0.538). All GT tests had findings, 5 pts were carriers of 6 variants of unknown significance (VUS) in BRCA2, PALB2, CHEK2, AXIN2, PDGFRA and VHL. One pt had a pathogenic variant in BRCA1. **Conclusion:** Our sample is small, and it was performed in highly selected patients. Nevertheless, we observed variants in genes of the Fanconi pathway. Those VUS are not considered actionable at this time, but a follow-up is guaranteed. 16% of our sample had a positive finding, even if if's complicated to establish a link between this variant and LC, this result will lead to a better surveillance and risk reduction for breast and ovary cancer in relatives. Besides, it remains to prove if iPARPs have a role in LC treatment, studies suggest PARP inhibitors may be a beneficial therapy for LC with HR deficiency and it would be important to identify pts with these features. We attempt to provide more evidence of clinical utility of germline GT in LC context.

Keywords: germline, BRCA1, Fanconi

P63.01 Lurbinectedin in Pre-Treated Patients With Small Cell Lung Cancer and Malignant Pleural Mesothelioma in a Real World Setting

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Introduction: Lurbinectedin, a selective inhibitor of oncogenic transcription is currently being investigated in patients with small cell lung cancer (SCLC) or malignant pleural mesothelioma (MPM) after failure of at least first-line therapy, with phase 2 studies showing promising results. In 2020, the FDA granted accelerated approval to lurbinectedin (Zepzelca®) for patients with metastatic SCLC with disease progression during or after platinum-based chemotherapy. Here, we present the first real-world data of lurbinectedin from two large heavily pre-treated patient cohorts, SCLC and MPM, treated in our tertiary referral university medical center. **Methods:** Lurbinectedin, a selective inhibitor of oncogenic transcription is currently being investigated in patients with small cell lung cancer (SCLC) or malignant pleural mesothelioma (MPM) after failure of at least first-line therapy, with phase 2 studies showing promising results. In 2020, the FDA granted accelerated approval to lurbinectedin (Zepzelca®) for patients with metastatic SCLC with disease progression during or after platinum-based chemotherapy. Here, we present the first real-world data of lurbinectedin from two large heavily pre-treated patient cohorts, SCLC and MPM, treated in our tertiary referral university medical center. **Results:** Between November 2019 and December 2020, a total of 95 patients (43 SCLC and 52 MM) started treatment with lurbinectedin. All patients with SCLC and 81% of MM received lurbinectedin as third or further line of therapy. The median number of cycles that was administered was 2 (range: 1-12) for SCLC and 3 (range: 1-13) for MM. After 12 weeks, in the SCLC cohort, the disease control rate (DCR) was 29% and the objective radiological response (ORR) was 17%. The median progression free survival (mPFS) was 1.5 months (95% CI: 1.4–3.0), and median overall survival (mOS) was 7.0 months (95% CI: 4.7-not reached). In the MPM cohort, the DCR after 12 weeks was 32% and no tumor responses were registered. The mPFS was 2.8 months (95% CI: 1.4–4.2), while mOS was 7.2 months (95% CI: 5.9–not reached). In general, lurbinectedin was well tolerated. Dose reductions were applied in 27% of patients, mainly because of fatigue or hematologic toxicity. **Conclusion:** Lurbinectedin appears to be a clinically meaningful therapeutic option in heavily pre-treated patients with SCLC and mesothelioma.

	Trigo et al. (SCLC) (n=105)	Erasmus MC (SCLC) (n=43)	Metaxas et al. (MPM) (n=42)	Erasmus MC (MPM) (n=52)
Patients number	105	43	42	52
Treatment line	2-3	3-4	2-3	2-3
Median follow-up	17.1 months	7.2 months	NA	7.3 m
Median chemotherapy-free interval	3.5 months	1.9 months	NA	1.6 months
DCR 12 weeks	68%	29%	52%	32%
ORR 12 weeks	35%	17%	4%	0%
Median PFS	3.5 months	1.5 months	4.1 months	2.8 months
Median OS	9.3 months	7.0 months	11.1 months	7.2 months

Table 1: comparison of our real-world data to the phase II clinical trials

Keywords: SCLC, Mesothelioma, lurbinectedin

P63.02 Exposure-Response Analysis of Lurbinectedin Alone or With Doxorubicin in Overall Survival in Small Cell Lung Cancer

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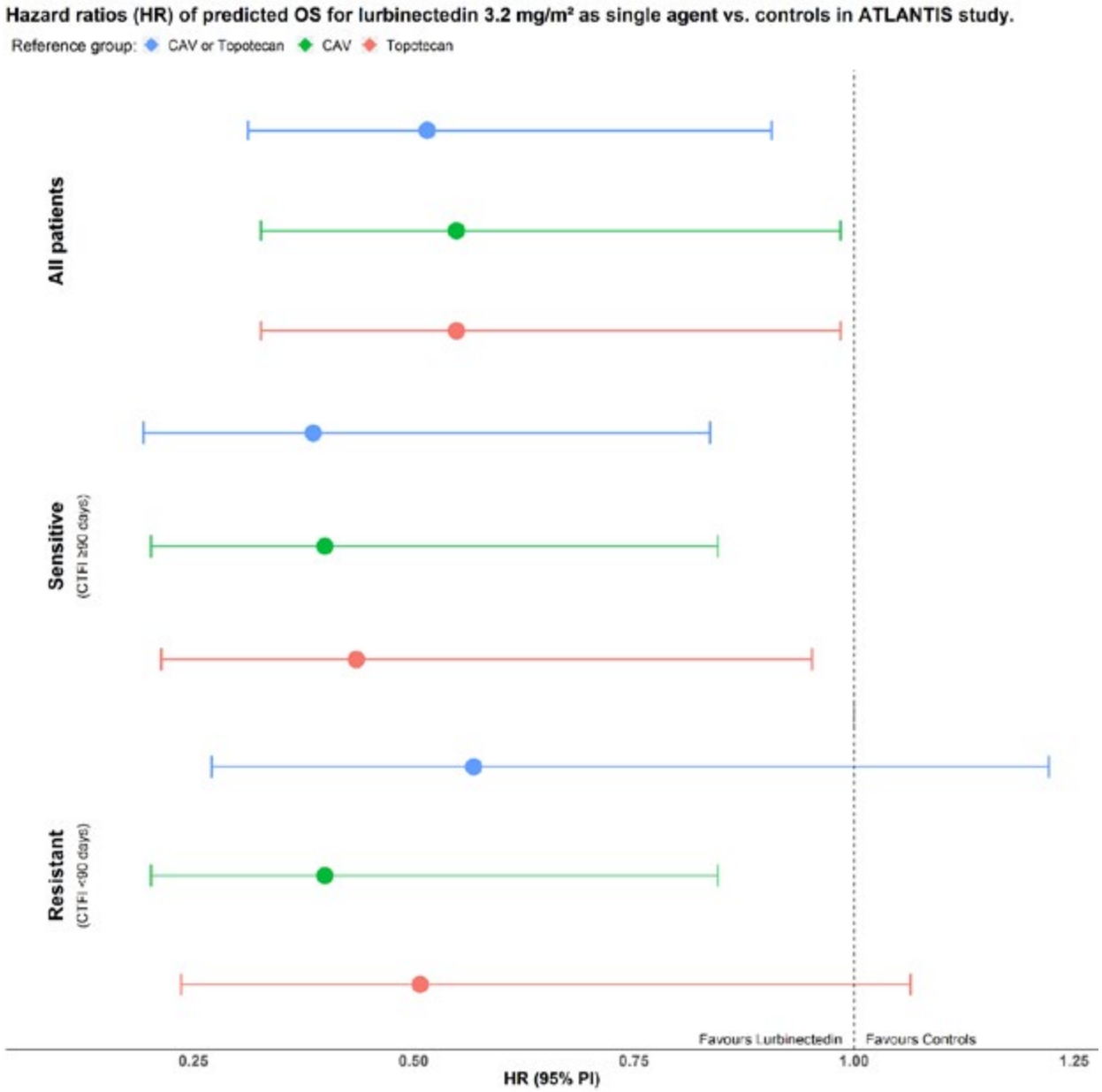
Introduction: In June 2020, FDA granted accelerated approval to lurbinectedin (Zepzelca™) as single agent at 3.2 mg/m^2 q3wk for patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy based on data from a phase 2 basket trial (study B-005). Phase 3 ATLANTIS study compared lurbinectedin 2.0 mg/m^2 plus doxorubicin 40 mg/m^2 vs. CAV (cyclophosphamide 1000 mg/m^2 plus doxorubicin 45 mg/m^2 plus vincristine 2.0 mg) or topotecan. The aim of the present analysis was to develop an exposure-response (E-R) model of OS with lurbinectedin alone or in combination with doxorubicin in second-line SCLC, and to compare predicted OS of single agent lurbinectedin at 3.2 mg/m^2 vs. ATLANTIS control arm, CAV and topotecan. **Methods:** Lurbinectedin and doxorubicin plasma concentration data from ATLANTIS study and study B-005, were pooled to build an E-R model for OS. Lurbinectedin unbound and doxorubicin total exposure (AUC_u and AUC_{Dox}) were used as exposure metrics. A log-logistic parametric survival model was developed to describe OS, exploring the relationship with AUC_u and AUC_{Dox}, and adjusting to potential prognostic factors. Model-based Monte Carlo simulations of study ATLANTIS with lurbinectedin 3.2 mg/m^2 alone as experimental arm were conducted. The median OS for each study arm and the corresponding hazard ratio (HR) with the 95% prediction interval (PI) of each virtual trial replicate were computed and then summarized across 500 replicates. **Results:** Patients with exposure metrics (over patients treated) in experimental arm of ATLANTIS and B-005 were 288 (95%) and 99 (94%). Patients treated in control arm of ATLANTIS were 289 (168 with CAV and 121 with topotecan). The log-logistic model was the best probability density function to parametrically describe the OS data. AUC_u of lurbinectedin, chemotherapy-free interval (CTFI) ≥90 vs. <90 days, LDH, albumin, CNS metastases, neutrophils/lymphocytes ratio (NLR), patients with refractory disease (CTFI <30 days) and combination with doxorubicin were found to be significantly associated with the scale parameter of the log-logistic model. Significant relationship between AUC_{Dox} and OS was not observed. HRs of predicted OS with lurbinectedin 3.2 mg/m^2 alone in study ATLANTIS study compared with control arm (CAV and/or topotecan), in all patients and those with resistant or sensitive disease, are depicted in the figure.



Conclusion: A relationship between lurbinectedin exposure and OS was established. Model-based simulation of lurbinectedin at 3.2 mg/m^2 as single agent in ATLANTIS study showed superiority of lurbinectedin over CAV and topotecan for OS. These results also confirm the findings of study B-005.

Keywords: Small cell lung cancer, lurbinectedin, Exposure Response

P63.03 Very Limited SCLC Benefits From Surgery and Adjuvant Chemotherapy – A Large Retrospective Analysis

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Introduction: Most SCLC patients are diagnosed with extensive disease (ED) and the prognosis in this cohort remains poor. However, some patients are diagnosed with limited (LD) or very limited (VLD, T1-2, N0-1, M0) disease and previous data suggest that surgical resection (anatomic resection and mediastinal lymphadenectomy) might improve outcomes in these patients. Most of the existing evidence comes from small case series. For this reason, we investigated clinical features and surgical outcomes in a large cohort of resected SCLC patients. **Methods:** We used a pseudonymized dataset provided by the Bavarian cancer registry. The dataset included 5043 SCLC patients diagnosed and treated at the Ludwigs-Maximilians university (LMU) clinic in Munich between 2002 and 2015. We categorized patients into resected and non-resected, and resections into oncological resection (lobectomy, bilobectomy, pneumectomy) and limited resection (segmentectomy and wedge resection). We analyzed clinical variables (tumor stage, age, gender, adjuvant- or neoadjuvant treatment, type of resection) and survival data and compared them to non-resected patients. In the univariate analysis, we used t-test to compare numerical variables and chis-square and fisher exact test to compare categorical variables between the groups. We used Kaplan-Meier curves with logRank test to compare survival times. In the multivariate analysis, we used linear regression to model time trends in the proportion of patients receiving surgical resection, and Cox regression to model differences in survival time. **Results:** In total 161 (3.2%) received either an oncological or limited resection. We found a significant trend suggesting that resections in SCLC patients are becoming less common in all stages of disease, and that the proportion of oncological resections is increasing. This suggests that preoperative staging is becoming more accurate in SCLC. In VLD resection was significantly associated with longer survival compared to non-surgical management of VLD (logRank p=0.013). Survival was better in patients who underwent oncological resection compared to atypical resection. The Cox regression showed that administration of adjuvant chemotherapy was associated with better outcome in all resected patients independent of tumor stage (p=0.01). **Conclusion:** VLD SCLC patients benefit from oncological resection. We recommend accurate and invasive staging in these patients to ensure VLD. Furthermore, adjuvant chemotherapy should be offered to all medically fit patients

Keywords: SCLC, Surgery, very limited disease

P63.04 Minimum Number of Lymph Node Dissections for Resectable Early-Stage Small Cell Lung Cancer

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Introduction: Because only a minority of small cell lung cancer (SCLC) cases undergo surgical resection, the minimum number of hilar/mediastinal lymph node (LN) dissections required for resectable SCLC has never been established **Methods:** using National Cancer Database (NCDB), patients with clinical stage I-II SCLC who had undergone primary tumor resection were screened. Eligibility included clinical stage I-II by American Joint Commission on Cancer 7th edition, resection with at least lobectomy, pathological T1-2, and pathological N0/NX. Cases with unknown size of primary tumor or survival follow up less than one month were excluded. Collected clinical information included number of dissected LNs (<3 vs. 3+), age (<70 vs. older), sex (male vs. female), type of institution (academic vs. other), race (white vs. other), insurance status (uninsured vs. insured), comorbidity score (<2 vs. higher), year of diagnosis (2010-2012 vs. later), histology type (SCLC not otherwise specified vs. other), tumor size (<30mm vs. larger), margin status (positive vs. negative), pT status (pT1 vs 2), pN status (pN0 vs. X), use of chest radiation (yes vs. no), and chemotherapy (yes vs. no). Correlations between the number of dissected nodes and clinical characteristics were assessed by chi-square test. Log-rank test and Kaplan-Meier curve analyses were used for overall survival (OS). A two-tailed p-value less than 0.05 was considered as statistically significant **Results:** A total of 926 cases met the screening criteria. LNs ≥ 3 group (N=837) was associated with insured status, pN0, and use of chest radiation. Univariate analysis showed LNs ≥ 3 group had better OS than those with fewer dissected LNs (median OS 77.8 and 36.0 months, respectively, Logrank p<0.0001). Multivariate analysis demonstrated patients with LN 3+ status as well as younger age, female sex, pT1, and use of chemotherapy were associated with improved OS. Propensity score matching analysis confirmed that those with LN 3+ status had better OS in both univariate and multivariate analysis. Further analysis showed the difference in OS was significant for cut-off of LNs 3 and 5, but not for 7 or 10 with Logrank p-values of <0.0001, 0.0207, 0.0570, 0.2652, respectively. **Conclusion:** Our retrospective analysis using the largest cancer database shows that those with greater than three dissected LNs have significantly longer survival than those who had undergone fewer LN dissections, suggesting its prognostic and therapeutic roles. Further research is warranted to validate the findings.

Keywords: lymph node dissection, Small cell lung cancer

P63.05 Treatment Pattern in Small Cell Lung Cancer: A Real-world Observational Study in the Era of Immune Checkpoint Inhibitors

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Introduction: The treatment landscape in small cell lung cancer (SCLC) had not changed in the last three decades until the approval of immune checkpoint inhibitors (ICI) for treating extensive stage SCLC (ES-SCLC) in 2018. In early October 2018, the National Comprehensive Cancer Network (NCCN) guidelines recommended atezolizumab in combination with carboplatin and etoposide for first line treatment (1LT) of ES-SCLC following the publication of IMpower 133 trial results. There is little information currently available regarding the treatment landscape in SCLC after the availability of this new standard of care in frontline. We conducted a real-world observational study to address this data gap. **Methods:** This study is a retrospective, observational cohort study using structured oncology electronic medical record (EMR) data available from IQVIA (the data cutoff was September 30, 2020). Patients with a confirmed diagnosis of limited stage SCLC (LS-SCLC) or ES-SCLC who initiated first systemic therapy between October 1, 2018 and December 31, 2019. The index date was defined as the date of initiation of first systemic anticancer therapy following the SCLC diagnosis. A validated tumor-agnostic algorithm, adapted for SCLC based on clinical knowledge, was used to define treatment regimen and line of therapy. ICI use was defined as any regimen that contained a PD-1/PD-L1 inhibitor and/or a CTLA-4 inhibitor. Descriptive analyses were conducted to describe baseline patient characteristics and treatment distribution by regimen and class across lines of therapy. **Results:** A total of 1,256 patients (LS-SCLC: n=339; ES-SCLC: n=917) were included in the study, with a mean age of 67.3 years and a median follow-up of 5.6 months. During the study period, among 339 patients with LS-SCLC who received first-line (1L) systemic therapies, 77 (22.7%) and 15 (4.4%) progressed to receive second-line (2L) and third-line (3L) treatments, respectively. Of 917 patients with ES-SCLC, 249 (27.2%) and 60 (6.5%) advanced to 2L and 3L treatments, respectively. Approximately 91% of patients with LS-SCLC at initial diagnosis first received chemotherapy without ICI, consistent with concurrent chemoradiation therapy as the standard of care for 1L LS-SCLC. Subsequently, 76.6% patients received ICI-containing regimens in 2L and 80.0% received ICI in 3L. In contrast, 59.9% patients with ES-SCLC at initial diagnosis received ICI in 1Lwhereas in 2L and 3L, 52.6% and 30.0% patients received ICI. **Conclusion:** Despite the availability of ICIs in the front-line treatment of ES-SCLC, a considerable proportion of ES-SCLC patients do not receive ICI therapies in this setting. As these patients continue to progress and are in need of agents that have demonstrated efficacy, there is substantial ICI use in 2L and beyond. In the 1L treatment of LS-SCLC, there is yet to be a role for ICI; though a proportion of these patients progress rapidly and necessitate other treatments. The real-world evidence from this study supports that ICI therapies provide a meaningful treatment option beyond the frontline for patients with SCLC who currently have a limited life expectancy and high unmet medical need.

Keywords: Small cell lung cancer, real-world evidence, Treatment landscape

P63.06 Immunotherapy Improved Pathological Response for Resectable Limited Stage Small Cell Lung Cancer- A Case Serial

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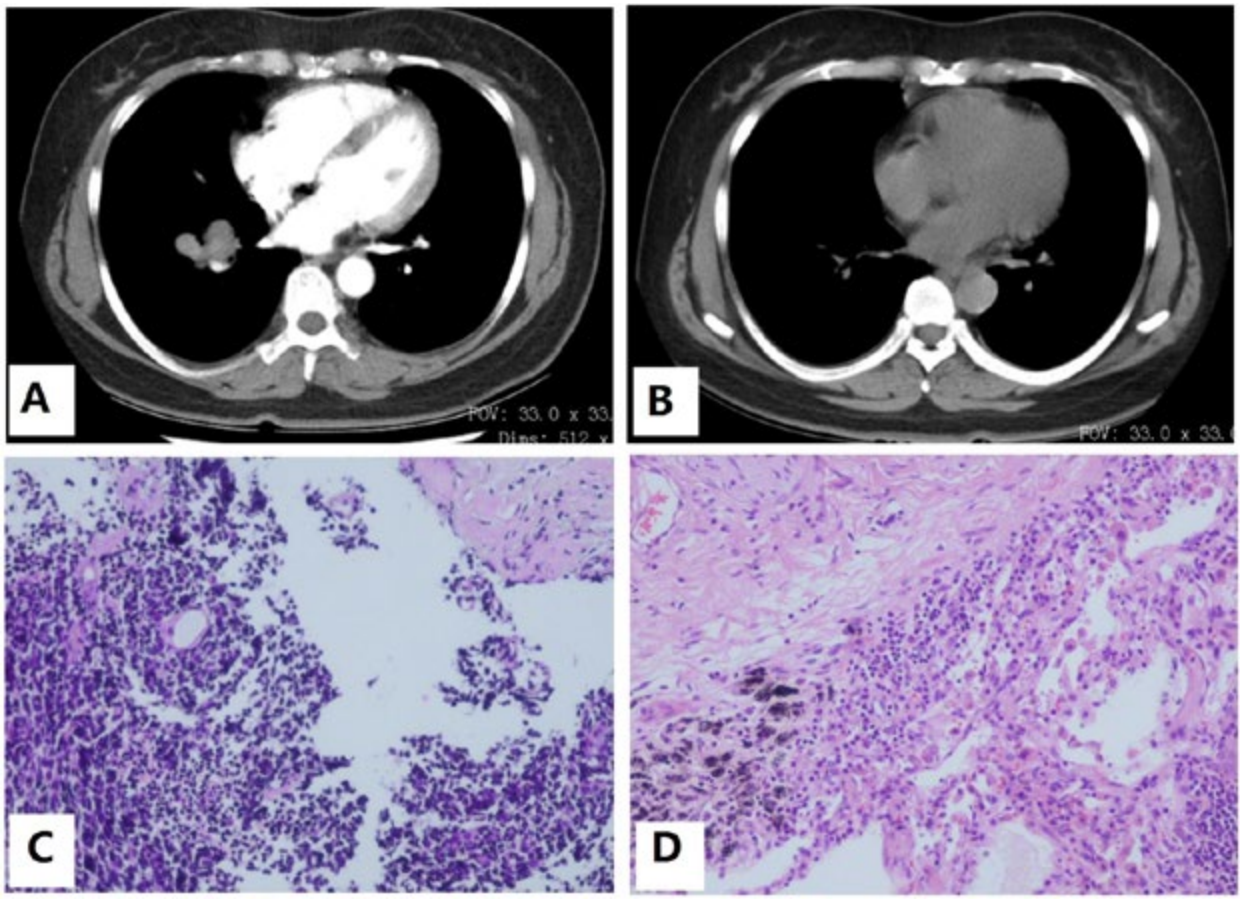
Introduction: As one of the most lethal cancers, small cell lung cancer (SCLC) stepped into the era of immunotherapy with the approval of anti-PD-L1 as standard therapy for extended stage SCLC. There are still some unmet needs for the limited stage SCLC. Here we report a small case series of the immunotherapy plus chemotherapy as neoadjuvant therapy for limited stage SCLC which achieved improved pathological response. **Methods:** Three patients were diagnosed as limited stage SCLC as nodal stage N1-N2 in Beijing Chest Hospital. All these patients received atezolizumab and standard chemotherapy (carboplatin plus etoposide) for 2-3 cycles, and underwent re-evaluation for the response and the possibility for R0 resection in Multi-disciplinary team (MDT). As the suggestion by MDT, all these patients underwent surgical resection after the neoadjuvant therapy. **Results:** The general baseline data was shown in Table 1. All three patients were re-evaluated down-staging as good PR after 2-3 cycles neoadjuvant therapy, especially for the nodal dowstaging in these patients. The possibility of R0 resection was fully discussed. As for the suggestion from MDT, these patients were evaluated as resectable and operable. They all received lobectomy and lymphadenectomy by the traditional thoracotomy instead of the video-assisted thoracic surgery (VATS).
The post-operation pathological results proved R0 resection for all these patients. Further, the results indicated pathological complete response in one patient (Figure 1) and pathological MPR in the other two patients, and all the dissected mediastinal lymph nodes were tumor free. Based on this result, we registered a single arm trial (ChiCTR2100042367) for the further study of this combination therapy for limited stage SCLC as neoadjuvant therapy.

Table 1 The General Data of Three patients received Neoadjuvant Thereapy

	Patient 1	Patient 2	Patient 3
Gender	Female	Male	Female
Age	49	51	43
Smoking status	Never	Never	Never
TNM stage	T2N1M0	T3N1M0	T2N2M0
Cycles before surgery	2	3	3
Pathological response	pCR	MPR	MPR



Conclusion: Immunotherapy combined with chemotherapy as neoadjuvant therapy could induce significant pathological response and give the opportunity of R0 resection in some limited stage SCLC patients, which is worth to be further explored.

Keywords: neoadjuvant therapy, Small cell lung cancer, immunotherapy

P63.07 Real World Predictors for Long Term Survival in Stage IV Small Cell Lung Cancer Treated With Standard of Care Chemotherapy

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Introduction: Stage IV small cell lung cancer (SCLC) has a median survival of less than 12 months, but rates of long term survival remain unclear. The importance of understanding long term survival increased recently with studies demonstrating improved survival with immune checkpoint inhibitors plus standard chemotherapy. We pursued an analysis of real world outcomes of patients in the province of Manitoba, Canada with stage IV SCLC treated with platinum-etoposide chemotherapy to clarify the likelihood of long term survival and predictive factors. **Methods:** Retrospective cohort study of Manitobans aged >18 years who received chemotherapy with cytologically confirmed, stage IV SCLC diagnosed 2004 – 2017. Comparisons between characteristics, treatment and survival duration (short term <6 months, medium term 6-24 months, long term >24 months) used Chi-square and Fisher Exact tests for categorical variables and Kruskal Wallis tests when variables were continuous and non-normally distributed. Overall survival was defined as the time between first treatment and death or end of follow-up (August 31, 2020). Overall survival estimates for 1-, 2-, and 5-year survival were plotted using Kaplan-Meier methods. **Results:** Our real world analysis of 427 stage IV SCLC patients in Manitoba, showed that 9.8% of patients had an ECOG performance status of 0, proportion of males and females was even, and poor prognostic factors (brain/liver metastases, high LDH, abnormal sodium, and low haemoglobin) were common. Cisplatin was the first line platinum drug for 60% of patients and 44% received thoracic radiotherapy (RT). When patients were classified by survival time (36.8% short term, 55.5% medium term, 7.7% long term), long term survivors were less likely to have ECOG 3-4 than ECOG 0 or 1-2, p<0.001or to have laboratory-based poor prognostic factors (elevated LDH, abnormal sodium, low haemoglobin, each p<0.02). Long term survivors were more likely to have initially been treated as limited stage disease, but ultimately were found to have stage IV disease instead. Further, 75.8% of long term survivors received lung RT and 48.5% received PCI. Survival in our cohort varied significantly by ECOG. Patients with ECOG 0 experienced 1, 2, and 5 year survivals of 45%, 21%, and 12%, while these survivals for ECOG 1-2 are 27%, 8%, 2% and for ECOG 3-4 are 16%, 3%, and 3%, p<0.01. For those who received lung RT, survival was 44%, 27%, and 12% at 1, 2, and 5 years, respectively. **Conclusion:** Though rare, long term survivors with stage IV SCLC treated with standard of care chemotherapy exist. Long term survival correlates with known prognostic factors, similar to reports from randomized trial populations assessing addition of immune checkpoint inhibitors. Two year survival in our cohort varied from 3-27% and 5-year survival from 3-12%, depending on patient characteristics. Poor performance status or other poor prognostic factors do not rule out long term survival, but they decrease the likelihood. Receipt of lung RT was associated with better survival, but these patients survived long enough to receive RT and likely had better performance status and fewer comorbidities.

Keywords: Chemotherapy, Long term survival, real world outcomes

P63.08 Real-World Utilization of Immune Checkpoint Inhibitors in Extensive Stage Small Cell Lung Cancer in Community Settings

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Introduction: Following the publication of IMpower 133 trial results (September 25, 2018) and the National Comprehensive Cancer Network (NCCN) guideline recommendation (October 10, 2018) of atezolizumab in combination with carboplatin and etoposide for first line treatment (1LT) of extensive stage SCLC (ES-SCLC), this combination therapy became the new standard of care for ES-SCLC. However, little is known regarding the subsequent changes in the SCLC treatment landscape, in particular, the utilization of immune checkpoint inhibitors (ICI). To address this data gap, we conducted a real-world observational study in community settings where the majority of patients with SCLC in the US are treated. **Methods:** This study is a retrospective, observational cohort study using structured oncology electronic medical record (EMR) data available from McKesson Specialty Health (the data cutoff date was November 30, 2020). The EMR data are collected from the US Oncology Network and Onmark practices, of which all are in community settings. Patients with a confirmed diagnosis of ES-SCLC (either de novo or progressed/recurred) who initiated first systemic anticancer therapy between October 1, 2018 to February 29, 2020 were identified. The index date was defined as the date of initiation of first systemic therapy following the initial diagnosis of SCLC. A validated tumor-agnostic algorithm was used to define treatment regimen and line of therapy. ICI use was defined as any regimen that contained a PD-1/PD-L1 inhibitor and/or a CTLA-4 inhibitor. Descriptive analyses were conducted to describe baseline patient characteristics and treatment distribution by regimen and class across lines of therapy. **Results:** A total of 1,496 patients (de novo ES-SCLC: n=1,268; progressed/recurred ES-SCLC: n=228) were included in the study, with a mean age of 67.9 years and a median follow-up of 6.3 months. Among patients with data available, 72.6% had an ECOG performance score of 0 or 1; 22.1% had brain metastases; and 92.5% had elevated lactate dehydrogenase (LDH). Of 1,496 patients who initiated first-line (1L) treatment, 703 (47%), 229 (15%), and 70 (5%) subsequently initiated second-line (2L), third-line (3L), and forth-line (4L) treatments, respectively. Approximately 59%, 53%, 29%, and 13% of patients received a regimen containing an ICI in 1L, 2L, 3L, and 4L, respectively. Among ICI-naïve patients, 77% and 67% received ICI in 2L and 3L, respectively. Notably, some patients were re-challenged with ICI regimens (15% in 2L and 17% in 3L). **Conclusion:** Despite the availability of ICI in combination with platinum-based chemotherapy as the standard of care for ES-SCLC in frontline, a considerable proportion of patients did not receive ICI in 1L and thus would be eligible for ICI-containing regimens when their disease progressed and required additional lines of treatment. There is substantial use of ICI in later lines of therapy, particularly among ICI-naïve patients. In conclusion, there remains an unmet need for SCLC patients with disease progression, and ICI has been an important option in the treatment paradigm.

Keywords: real-world evidence, Treatment landscape, Small cell lung cancer

P63.09 Surgical Management of Cushing's Syndrome Secondary to Lung Carcinoid Tumors: Changing Perspectives

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Introduction: Ectopic adrenocorticotropic hormone secretion from lung tumors causing Cushing's Syndrome engender profound morbidity. Optimal management remains obscure since knowledge is based on rare reports with few patients, with these tumors vaguely defined as more "aggressive" than non-hormonally active lung neuroendocrine tumors. This study's objective was to review our single institution's experience of lung carcinoids causing Cushing's Syndrome – the largest reported to date – to gain insights on treatment and outcomes in this rare subgroup. **Methods:** A retrospective observational case-series review of a prospectively maintained database at a single institution referral center (National Cancer Institute) from 1982 to 2020 was conducted. Included patients underwent curative-intent surgery for a lung neuroendocrine tumor causing Cushing's Syndrome during the study period. Fisher's exact test, Mehta's modification to Fisher's exact test, an exact Cochran-Armitage test, or a Wilcoxon rank-sum test were used depending on the variables to compare patients who underwent a lobectomy versus other procedures. Kaplan-Meier analysis estimated our primary outcome measure of disease-free survival. Disease-free survival was evaluated according to several clinicopathologic variables. **Results:** Sixty-eight patients met inclusion criteria. The mean age was 43 years, 57.4% (39/68) were female, 16.2% (11/68) were atypical carcinoid, 55.9% (38/68) were T1a, lymph node positivity was 37% (22/59) when evaluable, and mean follow-up was 53 months. Lobectomy was the most common procedure (70.6%, 48/68), followed by wedge resection (23.5%, 16/68) and segmentectomy (4.4%, 3/68). Video-assisted surgery was performed in 27.9% (19/68) of patients. Surgical morbidity was 19.1% (13/68), perioperative mortality was 1.5% (1/68). The overall incidence of persistence/recurrence of disease was 16.2% (11/68), with a mean recurrence time of 6.3 years. The 5-year disease-free survival for patients who underwent operative intervention with curative intent was 73%, and 10-year disease-free survival was 55%. The median disease-free survival was reached in 12.7 years. There were no statistical differences in disease free-survival based on the surgical approach. **Conclusion:** Despite neuroendocrine pulmonary tumors causing Cushing's Syndrome having increased nodal metastasis, higher recurrence, and lower disease-free survival than quiescent bronchopulmonary carcinoids, many patients enjoy favorable outcomes. Observing no difference in surgical techniques implies that a lung-sparing approach could suffice.

Keywords: Cushing's Syndrome, Neuroendocrine, Carcinoid

P63.10 Safety of Simultaneously Performed Radiotherapy in Patients With Small-Cell Lung Cancer Undergoing Atezolizumab Treatment

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Introduction: In September 2019 Atezolizumab was approved for extended disease small cell lung cancer (ED-SCLC) in combination with cytotoxic chemotherapy by the European Medicines Agency (EMA). In the clinical trial IMpower133 only 22 out of 201 patients received prophylactic cranial radiotherapy (PCI) during their treatment with Atezolizumab (either during induction chemo-/immunotherapy or during maintenance immunotherapy). To our knowledge, no other clinical studies have reported efficacy or safety regarding the combination of radiotherapy (PCI, whole brain radiotherapy (WBRT) or consolidating thoracic radiotherapy) with Atezolizumab as single agent or in combination with chemotherapy. In the clinical routine these safety data are urgently needed for treatment decisions of (radio)-oncologists. **Methods:** We performed a retrospective data analysis of all patients with SCLC who were treated at the Department of Medical Oncology, Evang. Kliniken Essen-Mitte from January 2019 until March 2021. Patients with combined chemo-/immunotherapy as induction treatment or with immunotherapy as maintenance were compared to those without any immunotherapy receiving similar radiotherapies. In case of thoracic radiotherapy, pulmonary function before and after irradiation was measured. Odds-Ratio for any documented adverse events were calculated. PFS for the different groups will be calculated. **Results:** 33 SCLC patients underwent cranial and/or thoracal irradiation (a group of 16 patients received both treatments yet) and were investigated. Atezolizumab was administered to 11 patients. There were no severe adverse events in patients with cranial radiotherapy regardless of simultaneously administered immunotherapy. In patients with thoracic radiotherapy, there was no significant difference in grade I to III adverse events. However, grade IV adverse events did only appear in patients without immunotherapy. Less than half of the patients had progression of their disease until March 2021.Therefore, PFS will be calculated in the next months and compared for the different subgroups. In five patients, who have already finished thoracic radiotherapy with immunotherapy maintenance and performed pulmonary function tests until March 2021, there is preliminary evidence for no deterioration of pulmonary function (forced one-second capacity (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, diffusing capacity for carbon monoxide (DLCO) and Carbon monoxide transfer coefficient (KCO)) compared to patients with thoracic radiotherapy without any immunotherapy. **Conclusion:** The addition of radiotherapy to immunotherapy seems not to be associated with increased toxicity in SCLC patients.

Keywords: immunotherapy, Small-cell lung cancer, radiotherapy

P63.11 Real-World Survival Outcomes of Patients with Limited Stage Small Cell Lung Cancer (LS-SCLC) by Choice of Platinum Chemotherapy

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Introduction: SCLC is an aggressive cancer with poor overall survival (OS). LS-SCLC is curable with concurrent chemoradiation (CRT). Cisplatin is the preferred chemotherapy backbone in national guidelines. Unfortunately, many patients with LS-SCLC are elderly, have co-morbidities, and have poor performance status (PS) which preclude cisplatin use. Carboplatin may be a suitable alternative. This analysis evaluates the overall survival (OS) and time to next treatment (TTNT) in LS-SCLC patients receiving concurrent CRT, by 1L platinum use. **Methods:** The study included LS-SCLC patients in the Flatiron Health nationwide de-identified electronic health record-derived database who received CRT in 2013-2019, with follow-up through May 2020. The study excluded patients with no documented visit or medication order within 90 days of diagnosis. Patient characteristics were compared between platinum chemotherapy groups using Wilcoxon rank sum tests and chi-squared tests. TTNT and OS were compared using both unadjusted and inverse propensity weighted Cox proportional hazards models. Propensity scores were built using boosted logistic regression minimizing standardized covariate distances for the covariates smoking history, prophylactic cranial irradiation (PCI), race, gender, age, relevant comorbidities, PS, and creatinine clearance (CrCl). **Results:** This study included patients treated with carboplatin (n=600) or cisplatin (n=572) in combination with etoposide and RT. Cisplatin patients were younger, had shorter time from diagnosis to radiation, and had less kidney disease. Propensity scores adequately balanced covariates between the two groups. In an unadjusted analysis, OS was greater in the cisplatin compared to the carboplatin group (mOS 22.3 vs. 19.2 m, HR 0.83, p=0.01). In the inverse propensity weighted analysis, this difference was no longer significant (HR 0.93, p=0.41). No differences were seen in TTNT.

		Carboplatin	Cisplatin	p	SMD
N		600	572		
Age (y)		69.1 [62.6, 75.1]	65.2 [59.0, 70.2]	<0.001	0.49
Comorbidities	Cardiomyopathy: N (%)	12 (2.0%)	10 (1.7%)	0.919	0.02
	Nephropathy: N (%)	27 (4.5%)	9 (1.6%)	0.006	0.17
	Otopathology: N (%)	6 (1.0%)	3 (0.5%)	0.550	0.05
	Neuropathy: N (%)	11 (1.8%)	9 (1.6%)	0.906	0.02
ECOG	0	171 (28.5%)	150 (26.2%)	0.083	0.15
	1	160 (26.7%)	172 (30.1%)		
	2-3	55 (9.2%)	33 (5.8%)		
CrCl		75.4 [58.3, 99.4]	87.9 [70.8, 111.8]	<0.001	0.41

*Categorical variables summarized as N (%) and compared via chi-squared tests, quantitative variables summarized as Median [Interquartile range] and compared via Wilcoxon rank sum tests **Conclusion:** When balancing on key clinical factors, we observe no statistical difference in OS or TTNT by platinum choice in real-world LS-SCLC patients treated with CRT. Although observational, the results from this large data set are consistent with the hypothesis that either cisplatin or carboplatin is appropriate therapy regardless of health status.

Keywords: Overall survival, Real-world data, SCLC

P63.12 Radiotherapy for Small Cell Lung Cancer in Current Clinical Practice Guidelines

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Introduction: Several guidelines for the treatment of small cell lung cancer (SCLC) exist worldwide. We conducted a review to evaluate whether there are major differences in radiotherapy recommendations between guidelines. **Methods:** PubMed and the sites of the different medical societies were searched for recent (≤3 years) SCLC guidelines published in either English, Chinese or Dutch. Data from these guidelines were extracted and compared regarding the guideline's development method and radiotherapy recommendations in SCLC. Reasons behind the differences in the guidelines regarding these recommendations were discussed. **Results:** Eleven guidelines were identified (PubMed n=4, societies n=7): 1 from Spain (SEOM, 2020), 1 from Canada (CCO, 2018), 3 from America (ASTRO, 2020; ARS, 2020; NCCN, 2021), 1 from England (NICE, 2019), 1 from Europe (ESMO, 2021), 1 from the Netherlands (FMS, 2019), and 3 from China (CSCO, 2020; CSTRO, 2020; CMA, 2019). Nine guidelines assessed the strength of evidence and specified the strength of recommendation, although methods were different. For patients with resected stage I–IIA, most applicable guidelines recommend thoracic radiotherapy (TRT) in patients with pathological N2 (n=8) or R1-2 (n=4), for pN1 recommendations are discrepant. PCI is recommended in two guidelines, one advises against, and others state it can be considered. For non-surgically treated stage I–IIA patients, chemoradiotherapy is recommended. Six guidelines further suggest stereotactic body radiation therapy (SBRT). Recommendation of PCI is controversial. PCI is recommended in CSCO, but not recommended in SEOM, four suggest it can be considered. Others manage it the same as stage IIB-IIIC. For patients with stage IIB–IIIC in good clinical condition, all guidelines prefer concurrent chemoradiotherapy (CCRT). Most guidelines advise to start radiotherapy (45Gy twice-daily [BID] or 60-70Gy once-daily [QD] [n=9]) preferably at the first or second cycle of chemotherapy (n=9). Two guidelines advise only 45Gy BID. As for the RT volume, six guidelines recommend that the primary tumor post-chemotherapy and the involved nodal regions before chemotherapy should be included. SEOM suggests primary tumor before-chemotherapy should be included. Four guidelines suggest omission of elective nodal irradiation (ENI), others have no related information (NI). All applicable guidelines recommend PCI (25Gy) in patients with response to initial therapy. PCI should be started 3-4 weeks after chemoradiotherapy (n=3), within 60 days after completing of chemotherapy (n=1), after initial therapy (n=2), or no time period is specified (n=4). For stage IV patients, consolidative TRT is advised in all of the guidelines. Either PCI or cranial MRI surveillance is recommended. Two guidelines recommend MRI surveillance regardless of PCI status. All applicable guidelines advise whole-brain radiotherapy in patients with brain metastases. **Conclusion:** Most recommendations regarding radiotherapy are similar across guidelines with some differences in controversial fields, such as TRT in pN1, PCI in very early or extensive stage. The existence of several overlapping guidelines for SCLC treatment suggests that work is (unnecessarily) repeated by the different organizations or societies. Improvement could be made by better international collaboration, which would spare a lot of time, effort and resources.

Keywords: radiotherapy, Small cell lung cancer, guideline

P63.13 Long Term Survival Characteristics in SCLC Patients Receiving Atezolizumab and Chemotherapy

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Introduction: First-line atezolizumab with platinum-based chemotherapy (Atezo-chemo) improves outcomes in clinical trials and the real world setting, but identifying those most likely to benefit is challenging. Immune-related adverse event (irAE) has been associated with improved survival among small cell lung cancer (SCLC) patients treated with immune checkpoint inhibitor 1. We explored factors linked with long term survival (LTS) in a cohort of extensive stage (ES) SCLC in receipt of Atezo-chemo **Methods:** Demographic and clinical data were extracted from the institutional Glans-Look Research Database. LTS versus non-LTS was defined as overall survival ≥12 vs < 12 months following systemic treatment initiation respectively. Disease progression referred to new or growing lesions by RECIST criteria and/or death from any cause. LTS versus non-LTS characteristics (Fisher's Exact) and outcomes including adverse events (CTCAE criteria v5), survival (Kaplan-Meier's Long-Rank and Cox proportional hazard ratio) were compared. **Results:** 34 patients who received Atezo-chemo were identified. Median follow-up time was 18 months as of Mar 24, 2021. 53% were LTS. 85% (29/34) have discontinued treatment, the leading reasons being development of new and/or growing lesions (52%, 15/29). 62% (21/34) had adverse event (AE). The distribution of AEs were: 57% (12/21) hematological, 24% (5/21) gastro-intestinal and 19% (4/21) for both skin and endocrine disorders. irAE accounts for 38% (8/21) of all AE, mostly seen in LTS (6/8). AE was the second leading cause of treatment termination (35%, 12/34), with grade ranging from 2-5. The median (range) treatment cycle at discontinuation was 5 (1-16 cycles). Half (4/8) of irAE led to permanent treatment discontinuation with equal proportion of LTS vs non-LTS. LTS versus non-LTS did not significantly differ in age, sex, or the presence of brain or liver metastasis at treatment initiation. However, non-LTS had more abrupt treatment discontinuation with all Grade 5 AE (died on treatment) limited to this group only. Progressive disease (PD) rate was 83% vs 100% in LTS vs non-LTS. 22% of LTS vs 38% non-LTS had concurrent intra and extra-thoracic disease progression while intrathoracic-only disease progression was seen in just LTS (33% LTS, p=0.09). Multivariate analysis revealed that good ECOG status (0-1), no distant metastasis and PCI receipt correlated with favorable survival prognoses. There was a trend in association between non-immune AE and worse survival (Table 1).

Table 1: Characteristics of long tem survivors (LTS) versus non-LTS, n (%)

	Non-LTS N=15	LTS N=18	P value (Fisher's test)	HR (OS)	Reference variable	P value for HR
Median Overall Survival, months	6	Not reached	<0.01**			
Still alive	1 (6)	11 (61)	<0.01			
Ongoing atezolizumab	0 (0)	5 (28)	0.05			
Median atezolizumab cycle (range)	5 (1-10)	14 (4-19)				
Maintenance atezolizumab	10 (63)	17 (94)	0.04			
Thoracic Radiotherapy (tRT)	0 (0)	4 (22)	0.11	<0.01	No tRT	0.91
Prophylactic Cranial Irradiation	1 (6)	3 (17)	0.60	0.02	No PCI	<0.01
Adverse events (AE)	10 (63)	11 (61)	>0.05			0.91
Immune-related AE	2 (13)	6 (33)	0.27	<0.01	No AE	0.88
Non-immune AE	8 (50)	5 (28)		30.92	No AE	0.05
≥ Grade 3 AE	7 (44)	8 (44)	>0.05			
Treatment discontinuation due to AE	9 (56)	3 (17)	0.03			
Age ≥65 yr.	8 (50)	9 (50)	>0.05	0.47	<65	0.30
ECOG 2-3	6 (38)	2 (11)	0.11	51.36	ECOG 0-1	0.02
No distant metastasis	3 (19)	4 (22)	0.18	0.30	>1 metastases	0.01
Second-line systemic treatment	3 (19)	7 (39)	0.27			

** Log-Rank p value (Kaplan-Meier Survival)

Conclusion: A higher rate of AE-related treatment termination in real-world than trial patients2. irAE does not seem to be associated with longer survival in our ES cohort of Atezo-chemo.

Keywords: Extensive stage SCLC, Immune checkpoint inhibitor, Real-world treatment safety

P63.14 Three Weekly Irinotecan for Refractory/Relapsed Small Cell Lung Cancer

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Introduction: Studies that evaluated Irinotecan for solid malignancies includes both weekly and three weekly regimens. However, NCCN guidelines support weekly irinotecan regimen for refractory/relapsed SCLC (small cell lung cancer). Current guidelines do not acknowledge three weekly regimen for SCLC due to insufficient data. We aimed to study clinical efficacy, side effect profile, and cost analysis of three weekly irinotecan regimens for refractory/relapsed SCLC. **Methods:** Retrospective analysis of relapsed/refractory SCLC or high-grade neuroendocrine carcinoma (HGNEC) patients treated with every 3 weekly irinotecan (300 mg/m^2) regimen between 2010 and 2020 at an National Cancer Institute designated cancer care center was performed. Median progression free survival(PFS) and adverse events per CTCAE 5.0 were determined. **Results:** A total of thirty-nine patients were included in our analysis, 33 with SCLC and 6 with HGNEC. Primary site for patients with HGNEC includes bladder (n=1), prostate(n=1), gastroesophageal junction(n=1) and unknown primary (n=3). The median age at diagnosis was 63 years (IQR = 14 years). The median prior line of therapies was 2 (IQR=0.5), and median number of irinotecan cycles was 2 (IQR=2). None of our study patients had a complete response to therapy. Stable disease was noted among 38.5% patients and the rest experienced disease progression. Median progression-free survival was 2.1 months (95% CI-1.6 to 8.1). Overall grade (G) 2 adverse events were noted among 20.5%, G3 in 35.9%, and G4 among 7.7% of study patients. Following G1, G2, G3 and G4 adverse events were noted. Nausea: 15.4%, 5.1%, 12.8% and 0% ; vomiting: 7.7% , 5.1%, 10.3% and 0%; diarrhea: 10.3%, 5.1%, 23.1% and 0%; neutropenia: 0%,0%,2.6% and 5.1%; transaminitis: 7.7%, 0%, 7.7% and 0% respectively. Ileus was noted among 5.3%; enterocolitis among 2.6%. None of study patients experienced mucositis, pneumonitis, skin rash and liver failure. Estimated overall costs per cycle to deliver three 100mg/m2 doses with every weekly regimen was $661 compared to only $268 for a single 300mg/m2 dose with every three-weekly regimen. **Conclusion:** In patients with progressive refractory / relapsed SCLC, every three weekly irinotecan regimen was found to have comparable efficacy and adverse event profile. Moreover, cost-effectiveness and reduced number of infusions with of every 3 weekly regimen might potentially benefit patients who live far from health care facility as is the case in rural Appalachia and also help reduce financial toxicity.

Keywords: high-grade neuroendocrine carcinoma, Small cell lung cancer, Irinotecan

P63.15 Clinical Analysis of 89 Female Patients With Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is a kind of tumor with obvious heterogeneity. Accurate classification is a prerequisite of appropriate selection of treatment. Females differ from males in several demographic, hormone and clinical characteristics, which may lead to different prognosis in SCLC. Our study is aimed at summarizing the clinicopathological characteristics, management and prognosis of female small cell lung cancer and contributing to the promotion of precision treatment of SCLC. **Methods:** The study collected female SCLC patients treated in Cancer Hospital, Chiniese Academy of Medical Sciences from May 1, 2015 to April 1, 2020. Eligible patients were required to be histologically or cytologically confirmed SCLC.The patients were analyzed in terms of age, pathological characteristics, TNM staging status, smoking history, family history, and treatment. **Results:** 89 female patients (47.2% limited-stage, 52.8% extensive-stage) were included, among whom 80 (89.8%) were never-smokers. Among 89 patients, the 1-, 3- and 5-year overall survival (OS) rates were 84.21%, 39.76% and 18.56%, respectively. The 1-, 2- and 3-year progression-free survival (PFS) rates were 42.7%, 21.71% and 13.23%, respectively. In the whole cohort, the median PFS was 10 months (8.03 months -11.97 months), the median OS was 34 months (26.6 months -41.4 months) At the time of data cut-off in February 1,2020, 45 patients were deceased and 44 patients were still alive. mPFS of limited disease of SCLC is better than that of extensive stage small cell lung cancer. The mPFS of LD-SCLC was 10month(3.71month -16.29 month),and mPFS of ED-SCLC was 9month(7.09month-10.91month).Chest radiotherapy and prophylactic cranial irradiation influence PFS.M group ,chest radiotherapy and prophylactic cranial irradiation influence female small cell lung cancer's OS. **Conclusion:** Compared to previously reported male patients, the survival of female small cell patients was longer than that of male patients in both limited and extensive stages. Chest radiotherapy and prophylactic brain irradiation are necessary to improve survival outcomes. We are deeply exploring biomolecular markers, looking forward to accurate treatment from clinical diagnosis and treatment to basic research.

Keywords: female, prophylactic cranial irradiation, Small cell lung cancer

P64 SMALL CELL LUNG CANCER/ NET - CLINICAL TRIAL IN PROGRESS

P64.01 The Canadian Small Cell Lung Cancer Database (CASCaDe): A Multi-Institutional Real-World Evidence Collaboration

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Introduction: Small cell lung cancer (SCLC), a poorly differentiated neuroendocrine tumor distinguished by rapid doubling time and early development of metastases, represents approximately 15% of all diagnosed lung cancers. Median survival is poor regardless of stage at diagnosis. Good evidence exists to guide upfront management of both limited (LS) and extensive stage (ES) SCLC, and several recent trials have shown significant survival benefits with the addition of immunotherapy to chemotherapy in ES-SCLC. However, upon relapse, there is modest prospective evidence available to guide management. Clinical trials are challenging due to the aggressive course of illness, high incidence of brain metastases, and frequent presence of significant comorbidities in the affected patient population. Real-world evidence (RWE) has a significant role to play in the optimal management of SCLC. It can be used to ensure therapies studied in a controlled trial setting have equal impact for patients seen in routine clinical practice. It can also inform treatment options in the 2nd line and beyond setting, where prospective evidence is limited. Generating optimal RWE involves collecting robust and detailed patient level data for a large number of patients seen in a variety of care settings. We have initiated a collaborative Canadian SCLC database, where data can be pooled from multiple sites across the country, in order to generate more powerful RWE. This database can be used to support regulatory issues, and primarily answer multiple research questions regarding population-based outcomes of SCLC, optimal management strategies, and quality of care indicators. **Methods:** With ethics approval at each centre and data sharing agreements in place, CASCaDe involves the creation of a multi-institutional database of patients with SCLC. We have engaged 8 institutions across the country who have committed to participating in CASCaDe: BC Cancer (Provincial cancer program for British Columbia), Tom Baker Cancer Centre (Calgary, Alberta), Cancer Care Manitoba (provincial cancer program for Manitoba), Princess Margaret Cancer Centre (Toronto, Ontario), Cancer Centre of Southeastern Ontario (Kingston, Ontario), the Ottawa Hospital Cancer Centre (Ottawa, Ontario), Jewish General Hospital (Montreal, Quebec), and the QEII Cancer Centre (Halifax, Nova Scotia). A variable list (data dictionary) has been generated and contains detailed baseline demographic factors, staging information, treatment details, and survival outcomes. Currently, there are 1848 patients in existing local databases that will be merged into CASCaDe, with an estimated additional 2100 patients from local sites where additional data collection is ongoing. Initial research questions for the database include: an overall descriptive analysis of SCLC in Canada; an analysis of post-1st line treatment; the use of stereotactic radiotherapy in limited stage SCLC **Results:** A full descriptive analysis of the database contents is expected to be available at the time of the conference.

Keywords: SCLC, real-world evidence

P64 SMALL CELL LUNG CANCER/ NET - CLINICAL TRIAL IN PROGRESS

P64.03 A Phase II Single-Arm Trial of Apatinib as Maintenance Treatment Following First-Line Chemotherapy in Extensive Stage Small Cell Lung Cancer

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Introduction: For half a century, there is no breakthrough in maintenance therapy after first-line chemotherapy of extensive stage small cell lung cancer(ED-SCLC). Even though first-line chemotherapy combined with immunotherapy can prolong the overall survival(OS) of ED-SCLC patients, the benefit is not satisfactory. The disease often progresses rapidly, and the therapy after the first-line treatment is very limited. The development of therapy to delay cancer progression and prolong survival after initial chemotherapy for SCLC is an unmet clinical need. Recently, small, orally administered multi-target TKIs , such as apatinib, have exerted promising effects on SCLC. **Methods:** This study enrolled 12 ED-SCLC patients to study the efficacy and toxicity of apatinib in maintenance therapy after standard first-line chemotherapy. The primary endpoints were OS and progression-free survival (PFS). The secondary endpoints included toxicity and safety. Apatinib was given 250 mg/day during the chemotherapy interval, and as maintenance therapy after 4–6 cycles until the patient progressed, died, or was intolerant to drug toxicity. **Results:** The patients who received apatinib as maintenance treatment exhibited a median PFS of 3.7 months (range=1.3–6.2). The median OS was 16.3 months (range=9.7-22.8). Two patients required dose reduction due to adverse effects. The most common AEs included hypertension (n = 4,33.33%) and hand-foot-skin reaction (n = 2, 16.67%). One patient developed diarrhea and one patient developed hemoptysis. The most serious side effect was intestinalobstruction **Conclusion:** As a maintenance treatment after first-line chemotherapy , apatinib not only showed anti-tumor activity for further tumor shrinkage, but also had the potential to prolong OS in ED-SCLC and would be a potent therapeutic option in future clinical practice.

Keywords: small cell lung cancer, apatinib, maintenance treatment

P64.04 Hypo-Fractionated Versus Conventionally Fractionated Radiotherapy for Patients with LS-SCLC: An Open-Label, Randomized, Phase 3 Trial

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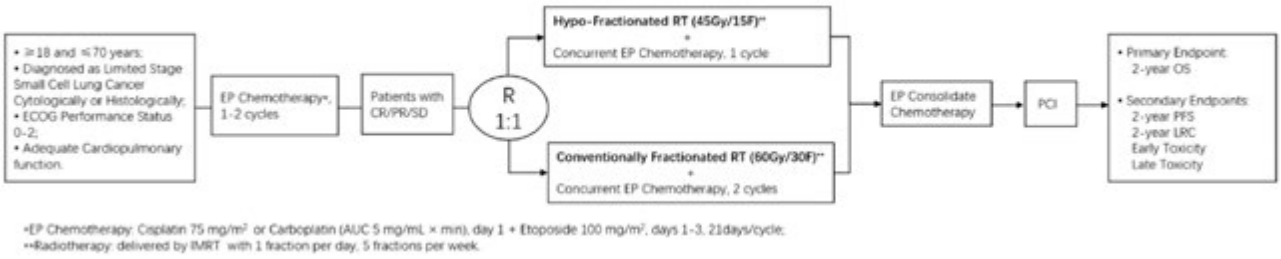
Introduction: Concurrent chemoradiotherapy (CRT) is the standard treatment of limited-stage small-cell lung cancer (LS-SCLC). Various radiation schedules in CRT are commonly used, because the CONVERT phase III trial suggested comparable survival outcomes with similar toxicity profiles of once-daily radiotherapy of 66 Gy (conventionally fractionated radiotherapy, CFRT) over twice-daily (BID) radiotherapy of 45 Gy. However, twice-daily radiotherapy has not been widely adopted clinically, due to logistical issues in its delivery. Recently, characterized by the improved dose conformality to tumor target and reduced normal tissue exposure, intensity-modulated radiation therapy (IMRT) has been used widely, making hypo-fractionated radiotherapy (HFRT) for LS-SCLC feasible and tolerable. Here, we aim to design a phase III trial to compare the efficacy and toxicity of HFRT and CFRT in LS-SCLC patients. **Methods:**

Figure1. Trial Design



*EP Chemotherapy: Cisplatin 75 mg/m^2 or Carboplatin (AUC 5 mg/mL × min), day 1 + Etoposide 100 mg/m^2, days 1-3, 21days/cycle;
**Radiotherapy: delivered by IMRT, with 1 fraction per day, 5 fractions per week.

This multicenter, open-label, phase III, randomized trial aims to enroll approximately 540 patients with cytologically or histologically confirmed LS-SCLC, aged 18 to 70 years, ECOG performance status 0-2, and adequate cadiopulmonary function. Stratified by institution and stage, participants are randomly assigned (1:1) to receive either HFRT (45 Gy/15 fractions) or CFRT (60 Gy/30 fractions). Both groups receive one fraction per day and five fractions per week. All patients complete four to six courses of intravenous cisplatin 75 mg/m2 or carboplatin (area under the curve 5 mg/mL × min, Calvert's formula) on day 1 and etoposide 100 mg/m2 on days 1-3 every 3 weeks. Thoracic radiotherapy starts no later than the first day of the 3rd course of platinum-etoposide. Responders are recommended prophylactic cranial irradiation of 25 Gy in 10 fractions. The primary endpoint is 2-year overall survival and the secondary objectives include 2-year progression-free survival, 2-year local-regional control and toxicities. **Results:** This study started in Feb 2016, and 373 patients have been accrued as of Mar 31, 2021. Trial registration: ClinicalTrials.gov: NCT02688036. Registered 23 February, 2016.

Keywords: Conventionally fractionated radiotherapy, Limited-stage small cell lung cancer, Hypo-fractionated radiotherapy

P64.02 EMERGE 402 Phase 4 Observational Study: Safety and Outcomes in Patients With SCLC Receiving Treatment With Lurbinectedin

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Introduction: Lurbinectedin, a selective inhibitor of oncogenic transcription, was approved on June 15, 2020 by the US Food and Drug Administration for the treatment of adult patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy; accelerated approval was based on the overall response rate (ORR; 35.2%) and duration of response (5.3 months) observed in a phase 2 clinical trial (NCT02454972). This trial, however, included a limited number of patients with metastatic SCLC who progressed on first-line platinum-based chemotherapy in combination with immunotherapy, which has since become standard of care. Thus, it is important to understand the effectiveness of lurbinectedin in patients with first-line immunotherapy exposure among a broader population with variable disease state and progression, and sensitivity to various treatments, as well as to collect data on health-related quality of life (HRQOL). Accordingly, the EMERGE 402 study will assess the effectiveness, safety, and HRQOL with lurbinectedin in a real-world setting among patients with SCLC who progressed on or after prior platinum-containing chemotherapy, with or without immunotherapy. **Methods:** EMERGE 402 is a prospective, observational, multicenter, phase 4 trial with a target enrollment of 300 patients with SCLC who have previously received ≥1 line of a platinum-based chemotherapy regimen at approximately 50 community- and academic-based centers throughout the United States. After a physician has prescribed lurbinectedin (in line with US prescribing information: 3.2 mg/m^2 by intravenous infusion over 60 minutes every 21 days), the patient may be assessed for enrollment in the study. Data will be collected at baseline and during the normal course of patient care from first infusion until death, withdrawal of consent, loss to follow-up, or until 24 months has elapsed, whichever occurs first. An ad hoc analysis is planned after the first 120 patients have been followed for ≥6 months after initial lurbinectedin infusion. Primary and secondary endpoints are listed in the Table. Additional analyses will be performed for key subgroups of interest: patients receiving prior immunotherapy (including specific immune checkpoint inhibitors); chemotherapy-free intervals of >180, >90, <90, and <30 days before lurbinectedin treatment; brain metastasis (baseline and progression); limited- versus extensive-stage disease at initial diagnosis; use of granulocyte colony-stimulating factor as prophylaxis (primary versus secondary and number of administrations); ages ≥65 versus <65 years; and current therapies, including lurbinectedin monotherapy, lurbinectedin in combination with other anti-cancer agents, line of lurbinectedin treatment, and lurbinectedin treatment through progression.

Table. Primary and Secondary Objectives and Endpoint Assessments in EMERGE 402	
Primary objective	• Assess effectiveness of lurbinectedin monotherapy by ORR (CR or PR) as assessed by the investigator according to the RECIST v.1.1 in the study population
Secondary objectives	• Assess other effectiveness measures (OS, PFS, DoR, and DCR) of lurbinectedin monotherapy in the study population • Assess patterns of lurbinectedin utilization (dose and number of lurbinectedin cycles, and previous, concomitant, and subsequent treatments) in the study population • Assess safety and tolerability (SAE and AESI) of lurbinectedin monotherapy in the study population • Assess HRQOL with lurbinectedin monotherapy in the study population using PRO questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-LC13) • Assess time to confirmed response (CR or PR) with lurbinectedin monotherapy in the study population • Assess effectiveness, safety, and HRQOL with lurbinectedin monotherapy in the second-line setting • Assess effectiveness (OS, PFS, ORR, DoR, and DCR) and safety in other subgroups of interest
ORR, overall response rate; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; OS, overall survival; PFS, progression-free survival; DoR, duration of response; DCR, disease control rate; SAE, serious adverse event; AESI, adverse event of special interest; HRQOL, health-related quality of life; PRO, patient-reported outcomes; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire.	

Keywords: lurbinectedin, post-platinum chemotherapy, Small-cell lung cancer

P65.01 Are Serum Markers Useful In Patients With Resected Pulmonary High-Grade Neuroendocrine Tumors?

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Introduction: Although pro-gastrin-releasing peptide (ProGRP), neuron-specific enolase (NSE), and carcinoembryonic antigen (CEA) have been reported to be useful markers for staging, monitoring treatment, and predicting relapse in patients with high-grade neuroendocrine tumors (HGNETs), the usefulness of these serum markers in patients with resected HGNET has not yet been evaluated. The aim of this study was to investigate the usefulness of these serum markers in these patients. **Methods:** One hundred eighty-five consecutive patients with HGNETs (82 with small cell carcinoma: SCLC and 103 with large cell neuroendocrine carcinoma: LCNEC) were investigated. Serum levels of ProGRP, NSE, and CEA before surgery and at relapse were evaluated in each histologic subtype. **Results:** Table 1 shows the preoperative status of serum markers. At relapse, in patients with SCLC, 33 (77.0%) of 43 patients had an elevated serum level of at least one of the three serum markers. Twenty-three (53.5%) of 43 had an elevated serum level of ProGRP, and of these 23, 9 had a normal level before surgery. Seventeen (39.5%) of 43 had an elevated serum level of NSE, and of these 17, 15 had a normal level before surgery. Eight (18.6%) of 43 had elevated serum levels of both ProGRP and NSE. Only one patient had an elevated serum level of CEA alone. In contrast, in patients with LCNEC, 31 (70.5%) of 44 patients with relapse had an elevated serum level of at least one of the three serum markers. Ten (22.7%) of 44 had an elevated serum level of ProGRP, and of these 10, 4 had a normal level before surgery. Seventeen (38.6%) of 44 had an elevated serum level of NSE, and of these 17, 15 had a normal level before surgery. Three (6.8%) of 44 had elevated serum levels of both ProGRP and NSE. Nine (20.5%) of 44 had an elevated serum level of CEA alone. (Table 1)

Variables	SCLC (n = 82)	LCNEC (n = 103)
Serum markers, n (%)		
Not elevated	37 (45.2)	46 (44.6)
CEA alone	13 (15.9)	27 (26.2)
ProGRP alone	14 (17.0)	5 (4.9)
NSE alone	5 (6.1)	5 (4.9)
CEA and ProGRP	9 (11.0)	9 (8.7)
CEA and NSE	2 (2.4)	8 (7.8)
ProGRP and NSE	1 (1.2)	1 (1.0)
CEA, ProGRP, and NSE	1 (1.2)	2 (1.9)

Conclusion: While both ProGRP and NSE may be useful for detecting the relapse of HGNETs after surgery, CEA might be useful in patients with LCNEC.

Keywords: high-grade neuroendocrine tumor, tumor marker, Surgery

P66.01 Characterize the Heterogeneity of the Immunophenotype in Different Neuroendocrine (NE) Subtypes of Small-Cell Lung Cancer (SCLC)

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Introduction: SCLC is a typical neuroendocrine carcinoma, however, a variant subtype of SCLC with low expression of NE markers and a variant morphology has been reported mainly based on cell lines and xenograft models. The difference of the tumor immune microenviroment (TIME) and other clinicopathological characteristics between the two subtypes in human specimens remain to be investigated. **Methods:** Forty-eight resected Formalin-Fixed and Paraffin-Embedded (FFPE) SCLC tissues were collected for mRNA detection using Nanostring technology. Patients were assigned into NE-high and NE-low group according to NE gene signature score, and the expression level of immune-related genes and abundance of immunocytes estimated by CIBERSORT was compared between the two groups. Nanostring digital spatial profiling (DSP) was performed in 6 NE score paired tumors to dissect the heterogeneity of spatial distribution of immune cells and immunotherapeutic drug targets between the two subtypes. Kaplan-meier method and COX regression model was used to compare the survival of the two subtypes and identify the independent prognostic factors and potential immunotherapeutic targets respectively. **Results:** Forty-eight patients were assigned into the NE-high and NE-low group respectively based on NE score. NE-low group had earlier clinical stages (P=0.030), higher positive rates of lymph nodes (P=0.017) and higher frequency of variant morphology (P=0.047) than that of NE-high group. Compared with NE-high tumors, most of the detected immune-related genes were up-regulated in NE-low tumors. CIBERSORT results indicated NE-high subtypes had a higher relative proportion of Treg cells and M2 macrophages. However, higher absolute abundance of activated mast cells, CD8+ T cells and M1 macrophages enriched in NE-low TME. DSP results showed NE-high tumors were lack of dendritic cells and macrophages in peritumor area and normal tissue compartments and also lack of effector T cells in tumor center and surrounding area. However, a set of targetable negative immune checkpoints were up-regulated in NE-low TME. The prognosis was better for NE-low patients with 5-year DFS% 75% vs.38.6% (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.08-1.46; P=0.130) and 5-year OS% 87.5% vs.53.9% (HR 0.19, 95% CI 0.03-1.43; P=0.073). **Conclusion:** SCLC patients exhibited heterogeneous NE gene expression profile, implicating two entities with distinct TIME and prognosis. Compared with NE-high subtypes, patients with NE-low tumors had higher expression of immune-related genes, showing T cell-inflamed immunophenotypes, which might be one of causes for longer survival and suggested a higher propensity to benefit from immunotherapy.

Keywords: Neuroendocrine (NE), tumor immune microenvironment (TIME), Small-cell lung cancer (SCLC)

P66.02 The Prognostic Implication of hes1 Protein Expression in Resected Small Cell Lung Cancers of 247 Cases

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Introduction: Small cell lung cancer (SCLC) is a highly aggressive malignancy prone to early recurrence and metastasis. Preclinical studies have found that Hes1, as a transcription repressor of the basic helix-loop-helix (BHLH) family, can not only prevent the proliferation and migration of SCLC tumor cells, but also inhibit the neuroendocrine transcription factor ASCL1. However, the prognostic implication of Hes1 protein on surgically resected SCLCs remains unclear. The current study aims to analyze the expression pattern and prognostic value of Hes1 protein in SCLC. **Methods:** Two hundred and forty seven surgically resected pure SCLC specimens were reviewed and included in this study by using tissue microarrays (TMA) for immunohistochemistry (IHC) analysis of Hes1 protein on a fully automatic Roche immunohistochemical instruments . And the corresponding clinicopathological features such as age, lymph node metastasis, major cell shape and tumor infiltrating lymphocytes(TILs), etc were reviewed and collected. Correlation analysis of Hes1 protein with clinic pathological features and survival analysis was performed using SPSS 25.0 and Graphpad Prism 5.0. **Results:** Among the 247 surgically resected pure SCLC patients, 175 (71%) were male and 202 (82%) were less than 65 years. According to the AJCC Cancer Staging Manual (seventh edition), 78 (31.6%) were stage I, 68 (27.5%) were stage II, and 101 (40.9%) were stage III. Hes1 expression was localized in the nucleus of SCLC tumor cells. A total of 129 of the 247 enrolled SCLC patients showed high expression of Hes1 with a positive rate of 52.2%(129/247), and was found positively correlated with a lower age(≤65 yrs., p=0.014), no lymph node metastasis(P=0.003), main cell morphology of round cells(p=0.002), and TILs≤30% (p=0.010). Univariate survival analysis revealed a favorable survival in high expression group for a significant disease free survival (DFS, HR=1.477,95%CI 1.025-2.129, P=0.036) and a positive trend of overall survival (OS, HR=1.181,95%CI 0.778-1.792,P=0.435). **Conclusion:** In limited stage pure small cell lung cancer, high expression of Hes1 protein is related to age, lymph node metastasis, main cell morphology and TILs , which contributes as a potential biomarker for the prognosis of SCLC patients.

Keywords: SCLC, HES1, prognostic implication

P66.03 The Functional Role of TGF-β Signaling in SCLC Heterogeneity and Metastasis

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Introduction: Small cell lung cancer (SCLC) is the most aggressive lung cancer and highly heterogeneous phenotypes have been observed in human and mouse SCLC cells. Tumor heterogeneity has been proven to contribute to SCLC malignant progression and/or metastasis in RP-based models. And the unique therapeutic vulnerabilities across different SCLC subtypes have been linked with their specific gene expression profile, indicating the need of personal therapeutic strategy in clinic. The TGF-β signaling consists of secreted TGF-β family members, receptors and SMAD proteins, and is implicated in multiple cell biological processes, such as cell proliferation and survival, epithelial to mesenchymal transition (EMT), cell fate control, immune response, and tumorigenesis. Dysregulation of the TGF-β signaling pathway has been reported in different cancer types and dual role of this pathway in cancer development and progression has been documented. Activation of this pathway results in cell cycle arrest and apoptosis at the early-stage of cancer development, indicating a tumor suppressive function. On the other hand, TGF-β could promote EMT as well as tumor malignant progression at the late-stage disease. Up to date, the contribution of the TGF-β pathway in SCLC development and progression remains elusive. **Methods:** Using the $Rb1^{L/L}$/$Trp53^{L/L}$ (RP) mouse model, we find that mouse SCLC cells with adherent growth pattern are composed of mesenchymal-like (Mes) and epithelial-like (Epi) subpopulations. Take advantage of in vitro functional assay and in vivo allograft assay, we find that the Mes cells harbor higher malignant transformation and metastatic capabilities than Epi cells. Through the analysis of microarray data, we find that the TGF-β signaling is enriched in Mes cells. And the inhibition of TGF-β signaling in Mes cells significantly abrogates its metastatic ability in allograft assay. Moreover, genetic deletion of the key components of the TGF-β signaling pathway, dramatically attenuated SCLC metastasis in the RP mouse model. **Results:** In this study, we find that mouse SCLC cells derived from RP autochthonous mouse model with adherent growth pattern are composed of Mes and Epi subpopulations. The Mes cells have increased ability to form colonies in soft agar and harbored stronger metastatic capability in vivo when compared to the Epi cells. Gene Set Enrichment Analysis (GSEA) reveals that the TGF-β signaling is enriched in the Mes cells. Inhibition of the TGF-β signaling through either ectopic expression of dominant negative Tgfbr2 (Tgfbr2-DN) or treatment with Tgfbr1 inhibitor SD-208 consistently greatly abrogates the tumor metastasis in allograft assays. Moreover, genetic deletion of Tgfbr2 or Smad4, key components of the TGF-β signaling pathway, dramatically attenuates SCLC metastasis in the RP autochthonous mouse model of SCLC. **Conclusion:** Our results suggest the critical role of TGF-β signaling in SCLC heterogeneity and metastasis. Importantly, inhibition of TGF-β signaling significantly abrogates SCLC metastasis, providing a potential therapeutic avenue for SCLC management in clinic.

Keywords: Small cell lung cancer, TGF-beta signaling, metastasis

P66.04 A Multimodal Biomarker Predicts Dissemination of Bronchial Carcinoid

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Introduction: Endobronchial treatment (EBT) for selected patients with bronchial carcinoids is gaining popularity. Currently, therapeutic decision making is mainly based on tumor morphology and patient characteristics. However, differentiation between prognostic favorable and unfavorable bronchial carcinoid tumors is essential for therapeutic decision making between EBT or surgery. Alternatives for subdivision of TC and AC into prognostic relevant categories are therefore desired. This study defined prognostic factors for patients with bronchial carcinoid tumors. **Methods:** Patients referred to Amsterdam University Medical Centers with available histology were included. Clinical and morphological characteristics relevant for classification such as tumor diameter, mitotic count (MAI) and prognostic immunohistochemical markers as Ki-67, P16, Rb, Orthopedia homebox (OTP) and CD44 were analyzed. **Results:** In a cohort of 171 patients, the vast majority were curatively treated with either EBT (n=61, 36%) or surgery (n=103, 60%). Seven (4%) patients presented with distant metastases at diagnosis. TC was diagnosed in 112 (65%) and AC in 59 (35%) patients. Nine (15%) patients treated with EBT had a intrabronchial recurrence of disease during follow up and none developed lymph node or distant metastasis. Of all surgically treated patients, 13 (13%) had level 1 or 2 lymph node metastasis. Additional 13 (13%) patients developed distant metastasis, 11 (85%) AC and 2 (15%) were TC. RB and p16 were not prognostic for lymph node nor distant metastasis. CD44 (AUC 0.8646, p=<0.0001) showed a better prognostic value than OTP (AUC 0.6845, p=0.008). Patients with tumor stage IA (tumor diameter ≤1cm) irrespective of tumor classification or immunohistochemical results and patients with typical carcinoid stage ≥ IB with Ki67<5% and positive CD44 did not develop distant metastasis. Patients with a Ki-67 of ≥2% had a higher chance of developing N1 or N2 lymph node metastasis (AUC 0.7125, p=0.0058). All patients with atypical carcinoid, Ki-67 of ≥5% (p=<0.000) and loss of CD44 (p=<0.0001) developed distant metastasis. Tumors stage ≥IB with either ≥2 mitoses, Ki-67>5% or loss of CD44 metastasized occasionally (11%). **Conclusion:** Patients with carcinoid stage IA or favorable histological tumor characteristics, irrespective of tumor diameter, did not metastasize and could be excluded from intensive follow up. On the other hand, patients with carcinoid with a diameter of >1 cm and either ≥2 mitoses, Ki-67 ≥5% or loss of CD44 are at risk of distant metastases and should kept in follow up. Hypothetically, these patients should be discouraged for EBT.

Keywords: Bronchial carcinoid, prognosis, immunohistochemical markers

P66.05 Correlation Between Expression of Immune Cell-Related Molecular Markers and Prognosis in Small Cell Lung Cancer (SCLC)

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Introduction: Current retrospective studies have found that the prognosis of patients with small cell lung cancer (SCLC) after surgical resection varies greatly. At present, the biological factors relevant to tumor immune microenvironment (TIME) that affect the prognosis of patients with SCLC remain to be explored. **Methods:** Content of 22 types of immune cells in TIME was estimated by CIBERSORT in a public dataset containing 77 postoperative SCLC patients. Correlation of each type of immune cells with overall survival (OS) was analyzed by univariate and multivariate Cox regression analysis. Vital cytokines and their receptors which correlated with gamma delta T cells (γΔT) and resting NK cells whose abundance significantly influence OS derived from public data analysis were detected at transcriptional level in tissue samples of 48 prognosis-based paired SCLC patients in our institute. Markers of activated NK cells, T cells, B cells, and immune effector molecules were also detected. Each marker was fitted into univariable Cox regression model. Molecular markers correlated with resting NK cells and γΔT and molecules whose coefficient reached statistical significance in univariate analysis were combined with clinicopathological factors for multivariate survival analysis. **Results:** Univariate Cox regression analysis for external dataset showed that high relative proportion of follicular helper T cells (Tfh) is protective for OS (HR 1.30e-05, 95% CI: 3.2e-09-0.52, P = 0.008), while high relative proportion of γ Δ T cells (HR 4e+03, 95% CI 6.5-2.5e+06, P=0.011) and resting NK cells (HR 1.2e+10, 95% CI 200-7.5e+17, P=0.011) were hazardous for OS. Significant distinct disease-free survival (DFS) and OS was observed between the two paired groups in our internal cohort (DFS: P=1.00e-12; OS: P=2.05e-09), but there was no significant difference in clinical characteristics such as age, gender, clinical stage, treatment methods between the two groups. However, it was found that the expression of IL17RB was significantly higher in the poor prognosis group (P=0.015), while the expression of interferon γ(IFNG) and perforin (PRF1) was significantly lower in the poor prognosis group (IFNG: P=0.045; PRF1: P=0.013). Univariable Cox regression analysis confirmed that high expression of IL17RB was hazardous for shorter DFS, while high expression of activating receptor of NK cells (NCR1, NKG7), markers of effector T cells (CD8A) and cytotoxic molecules (PRF1, GZMB, GZMH) and IFNG were favorable for DFS. Among these molecules, influence on OS was also significant for NKG7, PRF1 and GZMB. Multivariable Cox regression analysis combining clinicopathological and immunological factors identified high expression of IL6 mRNA was hazardous for both DFS and OS independent of clinicopathological factors. **Conclusion:** Abundance of NK cells and T cells in TIME significantly affected the postoperative DFS of SCLC patients. Content of NK cells in TIME also significantly influenced OS of resected SCLC patients. The prognosis of patients with high expression of IL6 and IL17RB mRNA was extremely dismal, which might be explained by impairment of NK cell activity and γΔT polarization.

Keywords: tumor immune microenvironment (TIME), NK cell, Small cell lung cancer (SCLC)

P66.06 GPNMB Associates With Inferior Prognosis in SCLC Patients Through Promoting Tumor Cell Metastasis

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Introduction: Glycoprotein non-metastatic melanoma protein B (GPNMB) is a type I transmembrane glycoprotein which is highly expressed in many tumors and plays a critical role in metastasis of malignant tumors. However, its cellular functions in small cell lung cancer (SCLC) remain unclear. The aim of this study was to investigate the role of GPNMB expression in SCLC cells and its prognostic value in patients with SCLC. **Methods:** Plasma concentration of GPNMB was performed by ELISA and the Kaplan–Meier method and Cox regression analyses was respectively used to evaluate the association with overall survival. Metastatic, proliferation and apoptosis ability of SCLC cells were evaluated using migration, matrigel invasion assays, cell proliferation assay and flow cytometry respectively. **Results:** 88 patients with SCLC were included into this study. Plasma GPNMB higher expression was correlated with extensive stage (P = 0.011), and metastasis (P = 0.032), especially liver metastasis (P = 0.007). Moreover, both univariate and multivariate analyses indicated GPNMB higher expression was an independent prognostic factor of inferior overall survival (OS) (P = 0.009). We also showed that the mRNA and protein expression of GPNMB in SCLC cell lines (H446, H196) was significantly higher than that in normal bronchial epithelial cell line (Beas-2b). Inhibit GPNMB expression by siRNA significantly suppressed SCLC metastatic and proliferation ability whereas increased apoptosis ability.

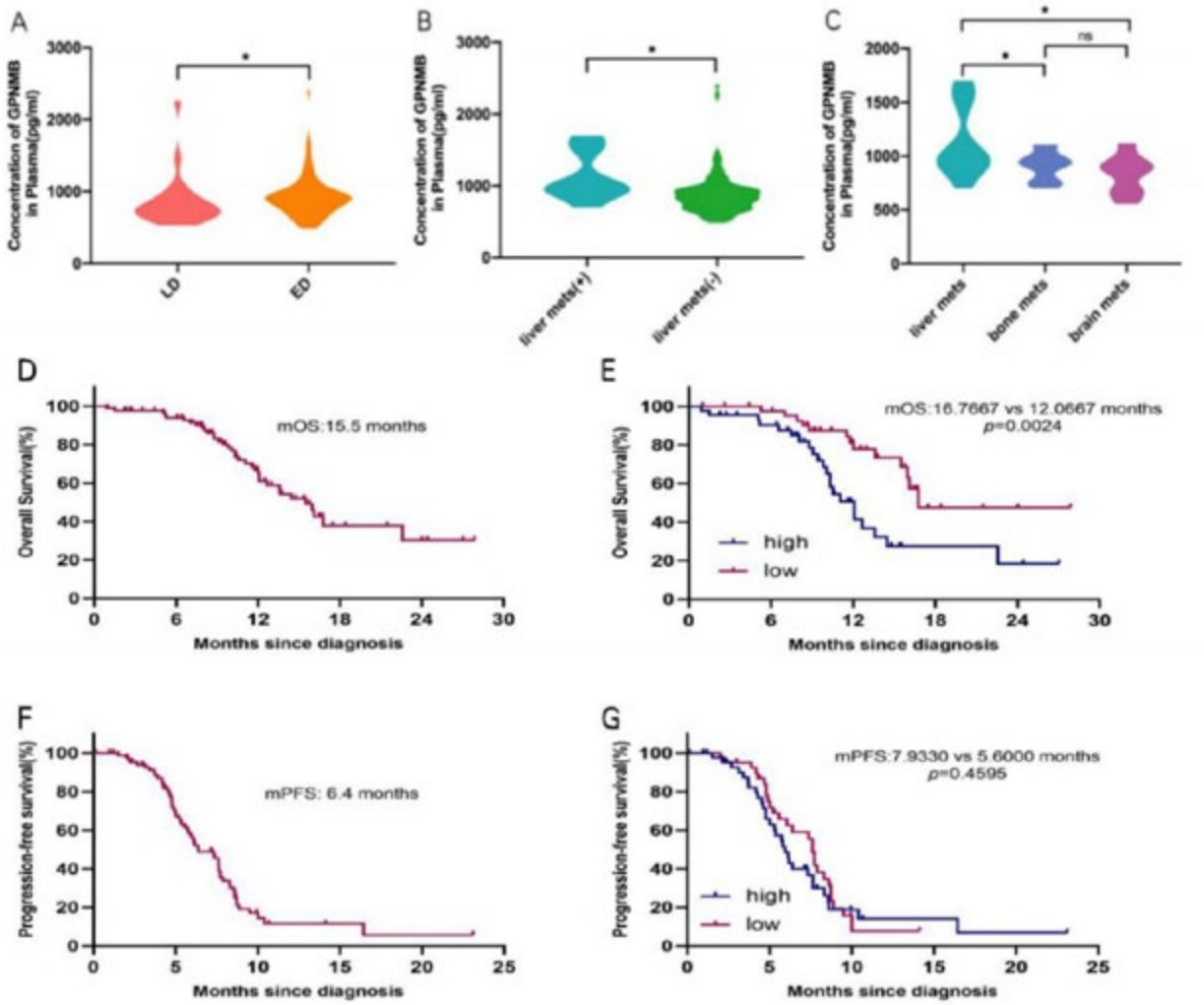

Figure1. GPNMB concentrations correlated with extensive stage, liver metastasis and higher GPNMB concentration correlates with dismal overall survival in SCLC patients.

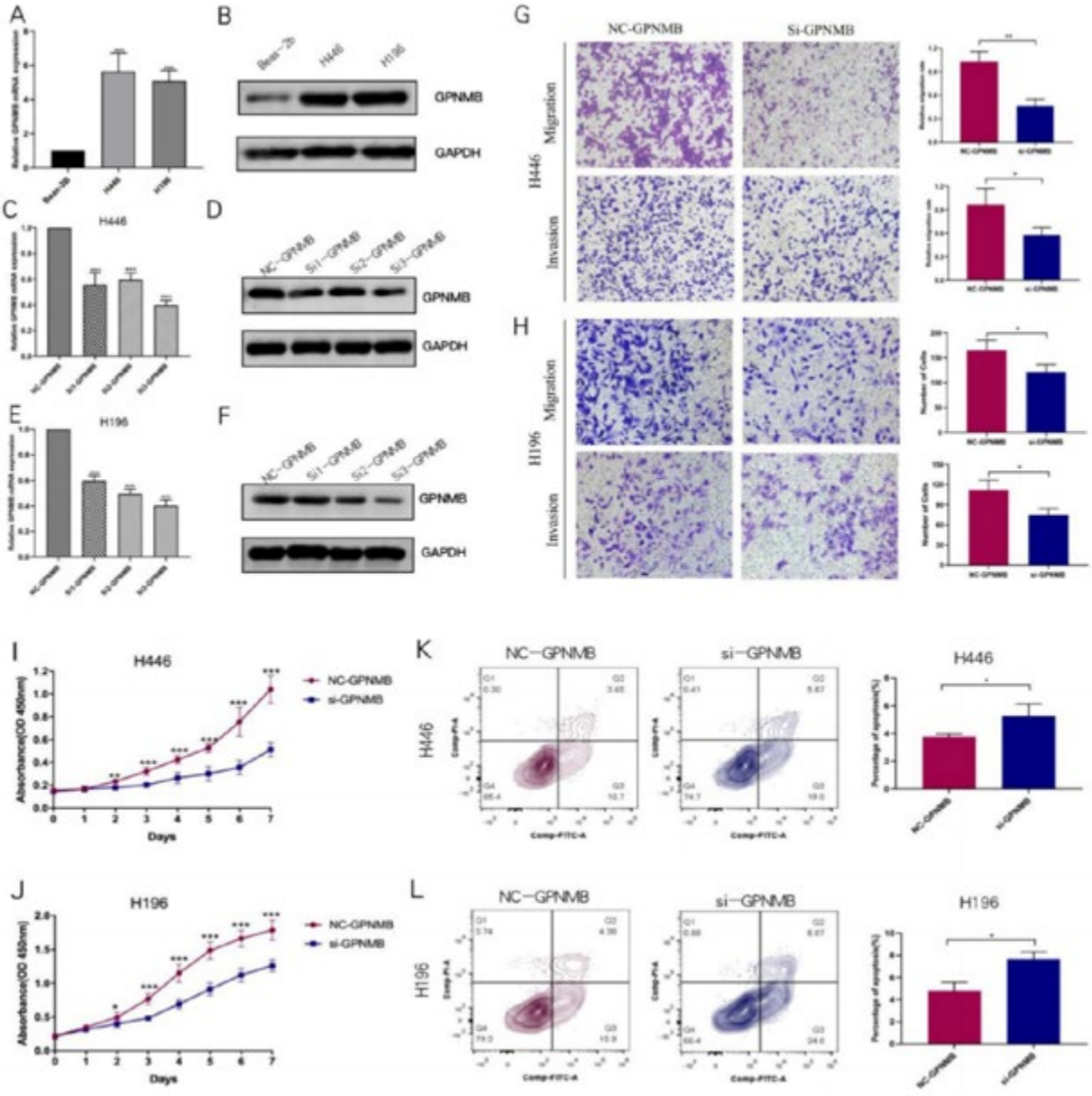

Figure2. GPNMB up-regulated in SCLC cells and promotes SCLC cells migration, invasion, proliferation, and inhibits apoptosis.

Conclusion: Our results suggest that expression of GPNMB is associated with metastasis and poor prognosis, and might be served as a novel potential therapeutic target in SCLC.

Keywords: GPNMB, prognosis, metastasis

P66.07 ASCL1 and DLL3 Expression and Their Clinicopathological Implications in Surgically Resected Pure Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is one of the most aggressive malignancies characterized by neuroendocrine (NE) differentiation. Our previous data revealed the achaete-scute homolog 1 (ASCL1) gene was a transcription factor in NE differentiation and highly expressed in SCLC. The Delta-like protein 3 (DLL3), as a direct downstream target of ASCL1, is involved in NE differentiation and carcinogenesis of SCLC. A DLL3-targeted antibody-drug conjugate, rovalpituzumab tesirine (Rova-T) has recently been developed for treatment of SCLC. This study was to investigate the relationship between ASCL1 and DLL3 protein expression and their clinicopathological implications in surgically resected pure SCLC. **Methods:** 247 surgically resected pure SCLC samples with limited clinical stage and follow-up data were retrieved in this retrospective study. ASCL1 and DLL3 protein expression was detected by immunohistochemistry staining in SCLC tissue microarrays. The correlation between ASCL1 and DLL3 protein expression as well as their clinicopathological features were analyzed by chi-square test. Disease-free survival (DFS) and overall survival (OS) in SCLC patients with ASCL1/DLL3 low and high expressions were compared by Kaplan-Meier method and Log-rank test. **Results:** Among the 247 surgically resected pure SCLC patients, 175 (70.9%) were male and 202 (81.8%) were less than 65 years. According to the AJCC Cancer Staging Manual (seventh edition), 78 (31.6%) were stage I, 68 (27.5%) were stage II, and 101 (40.9%) were stage III. ASCL1 expression was localized in the nucleus of SCLC tumor cells, and 105 (42.5%) patients showed high expression. ASCL1 high expression was associated with clinical stage (p=0.019) and nerve invasion (p=0.030). DLL3 expression was localized in the cytoplasm and membrane of tumor cells, and DLL3 high expression was observed in 188 (72.8%) patients. DLL3 high expression was correlated with vascular invasion (p=0.045). ASCL1 expression was positively associated with DLL3 expression (p=0.030). In addition, DLL3 expression has a strong association with expression of classic NE markers, Synapsin (Syn) and Chromogranin A (CgA). Survival analysis revealed that patients with ASCL1 high expression have a worse OS (p=0.047), whereas further multivariate cox regression analysis showed neither ASCL1 nor DLL3 expression was independent prognostic factors. **Conclusion:** ASCL1 and DLL3 were highly expressed in pure SCLC tumor cells, and their expression level was positively correlated. The patients with ASCL1 and DLL3 high expression may represent a distinct subgroup of SCLC benefit from targeted therapy. Therefore, ASCL1 and DLL3 could be potential biomarkers served for selection of related patients.

Keywords: DLL3, SCLC (small cell lung cancer), ASCL1

P66.08 Differential Expression of INSM1 Between Pure SCLC and LCNEC After Surgical Resection and Its Clinicopathological Significance

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Introduction: According to WHO diagnostic criteria, both Small cell lung cancer (SCLC) and Large cell neuroendocrine (LCNEC) are categorized into high grade neuroendocrine carcinoma, based on morphological features and immunostaining of neuroendocrine markers including CD56, chromogranin A (CgA) and synaptophysin (Syn). However, the above markers have limited satisfactory significance of specificity and sensitivity. Insulinoma-associated protein 1 (INSM1) is highly expressed in SCLC cells as a zinc finger protein, and numerous studies have shown that INSM1 positive staining has a strong correlation with NE differentiation in SCLC and an alternative diagnostic biomarker for SCLC, but few studies are involved in LCNEC and its significance remains unclear in LCNEC. The aim of this study was to investigate the potential of INSM1 as a neuroendocrine marker by comparing the expression of INSM1 in SCLC and LCNEC and its clinicopathological significance. **Methods:** 347 surgically resected lung cancer including 290 pure SCLC and 57 pure LCNEC samples were retrieved in this retrospective study. INSM1 expression was detected by immunohistochemistry staining in SCLC and LCNEC tissue microarrays. The different expression of INSM1 between SCLC and LCNEC as well as the correlation with clinicopathological features including gender, age, smoking history, tumor location, AJCC 7th stage, reginal lymph node metastasis, pleural invasion and tumor thrombosis were analyzed by chi-square test. **Results:** Of the included patients, male/female ratio was 2.33 (203/87) in SCLC and 10.4 (52/5) in LCNEC, the smoker rate was 64.5% (187/290) in SCLC and 43.9% (25/57) in NSCLC. According to the AJCC Cancer Staging Manual (7th edition), the SCLC patients were 29.0% (84/290) in stage I, 27.2% (79/290) in stage II, 40.7% (118/290) in stage III, and 3.1% (9/290) in stage IV, while the NSCLC patients were 49.1% (28/57) in stage I, 26.3% (15/57) in stage II, and 24.6% (14/57) in stage III, respectively. INSM1 was localized in the nucleus of lung cancer cells, a significant higher positive rate was detected in SCLC than that in LCNEC (271/290,93.4% in SCLC; 32/57,56.1% in LCNEC; $p<0.05$). INSM1 protein expression significantly correlated with smoking history ($p=0.023$), pleural invasion ($p=0.010$), and a positive trend of regional lymph node metastasis ($p=0.052$) in SCLC, but did not correlate with any of the clinicopathological features in LCNEC ($p>0.05$). INSM1 protein was found no prognostic significance neither in SCLC nor in LCNEC ($p>0.05$). **Conclusion:** INSM1 protein is highly expressed in SCLC and positively correlated with pleural invasion and smoking history. In contrast, INSM1 expression in LCNEC is significant lower and does not correlated with such clinicopathological features. Further research needs to be done on exploring the potential different underlying mechanisms and diagnostic significance of INSM1 in SCLC and LCNEC.

Keywords: SCLC, INSM1, IHC

P66.09 Differential Orthopedia Homeobox (OTP) Expression in Pulmonary Carcinoids is Regulated Through Methylation

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Introduction: Pulmonary carcinoids are well-differentiated neuroendocrine neoplasms with a general indolent behaviour. However, some patients with carcinoid develop recurrence of disease after curative surgery. Previously, loss of Orthopedia Homeobox (OTP) RNA and protein expression has been independently associated with a poor prognosis independent of histological subtype. The regulatory mechanism underlying OTP expression, however, remains to be elucidated. Here, we investigated OTP expression in 37 different cancer types and unmasked the mechanism regulating OTP expression in lung neuroendocrine neoplasms (LNENs). **Methods:** We have analysed publicly available multi-omics data (whole-exome sequencing, whole-genome sequencing, RNAseq, Epic 850K methylation array) of 88 carcinoid-, 69 large cell neuroendocrine carcinoma- (LCNEC) and 51 small cell lung cancer (SCLC) patients as well as TCGA (The Cancer Genome Atlas) data of 33 different cancer types. 850K array methylation analysis was cross-validated using targeted pyrosequencing on 35 carcinoids. **Results:** OTP proved to be expressed in lung carcinoids at higher levels in typical carcinoids (median 126.4, IQR 72.9 – 193.4 FPKM) than in atypical carcinoids (median 0.16, IQR 0.06- 57.7 FPKM). Both typical and atypical carcinoid groups included samples with high and low OTP expression. Other cancer types, including LCNEC (median 0.09, IQR 0.02 – 0.17 FPKM) and SCLC (median 0.09, IQR 0.02 – 0.17 FPKM), showed very low to no OTP expression. Bimodality testing showed a clear bimodal distribution of OTP in carcinoids suggesting the existence of two distinct groups (OTP^{high} versus OTP^{low} expression cluster) with different molecular and clinical features. No gene-inactivating somatic mutations, chimeric transcripts, or genomic rearrangements explaining differential expression were found in the OTP gene. 850K methylation array data analysis showed that 12/34 OTP Infinium probes harbour a significantly different methylation level between OTP^{high} and OTP^{low} carcinoids (fdr < 0.05 & delta > 0.2) possibly explaining the observed expression differences. OTP^{low} carcinoids have a high methylation level (based on beta-values) as compared to OTP^{high} carcinoids containing an overall low methylation level. Data were cross-validated using pyrosequencing showing no proportional difference. OTP^{high} carcinoids showed a significantly improved overall survival compared to OTP^{low} carcinoids (p=0.0052). Furthermore, gene set enrichment analysis for somatically mutated genes associated with hallmarks of cancer showed enrichment of gene mutations in three hallmarks in the OTP^{low} carcinoid cluster namely sustaining proliferative signaling, evading growth suppressor, and genome instability and mutation. No statistically significant enrichment was observed in the OTP^{high} cluster. **Conclusion:** Our data show that, in pulmonary carcinoids, two distinct patient cohorts can be identified based on OTP expression of which the OTP^{low} cluster is associated with poor prognosis. Differential OTP expression within pulmonary carcinoids was associated with DNA methylation suggesting that methylation is the underlying regulatory mechanism. These findings arouse curiosity about whether or not epigenetic therapies might be useful for pulmonary carcinoid patients in the future.

Keywords: pulmonary carcinoid, methylation, Orthopedia Homeobox (OTP)

P67.01 Cough in Patients After Thoracic Surgery: A Pilot Study

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Introduction: Cough is a challenging issue in patients after thoracic surgery, but little is known for the exact risk and the underline risk factors. The purpose of this study is to 1) prospectively assess the severity of cough and risk factors of Cough at baseline and 2) development or changes of cough in patients after thoracic surgery. **Methods:** This is part of prospective study of treatment toxicity, quality of life and biomarker study as part of a funded peacock project. Patients aged 18-year old and above requiring thoracotomy were eligible. The primary endpoint was cough which was evaluated by the treating physicians according to NIH/NCI CTCAE v4.0, prior to, immediately after surgery, at the time of discharge and at one-month follow-up. Patient and tumor factors as well as treatment factors including type of surgical procedures were collected prospectively. The variables of our interest included age, gender, body mass index, weight/weight loss, KPS, comorbidity score, tumor type, T stage, histology, N stage and type of surgery. Data are presented as mean (95% confidence interval) unless otherwise specified. Statistical significances were tested using pair-tests for changes and logistics regression for risk factors. P less than 0.05 were considered to be significant. **Results:** Between September 2019 and January 2020, a total of 40 patients scheduled to thoracic surgery enrolled this study. Before surgery, 11/40 (27.5%), 2/40 (5%) and 0/40 (0%) patients had grade 1, 2, and 3, respectively. At one month after surgery, 15/40 (37.5%), 3/40 (7.5%), and 2/40 (5%) had grade 1, 2, and 3, respectively. 14/40 (35%) and 4/40 (10%) had cough severity increased and decreased at the time of discharge. 14/40 (35%) and 5/40 (12.5%) had cough severity increased and decreased at one month after surgery. Type of surgery (p=0.084) and lung surgery (versus mediastinum or others) had a trend of association with postoperative cough at one month, while gender, age, BMI, smoking history, hypertension, diabetes, coronary heart disease, gout, previous history of lung cancer, previous history of other malignancy, COPD, liver disease and TNM stage were not. Twenty-two out of 40 (55%) patients versus 16/26 (62%) lung cancer patients had cough upgraded (p>0.05). Nodal stage in lung cancer (p=0.09) and the number of nodal dissected (p=0.045) was a significant risk factor for post-operative cough at 1 month follow-up. Worsening in cough was significantly/not significantly associated with the toxicity score during and end of treatment , and the total score of quality of life at the end of treatment. **Conclusion:** Majority of patients developed cough or had cough worsened after thoracic surgery in this pilot study. Nodal disease of lung cancer and type of surgery seemed to be risk factors. In addition to validate these findings, future study shall investigate the effect of cough on long-term complication and quality of life and define approaches of management to improve quality of life.

Keywords: Cough after Thoracic Surgery, toxicity score, quality of life

P67.02 Long-term Follow-up Data of Respiratory Function in Patients with Lung Cancer Undergoing Surgery

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Introduction: We often calculate the predicted postoperative respiratory function to evaluate respiratory function. However, there are a few reports of long-term follow-up data of postoperative respiratory function. We investigated the predicted postoperative respiratory function and long-term follow-up data of respiratory function in patients with lung cancer undergoing surgery. **Methods:** Sixty-five patients who underwent lobectomy for lung cancer between January 2017 and December 2018 at Sendai Medical Center were included. Respiratory function tests were performed at before surgery and 4 and 16 months after surgery. We analyzed the respiratory function in these 65 cases. **Results:** There were 31 men and 34 women, with ages ranging from 39 to 83years and a median age of 67years. The median Brinkman index was 100. The median preoperative vital capacity (VC) was 3.19 L and median preoperative forced expiratory volume in 1 second (FEV1.0) was 2.27 L. There were decreases in the VC of 470 mL in the short-term follow-up and of 310 mL in the long-term follow-up. The VC in the long-term follow-up improved compared with that in the short-term follow-up. Furthermore, there were decreases in the FEV1.0 of 330 mL in the short-term follow-up and of 270 mL in the long-term follow-up. The FEV1.0 in the long-term follow-up also improved compared with that in the short-term follow-up. On the other hand, the decrease in the VC was calculated as 670 mL and that in the FEV1.0 was calculated as 500 mL for the predicted postoperative respiratory function, and the postoperative respiratory function was better than predicted. **Conclusion:** Our study suggested that postoperative respiratory function improves over 1 year. Practical postoperative respiratory function may be better than predicted respiratory function because of the implementation of minimally invasive surgeries in recent years.

Keywords: lung cancer, Respiratory Function

P68.01 Tumor-Derived Exosomal miRNA-190b-5p Induces Microglia M2 Polarization to Promote Brain Metastasis of Lung Cancer

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Introduction: The severe complications caused by lung cancer metastasis to distant organs are the main cause of death in lung cancer patients, whereas the brain is the most acknowledged site of distant metastasis. Brain metastasis of lung cancer greatly affects the quality of life of patients and shortens the survival time of patients. At present, the specific mechanism of brain metastasis of lung cancer is still largely unknown, and the prevention and treatments are strenuous. More and more studies have confirmed that tumor-derived exosomes play an important role in the formation of pre-metastatic niche. However, the relationship between lung cancer-derived exosomal miRNAs and brain pre-metastatic niche formation and the molecular mechanism of brain metastasis are still indefinite and need to be further explored. **Methods:** The serum exosomes were extracted and purified by ultracentrifugation in four groups of NSCLC patients with or without brain metastasis. The exosomes were identified by transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and Western blot. Exo-miRNA-190b-5p was screened by high-throughput sequencing technology to predict and verify the downstream target genes and signaling pathways. Furthermore, the molecular mechanism of Exo-miRNA-190b-5p regulating M2 polarization of OGD/2h microglia (HMC3) was explored by RNA pull-down assay and dual-luciferase reporter assay. The MCAO model combined with the lung cancer in situ model was constructed for verifying the self-release of lung cancer-derived exosomes in vivo. **Results:** In this study, we confirmed that Exo-miRNA-190b-5p was abnormal overexpression in serum of NSCLC patients with brain metastasis, which was closely related to poor prognosis in non-small cell patients. Furthermore, we elucidated that activated microglia cells capture lung cancer-derived exosomes in the pathological state of cerebral ischemia. Exo-miRNA-190b-5p induces M2 polarization of microglia by downregulating ROCK1 expression and activating PI3K/AKT signaling pathway, which secretes a variety of cytokines IL-10, participates in NF-κB signaling pathway, and forms inflammatory pre-metastatic niche. Ultimately it promotes the formation of brain metastasis of lung cancer. **Conclusion:** Our results suggest that Exo-miRNA-190b-5p plays a key role in brain metastasis of lung cancer by regulating microglia function and forming inflammatory pre-metastatic niche. This study provides a new research strategy and theoretical basis for the occurrence and development mechanism of brain metastasis of lung cancer, which is of great significance to guide clinical early intervention, block the formation of brain metastasis and improve the therapeutic effect of lung cancer.

Keywords: brain metastasis of lung cancer, pre-metastatic niche, exosomes

P68.02 Losartan Enhances Lung Squamous Cell Carcinoma's Sensitivity to Cisplatin Treatment By Promoting Mesenchymal to Epithelial Transformation

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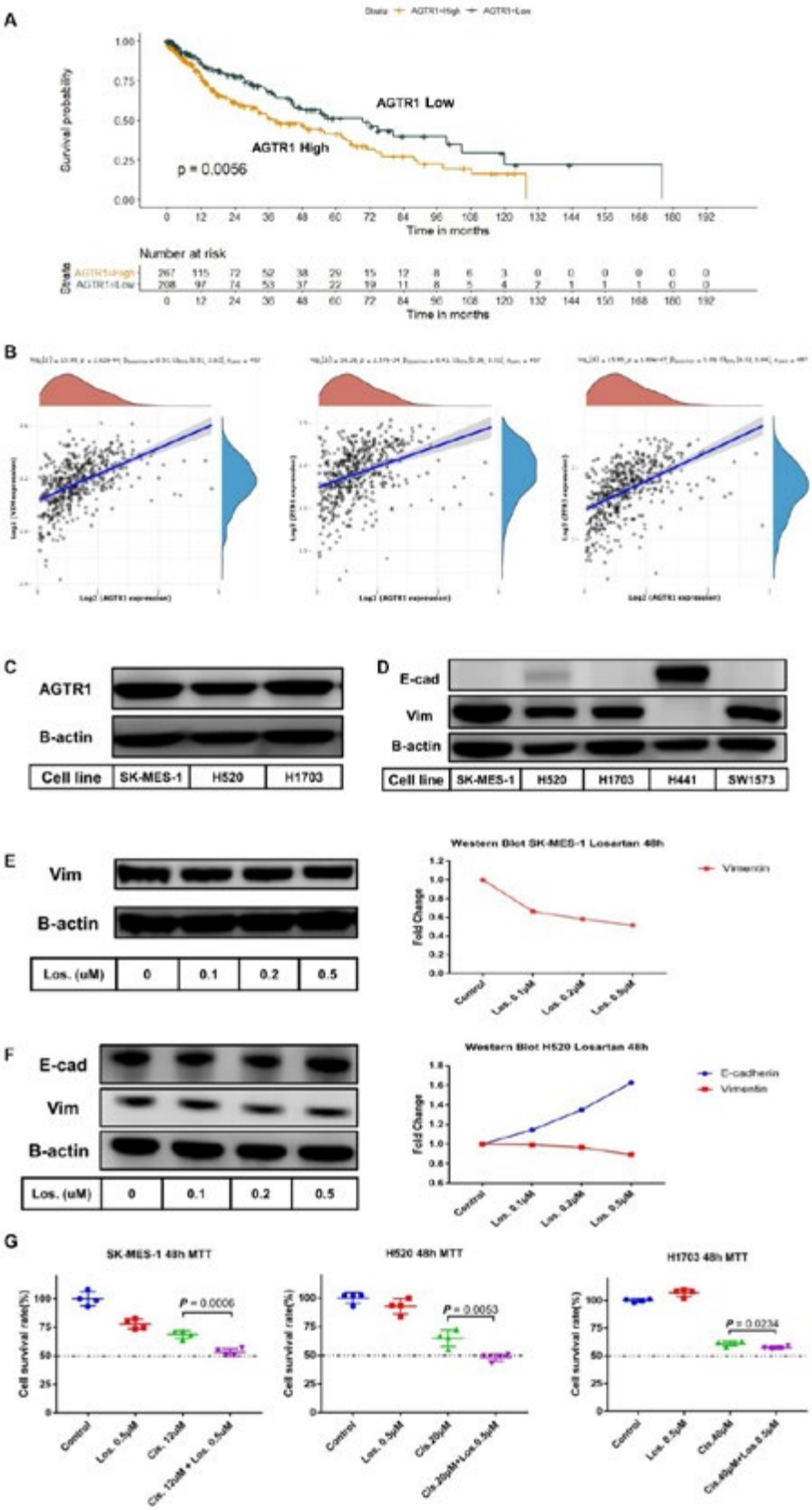
Introduction: Angiotensin II type 1 receptor (AT1R) overexpression has been associated with poor prognosis in patients with some solid organ cancers. The angiotensin II/AT1R axis is closely related to tumor proliferation, angiogenesis, invasion and metastasis. Platinum resistant non-small cell lung cancer shows significantly higher type I angiotensin II receptor (AGTR1) mRNA expression than their corresponding parent cells. Addition of angiotensin II receptor blocker (ARB) to platinum-based first-line chemotherapy may contribute to prolonged survival in patients with locally advanced squamous cell lung cancer. **Methods:** The TCGA database was analyzed for expression of AGTR1 in tumor tissue from resected lung squamous cell carcinoma (N=497) and correlated with overall survival. Multiple human lung squamous cancer cell lines (SK-MES-1, H520, H1703) with primary mesenchymal phenotype [Fig. 1D] were evaluated invitro for AGTR1 expression [Fig. 1C] and treated with losartan or combination losartan and cisplatin to assess cell survival and EMT expression by western blot. **Results:**


A
AGTR1 Low
AGTR1 High
p = 0.0056
Survival probability
Time in months
Number at risk
B
C
AGTR1
B-actin
Cell line
SK-MES-1
H520
H1703
D
E-cad
Vim
B-actin
Cell line
SK-MES-1
H520
H1703
H441
SW1573
E
Vim
B-actin
Los. (uM)
0
0.1
0.2
0.5
Western Blot SK-MES-1 Losartan 48h
Vimentin
Fold Change
F
E-cad
Vim
B-actin
Los. (uM)
0
0.1
0.2
0.5
Western Blot H520 Losartan 48h
E-cadherin
Vimentin
Fold Change
G
SK-MES-1 48h MTT
H520 48h MTT
H1703 48h MTT
Cell survival rate(%)
P = 0.0006
P = 0.0053
P = 0.0234
Control
Los. 0.5μM
Cis. 12uM
Cis. 12uM + Los. 0.5uM
Cis.20μM
Cis.20μM+Los.0.5μM
Cis.40μM
Cis.40μM+Los.0.5μM

Patients with stage I, II, and III lung squamous cell carcinoma (LUSC) demonstrated improved overall survival with low expression of AGTR1(P =0.0056) [Fig 1A]. When stratified by stage, stage II exhibited low AGTR1 expression and was associated with a better prognosis (P =0.0032). Expression of AGTR1 positively correlated with EMT expression of Vimentin (r=0.57, P <0.0001), ZEB1 (r=0.43, P <0.0001) and ZEB2 (r=0.59, P <0.0001) [Fig 1B]. SK-MES-1, H520 and H1703 express abundant AGTR1. Vimentin expression of SK-MES-1 decreased with losartan treatment [Fig. E] in a dose dependent fashion (0, 0.1, 0.2, 0.5μM). E-cad expression of H520 increased and Vimentin expression decreased with increasing losartan treatment [Fig. F]. Compared to cisplatin treatment alone, combination of Losartan and cisplatin significantly improved the cytotoxic effect in SK-MES-1(P=0.0006), H520 (P =0.0053) and H1703(P =0.0234) [Fig. G]. **Conclusion:** AGTR1 expression correlates with survival outcomes of lung squamous cell carcinoma in humans and is associated with a more mesenchymal phenotype in vivo and in vitro. Losartan treatment appears to promote a mesenchymal to epithelial transformation and enhances the anti-tumor effect of chemotherapy (cisplatin) compared to chemotherapy alone in lung squamous cancer cell.

Keywords: lung cancer, Chemotherapy, tumor biology

P68.03 An AI Workflow to Detect and Report Tumor Cell Proportion of H&E-Stained Tissue Samples

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Introduction: Before performing NGS-based genetic testing for lung cancer tissues, H&E-stained histopathology image reading by a specialized pathologist is usually required to ensure that sample quality can meet sequencing requirements, that is, the minimum threshold for the number of cells in the suspected tumor region. With the great progress of AI algorithms in processing digital images, it has become possible to automate the quality assessment of lung cancer histopathology slides using AI algorithms. **Methods:** We curated a dataset containing 357 H&E-stained histopathology images of lung cancer, in which the tumor regions were labeled by a professional pathologist. The dataset was randomly divided into a training set containing 307 images and a test set of 50 images. The deep learning algorithm was trained on the training set and its performance was evaluated on the test set. The predicted regions output by the algorithm were further quantified and compared with the pathologist's quality assessment report of the slides. **Results:** The tumor region segmentation performed by the deep learning algorithm achieved an iou of 0.7 on the test set. The correlation between the quantified results of the algorithm's predicted tumor region and the pathologist's slide quality report reached 0.52. **Conclusion:** The deep learning algorithm has good performance for the lung cancer tumor region segmentation after training on a certain amount of data. The strong correlation between the segmented regions output by the algorithm and the pathologist's slide quality report indicates that automated lung cancer tissue quality assessment using AI algorithms has great potential in the future. The model still has much room for improvement due to the morphological diversity of lung cancer tissue sections and the relatively low quality of the dataset.

Keywords: histopathology image, AI, tumor cell proportion

P68.04 Molecular Mechanism of MK2 Promoting Lung Adenocarcinoma Progression by Phosphorylating Transcription Regulator CRABP2

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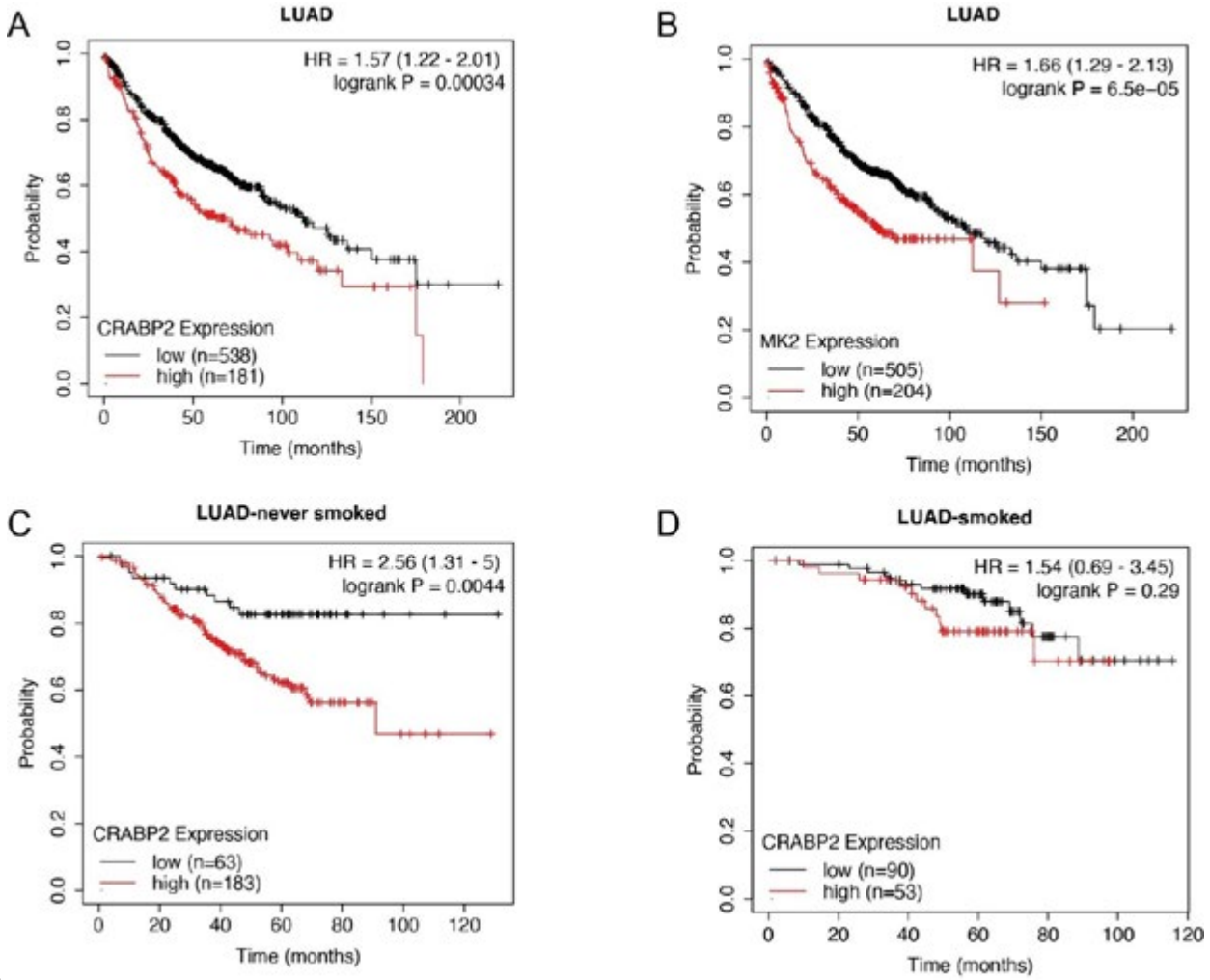
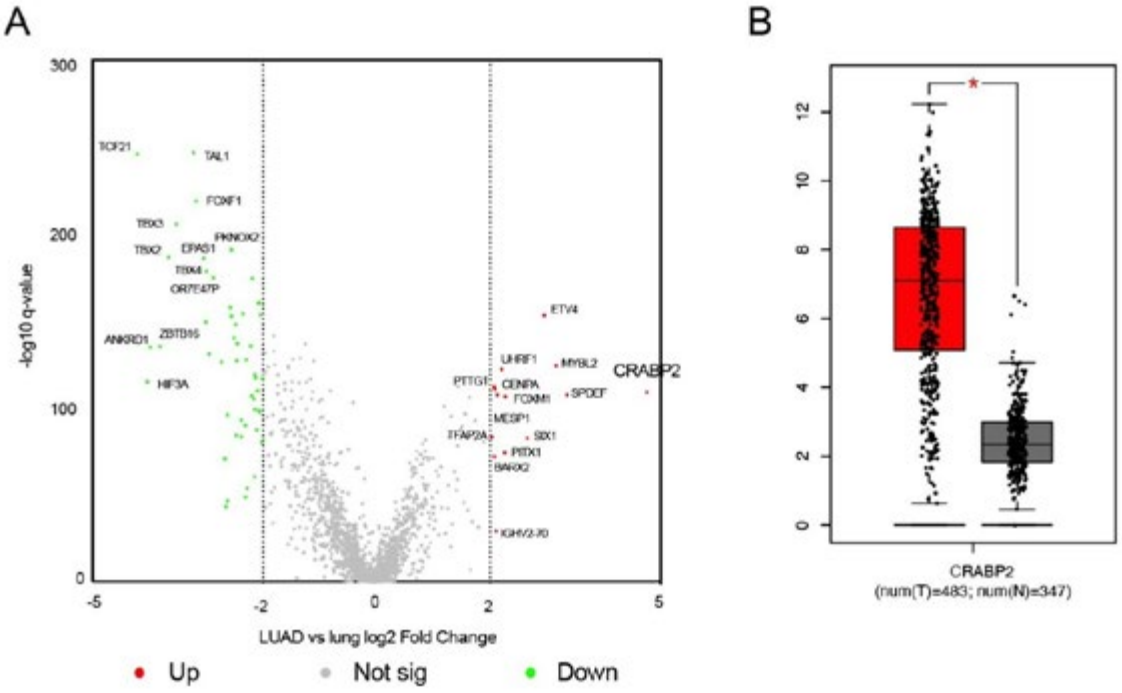
Introduction: The morbidity and mortality of lung cancer rank the first among malignant tumors in China. EGFR-TKIs has achieved good efficacy in advanced lung adenocarcinoma with EGFR-positive, however, drug resistance and rapid progress of some patients are still inevitable. Therefore, it is of great significance to find new therapeutic targets. Abnormally activated transcriptional regulators are involved in many biological processes of the development of malignant tumors, further exploration of their functional mechanisms is expected to provide a new direction for targeted tumor therapy. **Methods:** TRRUST and CHIPBase databases of transcriptional regulatory factor and TCGA databases were integrated to screen the transcriptional regulatory factors with significantly different expression in lung adenocarcinoma. The prediction of interacting molecules was performed on the Linkedomics, and preliminary verification was performed using WB. The clinicopathological data of lung adenocarcinoma patients with survival data from GEO and TCGA databases were downloaded to analyze the effect of CRABP2 and MK2 expression on survival prognosis. **Results:** Transcription and protein expression of CRABP2 were significantly up-regulated in lung adenocarcinoma (Figure 1). Bioinformatics analysis showed that MK2 interacted with CRABP2, and CRABP2 protein decreased significantly after knockdown of MK2 protein expression. The overall survival of lung adenocarcinoma patients with high CRABP2 and MK2 expressions were worse than that of the low expression group (P = 3.4e-04 and 6.5e-05, respectively)


A
LUAD
HR = 1.57 (1.22 - 2.01)
logrank P = 0.00034
Probability
CRABP2 Expression
low (n=538)
high (n=181)
Time (months)
B
LUAD
HR = 1.66 (1.29 - 2.13)
logrank P = 6.5e−05
Probability
MK2 Expression
low (n=505)
high (n=204)
Time (months)
C
LUAD-never smoked
HR = 2.56 (1.31 - 5)
logrank P = 0.0044
Probability
CRABP2 Expression
low (n=63)
high (n=183)
Time (months)
D
LUAD-smoked
HR = 1.54 (0.69 - 3.45)
logrank P = 0.29
Probability
CRABP2 Expression
low (n=90)
high (n=53)
Time (months)

(Figure 2).


A
-log10 q-value
CRABP2
LUAD vs lung log2 Fold Change
Up
Not sig
Down
B
CRABP2
(num(T)=483; num(N)=347)

Conclusion: MK2 may phosphorylate CRABP2 to mediate the progression of lung adenocarcinoma, and the MK2-CRABP2 signaling pathway is expected to become a biomarker or a new target for therapy of lung adenocarcinoma. However, further molecular experiments are needed for further exploration and verification.

Keywords: Transcription regulation, CRABP2, Lung adenocarcinoma

P68.05 Human Lung Carcinoma Primary Cultures From Malignant Pleural Effusions as a Tool for Drug Screening and Personalized Therapy

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Introduction: In recent years, new therapies have increased the number of treatment options available to the oncologist. However, the type and duration of response is still unpredictable in a significant number of patients and drug testing of patient-derived tumor cells can have clinical utility in this setting. A significant percentage of lung cancer (LC) patients show pleural effusion and viable malignant cells can be found in this fluid. Here, we present the results of the implementation of routine primary culture and drug testing from pleural effusions. **Methods:** Pleural effusions (PE) from 8 patients (p.) were collected, 7 adenocarcinomas and one small cell lung cancer. Total cells were isolated by centrifugation and cultured in complete RPMI medium. DNA and RNA were purified manually from cell pellets and genotyped by next generation sequencing (NGS), qPCR and nCounter. The fusions and amplifications were confirmed by FISH. Cell viability was determined by MTT assay, the antitumor effects of several drugs in primary tumor cells were tested, including ALK and MET tyrosine kinase inhibitors, PARP inhibitors and classical chemotherapeutic agents such as cis-platinum or pemetrexed. **Results:** Primary cultures were attempted from all lung cancer patients in our hospital presenting pleural effusion during a period of 6 months (n=8). In 5/8 cases (62.5%); cells grew ≥5 passages and were genotyped. Two primary cultures were pan-negative by NGS and nCounter, revealing that they were either non-tumor cells or a minor sub-clone within the tumor. In contrast, 3 primary cultures showed identical genetic alterations as the previous tumor biopsy, with allelic fractions ≥80%; namely a mutation p.M246I in TP53 together with a CD74-ROS1 fusion; a KRAS p.G12A mutation and a TP53 p.V73fs*50 mutation concomitant with a high-copy MYC amplification. The primary culture harboring the CD74-ROS1 fusion, corresponding to a patient in progression to crizotinib, was used for MTT assays in presence of crizotinib, lorlatinib, repotrectinib, olaparib, cisplatin and cabozantinib. Results indicated that the cultured tumor cells were resistant to crizotinib and olaparib, moderately sensitive to lorlatinib and cabozantinib and sensitive to cisplatin and repotrectinib. These results were concordant with the clinical history of the patient, with showed progressive disease to crizotinib, stable disease to lorlatinib and partial response to cisplatin. **Conclusion:** Primary culture of pleural effusions can be implemented in the clinical setting with a high success rate compared to other sources of material, such as fresh biopsies.

Keywords: primary culture, drug screening, pleural effusions

P68.06 Development and Validation of an NGS-Based MSI Detection Method

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Introduction: Microsatellite instability (MSI) is an important biomarker predictive of response to immune checkpoint blockade (ICB) across multiple solid cancers. Although next generation sequencing (NGS) based MSI detection method has been recommended by clinical practice guidelines, its testing results still need be validated using the gold standard MSI-PCR method. **Methods:** We designed a targeted NGS panel which incorporated 153 putative microsatellite loci consisting of short-tandem repeats of length 7 or more. MSI-H was defined as instability in 2 or more loci markers. We collected 5 MSI-H colorectal cancer patients and 34 patients with other types of cancers to validate our NGS-based MSI detection results. **Results:** All five colorectal cancer samples and one non-small cell lung cancer sample were detected as MSI-H (15.4%, 6/39) by the NGS-based method, while the remaining samples were defined as microsatellite stable (MSS) (84.6%, 33/39), which showed 100% concordance with the MSI-PCR results. Although the sample size is limited, NGS-based method showed quite high sensitivity and accuracy compared to MSI-PCR results. The selected 153 loci site may be used as predictive markers indicating instability for multiple cancer types. **Conclusion:** MSI detection using a custom NGS-panel is highly concordant with standard MSI-PCR method, enabling highly accurate detection of MSI status together with comprehensive genomic profiling, which will expand access to immunotherapy for patients with advanced cancers.

Keywords: MSI, NGS, immunotherapy

P68.07 Long Non-Coding RNA linc00665 Inhibits CDKN1C Expression by Binding to EZH2 and Affects Cisplatin Sensitivity of NSCLC

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Introduction: Long non-coding RNAs (lncRNAs) can play significant regulatory roles in cells that affect the development and acquired drug resistance of l non-small cell lung cancer (NSCLC). The purpose of this study was to investigate the role of linc00665 in the occurrence and development of NSCLC and its sensitivity to cisplatin. **Methods:** The expression level of LINC00665 was detected by qRT-PCR, and the effect of linc00665 on the occurrence and development of NSCLC and the sensitivity to cisplatin were detected by CCK-8, EDU, Transwell and other functional experiments, flow cytometry and in vitro animal experiments. Finally, the regulatory mechanisms of LINC00665, EZH2 and CDKN1c were explored by transcriptome sequencing, RIP and ChIP experiments. **Results:** LncRNA linc00665 is significantly upregulated in non-small cell lung cancer (NSCLC) tissues compared with adjacent normal tissues. Linc00665 affects the sensitivity of NSCLC cells to the chemotherapy drug cisplatin (DDP), making it a potential target for the treatment of NSCLC. Functional experiments showed that linc00665 enhanced the proliferation and migration of NSCLC cells in vivo and in vitro, and knocking down linc00665 could enhance the drug sensitivity of NSCLC cells to DDP. Further work revealed that linc00665 could recruit enhancer of zeste homolog 2 (EZH2) to the promoter region of cyclin dependent kinase inhibitor 1C (CDKN1C) to inhibit its transcription and thus carry out its tumorigenic role. **Conclusion:** Our study elucidated the carcinogenic role of the linc00665-EZH2-CDKN1C axis in NSCLC tumors and its ability to influence the sensitivity of these tumors to DDP.

Keywords: cisplatin sensitivity, non-small-cell lung cancer, linc00665

P68.08 ERK3/MAPK6 Does Not Contribute to Cell Proliferation in NSCLC

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Introduction: Lung cancer is the main cause of cancer-related death worldwide and non-small-cell lung cancer (NSCLC) represent 84% of the cases. The oncogene KRAS and the subsequent activation of the MAPK pathway is a main contributor to lung cancer progression. ERK3, or MAPK6, is an atypical MAPK with a poorly understood signaling pathway but highly expressed in lung cancer. Our aim is to study the expression of ERK3 in NSCLC and to understand if and how it may contribute to lung cancer progression. **Methods:** Calu-6 and Calu1 were plated for wound healing assay (WHA, n=3) or proliferation assay (PA, n=2). Calu-6 was also plated for Epidermal Growth Factor (EGF) Stimulation Assay (EGF-SA, n=3). siRNA against ERK3 (siERK3) or the control (siNEG) were transfected using SAINTTM-siRNA reagent, 48 hours(h) before each assay (WHA, PA). EGF at 100ng/ml was used in either complete media (WHA, PA) or serum free conditions (EGF-SA). Alamar blue was used to determine proliferation rate, after 24h incubation with or without EGF. WHA was done scratching with a 200µl tip and images were taken at 0h, 6h and 24h time points, with or without EGF. Wound healing area was measured using ImageJ. EGF-SA was performed in starvation and adding EGF at 15 minutes(min), 30min or 2h. Protein was extracted and analysed using Western Blot and incubating with antibodies anti-ERK3, anti-phosphoERK3, anti-phosphoBRAF, anti-phosphoMEK1/2, anti-phosphoERK1/2 and anti-βtubulin as loading control. Western blot data were normalized using Image Lab ® 6.0.1. Statistical analysis was done in GraphPad Prism 6 ®. EGF-SA and WHA were analysed using one- or two-way ANOVA, respectively. PA was analysed using t test. **Results:** The EGF-SA shows activation of the classical pathway phosphoBRAF ($P = 0.0074$), phosphoMEK1/2 ($P = 0.0274$) and phosphoERK1/2 ($P < 0.0001$) in an EGF-dependent manner. It also shows that ERK3 is phosphorylated independently of EGF ($P = 0.8314$), suggesting an alternative signaling pathway. In the WHA, siERK3 effect and EGF stimulation were verified by western blot. Effect of siRNA transfection was evaluated (siNEG vs non-transfected: $P = 0.7482$). Wound healing assay showed no significant effect between siERK3 and siNEG, and a tendency to be increased with EGF but not significant (siRNA effect: $P = 0.9494$; EGF effect: $P = 0.0742$; interaction: $P = 0.9275$). In the proliferation assay no significant effect was observed between siERK3 and siNEG ($P = 0.9557$), also no significant effect by EGF stimulation ($P = 0.9289$). These results combined suggest that ERK3 is not necessary for the proliferation of Calu-1 or Calu-6, and EGF is a neglectable contributor. **Conclusion:** Our data indicates that ERK3 is constitutively active in Calu-6, a representative of NSCLC with KRAS mutation. However, it does not contribute significantly to cell proliferation or to wound healing in NSCLC. It also suggests that ERK3 has a distinct intracellular signaling pathway from the classical ERK1/2. Considering the increased expression of ERK3 in lung cancer and its constitutive phosphorylation, it is important to keep elucidating its signaling pathway as well as understanding mechanistically which cellular functions is responsible for.

Keywords: NSCLC, ERK3, proliferation

P68.09 Precision Cut Lung Slices Models for Lung Cancer Chemoprevention Investigations

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Introduction: Chemoprevention of lung cancer is key to reducing the burden of lung cancer in high-risk populations. However, studying chemoprevention mechanisms currently relies largely on animal models of lung cancer. While these in vivo studies are critical to support chemoprevention clinical trials, they are costly, time consuming, and require large numbers of animals. Precision-cut lung slices (PCLS) address these challenges by retaining the complexity of living tissue while enabling ex vivo studies of pathogenesis. Developing models of PCLS will reduce the numbers of animals used and refine conditions to reduce suffering in preclinical lung cancer chemoprevention studies. Frizzled 9 (Fzd9) is a transmembrane receptor required for the chemopreventive effects of the prostacyclin analogue iloprost in mouse models of lung carcinogenesis. **Methods:** FVB wild type or Fzd9-/- mouse lungs were cleared with PBS, filled with 1ml agarose, placed on ice for 10 minutes, and them removed. Slices were produced using a vibratome on individual lobes in chilled growth media. Slices were punched with a 4mm biopsy punch to produce standardized sections of tissue for culture. Punches were transferred to a culture dish in growth media and agarose was removed with media washes. Punches were embedded in a PEG-hydrogel with soft or stiff modulus and cultured in 24-well plates, with media changes every 48 hours. For ex vivo carcinogen testing, vinyl carbamate and NTCU were applied to cells every 48 hours during culture at varying doses. PrestoBlue viability reagent was used to measure viability once per week during culture. The RNeasy Plus kit was used for RNA extraction from punches. **Results:** We are using PCLS from Fzd9-/- mice to explore the mechanism of iloprost activity and effects of cigarette smoke condensate (CSC) after Fzd9 loss. We found that Fzd9-/- PCLS can be cultured for one week with CSC or iloprost without loss of viability and RNA can be recovered for gene expression studies. An ex vivo inducible model of premalignant lung lesions would provide significant opportunity for mechanistic investigations, so we are developing a long term PCLS culture using hydrogel embedded tissues. With hydrogel embedding, viability of PCLS can be maintained for over 30 days. Initial tests of ex vivo vinyl carbamate or NTCU treated hydrogel embedded PCLS indicate that viability can be maintained for 5-6 weeks with carcinogen exposure and that RNA can be recovered for gene expression studies. **Conclusion:** These data present promising early-stage development of models that will improve capacity for chemoprevention drug efficacy testing prior to preclinical studies and provide opportunities for more relevant mechanistic studies.

Keywords: lung cancer, chemoprevention, precision cut lung slice

P68.10 PFN1 Induces Tumor Metastasis Through Promoting Secretion of Microvesicles By ROCK I/p-MLC Pathway in Non-Small Cell Lung Cancer

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Introduction: Profilin1(PFN1) plays confusing roles in metastasis of different cancers, here we explored the roles of PFN1 in metastasis of non-small cell lung cancer (NSCLC). Considering that PFN1 is an important mediator of membrane trafficking and microvesicles(MVs) have already been proved closely associated with tumor metastasis, we further explored relationship of PFN1 and MVs in NSCLC metastasis and the underlying mechanisms. **Methods:** We first detect PFN1 and p-MLC expression in tissue microarray. Then we extracted MVs of NSCLC patients' serums by continuous differential centrifugation, quantified MVs by WB, electron microscopy and spectral flow cytometry. And PFN1 was overexpression/ knockdown to study the effect of MVs secretion and cell migration. Protein interaction was tested by CO-IP. ROCK kinase assay was used to detect ROCK kinase activity. For in vivo experiment, intracardiac injection of H1299 cell lines were used to establish metastatic tumor model for in vivo assay. **Results:** PFN1 were highly expressed in late stage NSCLC tissues, and the expression of PFN1 is positively correlated with p-MLC in IHC. Overexpression of PFN1 promotes MVs secretion and metastasis in vitro. Further investigation found that PFN1 could interact with ROCK I and affect the activity of ROCK I to phosphorylate MLC, which could regulate the secretion of MVs. Inhibition of ROCK I activity by Y27632 partially reverse PFN1' s promotion of MVs secretion and NSCLC metastasis in vivo and in vitro. **Conclusion:** PFN1 affects NSCLC metastasis via promoting MVs' secretion, which provided us a new insight into PFN1's roles in cancer metastasis and a new target of therapy in NSCLC metastasis.

Keywords: profilin 1, microvesicles, NSCLC metastasis

P68.11 Correlation of CD26 With Pro-Fibrotic Mediators in Lung Tumors

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Introduction: CD26/dipeptidyl peptidase 4 (CD26) is a multifunctional enzyme containing collagen and fibronectin binding sites. CD26 is not only expressed on various malignancies, but also associated with the progression of organ fibrosis of the heart, liver, kidney, and lung. We previously showed a high expression of CD26 in lung adenocarcinoma and a significant association between CD26 expression and a worse survival of patients showing an active epithelial-mesenchymal transition status. Here, we extended our analysis on the correlation between CD26, fibrosis and inflammation mediators on patient lung tumors. **Methods:** Samples from patients with lung tumors (n=103) including adenocarcinoma (n=38), squamous carcinoma (n=26), secondary lung cancer from metastases (n=14), and others (n=25) were collected. We correlated CD26 levels with the expression of fibrosis related genes (TGFB1, TGFR1, TGFR2, CCL2) and immunity related genes (PDL1, PD1, IL6) by RT-qPCR, with the protein level for CD26 and TGF-β1 by ELISA, and by immunohistochemistry (IHC) for CD26 (n=80). The expression of CD26 on tumor cells was graded from 0 to 3. **Results:** Lung adenocarcinoma expressed significantly more CD26 than other thoracic malignancies (n=80, p=0.0001). While stage IA adenocarcinoma expressed significantly higher amounts of CD26 compared to stage IIIA (p=0.0019), levels of CD26 raised in stage IIIB and IV, however, without significance. Furthermore, we found a significant correlation between the gene expression of CD26 on adenocarcinoma for TGFB1 (p<0.0001), TGFR1 (p=0.0004), and TGFR2 (p<0.0001). Also, PDL1 and PD1 were significantly correlated with CD26 (p=0.03, p<0001 respectively), although CCL2 and IL6 were not significantly correlated. A similar correlation pattern was observed in squamous carcinoma (TGFB1 (p=0.6), TGFR1 (p=0.0015), TGFR2 (p<0.0001), PDL1 (p<0.0001), PD1 (p=0.5)). The co-expression of CD26 and TGF-β1 could be additionally confirmed on a protein level. **Conclusion:** Assessing clinical samples of lung tumors, we can confirm that CD26 is highly expressed in lung adenocarcinomas and found that the expression of pro-fibrotic genes are significantly correlated with CD26 expression. Moreover, the immune checkpoint proteins PD-L1 and PD-1 co-express with CD26. Together, we deem CD26 to be a prognostic marker in lung cancer and targeting CD26 might tackle a cancer-specific immune escape mechanism within the tumor microenvironments.

Keywords: CD26, Fibrosis, lung cancer

P68.12 Inter-Tumor Heterogeneity of CD44 Expression in Non-Small Cell Lung Cancers / EGFR Mutated Lung Adenocarcinomas

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Introduction: Epithelial to mesenchymal transition (EMT) is one of mechanisms of acquired resistance (AR) to EGFR-TKIs in EGFR-mutated lung cancers. In our previous study, we observed that homogeneous high CD44 expression will predict emergence of EMT-mediated AR to EGFR-TKIs in lung cancer cell lines with EGFR mutation as represented by HCC4006 and H1975 cells (PMID:30049789). In this study, we examined inter-tumor heterogeneity of CD44 status to evaluate if CD44 can be a potential biomarker with less sampling variation in the clinical setting. **Methods:** As a first cohort, we re-analyzed multi-lesion RNA sequencing data obtained from treatment naïve autopsied NSCLC patients (PMID:29933065). We then performed immunohistochemistry (IHC) for CD44 in surgically-resected lung adenocarcinoma patients with EGFR mutation who had pathologically confirmed lymph node (LN) metastases. IHC results were compared between primary lesions and respective LN metastases. **Results:** Analysis of the autopsied cohort revealed that mRNA expression of CD44 was similar between primary and metastatic lesions (Figure 1). Therefore, we evaluated 10 pairs (primary tumors and LN metastases) of EGFR-mutated lung adenocarcinomas by IHC and observed that one LN metastasis had homogeneous high CD44 expression while CD44 expression was negative in the corresponding primary tumor of that patient (Figure 2). The ratio of tumor cells with high CD44 expression were low (0 – 35%) and were similar between primary tumors and LN metastases in the remaining 9 patients (Figure 2). Two patients with low CD44 expression received gefitinib for their recurrent disease, and a T790M secondary mutation was detected at the time of AR to gefitinib in both patients (no EMT-mediated resistance)

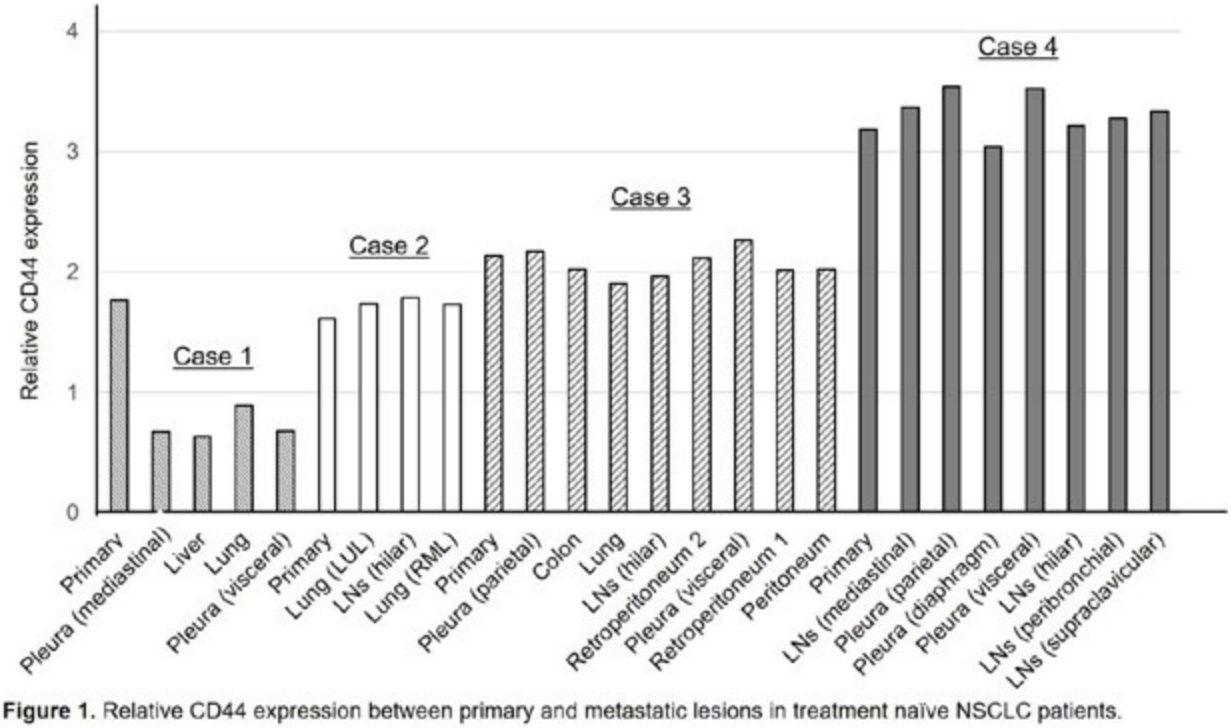

Figure 1. Relative CD44 expression between primary and metastatic lesions in treatment naïve NSCLC patients.

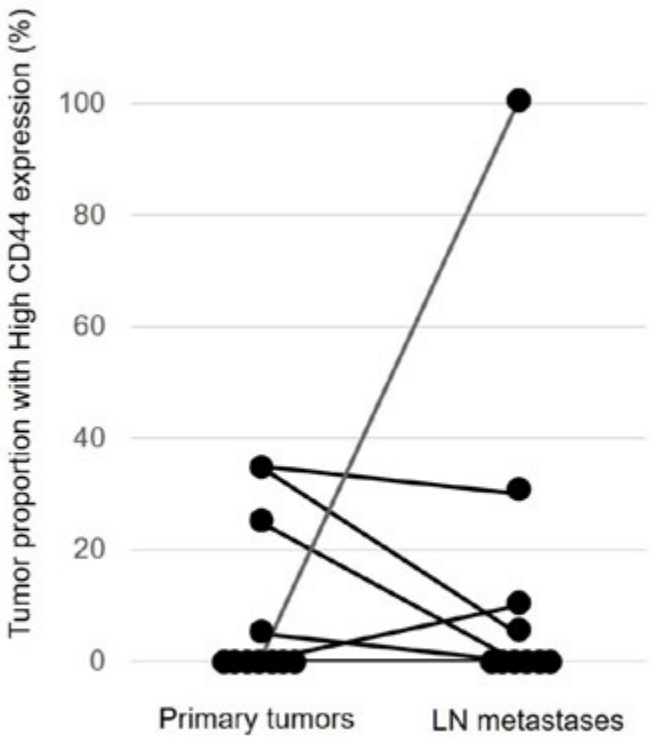

Figure 2. Comparison of high CD44 expression between primary tumors and LN metastases in surgically-resected lung adenocarcinoma patients.

Conclusion: In general, CD44 expression was similar between primary tumors and metastatic lesions with some exceptions in NSCLCs and in EGFR-mutated lung adenocarcinomas. However, unlike cell line models, the incidence of homogeneous high CD44 expression was rare in clinical specimens.

Keywords: acquired resistance, tumor heterogeneity, EGFR mutation

P68.13 Lung Cancer Prognosis and Cell Ratio Factors

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Introduction: We examined cell ratio factors (CRF) significantly affecting non-small cell lung cancer (LC) patients (LCP) survival. CRF - ratio between cancer cells (CC) and blood cells subpopulations. **Methods:** We analyzed data of 768 consecutive LCP (T1-4N0-2M0) (age=57.6±8.3 years; tumor size=4.1±2.4 cm) radically operated (R0) and monitored in 1985-2021 (m=660, f=108; upper lobectomies=277, lower lobectomies=177, middle lobectomies=18, bilobectomies=42, pneumonectomies=254, mediastinal lymph node dissection=768; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=193; only surgery-S=618, adjuvant chemoimmunoradiotherapy-AT=150: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=320, T2=255, T3=133, T4=60; N0=516, N1=131, N2=121, M0=768; G1=194, G2=243, G3=331; squamous=417, adenocarcinoma=301, large cell=50; right LC=412, left LC=356; central=290; peripheral=478. Variables selected for prognosis study were input levels of 45 blood parameters, sex, age, TNMG, cell type, tumor size. Survival curves were estimated by the Kaplan-Meier method. Differences in curves between groups of LCP were evaluated using a log-rank test. Multivariate Cox modeling, discriminant analysis, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence. **Results:** Overall life span (LS) was 2244.9±1750.3 days and cumulative 5-year survival (5YS) reached 72.9%, 10 years – 64.3%, 20 years – 43.1%. 502 LCP lived more than 5 years (LS=3128.7±1536.8 days), 145 LCP – more than 10 years (LS=5068.5±1513.2 days).199 LCP died because of LC (LS=562.7±374.5 days). Cox modeling displayed that LCP survival significantly depended on CRF: leucocytes/CC, segmented neutrophils/CC, lymphocytes/CC, healthy cells/CC (P=0.000-0.016). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and healthy cells/CC (rank=1), segmented neutrophils/CC (rank=2), erythrocytes/CC (rank=3), thrombocytes/CC (4), leucocytes/CC (5), lymphocytes/CC (6), eosinophils/CC (7), monocytes/CC (8), stick neutrophils/CC (9). Correct prediction of 5YS was 100% by neural networks computing (area under ROC curve=1.0; error=0.0). **Conclusion:** Lung cancer patients survival after radical procedures significantly depended on cell ratio factors.

Keywords: lung cancer, survival, cell ratio factors

P68.14 Sensitivity to Statin in EMT-Induced NCI-H322M Cells is Further Enhanced by Simultaneous Downregulation of HMGCR Expression

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Introduction: Statins, cholesterol-lowering drugs, can delay metastasis formation in vivo and attenuate the growth of tumor cells in vitro. The latter effect is stronger in tumor cells with a mesenchymal-like phenotype than in those with an epithelial phenotype. However, the effect of statins on epithelial cancer cells during epithelial-mesenchymal transition (EMT) remains unclear. In this study, we examined whether transforming growth factor-β (TGF-β)-induced EMT in epithelial-like cancer cells and concomitant downregulation of HMGCR expression counteracted their resistance to atorvastatin. **Methods:** NCI-H322M cells (a primary bronchioalveolar carcinoma) were incubated with or without 1 μM or 5 μM atorvastatin in serum-starved medium for 24 h prior to EMT induction with 10 ng/mL TGF-β1. Cell viability was defined at Day 6 by relative value obtained by dividing the cell number in each experimental group by that in the controls. In siRNA experiments, after 24 h of serum starvation, cells were treated with atorvastatin at concentrations of 1 μM or 5 μM for 24 h prior to EMT induction. EMT was induced with TGF-β1 for 6 days in the presence of 1 μM or 5 μM atorvastatin and HMGCR siRNA. Scrambled siRNA was used as a negative control for RNAi experiments. Cell numbers were counted on days 3 and 6 after EMT induction. **Results:** The difference in cell number between the TGF-β1 (+) and TGF-β1 (-) groups at 0 μM atorvastatin concentration was statistically insignificant. However, with increased concentration of atorvastatin, the cell numbers more significantly decreased in the TGF-β1 (+) group than that with same dosage of atorvastatin in the TGF-β1 (-) group ($p < 0.01$). In addition, siRNA-induced downregulation of HMGCR expression, observed at both the mRNA and protein levels, further enhanced the growth inhibitory effect of atorvastatin at both 1 and 5 μM concentrations in the TGF-β1 (+) group. **Conclusion:** Our study demonstrates that switching the phenotypic state of epithelial cancer cells and simultaneously downregulating HMGCR expression improves atorvastatin-induced attenuation of cell growth. One can hypothesize that dual inhibition of HMGCR by the attenuation of HMGCR expression and inhibition of HMGCR activity would delay metastasis formation to a greater extent than atorvastatin treatment alone.

Keywords: Statin, EMT, TGF-β

P68.15 Lung Cancer in Young Patients Under 45 Years: A French Study

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Introduction: Lung cancer is the leading cause of death by cancer in the world. The mean age at diagnosis is 63 years. The aim of this retrospective study was to describe the clinical, and molecular characteristics in patients under 45 years. **Methods:** All patients discussed at a French tumor board between 2008 and 2018 were included. The data collected were as follow: age, gender, histological type according to the 2015 WHO classification, TNM staging according to the 8th WHO classification, tobacco status (defined as follows: patients who had quit smoking for more than one year were considered ex-smokers, and patients who had smoked less than 100 cigarettes in their lifetime were defined as never smokers), and molecular (oncogenic drivers) characteristics. **Results:** We included 201 patients from a French tumor board, between 2008 and 2018, younger than 45 years. There were more men than women. The mean age at diagnosis was 39.55 years. The main histological type was adenocarcinoma, and more than half of the patients were diagnosed at advanced stages. Most of the patients were smokers. Thirty-four patients had oncogenic drivers (KRAS, EGFR et ALK). KRAS mutations were found in smokers, and men. ALK translocations, and EGFR mutations were more frequent in women, adenocarcinoma, and non-smokers.

	41-45 years		**31-40 years**		**Under 30 years**	
Characteristics	N=121	Percentages=60.2	N=64	Percentages=31.8	N=16	Percentages=8.0
Age in years	Mean=43.3 (41-45)		Mean=34.75 (31-40)		Mean=26.7 (16-30)	
Gender Men Women	63 58	52.0 48.0	36 28	56.25 43.75	10 6	62.5 37.5
Histological type Adenocarcinoma Squamous cell carcinoma Small cell carcinoma Non-small cell carcinoma Neuro-endocrine tumors Others	62 8 9 14 8 20	51.2 6.6 7.4 11.6 6.6 16.5	27 5 4 11 0 17	42.2 7.8 6.25 17.2 0 26.6	2 2 1 0 0 11	12.5 12.5 6.25 0 0 68.75
Stage I II III IV NA	15 8 26 67 5	12.4 6.6 21.5 55.4 4.1	7 1 17 36 3	11.9 1.6 26.6 56.25 4.7	2 1 3 9 1	12.5 6.25 18.75 56.25 6.25
Tobacco status Smokers Ex-smokers Non-Smokers Unknown	80 8 18 15	66.1 6.6 14.9 12.4	39 4 11 10	60.9 6.25 17.2 15.6	6 0 8 2	37.5 0 50.0 12.5

Clinical characteristics in the 3 groups of patients. **Conclusion:** Lung cancer in patients under 45 years are represented mostly by women, adenocarcinoma, advanced stage, and oncogenic drivers.

Keywords: oncogenic drivers, lung cancer, young patients

P68.16 Effect of GH / IGF1 System on Lung Cancer Cells A549

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Introduction: Lung cancer is a worldwide leading cause of death. The growth hormone (GH) – insulin like growth factor 1 (IGF1) axis has been observed to influence various stages and aspects of cancer development and behavior: cell proliferation and survival, angiogenesis and metastasis, and even resistance to chemotherapy. The combination of GH and IGF1 signaling, together with their interactions with other potentially oncogenic signaling proteins in tumor microenvironment, might be of great importance in the progression of cancer, and studies have been proposed for pharmacological targeting of the key molecules of GH-IGF1 axis. Pegvisomant (PEG), an antagonist of GH receptor, was initially developed to treat patients with acromegaly, but it has shown potential to treat some tumors. On the other hand, various antagonists aimed at tyrosine kinase domains have been mainly used in the inhibition of IGF1 signaling in breast, prostate and lung cancer cells; AG1024 is a selective inhibitor of the IGF1 receptor. **Methods:** In order to elucidate the participation of the GH / IGF1 axis in different hallmarks of lung cancer such as: proliferation, inhibition of apoptosis and cell migration, the effect generated by these two antagonists was investigated in the A549 cell line. Cells were incubated in DMEM supplemented with 10% FBS and antibiotics, 37ºC and 5% CO2 atmosphere; serum-depleted media were used for treatments with 100 ng/mL GH, 50 ng/mL IGF1, 5 µg/mL PEG and/or 32 µg/mL AG1024. Proliferation experiments were achieved by means of trypan blue exclusion method with neubauer chamber; cell scratch assay was performed in 6-well plates and images were registered with the light microscope; rt-PCR was performed with ThermoScientific and ZymoResearch kits, according to manufacturer instructions. **Results:** It was demonstrated that GH and IGF1 increased proliferation of A549 cells as expected, and both AG1024 and PEG generated a significant inhibition in proliferation in the different treatments, alone and combinated with GH and IGF1 (PEG only prevented the proliferation increment generated by GH and IGF1). On the other hand, in the scratch assay it was observed that AG1024 (alone and combined with IGF1 and/or GH) significantly inhibited the migration of A549 compared with the control group. Furthermore, the expression of GH mRNA was downwardly modified in the PEG+GH, IGF1, AG1024, AG1024+IGF1 treatments. In the expression of BCL2, a significant increment was only observed in the treatment with IGF1, but the expression of BAX showed an increase in PEG+GH, AG and PEG+AG groups. In turn, the pro-angiogenic factor VEGF showed significant differences only with the antagonist treatments. **Conclusion:** In conclusion, IGF1 antagonism is leading modulator in A549 lung cancer cells and autocrine/paracrine signaling in the GH/IGF1 axis is evidenced for adenocarcinoma cells, with changes in expression of GH and GH-receptor, which may imply that therapeutics need to be based on time changing kinase inhibitors and possible biomarkers to proper adjustments. Acknowledgements: the authors thank to I. Mendieta, J.E. Soto, J. Escobar, A.L. Gutiérrez for design and technical assistance; This work has been funded by Consejo Nacional de Ciencia y Tecnología (CONACYT) and UAQ-FCQ201820

Keywords: Somatotropin, IGF-1, tumor microenvironment

P68.17 Exosome-Mediated Transfer of SERPINE2 Regulates Non-Small Cell Lung Cancer Cells Repopulation After Ionizing Radiation

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Introduction: Radiotherapy plays important role in comprehensive treatment for lung cancer. However, approximately half of patients develop tumor resistance or recurrence. Repopulation is a major cause contributing to treatment failures. Studies on repopulation remains limited and the detailed mechanism is not well elucidated. **Methods:** This study established a repopulation model using a co-culture system with fluorescence-labeled H1975.luc cells. H1975.luc cells were termed as reporter cells. Irradiated H1975 cells were termed as feeder cells. Exosomes extracted from feeder cells were used to co-culture with reporter cells. Western blots were performed in exosomes, feeder cells, and reporter cells. **Results:** Feeder cells were co-culture with reporter cells after radiation with 0-8Gy. The luciferase assay showed luciferase activity of reporter cells was correlated with radiation dose in dose-dependent manner, indicating the dying cells after radiation could stimulated surround cells proliferation. RNAseq showed SERPINE2 were high expression in feeder cells. Over-expression SERPINE2 significantly promoted lung cancer cells proliferation. Further study showed exosomes from irradiated feeder cells could promote proliferation of reporter cells. An over-expression SERPINE2 feeder cells with tag were constructed. We determined high expression of SERPINE2-tag in exosomes from feeder cells and also in co-cultured reporter cells. Besides, Rad51 was elevated in reporter cells co-cultured with SERPINE2 over-expression exosomes. **Conclusion:** This study showed the role of exosome-mediated transfer of SERPINE2 on repopulation after ionizing radiation. This study provided evidence to better understand the underlying mechanisms of repopulation.

Keywords: Repupolation, SERPINE2, Exosome

P68.18 Relationship Between Cholesterol Synthesis in Cancer Cells and Anticancer Effect of Statins

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Introduction: Statins are blood cholesterol-lowering drugs that exert their effects through inhibiting cholesterol synthesis via the mevalonate pathway. In addition to cholesterol, this pathway produces intermediate products such as farnesyl diphosphate (FPP), geranylgeranyl diphosphate (GGPP), and squalene. It is reported that statins have an antiproliferative effect through depleting FPP and GGPP, suggesting that they could be useful for cancer treatment. Since FPP is located at a branch point between sterol and non-sterol production, squalene synthase (FDFT1) that converts FPP to squalene is thought to have an important role to control the flow of the mevalonate pathway; however, the effects of statins on this branch point remain unclear. In this study, we examined the variation in FDFT1 and GGPP synthase (GGPS1) expression, along with cholesterol levels, in statin-exposed cancer cells. **Methods:** We used two lung cancer-derived cell lines: statin-resistant NCI-H322M and statin-sensitive HOP-92. Cells were treated with atorvastatin at a final concentration of 1 μM for 24 hours. The effects of statins on GGPS1 and FDFT1 expression were analyzed with RT-qPCR and western blots. Total cholesterol, free cholesterol, and cholesterol ester were measured using a cholesterol assay kit. **Results:** Statin-resistant and statin-sensitive cancer cells did not differ in GGPS1 gene or protein expression. Statin treatment did not increase or decrease GGPS1 expression. Likewise, statin treatment did not alter FDFT1 gene and protein expression, but both were significantly lower in statin-sensitive cancer cells than in statin-resistant cancer cells. After statin treatment, cholesterol ester ratio (cholesterol ester/total cholesterol) did not change in statin-resistant cells, but decreased by approximately 35% in statin-sensitive cells. **Conclusion:** While GGPS1 expression did not differ between statin-resistant and statin-sensitive cancer cells, FDFT1 expression did. Our results suggested that in statin-sensitive cancer cells, originally-low FDFT1 levels, along with GGPP depletion, helped inhibit cholesterol synthesis. This cellular characteristic in turn strengthened the anticancer effect of statins.

Keywords: Drug repositioning, Cholesterol, Statin

P69.01 The Role of the Pregnancy Associated Protein Glycodelin and Its Influence on the Immune System in Non-Small-Cell Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer related death worldwide and the challenge of developing effective therapies especially for advanced stages remains. Novel approaches concentrating on immunotherapies showed a favorable response in lung cancer patients, making this an interesting and promising field for future research. Glycodelin is an immunosuppressive glycoprotein in reproduction and pregnancy maintenance. Interestingly, high expression levels were also observed in different cancer types, e.g. in non-small-cell lung cancer. **Methods:** To investigate whether glycodelin has similar immunomodulatory characteristics in NSCLC, 22 lectins were used to compare the glycosylation pattern of glycodelin secreted by NSCLC tumor cells to immunosuppressive glycodelin A isolated from amniotic fluid. Furthermore, tumor cell line supernatant containing high amounts of glycodelin was used to treat different immune cell lines. Binding assays were performed and possible effects of the treatment have been evaluated using microarray gene expression analyses. To investigate its influence on the efficiency of immunotherapy, glycodelin was measured in the serum of inoperable immunotherapy-treated NSCLC patients (n = 139) and progression-free survival analysis was performed. **Results:** We were able to show that the glycosylation of glycodelin from NSCLC is highly similar to glycodelin A and especially shares functional sialylation which is crucial for immune system regulation. In addition, we could validate that glycodelin binds to immune cells. The evaluation of microarray gene expression assays shall give hints for immune escape mechanisms induced by glycodelin. In patients, high serum concentrations of glycodelin were associated with a decreased progression-free survival (p = 0.048) of patients receiving an anti-PD-1-/ PD-L1 therapy. **Conclusion:** In conclusion, we demonstrate that glycodelin is a protein with a high potential of being a novel target in immuno-oncology especially for NSCLC patients.

Keywords: immunotherapy, NSCLC, immune escape

P69.02 Video-Assisted Mediastinoscopic Lymphadenctomy Improves Natural Killer Cytotoxicity in Non-Small Cell Lung Cancer

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Introduction: The aim of this study was to evaluate the effect of preoperative video-asissted mediastinoscopic lymphadenectomy (VAMLA) on effector functions and phenotypes of NK cell subsets in NSCLC patients. **Methods:** cIA-IIB NSCLC lung cancer patients (n=22, mean age: 64±7 years), undergoing preoperative mediastinal staging by VAMLA were included. Peripheral blood mononuclear cells were isolated from peripheral blood before and after VAMLA before resectional surgery. PD-1 and CTLA-4 molecule expressions, intracellular IL-10, TNF-α and IFN-γ levels were analyzed in cytokine secreting and cytotoxic NK cell subsets. Cytotoxic capacity of NK cells was assessed by granzyme A secretion and CD107a-based degranulation assay by flow-cytometry. The plasma soluble PD-1 and CTLA-4 concentrations were measured by ELISA. Twenty out 22 patients (90.9%) underwent anatomical pulmonary resection. **Results:** The ratio of cytokine-secreting NK subset ($CD56^{bright/dim}CD16^{-}$) increased in blood after VAMLA (p=0.027), while cytotoxic $CD16^{bright}CD56^{dim}$ and $CD16^{bright/}CD56^{-}$ NK subsets remained relatively unchanged. PD-1 and CTLA-4 expressions were diminished in all NK cell subsets after VAMLA (p<0.05). After VAMLA, IL-10 secreting $CD56^{bright/dim}CD16^{-}$ NK cells were significantly reduced (p=0.001), while TNF-α and/or IFN-γ secreting cells remained unchanged (p>0.05). NK cell cytotoxic activity increased significantly in K562 stimulated conditions (p=0.042). IFN-γ secretion was significantly increased in unstimulated (p=0.012) and K562 stimulated (p=0.003) conditions after VAMLA. **Conclusion:** This study demonstrated that removal of mediastinal lymph nodes decreased both IL-10 secreting regulatory NK cells as well as PD-1 and CTLA-4 expressing NK cell subsets implicating that VAMLA improves anti-tumor responses of NK cells.

Keywords: bilateral lymph node dissection, natural killer cells, anti-tumor immunity

P69.03 Chemotherapy Upregulates PD-L1 Expression and Activates cGAS-STING Pathway in Non-Small Cell Lung Cancer Models

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Introduction: Tumour cell expression of the PD-L1 may allow it to evade T-cell mediated killing, and therefore plays an important role in cancer progression. The clinical efficacy of PD-1/PD-L1 inhibitor therapy in non-small cell lung cancer (NSCLC) patients is greatest in high PD-L1 expressing tumours. Additionally, pembrolizumab (anti-PD-1; Keynote-189) and atezolizumab (anti-PD-L1; Impower130 Trial) combined with chemotherapy has also demonstrated greater clinical efficacy than chemotherapy alone, even in patients with low-PD-L1 tumours. The underlying mechanism mediating the enhancement of anti-PD-1/PD-L1 response by chemotherapy is unknown. We hypothesize that chemotherapy can sensitize the NSCLC tumours to anti-PD-1/PD-L1 therapy by inducing PD-L1 expression via activation of cyclic AMP-GMP synthase and stimulator of interferon genes (cGAS-STING) pathway, which has been shown to enhance tumour immunogenicity. We investigate the effect of chemotherapy on cGAS-STING and PD-L1 expression in patient-derived NSCLC models. **Methods:** Models investigated include NSCLC cell lines H226, HCC4006, MGH7, H1944, H2122, patient-derived xenograft (PDX) PHLC315 and PHLC169, and PDX-derived organoids PDXO377 and PDXO274. Cell lines and organoid models were treated with cisplatin. PDX models were treated with various chemotherapies used to treat NSCLC patients. Cell and tumor protein and mRNA extracts were analysed by Western blot and RT-qPCR, respectively. **Results:** Cisplatin treatment significantly upregulated PD-L1 protein expression after 72 hrs in H1944, H2122, H226, HCC4006, and MGH7 cell lines. The protein expression of cGAS, STING, TBK1, and p-TBK1 (a kinase activated downstream of STING signalling) was upregulated in H226, HCC4006, and MGH7 at 48 and 72 hrs after cisplatin treatment, and PD-L1 protein expression was also upregulated at these time points. At 48 hours of cisplatin treatment PD-L1 mRNA significantly increased 9-fold and 4-fold in PDXO377 and PDXO274, respectively. Cisplatin also significantly increased Interferon-beta (IFNB1) levels in the organoid models. Results in PDX models will be reported at the meeting. **Conclusion:** Chemotherapies used to treat NSCLC patients may upregulate PD-L1 expression and also activate the cGAS-STING pathway in NSCLC lung cancer models. The mechanistic relationship between these two events warrants further investigation.

Keywords: PD-L1, Chemotherapy, cGAS-STING

P69.04 Immune-Related Genomic Features in Non-Small-Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors have been being widely applied in clinical practice. However, the immune-related genomic features are not fully studied. This study aimed to investigate immune-related genomic features through testing PD-L1 expression and cancer-relevant genes. **Methods:** The Chinese patients with lung cancer enrolled from May 2016 to January 2021 at the Second Affiliated Hospital of Nanjing Medical University were collected. And the tumor tissue samples of 425 cancer-relevant genes from 148 patients were tested with targeted next-generation sequencing. Besides, 33 samples were stained with PD-L1 antibody clone 22C3. To be specific, 28 samples were examined for both NGS and PD-L1 expression. **Results:** Of all the samples which underwent PD-L1 test, 64% demonstrated PD-L1 positive (defined by > 1% of PD-L1 staining) and the rest 36% showed PD-L1 negative (<1% PD-L1 staining). Tumor mutation burden was not significantly associated with PD-L1 expression. APC mutations was significantly more prevalent in the group with PD-L1 positive comparing to the PD-L1 negative group (40% vs 0%, P=0.01). In addition, LRP1B (16.7% vs 0%) were enriched in PD-L1 positive group, whereas some of the known negative predictors of immunotherapy, such as JAK2 mutations (0% vs 20%) and MDM2 amplification (0% vs 20%), were enriched in patients of PD-L1 negative. **Conclusion:** This study identified several differentially enriched genetic alterations associated with high and low PD-L1 expression, which may provide future guidance to predict the efficacy of immunotherapy in patients with different PD-L1 expression levels.

Keywords: Immune, genomic features, non-small-cell lung cancer

P70.01 KRAS G12C Mutations Among NSCLC Patients Present With a High Intrerregional Variation, Indicating a Population Substructure

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Introduction: Molecular profiles of Non-small cell lung cancer (NSCLC) patients differ regarding sex, ethnic background, age, and exposure to tobacco smoke, among others. By extensively characterizing specific NSCLC populations, resource allocation and new molecular target exploration become more feasible. KRAS G12C mutations have become treatable in the last months, warranting a large-scale estimation of mutation prevalence and identifying possible interregional variability in its positivity, as observed in other molecular targets **Methods:** To determine geographical discrepancy with regards to KRAS G12C mutation status, patients with advanced/metastatic NSCLC, previously identified as EGFR (-) and ALK (-), were evaluated. Samples were collected from across the national territory of Colombia, warranting representation of several administrative regions. Mutational status was determined by ddPCR on formalin-fixed paraffin-embedded tissue. **Results:** A total of 1,002 KRAS G12C evaluations were conducted across 26 of the 32 administrative regions, identifying 80 positive samples, yielding a national prevalence of 8%. (95%CI 6.3-9.7%) By excluding regions without a representative number of individuals, 979 samples across 18 administrative regions were included in the analyses. National positivity reached 7.97% (95%CI 6.27-9.66%). Three administrative regions presented with prevalence's that differed from the national average. Bolivar (41 samples) had a 4.19% of positivity (95%CI 0-7.2%), similar to Bogota DC (Capital Region) with 259 samples and 5.4% of mutation prevalence (95%CI 2.7-8.2%). On the other hand, Antioquia (338 samples) debuted with 12.7% of KRAS G12C mutated samples (95%CI 9.1-16.3%) with a statistically significant difference among the first two and the last (p-value = 0.00262). **Conclusion:** Among NSCLC patients, interregional variability regarding KRAS G12C mutation frequencies indicates a distribution substructure, indicating that population composition and ethnicity could lead to varying prevalence in the same nation.

Keywords: Non Small Cell Lung Cancer, KRAS G12C, Population predisposition

P70.02 Clinicopathological and Genetic Ancestry Impact of TP53 Mutations in Brazilian Lung Adenocarcinoma Patients

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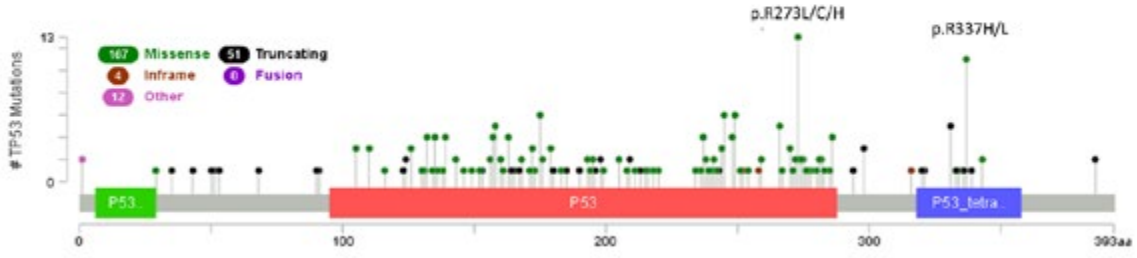
Introduction: TP53 is the most mutated gene in lung adenocarcinoma tumors. TP53 gene plays a crucial role in maintaining genome stability, and the presence of alterations in this gene may lead to uncontrolled cell proliferation and cancer. However, the frequency of TP53 mutation and its clinical impact in admixture lung adenocarcinoma populations, such as the Brazilian population, is unclear. Aim: To describe the frequency of TP53 mutations and their association with clinicopathological and genetic ancestry background data in lung adenocarcinoma patients in Brazil. **Methods:** We evaluated a retrospective FFPE series of lung adenocarcinoma (n=363) diagnosed at Barretos Cancer Hospital, Barretos, Brazil, between 2018 and 2020. TP53 mutational status was assessed by NGS (TruSight Tumor 15, Illumina). The genetic ancestry analysis was assessed on tumor DNA by a specific panel of 46 ancestry informative markers, and the ancestry proportions for Asian, African, European, and Native American was calculated. **Results:** In accordance with the AJCC 7thedition, the following disease stage was present at diagnosis: I/II (n=51); III (n=43), and IV (n=245). We observed the presence of TP53 mutations in 59% (n=215) of cases. About 71.0% of mutations were missense variants and the majority were located in the DNA-binding domain of the TP53 gene (Figure1). Furthermore, the codon Arg273 was the most mutated (n=13), and the R337H variant (founder-effect in Brazil) was identified in 10 cases (4.65%). TP53 mutations were associated with younger age at diagnosis(p=0.006) quitter and current smokers(p=0.006 and p=0.001), and intermedium and high African genetic ancestry(p=0.012 and p<0.0001). TP53 mutated patients presented a significantly worse overall survival (14 months) compared to wild-type patients (22months) (p=0.024). The adjusted cox regression model showed TP53 mutational status(TP53m HR=1.15, p=0.386) was not independently associated with worse outcomes. Apart from, EGFR mutational status(EGFRm HR=0.44, p<0.0001), advanced disease at diagnosis(HR=15.78, p<0.0001), and PS ECOG at diagnosis(PS1 HR=2.25, p=0.032; PS2 HR=3.71, p=0.01; PS3/4 HR=5.91, p<0.0001) were independently associated with worse outcomes regardless of disease course.

Figure 1- *TP53* gene lolipop showing all mutations identified. (n=234)



Conclusion: TP53 mutations are present in 59.0% in Brazilian lung adenocarcinoma patients. TP53 mutations are associated with younger patients, quitter and current smokers, patients with African genetic ancestry background.

Keywords: TP53, Lung adenocarcinoma, Brazil

P70.03 Computational Omics Biology Model (CBM) Identifies Amplifications of Chromosome 6p to Predict Chemotherapy Resistance

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Introduction: Gemcitabine and carboplatin/cisplatin ("platinum")-based combinations are used to treat a wide variety of malignancies including gynecologic, breast, lung, and occult primary cancers. In Non-Small Cell Lung Cancer (NSCLC), these combinations led to a substantial improvement in overall survival. Nevertheless, a large proportion of patients do not respond. An optimal cytotoxic strategy for managing NSCLC and the discovery of predictive biomarkers for cytotoxic chemotherapy to guide treatment selection remain unmet needs in the clinic. The Cellworks Computational Omics Biology Model (CBM) platform identified a unique chromosomal signature which permits a stratification of patients that are most likely to respond to gemcitabine and platinum treatments. **Methods:** Twenty patients treated with gemcitabine and platinum were identified from a TCGA dataset and analyzed. The mutation and copy number aberrations from individual cases served as input into the CBM to generate a patient-specific protein network map from PubMed and other online resources. Disease-biomarkers unique to each patient were identified within patient-specific protein network maps. Digital drug biosimulations were conducted by measuring the effect of gemcitabine and platinum on a cell growth score comprised of a composite of cell proliferation, viability, apoptosis, metastasis, and other cancer hallmarks. Drug biosimulations were conducted by mapping the drug combination to the patient genome along with a rational mechanism of action and validated based on the patient's genomic profile and biological consequences. **Results:** Of the 20 patients treated with gemcitabine and platinum, 12 had clinical responses while 8 were non-responders. The CBM correctly predicted response in 17/20 patients with 85% accuracy, 63% specificity and 100% sensitivity. The CBM identified that novel amplified segments of Chromosome 6p were associated with non-responsiveness to gemcitabine and platinum therapy. Key genes on these segments include E2F3, MDC1, TAP1 and TNF. Amplification of E2F3 leads to activation of MSH2/6, which enhances mismatch repair thereby causing resistance. Amplification of MDC1 leads to activation of CHECK2, BRCA1, ATM, and NBN_RAD51_MRE1 Complex which stimulates homologous recombination repair. Amplification of TAP1 reduces gemcitabine transport. Besides 6p amplification, PRMT7 deletion was also associated with gemcitabine resistance. Notably, BRCA2-del, RB1-del, NPM1-del, LIG4-del, XRCC4-del, RAD50-del, ATRX-Del, RBBP8-del, XRCC6-del, and FBXW7-del were also prevalent among gemcitabine non-responders. Interestingly, these aberrations also happen to be key criteria for predicting response to etoposide. Therefore, etoposide and platinum combinations might have provided better disease control for these patients. **Conclusion:** Amplification of chromosome 6p appears to be an important cause of treatment failure for patients receiving gemcitabine-platinum combinations. In this small patient group, the Cellworks CBM was especially useful for identifying non-responders. Biosimulation can identify novel patient subgroups for therapy response prediction and has promise to help select more effective therapies.

Keywords: Multi-omics Therapy Biosimulation, Personalized Cancer Therapy, Cancer Therapy Biosimulation

P70.04 Results From a Patient Avatar Program Utilizing Murine Xenografts and Organoids After Neoadjuvant Therapy for Operable NSCLC

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Introduction: Patient-derived xenografts (PDX) and organoids (PDO) are well described methods of propagating patient tumors. While propagation of such models are well established in treatment naïve patients after surgical resection, little is known of the prognostic utility of such methods in the context of patients who have undergone neoadjuvant therapy with conventional therapy (chemotherapy +/- radiation), immune checkpoint blockade (ICB) or tyrosine kinase inhibitor (TKI) for patients with operable non-small cell lung cancer (NSCLC). This study aims to evaluate PDX and PDO propagation rates after surgical resection from patients treated with a variety of conventional and emerging ICB neoadjuvant treatment regimens, as well as correlation with extent of pathological response. **Methods:** All trials of PDX and PDO implantation performed at the McGill University, Goodman Cancer Research Centre since 2017 from samples of lung cancer patients treated at the Montreal General Hospital were reviewed. After intraoperative specimen evaluation by a clinical pathologist, tumor pieces of 5 mm^3 were taken for live banking PDX and PDO procedures. A retrospective chart review was then performed to obtain patient demographic and treatment data. **Results:** A total of 80 PDX implantation and 28 PDO culture trials were performed, with respective take rates of 25% and 82%. Overall, 35/80 PDX trials (20 chemotherapy only, 2 chemotherapy +/- ICB, 2 chemoradiation, 10 ICB, and 1 TKI) and 23/28 PDO trials (11 chemotherapy only, 3 chemotherapy +/- ICB, 1 chemoradiation, 7 ICB, and 1 TKI) were from patients who received neoadjuvant treatment. In these patients, our take rates were 17% for PDX and 78% for PDO. 5 neoadjuvant-treated patients had a major pathological response (MPR) and 2 patients, a pathological complete response (pCR). Of those with MPR, 1/5 sample was successfully propagated in PDXs, and another 1/5 sample failed to propagate in PDXs, but grew organoids. Interestingly, 0/10 patients who received neoadjuvant ICB grew in PDXs versus 3/10 where PDOs were successfully propagated. **Conclusion:** PDX and PDO models offer tangible opportunities to create living patient avatars. Our study suggests that PDX and PDO propagation is possible after a variety of neoadjuvant treatment regimens, though we were unable to propagate PDX from ICB-treated patients. Furthermore, MPR did not preclude subsequent tumor propagation in PDX or PDO. The clinical relevance of these findings and biology underlying our findings remains to be further explored.

Keywords: patient-derived xenografts, patient-derived organoids, neoadjuvant therapy

P70.05 Identification of Germline Mutations in Young Never Smokers With Lung Adenocarcinoma by Whole Exome Sequencing

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Introduction: Recently, an increasing number of young never-smokers were diagnosed with lung cancer. Although environmental risk factors such as second-hand smoke, radon, and indoor air pollutants might cause never-smoking lung cancer, a large proportion of these patients do not have a definite association with established environmental risk factors. The aim of this study was to investigate the genetic predisposition of lung cancer in these patients and discover candidate pathogenic variants for lung adenocarcinoma in young never-smokers. **Methods:** We collected peripheral blood cells from 123 never-smoking patients who were diagnosed with lung adenocarcinoma before the age of 40. The germline DNA, extracted from peripheral blood cells, were sequenced by whole exome sequencing. **Results:** 5334 variants from 2368 genes were identified. Using bioinformatical tools and published germline variants of lung cancer, nine pathogenic mutations (ATR-L1673V, FANCD2-E369Q, GATA2-H169R, HFE-Q82X, MSH2-V817M, PDGFRA-E494V, SDHB-P37L, WAS-P315L, and PPIL2-W346S) were identified in ten patients with lung adenocarcinoma. The majority of patients with pathogenic mutation were females (9/10, 90%).

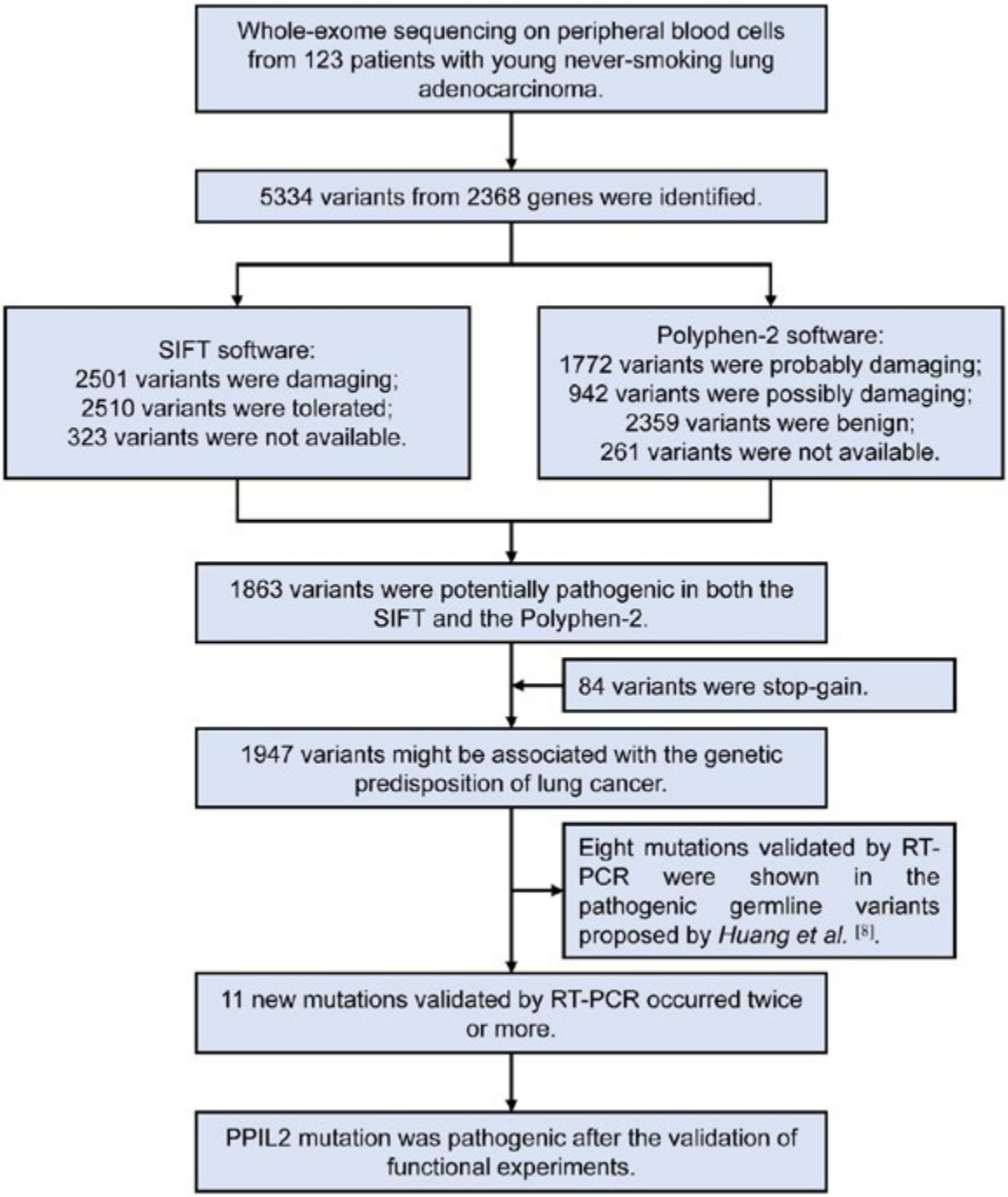

Figure 1. The workflow of this study.

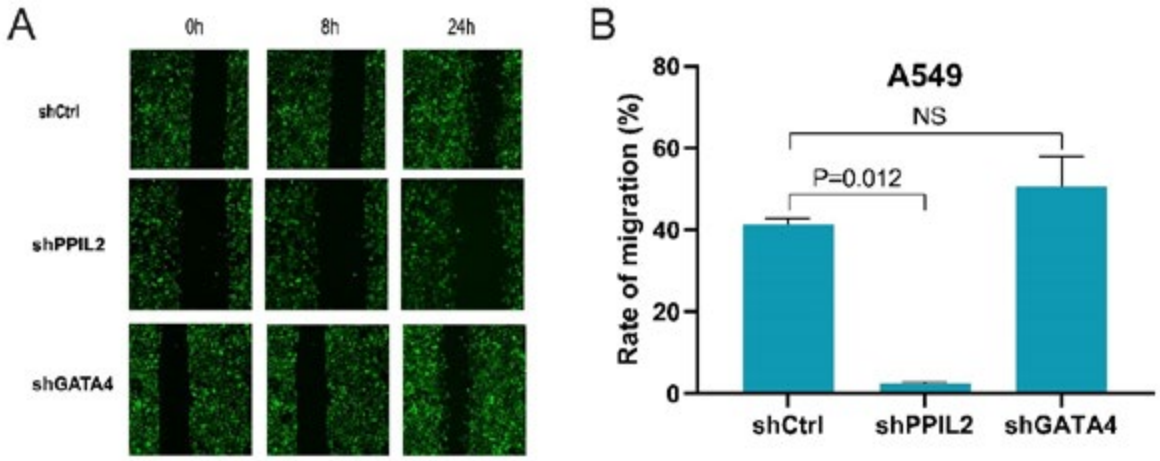

Figure 2. Downregulation of PPIL2 suppressed cell migration in A549. (A) Typical images of migration assays in 0h, 8h, and 24h. (B) Rate of migration in different groups. NS: none sense. **Conclusion:** In this study, we identified and confirmed PPIL2-W346S as a new germline mutation for lung adenocarcinoma. Furthermore, we established a public database for the predisposition of lung adenocarcinoma in young never smokers, which could be used for early diagnosis and individual management of lung cancer.

Keywords: germline mutation, never smoker, Lung adenocarcinoma

P70.06 m6A reader IGF2BP1 High Protein Expression level Indicates a Poor Recovery for Lung Adenocarcinoma Patients

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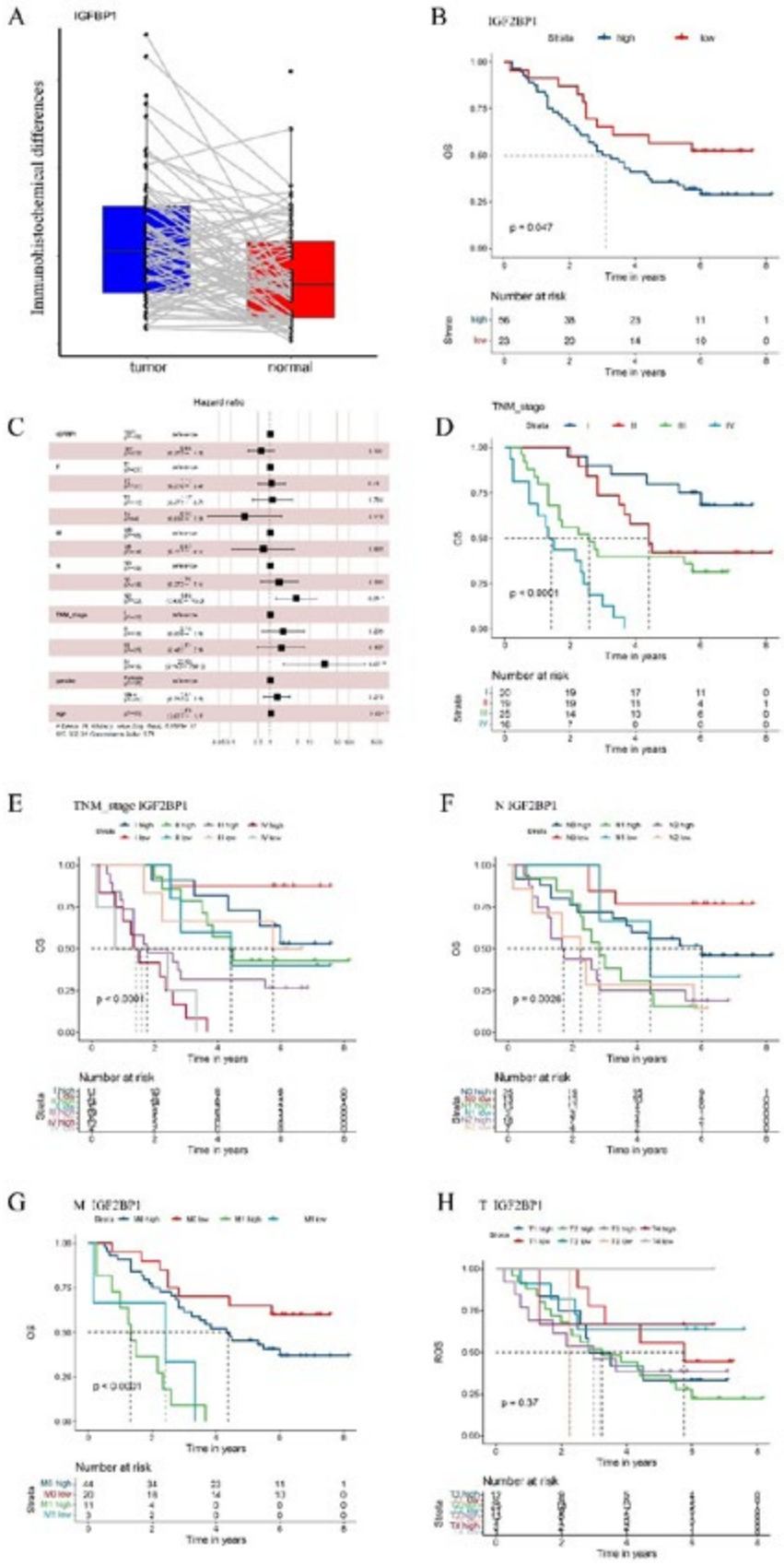
Introduction: Previous studies we found that IGFII mRNA-binding protein 1 (IGF2BP1) were highly expressed in Lung Adenocarcinoma (LUAD) patients tumor tissues compared with normal lung tissues and high expression related to LUAD various clinical pathological stages in transcription level[Wang, X. , et al. WCLC2020]. In this study, we analyzed in the translation level of patients with LUAD , in order to further obtain the impact of IMP1 on the prognosis of LUAD patients. **Methods:** In order to evaluate the differential expression and prognosis value of IGF2BP1 in LUAD, a tissue microarray (TMA) (LUC1601) containing 80 pair LUAD tumor tissues and paratumor tissues with overall survival rate follow-up, detailed TNM staging information was obtained from Superbiotek (Shanghai, China). Standard Immunohistochemical methods were used to detect the expression of IGF2BP1 in paraffin specimens of each samples. Aperio ImageScope viewing software were used for analyzing Immunohistochemical intensity created by the Aperio scanner for the TMA. Then the clinical role of IGF2BP1 Immunohistochemical intensity on the overall survival of LUAD patients was illustrated by multivariate Cox hazards regression and Kaplan-Meier analysis. **Results:** IGF2BP1 Immunohistochemical analysis demonstrated that LUAD tumor tissues was highly stained comparable with normal paratumor tissues. According to the immunohistochemistry score the tumor samples were divided into two groups with a score = 1.2 as cut off and 56 tumor samples were highly stained. Kaplan-Meier analysis showed that high score group patients owned poorer overall survival than patients with low stained samples and more than 50 percent of low risk patients survived during the follow-up period (> 7 years). Due to the low sample size, the multivariate analysis shows that IGF2BP1 is not an independent prognostic factor, which may also be related to the influence of IGFBP1 on clinical staging.


A
IGF2BP1
Immunohistochemical differences
tumor
normal
B
IGF2BP1
Strata
high
low
OS
p = 0.047
Time in years
Number at risk
C
Hazard ratio
D
TNM_stage
p < 0.0001
E
TNM_stage IGF2BP1
p < 0.0001
F
N IGF2BP1
p = 0.0026
G
M IGF2BP1
p < 0.0001
H
T IGF2BP1
ROS
p = 0.37

Conclusion: Our study found that highly IGF2BP1 protein level heralds a poor prognosis in LUAD. These results provides new clinical evidence for the role of IGF2BP1 on LUAD and may lay a theoretical foundation for LUAD corresponding countermeasures.

Keywords: Lung Adenocarcinoma, m6A, IGF2BP1

P70.07 Examples of Population Kinetics (PopKin) Assessments of Progression-Free (PFS) and Overall Survival (OS)

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Introduction: Most PFS/OS curves approximate first order kinetics and are fit by exponential decay nonlinear regression analysis (EDNLRA) models. Here we describe recent PopKin analyses. **Methods:** Published PFS and OS curves were digitized using https://apps.automeris.io/wpd/. EDNLRA 1-phase-, 2-phase-, and/or 3-phase-decay modelling was performed using GraphPad Prism 7. Using 1-phase-decay models, we calculated PFS and OS half-life (time to progression/death of half the remaining patients) for entire populations and calculated relative size and half-life for each subgroup in 2-phase- and 3-phase-decay models. **Results:** In studies with <20% crossover using multiple types of systemic therapies across a wide range of metastatic malignancies, PFS half-life gain ≥1.5 months predicted OS half-life gain ≥2 months, with a positive predictive value (PPV) of 82% and negative predictive value (NPV) of 85%.[1] Higher PFS gains predicted progressively higher OS gains. For example, PFS half-life gain ≥4 months predicted OS gain ≥5 months (PPV 84%, NPV 83%). PFS half-life gains performed much better than hazard ratios or gains in median PFS (PPV 55%; NPV 69%) in predicting OS gains. Across 887 PFS curves involving multiple systemic therapies and metastatic malignancies, shape on log-linear plots and probability of curves fitting 2-phase-decay models varied significantly with therapy type.[2] Late acceleration of growth after chemotherapy interruption characterized extensive small cell lung cancer, with highly convex log-linear plots.[2,3] Immune checkpoint inhibitors were particularly likely to fit 2-phase-decay models, with log-linear curve inflection to the right, suggesting 2 distinct populations (one with rapid progression, with PFS half-life similar to placebo, and one with slow progression). For other therapies, 2-phase-decay could be explained by presence-vs-absence of a sensitizing mutation, and curve log-linear shape may indicate for which new therapies we should put particular effort into identifying a present-vs-absent predictive biomarker. The 2-phase-decay with PD-1/PDL-1 inhibitors could potentially be driven by a not-yet-defined present-vs absent sensitizing/resistance factor.[2] 2-phase-decay was generally not seen when PD-1/PDL-1 inhibitors improved outcome when added to chemotherapy, suggesting that PD-1/PDL-1 inhibitors may be less limited by the putative not-yet-identified sensitizing/resistance factor when combined with chemotherapy.[4] EDNLRA 3-phase-decay models did not support the concepts of hyperprogression or potential cure with PD-1/PDL-1 inhibitors.[5] In advanced non-small cell lung cancer, EDNLRA assessment of placebo/best supportive care trial arms indicated that 4% of remaining patients die each week therapy initiation is delayed,[6] highlighting importance of avoiding excessive systemic therapy delays while screening patients for clinical trials, or while undergoing cranial radiation, etc. We also used PFS EDNLRA to calculate proportion of remaining patients who would progress in each subsequent week, to determine the optimal frequency of follow-up scans for patients receiving various therapies,[7] rather than basing this decision on expert consensus or standard practice. Additional projects are underway. **Conclusion:** PopKin assessments by PFS/OS curve EDNLRA and log-linear plots can offer helpful therapeutic insights. 1. Stewart. Crit Rev Oncol Hematol 2020[Feb 8];148:102896 2. Stewart. Crit Rev Oncol Hematol 2020[June 20];153:103039 3. Stewart. Proc ASCO 2020; Abstract#e21101 4. Stewart. Proc AACR 2021; Abstract#441 5. Stewart. WCLC 2021: submitted 6. Stewart. Proc AACR 2020; Abstract#1510 7. Stewart. Cancer Med 2019;8:6871

Keywords: population kinetics, Overall survival, progression-free survival

P70.08 Allelic Frequencies of Population Markers Correlate with KRAS G12C Prevalence: Considerations for Ancestries and Molecular Epidemiology

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Introduction: KRAS G12C mutation frequencies are not constant among all NSCLC patients. Recent studies suggest that specific ethnic differences play a role in varying population frequencies of specific mutations. **Methods:** A multiple stepwise regression analysis was conducted on samples evaluated for KRAS G12C mutations by ddPCR on a national study with specific regional representation. Independent variables were allelic frequencies for all CODIS short tandem repeats (STR) markers, used for individual, ancestral, and population identification. The best model and which markers to include were determined by a tradeoff of several markers and best-adjusted R2. Regional tobacco consumption rates were also analyzed. **Results:** A total of 979 samples across 18 administrative regions were included in the analyses. National positivity reached 7.97% (95%CI 6.27-9.66%). Tobacco consumption was relatively constant among all included regions, oscillating around 15,6%. Interregional variability with regards to G12C mutation frequencies ranged from 0% to 12.72%, confirming population substructures. Regression analyses revealed a strong relationship with regional STR markers allelic frequencies and KRAS G12C mutation frequencies. Selected STR were D22S1045 15, D22S1045 17, D2S441 12, D2S441 12.3, D7S820 11, D8S1179 13, TH01 6 and Vwa 20. Performance metrics revealed an adjusted R2 of 0.945 with a p value < 0.0001. **Conclusion:** Expected KRAS G12C mutation frequencies can be calculated based on population identification markers. Successively, the role of population composition and ancestries is suggested as having a pivotal role in determining specific NSCLC disease genotypes.

Keywords: Non Small Cell Lung Cancer, Population markers, KRAS G12C

P70.09 NOTCH1 Mutations in East Asian Patients With Non-Small-Cell Lung Cancer

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Introduction: NOTCH1 is a class I transmembrane (TM) protein which directly transduce extracellular signal into gene expression changes which function as ligand activated transcription factors. Interaction of the receptor with D like and Jagged ligands expressed on the surface of neighboring cells initiate NOTCH1 signal. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring NOTCH1 mutations. **Methods:** A total of 976 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of NOTCH1 mutations and other genes were detected by next generation sequencing. **Results:** NOTCH1 gene mutation rate was 4.41% (43/976) in non-small cell lung cancer, including Y1738N(1 patient), A2256V(1 patient), M2318T(1 patient), P1257L(1 patient), S1140Afs*39(1 patient), N1460I(1 patient), V874G(1 patient), M2363I(1 patient), R1758H(1 patient), V2007M(1 patient), N41I(1 patient), N2248I(1 patient), R1662Q(1 patient), C768Y(1 patient), P1731L(2 patients), L1593P(1 patient), R79L(1 patient), D573A plus D1880N(1 patient), A2256V(1 patient), Y202S(1 patient), D388N(1 patient), A1418T(1 patient), C1363G(1 patient), V354E(1 patient), T445M(1 patient), A208T(1 patient) (1 patient), R2104H(1 patient), E1294*(1 patient), R1991H(2 patients), R203H(1 patient), T2132M(1 patient), G925Afs*254(1 patient), Y1738N(1 patient), P460Q(1 patient), R1991Pfs*9(1 patient), T1079Pfs*23(1 patient), V1307I(1 patient), M2318T(1 patient), G1437W(1 patient), E455K(1 patient) and V1750M, and median overall survival (OS) for these patients was 26.0 months. Among them, all patients were NOTCH1 gene with co-occurring mutations. Briefly, patients with (n=6) or without (n=37) co-occurring EGFR mutations had a median OS of 26.0 months and 16.0 months respectively (P=0.26); patients with (n=31) or without (n=12) co-occurring TP53 mutations had a median OS of 26.0 months and not up to now respectively (P=0.60); patients with (n=11) or without (n=32) co-occurring KRAS mutations had a median OS of not up to now and 16.0 months respectively (P=0.08); patients with (n=9) or without (n=34) co-occurring NF1 mutations had a median OS of not up to now and 26.0 months respectively (P=0.97). **Conclusion:** EGFR, TP53, KRAS, NF1 gene accompanied may have less correlation with NOTCH1 mutation in NSCLC patients. We report different mutations than those previously reported, which emphasizes the importance of personalized medicine that could be empowered by the use of bioinformatics tools in the diagnostic process and therapeutic approaches.

Keywords: non-small-cell lung cancer, NOTCH1 mutation, prognosis

P70.10 Prevalence of KRAS and Concomitant Mutations in Advanced Lung Adenocarcinoma Patients

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Introduction: One of the most frequently mutated oncogenes in cancer belongs to the Ras family of proto-oncogenes and encodes distinct key signalling events. RAS gain-of-function mutations are present in ~30% of all human cancers, where KRAS is the most frequent mutated isoform being altered in different cancer types including lung cancer. This study aims to analyse, retrospectively, the incidence of KRAS mutations, with emphasis in the evaluation of G12C mutations and the presence of KRAS concomitant mutations. **Methods:** In this retrospective study, we analysed genomic DNA extracted from paraffin embedded tumour tissues from 121 Brazilian advanced lung adenocarcinoma patients in order to evaluate via Next Generation Sequencing (NGS) the incidence of KRAS mutations and correlate, when possible, to clinicopathological characteristics such as sex. The prevalence of co-occurring mutations alongside KRAS was also investigated. Statistical analysis was performed to investigate the association between mutation status, mutation types and sex. **Results:** There was a prevalence of male (N= 63; 54.8%) in comparison to female (N= 52, 45.2%) patients in our cohort. KRASwas mutated in 20.86% (24/115) of all samples. Of the total number of KRAS mutants (N=24), G12D (N= 6; 24%) was the most frequent mutation type, whereas G12C came in third place alongside G12A (N=3; 12,5%). Interestingly, 33,3% of the mutant KRAS samples showed other co-occurring mutations. There was no significant association with sex. **Conclusion:** This study further confirms the prevalence of the most frequent KRAS mutations in advanced lung cancer and reveals the presence of rare concomitant mutations alongside KRAS. Further investigation on the importance of these concurrent genomic alterations in patient prognosis and treatment response is warranted.

Keywords: KRAS, advanced lung adenocarcinoma, concomitant mutations

P70.11 Prevalence and Clinicopathological Characteristics of ARID1A Mutations in East Asian Patients With Non-Small Cell Lung Cancer

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Introduction: The AT-rich interacting domain-containing protein 1A gene (ARID1A) encodes ARID1A, a member of the SWI/SNF chromatin remodeling complex. Notably, ARID1A is mutated in over 50% of ovarian clear cell carcinomas and 30% of ovarian endometrioid carcinomas. ARID1A mutation is a known genetic driver of ovarian cancer. However, the role of ARID1A in the angiogenesis of human non-small cell lung cancer (NSCLC) remains unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring ARID1A mutations **Methods:** A total of 234 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of ARID1A mutations and other genes were detected by next generation sequencing. **Results:** ARID1A gene mutation rate was 2.56% (6/234) in non-small cell lung cancer, including Q909*(1 patient), S634*(1 patient), E1104*(1 patient), H1384Tfs*97(1 patient), S1791L(1 patient) and G1711A plus Q611*(1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, all patients were ARID1A gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=4) co-occurring ALK mutations had a median OS of 23.0 months and 11.0 months respectively (P=0.35); patients with (n=2) or without (n=4) co-occurring BRCA2 mutations had a median OS of 23.0 months and 11.0 months respectively (P=0.35); patients with (n=3) or without (n=13) co-occurring SMARCA4 mutations had a median OS of 23.0 months and 11.0 months respectively (P=0.35); patients with (n=2) or without (n=4) co-occurring KEAP1 mutations had a median OS of 18.0 months and 16.0 months respectively (P=0.73). **Conclusion:** Our data reveal ARID1A mutations represent a distinct subset of NSCLC, and improved understanding of the implications of ARID1A aberrations is critical for the identification of therapeutic target candidates.

Keywords: non-small-cell lung cancer, prognosis, ARID1A mutation

P70.12 NTRK Gene Fusion in Advanced Non Small Cell Lung Cancer at Pham Ngoc Thach Hospital - Viet Nam

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Introduction: The NTRK gene fusion in lung cancer has been reported in more recent years, although this is a rare genetic alternation. We have conducted research for the following goals: 1. Investigation of the rate of NTRK gene fusion in advanced NSCLC patients. 2. Evaluate the ability to diagnose NTRK gen fusion by IHC compared to NGS. **Methods:** Retrospective research, cross-sectional descriptive statistics. **Results:** General data: - Total number of research cases: 497 cases advanced NSCLC in 2020 - All researched cases have been diagnosed at hospital admission have not received specific treatment (chemotherapy, targeted therapy, immunotherapy ect.) - Male: 283 cases (56.94%) - Female: 214 cases (43.06%) - Average age: 58.35 ± 6.89 years - Patients with smoking: 207 cases (41.65%) - Number of cases with NTRK gene fusion, those have been diagnosed: IHC: 18 cases (3,62%) - NGS: 18 cases (3,62%) Histological distribution in NSCLC and associated expression of NTRK genes: - Adenocarcinoma: 386 cases [11 cases NTRK (+)] - Squamous cell carcinoma: 59 cases [3 cases NTRK (+)] - Adonosquamous carcinoma: 28 cases [1 case NTRK (+)] - Large cell carcinoma: 15 cases [2 cases NTRK (+)] - Carcinoma is not classified as NOS: 9 cases [1 case NTRK (+)] Distribution of NTRK gene fusion have expressioned on adenocarcinoma type: - Leipidic adenocarcinoma: 2 cases - Papillary adenocarcinoma: 1 case - Acinar adenocarcinoma: 4 cases - Micro-papillary adenocarcinoma: 1 case - Solid adenocarcinoma: 2 cases - Adenocarcinoma, poorly differentiated: 1 case Comments: - The rate of expression of the NTRK gene fusion in NSCLC at PNTH: 3.62% (Equivalent to other researches on the world (P = 0.0589 - 0.1564 > 0.05) - The rate of expression of NTRK gene fusion on adenocarcinoma is highest (11/18 cases # 61.11%), similar to other researches on the world (P = 0.0775 - 0.2513 > 0, 05) - Distribution of NTRK gene fusion on adenocarcinoma has differenced among histological types: acinar adenocarcinoma has the highest rate (4/11 cases # 36.36%) - Similarity between diagnosis with IHC & NGS: 100% (No false positives or false positives) **Conclusion:** Currently in NSCLC, the diagnostic NTRK gene fusion has many methods: IHC, FISH, RT-PCR, NGS in which NGS is the most supported technique due to detection of most NTRK lines. However, there are still difficulties in diagnosis due to many factors: professional experience, equipment, Test-Kit ect. IHC with specific markers shows high similarity to NGS. So in the future, can it be used this diagnostic method to indicate NTRK TKIs or not? Feasibility studies are still waiting for diagnostic tests and drugs to treat NTRK Gene Fusion.

Keywords: NTRK Gene Fusion, IHC: Immunohistochemistry, FISH: Fluorescence In Situ Hybridization, RT-PCR: RealTime Polymerase chain reaction, NGS: Next Generation Sequencing

P70.13 Different Types of ERBB3 Mutations in Chinese Non-Small Cell Lung Cancer Patients

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Introduction: HER3, a member of the EGFR family of receptor tyrosine kinases coded by the ERBB3 gene, plays an important role in cancer, despite its lack of intrinsic kinase activity. As with genes coding for potential heterodimeric partners of HER3, EGFR, and HER2, oncogenic mutations of ERBB3 have been explored by several studies. The prevalence of these mutations in non-small-cell lung cancer (NSCLC) is unknown. The aim of this study is to investigate mutations and prognosis of NSCLC harboring ERBB3 mutations. **Methods:** A total of 1402 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of ERBB3 mutations and other genes were detected by next generation sequencing. **Results:** ERBB3 gene mutation rate was 1.14% (16/1402) in non-small cell lung cancer, including D297N (1 patient), L841I (1 patient), R833G (1 patient), V653I (1 patient), R81Efs*3 (1 patient), R391L (1 patient), D1155E (1 patient), G994S (1 patient), Q849R (1 patient), C246* (1 patient), R1125W (1 patient), R541Q (1 patient), P276H (1 patient), L841I (1 patient), A232V (1 patient) and C327S (1 patient), and median overall survival (OS) for these patients was 17.0 months. Among them, all patients were ERBB3 gene with co-occurring mutations. Among them, all patients were ERBB3 gene with co-occurring mutations. Briefly, patients with (n=5) or without (n=11) co-occurring EGFR mutations had a median OS of not up to now and 17.0 months respectively (P=0.90); patients with (n=13) or without (n=3) co-occurring TP53 mutations had a median OS of 17.0 months and 14.5 months respectively (P=0.88); patients with (n=5) or without (n=11) co-occurring KRAS mutations had a median OS of 3.0 months and not up to now respectively (P=0.04); patients with (n=3) or without (n=13) co-occurring BRCA2 mutations had a median OS of 17.0 months and not up to now respectively (P=0.74). **Conclusion:** KRAS accompanied mutations might play a good prognosis in ERBB3 gene mutation NSCLC. Our results show that ERBB3 mutations delineate an aggressive subtype of lung cancer for which a targeted treatment through ERBB3 inhibition might offer new opportunities.

Keywords: prognosis, non-small-cell lung cancer, ERBB3 mutation

P70.14 PRKDC Mutations Recurrently Found in Non-Small Cell Lung Cancer in East Asian Patients

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Introduction: Protein kinase, DNA-activated, catalytic polypeptide (PRKDC) encodes a 465 kDa catalytic subunit of DNA-dependent protein kinase (DNA-PKcs) that plays a pivotal role in the maintenance of genomic stability and is a critical component of DNA double-strand break repair and recombination. Because of the rarity of those mutations, associated clinical features and prognostic significance have not been thoroughly described so far. The aim of this study is to investigate mutations and prognosis of NSCLC harboring PRKDC mutations. **Methods:** A total of 328 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of PRKDC mutations and other genes were detected by next generation sequencing. **Results:** PRKDC gene mutation rate was 1.22% (4/328) in non-small cell lung cancer, including D3411N(1 patient), D2724H(1 patient), M4002L(1 patient) and A1634T(1 patient), and median overall survival (OS) for these patients was 14.0 months. Among them, all patients were PRKDC gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=2) co-occurring BCOR mutations had a median OS of 15.5 months and 22.0 months respectively (P=0.64); patients with (n=2) or without (n=2) co-occurring TP53 mutations had a median OS of 12.5 months and 19.0 months respectively (P=0.23); patients with (n=2) or without (n=2) co-occurring ARID1A mutations had a median OS of 17.5 months and 14.0 months respectively (P=0.81); patients with (n=2) or without (n=2) co-occurring KRAS mutations had a median OS of 12.5 months and 19.0 months respectively (P=0.23). **Conclusion:** BCOR, TP53, ARID1A, KRAS gene accompanied may have less correlation with PRKDC mutation in NSCLC patients. Next generation sequencing provides a simplified strategy and reasonably high detection rate for PRKDC mutation, which suggested application of the strategies into clinical molecular diagnostics.

Keywords: prognosis, non-small-cell lung cancer, PRKDC mutation

P70.15 Mutational Subtypes and Prognosis of East Asian Non-Small-Cell Lung Cancer Harboring NF2 Mutations

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Introduction: Neurofibromatosis type 2 (NF2) is an autosomal-dominant disorder caused by mutations in the NF2 gene and predisposing to the development of nervous system. The aim of this study is to investigate mutations and prognosis of NSCLC harboring NF2 mutations. **Methods:** A total of 411 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of NF2 mutations and other genes were detected by next generation sequencing. **Results:** NF2 gene mutation rate was 1.70% (7/411) in non-small cell lung cancer, including S138F(1 patient), N563D(1 patient), E530*(1 patient), E392*(1 patient), W74*(1 patient), C300S(1 patient) and E260*(1 patient), and median overall survival (OS) for these patients was 14.0 months. Among them, all patients were NF2 gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=5) co-occurring PTPRD mutations had a median OS of 17.0 months and 14.0 months respectively (P=0.99); patients with (n=2) or without (n=5) co-occurring CIC mutations had a median OS of not up to now and 14.0 months respectively (P=0.27); patients with (n=2) or without (n=5) co-occurring APC mutations had a median OS of 18.5 months and 14.0 months respectively (P=0.44); patients with (n=2) or without (n=5) co-occurring ERBB4 mutations had a median OS of 17.0 months and 14.0 months respectively (P=0.99). **Conclusion:** NF2 oncogenic activation through mutation defines a novel and distinct subset of NSCLC. Targeted therapy may be considered as a possible treatment for carriers of the mutation. PTPRD, CIC, APC, ERBB4 gene accompanied may have less correlation with NF2 mutation in NSCLC patients.

Keywords: prognosis, NF2 mutation, non-small-cell lung cancer

P70.16 Epidemiological Study of FGFR3 Mutations Among Non-Small Cell Lung Cancer Patients in China

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Introduction: Fibroblast growth factor receptors (FGFR) are transmembrane kinase proteins with growing importance in cancer biology given the frequency of molecular alterations and vast interface with multiple other signaling pathways. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer harboring FGFR3 mutations. **Methods:** A total of 976 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of FGFR3 mutations and other genes were detected by next generation sequencing. **Results:** FGFR3 gene mutation rate was 1.23% (12/976) in non-small cell lung cancer, including Q29H (1 patient), G65R (1 patient), Q95K (1 patient), A169S (1 patient), S249C (1 patient), N262T (1 patient), W287delinsIVGL (1 patient), V291M (1 patient), V329I (1 patient), T450M (1 patient), D512V (1 patient) and D513N (1 patient), and median overall survival (OS) for these patients was 21.0 months. Among them, all patients were FGFR3 gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=9) co-occurring EGFR mutations had a median OS of 11.0 months and 23.0 months respectively (P=0.07); patients with (n=3) or without (n=9) co-occurring KRAS mutations had a median OS of 9.0 months and 21.0 months respectively (P=0.13); patients with (n=2) or without (n=10) co-occurring ATM mutations had a median OS of 17.0 months and 21.0 months respectively (P=0.54); patients with (n=2) or without (n=10) co-occurring SMARCA4 mutations had a median OS of 15.0 months and 23.0 months respectively (P=0.19). **Conclusion:** EGFR, KRAS, ATM, SMARCA4 gene accompanied may have less correlation with FGFR3 mutation in NSCLC patients. The findings of this study could facilitate both clinical trial design and therapeutic strategies.

Keywords: FGFR3 mutation, non-small-cell lung cancer, prognosis

P70.17 Molecular Characteristics and Prognosis TERT Mutations in East Asian Non-Small-Cell Lung Cancer Patients

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Introduction: Mutations in the TERT promoter (TERTp) are a common mechanism of TERT reactivation in many solid cancers, The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring TERT promoter mutations. **Methods:** A total of 429 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of TERT promoter mutations and other genes were detected by next generation sequencing. **Results:** TERT gene promoter mutation rate was 3.73% (16/429) in non-small cell lung cancer, including c.-58-u5858A>T plus c.-58-u6149C>T(1 patient), c.-58-u6149C>T(1 patient), c.-58-u533T>G(1 patient), c.58-u66C>A plus c.-58-u3358G>A(1 patient), c.-58-u3363G>T(1 patient), c.-58-u2785C>T plus c.-58-u2257C>T(1 patient), c.-58-u760T>A(1 patient), c.-58-u4217G>C plus c.-58-u2692G>A plus c.-58-u1597G>A(1 patient), c.-58-u1324T>C(1 patient), c.-58-u900C>T(1 patient), c.-59-u5461C>G plus c.-58-u5438C>G plus c.-58-u5427C>T(1 patient), c.-58-u1160C>T(1 patient), c.-58-u6544G>A(2 patients), and c.-58-u66C>T(2 patients), and median overall survival (OS) for these patients was 18.5 months. Among them, all patients were TERT gene with co-occurring mutations. Briefly, patients with (n=7) or without (n=9) co-occurring TP53 mutations had a median OS of 8.0 months and 18.0 months respectively (P=0.04); patients with (n=3) or without (n=13) co-occurring PTPRT mutations had a median OS of not up to now and 18.0 months respectively (P=0.67); patients with (n=3) or without (n=13) co-occurring STK11 mutations had a median OS of not up to now and 18.0 months respectively (P=0.90); patients with (n=3) or without (n=13) co-occurring ARID1A mutations had a median OS of 12.0 months and 18.0 months respectively (P=0.30). **Conclusion:** TERT gene promoter mutation represent a distinct subset of NSCLC. Next generation sequencing showed that TERT mutations commonly co-existed with other driver genes. Our finding expands the mutant spectrum of TERT gene and adds new understanding of the phenotype.

Keywords: TERT mutation, non-small-cell lung cancer, prognosis

P70.18 Distribution of GNAS Mutations in Chinese Patients With Non-Small Cell Lung Cancer

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Introduction: G protein αs (GNAS) mediates receptor-stimulated cAMP signalling, which integrates diverse environmental cues with intracellular responses. GNAS is mutationally activated in multiple tumor types, although its oncogenic mechanisms remain elusive. The aim of this study is to investigate mutations and prognosis of NSCLC harboring GNAS mutations. **Methods:** A total of 864 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of GNAS mutations and other genes were detected by next generation sequencing. **Results:** GNAS gene mutation rate was 1.27% (11/864) in non-small cell lung cancer, including M139I(1 patient), R265H(1 patient), R506Q(1 patient), A331V(1 patient), R201H(1 patient), L156P(1 patient), H41R(1 patient), Q286K(1 patient), Q237H(1 patient), R206G(1 patient) and G334S(1 patient), and median overall survival (OS) for these patients was 23.0 months. Among them, all patients were GNAS gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=8) co-occurring EGFR mutations had a median OS of 26.5 months and 11.0 months respectively (P=0.08); patients with (n=6) or without (n=5) co-occurring TP53 mutations had a median OS of 11.5 months and not up to now respectively (P=0.12); patients with (n=4) or without (n=7) co-occurring KEAP1 mutations had a median OS of 7.5 months and 23.0 months respectively (P=0.32); patients with (n=2) or without (n=9) co-occurring CIC mutations had a median OS of 16.5 months and 23.0 months respectively (P=0.04). **Conclusion:** CIC accompanied mutations might play a good prognosis in GNAS gene mutation NSCLC. Results of ongoing studies will provide a platform for further research to offer individualized therapy with the purpose of improving outcomes.

Keywords: prognosis, non-small-cell lung cancer, GNAS mutation

P70.19 Clinicopathologic Characteristics of Patients with LRP1B Mutations in Chinese Non-Small Cell Lung Cancer Patients

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Introduction: The low-density lipoprotein receptor-related protein 1B (LRP1B), which encoding endocytic LDL-family receptor, is among the top 10 significantly mutated genes in human cancer. It has been demonstrated that LRP1B could bind to multiple extracellular ligands. Frequently inactivationmutation of LRP1B was observed in melanoma, lung cancer, esophagus squamous-cell carcinoma, head and neck squamous cancer, gastric cacner, and so on. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer (NSCLC) harboring LRP1B mutations. **Methods:** A total of 217 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of LRP1B mutations and other genes were detected by next generation sequencing. **Results:** LRP1B gene mutation rate was 11.98% (26/217) in non-small cell lung cancer, including C922Y(1 patient), R1857K plus W1622L(1 patient), R1388I(1 patient), C4415S plus S2164*(1 patient), V751M(1 patient), H564Q plus P2218Q(1 patient), T1091A(1 patient), S977I(1 patient), S983N(1 patient), E1327*(1 patient), D1365Y(1 patient), E1229K(1 patient), D951Y(1 patient), G873V(1 patient), I1892L(1 patient), R4120K(1 patient), I719N(1 patient), C2182* plus P1539H(1 patient), R1278T plus S2974L(1 patient), Y750D plus I3898M (1 patient), C180F (1 patient), C2182S(1 patient), D1162N(1 patient), W1665* plus P3761H(1 patient), P4313Q(1 patient) and H302N(1 patient), and median overall survival (OS) for these patients was 19.0 months. Among them, all patients were LRP1B gene with co-occurring mutations. Briefly, patients with (n=18) or without (n=8) co-occurring TP53 mutations had a median OS of 19.0 months and 18.5 months respectively (P=0.61); patients with (n=2) or without (n=24) co-occurring KRAS mutations had a median OS of 18.8 months and 19.3 months respectively (P=0.78); patients with (n=3) or without (n=23) co-occurring PIK3CA mutations had a median OS of 21.0 months and 17.0 months respectively (P=0.92); patients with (n=3) or without (n=23) co-occurring APC mutations had a median OS of 15.5 months and 8.0 months respectively (P=0.67). **Conclusion:** LRP1B gene mutation coexists with other gene mutation in NSCLC. LRP1B gene mutation may define a subset of patients with lung cancer appropriate for immunotherapeutic strategies.

Keywords: prognosis, LRP1B mutation, non-small-cell lung cancer

P70.20 Impact of KRAS and Co-occurring Mutations on NSCLC Master Regulator Network as Determined by Computational Omics Biology Model.

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Introduction: KRAS is a frequent oncogenic driver in solid tumors, including Non-Small Cell Lung Cancer (NSCLC). KRAS is involved in various signaling pathways that could allow for targeting of KRAS by targeting downstream key transcription factors that mediate oncogene signaling. At the same time, co-occurrence of other mutations alters the signaling pathways and the key transcription factors involved in the disease network. The convergence of these dysregulated pathways to activate key kinases and transcription factors defines master regulators, forming the regulatory logic (i.e. oncotecture) of the tumor cell that maintains the malignant phenotype, its hallmark behaviors, and homeostasis in the face of treatment, while also providing a new set of potential therapeutic targets. In this study, we describe the impact of KRAS and a variety of co-mutations on the tumor's oncotecture. **Methods:** 248 NSCLC patients with KRAS mutations were selected from TCGA: 110 had only KRAS mutations, 138 had co-occurrence of other mutations: EGFR 55, MET 44, and PIK3CA 39. Mutation and CNV from each case served as input for the Cellworks Computational Omics Biology Model (CBM) to generate a patient-specific protein network map from PubMed and other resources. Disease-biomarkers unique to each patient were identified within protein network maps. The CBM identified the top 25 master regulators for each patient. We calculated the frequency of occurrence of each of the selected master regulators for KRAS alone and KRAS with other mutation co-occurrences. **Results:** Comparative networks analyses of KRAS alone and KRAS with another mutation were performed. We identified that FOXM1, IKBKB, PLK1, PAK1, MTOR, AURKA, PIK3CA, CSNK2A1 function as master regulators in more than 70% of KRAS-only mutated cancers (Table 1). When co-mutations were present, the master regulator network was upregulated, e.g.: (1) MET: RPS6KA3, STAT3, NEK2 (2) EGFR: NFKB1, CEBPA, NEK2 (3) PIK3CA: SRPK1, GLI2, AKT

Table 1: KRAS mutation and co-mutations with EGFR, MET, and PIK3CA impact the master regulator network.

Master Regulators	KRAS	KRAS + MET	(KRAS + MET) - KRAS	KRAS + EGFR	(KRAS + EGFR) - KRAS	KRAS + PI3K	(KRAS + PI3K) - KRAS
AKT	3.6%	12.6%	10.0%	7.3%	3.6%	26.4%	70.7%
AP1	35.5%	50.0%	14.5%	50.9%	15.3%	17.9%	17.5%
ATF4	28.2%	50.0%	21.8%	61.8%	33.6%	82.1%	53.9%
AURKA	75.5%	88.6%	13.2%	68.1%	6.4%	20.5%	54.9%
AURKB	69.1%	61.4%	7.7%	69.1%	0.0%	62.5%	7.6%
CDK5	3.6%	26.4%	22.7%	27.3%	23.6%	2.6%	1.1%
CEBPA	22.7%	20.5%	2.3%	60.0%	37.3%	7.7%	15.0%
CSNK2A1	74.5%	84.1%	9.3%	23.8%	52.7%	10.2%	64.3%
E2F1	65.5%	97.7%	32.3%	98.2%	32.7%	96.9%	29.4%
ELK1	2.7%	0.0%	2.7%	1.8%	0.9%	0.0%	2.7%
ESR1	30.9%	43.2%	12.3%	58.2%	27.3%	48.7%	17.8%
FOXM1	73.6%	88.6%	15.0%	94.5%	20.9%	97.4%	23.8%
GLI1	74.5%	93.2%	18.6%	94.5%	20.0%	96.9%	20.3%
GLI2	21.8%	56.8%	35.0%	52.7%	30.9%	92.3%	70.5%
GLI3	0.0%	11.4%	11.4%	14.5%	14.3%	2.6%	2.6%
HIF1A	54.5%	70.5%	15.9%	36.4%	18.2%	84.6%	30.1%
HK2	60.0%	81.8%	21.8%	1.8%	58.2%	7.7%	52.3%
IKBKB	72.6%	93.2%	19.5%	89.1%	15.3%	100.0%	26.4%
ILK	24.5%	43.2%	18.6%	3.6%	20.9%	10.3%	14.3%
JUN	60.0%	77.3%	17.3%	81.8%	21.8%	97.4%	37.4%
MAFK_NFE2L2	3.6%	0.0%	3.6%	0.0%	3.6%	2.6%	1.1%
MAP2K1	12.7%	4.5%	8.2%	7.3%	5.5%	2.6%	10.2%
MAP3K8	10.9%	29.5%	18.6%	10.9%	0.0%	30.8%	19.9%
MAPK8	19.1%	52.3%	33.2%	45.5%	26.4%	41.0%	21.9%
MECOM	2.7%	0.0%	2.7%	1.8%	0.9%	0.0%	2.7%
MTOR	72.7%	95.5%	22.7%	70.9%	1.8%	64.1%	8.6%
MYC	0.9%	20.5%	19.5%	10.9%	10.0%	2.6%	1.7%
NEK2	11.8%	54.5%	42.7%	58.2%	46.4%	25.6%	13.8%
NFKB1	26.4%	50.0%	23.6%	60.0%	33.6%	59.0%	32.6%
PAK1	75.5%	90.9%	15.5%	72.7%	2.7%	84.6%	9.2%
PIK3R3	27.3%	43.2%	15.9%	1.8%	25.5%	0.0%	27.3%
PIM1	52.7%	79.5%	26.8%	21.8%	30.9%	25.6%	27.1%
PIK3CA	74.5%	81.8%	7.3%	36.4%	38.2%	28.2%	46.3%
PIK3CB	5.5%	15.9%	10.5%	10.9%	5.5%	0.0%	5.5%
PIK3CD	18.2%	27.3%	9.1%	47.3%	29.1%	30.8%	12.6%
PLK1	90.9%	77.3%	13.6%	25.5%	65.5%	2.6%	88.3%
PRKCA	14.5%	20.5%	5.9%	10.9%	3.6%	2.6%	12.0%
PRKCE	57.3%	86.4%	29.1%	36.4%	20.9%	35.9%	21.4%
PRKCI	59.1%	81.8%	22.7%	18.2%	40.9%	41.0%	18.1%
PRKCQ	25.5%	52.3%	26.8%	36.4%	10.9%	23.1%	2.4%
PRKCZ	9.1%	13.6%	4.3%	10.9%	1.8%	28.2%	19.1%
PRKG1	14.5%	45.5%	23.6%	21.8%	0.0%	7.7%	14.1%
ROCK1	65.5%	88.6%	23.2%	49.1%	16.4%	17.9%	47.5%
RPS6KA3	36.4%	72.7%	36.4%	67.2%	30.9%	92.3%	55.9%
SIK2	0.9%	9.1%	8.2%	0.0%	0.9%	33.3%	32.4%
SNAI1	21.8%	4.5%	17.3%	25.5%	3.6%	43.6%	21.8%
SNAI2	2.7%	0.0%	2.7%	0.0%	2.7%	0.0%	2.7%
SOX2	14.5%	34.1%	19.5%	12.7%	1.8%	17.9%	3.4%
SRC	6.4%	4.5%	1.8%	5.5%	0.9%	2.6%	3.8%
SRPK1	11.8%	20.5%	8.6%	10.9%	0.9%	71.8%	60.0%
STAT3	19.1%	61.4%	42.3%	29.1%	10.0%	17.9%	1.1%
TP53	23.6%	20.5%	3.2%	18.2%	5.5%	35.9%	12.3%
TWIST1	5.5%	18.2%	12.7%	23.6%	18.2%	2.6%	2.9%
YES1	16.4%	18.2%	1.8%	12.7%	3.6%	5.1%	11.2%
ZEB1	20.9%	18.2%	2.7%	14.5%	6.4%	28.2%	7.3%

Conclusion: The Cellworks CBM can reveal transcription factor addiction by identifying the convergence points of numerous upstream dysregulated pathways. These master regulators reveal another set of potential treatment vulnerabilities or Achilles heels in the network that can inform specific treatment options. This study identifies the key transcriptional mediators of KRAS mutations and how they are shuffled by the presence of co-mutations in other common oncogenes. The CBM biosimulation platform identifies the regulatory network in the cancer laying the foundation for new therapeutic strategies targeting key master regulators.

Keywords: Cancer Therapy Biosimulation, Multi-omics Therapy Biosimulation, Personalized Cancer Therapy

P71.01 Targeting HSPA1A in ARID2-Deficient Lung Adenocarcinoma

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Introduction: Chromatin remodeling is known to play important roles in multiple physiological as well as pathological settings. Conserved from yeast to human, the SWI/SNF complex, as the essential components of chromatin remodelers, is involved in cell differentiation, proliferation and DNA repair process. BAF and PBAF are two variant forms of the SWI/SNF chromatin-remodeling complex. These two forms share many subunits but have also subtype specific subunits: BAF250 and hBRM are only found in BAF, whrereas BAF180 and BAF200 only found in PBAF. BAF200, encoded by ARID2, is required for the function and selectivity of PBAF. ARID2 is listed as one of the most frequently mutated genes after TP53, KRAS, EGFR, CDKN2A and STK11 (or LKB1) with an inactivating mutation rate about 7.3% in lung adenocarcinoma (LUAD), the major subtype of lung cancer. However, the contribution of ARID2 to the malignant progression of LUAD remains largely uncharacterized.
Methods: By using $Kras^{G12D}$-based de novo genetically engineered murine models as well as non-small cell lung cancer cell lines, we provided substantial evidence supporting that ARID2 deficiency significantly promoted lung cancer malignant progression. Both in vitro and in vivo data clearly demonstrated a tumor suppressive role for ARID2 in lung cancer. In an attempt to search for the molecular events involved in mediating the effect of ARID2 knockout, we performed the ChIP-Seq and RNA-Seq, and found that HSPA1A is up-regulated by ARID2 loss. By using ChIP-PCR and luciferase reporter assay, we found that ARID2 negatively regulated HSPA1A expression through binding to its promoter region. The potential link between ARID2 and HSPA1A is further supported by human lung cancer specimen analyses. To determine whether HSPA1A is required for mediating the phenotype of ARID2 deficiency, we inhibited HSPA1A expression genetically and pharmacologically. Notably, both genetic knockdown and pharmacologic inhibition of HSPA1A greatly dampened the malignant progression of ARID2-deficient lung cancer in allograft assays and genetically engineered murine model, whereas without significant impact upon the proliferation and/or apoptosis in ARID2-WT cancer cells. **Results:** We find that ARID2 expression is decreased during the malignant progression of both human and mice LUAD. Using two $Kras^{G12D}$-based genetically engineered murine models (GEMM), we demonstrate that ARID2 knockout significantly promotes lung cancer malignant progression and shortens the overall survival. Consistently, ARID2 knockdown significantly promotes cell proliferation in human and mice lung cancer cells. Through integrative analyses of ChIP-Seq and RNA-Seq data, we find that HSPA1A is up-regulated by ARID2 loss. Knockdown of HSPA1A specifically inhibits malignant progression of ARID2-deficient but not ARID2-WT lung cancers in both cell lines as well as animal models. Treatment with HSPA1A inhibitor could significantly inhibit the malignant progression of lung cancer with ARID2 deficiency. **Conclusion:** Our findings establish ARID2 as an important tumor suppressor in LUAD with novel mechanistic insights, and further identify HSPA1A as a potential therapeutic target in ARID2-deficient LUAD.

Keywords: Lung adenocarcinoma, ARID2, HSPA1A

P71.02 Molecular and Cellular Dynamics of Drug-Tolerant Persister (DTP) Cells During Osimertinib Therapy in EGFR Mutant Lung Adenocarcinoma

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Introduction: The acquisition of drug resistance to molecular targeted therapies is a major obstacle in the treatment of EGFR mutant lung cancer. One proposed mechanism to develop resistance to EGFR-tyrosine kinase inhibitor (TKI) involves subpopulations of tumor cells to enter a drug-tolerant persister (DTP) state while on the therapy, leading to eventual acquisition of diverse resistance mechanisms. Thus, understanding and targeting this mechanism may provide a therapeutic opportunity to prevent tumor relapse. However, properties of DTPs, including genetic and transcriptomic architecture and intra-tumor heterogeneity, leading to the generation of DTPs remains unknown. The aim of this study is to investigate key properties and molecular characteristics of DTPs in 2 patient-derived xenograft (PDX) models. **Methods:** DTPs were generated through chronic exposure to osimertinib in a lung adenocarcinoma PDX models with EGFR exon-19 deletion and exon-19 deletion+T790M mutation, respectively. Histological analysis, genomic clonal structure analysis using whole-exome sequencing (WES), transcriptomic analysis with single-cell RNA-seq were conducted on DTPs and compared to pre-treatment baseline (BL) tumors. To examine the reversibility of DTP feature and the detail clonal changes, DTPs were repopulated upon drug discontinuation and the regrowth tumors were compared to BL and DTPs. **Results:** EGFR-mutant PDXs showed significant response to osimertinib. However, all PDX tumors regrew after drug release, indicating EGFR-TKI cannot eradicate EGFR-mutant lung cancer cells. The regrowth tumors consistently showed sensitivity to repeat treatment. Although DTPs exhibited distinct histologic features from BL, with small number of persister tumor cells and significantly increased stromal fibrosis, the histologic findings of regrowth tumors closely resembled the BL, indicating DTPs are phenotypically reversible. WES demonstrated no new known resistant mutations arising in DTPs and regrowth tumors. In genomic clonal structure analysis, dynamic clonal change was not observed across the treatment state and most of genomic subclones observed in BL were retained in DTPs and regrowth tumors. single-cell RNA-sequencing revealed that DTPs consisted of several transcriptomically-defined clusters, with majority of DTPs formed distinct clusters from BL, while some overlapped with BL, demonstrating DTPs are generated through mixed process of transcriptomic reprogramming and clonal selection of pre-existing cells in BL. Regrowth tumors demonstrated mostly overlapped transcriptomic feature with BL tumors, indicating DTPs have reversible biological capacity. **Conclusion:** In EGFR-mutant PDX models, DTPs have phenotypically and transcriptomically reversible feature. Genetic clonal selection does not mainly contribute to the generation of DTP. DTPs consist of transcriptomically heterogeneous subpopulations, and each subclone could potentially survive EGFR-TKI therapy through different molecular mechanisms.

Keywords: Lung adenocarcinoma, EGFR-TKIs, drug tolerant persister

P71.03 A New Combination Therapy for FGFR1-Amplified Lung Cancer

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Introduction: Background: FGFR signaling is frequently deregulated in cancers. Compelling evidence has demonstrated the oncogenic potential of deregulated FGFR signaling in driving tumor growth. In particular, FGFR1 amplifications occur in 10–20% of lung cancer, primarily squamous cell lung carcinoma (SQLC), making FGFR1 the biggest class of "druggable" targets in SQLC. However, FGFR-TKIs as single therapeutics benefit only a small fraction of patients, with reported clinical responses in approximately 11% of FGFR1-amplified NSCLC. While these data support the notion that FGFR alterations are associated with tumor sensitivity to FGFR-TKIs, they also highlight the need to identify complementary targets for combination treatment with FGFR-TKIs. **Methods: Methods:** By exploiting a kinome-wide CRISPR knockout screen, we identify PLK1 as a novel drug target to promote FGFR1-target therapy and endurance in FGFR1-amplified lung cancer. **Results:** Pharmacological combination of FGFR1 with PLK1 inhibitor (BI2536/BI6727) shows synergistic anti-proliferative effects in FGFR1-amplified lung cancer cells. Combination treatment (FGFRi/PLK1i) potently suppresses FGFR1-amplified lung cancer growth in mouse xenograft models. Specifically, in H1703, H520 cell lines xenografts and a PDX model of FGFR1-amplified lung cancer cells, the combination treatment (AZD4547 plus BI2536/BI6727) led to significantly greater inhibition of tumor growth than single agents, while there are no apparent toxicities (monitored by mouse body weights) associated with the drug combination. Accompanying the anti-cancer efficacy, AZD4547/BI2536 or BI6727 combination increased DNA damage (γH2AX) and apoptotic cell death (caspase 3 cleavage) in residual tumors compared to single drugs. **Conclusion:** s: Our results suggest a synergistic combination strategy for the treatment of FGFR1-amplified lung cancer.

Keywords: FGFR, lung cancer, CRISPR-Cas9

P71.04 MiR-1243 Increases Radiosensitivity in EGFR-TKI Resistant Non-Small Cell Lung Cancer Cells

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Introduction: Acquired resistance is an important issue which limits the application of EGFR-TKI in advanced non-small cell lung cancer (NSCLC). Our data showed nearly half of EGFR-mutant patients develop local relapse or limited metastases at disease progression. Previous studies have confirmed the value of radiotherapy in advanced lung cancer patients. EGFR-TKI resistant cells with T790M exhibited enhanced sensitivity to radiation. Studies have shown that microRNAs are involved in DNA damage repair mechanisms and thus affect the sensitivity of radiotherapy. Therefore, it is important to explore the detailed mechanism on miRNAs regulating radiosensitivity in EGFR-TKI resistant NSCLC. **Methods:** We performed miRNA microarray to screen miRNAs differentially expressed in the paired gefitinib-sensitivity PC-9 cells and gefitinib-resistant PC-9-GR cells (T790M mutation). Furthermore, we use bioinformatics to screen out target proteins and verify the expression differences of these target proteins. The proliferation of lung cancer cells was determined by CCK-8 assay. Proteins and the phosphorylation of proteins were evaluated by western blot assay. **Results:** Colony formation assay showed PC-9-GR cells were more sensitive to radiation than PC-9 cells. MiRNA microarray showed 156 differentially expressed miRNAs between PC-9 and PC-9-GR cells. miR-1243 was in the top10 differentially expressed miRNAs and it was up-regulated in PC-9-GR cells. Stable knock-down miR-1243 PC-9-GR cells were further constructed using, termed as PC-9-GR-miR1243KD. CCK-8 assay showed similar proliferation kinetics between PC-9-GR and PC-9-GR-miR1243KD. It was found that PC-9-GR-miR1243KD cells showed a significant reduction in clone formation compared with PC-9-GR and PC-9-GR-NC cells after radiation, indicating higher radiosensitivity. Bioinformatics showed miR-1243 may function as a tumor oncogene to regulate apoptosis of gefitinib resistant cell with T790M mutation. SPOCK1 was one of its targeting gene. Western blots showed SPOCK1 was high expression in PC-9-GR-miR1243KD cells. **Conclusion:** This study found novel molecular mechanism might correlate with increase of radiosensitivity in EGFR-TKI resistant NSCLC cells. It could be a new therapeutic strategy for patients in advanced NSCLC to aid expansion of the effectiveness of TKI treatment through radiotherapy.

Keywords: NSCLC, miR-1243, radiosensitivity

P71.05 Use of a Multiscale NSCLC Tumor Heterogeneity Model to Predict Tumor Growth Under Gefitinib

A. L'Hostis, J. Palgen, N. Ceres, E. Peyronnet, A. Perrillat-Mercerot, A. Schneider, M. Margreiter, E. Jacob, R. Kahoul, B. Illigens, M. Hommel, J. Boissel, J. Bosley, C. Monteiro

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Introduction: Novel high-throughput techniques, advanced tumor micro-environment analyses and new insights in tumor cell heterogeneity have significantly increased understanding of regulatory processes in Non-small cell lung cancer (NSCLC): NSCLC treatment response to Gefitinib depends on the epidermal growth factor receptor (EGFR), but differs depending on EGFR gene mutations making clinical prognosis challenging. We therefore developed an in silico EGFR+ lung adenocarcinoma (LUAD) model to predict the effect of EGFR-related mutations on tumor size in advanced-stage adenocarcinoma patients (IIIb or higher), using a mechanistic representation of tumor evolution, including response to Gefitinib. Tumor heterogeneity, age, gender, initial clinical stage, and smoking status are included as covariates. **Methods:** 5-step in silico model development:
1. Model Building: Pathophysiology of EGFR+LUAD was characterized by extracting biological features and their functional relationships from literature and translating them into ordinary differential equations (ODEs). Mutational burden, EGFR downstream-pathways, tumor growth and heterogeneity, Gefitinib-PK/PD, treatment-induced resistance and clinical outcome were modeled in a computational simulation with 43 variables, 170 parameters and 18 to 83 ODEs reflecting intra-tumor heterogeneity.
2. Calibration: Published spheroid, xenograft and clinical data were used for stepwise calibration.
3. Virtual populations (VPOP): VPOPs were generated for validation and benchmarking respectively, adapting baseline characteristics of a real population.
4. Validation: A VPOP with comparable baseline characteristics was tested against published patient data[1].
5. Benchmarking against a Bayesian reference model[2]: (1) coverage of experimental interquartile range (IQR) with simulated IQR (precision) assesses model fit with experimental data, (2) coverage of simulated IQR with experimental IQR (overlap) assesses model fit with experimental variability. **Results:** Our model computed in silico data comparable to the reference model[2] without use of original data for calibration (Figure 1B.2: experimental vs. simulated, precision of 68%, overlap of 91%). The reference model reported precision of 72% and overlap of 86%.

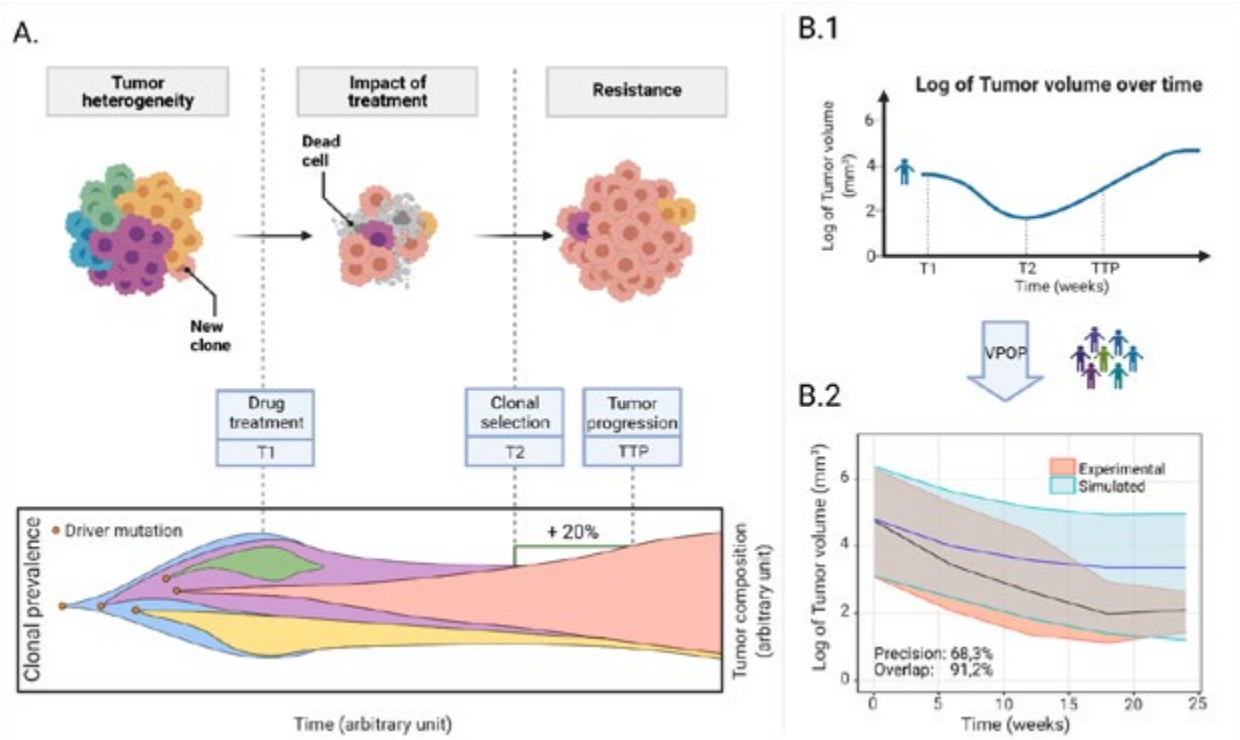

Figure 1: Quantification of tumor progression measured by clonal prevalence and size. Panel A: Tumor growth and heterogeneity. Panel B: Logarithmic tumor volume progression computed (B.1, blue) on the virtual population and compared to the experimental logarithmic tumor volume (orange), assessed by median, first and third quartile as reported[2] (B.2). [Precision=Common_IQR/Experimental_IQR; Overlap=Common_IQR/Simulated_IQR] **Conclusion:** We simulated tumor growth and treatment response in advanced-stage adenocarcinoma patients and successfully validated results with a published study[2]. Access to patient-level data for calibration would have improved precision of our model. References: [1]: Paz-Ares L, et al. 2017 [2]: Nagase M, et al. 2020

Keywords: MechanisticModeling, Benchmark, NSCLC

Workshop Sessions

WS02 EARLY CAREER WORKSHOP
SATURDAY, SEPTEMBER 11, 2021 - 11:30-13:00

WS02.02 How to Maximize Success in Publications for JTO - Writing a Compelling Manuscript

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JTO and JTO CRR are premier journals focusing on thoracic malignancies. The editorial board carefully scrutinize manuscripts to ensure that high quality research, relevant to our readership, is published in the IASLC journals. There are a few key aspects that flag a manuscript for further consideration. With a multitude of submissions, it is critical to catch the editor's interest. The abstract is perfect opportunity to emphasize the key findings of your research. The figures and tables act as visual lures to engage the reader and encourage a more in-depth review. They should help communicate complex findings in a simple and straightforward manner and rouse curiosity to explore the findings in the manuscript. Once the reader's interest is piqued, the author can promote engagement by telling story. Explain what is known, what is not known and what is novel about your research. The introduction is the opportunity to set the stage for your findings and why they should be considered important and publishable. A strong manuscript has succinct and pertinent methods. Editors like to have a good understanding of how the research was done to be able to critically appraise the results. Study design, data collection and statistical methods are necessary components to understand the research validity and need to be clearly linked to the results. The results should be presented in concisely, in scientific language, free of interpretation. Spend time on the figures and tables early in the preparation of the manuscript. Experienced editors and reviewers often go to this section first. Figures and tables should be able to stand alone; the reader should be able to interpret them separately, without relying on the text of the manuscript. The discussion in the manuscript provides the opportunity to interpret the results. In this section the authors help place their results in the context of the current landscape. Connecting your finding to other research helps frame your finding and also interpret the results appropriate. Converge and divergence from the existing knowledge should be discussed and explained so that the importance of your work is clear. With all research there are aspects that cannot be fully addressed. It is important to acknowledge your limitations and resist the temptation to overstate your conclusions. Limitations are not necessarily weaknesses, they show the editor and the reader that the authors have critically appraised their own work. While this is humbling it is also a necessary component and can help fuel the next project of interest. The conclusions of your research should reflect the limitations in the certainty in which they are stated. If you made it past the hurdle of catching the editors' interest and you have received feedback, respond to your reviewers. Remember that the reviewer represents the readership and what questions they might have after considering your research. The feedback is constructive criticism to strengthen your publication. Finally, don't get discouraged if your research does not get accepted to JTO or JTO CRR. There are so many meritorious submissions we cannot publish them all. Use the feedback to make your paper stronger so that you will be successful in your next submission.

WS04.02 Access to Biomarker Testing in Latin America

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Lung cancer kills more people in Latin America (LATAM) than any other malignancy, with rising incidence and mortality rates. There are major differences in lung cancer molecular epidemiology across LATAM countries, with recent studies demonstrating how genetic ancestry, with or without ancestry-specific environmental exposure, affects somatic events in lung cancer.[1,2] A local Native American ancestry risk score was more strongly correlated with EGFR mutation frequency compared with global ancestry correlation.[1] Molecular testing and access to drugs also varies significantly across LATAM countries. Indeed, genomically-guided therapies and immunotherapies have dramatically increased disparities in access to best available care. It is estimated that less than 50% of lung adenocarcinomas are tested for EGFR mutations, ALK fusions and PDL1 expression. Most tests are supplied by pharmaceutical companies. Reasons for not testing include lack of sufficient tissue in up to 30% of the cases, difficulties with logistics, long turn-around time, high cost and limited drug reimbursement.[3] Median time from diagnosis to test request is one month, while turn-around time from test request to results ranges from 7 to 14 days for non-NGS assays, and frequently exceed 40 days for comprehensive genomic profiling, generally performed in the USA. Major challenges for access to biomarker testing in LATAM are summarized in the table below[4,5]:

Cost	Healthcare inequities, socio-economic determinants of health Public system fragmented and under-financed
Logistics	Delayed diagnosis Small tissue and poor quality for NGS Need to send samples abroad Long turn-around time
Lab infrastructure	Limited number of certified labs Lack of resource-stratified and companion diagnostic-specific guidelines
Access to targeted therapies	Complex, slow and cumbersome regulatory system Limited and delayed access to novel therapies and clinical trials
Patient and (bio)medical education	Difficulties interpreting NGS Few molecular tumor board networks Lack of trained personnel and bioinformatics support

In Brazil, the industry-sponsored support program “Lung Mapping” comprises seven pharmaceutical companies working together to provide timely and accurate molecular diagnosis of advanced lung adenocarcinomas in the public and private healthcare settings. Oncologists are able to select from different providers, including a local lab with “fast-track” biomarker results based on non-NGS technology followed by large NGS gene panel, or upfront shipment of the samples abroad for comprehensive genomic profiling, either tissue or liquid biopsies. These biomarker access programs must be linked to national initiatives to promote lab infrastructure, governance, regulation, clinical research and (bio)medical education[5]. Combined effort of the governments and the private health care sector in collaboration with molecular diagnostic companies and the pharmaceutical industry are critical to create a favourable ecosystem and increase access to comprehensive genomic profiling in LATAM. Beyond biomarker prevalence and testing rates, we need to measure the impact of precision medicine in terms of real-world pragmatic actionability, outcomes research and cost-effectiveness analysis[6]. In parallel, the roadmap to lung cancer personalized healthcare in LATAM includes building multi-disciplinary teams that promote medical awareness of molecular diagnosis as fundamental for high-value care and empowering patients to increase accessibility to high-quality testing and accessibility to drugs[5]. References: 1. Carrot-Zhang J, Soca-Chafre G, Patterson N, et al. Genetic Ancestry Contributes to Somatic Mutations in Lung Cancers from Admixed Latin American Populations. Cancer Discov 2021;11(3):591-598 2. Sepúlveda-Hermosilla G, Blanco A, Freire M, et al.

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Keywords: Latin America, Biomarker, lung cancer

WS05 SOUTH/SOUTH-EAST ASIA WORKSHOP: LUNG CANCER DIAGNOSIS AND MANAGEMENT WITH RESOURCE CONSTRAINTS IN SOUTH AND SOUTH-EAST ASIA
SATURDAY, SEPTEMBER 11, 2021 - 20:00-21:30

WS05.03 Treatment of Advanced and Metastatic NSCLC without Oncogenic Drivers: Balancing Cost and Efficacy

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The goals of treatment in advanced non-small cell lung cancer (NSCLC) are survival prolongation, symptom palliation, and improvement of the quality of life. Before immunotherapy era, we had only couple choices of treatment, such as, doublet platinum-based chemotherapy with or without adding bevacizumab or cetuximab then continuation with maintenance therapy. These treatments have been accepted as the standard therapy in the past decades.[1-5] One of the acquired capability of cancer cells is avoiding immune destruction. [6] The immunotherapy has played the crucial role in NSCLC since 2015. In 2021 era, we are able to categorize treatment of advanced NSCLC into 2 specific populations which are targetable driver group and non-oncogenic driver group. Immunotherapy has demonstrated the survival benefits in the latest group either monotherapy or combination with chemotherapy or combination with the other immunotherapies compared to chemotherapy alone according to PD-L1 protein expression. Regarding KETNOTE-024, KEYNOTE-042, IMPOWER-110, and the recent study (EMPOWER-Lung 1), these clinical studies showed the significantly longer overall survival (OS) and progression-free survival (PFS) of single agent immunotherapy over standard doublet platinum-based chemotherapy in PD-L1 high expression (≥ 50%) advanced NSCLC patients.[7-10] However, we noticed from these landmark clinical studies that some of the patients had developed rapid progression of disease during receiving the immunotherapy. Thus, there were the development in combination of immunotherapy and doublet platinum-based chemotherapy to overcome the hyper-progressive disease in these landmark studies (KETNOTE-189, KEYNOTE-407, IMPOWER-130, IMPOWER-150, CHECKMATE-9LA) [11-15] with the hypothesis that chemotherapy could enhance anti-cancer immune response.[16] All of these chemotherapy plus immunotherapy studies demonstrated the significantly better survivals in advanced non-oncogenic driven NSCLC regardless of PD-L1 expression.[11-15] The combination of immunotherapies was also explored in CHECKMATE-227 and KEYNOTE-598. Nivolumab plus Ipilimumab also showed significantly better survival compared to chemotherapy regardless of PD-L1 expression but Pembrolizumab plus Ipilimumab did not show the significant difference in OS compared to chemotherapy alone.[17, 18]

Even though, nowadays we have many choices of first-line treatment in non-oncogenic driven advanced NSCLC, but more drugs come together with more toxicities and more expenses. As one of the physicians in oncology field, we need to balance efficacy, toxicity, and cost of treatment, especially, in the limited budget situation which is one of the key considerations for first-line treatment selection. For example, in developing country like Thailand, we have 3 healthcare schemes which are Civil Servant Medical Benefit Scheme (CSMBS), Social Security Scheme (SSS), and Universal Coverage Scheme (UC).[19] The best public healthcare scheme is CSMBS, followed by SSS, and UC. In Thailand, the majority of our population are under UC system (72%), followed by SSS (21%), and only 7% of population have CSMBS system.[19] UC and SSS patients have faced a lot of limitation of cancer drugs access. Only CSMBS patients could reimburse atezolizumab as the single agent in only 2nd or 3rd- line treatment in non-oncogenic driven lung cancer. UC and SSS patients could not reimburse immunotherapy in every indication and in any line of treatments. The backbone doublet platinum-based chemotherapy +- anti-angiogenesis then +- maintenance therapy are still the available options to consider in the limited budget situation.

Furthermore, even we are in the era of immuno-oncology with the complexity of the microenvironment and the human immune system. The true predictive biomarker should be continued to explore for best patient selection to receive immunotherapy.

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WS06 JOINT IASLC - CAALC - CSCO WORKSHOP: LOOKING TOWARD THE FUTURE: RECOGNIZING AND CURING LUNG CANCER
SATURDAY, SEPTEMBER 11, 2021 - 22:15-23:45

WS06.05 RATIONALE-307: Updated Biomarker Analysis of Phase 3 Study of Tislelizumab Plus Chemo vs Chemo Alone For 1L Advanced Sq-NSCLC

J. Wang[1], S. Lu[2], Z. Wang[3], C. Hu[4], Y. Sun[5], K. Yang[6], M. Chen[7], J. Zhao[8], L. Liang[9], Y. Huo[9], Y. Zhang[9], R. Huang[9], X. Wu[9], X. Ma[9], S.J. Leaw[9], F. Bai[9], Z. Shen[9]

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Introduction: In the RATIONALE-307 trial (NCT03594747), tislelizumab plus platinum-based chemotherapy significantly improved clinical outcomes vs chemotherapy alone in treatment-naïve advanced squamous non-small cell lung cancer (sq-NSCLC). Previously, we showed superior clinical efficacy of tislelizumab plus chemotherapy vs chemotherapy alone regardless of PD-L1 expression (J Clin Oncol 38:2020[suppl; Abstr 9554]) and blood tumor mutational burden (Ann Oncol 2020;31[4]:S754–S840). Here we report the updated biomarker analysis of PD-L1 expression, tissue tumor mutational burden (tTMB) and gene expression profiling (GEP) in baseline tumor samples. **Methods:** Biomarkers were assessed in 360 patients randomized in RATIONALE-307. The association of the above-mentioned biomarkers and progression-free survival (PFS) between and within the two treatment groups was assessed using a stratified Cox proportional hazards model. P-values < 0.05 were considered statistically significant without multiplicity adjustment. **Results:** A total of 263 (73%) randomized patients had evaluable tTMB and 275 (76%) had evaluable GEP. Baseline characteristics were similar to that of the overall study population. PFS benefits of tislelizumab plus chemotherapy vs chemotherapy alone were not associated with tTMB status (Table). Significant treatment-specific differences in PFS were observed in patients with high expression levels of interferon-related genes, including PSMB9, HERC6, OAS2 (Interaction P-value: 0.029, 0.037, 0.025, respectively), etc., and an 18-gene tumor inflammation signature (TIS) (Interaction P-value: 0.001). High TIS score was associated with significantly longer PFS in the tislelizumab plus chemotherapy group, but not in the chemotherapy alone group. The association of TIS score and PFS was independent from PD-L1 and tTMB status. Additional analysis on GEP signatures and genomic alterations, including their association with TIS, PD-L1 expression and clinical efficacy, will be presented. **Conclusion:** This exploratory analysis of RATIONALE-307 is the first Phase 3 trial indicating a strong association between TIS score and clinical benefit of PD-1 blockade plus chemotherapy vs chemotherapy alone in sq-NSCLC. These data support TIS score as a potential predictive biomarker for PD-1 inhibitor response, regardless of PD-L1 and tTMB status.

Table: Association of biomarkers with PFS in tislelizumab plus chemotherapy vs chemotherapy alone treatment groups.

Biomarkers*	N	mPFS, Mo (95% CI) Tislelizumab + chemo vs chemo alone	PFS HR (95% CI)	Interaction P-value
PD-L1 positive	213	7.62 (6.74–11.01) vs 4.96 (4.14–5.59)	0.41 (0.28–0.60)	0.143
PD-L1 negative	136	7.56 (5.68–9.69) vs 5.45 (4.21–6.97)	0.64 (0.40–1.02)	
tTMB-high	131	9.69 (7.59–NR) vs 5.42 (4.17–5.78)	0.44 (0.27–0.72)	0.463
tTMB-low	132	6.90 (5.55–7.69) vs 5.39 (3.71–5.88)	0.57 (0.36–0.91)	
TIS-high†	138	9.79 (65.75–NR) vs 4.17 (4.04–5.55)	0.26 (0.16–0.43)	0.001
TIS-low†	137	6.9 (5.49–7.59) vs 5.78 (4.30–7.43)	0.84 (0.53–1.35)	

*PD-L1 positive: TC ≥ 1%; PD-L1 negative: TC < 1%; tTMB-high: ≥ 10 mutations/Mb; tTMB-low: < 10 mutations/Mb; TIS-high: ≥ median score; TIS-low: < median score.
†18-gene TIS included: TIGIT, CD27, CD8A, PDCD1LG2, LAG3, CD274, CXCR6, CMKLR1, NKG7, CCL5, PSMB10, IDO1, CXCL9, HLA-DQA1, CD276, STAT1, HLA-DRB1, HLA-E. Abbreviations: CI, confidence interval; HR, hazard ratio; Mb, megabase;NMo, month; mPFS, median progression-free survival; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; TIS, tumor inflammation signature; tTMB, tissue tumor mutational burden.

Keywords: biomarkers, immunotherapy, pd-1 inhibitor

WS06 JOINT IASLC - CAALC - CSCO WORKSHOP: LOOKING TOWARD THE FUTURE: RECOGNIZING AND CURING LUNG CANCER
SATURDAY, SEPTEMBER 11, 2021 - 22:15-23:45

WS06.06 Drug Holiday Based on Minimal Residual Disease Status After Local Therapy Following EGFR-TKI Treatment for Patients With Advanced NSCLC

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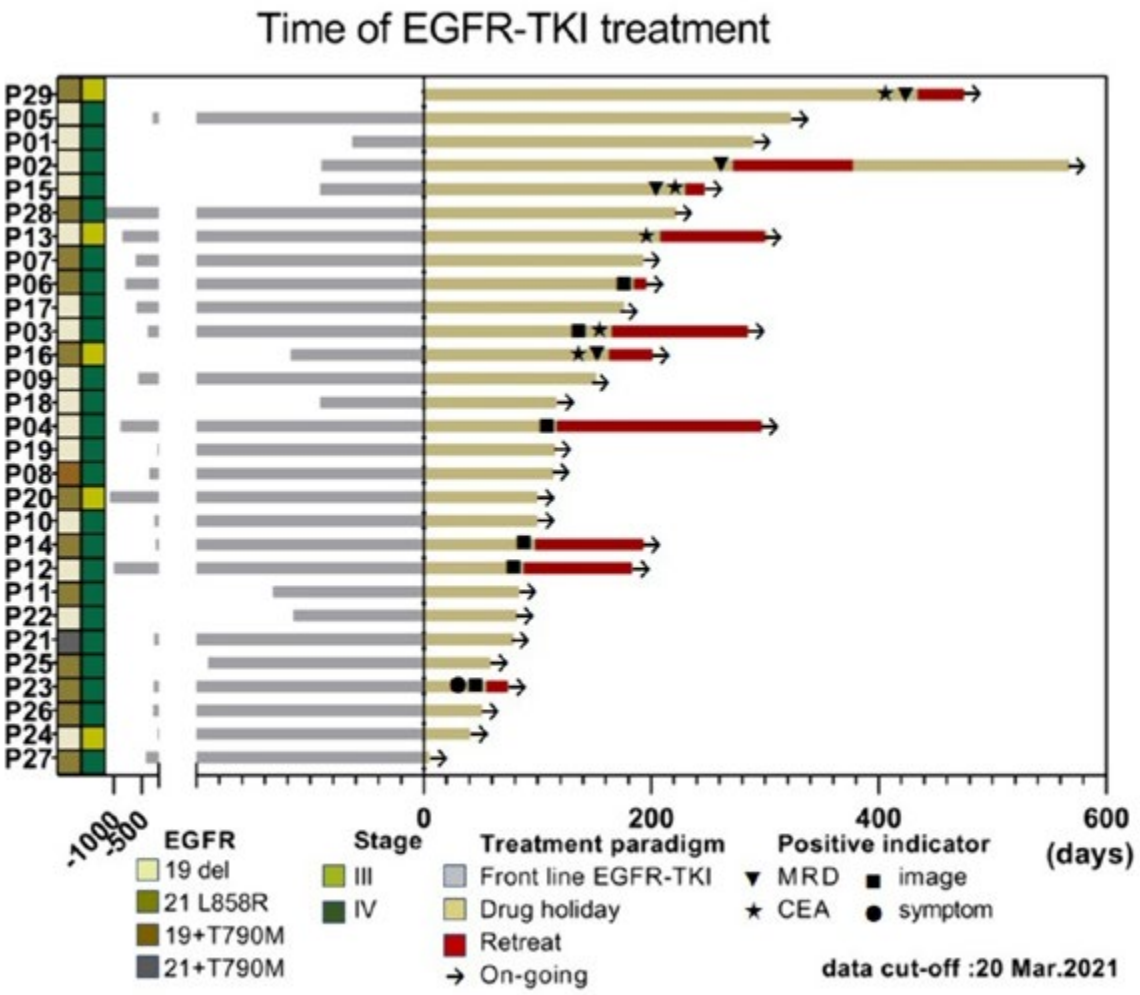
Introduction: Local consolidative therapy (LCT)has been confirmed to improve the overall survival of patients with non-small cell lung cancer (NSCLC) receiving targeted therapy and continuation of target therapy is currently recommended. it is unknown whether patients could benefit from targeted therapy holiday if no visible lesions and negative minimal residual disease (MRD) after LCT. **Methods:** Detection of ctDNA in periphery blood was performed to identify MRD in patients with EGFR mutant oligo-residual disease after LCT. EGFR-TKIs were ceased for patients who met criteria: (1) no imagery lesions after surgery; (2) negative MRD; (3) normal serum carcinoembryonic antigen (CEA); (4) asymptomatic. Negative MRD was defined as no driver genes or a maximum of one cancer-related gene was detected. Follow-up would be done every three months and EGFR-TKIs would be retreated If any of the above drug holiday criteria were missed. This study was exploring part of CTONG 1602 (NCT03046316), which was approved by Research Ethics Committee of Guangdong General Hospital&Guangdong Academy of Medical Sciences. **Results**: 38 patients with stage IIIB or IV NSCLC were screened for MRD after LCT following targeted therapy between June 2019 to February 2021. Except for 2 patients with positive MRD, 36 patients met drug holiday criteria. 7 patients refused participation. For 29 patients enrolled the median duration of front-line treatment with EGFR-TIKs was 298 days (0-1699 days). The median drug holiday was 117 days (5-434 days). Eleven (37.9%) patients met at least one issue of drug holiday criteria during follow-up with median drug holiday 165 days (55-434 days), and six of them presented with imagery lesions, five relapsed in previous sites of disease (2 in lung, 3 in brain), one patient relapsed in new site (brain). all these six patients (100%) were responsive to EGFR-TKI retreatment. The other five patients with positive MRD (EGFR mutation) and/or increased levels of CEA met drug holiday criteria again after 3 months of EGFR-TKI retreatment, and two of them(P02 and P13) therefore gained second drug holiday(Fig 1).



Conclusion: Drug holiday based on MRD status was feasible for patients treated with EGFR-TKI on the basis of LCT. Brain metastases were higher risk of recurrence after drug holiday.

Keywords: Local consolidative therapy, Drug holiday, minimal residual disease

WS06 JOINT IASLC - CAALC - CSCO WORKSHOP: LOOKING TOWARD THE FUTURE: RECOGNIZING AND CURING LUNG CANCER
SATURDAY, SEPTEMBER 11, 2021 - 22:15-23:45

WS06.07 Lorlatinib for Previously Treated ALK-Positive Advanced NSCLC: Primary Efficacy and Safety Data from a Phase 2 Study in China

S. Lu[1], Q. Zhou[2], X. Liu[3], Y. Du[4], Y. Fan[5], Y. Cheng[6], J. Fang[7], Y. Lu[8], C. Huang[9], J. Zhou[10], Y. Song[11], K. Wang[12], H. Pan[13], N. Yang[14], J. Li[15], G. Chen[16], J. Chang[17], J. Cui[18], Z. Liu[19], C. Bai[20], H. Zhang[21], H. Thurm[22], G. Peltz[22], H. Li[23], H. Zhao[23], Y. Wu[2]

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Introduction: Lorlatinib, a third-generation inhibitor of anaplastic lymphoma kinase (ALK), was shown in a global Phase 2 study to have potent overall and intracranial (IC) anti-tumor activity in patients with ALK-positive advanced non-small cell lung cancer (NSCLC) after progression on first- and/or second-generation ALK inhibitors (NCT01970865). Here we report primary data from a multicenter Phase 2 study conducted in China that investigated lorlatinib in ALK inhibitor-treated patients with ALK-positive NSCLC (NCT03909971). **Methods:** This ongoing, open-label, Phase 2 study enrolled patients in China with ALK-positive locally advanced/metastatic NSCLC and disease progression after crizotinib as the only ALK-inhibitor (Cohort 1), or after one ALK-inhibitor other than crizotinib, with or without prior crizotinib (Cohort 2). Patients with CNS metastases were eligible to enroll; one prior line of chemotherapy was permitted. All patients received lorlatinib 100 mg QD in a continuous 3-week cycle. The primary endpoint was objective response rate (ORR) by independent central review (ICR) per RECIST v1.1 in Cohort 1. Secondary endpoints included ORR in Cohort 2, IC-ORR, PFS, overall survival (OS), and safety. **Results:** In total, 109 patients were enrolled: 67 to Cohort 1 and 42 to Cohort 2. Among these, 36 patients in Cohort 1 and 21 patients in Cohort 2 had ≥1 intracranial lesion at baseline per ICR assessment. At data cutoff (August 10, 2020), ORR (95% CI) by ICR in Cohort 1 was 70.1% (57.7–80.7) and in Cohort 2 was 47.6% (32.0–63.6). IC-ORR was 80.6% in Cohort 1 and 47.6% in Cohort 2. See Table for additional response data. Median DOR by ICR was not reached in Cohort 1, and was 11.2 months in Cohort 2. Median PFS by ICR was not reached in Cohort 1, and was 5.6 months in Cohort 2. OS data were immature and median OS was not estimatable in either cohort. Median treatment duration was 11.4 months in Cohort 1 and 8.4 months in Cohort 2. Grades 3–4 treatment-related adverse events (TRAEs) occurred in 36 (53.7%) patients in Cohort 1 and 17 (40.5%) patients in Cohort 2; serious TRAEs occurred in 4 (6.0%) and 5 (11.6 %) patients in each cohort, respectively. No Grade 5 TRAE were reported in either cohort. The most commonly-reported any-grade AEs overall were hypercholesterolemia (92.7%) and hypertriglyceridemia (91.7%). Table 1. Summary of response data

	Cohort 1	Cohort 2	Total
Best overall response by ICR			
Patients in analysis	N=67	N=42	N=109
ORR, n (%)	47 (70.1)	20 (47.6)	67 (61.5)
95% CI	57.7–80.7	32.0–63.6	51.7–70.6
CR	8 (11.9)	2 (4.8)	10 (9.2)
PR	39 (58.2)	18 (42.9)	57 (52.3)
SD	8 (11.9)	6 (14.3)	14 (12.8)
Best overall intracranial response in patients with any intracranial lesions			
Patients in analysis	N=36	N=21	N=57
IC-ORR, n (%)	29 (80.6)	10 (47.6)	39 (68.4)
95% CI	64.0–91.8	25.7–70.2	54.8–80.1
CR	19 (52.8)	6 (28.6)	25 (43.9)
PR	10 (27.8)	4 (19.0)	14 (24.6)
SD	0	2 (9.5)	2 (3.5)

CI, confidence interval; CR, complete response; IC, intracranial; ICR, independent central review; ORR, objective response rate; PR, partial response; SD, stable disease

Conclusion: Lorlatinib showed robust clinical activity in Chinese patients with previously treated ALK-positive NSCLC, including those with CNS metastases. Safety data were consistent with previous findings.

Keywords: CNS metastases, Lorlatinib, ALK-positive NSCLC

Joint IASLC-Estro Session

JIES01 JOINT IASLC – ESTRO SESSION: ADVANCES IN RADIOTHERAPY FOR LUNG CANCER
FRIDAY, SEPTEMBER 10, 2021 - 07:00-08:00

JIES01.02 Radiomics and Radiotherapy: State of the Art and Future Challenges

D. De Ruysscher

Department of Radiation Oncology (Maastro), Grow School for Oncology, Maastricht University Medical Centre+, Maastricht/NL

In radiomics, large numbers of quantitative features from images (e.g. CT or MRI scans) are extracted and analyzed. These image features cannot be identified by the human eye, i.e. there is much more information in an image than intuitively appreciated. These radiomic features can be used for many applications in medicine, such as prognostication of individual patients, as a predictive test, for response assessment, for automatic contouring of anatomical structures including tumors etc. Radiomics and deep learning are not the same, but have overlapping characteristics, of which the ability of deep learning to select features independent of human interaction is one of the most striking. A typical radiomics pipeline involves the acquisition of images, segmentation of a region of interest (ROI), e.g. a tumor, feature extraction, statistics and predictive modelling and finally validation. Radiomics is shown to give information that relates to biological characteristics of the tumor such as hypoxia, PD-L1 expression and CD8 T-cell infiltration. The prediction of these features was shown to correlate with the survival of patients. In line with the biological correlate of radiomics, response evaluation in situations where RECIST criteria perform modest such as in case of immune therapy, radiomics helps in classifying patients and correlates with survival. Radiomics has therefore a role to play the clinical cycle where at several points decisions have to be made, with or without patient involvement, e.g. prognostication of patients to allocate the optimal treatment, segmentation of organs at risk and tumors, response assessment etc. Moreover, as radiomics relies on standard images, including cone-beam CT scans that are made on a daily base in standard practice, the changes of the image over time in an individual patient will increase the predictive accuracy of radiomics. Even though radiomics has shown to have big potential, the majority of publications are of inferior quality, being in over 90 % based on retrospective, i.e. highly biased, data sets, with again over 90 % single-center and mostly not externally (ideally at least twice) validated. Mostly, the AUC of the model is only 0.55-0.60, with significant heterogeneity. The latter may also partly be due to differences in scanners and image protocols. Nevertheless, although radiomics is a novel scientific field, already at present, it has shown its big potential impact for it allows to give even standard non-contrast-enhanced Imaging insight in biological mechanisms and helps in prognostication and response prediction together with other known variables. The major caveat in a lot of radiomic literature is the lack of multiple external validation and reproducibility. The exciting new data coming from radiomics will be part of the ongoing move towards AI-driven radiation oncology. **References** Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, Zegers CM, Gillies R, Boellard R, Dekker A, Aerts HJ. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012 Mar;48(4):441-6 Coates JTT, Pirovano G, El Naqa I. Radiomic and radiogenomic modeling for radiotherapy: strategies, pitfalls, and challenges. J Med Imaging (Bellingham). 2021 May;8(3):031902. Grossmann P, Stringfield O, El-Hachem N, Bui MM, Rios Velazquez E, Parmar C, Leijenaar RT, Haibe-Kains B, Lambin P, Gillies RJ, Aerts HJ. Defining the biological basis of radiomic phenotypes in lung cancer. Elife. 2017 Jul 21;6:e23421. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, Hoebers F, Rietbergen MM, Leemans CR, Dekker A, Quackenbush J, Gillies RJ, Lambin P. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014 Jun 3;5:4006 Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, Verlingue L, Brandao D, Lancia A, Ammari S, Hollebecque A, Scoazec JY, Marabelle A, Massard C, Soria JC, Robert C, Paragios N, Deutsch E, Ferté C. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol. 2018 Sep;19(9):1180-1191. Dercle L, Henry T, Carré A, Paragios N, Deutsch E, Robert C. Reinventing radiation therapy with machine learning and imaging bio-markers (radiomics): State-of-the-art, challenges and perspectives. Methods. 2021 Apr;188:44-60. Trebeschi S, Drago SG, Birkbak NJ, Kurilova I, Călin AM, Delli Pizzi A, Lalezari F, Lambregts DMJ, Rohaan MW, Parmar C, Rozeman

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Keywords: radiomics, prediction models, radiotherapy

JIES01 JOINT IASLC – ESTRO SESSION: ADVANCES IN RADIOTHERAPY FOR LUNG CANCER
FRIDAY, SEPTEMBER 10, 2021 - 07:00-08:00

JIES01.04 Prophylactic Cranial Irradiation in Lung Cancer: Where We Are

B. Slotman

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Prophylactic cranial irradiation (PCI) has been used in small cell lung cancer (SCLC) to reduce the high risk (~60%) of brain metastases in these patients. Early trials on PCI have focused on patients in complete remission after treatment for limited stage (LS). Individual studies showed unequivocally a significant reduction in the risk of brain metastases, but a survival benefit was only seen in a meta-analysis [1]. In this analysis. An absolute increase in survival rate of 5.4% at 3 years [1]. The vast majority of patients in these studies had a complete remission (often based on chest radiographs) after chemotherapy. Based on these studies, PCI became part of standard treatment of LS-SCLC patients with a complete response. To reduce the risk of neurocognitive toxicity, PCI was not simultaneously given with chemotherapy and started within 6 weeks after last chemotherapy. A study on the effectiveness of higher dose PCI (36 Gy) showed no benefit over standard dose (25 Gy) PCI [2]. Since most patients with SCLC present with extensive stage (ES) disease, and the risk of brain metastases is even higher in this group of patients, the EORTC performed a study on PCI in patients with any response after chemotherapy for ES-SCLC. In this trial, PCI not only significantly reduced the risk of symptomatic brain metastases (15 vs 40%), but also significantly improved survival (1 year survival 27 vs 13%) [3]. This study was pragmatic and in line with existing guidelines not to repeat brain imaging and to focus on symptomatic disease. It was argued that some individuals with asymptomatic, but radiologically detectable brain metastases may have been included in the study and that could, at least partially, have contributed to the outcome. In a Japanese study on PCI in ES-SCLC patients, all patients had a brain MRI to excluded presence of asymptomatic brain metastases [4]. In addition, regular brain MR imaging was performed during follow-up and when appropriate, brain metastases that appeared were treated. The study showed a significant reduction in the rate of brain metastases when using PCI (33 vs 59%), but no survival benefit. In the observation arm that did not receive PCI, many patients (83%) who developed brain metastases were treated with radiotherapy [4]. A SWOG trial (SWOG 1827/"MAVERICK") has opened in 2020 to compare a strategy of MRI surveillance with early treatment to MRI surveillance with PCI. Interestingly, this study is not only enrolling patients with ES-SCLC but also with LS-SCLC. In it well known that the disease SCLC and PCI can be associated with cognitive decline. Studies aiming at sparing brain regions involved in memory and cognitive functions, esp. hippocampal region, led to attempt of using hippocampal avoiding PCI (HA-PCI). Whole brain radiotherapy with hippocampal avoidance was associated with better preservation of memory and quality of life [5]. Studies on the benefit of HA-PCI are less conclusive [6,7] and the results of an ongoing trails (NRG CC003) are awaited. In conclusion, PCI is very effective in reducing the risk of brain metastases in SCLC. There are questions whether the beneficial effect on survival is maintained in the era of MR screening and MR surveillance with early treatment of (asymptomatic) brain metastases. Studies to re-evaluate the role of PCI in the current era of immunotherapy are underway. In the meantime, PCI or MRI surveillance should be considered guideline-recommended treatment. In NSCLC, the role of PCI was also addressed in a number of studies. In a recent trial with long term follow-up (NRG/RTOG0214) and a meta-analyses, earlier findings of a significant reduction in the rate of brain metastases, improvement in diseasefree survival, but absence of improved overall survival after PCI, were confirmed [8,9]. Literature 1. Auperin A, Arriagada R, Pignon JP, et al. N Engl J Med 341, 476-84, 1999. 2. Le Pechoux C, Dunant A, Senan S, et al. Lancet Oncol 10, 467-74, 2009. 3. Slotman BJ. Faivre-Finn C, Kramer G, et al. N Engl J Med 357, 664-72, 2007. 4. Takahashi T, Yamanaka T, Seto T, et al. Lancet Oncol 18, 663-71, 2017. 5. Gondi V, Pugh SL, Tome WA. J Clin Oncol 3, 3810-6, 2014. 6. De Dios ND, Counago F, Lopez JL, et al., Int J Radiat Oncol Biol Phys 105, S35-6, 2019. 7. Belderbos JS, De Ruysscher DK, de Jaeger K, et al. T Thor Oncol 16, 840-9, 2021. 8. Sun A, Hu C, Wong SJ. JAMA Oncol 5, 847-55, 2019. 9. Witlox WJA, Ramaekers BLT, Lacas B, et al., Radiother Oncol. 158, 40-7. 2021.

Keywords: brain metastases, PCI, prophylactic cranial irradiation

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Zotenko Elena	FP05.03
Zou Wei	MA07.02, P22.02
Zou Zihua	P06.04, P45.15
Zu Ke	P63.05, P63.08
Zulato Elisabetta	MA07.01
Zu Lingling	P57.14
Zullo Lodovica	OA01.02
Zuo Xuerong	FP10.01
Zurawski Bogdan	OA09.01