Scientific Advances in Lung Cancer 2015

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ABSTRACT

Lung cancer continues to be a major global health problem; the disease is diagnosed in more than 1.6 million new patients each year. However, significant progress is underway in both the prevention and treatment of lung cancer. Lung cancer therapy has now emerged as a "role model" for precision cancer medicine, with several important therapeutic breakthroughs occurring during 2015. These advances have occurred primarily in the immunotherapy field and in treatments directed against tumors harboring specific oncogenic drivers. Our knowledge about molecular mechanisms for oncogene-driven tumors and about resistance to targeted therapies has increased quickly over the past year. As a result, several regulatory approvals of new agents that significantly improve survival and quality of life for patients with lung cancer who have advanced disease have occurred. The International Association for the Study of Lung Cancer has gathered experts in different areas of lung cancer research and management to summarize the most significant scientific advancements related to prevention and therapy of lung cancer during the past year.

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Introduction

Ongoing Efforts in Lung Cancer Research and Treatment

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The decoding of the human cancer genome and advent of therapies targeting driver mutations represent two major milestones for the clinical implementation of precision medicine in patients with lung cancer. This requires an understanding of cancer genes and mutational processes, as well as an understanding of their evolution during tumor development and an appreciation for the genetic heterogeneity among cancer cells. Ongoing global efforts to systematically search for the most relevant genetic changes in each subtype of thoracic cancer will, it is hoped, increase the percentage of tumors that will respond better to new drugs targeting distinct genetic profiles. Many of the genetic alterations can be targeted by oral medications that have much higher response rates and much lower toxicity compared with chemotherapy. Although targeted drugs dramatically improve the outcome of patients with tumors harboring specific alterations, molecular and clinical resistance almost invariably develops. New drugs specifically active in the resistance setting have now been developed and, it is hoped, will further contribute to making lung cancer a chronic disease. Additionally, the development of rational combinations may further improve outcomes.

Even more recently, it has become evident that interactions between malignant and neighboring nonmalignant cells create a dynamic tumor microenvironment that can be therapeutically exploited. Important intercellular communications are driven by a complex and dynamic network of cytokines, chemokines, growth factors, and inflammatory and matrix remodeling enzymes against a background of major perturbations in the physical and chemical properties of lung tumor tissue. A better understanding of the interaction between cancer cells and the immune system has already generated drugs that use the body's immune system to fight the cancer. For example, cancer cells often have a protein called programmed death ligand 1 (PD-L1) on their surface that helps them evade the immune system. New drugs that block the PD-L1 protein, or the corresponding programmed cell death protein 1 (PD-1) protein on immune cells, T cells, can help the immune system recognize the cancer cells and attack them. Although robust data on these new drugs have already been generated in the setting of second-line therapy of non–small cell lung cancer (NSCLC), as discussed in the "Immunotherapy" section, their role in the front-line and earlier disease settings, as well as their combination with existing and newer targeted therapies, are promising areas of ongoing clinical research. Future research also needs to explore new and potentially better predictive assays than PD-L1 immunohistochemical (IHC) assays for selection of patients to receive immunotherapy.

In this volume of the *Journal of Thoracic Oncology*, the International Association for the Study of Lung Cancer (IASLC) has introduced another valuable educational resource to keep busy practitioners, scientists, and others interested in lung cancer up-to-date with the newest advances in lung cancer, with the primary focus on NSCLC, as expert leaders in the field and the IASLC have recently published a separate extensive and up-to-date review on small cell lung cancer (SCLC) in the *Journal of Thoracic Oncology*,[1] which the reader is encouraged to peruse. This current article is meant not to be an all-encompassing review but to cover the highlights of the field along with the necessary references for further reading. The Editors, Anne Tsao and Harvey Pass, along with the Managing Editor, Murry Wynes, are grateful to all of the contributors, who not only provided superlative commentary but also did so in an expeditious fashion. We hope that this ongoing annual series will be a *Journal of Thoracic Oncology* feature that you will look forward to, and that it will serve to help you in the management of your patients or stimulate provocative questions in the laboratory.

Prevention and Early Detection

Tobacco Control and Lung Cancer Prevention

Section Authors: Graham W. Warren, MD, PhD, Chunxue Bai, MD, PhD

Tobacco control is essential to preventing lung cancer and improving outcomes for patients in whom lung cancer is diagnosed. Comprehensive reviews clearly demonstrate that combustible tobacco is the primary causative risk factor for the development of 80% to 90% of lung cancer in men and women and that smoking cessation reduces the risk for lung cancer in a time- and dose-dependent manner.[2–4] Among smokers, there are significantly increased risks for several major cancers, including lung cancer.[5] Smoking not only causes cancer, but continued smoking alters cancer biology, leading to tumors that are resistant to cancer treatment and thereby leading to increases in overall and cancer-specific mortality.[2,6] Examples of proven methods that reduce the burden of tobacco and lung cancer include primary prevention of tobacco use in youth, regulation and taxation of tobacco products, antismoking campaigns and legislation (such as indoor air laws and smoking bans), and provision of evidence-based smoking cessation support before and after a diagnosis of

cancer.[2,4,6,7] Unfortunately, worldwide tobacco control is highly variable and highly dependent on a complex interaction between governmental regulation, taxation, public awareness, social patterns, the tobacco industry, and people who consume tobacco products.[8] In countries with stronger tobacco control laws, reductions in lung cancer incidence and mortality lag behind reductions in smoking prevalence by approximately 20 years.[2,4] However, tobacco consumption continues to rise in several developed countries, including the People's Republic of China, where the health burden caused by tobacco is also expected to continue to rise.[2,9] Fortunately, recent changes in tobacco control in the People's Republic of China, such as indoor smoking bans enacted in Beijing in 2015, are expected to curtail future adverse health effects of tobacco.

Early diagnosis through screening for lung cancer is a proven method of reducing mortality,[10] and recent data show that smoking cessation for 7 years had a survival benefit comparable to that of screening.[11] Unfortunately, recent data from IASLC surveys demonstrate that lack of resources, training, and time are primary barriers to providing cessation support.[12] However, integrating tobacco control and cessation support into the diagnosis and management of patients with lung cancer does not have to be difficult and can be tailored to patient- and institution-specific needs.[6,13] Collectively, addressing tobacco use in conjunction with advances in lung cancer therapy will provide the greatest benefit to patients and society.

Lung Cancer Screening

Section Authors: Harry J. de Koning, MD, PhD, A. Uraujh Yousaf-Khan, MD, Annette McWilliams, M.B.B.S., FRACP

Status of the NELSON Trial. Lung cancer screening with low-dose computed tomography (LDCT) is recommended in the United States by the U. S. Preventive Services Task Force on the basis of the results of the National Lung Screening Trial (NLST), which showed a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality.[10,14] In Europe, smaller underpowered trials showed no significant mortality reduction.[15–17] The largest European trial, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), aimed to determine whether LDCT screening can reduce lung cancer mortality by at least 25%.[18,19] The screened group received LDCT at years 1, 2, 4, and 6.5.[20,21] Currently, all rounds have been completed. The lung cancer detection rate was 3.2% and the number needed to screen for the detection of lung cancer was 85 to 123 per round.[20,22] The final mortality and cost analyses are expected within 2 years.

Technical Contributions of the NELSON Trial. NELSON utilized a nodule protocol based on volumetric assessment, nodule growth (defined as a change in volume of $\geq$25%), and volume doubling time (VDT).[18,20,21] LDCT results were defined as follows: (1) *negative*, screened at next round (new nodules $<$50 mm^3 or previously detected nodule with growth $<$25% or growth $\geq$25% and VDT $>$600 days); (2) *positive*, referred to pulmonologist (new nodules $>$500 mm^3 or previously detected nodule with growth $\geq$25% and VDT $<$400 days); and (3) indeterminate, referred for a short-term follow-up computed tomography (CT) (new nodules 50–500 mm^3 or previously detected nodule with VDT 400–600 days). The use of this nodule management strategy resulted in a higher positive predictive value (40.6% versus 3.6%) and a substantially lower false-positive result (59.4% versus 96.4%) than in the NLST.[10,22,23]

Modeling of Risk for Screening Participation and Management of CT-Detected Pulmonary Nodules. Selection criteria for LDCT screening have largely been based on age and smoking history, but screening is most effective when applied to people at high risk.[24,25] The use of multivariate risk-prediction models to select participants who will most benefit will likely be the more cost-effective strategy.[24–28] Multiple risk prediction models exist, but only two are based on large prospective population-based samples: the Tammemagi prostate, lung, colorectal, and ovarian (PLCO) model and the Hoggart European Prospective Investigation into Cancer and Nutrition model.[24,29–31] Retrospective analysis has shown the PLCOm2012 model to be more accurate and efficient than the NLST/U. S. Preventive Services Task Force selection criteria.[24,28,30] There was an observed risk threshold at which CT-screened participants had reduced lung cancer mortality.[30] The Pan Canadian Early Detection of Lung Cancer Study used an earlier version (PLCOm2008) for recruitment. It was accurate and cost-effective, with an incremental cost-effectiveness ratio of $9410 per quality-adjusted life-year compared with $81,000 per quality-adjusted life-year in the NLST.[32–34]

LDCT screening frequently detects pulmonary nodules for which there is no universally accepted management protocol. The only evidence-based lung nodule risk calculator was published by the Pan Canadian team.[35] It was designed to assist in the management of nodules when first detected in a screening setting by using a probabilistic approach.[26,35] This calculator has been validated in two cohorts and has been suggested to have performance superior to that of the Lung CT screening reporting and data system classification.[36–38] It is recommended by the American College of Radiology Lung CT Screening Reporting and Data System and the British Thoracic Society Guidelines.[39,40]

The use of risk-prediction models, including the Tammemagi PLCO[29] and the Hoggart European Prospective Investigation into Cancer and Nutrition model[31] to select screening participants and the McWilliams models for nodule triage,[35] combined with volumetric analysis of higher-risk nodules over short-term follow-up is the likely future direction for a lung cancer screening program.

Stage I through III NSCLC

Pathology

Section Authors: Ming Sound Tsao, MD, FRCPC, Prasad S. Adusumilli, MD, FCCP

In 2015, the World Health Organization published the fourth edition of the *Classification of Tumours of the Lung, Pleura, and Thymus*.[41,42] The new classification was developed by an international panel of multidisciplinary experts. Compared with the third edition published in 1999 and 2004, the new classification included several important changes: (1) classification applied to small biopsy and cytologic samples, (2) molecular testing for treatment selection, (3) inclusion of IHC markers for more precise classification of NSCLC, (4) changes in the classification of squamous carcinoma and adenocarcinoma (ADC), and (5) new genomic information for various types of lung cancers.

The new World Health Organization classification for lung ADC was based on the 2011 classification recommended by the IASLC/American Thoracic Society/European Respiratory Society.[43] Subsequent to its initial publication, many studies worldwide have validated the prognostic value of this classification.[44–61] In particular, the high risk for distant recurrence in solid predominant lung ADC,[53] local or regional recurrence in lung ADC with a micropapillary component, and presence of an invasion pattern of spread through alveolar spaces beyond the edge of the tumor into the surrounding lung parenchyma, especially after limited resection, were reported.[62–66] In contrast, ADC with a purely lepidic pattern (ADC in situ [AIS]) or with an invasive area of 0.5 cm or less (minimally invasive ADC) are associated with 100% survival after complete surgical resection.[48,57,58] Furthermore, the size of the invasive area in lepidic predominant ADC appeared to be correlated with disease-free survival (DFS).[57] However, recognition of the predominant histological subtype in preoperative small biopsy specimens and on frozen sections remains a challenge.[67,68] Importantly, pooled analyses of retrospectively reclassified lung ADC cases (n = 575) from four pivotal adjuvant chemotherapy trials by the Lung Adjuvant Cisplatin Evaluation Biology group showed significant benefit from adjuvant chemotherapy for DFS and specific DFS for patients with micropapillary and solid predominant tumors, but not for patients with acinar or papillary predominant tumors (Fig. 1).[51]

The past few years have also witnessed advances in deciphering the genetics of lung cancers through completion of multiplatform genomic profiling studies. The Cancer Genome Atlas Research Network completed comprehensive profiling of 500 resected lung squamous carcinomas and ADCs.[69,70] Other groups have reported multi-omics profiling of other types of lung carcinomas, including small cell carcinoma.[71–78] These, together with targeted mutation analyses of large numbers of NSCLCs (Fig. 2),[79–81] have advanced lung cancer diagnosis and treatment in the context of personalized medicine.

Staging

Section Authors: Ramón Rami-Porta, MD, Hisao Asamura, MD

The seventh edition of the tumor, node, and metastasis (TNM) classification was revised according to the analyses of the new database of the IASLC. The new eighth edition includes retrospective data from 73,251 patients and prospective data from 3905 in whom lung cancer was diagnosed from 1999 to 2010 and registered in 35 data sources in 16 countries around the world.[82] The T, N, and M components of the classification were analyzed separately.[83–85] The recommendations for changes derived from these analyses are summarized in Table 1.

The most relevant innovation for the T component is that tumor size is an important prognostic factor and is now a descriptor in all T categories. Endobronchial location less than 2 cm from the carina and total atelectasis/pneumonitis become T2 descriptors, invasion of the diaphragm becomes T4 as its prognosis is more similar to this category than to T3, and mediastinal pleural invasion disappears as a T descriptor because it is rarely used.[85]

The categories of the N component remain the same because they separate groups of tumors with different prognosis, at both clinical and pathological staging. In addition, the analyses of survival in patients with pathologically staged tumors showed that quantification of nodal disease according to the number of involved nodal stations has a prognostic impact.[83] Finally, the analyses of survival of patients with disseminated disease validated the M1a descriptors and allowed for the separation of those with a single extrathoracic metastasis (M1b) from those with multiple extrathoracic metastases in one or several organs (M1c).[84]

The recommended changes implied the subdivision of stage IA, the creation of stage IIIC for T3 and T4 tumors with N3 disease, and the subdivision of stage IV into stage IVA and IVB to include intrathoracic

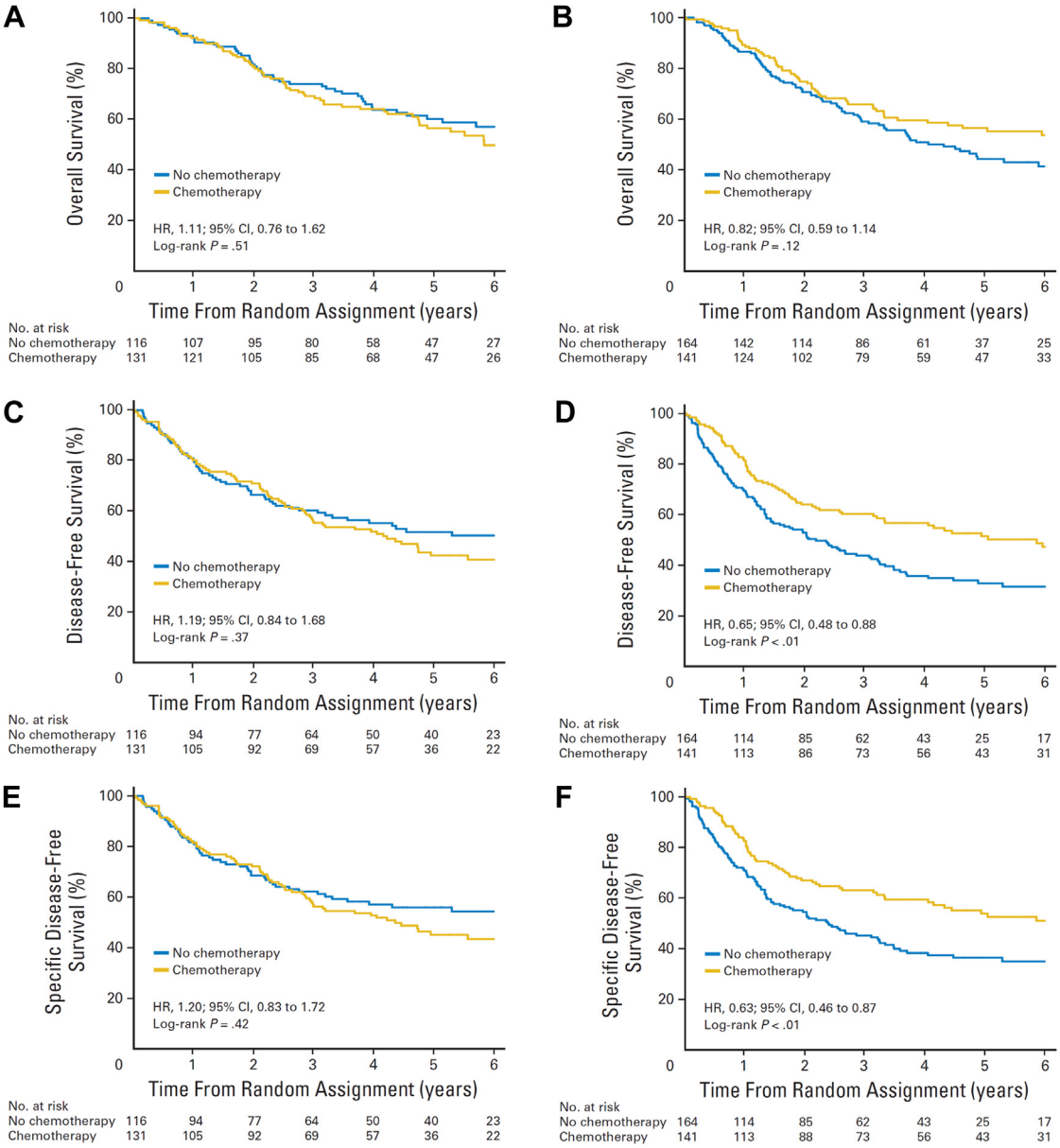


Figure 1. Survival curves according to treatment arm (chemotherapy versus observation) in the acinar/papillary (*A*, *C*, and *E*) and micropapillary/solid (*B*, *D*, and *F*) subgroups for overall (*A* and *B*), disease-free (*C* and *D*), and specific disease-free survival (*E* and *F*). *p* Values from log-rank test, hazard ratios (HRs), and 95% confidence intervals (CIs) of treatment effect, which were estimated through a univariable Cox model stratified on trial, are reported for each subgroup and end point. Reprinted with permission from Tsao et al.[51]

metastases/single extrathoracic metastasis and multiple extrathoracic metastases, respectively. Figures 3 and 4 show weighted survival by stage according to the seventh edition of the TNM classification and the newly proposed eighth edition of TNM stage based on the entire set of cases available for reclassification.[86] These changes are applicable to SCLC.[87] Other recommendations are the inclusion of AIS in the Tis category and the utilization of size of the solid/invasive component to determine the T category for part-solid ADCs.

Role of Surgery

Section Authors: Paul E. Van Schil, MD, PhD, Gail E. Darling, MD, FRCSC

LDCT screening and management of screen-detected small nodules were dominant themes in 2015, but surgical quality remains an important topic. Lobectomy with R0 resection and lymph node dissection remains the accepted standard for treatment of NSCLC against which all other treatment must be compared.[88] However, sublobar resection appears to provide equivalent

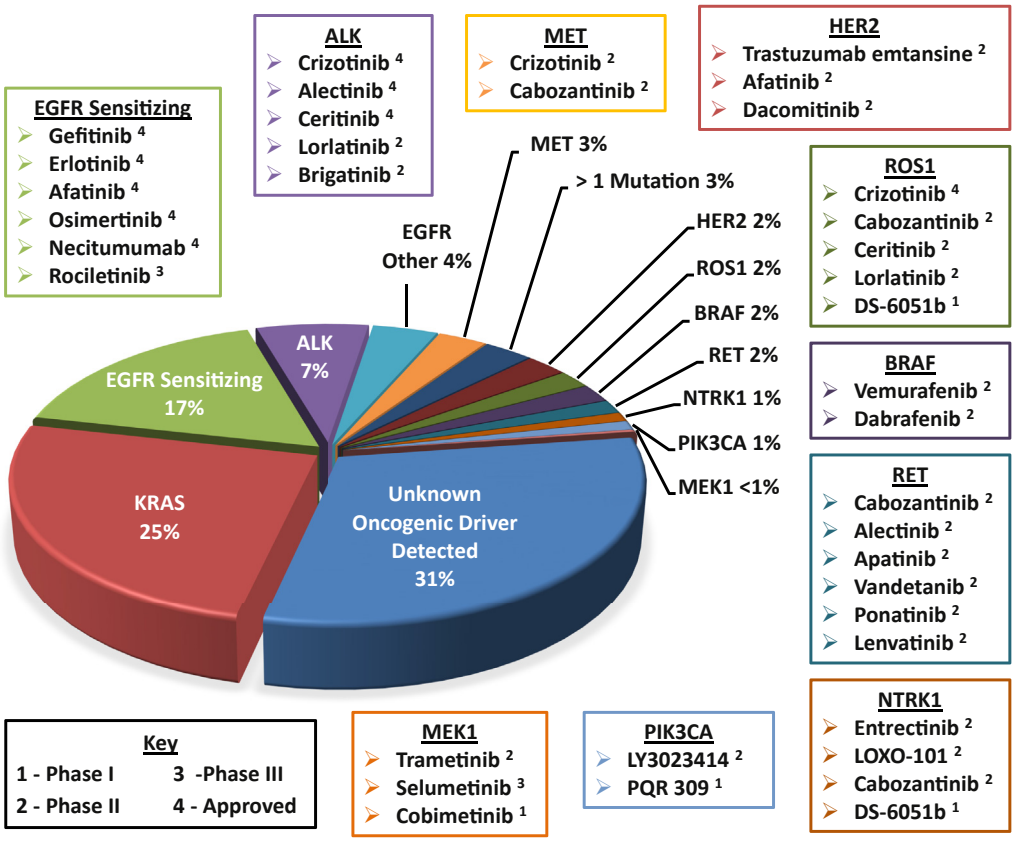


Figure 2. Frequency of molecular aberrations in various driver oncogenes in lung adenocarcinomas and current available drugs against these oncogenic proteins. These frequencies are a combination of data from the Lung Cancer Mutation Consortium and frequencies listed in Shea et al.[81] Shown in the boxes are the available drugs in addition to their developmental phase. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma receptor tyrosine kinase; MET, mesenchymal-to-epithelial transition factor; HER2, erb-b2 receptor tyrosine kinase 2; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; RET, ret proto-oncogene; NTRK1, neurotrophic tyrosine kinase receptor type 1; PIK3A, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; MEK1, mitogen-activate protein kinase kinase 1; KRAS, Kirsten rat sarcoma viral oncogene homolog.

survival for ground glass nodules (GGNs) and patients with limited life expectancy.[89–93] Minimally invasive surgery allows an operation, including lobectomy, to be offered to those previously considered to be high risk.[94] Whether sublobar resection is oncologically equivalent to lobectomy awaits the results of large randomized trials (JCOG0802/WJOG4607L and Cancer and Leukemia Group B 140503).[95,96]

Pure GGNs are predominantly AIS or minimally invasive ADC. Resection is required if growth occurs or a solid component develops. Segmentectomy is acceptable if the lesion is smaller than 2 cm, the lesion has a positron emission tomography maximum specific uptake value less than 2.0, and the results of examination of a frozen section of hilar and mediastinal nodes are negative. Ongoing research (JCOG0804/WJOG4507L) will address management of pure GGNs.[10,22,24,27,43,97–108]

Stereotactic radiotherapy (SRT) is increasingly being used to treat NSCLC, but whether it is oncologically equivalent to an operation remains debated, with conflicting evidence in the literature. A pooled analysis of two small randomized trials that both closed on account of poor accrual reported superior overall survival (OS) with SRT but no difference in recurrence-free survival. This is critically discussed further in the Advances in Radiotherapy section.

Management of locally advanced stage IIIA-N2 NSCLC remains controversial. A systematic review and meta-analysis found that both surgical and radiotherapy options were valid in bimodality trials focusing on the specific role of surgery versus radiotherapy. In trimodality regimens, however, surgical results were found to be superior, with a 13% relative improvement in OS.[109–117] The general consensus is that patients with single-station N2 disease found during a surgical procedure should have postoperative chemotherapy and patients with single-station ipsilateral N2 disease found during pre-resection invasive staging, in whom R0 resection would be accomplished with a lobectomy, should be considered for induction chemotherapy.

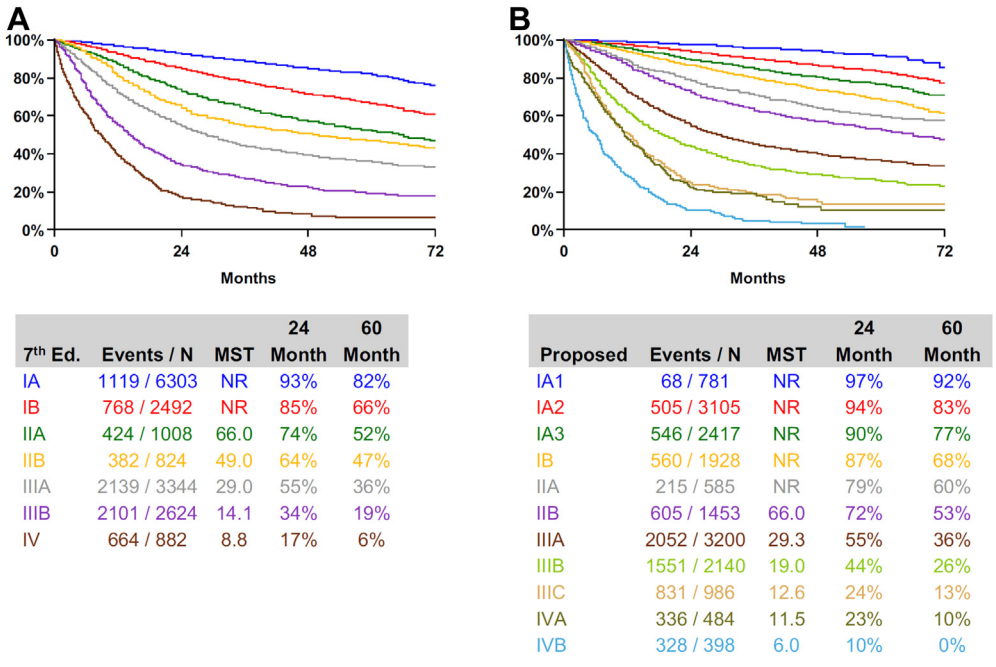
Table 1. Recommended Changes for the Descriptors and Stages for the Eighth Edition of the TNM Classification for Lung Cancer

		N Categories Overall Stage			
Descriptor in Seventh Edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

Note: Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
TNM, tumor node, and metastasis; T, tumor; M, metastasis.
Reprinted with permission from Goldstraw et al.[86]

Whether radiotherapy should be combined with chemotherapy for induction purposes remains controversial and is discussed in the "Radiotherapy" section of this article.

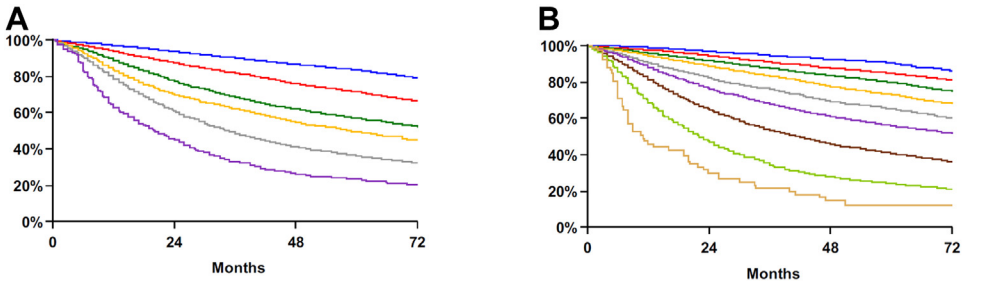
Resection for patients with oligometastatic disease represents a relatively new concept in thoracic surgery, and long-term survival may be obtained when complete resection of the primary and metastasis are performed. In the upcoming eighth TNM classification a new subcategory M1b, consisting of patients with a single metastasis in a single organ, will be introduced. M1c will be defined as multiple metastases in a single organ or multiple organs. Further trials are needed to determine



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Figure 3. Overall survival by clinical stage according to the seventh edition (*A*) and the proposed eighth edition (*B*) of the tumor, node, and metastasis (TNM) classification. Groupings use the entire database available for the eighth edition. Survival is weighted by type of database submission: registry versus other. Reprinted with permission from Goldstraw et al.[86]



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1837 / 11423	NR	94%	83%
IB	2168 / 7711	NR	87%	71%
IIA	1514 / 3702	NR	77%	57%
IIB	1325 / 2776	58.9	70%	49%
IIIA	3467 / 5818	35.0	61%	36%
IIIB	364 / 506	20.0	45%	23%

Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Figure 4. Overall survival by pathological stage according to the seventh edition (*A*) and the proposed eighth edition (*B*). Groupings use the entire database available for the eighth edition. Survival is weighted by type of database submission: registry versus other. MST, median survival time; NR, not reached. Reprinted with permission from Goldstraw et al.[86]

optimal treatment and long-term follow-up in this patient population.[84,118,119]

In conclusion, the role of surgery remains important in the management of early, locally advanced, and oligometastatic lung cancer. Ongoing research will refine screening algorithms and the role of surgery in screen-detected nodules. Minimally invasive surgery allows safe surgical management for elderly and high-risk patients. Every patient should be discussed within multidisciplinary teams to determine the optimal diagnostic and therapeutic strategy.

Role of Adjuvant Chemotherapy

Section Authors: Suresh S. Ramalingam, MD, Giorgio V. Scagliotti, MD, PhD

Cisplatin-based adjuvant chemotherapy is the standard of care for patients with large tumors (>4 cm) and lymph node–positive NSCLC after surgical resection. Adjuvant chemotherapy results in an absolute improvement in the 5-year survival rate of approximately 5% to 15%.[120–123] The next generation of clinical trials in the adjuvant setting can be broadly categorized into three major thematic areas: (1) integration of targeted therapy, (2) customization of chemotherapy on the basis of tumor characteristics, and (3) immunotherapy.

Integration of Targeted Therapy. The results of a phase III trial that evaluated the role of bevacizumab in patients with early-stage NSCLC were recently reported (Eastern Cooperative Oncology Group 1505).[124] Patients (N = 1500) with stages IB, II, and IIIA were randomized after surgery to receive four cycles of cisplatin-based chemotherapy given alone or in combination with bevacizumab. The results were disappointing, with no difference in OS (hazard ratio [HR] = 0.99, $p = 0.93$) or DFS (HR = 0.98, $p = 0.75$) between the two study arms. The RADIANT study evaluated the role of adjuvant therapy with erlotinib, an epidermal growth factor (EGFR) inhibitor, after surgery for early-stage disease.[125] There was no improvement in DFS for erlotinib compared with placebo (HR = 0.90, $p = 0.324$), although there was a promising trend toward improved DFS for patients with activating mutations in *EGFR* (HR = 0.61, $p = 0.039$). Several ongoing studies in Asia are comparing an EGFR inhibitor to chemotherapy in patients with *EGFR*-activating mutations in the adjuvant setting.

Customization of Chemotherapy. Selecting chemotherapy on the basis of baseline expression of DNA repair pathway markers has been a major focus in investigations.[126] A recent study that randomized patients to receive customized chemotherapy on the basis of breast cancer 1 expression levels (BRACA1) failed to meet its primary end point.[127] Another study by the French Intergroup that evaluated customization of chemotherapy based on excision repair cross-complementation group 1 (ERCC1) was discontinued on account of unreliability of the ERCC1 assay.[128] The results of an Italian study (ITACA) that addresses customized chemotherapy based on thymidylate synthase and ERCC1 levels in the tumor are eagerly awaited.

Immunotherapy. The recent approval of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway

in patients with advanced stage NSCLC has prompted studies of these agents in the adjuvant therapy setting. Phase III studies with several immune checkpoint inhibitors have been initiated across the world.

In 2014, the MAGRIT trial, a phase III placebo-controlled randomized study of melanoma-associated antigen 3 (MAGE-A3) vaccine in patients with stage IB–IIIA resected NSCLC who express the MAGE family member 3 gene (*MAGE-A3*), failed to meet its first or second coprimary end points of improving DFS compared with placebo in the overall group of MAGE-A3–positive patients or in the group of MAGE-A3–positive patients who did not receive chemotherapy.[129] The trial was still continued to assess the third coprimary end point of assessing DFS in a gene signature–positive subpopulation. Unfortunately, the updated information indicated that the MAGE-A3 vaccine did not improve survival outcomes and the trial was subsequently closed.[130]

ALCHEMIST Study. The National Clinical Trials Network in the United States is conducting a large adjuvant therapy study that individualizes therapy on the basis of the genomic features of the patient's tumor (Fig. 5). Patients with early-stage NSCLC are screened for *EGFR* mutations and anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) rearrangements after surgery and are randomized to receive the relevant targeted therapy versus placebo. A third arm will be introduced for patients with *EGFR* and *ALK* wild type, with randomization to receive the immune checkpoint inhibitor nivolumab versus observation after adjuvant chemotherapy. The study has the relevant objective of performing in-depth genomic analyses on tumor specimens on all patients. Ultimately, this will greatly enhance our understanding of genomic factors that drive recurrence and sensitivity to adjuvant therapy.

Advances in Radiotherapy

Section Authors: Daniel R. Gomez, MD, Kenneth E. Rosenzweig, MD

SBRT for Lung Cancer. Multiple retrospective and phase I–II trials of stereotactic body radiation therapy (SBRT) have demonstrated excellent local control in early stage lung cancer.[131] To further test its efficacy, three phase III randomized trials were initiated to compare SBRT against surgery: the STARS trial, the ROSEL trial, and ACOSOG Z4099. Unfortunately, all three trials were closed early on account of poor accrual. Chang et al.[132] reported on the pooled results of the first two trials. There were 58 patients randomized to receive either an operation or SBRT, and the median follow-up time was 40 months. Surprisingly, there was improved OS at 3 years in the SBRT arm (95% versus 79% with surgery, $p = 0.037$). Recurrence-free survival was similar in both groups. From a surgical viewpoint, this analysis was flawed by small sample size, short follow-up period, and lack of histological confirmation of cancer. Moreover, in a retrospective propensity-matched analysis of patients with NSCLC that compared SBRT and an operation, an operation provided significantly

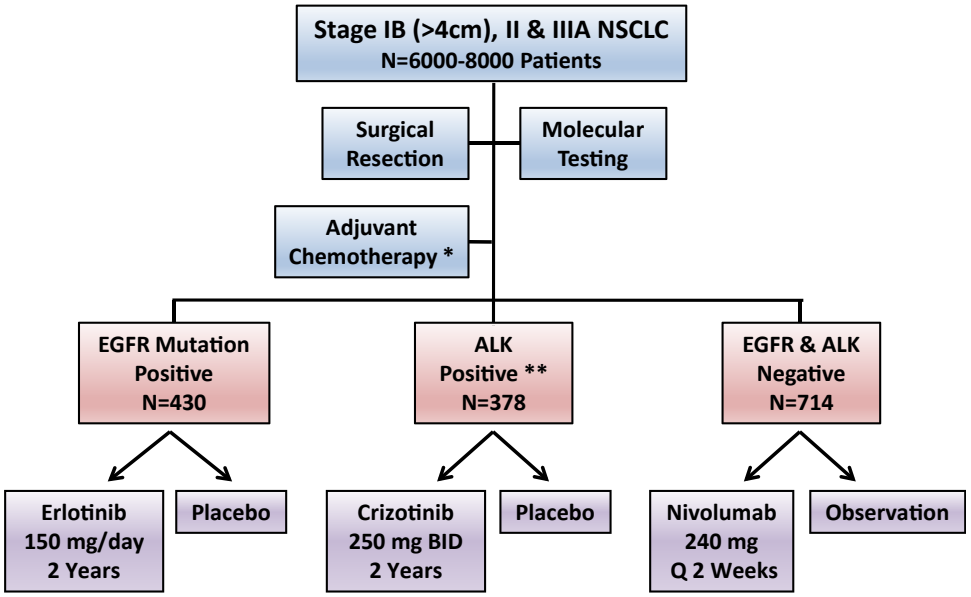


Figure 5. Schema of the ALCHEMIST study. *Adjuvant radiotherapy is allowed if indicated; patients who decline adjuvant chemotherapy are eligible. **ALK positivity defined by fluorescence in situ hybridization test. NSCLC, nonsmall cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma receptor tyrosine kinase; BID, twice daily; Q 2 weeks, every 2 weeks.

better overall and recurrence-free survival; however, 5-year OS was not different in a similar analysis of high-risk patients treated with SBRT or sublobar resection.[132–135] Needless to say, because of the small sample size of the Chang study, further trials are needed, but this work does support SBRT as a viable treatment option for early-stage NSCLC in patients *who refuse an operation* but are resection candidates. Future trials, possibly with novel designs that would support increased accrual, are needed to recommend it as equivalent to the standard of care, which is an operation.

The treatment of central early-stage NSCLC remains a challenge because of toxicity. At the 2015 American Society for Therapeutic Radiology and Oncology meeting, two abstracts on the treatment of these lesions were presented. NRG Oncology/RTOG 0813[136] demonstrated a 7.2% dose-limiting toxicity for 12 Gy × 5, including one toxic death. A Washington University phase II trial[137] demonstrated excellent local control and acceptable toxicity using a dose of 11 Gy × 5.

Locally Advanced NSCLC. A multicenter phase III randomized trial from Europe tested induction chemotherapy alone versus induction chemotherapy with radiation in patients with stage IIIA (N2) NSCLC who were scheduled to undergo an operation.[116] In the 232 patients who were enrolled, the median event-free survival (12.8 versus 11.6 months) and OS (37 versus 26 months) were slightly, but not significantly, improved with the addition of preoperative radiation therapy, suggesting that chemotherapy alone should be used as preoperative treatment for resectable stage III NSCLC. Justifiable criticisms, however, have been raised regarding this trial, including the slow recruitment from 23 centers over 12 years. Moreover, the quality of delivery of radiotherapy in such a trial (very slow recruitment and many centers) is very problematic. In spite of all its methodological imperfections, the trial did show a nonsignificant improvement in the trimodality arm (median OS 37.1 versus 26.2 months) and critics would argue that the conclusion that radiotherapy does not add any benefit to these patients is not justified; rather, the conclusion should be that a larger trial with modern standardized radiotherapy is warranted.

Advanced Stage

Introduction to Personalized Medicine and Targeted Therapies

Section Authors: Stefan Zimmermann, MD, Solange Peters, MD, PhD

Our understanding of NSCLC has evolved from a single disease entity to a disease comprising genetically and clinically distinct subgroups.[138] Lung ADC in particular can now be considered a cluster of discrete molecular subtypes, with most being defined by a single oncogenic driver alteration (see Fig. 2). These oncogenic alterations mainly result in a downstream activation of canonical mitogen-activated protein kinases (MAPKs)/extracellular signal–regulated kinases or phosphatidylinositol 3 kinase (PI3K)/protein kinase B cancer pathways, and include Kirsten rat sarcoma viral oncogene homolog gene (*KRAS*), *EGFR*, B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*), MET proto-oncogene, receptor tyrosine kinase (*MET*) exon14, erb-b2 receptor tyrosine kinase 2 gene (*ERBB2*), neuroblastoma RAS viral (v-ras) oncogene homolog gene (*NRAS*), harvey rat sarcoma viral oncogene homolog (*HRAS*), mitogen-activated protein kinase kinase 1 (*MEK1*), fibroblast growth factor receptor 2 gene (*FGFR2*), fibroblast growth factor receptor 3 gene (*FGFR3*), and neurotrophic tyrosine kinase receptor type 2 (*TrkB*) mutations, ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*), ret proto-oncogene gene (*RET*), and neurotrophic tyrosine kinase, receptor, type 1 gene (*NTRK1*) fusions, as well as *MET* and *ERBB* and *FGFR1/2* amplifications, some of which are characterized by an extremely low prevalence.[69,139] Advances in multiplex genotyping and high-throughput genomic profiling by next-generation sequencing allow physicians to routinely gather therapy-relevant molecular information in a timely fashion, a condition that is required for true personalized medicine in the face of a growing list of molecularly targeted drugs.

The transition from empirical to mechanism-based biomarker-driven therapeutic decisions has had a profound impact on patients' clinical outcomes. A historical comparison of patients with *EGFR*-mutated NSCLC treated before and after the approval of gefitinib in Japan demonstrated a doubling of median survival time, 27.2 months versus 13.6 months.[140] In the second- and third-line setting, patients with *ALK*-positive NSCLC receiving crizotinib therapy experienced a 1-year survival rate of 70% versus 44% in crizotinib-naive *ALK*-positive controls.[141] The magnitude of benefit is expected to be even greater in the future thanks to the accessibility of second- and third-generation agents for the treatment of patients with *EGFR*-mutated and *ALK*-translocated NSCLC, allowing for multiple lines of targeted therapy beyond resistance to initial targeted compound.

This initial success has also brought new challenges. Because many of the known genetically determined NSCLC subtypes represent small subsets of NSCLC, novel clinical trial designs are needed. This has recently led to the development of innovative and complex large umbrella trials, which can study multiple arms/strategies in parallel (see the "Master Protocols" section).

Future regulatory approval will have to rely on single-arm trials using nonclassical "surrogate end points," as was the case initially for crizotinib in 2011 for

ALK-rearranged NSCLC and osimertinib, which received U. S. Food and Drug Administration (FDA) approval in late 2015 for the treatment of patients with *EGFR* T790M mutation-positive NSCLC whose disease has progressed while or after receiving they were EGFR tyrosine kinase inhibitor (TKI) therapy.[142,143]

Intrapatient and intratumor heterogeneity add another layer of complexity, in some cases predicting acquired resistance mechanisms.[144] Although yet to be validated and achieve regulatory approval, peripheral blood circulating tumor DNA may provide more accurate biomarker testing than do tumor biopsy specimens, in particular in the setting of drug resistance.[145]

Still, progress has largely lagged behind for some subgroups of NSCLC, like squamous cell lung cancer, specific subtypes of ADC, such as *KRAS*-mutated tumors, and those without any known targetable alteration.

Lastly, in all NSCLCs and across various solid cancers, elucidating the ideal timing and sequence of various lines of targeted therapy, immunotherapy, and chemotherapy will remain an ongoing challenge for clinicians.

ALK and ROS1

Section Authors: Sai-Hong Ignatius Ou, MD, PhD, Thanyanan Reungwetwattana, MD, MSc

In the past year, there have been developments in understanding the molecular biology and resistance mechanisms of *ALK*-positive NSCLC, regulatory approval of a new IHC assay, and FDA approval of a third ALK inhibitor. Eight new fusion partners to *ALK* gene (*SOCS5*, *CLIP4*, *BIRC6*, *DCTN1*, *SQSTM1*, *EIF2AK*, *PPM1B*, *PRKAR1A*) were reported in *ALK*-positive NSCLC.[146–149] The importance of fusion partners in *ALK*-positive NSCLC is demonstrated by evidence that the HELP domain in echinoderm microtubule associated protein like 4 (EML4) plays a role in engaging the RAS-MAPK pathway as a potential resistance mechanism to ALK inhibitors.[150] MAPK, SRC proto-oncogene non-receptor tyrosine kinase, and EGFR signaling pathways have also been shown to provide bypass mechanisms to ALK inhibitors in tumors that do not harbor resistant *ALK* mutations.[151] On June 15, 2015, the FDA-approved the Ventana ALK (D5F3) IHC assay (Ventana Medical Systems, Tucson, AZ) as a companion diagnostic test to detect *ALK* rearrangement in NSCLC.[152]

Alectinib, a second-generation ALK inhibitor, which has higher intracranial activity than does crizotinib,[153] including against leptomeningeal carcinomatosis,[154,155] was approved by the FDA for patients with *ALK*-positive NSCLC who are refractory to/intolerant of crizotinib.[156,157] Sequential use of ALK inhibitors has led to increased OS, with some *ALK*-positive patients reaching an OS of approximately 5 years.[158,159] Lorlatinib (PF06463922), a third-generation ALK/ROS1 inhibitor that can overcome certain resistant *ALK* mutations (but not *ALK* L1198F), is now in a phase II clinical trial for patients with *ALK*-positive and *ROS1*-positive NSCLC (ClinicalTrials.gov identifier NCT01970865).[160–162] *ALK* I1171X and *ALK* F1174X resistance mutations have differential sensitivities to alectinib and ceritinib, which may determine which one of the two inhibitors to use.[163,164] Other resistant *ALK* mutations have been reported.[165,166] In a case report, Shaw et al.[167] recently reported that C1156Y-L1198F mutations confer resistance to lorlatinib, ceritinib, alectinib, and brigatinib but resensitize cells to crizotinib. In this analysis, studies of cocrystal structure indicated that the L1198F mutation has greater binding to crizotinib that overcomes the increased kinase activity of C1156Y.[167]

Four new fusion partners (*CLTC*, *LIMA1*, *MSN*, *TMEM106B*) to *ROS1* were identified in 2014 and 2015.[69,168–170] and the incidences and clinicopathologic characteristics of patients with *ROS1*-positive NSCLC were described in a comprehensive meta-analysis.[171] Crizotinib was granted priority review designation for a supplemental New Drug Application for patients with advanced metastatic *ROS1*-positive NSCLC on the basis of the efficacy results reported from an expanded cohort of patients with *ROS1*-positive NSCLC from the original crizotinib phase I trial.[169,172] Retrospective analysis of crizotinib in *ROS1*-positive patients confirmed the high overall response rate to crizotinib.[173] Crizotinib was subsequently approved by the U.S. FDA on March, 11 2016 for the treatment of patients with *ROS-1* gene alteration positive metastatic NSCLC.[174] A novel crizotinib-resistant mutation, *ROS1* D2033N, that is distinct from G2032R[175,176] has been discovered in a patient with *ROS1*-positive NSCLC.[177]

EGFR

Section Authors: Pasi A. Jänne, MD, PhD, Tony S. Mok, MD

Targeting EGFR continues to be an active area of clinical trials and novel drug development. Two EGFR-targeted therapies (osimertinib and necitumimab) were recently approved, and the result of the first ever trial comparing first- and second- generation EGFR TKI was presented. The LUX Lung 7 study[178] compared afatinib with gefitinib in 319 treatment-naive patients with activating *EGFR* mutations; the primary end points included progression-free survival (PFS), time to treatment failure, and OS. Sample size was not justified statistically. The results demonstrated improvement in PFS (HR = 0.73, 95% confidence interval [CI]: 0.57–0.95, $p = 0.017$); however, the median PFS times were 11.0 and 10.9 months for the afatinib and gefitinib arms, respectively. Tumor response rate was also statistically different at 70% versus 56%, favoring afatinib. The data

on OS are still immature. Severe EGFR TKI–related toxicities, including skin rash, stomatitis, and diarrhea, were more common with afatinib. This second-generation TKI is considered one of the first-line options for *EGFR* mutation–positive lung cancer but is unlikely to fill the role of first-generation EGFR TKIs.

The most common mechanism of acquired resistance to EGFR TKIs (in ~60% of cases) that develops in patients with *EGFR* mutations after drug treatment is the *EGFR* T790M mutation.[179] A mutant-selective EGFR inhibitor, osimertinib (AZD9291), is clinically effective in this patient population and received accelerated approval by the FDA. The approval was based on the results of two studies in patients with advanced disease and EGFR mutations whose disease had progressed while they were receiving prior systemic therapy, including a prior EGFR TKI, and whose tumors harbored the *EGFR* T790M mutation.[180] In the 411 patients with *EGFR* T790M in the two studies, the confirmed response rate by blinded independent central review was 59%. The most common side effects included diarrhea and rash; less than 5 % of patients experienced grade 3/4 toxicities.

Although *EGFR* mutations are rare in squamous cell lung cancer, EGFR expression is common. The anti-EGFR–directed antibody necitumumab was evaluated in a phase III clinical trial in combination with cisplatin and gemcitabine in 1093 patients. Patients treated with the combination of cisplatin, gemcitabine, and necitumumab had a prolonged OS (11.5 versus. 9.9 months, HR = 0.84, 95% CI: 0.74–0.96, $p < 0.01$) and PFS (5.7 versus. 5.5 months, HR = 0.85, 95% CI: 0.74–0.98, $p = 0.02$) compared with patients treated with cisplatin/gemcitabine alone.[181] Patients treated with the necitumumab combination experienced a higher rate of rash and aceneiform dermatitis than did patients treated with chemotherapy alone. Additionally, for advanced squamous cell carcinoma of the lung, the LUX Lung 8 open-label, phase III randomized controlled trial (N = 795) was published; it reported that afatinib improved PFS (2.6 versus 1.9 months, HR = 0.81, $p = 0.0103$) and OS (7.9 versus 6.8 months, HR = 0.81, $p = 0.0077$) over erlotinib as second-line treatment for patients.[182] Regulatory submissions to the FDA and European Medicines Agency have been filed for use of afatinib in patients with advanced squamous cell lung cancer whose disease progressed after first-line chemotherapy.[183]

Other Targets

Section Authors: Heather A. Wakelee, MD, Robert Pirker, MD

BRAF Mutation. Mutations (most commonly V600E) in *BRAF*, a serine-threonine kinase belonging to the RAF kinase family downstream of KRAS, are estimated to be present in 1% to 3% of NSCLC, more commonly in smokers.[184–188] Supporting early case series data,[186] the first prospective trial (BRF113928) reported a response rate of 40% with dabrafenib in BRAF V600E-mutated NSCLC.[189] The addition of the MEK inhibitor trametinib increased the overall response rate to 63%,[190] Vemurafenib is also active.[191–194]

KRAS Mutation. More common in smokers, *KRAS* mutations are present in approximately 20% to 25% of lung ADCs and 4% of lung squamous cell carcinomas.[79,195–198] To date, there are no established targeted therapies for *KRAS* mutations. In randomized phase II trials, the addition of the MEK inhibitor selumetinib to docetaxel improved median survival (9.4 months versus 5.2 month)[199] but failed to improve outcomes when added to erlotinib.[200] The combination of trametinib, a MEK inhibitor, plus either pemetrexed or docetaxel showed promising activity.[201–203] The MET inhibitor tivantinib plus erlotinib failed in a phase II trial after initial promise.[204,205] Preclinical data support the use of mammalian target of rapamycin inhibition and focal adhesion kinase inhibition as potential strategies,[196,206] and immune checkpoint inhibitors may be particularly active. Three major subgroups of *KRAS*-mutant ADCs with distinct biology and therapeutic vulnerabilities have been characterized on the basis of co-occurring genetic alterations in serine/threonine kinase 11 (liver kinase B1), tumor protein p53, and cyclin-dependent kinase inhibitor 2A/B.[207]

RET Rearrangement. RET proto-oncogene (*RET*) is estimated to be rearranged in 1% to 2% of patients with NSCLC,[208–210] and is associated with younger age and light smoking history in some series,[210,211] although a median age of 62 years old and some patients with a heavy smoking history were reported in a large series from Europe.[212] *RET* lung cancers have responded well to pemetrexed,[213] cabozantinib,[214] and vandetanib.[215,216] Preclinical models also support activity with alectinib, sunitinib, and sorafenib.[208,217,218]

MET. MET proto-oncogene, receptor tyrosine kinase (MET) is a tyrosine kinase receptor for hepatocyte growth factor. Amplification of *MET*, which is associated with poor prognosis, is detected in up to 20% of lung cancer cases,[219–223] and various MET inhibitors, including crizotinib[222,224,225] and less so tivantinib, have shown activity.[205,226,227] In the first reports of *MET* exon 14 splice variants, which are found in approximately 4% of lung ADCs, striking activity has been reported with crizotinib as well as with cabozantinib.[228] The frequency of *MET* exon 14 skipping mutations is especially high in sarcomatoid carcinoma,[229] an uncommon poorly

differentiated non–small cell carcinoma with a known poor prognosis.[41]

NTRK1. Oncogenic high-affinity nerve growth factor receptor (tropomyocin receptor kinase A) fusion proteins caused by rearrangements in neurotrophic tyrosine kinase 1 (*NTRK1*) are a rare oncogenic driver in NSCLC, with frequencies ranging from less than 1% to 3% reported in the literature.[230,231] Ongoing clinical trials with tropomyocin receptor kinase inhibitors, including entrectinib and LOXO-101, are open to patients with NSCLC as well as to those with other histological diagnoses, with initial responses seen.[230]

Immunotherapy

Section Authors: Julien Mazières, MD, PhD, Julie R. Brahmer, MD, Fred R. Hirsch MD, PhD

Introduction. Activation of the immune system to treat cancer has long been investigated, and after decades of disappointment, the tide has undoubtedly changed in 2015 with the success of recent clinical trials.

Rational. Multiple mechanisms of immune suppression prevent effective antitumor immunity.[232] Antibody therapies directed against negative immunologic regulators (checkpoints) have thus been developed. Blocking PD-1 (Fig. 6) and its ligands (PD-L1 and/or PD-L2) restores cytotoxic antitumor T-cell activity and, subsequently, acts as an effective antitumor response. A number of antibodies that disrupt the PD-1 axis have entered clinical development. They can be split into two main categories: those that target PD-1 (nivolumab and pembrolizumab) and those that target PD-L1 (atezolizumab, durvalumab, and avelumab).

Results from Recent Trials in NSCLC. Nivolumab is the first anti-PD-1 targeted drug approved for the treatment of pretreated NSCLC. A phase II and two large phase III studies have been reported this year (for details on this and the other trials mentioned in this section, see Table 2). Checkmate 063 tested nivolumab as a monotherapy for pretreated squamous NSCLC and showed interesting response and survival rates,[234] and Checkmate 017 was a phase III randomized trial that compared nivolumab to docetaxel in patients with pretreated squamous NSCLC. The OS was prolonged with immunotherapy, and the toxicity profile was much more favorable.[235] CheckMate 057, a trial with a similar design, was conducted on patients with pretreated nonsquamous NSCLC and also reported a benefit in terms of survival.[236]

Pembrolizumab has recently been approved by the FDA to treat PD-L1–positive metastatic NSCLC after failure of platinum-based chemotherapy. A large phase I trial reported a very promising response rate and durable response.[237] A phase III study has been recently completed and confirmed the results observed with

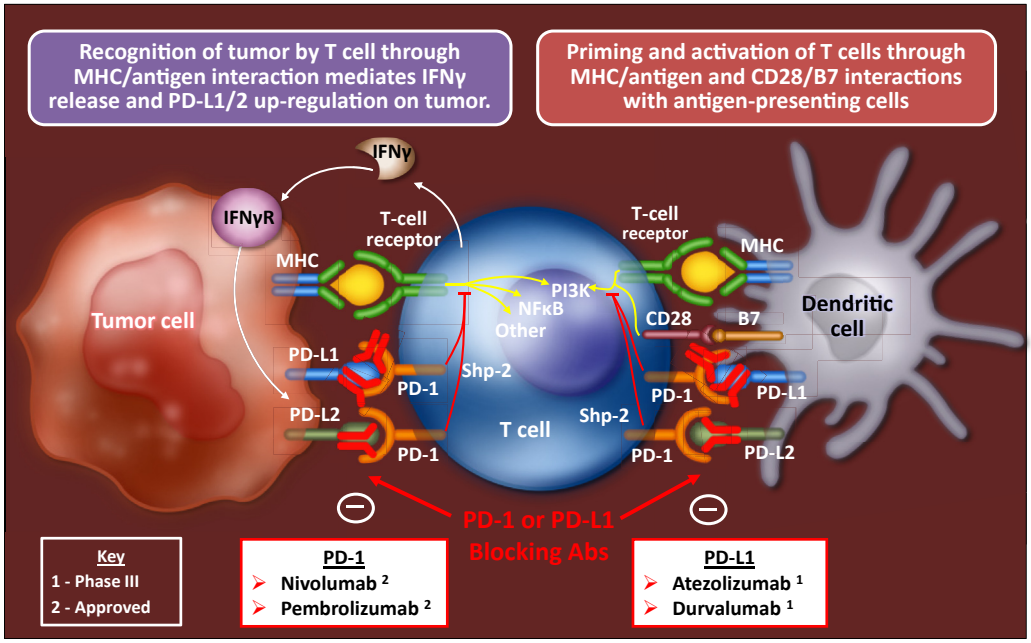


Figure 6. Illustration showing the role of the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway in suppressing antitumor immunity. Available therapies against PD-1 and PD-L1 are shown in the boxes along with their phase of development. IFNγ, interferon gamma; MHC, major histocompatibility complex; PD-L2, programmed death ligand 2; Abs, antibodies; NFκB, nuclear factor kappa light-chain enhancer of activated B cells. Modified with permission from Sznol et al.[233]

Table 2. Main Results of Phase II and III Immunotherapy Clinical Trials in NSCLC

Drug	Trial	Population	ORR	Median OS, mo	ORR PD-L1-Negative	ORR PD-L1-Positive	Grade 3/4 Side Effects
Nivolumab (PD-1 inhibitor)	CheckMate 063 phase II	117 patients with pretreated SCC	14.5%	8.2	14% (cutoff 5%)	24% (cutoff 5%)	17%
	CheckMate 017 phase III vs. docetaxel	272 patients with pretreated SCC	20% vs. 9%	9.2 vs. 6	17% (cutoff 1%) 15% (cutoff 5%) 16% (cutoff 10%)	17% (cutoff 1%) 21% (cutoff 5%) 19% (cutoff 10%)	9% vs. 71%
	CheckMate 057 phase III vs. docetaxel	582 patients with pretreated nonsquamous NSCLC	19% vs. 12%	12.2 vs. 9.4	9% (cutoff 1%) 10% (cutoff 5%) 11% (cutoff 10%)	31% (cutoff 1%) 36% (cutoff 5%) 37% (cutoff 10%)	10.5% vs. 53.7%
Pembrolizumab (PD-1 inhibitor)	KEYNOTE 001 phase I	495 patients with NSCLC (101 in first- line setting, 394 with pretreated NSCLC)	19.5% (24.8% first line)	12	10%	45.2% (cutoff 50% IC or TC)	9.5%
	KEYNOTE 010 phase II/III vs. Docetaxel	1034 patients with advanced NSCLC (pembro 2 mg vs. pembro 10 mg vs. docetaxel)	18% vs. 18% vs. 9%	10.4 vs. 12.7 vs. 8.5	Total 18% vs. 18.5% vs. 9.3%	Cutoff 50% 30.2% vs. 29.1% vs. 7.9%	13% vs. 16% vs. 35%
Atezoluzimab (PD-L1 inhibitor)	POPLAR phase II vs. docetaxel[239]	287 patients with pretreated NSCLC	NA	12.6 vs. 9.7	8% (TC0, IC0)	38% (TC3, IC3) 22% (TC2/3, IC2/3)	11%

ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; SCC, small cell cancer; NSCLC, non-small cell lung cancer; IC, immune cells; TC, tumor cells; NA, not available.

nivolumab, showing a significant improvement in OS with pembrolizumab versus with docetaxel.[238]

Atezolizumab, an antibody that targets PD-L1, showed encouraging results in a phase I study, leading to durable responses in pretreated patients. In a subsequent phase II randomized study (POPLAR), in which pretreated patients were randomized to receive either atezolizumab or docetaxel, it also showed a benefit in terms of survival.[239] A phase III study of similar design (the OAK study) was recently completed.

Durvalumab, which also targets PD-L1, has been tested as monotherapy with durable clinical activity in a dose escalation study[240] and also in combination with tremelimumab (a cytotoxic T-lymphocyte-associated protein 4 inhibitor) with promising results.[241] Phase II and III trials are ongoing in metastatic NSCLC (the ATLANTIC study), in locally advanced NSCLC (the PACIFIC trial), and in an adjuvant setting (the BR31-IFCT1401 trial).

Active Clinical Trials in NSCLC. Many trials are currently being conducted in thoracic oncology; there are trials examining almost all tumor types and tumor stages. Briefly, PD-1 and PD-L1 inhibitors are currently being tested in advanced NSCLC in the first-line setting in comparison with chemotherapy in patients selected on the basis of their PD-L1 expression status, in locally advanced NSCLC after chemoradiotherapy, and in early-stage NSCLC in the neoadjuvant or adjuvant setting. Combination trials are also ongoing in most of the previous settings.

Toxicity. Targeting immune checkpoints has led to the emergence of a new form of toxicity.[242,243] These autoimmune side effects are less frequent and less severe than the toxicities observed with chemotherapy and essentially concern endocrine glands (hypophysitis and hypothyroidism), the skin (rash), the gastrointestinal tract (diarrhea and colitis), the lung (pneumonitis), the liver (hepatitis), and the kidneys (renal insufficiency). However, significant patient education and vigilant oversight are needed to address these autoimmune-related toxicities quickly to avoid development of severe symptoms.

Predictive Biomarkers. Not all patients with advanced NSCLC benefit from these drugs. It is necessary to improve the selection of patients in this era of

personalized therapies and high costs. In most of the aforementioned recent trials, PD-L1 expression can be used to identify good responders and long-term survivors (for details see Table 2). Despite the fact that the PD-L1 IHC assay seems to be a good predictive assay, PD-L1 expression is not yet a perfect test. Many questions are still unresolved concerning the best antibody, the right cutoff for positivity versus negativity, the relevance of PD-L1 expression on immune cells versus tumor cells, and the heterogeneity of PD-L1 expression.[244–246] An academic effort is being conducted by IASLC, together with pharmaceutical and diagnostic companies, to optimize and homogenize this test.[244,245] Other potential molecular biomarkers under investigation, such as nonsynonymous mutation burden, could also be used to help select the best candidates for therapy.[247]

Future Efforts. Immunotherapy is an important advancement in the treatment of advanced pretreated NSCLC and is a new standard of care for second-line treatment of NSCLC. Future research initiatives to improve clinical outcomes are the (1) introduction of immunotherapies into the first-line setting for patients with advanced disease as clinical trials are ongoing and results should be released over the next 1 to 2 years; (2) use of immunotherapies during earlier stages of NSCLC (stages I–IIIA); (3) extension of indications toward other thoracic malignancies such as SCLC, mesothelioma, and thymic carcinoma; (4) combination of immunotherapy with standard therapies; (5) combination of checkpoint inhibitors (inhibitors of PD-L1/PD-1) with other immunotherapy inhibitors (inhibitors of cytotoxic T-lymphocyte-associated protein 4 and killer cell immunoglobulin-like receptors); (6) combination of immunotherapy with targeted therapy to combine the good response rate of targeted therapy in selected patients and the durable effects of immunotherapy; and (7) translational studies to optimize predictive biomarkers, such as PD-L1 expression[245,246] or other markers developed through DNA/RNA sequencing.

Specific Future Perspectives

Master Protocols

Section Authors: Yang Zhou, PhD, MPH, Roy S. Herbst, MD, PhD, Vassiliki A. Papadimitrakopoulou, MD, Mary W. Redman, PhD, David R. Gandara, MD, Fred R. Hirsch, MD, PhD

The development of a new cancer therapy from the initial stages of discovery to regulatory approval is a complex and expensive process that can take more than a decade. Clinical trials face many challenges, including lengthy start-up time, high upfront expense, and inability to recruit an adequate number of participants in a timely manner. This process is particularly difficult when attempting to develop targeted therapies for rare genotype subtypes of lung cancer. With this in mind, modernizing the clinical trials process to keep up with the molecular age by using innovative approaches and new trial designs is of high importance. The research community, along with government and patient advocates, have risen to the challenge to create "master protocols" that can screen large numbers of patients and then simultaneously test multiple new drugs or combinations, with resultant efficiencies in patient recruitment and regulatory approval.[248]

In the advanced metastatic stage, one of the first master protocols to have been developed is the Lung-MAP (S1400) study for previously treated squamous cell lung cancer. Lung-MAP is a registration-intent umbrella trial that simultaneously evaluates multiple treatments through a series of genotypically driven phase II/III substudies, with "rolling" opening and closing so that each functions in an independent manner. The current schema for Lung-MAP is shown in Figure 7. The project is a unique public-private partnership led by SWOG (formerly the Southwest Oncology Group) together with the National Cancer Institute and its National Cancer Trials Network, the Friends of Cancer Research, and the Foundation of the National Institutes of Health.[249,250]

This master protocol provides a mechanism to genomically test a large population of patients with squamous lung cancer for genetic alterations. Although most of the substudies evaluate therapies specifically targeted at the particular alteration found in a specimen of a patient's tumor, patients who do not have one of the genetic alterations currently being studied are assigned to a "nonmatch" substudy. Lung-MAP was first launched on June 16, 2014, and has undergone several protocol amendments to address the evolving therapeutic landscape and the emergence of immunotherapy as one of the prime treatment modalities for NSCLC.

An example of a master protocol in the early-stage setting, the ALCHEMIST (see Fig. 5) trial, which was described previously in the "Role of Adjuvant Therapy" section, randomizes patients with resected stage IB–IIIA NSCLC with *EGFR* mutations or *ALK* translocations to receive either placebo or adjuvant erlotinib or crizotinib, respectively. The duration of administration of the adjuvant targeted therapy treatment or placebo is 2 years.

Quality and Value of Therapy

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In 2013, the Institute of Medicine declared the cancer treatment delivery system in the United States to be a system in crisis and proposed a conceptual framework to improve the quality of care.[251,252] A key recommendation was that continuous quality measurement and

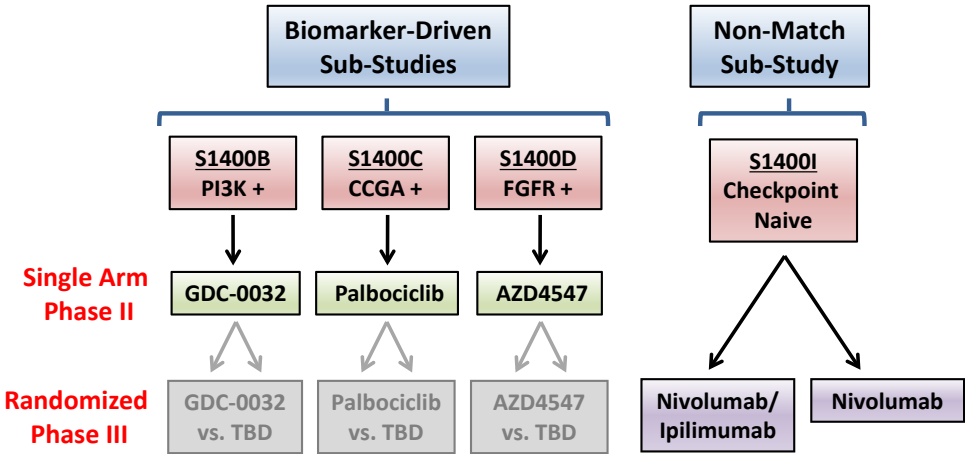

Figure 7. Schema of the Lung-MAP (S1400) study. Biomarker-driven substudies will progress to phase III if the study meets its end point and a phase III is feasible, at which point the standard of care arm will be determined. TBD, to be determined; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase positive; CCGA, cell cycle gene alteration positive; FGFR, fibroblast growth factor receptor positive.

clinical improvement strategies had to be at the center of day-to-day oncology practice. An earlier report from the National Quality Forum identified a lack of available outcomes versus process metrics in addition to the difficulties of collecting and managing data as fundamental weaknesses.[253] The widespread adoption of electronic medical records both in the United States and overseas means that we now have the ability to adequately measure the adoption and utilization of key quality metrics. The high cost of recently approved drugs for lung cancer has heightened the importance of value as a consideration in treatment decisions and has placed lung cancer at the center of emerging and evolving paradigms of care delivery.[254]

In 2015, we saw a number of innovative efforts from the American Society of Clinical Oncology, European Society for Medical Oncology, and National Comprehensive Cancer Network to address escalating and unsustainable drug costs with credible data-driven analyses.[255,256] These initiatives allied with the introduction of the Medicare Access and Chip Reauthorization Act mean that not only has the cost-benefit debate finally come of age, but that physicians will increasingly be held responsible for quality of care and cost control in the years ahead. The management of lung cancer is no exception. Given the number of drugs that are now available to the treating oncologist, as well as the incidence and demographics of thoracic tumors, it is likely that significant treatment changes will be required if we are to comply with federally mandated initiatives such as pathway-directed treatment, episodic bundled payments, and merit-based incentive payment schemes. As a result, the IASLC has formed a quality and value task force and has partnered with the American Society of Clinical Oncology to jointly develop lung cancer treatment quality measures. The IASLC will continue to lead transformative efforts in the management of lung cancer as we look to achieve value-based health care both in the United States and internationally.

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