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Scientific Advances in Thoracic Oncology 2016

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Drs. Stone, Jett, Field, Mulshine, Dacic, Rami-Porta, Detterbeck, Donington, Higgins, Kim, Johnson, Ahn, Peters, Wynes, Baas, Leighl, Gandara, and Spigel have nothing to disclose.

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Abstract

Lung cancer care is rapidly changing with advances in genomic testing, the development of next-generation targeted kinase inhibitors, and the continued broad study of immunotherapy in new settings and potential combinations. The IASLC and the Journal of Thoracic Oncology publish this annual update to help readers keep pace with these important developments. Experts in thoracic cancer and care provide focused updates across multiple areas including prevention and early detection, molecular diagnostics, pathology and staging, surgery, adjuvant therapy, radiotherapy, molecular targeted therapy, and immunotherapy for non-small cell lung cancer, small cell lung cancer, and mesothelioma. Quality and value of care and perspectives on the future of lung cancer research and treatment have also been included in this concise review.

Introduction

A very exciting time exists in the field of thoracic malignancies. In the past year, we have witnessed tremendous advances in thoracic cancer research and treatment. In this annual report, now in its second year, we are pleased and excited to bring together leaders in the field to summarize recent major breakthroughs and significant advances in prevention and early detection, molecular diagnostics, pathology, staging, surgery, adjuvant therapy, radiotherapy, molecular targeted therapy, and immunotherapy. Important progress has been made in small cell lung cancer and malignant mesothelioma and has also been included. With more novel treatment options, we reviewed the quality and value of such therapy and lastly, a perspective on emerging trends and future directions in lung cancer research and treatment is provided. The Editors would like to acknowledge all co-authors for providing a succinct and expert commentary in a swift manner and thank Managing Editor, Murry Wynes, for outstanding editorial assistance.

Prevention and Early Detection

Cigarettes, E-cigarettes, and Cannabis

Emily CA Stone, MBBS MMed; K Michael Cummings, PhD, MPH; and James R Jett, MD.

Cigarettes
Tobacco cigarettes account for the vast majority of tobacco consumed worldwide and is by far the most lethal type of tobacco product consumed and costs global economies $1 trillion annually through loss of productivity and health care expenditure. Tobacco control interventions such as higher taxes, graphic health warnings, mass media campaigns and bans have led to a fall in smoking rates in developed countries, but less so in low income countries where the tobacco industry is building market share. However, when such declines in smoking rates do occur, they result more from reduced youth uptake than from smoking cessation. Smokers are clearly looking for viable options to move away from cigarettes, but until recently few alternatives were available. The rapid uptake of e-cigarettes by smokers over the past decade has posed some interesting challenges for the medical profession. Will these new nicotine delivery products offer smokers an escape from cigarettes? Will nonsmokers (especially the young) be led into smoking? Another issue confronting the lung health field is the movement to legalize cannabis, which appears to be changing how cannabis is perceived and used in ways that could have important health consequences down the line.

**E-cigarettes**

Electronic cigarettes, “e-cigarettes”, are a form of electronic nicotine delivery system (ENDS) that have emerged as a potential alternative to conventional tobacco cigarettes and as a possible aid to tobacco cessation. A newly published systematic review identifies the need for frequent re-evaluation of evidence in a field characterized by rapid change. The regulatory status of e-cigarettes, an industry appropriated by global tobacco companies, varies around the world, with restrictions ranging from minimum age-of-purchase to a ban on sales altogether. While it does appear that e-cigarettes can help some smokers to quit or reduce their smoking, the evidence is mixed. The recent United States (US) Surgeon General’s report on e-cigarettes discourages the sale and use of any nicotine-containing product by nonsmokers, especially the young. Conversely Public Health England cited e-cigarettes as “95% safer” than tobacco cigarettes, identifying their adoption by smokers as a key strategy for tobacco cessation. A 2016 Cochrane review of e-cigarettes for smoking cessation identified two studies that showed an increased chance of smoking cessation with the use of nicotine e-cigarettes compared with nicotine-free e-cigarettes, but acknowledged a lack of evidence for long-term safety. The likelihood of cigarette cessation was shown to be lower in those using e-cigarettes compared to other methods in a recent small study of cancer patients. A 2014 review of e-cigarettes in lung cancer patients noted the urgency for smoking cessation after a diagnosis of lung cancer, but advised against recommending e-cigarette uptake after diagnosis given the lack of safety and efficacy data.
Cannabis

Cannabis, also known as marijuana, has been legalized in 28 states in the United States for medical purposes. Recreational cannabis use is now permitted in 8 states and Washington, DC. A number of states have also decriminalized possession of small amounts for personal use. Similar legalization efforts have occurred in Canada, Uruguay, Germany, Israel, and other countries. Between 2002 and 2014, the prevalence of past 30-day cannabis use in the US increased 35%. In 2014, 8.4% of those 12 years of age and older reported past 30 day use of cannabis and 3.5% reported daily use.

Cannabis is most commonly smoked, but can be vaped, ingested or used topically. Cannabinoids enter the blood stream and reach the brain within seconds to a few minutes when smoked. Oral ingestion of cannabis takes 30 minutes or longer to have its effects in the brain.

The most recent and most comprehensive review of the health effects of cannabis use was recently published by the National Academies of Sciences, Engineering and Medicine. There is at least moderate evidence that cannabis is beneficial for chronic pain, neuropathic pain, and muscle spasms, especially related to multiple sclerosis. There is also moderate evidence that cannabis improves nausea and vomiting related to chemotherapy. There is less certain evidence that cannabis can increase appetite and prevent weight loss.

Cannabis usage has been found to impair driving ability, increase drowsiness, cause addiction in approximately 10% of users, and increase psychotic episodes and hyperemesis in heavy long-term users.

Cannabis smoke contains many of the same toxins as tobacco smoke such as polycyclic aromatic hydrocarbons (PAHs). Studies have shown that frequent cannabis use can cause chronic bronchitis (cough, sputum, wheeze) but there is no established causality with chronic obstructive pulmonary disease. There is also no conclusive evidence that cannabis usage increases the risk of lung cancer, although cannabis users often smoke cigarettes making it difficult to isolate the impact of regular cannabis use on the risks for chronic lung disease. The best evaluation of the association between smoking cannabis and lung cancer risk, after adjusting for tobacco usage, is a pooled analysis of six case controlled studies with 2,159 patients with lung cancer and 2,985 controls which failed to find evidence of an increased risk of lung cancer among long term cannabis smokers. Given the changing potency and patterns of use of cannabis, including use by non-cigarette smokers, there is an urgent need to conduct research to assess its effects on lung health.
Lung Cancer Screening

John K Field, PhD, FRCPath; Harry JM Groen, MD, PhD; and James L Mulshine, MD

This is a very dynamic time for both computed tomography (CT)-based lung cancer screening research and the process of clinical implementation of routine CT lung cancer screening. Notable improvements in efficient screening detection rates have been reported, thus addressing concerns about high-false positivity in screening work-ups. These reports, including the British pilot study, UKLS, the NELSON trial group, the I-ELCAP and the preliminary experiences with the ACR LungRADS approach, cite false-positive diagnostic detection rates of less than 10%. In addition, the field recognized that non-standardized terms for characterizing the efficiency screening process were also confusing. Some investigators consider the finding of lung nodules on a CT scan as being equivalent to a cancer diagnosis; and since lung nodules are common in smokers, this misconception resulted in the perception of a high false diagnosis rate. From a screening subject perspective this situation leads to unnecessary distress; however, this situation in lung cancer screening could benefit from education for subjects and those involved in screening about the fact that pulmonary nodules are not equivalent to lung cancer, most pulmonary nodules are benign in origin, and lung cancer is a pathology diagnosis, not an imaging diagnosis. A consensus is emerging that working towards more systematic definitions for key parameters for a lung cancer screening is a near term priority that could reset screening subject expectations and reduce anxiety with the process.

Additional areas of progress include a number of research efforts to effectively integrate tobacco cessation, both as a service and as a research focus, within the process of lung cancer screening. Dr. Jamie Ostroff of Memorial Sloan Kettering Institute is leading an exciting new research effort to address this vital aspect of lung cancer screening research.

A major Canadian effort buttressed the growing evidence on the cost efficiency of providing high quality lung cancer screening services while still providing public health benefit. Using conservative assumptions, an analysis of screening benefit was favorable relative to its impact on person-years of life saved. However, each nation has to make its own decision relative to the complex array of health priorities in each distinctive national setting.
Pathology and Staging

Pathology and Diagnostics

Yasushi Yatabe, MD, PhD; Lukas Bubendorf, MD; and Sanja Dacic, MD, PhD

The acquisition of appropriate tumor material is crucial for accurate diagnosis and molecular testing of lung cancer. To meet the clinical demand, new methods have been developed. Electromagnetic navigation bronchoscopy using assisted-CT allows to precisely target peripheral nodules, while transbronchial cryo-biopsy is a promising tool to obtain large and high-quality specimens. Several studies have reported cytological specimens obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or fine-needle aspiration (FNA) are equally suitable for molecular testing. The upcoming molecular testing guideline has been updated to include newer targetable genes (ROS1, RET, BRAF, HER2 and MET), resistant mutations, advances in technology including liquid biopsy and next generation sequencing (NGS), as well as reaffirming or updating the previous recommendations. The draft was published on the College of American Pathologists, IASLC, and Association for Molecular Pathology websites for open comment and the final recommendations are planned to be published in 2017.

In addition to the traditional specimens, liquid biopsies, especially circulating tumor cell DNA (ctDNA), have been increasingly used in clinical practice. Although the liquid biopsies have been investigated for various targetable genes in NSCLC, it is mainly used in the detection of EGFR mutations when there is inadequate tumor sample or when the risk of biopsy is high. While plasma EGFR testing has high specificity, the main concern remains concordance with tissue biopsies and its relatively low sensitivity, especially for T790M. This situation has improved with the use of advanced Next-Generation Sequencing (NGS) platforms. The US Food and Drug Administration (FDA) has recently approved the cobas EGFR Mutation Test v2 plasma-based assay as a companion diagnostic for erlotinib. If the plasma EGFR results are negative, a tissue based testing should be performed. Saliva and urine have also been used to detect EGFR mutations.

Clinically, immune checkpoint inhibitors provide an additional treatment option in advanced NSCLC and PD-L1 immunohistochemistry (IHC) is used as a biomarker to select patients who are more likely to respond to such treatment in either the first or second line setting. However, the development of different PD-L1 IHC assays with individual cut-off values, antibodies, and platforms for the immune checkpoint inhibitors have raised concerns among pathologists and oncologists, in order to
obtain some clarity, the individual five assays have been, and are currently being, compared to one another. Among these studies, first insights for possible harmonization of different PD-L1 IHC assays were provided with the BluePrint project, which was conducted in collaboration with pharmaceutical companies, diagnostic partners, AACR and IASLC. Three clones (22C3, 28-8 and SP263) showed similar results in tumor cell staining, while the SP142 assay displayed significantly less tumor cell staining. All assays stained immune cells with greater variability than tumor cells. Recently, tumor mutation burden was focused on as an alternative predictive biomarker for immune checkpoint inhibitor treatment, as a high non-synonymous mutational load is expected to lead to more tumor-specific T-cell responses though expression of neoantigens. Indeed, the mutation burden enriched the patients who benefit from first-line therapy with nivolumab and the combination of mutation burden plus high PD-L1 expression appeared to be more predictive.

**TNM staging system**

Ramon Rami-Porta, MD; Frank C Detterbeck, MD; and Eric Lim, MB ChB, MD, MSc, FRS (C-Th)

The 8th edition of the tumor, node and metastasis (TNM) classification of lung cancer includes adenocarcinoma in situ (Tis[AIS]) and minimally invasive adenocarcinoma (T1mi); incremental categories based on 1 cm increase in tumor size from T1a-c to T2a-b, with tumors >5 to ≤7 cm and >7 cm reclassified as T3 and T4, respectively; reclassification of endobronchial location <2 cm from the carina and total atelectasis-pneumonitis as T2, and diaphragmatic invasion as T4. Nodal classification and intrathoracic metastasis remain unchanged. Single extrathoracic metastasis is now classified M1b separately from multiple extrathoracic metastases as M1c. Amendments were made to stage grouping, as well as classification of lung cancers with multiple lesions. Overall survival by clinical stage according to the 7th edition and the 8th edition is shown in Figure 1.

The revised TNM for mesothelioma included combination of T1a and T1b into the new T1 category; collapse of N1 and N2 into N1 category; and reclassification of N3 as N2. The M categories remain unchanged and stage grouping modified for improved stratification.

The TNM classification of thymic epithelial malignancies was a joint effort of the IASLC and the International Thymic Malignancies Interest Group. The T component is classified according to the involved organs. Nodal involvement is divided into N1 (anterior –perithymic– nodes) and N2 (deep intrathoracic or supraclavicular nodes). Stages I, II, IIIA and IIIB are based on increasing local organ
invasion; with stage IVA, including N1 and M1a (separate pleural or pericardial nodules); and stage IVB, including N2 and M1b (intrapulmonary or distant organ metastasis) \(^85\).

For esophageal and esophagogastric junction cancers (cancers with their epicenter within the proximal 2 cm of the cardia) \(^86\), tumors were staged clinically \(^87\), pathologically \(^88\) or pathologically after induction treatment \(^89\). This edition included subdivision of T4 into T4a and T4b depending on invaded organ; differentiation of clinical and pathologic stages for squamous and adenocarcinoma; introduction of pathologic stages after induction for both cancers, and of prognostic sub-groups based on anatomic extent, location and differentiation grade \(^90\)-\(^92\).

**Therapy**

**Surgery**

Hisao Asamura, MD and Jessica Donington, MD

*Minimally Invasive Lobectomy*

Over the past 2 decades, video-assisted thoracic surgery (VATS) has become a common surgical technique. Along with this came improvements in operative and visual instruments. Although a definition of VATS has been conflicting, VATS generally means operating using thoracoscopy with a minimal number of small incisions and without rib spreading. Treatment of lung cancer via VATS has been performed on the assumption that it has equivalent oncological outcome compared to open thoracotomy but is a less invasive method. However, scientifically supported comparisons between VATS and open thoracotomy with randomized controlled trials have been scarcely reported. Some studies using large national or regional databases reported that VATS had lower incidence of postoperative complications or shorter length of hospital stay by 1-2 days, but there is uncertainty on whether this is clinically meaningful \(^93\)-\(^96\). On the other hand, some reports concluded that more incidence of nodal upstaging was observed in thoracotomy than VATS, indicating the possibility of insufficient nodal evaluation in VATS \(^97\), \(^98\). Of note, these conclusions were derived from retrospective studies, therefore they always harbor hidden biases that may affect the outcome.

A randomized controlled trial from Denmark concluded that VATS was associated with less postoperative pain and better quality of life (QOL) compared with thoracotomy for the first year after surgery \(^99\). This study focused on the self-reported scoring systems of pain and QOL as outcomes.
Further randomized studies would be required that compare VATS to thoracotomy using objective outcomes.

Robot-assisted thoracic surgery (RATS) is defined as a surgery that utilizes a robotic system for all or mostly all of the crucial aspects of the operation. In a recent retrospective study, RATS was reported to be equivalent as VATS in all measures of quality for treatment of lung cancer. To date, no randomized trials have reported the comparative data between RATS and VATS/thoracotomy for lung cancer.

The extent of parenchymal resection remains an area of evolution. There are several situations where sublobar resection should be considered as primary treatment for early stage NSCLC. In patients with limited pulmonary reserve or with poor physical conditions, sublobar resection, either as segmentectomy or wedge resection, can be reasonably selected as a surrogate for lobectomy. In case of multiple primary NSCLCs, sublobar resections should be considered as well. Of course, there are anatomic limitations for such resection, there is no doubt that such surrogate resections could be selected.

**Surgical Quality**

The importance of surgical quality measures (QM) in NSCLC was highlighted in 2016. Two independent studies from the National Cancer Database (NCDB) found compliance with basic QMs was associated with improved OS following NSCLC resections. A study examining stage I NSCLC looked at: 1) anatomic resection; 2) operation within 8 weeks of diagnosis; 3) R0 resection; and 4) > 10 lymph nodes sampled. While 99% of resections met at least one QM, only 22% satisfied all four. Median OS varied from 31 to 89 months for those who met none compared to four QMs. Similarly, in clinical stage IIIA, adherence to four QMs: (1) neoadjuvant therapy; 2) lobectomy or greater; 3) R0 resection; and 4) > 10 lymph nodes sampled was examined and only 12.8% of stage IIIA resections satisfied all QMs. Median OS varied from 12 to 43.5 months for those that met none compared to four QMs. Compliance with QMs was associated with age, insurance type, hospital volume and comorbidity score, but remained a strong independent predictor of survival in both studies. The benefit of thorough thoracic lymphadenectomy in early stage NSCLC was further emphasized with multiple meta-analysis and population-based studies demonstrating improved OS when greater numbers of lymph nodes were resected and examined.

**Adjuvant Therapy in Completely Resected NSCLC**
Heather Wakelee, MD; and Yi Long Wu, MD

Cisplatin-based adjuvant chemotherapy is the standard of care for patients with resected stage II and IIa NSCLC and is commonly used for patients with larger (at least 4 cm in size) stage IB tumors. In 2016 we learned from a subset analysis of the E1505 trial that the 4 platinum-based doublets utilized (cisplatin with either vinorelbine, gemcitabine, docetaxel, or pemetrexed) had comparable efficacy but differing toxicity profiles. Further data to support the 4 cm cut-off to recommend adjuvant chemotherapy came from a propensity score-matched analysis performed in Korea which divided stage IB patients into those with a tumor of 3 cm or smaller with visceral pleural invasion, tumors 3-4 cm in size and those 4-5 cm in size. The study reported that the only group with a clear differential benefit from adjuvant chemotherapy were those with the tumors 4-5 cm in size. A Chinese study which utilized carboplatin/docetaxel and randomized nearly 200 patients to pre-operative or post-operative therapy was presented at IASLC WCLC 2016. Both DFS and OS trended in favor of the adjuvant approach, but the trial was too small to draw any definitive conclusions and leaves us with continued questions about the ideal strategy. Recent studies with strategies including the addition of bevacizumab in E1505 and the use of the MAGE-A3 vaccine in MAGRIT failed to demonstrate any improvement in survival with these approaches.

Encouraging data from retrospective and non-randomized trials of adjuvant EGFR TKIs in patients with EGFR-mutant NSCLC has led to randomized trials including the phase III RADIANT trial of adjuvant erlotinib or placebo. In the EGFR mutated subset (N=161) DFS favored erlotinib (HR 0.61, NS); however; OS did not trend favorably, but was immature. Table 2 includes multiple ongoing trials of adjuvant EGFR TKI (and adjuvant ALK TKI) therapy for resected early stage NSCLC patients with tumors harboring the appropriate molecular marker. With approvals in advanced stage disease, multiple PD-1/PD-L1 immune checkpoint inhibitors are now being studied in the adjuvant setting.

Advances in Radiotherapy

Kristin Higgins, MD; and Suresh Senan, MD

Locally Advanced Stage III

The standard of care for locally advanced NSCLC remains concurrent platinum-based chemotherapy and radiation to 60-66 Gy. The PROCLAIM study evaluated two concurrent chemotherapy schemes, pemetrexed-cisplatin versus cisplatin-etoposide, with thoracic radiation therapy (TRT) in stage IIIA/IIIB
non-squamous NSCLC. Survival with pemetrexed-cisplatin-TRT was not superior, although less ≥ grade 3 neutropenia occurred in the pemetrexed arm \(^{115}\). A randomized study comparing intensity modulated radiotherapy (IMRT) to passively scattered proton therapy reported no differences in the primary study endpoint of treatment failure (defined as either local progression or ≥ grade 3 radiation pneumonitis) \(^{116}\). Secondary analyses of the RTOG 0617 study found less high-grade pneumonitis, and lower cardiac doses with use of IMRT versus 3D-CRT \(^{117}\), and also less clinically meaningful decline in QOL with IMRT \(^{118}\).

**SBRT for early stage and for oligometastatic disease**

The impact of stereotactic body radiotherapy (SBRT) for peripheral early-stage NSCLC is reflected in a SEER analysis showing that RT rates for stage IA NSCLC increased from 13% to 29% between 2004-2012, with significant improvements in OS in the RT cohort \(^{119}\). A systematic review reported only limited changes in health-related QOL following SBRT \(^{120}\). For patients with centrally located lung tumors, both a prospective trial \(^{121}\) and a literature overview \(^{122}\) suggested that the toxicity rates of SBRT were acceptable, but the HILUS trial reported significant rates of fatal hemoptysis \(^{123}\). Mature data from prospective trials of SBRT for central tumors are awaited. In stage IV oligometastatic NSCLC (1-3 metastatic lesions), a randomized phase II trial in patients not progressing after first-line systemic therapy, demonstrated a significant improvement in PFS with local consolidative therapy ((chemo)RT or resection of all lesions) compared with standard therapy (11.9 months vs. 3.9 months; log-rank p = 0.0054) \(^{124}\).

**Use of WBRT in NSCLC**

Up to 50% of patients with NSCLC will develop brain metastases \(^{125,126}\). In selected patients, surgery or radiosurgery offers the best results. However, patients with large volume metastatic brain disease have traditionally been treated with whole brain radiotherapy (WBRT). In the QUARTZ trial, 538 patients with brain metastases from NSCLC, who were ineligible for surgery or radiosurgery were randomized to WBRT (20 Gy/5 fractions) or best supportive care \(^{127}\). The primary outcome measure was quality-adjusted life-years (QUALYs), and no differences in OS, QOL, or dexamethasone use were observed between the two groups. This study provides evidence that poor prognosis patients with brain metastases from NSCLC do not benefit from WBRT. However, the QUARTZ data are not applicable to younger patients, those with limited extra-cranial disease, and when radiosurgery remains an option.
ALK

Benjamin Solomon MBBS, PhD; and Dong Wan Kim, MD, PhD

New generation TKIs

Currently, ceritinib and alectinib are approved by the US FDA as subsequent treatment options after crizotinib failure in ALK-positive patients. Several recent trials have provided clinical data on these drugs in the crizotinib naive setting. In the ASCEND-4 study, a phase 3 study comparing ceritinib with chemotherapy, the median PFS was 16.6 months for ceritinib compared with 8.1 months for chemotherapy (HR 0.55 [95% CI 0.42-0.73]; p<0.00001) 128. The randomized phase II J-ALEX study compared alectinib 300 mg bid and crizotinib in Japanese patients without prior ALK inhibitor treatment. Alectinib was significantly superior to crizotinib with PFS not reached vs 10.8 months, respectively (HR 0.34) 129. Results from a global phase 3 study (ALEX study) comparing alectinib 600 mg bid and crizotinib will likely be reported soon. Lorlatinib and brigatinib showed efficacy in patients with brain metastasis and/or resistant mutations including G1202R 130, 131. Phase 3 trials comparing these agents with crizotinib are ongoing.

ALK resistance and sequencing of therapies

Resistance to first and second generation ALK TKIs may occur through ALK-dependent mechanisms, primarily ALK kinase secondary mutations or amplification; or ALK-independent mechanisms, including activation of oncogenic bypass tracts or cell lineage change (small cell or epithelial to mesenchymal transformations) 132, 133. Recently, Gainor et al. extensively characterized mutations in post TKI biopsies and identified differences in the frequency and type of secondary mutations occurring in patients progressing on crizotinib compared to second generation ALK TKIs 134. Secondary ALK mutations were present in 20-30% of patients progressing on crizotinib, compared with over 50% of patients progressing on a second generation ALK TKI. Mutations such as L1196M and G1269A were frequent in post-crizotinib biopsies, they were less common after second generation ALK TKIs. In contrast, G1202R, which was only found in 2% post-crizotinib, was the most frequent mutation after second generation TKIs. Interestingly, the mutation profile of tumors changes with time and with the influence of sequential ALK TKIs 134, 135. While the empirical use of sequential ALK TKI such as crizotinib followed by ceritinib or alectinib has resulted in long-term disease control and excellent survival, characterization of resistance mechanisms using serial tumor biopsies has potential to guide selection of multiple, sequential lines of ALK inhibitor therapy 136, 137. For example, the I1171 mutation that is associated with resistance to crizotinib and
alectinib may be sensitive to ceritinib; or the G1202R mutation that is associated with resistance to crizotinib, alectinib, and ceritinib may be sensitive to the third generation ALK TKI lorlatinib.\textsuperscript{130}

### EGFR

Melissa Johnson, MD; James CH Yang, MD, PhD; and Lecia V Sequist, MD

The optimal treatment for patients with \textit{EGFR} mutations continued to be refined in 2016. Key research findings centered around comparing first-line \textit{EGFR} TKIs, solidifying the role of the newly approved osimertinib for acquired resistance, development of novel \textit{EGFR} TKIs, and the use of plasma to genotype \textit{EGFR}.

The LUX-Lung 7 trial compared first-line afatinib to geftinib among \textit{EGFR}-mutant patients. A slight PFS benefit for afatinib with HR 0.73 (95% CI 0.57-0.95), p=0.017 was seen but the median PFS was 11 months in both arms.\textsuperscript{138} Furthermore the OS was similar in both treatment arms, including analyses within exon 19 deletion and L858R.\textsuperscript{139} At this time, it is unclear if there are clear differences between the first-line \textit{EGFR} TKIs; therefore, afatinib, erlotinib and gefitinib are all reasonable options.

Osimertinib became the first US FDA-approved T790M-mutant specific, WT sparing (3rd-generation) \textit{EGFR} TKI in November 2015. This year we saw mature results from two large single-arm phase II studies of osimertinib at 80mg daily in patients with T790M-mediated acquired resistance. The AURA extension and AURA2 trials showed an ORR of 62% and 58%, DCR of 90% and 92%, and PFS of 12.3 and 9.9 months, respectively.\textsuperscript{140, 141} The phase III AURA3 trial randomized 419 \textit{EGFR}-mutant patients with T790M after failure of first-line \textit{EGFR} TKIs to osimertinib or platinum/pemetrexed with a PFS was 10.1 months and 4.4 months, respectively (HR 0.30; 95% CI, 0.23 to 0.41; P<0.001).\textsuperscript{142} Osimertinib may also have unique CNS activity.\textsuperscript{143} \textit{EGFR}-mutant patients (\textit{EGFR} T790M not required) with leptomeningeal disease were treated with osimertinib 160 mg (BLOOM study).\textsuperscript{144} Nine of 20 patients had radiographic responses; improvements in neurologic examination and declining levels of ctDNA in the CSF were also reported. Promising PFS was seen with first-line osimertinib in \textit{EGFR}-mutant NSCLC patients\textsuperscript{145} and results of a phase III study comparing osimertinib to erlotinib/ gefitinib (FLAURA) are greatly anticipated.

The need for tissue re-biopsy to determine T790M status can be a barrier to appropriate treatment selection. Plasma detection and semi-quantitation of the activating \textit{EGFR} and T790M mutation is a
useful tool to predict for the efficacy of osimertinib and an assay for T790M in ctDNA was US FDA-approved in 2016 as a companion diagnostic to osimertinib. Novel techniques for T790M detection in both plasma and urine have been studied and minimally-invasive assays are expected to gain prominence in the future.

Several other novel EGFR TKIs reported updates in 2016. Olmutinib was approved in Korea, but global development has been halted. EGF816 and ASP8273 are active in T790M positive patients. Rociletinib development has been ceased due to low activity in T790M patients. A novel EGFR TKI, AZD3759 has increased CNS penetration, but does not inhibit T790M.

Finally, although immune therapy checkpoint inhibitors have had a huge impact in advanced NSCLC in 2016, the studies to date show little, if any, benefit for EGFR mutation-positive patients.

ROS1

Alice Shaw, MD, PhD and Myung-Ju Ahn, MD, PhD

Almost all patients with ROS1-rearranged NSCLC develop resistance to crizotinib. Although the mechanisms of acquired resistance are incompletely understood, several case series of repeat biopsies with supporting preclinical studies have identified missense mutations within the ROS1 kinase domain, such as G2032R, D2033N, S1986Y/F, and L2155S, which can mediate crizotinib resistance. The ROS1 G2032R mutation which is located at the solvent front of the kinase hinge, confers high level resistance to crizotinib and appears to be the most common resistance mechanism in crizotinib-treated patients. Preclinical studies suggest that cabozantinib, foretinib, and lorlatinib may be able to overcome this resistance mutation. The ROS1 D2033N resistance mutation was identified in a patient with CD74-ROS1 fusion who relapsed on crizotinib. Like G2032R, D2033N is located at the solvent front of the kinase hinge. Notably, this patient was highly responsive to the multitargeted inhibitor cabozantinib, experiencing a rapid and durable clinical response. Recently, a dual ROS1 kinase domain mutation, S1986Y and S1986F, was discovered in a ROS1-positive patient who had relapsed on crizotinib. This patient subsequently responded to lorlatinib. Finally, the novel resistance mutation, L2155S, was identified in crizotinib-resistant HCC78 cell lines harboring the SLC34A2-ROS1 fusion. Whether this ROS1 mutation will emerge in patients exposed to crizotinib remains to be determined. To date, the lorlatinib phase 1/2 trial represents the largest study to examine crizotinib-resistant, ROS1-positive NSCLC patients. Preliminary data suggest that lorlatinib can induce responses in some patients,
but ROS1 mutation status in these responders has not been reported. A newer next-generation ROS1 inhibitor, TPX-0005, will soon enter phase 1 clinical testing. TPX-0005 has been specifically designed to overcome the solvent front mutations in ALK and ROS1, including ROS1 G2032R. In addition to secondary mutations within ROS1, several different off-target mechanisms of resistance have also been reported in crizotinib-resistant tumors, including a KIT D816G activating mutation and EGFR pathway activation. Further studies of crizotinib-resistant tumor specimens are needed to fully define the spectrum of on-target and off-target resistance mechanisms in ROS1-positive NSCLC. Elucidating these mechanisms may inform the rational development of new treatment strategies for crizotinib-resistant, ROS1-positive NSCLC.

Other targets (BRAF, MET, ERBB2/HER2, RET, NTRK, FGFR, others)

Daniel B. Costa, MD, PhD and Jyoti D. Patel, MD

Although the approval of tyrosine kinase inhibitors (TKIs) matched to a driver oncogene - until 2016 - has been restricted to tumors with genomic aberrations in EGFR, ALK and ROS1, other putative driver events can predict for response to targeted therapies in advanced NSCLC, particularly in lung adenocarcinoma (Table 3).

The genotype/inhibitor duo closest to receiving approval by the US FDA and other worldwide regulatory agencies is the B-Raf proto-oncogene serine/threonine kinase (BRAF) V600E mutation (~1-2% of adenocarcinomas) with dabrafenib+trametinib, as the overall response rate (ORR) of this BRAF+MEK inhibitor combination is over 60% and is associated with prolonged disease control. The European Union approved the aforementioned combination in April 2017.

Another promising treatable target is MET Proto-Oncogene, Receptor Tyrosine Kinase, also known as Hepatocyte Growth Factor Receptor. MET can be activated as a primary oncogenic driver in NSCLC by two independent mechanisms: high level MET gene amplification (~1% of adenocarcinomas) and MET exon 14 alterations (~3-4% of adenocarcinomas and >10% of sarcomatoid carcinomas). Crizotinib, the US FDA-approved ALK/ROS1/MET TKI, induces responses in close to half of the patients with advanced cancers with MET alterations, and there are ongoing clinical trials of multiple other multitargeted MET TKIs (Table 3).
The activity of TKI monotherapy in other subgroups of lung cancer is less clear. The oncogene rearranged during transfection (RET) is seen in ~1-2% of patients with NSCLC, however, the ORR is <30% with the currently available multitargeted RET TKIs. ErbB2 receptor tyrosine kinase 2 (ERBB2 or HER2) exon 20 mutations occur in ~2% of lung adenocarcinomas. Currently available ErbB TKIs and monoclonal antibodies are minimally active and seldom reach ORR >20%. More specific TKIs and rationale combination approaches may hold the promise of eventually leading to regulatory approval of precision therapies in these tumors (Table 3).

The drug development platform for driver oncogenes with prevalence of <1% in lung cancer, such as neurotrophic receptor tyrosine kinase (NTRK) or fibroblast growth factor receptor (FGFR) rearrangements, is more challenging (Table 3) and may require large umbrella or basket trials that capture different molecular subgroups of lung cancer, such as Lung-MAP (NCT02154490) and the UK-National Lung Matrix (NCT02664935), or that involve multiple cancer primaries binned by molecular alterations, such as NCI-MATCH (NCT02465060).

**Immunotherapy**

Leora Horn, MD, MSc; Scott Gettinger, MD; and Solange Peters; MD, PhD

In 2016 the first anti-PD-L1 antibody, atezolizumab, received approval as a second-line treatment option for patients with metastatic NSCLC with a significant improvement in OS compared to docetaxel (13.8 vs 9.6 months, HR 0.73, p = 0.0003). Contrary to data with nivolumab in patients with nonsquamous NSCLC, atezolizumab demonstrated a significant benefit in patients with tumors that were negative for PD-L1 expression. However, this may be due to the differential sensitivity between the complimentary diagnostic antibody approved for atezolizumab (SP142) compared to both the companion diagnostic approved for pembrolizumab (22C3) and the complimentary diagnostic approved for nivolumab (28-8). Pembrolizumab became the first checkpoint inhibitor to be approved as a first line treatment option for patients with newly diagnosed stage IV NSCLC, with a superior PFS (10.3 vs 6.0, HR 0.50, p < 0.001), OS (HR 0.60, p = 0.005), health-related QOL and the time to deterioration for dyspnea, cough, and chest pain compared to platinum-based chemotherapy in patients with tumors that were EGFR and ALK negative and strongly PD-L1 positive (≥ 50%). A similarly designed study did not show efficacy when nivolumab was compared to chemotherapy; however, in this first-line study, patients with tumors expressing PD-L1 at a lower level of expression, greater than 1% of tumor cells,
were enrolled. First line avelumab demonstrated similar efficacy to currently approved agents with a 21.2% RR and PFS of 4.2 months (95% CI: 2.8, 5.6) in an unselected cohort of NSCLC patients.

**Benefit in EGFR/ALK+**

The role of immunotherapy, and in particular, immune checkpoint inhibitors, in EGFR mutant and ALK rearranged NSCLC, has yet to be determined. Retrospective subset analyses from several trials suggest lower response rates to PD-1 axis inhibitors, without better outcome than standard second line chemotherapy. That said, some patients benefit from such therapy, as demonstrated in the CheckMate 012 trial. One arm of this trial treated 20 patients with EGFR-mutant NSCLC and acquired resistance to EGFR TKI therapy as last therapy with erlotinib and nivolumab; four experienced prolonged tumor regression. Combination therapy was tolerated well; however, increased toxicity, particularly pneumonitis, has been suggested with other TKI/PD-L1 axis inhibitor combinations. Additional arms on the CheckMate 012 trial evaluated combination therapy with nivolumab and ipilimumab; among eight patients with EGFR-mutant NSCLC, four achieved response. Less clinical information exists concerning ALK rearranged NSCLC, although preclinical studies suggest intrinsic PD-L1 upregulation in such tumors, and responsiveness to PD-1 axis inhibition. Currently, it is uncertain if high tumor PD-L1 expression trumps EGFR or ALK status. One retrospective analysis suggested this may not to be the case, with poor outcome with pembrolizumab among 19 patients with high PD-L1 expressing EGFR-mutant NSCLC.

**Immunotherapy: novel combinations and future directions**

Immune escape is a critical gateway to malignancy. While the recent clinical developments in immunotherapy for lung cancer have improved the outcome of patients with metastatic disease, further improvements are still required. So what approaches can be taken to improve outcomes? Combination therapy with nivolumab every two weeks and ipilimumab (every 12 or 6 weeks) has demonstrated promising results with increasing response rates compared to nivolumab alone, 47%, 38% and 23%, respectively, and durable responses, albeit with higher grade 3/4 adverse events. Combination strategies with both anti-PD-1 or PD-L1 inhibitors and anti-CTLA-4 are being explored further in phase II and III clinical trials (NCT02477826, NCT02659059, NCT02542293, NCT02453282). To further build on successes of the PD-1/PD-L1 blockade and taking advantage of the multiple negative feedback mechanisms that regulate the adaptive immune response, numerous clinical trials of immunotherapy combinations are in progress. New modulatory monoclonal antibodies are currently being tested in
phase I/II in NSCLC or solid tumors, including LAG3 (NCT01968109 / NCT02460224), TIM3 (NCT02817633 / NCT02608268), OX40 (NCT02318394 / NCT02410512), GITR (NCT02583165 / NCT02697591), and IDO inhibitors (NCT02460367). Finally, a small phase II trial demonstrated superior response rates (55% vs 29%) and PFS (median 13.0 months vs 8.9 months, HR 0.53 [95% CI, 0.31-0.91; p=0.0205]) for patients treated with pembrolizumab plus pemetrexed and carboplatin compared to chemotherapy alone, with a similar incidence of grade 3 or higher adverse events. This led to the US FDA giving accelerated approval for pembrolizumab in combination with pemetrexed and carboplatin for the first-line treatment of metastatic nonsquamous NSCLC, irrespective of PD-L1 expression. Multiple trials are ongoing comparing this approach.

The second approach, designing studies that target specific defects in the cancer-immune interaction. Currently mutational burden, tumor infiltrating lymphocytes, and high PD-L1 expression in the tumor micro-environment are associated with sensitivity to immune checkpoint inhibition. Therefore, research efforts should be directed at mapping the state of the cancer immune interaction in a comprehensive manner.

A third approach is to create publicly available, open source inventories of large numbers of tissue and blood samples from patients prior to initiation of immunotherapy and subject such samples to genomics (whole exome sequencing, RNA seq), multiplex IHC, flow cytometry, and proteomics analyses, with the results coupled to clinical outcomes. These studies will aid in the characterization of predictors of response and progression. Based on these signatures, clinical trials should be performed testing combinations that have shown to overcome the specific defect in the cancer-immune interaction present in that particular patient population.

Another approach is to treat in earlier disease stages with the aim of increasing cure rates. Early results from melanoma studies suggest the general immune state of stage III disease patients is better than that of stage IV patients, resulting in a higher response rate and more toxicities. Interestingly pathological responses have also been observed after neo-adjuvant anti-PD1 in early NSCLC. Earlier stage patients may require shorter treatment duration than stage IV patients. Immunotherapy is being actively studied in the neoadjuvant (NCT02259621 / NCT02998528) and the adjuvant setting in NSCLC (NCT02504372 / NCT02273375).
Finally, as pricing of new immune-oncology drugs is unlikely to change soon, the above-mentioned future directions will certainly lead to a much more cost-effective utilization of our resources as chances for best outcome will be optimal.

Small Cell Lung Cancer

Corinne Faivre-Finn, MD, PhD and Charles M Rudin, MD, PhD

Radiotherapy for Small Cell Lung Cancer

The optimal timing and schedule of thoracic radiation in the management of limited-stage (LS) SCLC continues to provoke debate. Since the publication of Intergroup 0096 in 1999, there has been controversy about the standard chemo-radiotherapy regimen in LS disease. At ASCO 2016, the CONVERT trial was presented. This multicenter, international, randomized, phase III trial aimed to establish a standard chemo-radiotherapy regimen in LS-SCLC. Patients were randomized 1:1 to receive either 45Gy in 30 twice-daily (BD) fractions over 3 weeks or 66Gy in 33 once daily (OD) fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy, followed by prophylactic cranial irradiation. The study enrolled 547 patients, recruited from 73 centers in 7 European countries and Canada, between 2008 and 2013. OD RT did not result in superior survival or worse toxicity than BD RT (2-year survival 56% compared to 51%, HR for death OD group=1.18 p=0.14). The survival for both regimens was higher than previously reported and radiation toxicities were lower than expected, likely due to the use of modern RT techniques. The implications of CONVERT are important. As CONVERT was not an equivalence trial and since the only study to date that has shown superiority for one RT regimen over another in LS-SCLC was the Intergroup 0096 trial, which showed no major differences in toxicity, BD RT should continue to be regarded as standard of care. However, OD RT at a dose of 66Gy in 33 fractions can certainly be considered an alternative regimen if 45Gy in 30 fractions BD cannot be delivered due to patient choice, departmental logistics or other factors. Given the importance of keeping the overall treatment time short, future studies could investigate dose-escalated twice-daily or hypofractionated radiotherapy concurrently with chemotherapy.

For extensive stage (ES) SCLC patients with residual intra-thoracic disease who have responded after induction chemotherapy, addition of thoracic radiotherapy reduces the risk of intra-thoracic recurrence and improves 2-year survival; however, the primary endpoint of 1 year survival was not met. A survey of routine practice presented at ESTRO 2016 showed that following publication of the CREST trial there
has been a dramatic increase in the use of TRT from 25% to 81%. Subsequently a sub-analysis of CREST was presented at ASTRO 2016 investigating the prognostic importance of the number and sites of metastases. It suggested that future studies evaluating more intensive thoracic and extrathoracic radiotherapy in ES-SCLC should focus on patients with less than 3 metastases, which are not in the liver or bone.

**Advances in novel systemic therapies for small cell lung cancer**

Several new approaches to systemic treatment of small cell lung cancer have recently emerged and have been the subject of recent reviews. These will be only briefly touched on here, but include combination immunotherapy approaches that have shown substantial efficacy in other diseases, as well as a novel antibody drug conjugate against a cell surface determinant, DLL3, relatively unique to SCLC.

In the immunotherapy domain, several of the same PD-1-directed T-cell checkpoint inhibitors discussed above under NSCLC, including both pembrolizumab and nivolumab, have demonstrated initial activity in SCLC. Early data with the combination of nivolumab with ipilimumab appears particularly promising. In a 216 patient randomized phase II study of nivolumab versus various schedules of nivolumab and ipilimumab, the combination arms demonstrated response rates of 19 – 23% and disease control rates of 36-42%. Toxicities observed were similar to those reported in other diseases. Based on these data, the combination of nivolumab and ipilimumab has been included as a treatment option for recurrent SCLC in the most recent National Comprehensive Cancer Network treatment guidelines for SCLC, and confirmatory trials are ongoing.

DLL3 is an inhibitory Notch ligand normally confined to intracellular compartments but which is markedly upregulated and becomes aberrantly cell surface expressed in the majority of SCLC. Rovalpituzumab teserine, or Rova-T, is an antibody drug conjugate directed against DLL3 that demonstrated remarkable preclinical efficacy against SCLC in vivo, and promising activity in a first-in-human phase I clinical trial in patients with recurrent metastatic SCLC. Early data suggests that high level expression of the target, DLL3, may serve as a predictive biomarker for the activity of this agent as a response rate of 38% (10/26) and disease control rate of 88% (23/26) were observed in two thirds of patients with DLL3 expressed in over 50% of the cells. Larger confirmatory trials of Rova-T in SCLC are ongoing.

**Mesothelioma**
Anne Tsao, MD and Paul Baas, MD, PhD

In the last year, the field of mesothelioma has seen a dramatic increase in therapeutic clinical trials. Several basket trials in immunotherapy with mesothelioma cohorts have reported on the preliminary results of monotherapy PD-1/PD-L1 inhibitors (Table 4)\(^{240-243}\). In general, the reported response rates vary between 9-28% with a disease control rates of 50-77% in unselected mesothelioma patients. Similar to NSCLC, checkpoint inhibitors seem to be more active in PD-L1 IHC positive patients but the association is not strong. Unfortunately, the CTLA4 inhibitor tremelimumab did not show any benefit over placebo in the DETERMINE trial (NCT01843374)\(^{244}\). While there is a preliminary modest signal with PD-1/PD-L1 inhibitors, there is still a critical need to understand the biology and develop novel combination therapies. Combination regimens such as ipilimumab-nivolumab and platinum-pemetrexed combinations with PD-1/PD-L1 inhibitors are being investigated in the frontline and salvage settings (Table 5). Other approaches encompass neoadjuvant trials with atezolizumab or adjuvant trials with a WT-1 vaccine, galinpepimut-S\(^{245}\).

In the field of angiogenesis, the French MAPS trial\(^{246}\) demonstrated a PFS and OS benefit with the addition of bevacizumab to cisplatin-pemetrexed for 6 cycles of therapy followed by bevacizumab maintenance. Based on the survival benefit, cisplatin-pemetrexed-bevacizumab is now listed in the NCCN guidelines as an approved frontline therapy. Based on a significant improvement of PFS, nintedanib combined with cisplatin-pemetrexed has proceeded to a phase III international randomized trial (NCT 01907100). In Europe the EORTC is currently studying nintedanib in a phase 2 switch maintenance setting (NCT02863055). The phase II study of cisplatin-pemetrexed ± cediranib (S0905 trial) has completed enrollment and results are anticipated in 2017.

Agents that inhibit metabolism or other novel targets under active investigation include ADI-PEG20 in ASS-1 deficient mesothelioma (ATOMIC trial, NCT02709512), mesothelin-targeted agents (SS1P, anetumab ravtansine, LMB-100), tazemetostat in BAP1 deficient mesothelioma (NCT02860286), trabectedin (ATREUS trial, NCT 02194231), alisertib targeting aurora kinase (NCT02293005), and brentuximab in CD30 positive disease (NCT03007030). Two studies with amatuximab or CRS-207 have currently been suspended for efficacy analysis. Of note, the IASLC has formed a mesothelioma task force that is charged with uniting researchers in the field and furthering investigational efforts.

**Quality and Value in Lung Cancer**
Quality and value are emerging as key priorities in cancer care. Value in cancer, the relationship between treatment benefit and cost, remains a challenging subject worldwide. Regulatory agencies like the US FDA or EMA focus on efficacy and safety of novel interventions, approving new treatments that yield statistically better outcomes. Other bodies like the National Institute for Health Care Excellence (UK) or pan-Canadian Oncology Drug Review focus on value, including cost and clinical relevance of these improved outcomes. By contrast, the US Centers for Medicare and Medicaid Services do not consider cost when making treatment funding decisions. Furthermore, the Affordable Care Act forbids the use of cost effectiveness thresholds at the Patient Centered Outcomes Research Institute (PCORI) when making funding recommendations.

However, there is a growing recognition that value in cancer care is important to patients and clinicians. Several international bodies including ASCO and ESMO have developed standardized value frameworks to help determine the value of treatments, incorporating the magnitude of clinical benefit, toxicity and quality of life gain without aggregating these measures as a formal cost-effectiveness analysis. For example, the ESMO magnitude of clinical benefit scale (MCBS) uses a structured approach to rank treatments using a 4-point scale based on relative and absolute survival gain, toxicity rates, QOL, and use of intermediate endpoints such as PFS.

With a record number of drug approvals, meaningful progress is being made in the areas of targeted and immune therapy in lung cancer. Cost effectiveness studies suggest that the costs of many new treatments are above traditional willingness to pay thresholds (WTP), including multiplex genomic testing, novel targeted kinase inhibitors and checkpoint inhibitors. Each jurisdiction must determine their own WTP for new treatments, which varies across countries and health care systems. Given that severe financial toxicity is recognized as a potential predictor of early mortality in lung and other cancers, implementing strategies to ensure affordable access to treatment has never been more important for patients with lung cancer and their families.

**Specific Future Perspectives**

Fred R Hirsch, MD, PhD; Giorgio V Scagliotti, MD, PhD; and David R Gandara, MD
The last year led to significant progress for new therapies for lung cancer based on genomic characterization of patients’ tumors and further clinical developments of immunotherapies.

The growing concept of "precision medicine" addresses this challenge by recognizing the vast yet fractured state of biomedical data, and calls for a patient-centered view in which molecular, clinical, and environmental measurements are stored in large shareable databases. Such efforts have already enabled large-scale knowledge advancement, but they also risk enabling large-scale misuse.

There is still a huge unmet need for identifying new “druggable” molecular targets, particularly in squamous lung cancer and small cell lung cancer. Furthermore, much focus has so far been on single drug development, which for certain subgroups of patients has been very encouraging, but in the vast majority of patients, combination therapy may be required to convert treatment intent into the “curable” category. Despite the early successes of targeted therapies, it is also becoming evident that primary and acquired resistance are major limitations to long-term survival. Most lung cancers will not be cured by single-agent targeted therapies due to the inherent genomic complexity, now complicated by recognition of heterogeneity in immune-biology as well.

Clearly, there is much yet to understand about in vivo tumor biology, and exploring resistance mechanisms is essential to determine what combination of drugs will best treat resistant tumors or prevent the emergence of resistance.

While pharmaceutical companies are still pursuing many phase II/III combination studies that assess molecular targeted therapies or immunotherapy in combination with chemotherapy, or in combination with each other, study designs remain largely empiric, often without sufficient biological scientific background or rationale for dosing/scheduling for the combinations. Selection of the right therapy for the right patient is crucial as the new treatments are costly; but most of all, patients with advanced lung cancer have a limited life span and optimizing therapy on an individual basis should be the goal. This is, after all, the definition of precision medicine.

Improved understanding of the cancer immune landscape, including immune-evasion strategies, have led to breakthrough therapeutic advances for patients with NSCLC and provide a platform for future therapeutic developments. Better pre-clinical models need to be developed to study tumor-environmental interactions and potential intervention opportunities. While PD-L1 IHC assessment is used today for PD-L1/PD-1 antibody therapies, with some merit (biomarker assays already regulatory
approved and used in clinical practice), other biomarkers and synergistic combinatorial biomarker assays need to be explored as predictive “immune-signatures”.

Several scientific societies and regulatory bodies are concerned about the cost of newer therapies and quantitating “value” of each new therapy. While cost-benefit analysis is increasingly justified, such algorithms are preferably developed by the scientific community rather than dictated by governmental or insurance-based policies.

Lung cancer screening with low-dose CT has demonstrated very encouraging results. However, much research is still needed, particularly as guidelines and new technology develop. Screening opportunities for never-smokers and younger people also needs to be explored. It remains crucial to foster future research in lung cancer prevention, early detection and screening. While most of the excitement regarding new therapies today focuses on patients with advanced disease, the odds for making lung cancer a curable disease favor moving these advances towards early stage disease. New biomarkers, most likely blood-based assays, to complement the lung cancer screening process are strongly needed in order to improve the sensitivity and specificity of low-dose CT screening.

Regarding “other thoracic malignancies”, such as mesothelioma and thymoma, lessons learned in lung cancer are now increasingly being applied toward advancing our knowledge about biology, epidemiology, diagnosis and therapy. Although the future appears to be bright for patients with lung cancer and research, much work remains to be done.

Figure Legends.

Figure 1. Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) of the TNM staging system using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other 72.

References

Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.


212. Socinski M, Creelan B, Horn L, et al. NSCLC, metastaticCheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)–positive NSCLC. *Ann Oncol* 2016;27:LBA7_PR-LBA7_PR.


**Table 1. Immune checkpoint inhibitors and PD-L1 IHC assays in NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>MERCK</th>
<th>ROCHE</th>
<th>AstraZeneca</th>
<th>Pfizer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
<td>Durvalumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td><strong>Antibody clone</strong></td>
<td>Dako 28-8</td>
<td>Dako 22C3</td>
<td>Ventana SP142</td>
<td>Ventana SP263</td>
<td>Dako 73-10</td>
</tr>
<tr>
<td><strong>US FDA Status</strong></td>
<td>Complementary</td>
<td>Companion</td>
<td>Complementary</td>
<td>Not approved</td>
<td>Not approved</td>
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<tr>
<td><strong>Cell type scored</strong></td>
<td>Tumor cells</td>
<td>Tumor cells</td>
<td>Tumor cells and TIL</td>
<td>Tumor cells</td>
<td>Tumor cells</td>
</tr>
<tr>
<td><strong>PD-L1 threshold</strong></td>
<td>All patients</td>
<td>&lt;50% or ≥50%</td>
<td>TC1/2/3 or IC1/2/3 ≥1%</td>
<td>≥25%</td>
<td>≥1%</td>
</tr>
<tr>
<td><strong>Validation trial</strong></td>
<td>CM-057 All comers</td>
<td>KN-001: PD-L1 ≥ 1%</td>
<td>BIRCH: TC or IC 2/3 POPLAR: all comers</td>
<td>NCT01693562: All comers</td>
<td>NCT02395172 (JAVELIN Lung 200) ≥1%</td>
</tr>
</tbody>
</table>
Table 2. Ongoing Phase III Targeted and Immunotherapy Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population*</th>
<th>Adjuvant therapy</th>
<th>Primary Endpoint(s)</th>
<th>Estimated Enrollment</th>
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<tbody>
<tr>
<td>C-TONG 1104 NCT01405079</td>
<td>EGFR deletion 19 or exon 21 L858R mutation</td>
<td>Gefitinib vs. Vinorelbine / Cisplatin</td>
<td>3-year DFS</td>
<td>220</td>
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<tr>
<td>GASTO1002 NCT01996098</td>
<td>EGFR deletion 19 or exon 21 L858R mutation</td>
<td>Chemotherapy then Icotinib vs Observation</td>
<td>5-year DFS</td>
<td>477</td>
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<tr>
<td>BD-IC-IV-59 NCT02125240</td>
<td>EGFR deletion 19 or exon 21 L858R mutation</td>
<td>Chemo then Icotinib vs. Placebo</td>
<td>2-year DFS</td>
<td>300</td>
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<tr>
<td>WJOG6401L IMPACT</td>
<td>EGFR deletion 19 or exon 21 L858R mutation</td>
<td>Gefitinib vs. Cisplatin/Vinorelbine</td>
<td>5-year DFS</td>
<td>230</td>
</tr>
<tr>
<td>ADAURA NCT02511106</td>
<td>EGFR deletion 19 or exon 21 L858R mutation with or without T790M</td>
<td>+/- Chemotherapy then Osimertinib vs. Placebo</td>
<td>DFS</td>
<td>700</td>
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<tr>
<td>ALCHEMIST A081105 NCT02193282</td>
<td>EGFR deletion 19 or exon 21 L858R mutation</td>
<td>Erlotinib vs. Placebo, OS</td>
<td>OS</td>
<td>450</td>
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<tr>
<td>ALCHEMIST E4512 NCT02201992</td>
<td>ALK+ by FISH</td>
<td>Crizotinib vs Placebo</td>
<td>OS</td>
<td>378</td>
</tr>
<tr>
<td>ALCHEMIST/AN VIL NCT02595944</td>
<td>EGFR/ALK wildtype, regardless of PD-L1 status</td>
<td>Chemotherapy then Nivolumab vs Observation</td>
<td>OS/DFS</td>
<td>714</td>
</tr>
<tr>
<td>Impower010 NCT02486718</td>
<td>Regardless of PD-L1 status</td>
<td>Chemotherapy then Atezolizumab vs. Placebo</td>
<td>DFS</td>
<td>1127</td>
</tr>
<tr>
<td>BR31 NCT02273375</td>
<td>Regardless of PD-L1 status</td>
<td>+/- Chemotherapy then Durvalumab vs Placebo</td>
<td>DFS</td>
<td>1100</td>
</tr>
<tr>
<td>Keynote-091 NCT02504372</td>
<td>Regardless of PD-L1 status</td>
<td>+/- Chemotherapy Pembrolizumab vs Placebo</td>
<td>DFS</td>
<td>1380</td>
</tr>
</tbody>
</table>

*All include stage II-IIIA, all PD-1/PD-L1 studies open to IB (4cm) – IIIA after adjuvant chemotherapy

DFS: disease-free survival; OS: overall survival
Table 3. Driver oncogene mutations, inhibitors, response, and clinicaltrials.gov registration for other targets in lung cancer

<table>
<thead>
<tr>
<th>Driver Oncogene</th>
<th>Prevalence Lung Adenocarcinoma</th>
<th>Inhibitor(s)</th>
<th>ORR</th>
<th>NCT Number</th>
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</thead>
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<tr>
<td><strong>BRAF</strong> V600E mutation</td>
<td>1-2%</td>
<td>vemurafenib</td>
<td>42% (n=19)&lt;sup&gt;177&lt;/sup&gt;</td>
<td>NCT01524978</td>
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<tr>
<td></td>
<td></td>
<td>dabrafenib</td>
<td>35% (n=84)&lt;sup&gt;178&lt;/sup&gt;</td>
<td>NCT01336634</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dafrafenib+ trametinib*</td>
<td>63% (n=57)&lt;sup&gt;179&lt;/sup&gt;</td>
<td>NCT01336634</td>
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<tr>
<td><strong>BRAF</strong> non-V600E mutations</td>
<td>1-2%</td>
<td>trametinib</td>
<td>NR</td>
<td>NCT02465060</td>
</tr>
<tr>
<td><strong>MET</strong> exon 14 skipping</td>
<td>3-4%</td>
<td>crizotinib</td>
<td>44% (n=18)&lt;sup&gt;188&lt;/sup&gt;</td>
<td>NCT00585195</td>
</tr>
<tr>
<td></td>
<td></td>
<td>crizotinib</td>
<td>NR</td>
<td>NCT02465060</td>
</tr>
<tr>
<td></td>
<td></td>
<td>capmatinib</td>
<td>NR</td>
<td>NCT01324479</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tepotinib</td>
<td>NR</td>
<td>NCT02864992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>savolitinib</td>
<td>NR</td>
<td>NCT02897479</td>
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<tr>
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<td></td>
<td>glesatinib</td>
<td>NR</td>
<td>NCT02544633</td>
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<tr>
<td></td>
<td></td>
<td>cabozantinib</td>
<td>NR</td>
<td>NCT01639508</td>
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<tr>
<td></td>
<td></td>
<td>merestinib</td>
<td>NR</td>
<td>NCT02920996</td>
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<td><strong>MET</strong> high level amplification</td>
<td>1%</td>
<td>crizotinib</td>
<td>66% (n=6)&lt;sup&gt;187&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>capmatinib</td>
<td>NR</td>
<td>NCT01324479</td>
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<td>glesatinib</td>
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<td></td>
<td></td>
<td>cabozantinib</td>
<td>NR</td>
<td>NCT01639508</td>
</tr>
<tr>
<td><strong>RET</strong> rearrangements</td>
<td>1-2%</td>
<td>cabozantinib</td>
<td>28% (n=25)&lt;sup&gt;192&lt;/sup&gt;</td>
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<td>vandetanib</td>
<td>47% (n=19)&lt;sup&gt;194&lt;/sup&gt;</td>
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<td>17% (n=18)&lt;sup&gt;195&lt;/sup&gt;</td>
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<td>sunitinib</td>
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<td>NR</td>
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<td></td>
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<td>NR</td>
<td>UMIN20628 (Japan)</td>
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<td></td>
<td></td>
<td>vandetanib+ everolimus</td>
<td>83% (n=6)&lt;sup&gt;203&lt;/sup&gt;</td>
<td>NCT01582191</td>
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<tr>
<td><strong>ERBB2</strong> (HER2) exon 20 mutations</td>
<td>2%</td>
<td>dacomitinib</td>
<td>12% (n=26)&lt;sup&gt;199&lt;/sup&gt;</td>
<td>NCT00818441</td>
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<tr>
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<td>afatinib</td>
<td>33% (n=3)&lt;sup&gt;200&lt;/sup&gt;</td>
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<td>NCT02465060</td>
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<td>ado-trastuzumab emtansine</td>
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<td>NCT02675829</td>
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<td>Drug</td>
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<td>Trial ID</td>
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<td>neratinib</td>
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<td>AP32788</td>
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<td>NCT02716116</td>
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<td>NTRK1/2/3</td>
<td>&lt;1%</td>
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<td>rearrangements</td>
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<td>PLX7486</td>
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<td>&lt;1%</td>
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<td>mutations or</td>
<td></td>
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<td>BGJ398</td>
<td>NR</td>
<td>NCT02160041</td>
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</table>

ORR, overall response rate; NR, not reported/ongoing trial; * approved by European Union on 2017 and pending review for formal regulatory approval elsewhere
Table 4. Selected monotherapy immunotherapy trials and preliminary reported results.

<table>
<thead>
<tr>
<th>Agent</th>
<th>NCT Number</th>
<th>Type</th>
<th>Setting</th>
<th>ORR</th>
<th>DCR</th>
<th>PFS</th>
<th>OS</th>
<th>PD-L1 IHC status</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab (KEYNOTE-028)</td>
<td>02054806</td>
<td>PD-1</td>
<td>2\textsuperscript{nd} line</td>
<td>28%</td>
<td>76%</td>
<td>5.8 months</td>
<td>18 months</td>
<td>All patients were PD-L1 IHC (+)</td>
</tr>
<tr>
<td>Pembrolizumab\textsuperscript{41}</td>
<td>02399371</td>
<td>PD-1</td>
<td>2\textsuperscript{nd} line</td>
<td>21%</td>
<td>77%</td>
<td>6.2 months</td>
<td>NR</td>
<td>Did not correlate to response.</td>
</tr>
<tr>
<td>Nivolumab (NivoMes trial)\textsuperscript{242}</td>
<td>02497508</td>
<td>PD-1</td>
<td>1 prior therapy</td>
<td>24%</td>
<td>50%</td>
<td>3.6 months</td>
<td>NR</td>
<td>Trend for a correlation with OR</td>
</tr>
<tr>
<td>Avelumab (JAVELIN)\textsuperscript{243}</td>
<td>01772004</td>
<td>PD-L1</td>
<td>salvage, any line</td>
<td>9.4%</td>
<td>57%</td>
<td>4.3 months</td>
<td>NR</td>
<td>Trend to correlate with median PFS</td>
</tr>
<tr>
<td>Agents</td>
<td>Phase</td>
<td>NCT Number</td>
<td>Target</td>
<td>Setting</td>
<td>Planned N</td>
<td>Primary Endpoint</td>
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<td>---------------------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------------</td>
<td></td>
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<tr>
<td>Ipilimumab-nivolumab vs platinum-pemetrexed</td>
<td>III</td>
<td>02899299</td>
<td>PD-1+CTLA4 inhibitors vs chemo</td>
<td>Frontline</td>
<td>600</td>
<td>OS</td>
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<td>Durvalumab + cisplatin-pemetrexed (PrE0505)</td>
<td>II</td>
<td>02899195</td>
<td>PD-L1 inhibitor + chemo</td>
<td>Frontline</td>
<td>55</td>
<td>OS</td>
<td></td>
<td></td>
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<tr>
<td>Pembrolizumab + cisplatin-pemetrexed vs cisplatin-pemetrexed vs pemetrexed alone (Canadian Cancer Trials Group)</td>
<td>II</td>
<td>02784171</td>
<td>PD-1 inhibitor + chemo</td>
<td>Frontline</td>
<td>126</td>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONCOS-102 + cisplatin-pemetrexed (Spain)</td>
<td>Ib/Ii</td>
<td>02879669</td>
<td>Immune-priming GM-CSF coding oncolytic adenovirus + chemo</td>
<td>Frontline</td>
<td>30</td>
<td>Safety Toxicity</td>
<td></td>
<td></td>
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<tr>
<td>Tremelumumab - durvalumab (Italy NIBIT-MESO-1)</td>
<td>II</td>
<td>02588131</td>
<td>PD-L1+CTLA4 inhibitors</td>
<td>0 or 1 prior therapy</td>
<td>40</td>
<td>ORR (immune related)</td>
<td></td>
<td></td>
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<tr>
<td>Pembrolizumab vs gemcitabine or vinorelbine (PROMISE-meso ETOP)</td>
<td>III</td>
<td>02991482</td>
<td>PD-1 inhibitor vs chemo</td>
<td>2nd line</td>
<td>142</td>
<td>PFS</td>
<td></td>
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<tr>
<td>Nivolumab vs Nivolumab-Ipilimumab (IFCT MAPS2)</td>
<td>II</td>
<td>02716272</td>
<td>PD-1 vs PD-1 + CTLA4 inhibitor</td>
<td>1 or 2 prior therapies</td>
<td>125</td>
<td>Disease Control Rate</td>
<td></td>
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<tr>
<td>Ipilimumab + Nivolumab (INITIATE, NKI Netherlands)</td>
<td>II</td>
<td>03048474</td>
<td>CTLA 4 and PD1 with translational reaserch biopsies</td>
<td>1 or 2 prior therapies</td>
<td>33</td>
<td>Disease Control Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + nintedanib (PEMBIB, Gustave Roussy)</td>
<td>Ib</td>
<td>02856425</td>
<td>PD-1 and VEGFR, PDGF, FGFR inhibitor</td>
<td>At least 1 prior therapy</td>
<td>18</td>
<td>Safety Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab (basket trial)</td>
<td>II</td>
<td>02458638</td>
<td>PD-L1 inhibitor</td>
<td>At least 1 prior therapy</td>
<td>725</td>
<td>Disease Control Rate</td>
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<td>Study Description</td>
<td>Phase</td>
<td>NCT ID</td>
<td>Summary</td>
<td>Requirements</td>
<td>Outcomes</td>
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<td>CART-meso (U of Penn)</td>
<td>I</td>
<td>02159716</td>
<td>Autologous T cells transduced with anti-mesothelin immunoreceptor</td>
<td>At least 1 prior therapy</td>
<td>Safety Toxicty</td>
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<td>Autologous Redirected RNA Meso-CIR T cells (U of Penn)</td>
<td>I</td>
<td>01355965</td>
<td>Autologous T cells transfected with anti-mesothelin mRNA</td>
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<td>Safety Toxicty</td>
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<td>Autologous T cells to target mesothelin (MSKCC)</td>
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<td>02414269</td>
<td>Mesothelin-targeted T cell infusions iCasp9M28z</td>
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<td>Defactinib + Pembrolizumab Mesothelioma cohort (United Kingdom)</td>
<td>I/IIA</td>
<td>02758587</td>
<td>FAK and PD-1 inhibitor</td>
<td>Any</td>
<td>Safety Toxicty</td>
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<td>Atezolizumab + Bevacizumab (MDACC)</td>
<td>II</td>
<td>Pending</td>
<td>PD-L1 inhibitor + VEGF inhibitor</td>
<td>Any</td>
<td>Safety Toxicty</td>
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<td>Atezolizumab (basket trial)</td>
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<td>02458638</td>
<td>PD-L1 inhibitor</td>
<td>1 prior therapy</td>
<td>Disease Control Rate</td>
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<td>Durvalumab vs Tremelimumab + durvalumab</td>
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<td>02592551</td>
<td>PD-1 inhibitor vs PD-1 + CTLA4 inhibitor</td>
<td>Neoadjuvant</td>
<td>Biomarker modification</td>
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<td>S1619 cisplatin-pemetrexed-atezolizumab (SWOG)</td>
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<td>PD-L1 inhibitor + chemo</td>
<td>Neoadjuvant</td>
<td>Safety Feasibility</td>
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<td>Pembrolizumab</td>
<td>Pilot</td>
<td>02707666</td>
<td>PD-1 inhibitor</td>
<td>Neoadjuvant</td>
<td>Safety Feasibility</td>
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<td>Pembrolizumab (MDACC)</td>
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<td>PD-1 inhibitor</td>
<td>Adjuvant with XRT</td>
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### A

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<th>Events / N</th>
<th>MST</th>
<th>24 Month</th>
<th>60 Month</th>
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<td>82%</td>
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<td>768 / 2492</td>
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<tr>
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<td>II B</td>
<td>2101 / 2624</td>
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### B

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<tr>
<td>IA2</td>
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<td>IA3</td>
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<td>II C</td>
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