REVIEW ARTICLE

Scientific Advances in Thoracic Oncology 2016

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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 International Association for the Study of Lung Cancer 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

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and early detection, molecular diagnostics, pathology and staging, surgery, adjuvant therapy, radiotherapy, molecular targeted therapy, and immunotherapy for NSCLC, SCLC, 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.

Keywords: NSCLC; Malignant mesothelioma; SCLC; Smoking cessation; Cancer prevention; Targeted therapy; Immunotherapy; Screening; Pathology; Staging; Surgery; Adjuvant therapy; Radiotherapy; Molecular diagnostics; Biomarkers; Value of therapy

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 (RT), molecular targeted therapy, and immunotherapy. Important progress has been made in SCLC 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.

Prevention and Early Detection

Cigarettes, E-cigarettes, and Cannabis

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Cigarettes. Tobacco cigarettes account for the vast majority of tobacco consumed worldwide and are by far the most lethal type of tobacco product consumed, costing global economies $1 trillion annually through loss of productivity and health care expenditure.[1] 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, which in turn could have important health consequences in the future.

E-cigarettes. Electronic cigarettes (e-cigarettes) are a form of electronic nicotine delivery that has 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 reevaluation of evidence in a field characterized by rapid change.[2] The regulatory status of the e-cigarette industry, 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.[3] Although it does appear that e-cigarettes can help some smokers quit or reduce their smoking, the evidence is mixed. The recent U.S. surgeon general's report on e-cigarettes discourages the sale and use of any nicotine-containing product by nonsmokers, especially the young.[4] 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.[5] 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.[6] The likelihood of cigarette cessation was shown to be lower in those using e-cigarettes compared with other methods in a recent small study of patients with cancer.[7] A 2014 review of e-cigarettes in patients with lung cancer noted the urgency of 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.[8]

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 eight 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 cannabis use in the past 30 days in the United States increased by 35%. In 2014, 8.4% of those 12 years of age and older reported use of cannabis in the past 30 days and 3.5% reported daily use.[9]

Cannabis is most commonly smoked but can be vaped, ingested, or used topically. Cannabinoids enter the bloodstream 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.[10] There is at least moderate evidence that cannabis is beneficial for chronic pain, neuropathic pain, and muscle spasms, especially related to multiple sclerosis.[11–14] 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.[12,15]

Cannabis use 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.[10,15,16]

Cannabis smoke contains many of the same toxins as tobacco smoke, such as polycyclic aromatic hydrocarbons. Studies have shown that frequent cannabis use can cause chronic bronchitis (cough, sputum, and wheeze), but there is no established causality with chronic obstructive pulmonary disease.[17,18] There is also no conclusive evidence that cannabis use increases the risk for 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.[19–21] The best evaluation of the association between smoking cannabis and lung cancer risk, after adjustment for tobacco use, is a pooled analysis of six case-control studies with 2159 patients with lung cancer and 2985 controls that failed to find evidence of an increased risk for lung cancer among long-term cannabis smokers.[20] 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.[11]

Lung Cancer Screening

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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,[22] the NELSON trial group study,[23,24] the I-ELCAP study,[25] and the preliminary experiences with the American College of Radiology LungRADS approach,[26,27] cite false-positive diagnostic detection rates of less than 10%. In addition, the field recognized that nonstandardized terms for characterizing efficiency of the 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 because lung nodules are common in smokers, this misconception has 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 pathologic diagnosis rather than an imaging diagnosis. A consensus is emerging that working toward more systematic definitions for key parameters for a lung cancer screening is a near-term priority that could reset screening subjects's expectations and reduce anxiety regarding the process.[24,28–35]

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.[36,37] 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 a public health benefit.[38,39] When conservative assumptions were used, 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

Section Authors: Yasushi Yatabe, MD, PhD, Lukas Bubendorf, MD, 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 precise targeting of peripheral nodules,[40] whereas transbronchial cryobiopsy is a promising tool to obtain large and high-quality specimens.[41] Several studies have reported that cytologic specimens obtained by endobronchial ultrasound–guided transbronchial needle aspiration or fine-needle aspiration are equally suitable for molecular testing.[42] The upcoming molecular testing guideline has been updated to include newer targetable genes (*ROS1,* rearranged during transfection proto-oncogene [*RET*],

Table 1. Immune Checkpoint Inhibitors and PD-L1 IHC Assays in NSCLC

Characteristic	Pharmaceutical Company				
	BMS	Merck	Roche	AstraZeneca	Pfizer
Drug	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Antibody clone	Dako 28-8	Dako 22C3	Ventana SP142	Ventana SP263	Dako 73-10
US FDA status	Complementary	Companion	Complementary	Not approved	Not approved
Cell type scored	TCs	TCs	TCs and TILs	TCs	TCs
PD-L1 threshold	All patients	<50% or ≥50%	TC1/2/3 or IC1/2/3 ≥1%	≥25%	≥1%
Validation trial	CM-057: all comers CM-026: ≥1%	KN-001: PD-L1 ≥1% KN-010: PD-L1 ≥1% KN-024: PD-L1 ≥50%	BIRCH: TC or IC 2/3 POPLAR: all comers	NCT01693562: All comers	NCT02395172 (JAVELIN Lung 200) ≥1%

PD-L1, programmed death ligand 1; IHC, immunohistochemistry; BMS, Bristol-Myers Squibb; US FDA, U.S. Food and Drug Administration; TIL, tumor-infiltrating lymphocyte; IC, immune cell; TC, tumor cell.

BRAF, erb-b2 receptor tyrosine kinase 2 [*HER2*], and MET proto-oncogene, receptor tyrosine kinase [*MET*]), resistant mutations, and advances in technology, including liquid biopsy and next-generation sequencing; as well as to reaffirm or update the previous recommendations. The draft was published on the College of American Pathologists, International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology websites for open comment,[43] and publication of the final recommendations is planned in 2017.

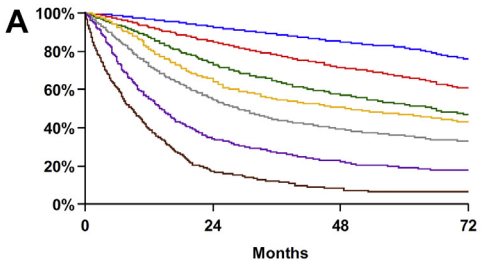
In addition to the traditional specimens, liquid biopsies (especially circulating tumor cell DNA [ctDNA]) have been increasingly used in clinical practice. Although the liquid biopsy has been investigated for use in relation to various targetable genes in NSCLC, it is mainly used in the detection of *EGFR* mutations when there is inadequate tumor sample or when the risk associated with biopsy is high. Although plasma EGFR testing has high specificity, the main concerns remain concordance with tissue biopsy results and its relatively low sensitivity, especially for T790M. This situation has improved with the use of advanced next-generation sequencing platforms.[44–49] The U.S. Food and Drug Administration (FDA) has recently approved the cobas EGFR Mutation Test v2 plasma-based assay as a companion diagnostic for erlotinib.[50] If the plasma EGFR results are negative, tissue-based testing should be performed.[51] Saliva and urine have also been used to detect *EGFR* mutations.

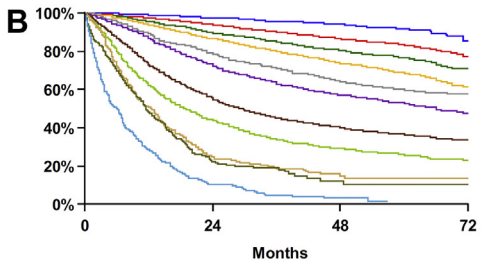
Clinically, immune checkpoint inhibitors provide an additional treatment option in advanced NSCLC, and programmed death ligand 1 (PD-L1) immunohistochemistry (IHC) is used as a biomarker to select patients who are more likely to respond to such treatment in either the first- or second-line setting.[52,53] However, the development of different PD-L1 IHC assays with individual cutoff values, antibodies, and platforms for the immune checkpoint inhibitors has raised concerns among pathologists and oncologists (Table 1).[54–56] To obtain some clarity, the five individual assays have been, and are currently being, compared with one another.[57–62] 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, the American Association for Cancer Research, and the IASLC. Three clones (22C3, 28-8, and SP263) showed similar results in tumor cell staining, whereas the SP142 assay displayed significantly less tumor cell staining. All assays stained immune cells with greater variability than tumor cells.[57] Recently, tumor mutation burden was focused on as an alternative predictive biomarker for immune checkpoint inhibitor treatment, as a high nonsynonymous mutational load is expected to lead to more tumor-specific T-cell responses though expression of neoantigens.[63] 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.[64]

TNM Staging System

Section Author: Ramon Rami-Porta, MD, Frank C. Detterbeck, MD, Eric Lim, MBChB., MD, MSc

The eighth edition of the TNM classification of lung cancer[65–67] includes adenocarcinoma in situ (Tis[AIS]) and minimally invasive adenocarcinoma (T1mi)[68]; incremental categories based on a 1-cm increase in tumor size from T1a–c to T2a–b, with tumors smaller than 5; 5 to no larger than 7 cm and those larger than 7 cm reclassified as T3 and T4, respectively; reclassification of endobronchial location less than 2 cm from the carina and total atelectasis-pneumonitis as T2; and diaphragmatic invasion as T4.[69] Nodal classification and





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

intrathotracic metastasis remain unchanged.[70] Single extrathoracic metastasis is now classified as M1b separately from multiple extrathoracic metastases as M1c.[71] Amendments were made to stage grouping,[72] as well as to classification of lung cancers with multiple lesions.[73–76] Overall survival (OS) by clinical stage according to the seventh and eigth editions is shown in Figure 1.

The revised TNM classification for mesothelioma includes combination of T1a and T1b into the new T1 category,[77,78] collapse of N1 and N2 into the category N1, and reclassification of N3 as N2.[79] The M categories remain unchanged and stage grouping has been modified for improved stratification.[80]

The TNM classification of thymic epithelial malignancies was a joint effort of the IASLC and the International Thymic Malignancies Interest Group.[81] The T component is classified according to the involved organs.[82] Nodal involvement is divided into N1 (anterior [perithymic] nodes) and N2 (deep intrathoracic or supraclavicular nodes).[83,84] 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 introduction of prognostic subgroups based on anatomic extent, location, and differentiation grade.[90–92]

Therapy

Surgery

Section Authors: Hisao Asamura, MD, Jessica Donington, MD

Minimally Invasive Lobectomy. Over the past 2 decades, video-assisted thoracic surgery (VATS) has become a common surgical technique. Along with it came improvements in operative and visual instruments. Although definition of VATS has been conflicting, VATS generally means operating by using thoracoscopy with a minimal number of small incisions and without rib spreading. Treatment of lung cancer by VATS has been performed under the assumption that it has an oncologic outcome equivalent to that of 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 have reported that VATS had a lower incidence of postoperative complications or shorter length of hospital stay by 1 to 2 days, but there is uncertainty as to

whether this is clinically meaningful.[93–96] On the other hand, some reports concluded that a higher incidence of nodal upstaging has been observed in thoracotomy than in 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 that compare VATS to thoracotomy would be required to definitively demonstrate the prognostic equivalence and any differences in QOL or postoperative complications for these two surgical modalities.

Robot-assisted thoracic surgery (RATS) is defined as a surgical procedure 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 to VATS in all measures of quality for treatment of lung cancer.[100] To date, no randomized trials have reported the comparative data between RATS and VATS/thoracotomy for lung cancer.[101]

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 cases of multiple primary NSCLCs, sublobar resections should be considered as well. Of course, there are anatomic limitations for such resection; however, there is no doubt that such surrogate resections could be selected.

Surgical Quality. The importance of surgical quality measures (QMs) in NSCLC was highlighted in 2016. Two independent studies from the National Cancer Database found that compliance with basic QMs was associated with improved OS after 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) more than 10 lymph nodes sampled. Whereas 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 no QMs as opposed to four QMs.[102] Similarly, in clinical stage IIIA, adherence to four QMs (neoadjuvant therapy, lobectomy or more extensive procedure, R0 resection, and >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 who met no QMs compared with for those who met four.[103] 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.[104–108]

Adjuvant Therapy in Completely Resected NSCLC

Section Authors: Heather Wakelee, MD, and Yi-Long Wu, MD

Cisplatin-based adjuvant chemotherapy is the standard of care for patients with resected stage II and IIIA NSCLC and is commonly used for patients with larger (at least 4 cm) stage IB tumors. In 2016 we learned from a subset analysis of the E1505 trial that the four platinum-based doublets utilized (cisplatin with either vinorelbine, gemcitabine, docetaxel, or pemetrexed) had comparable efficacy but differing toxicity profiles.[109] Further data to support the 4-cm cutoff to recommend adjuvant chemotherapy came from a propensity score–matched analysis performed in the Republic of Korea that divided stage IB patients into those with tumors 3 cm or smaller with visceral pleural invasion, tumors 3 to 4 cm in size, and tumors 4 to 5 cm in size. The study reported that the only group with a clear differential benefit from adjuvant chemotherapy was that with tumors 4 to 5 cm in size.[110] A Chinese study that utilized carboplatin/docetaxel and randomized nearly 200 patients to preoperative or postoperative therapy was presented at the IASLC World Conference on Lung Cancer 2016.[111] Both disease-free survival 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.[109,112]

Encouraging data from retrospective and non-randomized trials of adjuvant EGFR tyrosine kinase inhibitors (TKIs) in patients with *EGFR*-mutant NSCLC have led to randomized trials, including the phase III RADIANT trial of adjuvant erlotinib or placebo.[113] In the *EGFR*-mutated subset (n = 161) disease-free survival favored erlotinib (hazard ratio [HR] = 0.61 [not significant]); OS did not trend favorably but was immature. Table 2 includes multiple ongoing trials of adjuvant EGFR TKI (and adjuvant anaplastic lymphoma kinase [ALK] TKI) therapy for patients with resected early-stage NSCLC with tumors harboring the appropriate molecular

Table 2. Ongoing Phase III Targeted and Immunotherapy Adjuvant Trials

Trial	Patient Population[a]	Adjuvant Therapy	Primary End Point(s)	Estimated Enrollment
C-TONG 1104 NCT01405079	*EGFR* deletion 19 or exon 21 L858R mutation	Gefitinib vs. vinorelbine/cisplatin	DFS	220
GASTO1002 NCT01996098	*EGFR* deletion 19 or exon 21 L858R mutation	Chemotherapy then Icotinib vs. observation	DFS	477
BD-IC-IV-59 NCT02125240	*EGFR* deletion 19 or exon 21 L858R mutation	Chemotherapy, then Icotinib vs. placebo	DFS	300
WJOG6401L IMPACT	*EGFR* deletion 19 or exon 21 L858R mutation	Gefitinib vs. cisplatin/vinorelbine	DFS	230
ADAURA NCT02511106	*EGFR* deletion 19 or exon 21 L858R mutation with or without T790M	Chemotherapy or no chemotherapy, then osimertinib vs. placebo	DFS	700
ALCHEMIST A081105 NCT02193282	*EGFR* deletion 19 or exon 21 L858R mutation	Erlotinib vs. placebo	OS	450
ALCHEMIST E4512 NCT02201992	*ALK*-positive by FISH	Crizotinib vs. placebo	OS	378
ALCHEMIST/ANVIL NCT02595944	*EGFR*/*ALK* wildtype, regardless of PD-L1 status	Chemotherapy, then nivolumab vs. observation	OS/DFS	714
Impower010 NCT02486718	Regardless of PD-L1 status	Chemotherapy, then atezolizumab vs. placebo	DFS	1127
BR31 NCT02273375	Regardless of PD-L1 status	Chemotherapy or no chemotherapy, then durvalumab vs. placebo	DFS	1100
Keynote-091 NCT02504372	Regardless of PD-L1 status	Chemotherapy or no chemotherapy, then pembrolizumab vs. placebo	DFS	1380

[a]All include stage II to IIIA, all PD-1/PD-L1 studies open to stage IB (4 cm) to IIIA after adjuvant chemotherapy.
DFS, disease-free survival; OS, overall survival; *ALK*, ALK receptor tyrosine kinase gene; FISH, fluorescence in situ hybridization; PD-L1, programmed death ligand 1; PD-1, programmed cell death 1.

marker. With approvals in advanced-stage disease, multiple programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint inhibitors are now being studied in the adjuvant setting.

Advances in RT

Section Authors: Kristin Higgins, MD, Suresh Senan, MD

Locally Advanced Stage III Disease. The standard of care for locally advanced NSCLC remains concurrent platinum-based chemotherapy and radiation to 60 to 66 Gy.[114] The PROCLAIM study evaluated two concurrent chemotherapy schemes, pemetrexed-cisplatin versus cisplatin-etoposide, with thoracic radiation therapy (TRT) in stage IIIA/IIIB nonsquamous NSCLC. Survival with pemetrexed-cisplatin-TRT was not superior, although grade 3 or lower neutropenia occurred less frequently in the pemetrexed arm.[115] A randomized study comparing intensity-modulated RT (IMRT) with passively scattered proton therapy reported no differences in the primary study end point of treatment failure (defined as either local progression or grade 3 or higher radiation pneumonitis).[116] Secondary analyses of the RTOG 0617 study found less high-grade pneumonitis, lower cardiac doses with use of IMRT versus three-dimensional conformal radiation therapy,[117] and also less clinically meaningful decline in QOL with IMRT.[118]

SBRT for Early-Stage and Oligometastatic Disease. The impact of stereotactic body RT (SBRT) for peripheral early-stage NSCLC is reflected in a Surveillance, Epidemiology, and End Results analysis showing that RT utilization rates for stage IA NSCLC increased from 13% to 29% between 2004 and 2012, with significant improvements in OS in the RT cohort.[119] A systematic review reported only limited changes in health-related QOL after 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 (one to three metastatic lesions), a randomized phase II trial in patients not progressing after first-line systemic therapy demonstrated a significant improvement in progression-free survival (PFS) with local consolidative therapy (chemoradiotherapy or resection of all lesions) compared with standard therapy (11.9 months versus 3.9 months, log-rank $p = 0.0054$).[124]

Use of WBRT in NSCLC. Brain metastases will develop in up to 50% of patients with NSCLC.[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 RT (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 in five fractions) or best supportive care.[127] The primary outcome measure was quality-adjusted life-years, 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 extracranial disease, and those for whom radiosurgery remains an option.

ALK

Section Authors: Benjamin Solomon, M.B.B.S., PhD, Dong-Wan Kim, MD, PhD

New-Generation TKIs. Currently, ceritinib and alectinib are approved by the U.S. 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, which was 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% confidence interval [CI]: 0.42–0.73, $p < 0.00001$).[128] The randomized phase 3 J-ALEX study compared alectinib, 300 mg twice daily, and crizotinib in Japanese patients without prior ALK inhibitor treatment. Alectinib was significantly superior to crizotinib, with PFS not reached versus 10.8 months, respectively (HR = 0.34).[129] Results from a global phase 3 study (ALEX study) comparing alectinib, 600 mg twice daily, 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 biopsy specimens and identified differences in the frequency and type of secondary mutations occurring in patients progressing while receiving crizotinib compared with second-generation ALK TKIs.[134] Secondary *ALK* mutations were present in

20% to 30% of patients progressing while taking crizotinib compared with in more than 50% of patients progressing during treatment with a second-generation ALK TKI. Mutations such as L1196M and G1269A were frequent in post–crizotinib treatment biopsy specimens; they were less common after treatment with second-generation ALK TKIs. In contrast, G1202R, which was found in only 2% of post–crizotinib treatment specimens, was the most frequent mutation after treatment with second-generation TKIs. Interestingly, the mutation profile of tumors changes with time and with the influence of sequential ALK TKIs.[134,135] Although the empirical use of sequential ALK TKIs such as crizotinib followed by ceritinib or alectinib has resulted in long-term disease control and excellent survival, characterization of resistance mechanisms by using serial tumor biopsy specimens 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; alternatively, the G1202R mutation that is associated with resistance to crizotinib, alectinib, and ceritinib may be sensitive to the third-generation ALK TKI lorlatinib.[130]

EGFR

Section Authors: Melissa Johnson, MD, James C. H. Yang, MD, PhD, Lecia V. Sequist, MD

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

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

In November 2015, osimertinib became the first U.S. FDA–approved T790M mutant–specific, wild-type–sparing (third-generation) EGFR TKI. This year we saw mature results from two large single-arm phase II studies of osimertinib, 80 mg daily, in patients with T790M-mediated acquired resistance. The AURA extension and AURA2 trials showed overall response rates (ORRs) of 62% and 58%, disease control rates (DCRs) of 90% and 92%, and PFS times of 12.3 and 9.9 months, respectively.[140,141] The phase III AURA3 trial randomized 419 *EGFR*-mutant patients with T790M after failure of first-line EGFR TKIs to osimertinib or platinum/pemetrexed; the PFS times were 10.1 and 4.4 months, respectively (HR = 0.30, 95% CI: 0.23–0.41, $p < 0.001$).[142]

Osimertinib may also have unique central nervous system activity.[143] *EGFR*-mutant patients (*EGFR* T790M not required) with leptomeningeal disease were treated with osimertinib, 160 mg (BLOOM study).[144] Nine of 20 patients had radiographic responses; improvements in neurologic examination findings and declining levels of ctDNA in the cerebrospinal fluid were also reported. Promising PFS was seen with first-line osimertinib in patients with *EGFR*-mutant NSCLC,[145] and the results of a phase III study comparing osimertinib to erlotinib/gefitinib (FLAURA) are greatly anticipated.

The need for tissue rebiopsy to determine T790M status can be a barrier to appropriate treatment selection. Plasma detection and semiquantitation of the activating *EGFR* and T790M mutation is a useful tool to predict the efficacy of osimertinib,[146] and an assay for T790M in ctDNA was U.S. FDA–approved in 2016 as a companion diagnostic to osimertinib. Novel techniques for T790M detection in both plasma and urine have been studied,[147] and minimally invasive assays are expected to gain prominence in the future.

Updates regarding several other novel EGFR TKIs were published in 2016.[148] Olmutinib was approved in the Republic of Korea, but global development has been halted. EGF816[149] and ASP8273[150] are active in T790M-positive patients. Rociletinib development has ceased owing to low activity in T790M-positive patients.[151,152] A novel EGFR TKI, AZD3759, has increased central nervous system penetration but does not inhibit T790M.[153,154]

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.[155–157]

ROS1

Section Authors: Alice Shaw, MD, PhD, Myung-Ju Ahn, MD, PhD

Resistance to crizotinib develops in almost all patients with *ROS1*-rearranged NSCLC. 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,[158] D2033N,[159] S1986Y/F,[160] and L2155S,[161] 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

Table 3. Driver Oncogene Mutations, Inhibitors, Response, and ClinicalTrials.gov Registration for Other Targets in Lung Cancer

Driver Oncogene	Prevalence of Lung Adenocarcinoma	Inhibitor(s)	ORR	NCT No.
BRAF V600E mutation	1%-2%	Vemurafenib	42% (n = 19)[176]	NCT01524978
		Dabrafenib	35% (n = 84)[177]	NCT01336634
		Dafrafenib + trametinib[a]	63% (n = 57)[178]	NCT01336634
BRAF non-V600E mutations	1%-2%	Trametinib	NR	NCT02465060
MET exon 14 skipping	3%-4%	Crizotinib	44% (n = 18)[179]	NCT00585195
		Crizotinib	NR	NCT02465060
		Crizotinib	NR	NCT02664935
		Capmatinib	NR	NCT01324479
		Tepotinib	NR	NCT02864992
		Savolitinib	NR	NCT02897479
		Glesatinib	NR	NCT02544633
		Cabozantinib	NR	NCT01639508
		Merestinib	NR	NCT02920996
MET high-level amplification	1%	Crizotinib	66% (n = 6)[180]	NCT00585195
		Capmatinib	NR	NCT01324479
		Glesatinib	NR	NCT02544633
		Cabozantinib	NR	NCT01639508
RET rearrangements	1%-2%	Cabozantinib	28% (n = 25)[181]	NCT01639508
		Vandetanib	47% (n = 19)[182]	UMIN10095 (Japan)
		Vandetanib	17% (n = 18)[183]	NCT01823068
		Lenvatinib	16% (n = 25)[184]	NCT01877083
		Sunitinib	NR	NCT01829217
		Apatinib	NR	NCT02540824
		Ponatinib	NR	NCT01813734
		Alectinib	NR	NCT02314481
		Alectinib	NR	UMIN20628 (Japan)
		Vandetanib + everolimus	83% (n = 6)[185]	NCT01582191
ERBB2 (*HER2*) exon 20 mutations	2%	Dacomitinib	12% (n = 26)[186]	NCT00818441
		Afatinib	33% (n = 3)[187]	NCT02369484
		Afatinib	NR	NCT02465060
		Ado-trastuzumab emtansine	NR	NCT02675829
		Neratinib	0% (n = 13)[188]	NCT01827267
		Neratinib + temsirolimus	21% (n = 14)[188]	NCT01827267
		AP32788	NR	NCT02716116
NTRK1/2/3 rearrangements	<1%	Entrectinib	NR	NCT02568267
		Entrectinib	NR[189]	NCT02097810
		Larotrectinib	NR	NCT02122913
		Larotrectinib	NR	NCT02576431
		Plx7486	NR	NCT01804530
		Ds6051b	NR	NCT02279433
		Altiratinib	NR	NCT02228811
		Sitravatinib	NR	NCT02219711
		Cabozantinib	NR	NCT01639508
		Merestinib	NR	NCT02920996

(continued)

resistance mechanism in crizotinib-treated patients.[162] Preclinical studies suggest that cabozantinib,[163] foretinib,[164] and lorlatinib[165] may be able to overcome this resistance mutation. The *ROS1* D2033N resistance mutation was identified in a patient with CD74 molecule gene (*CD74*)-*ROS1* fusion who relapsed while taking crizotinib. Like G2032R, D2033N is located at the solvent front of the kinase hinge. Notably, this patient was

Table 3. Continued

Driver Oncogene	Prevalence of Lung Adenocarcinoma	Inhibitor(s)	ORR	NCT No.
FGFR1/2/3 mutations or rearrangements	<1%	AZD4547	NR	NCT02465060
		AZD4547	NR	NCT02154490
		AZD4547	NR	NCT02664935
		Erdafitinib	NR	NCT02699606
		Lucitanib	NR	NCT02109016
		Nintedanib	NR	NCT02299141
		BGJ398	NR	NCT02160041

[a]Approved by European Union and FDA in 2017 and pending review for formal regulatory approval elsewhere.
ORR, overall response rate; NCT No., ClinicalTrials.gov identifier; NR, not reported/ongoing trial; *MET*, MNNG HOS Transforming gene; *RET*, ret proto-oncogene; *ERBB2*, erb-b2 receptor tyrosine kinase 2 gene; *NTRK1/2/3*, neurotrophic receptor tyrosine kinase 1/2/3 gene; *FGFR1/2/3*, fibroblast growth factor receptor 1/2/3 gene.

highly responsive to the multitargeted inhibitor cabozantinib, experiencing a rapid and durable clinical response.[159] Recently, a dual *ROS1* kinase domain mutation, S1986Y and S1986F, was discovered in a *ROS1*-positive patient who had relapsed while receiving crizotinib. This patient subsequently responded to lorlatinib.[160] Finally, the novel resistance mutation, L2155S, was identified in crizotinib-resistant HCC78 cell lines harboring the solute carrier family 34 member 2 gene (*SLC34A2*)-*ROS1* fusion.[161] 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 patients with crizotinib-resistant, *ROS1*-positive NSCLC. Preliminary data suggest that lorlatinib can induce responses in some patients, but *ROS1* mutation status in these responders has not been reported.[130] 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.[166] 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 proto-oncogene receptor tyrosine kinase gene (*KIT*) D816G activating mutation[167] and EGFR pathway activation.[168] 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

Section Authors: Daniel B. Costa, MD, PhD, Jyoti D. Patel, MD

Although in 2016 approval of TKIs matched to a driver was restricted to tumors with genomic aberrations in *EGFR, ALK* and *ROS1*,[169–175] other putative driver events could predict for response to targeted therapies in advanced NSCLC, particularly in lung adenocarcinoma (Table 3[176–189]).

The genotype/inhibitor duo closest to receiving approval by the U.S. FDA and other worldwide regulatory agencies is the *BRAF* V600E mutation (found in ~1% to 2% of adenocarcinomas) with dabrafenib plus trametinib, as the ORR of this BRAF plus MEK inhibitor combination is higher than 60% and is associated with prolonged disease control.[176–178,190] The European Union approved the aforementioned combination in April 2017 and the FDA in June 2017.

Another promising treatable target is MET proto-oncogene receptor tyrosine kinase, which is 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 (in ~1% of adenocarcinomas) and *MET* exon 14 alterations (in ~3%–4% of adenocarcinomas and >10% of sarcomatoid carcinomas).[191–197] Crizotinib, the U.S. FDA–approved ALK/ROS1/MET TKI, induces responses in close to half of patients with advanced cancers with MET alterations,[179,180,198] and there are ongoing clinical trials of multiple other multitargeted MET TKIs (see Table 3).

The activity of TKI monotherapy in other subgroups of lung cancer is less clear.[199,200] The oncogene rearranged during transfection (RET) is seen in approximately 1% to 2% of patients with NSCLC; however, the ORR is less than 30% with the currently available multitargeted RET TKIs.[181–184,201,202] ErbB2 receptor tyrosine kinase 2 (ERBB2 or HER2) exon 20 mutations occur in approximately 2% of lung adenocarcinomas. Currently available ERBB TKIs and monoclonal antibodies are minimally active and seldom reach an ORR higher than 20%.[186–188,203,204] More specific TKIs and rational combination approaches[185] may hold the promise of eventually leading to regulatory approval of precision therapies in these tumors (see Table 3).

The drug development platform for driver oncogenes with a prevalence less than 1% in lung cancer, such as neurotrophic receptor tyrosine kinase (*NTRK*) or fibroblast growth factor receptor (*FGFR*) rearrangements,[189,205–207] is more challenging (see 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 U.K. National Lung Matrix (NCT02664935), or that involve multiple cancer primaries binned by molecular alterations, such as NCI-MATCH (NCT02465060).[208]

Immunotherapy

Section Authors: Leora Horn, MD, MSc, Scott Gettinger, MD, 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 that provides a significant improvement in OS compared with docetaxel (13.8 versus 9.6 months, HR = 0.73, $p = 0.0003$).[209] Contrary to the data on nivolumab in patients with nonsquamous NSCLC,[156] the data on 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) and both the companion diagnostic approved for pembrolizumab (22C3) and the complimentary diagnostic approved for nivolumab (28-8).[57] 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 versus 6.0, HR = 0.50, $p < 0.001$), OS (HR = 0.60, $p = 0.005$), health-related QOL, and time to deterioration for dyspnea, cough, and chest pain compared with platinum-based chemotherapy in patients with tumors that were EGFR and ALK negative and strongly PD-L1–positive ($\geq$50%).[210,211] A similarly designed study did not show efficacy when nivolumab was compared with chemotherapy; however, in this first-line study, patients with tumors expressing PD-L1 at a lower level of expression (>1% of tumor cells) were enrolled.[212] First-line avelumab demonstrated efficacy similar to that of 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 patients with NSCLC.[213]

Benefit with EGFR/ALK Positivity. 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 rates of response to PD-1 axis inhibitors, without better outcome than standard second-line chemotherapy.[214–216] That said, some patients benefit from such therapy, as demonstrated in the CheckMate 012 trial. One arm of this trial, 20 patients with *EGFR*-mutant NSCLC and acquired resistance to EGFR TKI therapy as last therapy were treated with erlotinib and nivolumab; four experienced prolonged tumor regression.[217] Combination therapy was tolerated well; however, increased toxicity, particularly pneumonitis, has been suggested with other TKI and PD-L1 axis inhibitor combinations.[218] Additional arms on the CheckMate 012 trial evaluated combination therapy with nivolumab and ipilimumab; among eight patients with *EGFR*-mutant NSCLC, four achieved response.[219] 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.[220] Currently, whether high tumor PD-L1 expression trumps *EGFR* or *ALK* status is uncertain. 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.[221]

Immunotherapy: Novel Combinations and Future Directions. Immune escape is a critical gateway to malignancy. Although 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 2 weeks, and ipilimumab, every 12 or 6 weeks, has demonstrated promising results with increasing response rates (RRs) compared with nivolumab alone, 47%, 38%, and 23%, respectively, and durable responses, albeit with a higher number of grade 3 and grade 4 adverse events.[219] Combination strategies with both anti–PD-1 or anti–PD-L1 inhibitors and anti–cytotoxic T-lymphocyte associated protein 4 are being explored further in phase II and III clinical trials (NCT02477826, NCT02659059, NCT02542293, and NCT02453282). To further build on successes of the PD-1/PD-L1 blockade and take 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 or II in NSCLC or solid tumors, including lymphocyte activation gene 3 (NCT01968109/NCT02460224), hepatitis A virus cellular receptor 2 (NCT02817633/NCT02608268), tumor necrosis factor superfamily member 4 (NCT02318394/NCT02410512), tumor necrosis factor receptor superfamily member 18 (NCT02583165/NCT02697591), and indoleamine 2,3-dioxygenase inhibitors (NCT02460367). Finally, a small phase II trial demonstrated superior RRs (55% versus 29%) and PFS times (median 13.0 months versus 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 with chemotherapy alone, with a similar incidence of grade 3 or higher adverse events.[222] This led to the U.S. 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 comparing this approach are ongoing.

The second approach is designing studies that target specific defects in the cancer-immune interaction. Currently mutational burden,[63] tumor-infiltrating lymphocytes,[223] and high PD-L1[224] expression in the tumor microenvironment 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.[225]

A third approach is to create publicly available, open source inventories of large numbers of tissue and blood samples from patients before initiation of immunotherapy and subject such samples to genomics (whole exome sequencing and RNA sequencing), 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. On the basis of these signatures, clinical trials should be performed to test combinations that have been 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 that the general immune state of stage III disease patients is better than that of stage IV patients, resulting in a higher RR and more toxicities.[226] Interestingly, pathologic responses have also been observed after neoadjuvant anti–PD-1 in early NSCLC.[227] Earlier-stage patients may require a shorter treatment duration than stage IV patients. Immunotherapy is being actively studied in the neoadjuvant (NCT02259621/NCT02998528) and the adjuvant (NCT02504372/NCT02273375) settings in NSCLC.

Finally, as pricing of new immuno-oncology drugs is unlikely to change soon, the aforementioned future directions will certainly lead to a much more cost-effective utilization of our resources, as chances for best outcome will be optimal.

SCLC

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RT for SCLC. 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 chemoradiotherapy regimen in LS disease.[228,229] At the American Society of Clinical Oncology 2016 annual meeting, the CONVERT trial was presented.[230] This multicenter, international, randomized, phase III trial aimed to establish a standard chemoradiotherapy regimen in LS SCLC. Patients were randomized 1:1 to receive either 45 Gy in 30 twice-daily fractions over 3 weeks or 66 Gy in 33 once-daily fractions over 6.5 weeks starting on day 22 of cycle 1 of chemotherapy, followed by prophylactic cranial irradiation. The study enrolled 547 patients, who were recruited from 73 centers in seven European countries and Canada between 2008 and 2013. Once-daily RT did not result in superior survival or worse toxicity than twice-daily RT (2-year survival of 56% compared with 51% [HR for death in the once-daily group = 1.18, $p = 0.14$]). The survival for both regimens was higher than previously reported and radiation toxicities were lower than expected, likely because of the use of modern RT techniques. The implications of CONVERT are important. As CONVERT was not an equivalence trial and because the only study to date that has shown superiority for one RT regimen over another in LS SCLC is the Intergroup 0096 trial (which showed no major differences in toxicity), twice-daily RT should continue to be regarded as the standard of care. However, once-daily RT at a dose of 66 Gy in 33 fractions can certainly be considered an alternative regimen if 45 Gy in 30 fractions twice daily cannot be delivered because of 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 RT concurrently with chemotherapy.

For patients with extensive-stage SCLC with residual intrathoracic disease who have responded after induction chemotherapy, addition of thoracic RT reduces the risk for intrathoracic recurrence and improves 2-year survival[231]; however, the primary end point of 1-year survival was not met. A survey of routine practice presented at the European Society for Radiotherapy and Oncology 2016 conference showed that since publication of the CREST trial there has been a dramatic increase in the use of TRT (from 25% to 81%).[232] Subsequently, a subanalysis of CREST investigating the prognostic importance of the number and sites of metastases was presented at the ASTRO 2016 annual meeting.[233] It suggested that future studies evaluating more intensive thoracic and extrathoracic RT in extensive-stage SCLC focus on patients with fewer than three metastases that are not in the liver or bone.

Advances in Novel Systemic Therapies for SCLC. Several new approaches to systemic treatment of SCLC have recently emerged and have been the subject of recent

Table 4. Selected Monotherapy Immunotherapy Trials and Preliminary Reported Results

Agent	NCT No.	Type	Setting	ORR	DCR	PFS	OS	PD-L1 IHC status
Pembrolizumab (KEYNOTE-028)[240]	02054806	PD-1 inhibitor	Second line	28%	76%	5.8 mo	18 mo	All patients were PD-L1 IHC-positive
Pembrolizumab[241]	02399371	PD-1 inhibitor	Second line	21%	77%	6.2 mo	NR	Did not correlate with response
Nivolumab (NivoMes trial)[242]	02497508	PD-1 inhibitor	1 prior therapy	24%	50%	3.6 mo	NR	Trend for a correlations with OR
Avelumab (JAVELIN)[243]	01772004	PD-L1 inhibitor	Salvage, any line	9.4%	57%	4.3 mo	NR	Trend to correlate with median PFS

NCT No., ClinicalTrials.gov identifier; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survivial; PD-L1, programmed death ligand 1; IHC, immunohistochemistry; PD-1, programmed cell death; NR, not reported/ongoing trial.

reviews.[234,235] These will be touched on here only briefly, but they 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, which is relatively unique to SCLC.

In the immunotherapy domain, several of the same PD-1–directed T-cell checkpoint inhibitors already discussed in relation to NSCLC, including both pembrolizumab and nivolumab, have demonstrated initial activity in SCLC.[236,237] Early data with the combination of nivolumab plus ipilimumab appear particularly promising. In a 216-patient randomized phase II study of nivolumab versus various schedules of nivolumab and ipilimumab, the combination arms demonstrated RRs of 19% to 23% and DCRs of 36% to 42%.[236] The toxicities observed were similar to those reported in other diseases. On the basis of 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 that is normally confined to intracellular compartments but is markedly up-regulated and becomes aberrantly cell surface–expressed in most SCLC.[238] Rovalpituzumab teserine, or Rova-T, is an antibody drug conjugate directed against DLL3 that demonstrated remarkable preclinical efficacy against SCLC in vivo[238] and promising activity in a first-in-human phase I clinical trial in patients with recurrent metastatic SCLC.[239] Early data suggest that high-level expression of the target, DLL3, may serve as a predictive biomarker for the activity of this agent, as a 38% RR (10 of 26) and DCR of 88% (23 of 26) were observed in two-thirds of patients with DLL3 expressed in more than 50% of the cells. Larger confirmatory trials of Rova-T in SCLC are ongoing.

Mesothelioma

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In the past year, the field of mesothelioma treatment 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 RRs vary between 9% and 28%, with DCRs of 50% to 77% in unselected patients with mesothelioma. As in NSCLC, checkpoint inhibitors seem to be more active in PD-L1 IHC–positive patients, but the association is not strong. Unfortunately, the cytotoxic T-lymphocyte associated protein inhibitor tremelimumab did not show any benefit over placebo in the DETERMINE trial (NCT01843374).[244] Although 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 Wilms' tumor 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 six cycles of therapy followed by bevacizumab maintenance. On the basis of survival benefit, cisplatin-pemetrexed-bevacizumab is now listed in the National Comprehensive Cancer Network guidelines as an approved frontline therapy. On the basis of a significant improvement of PFS, nintedanib combined with cisplatin-pemetrexed has proceeded to a phase III international randomized trial (NCT01907100). In Europe the EORTC is currently studying nintedanib in a phase 2 switch maintenance setting (NCT02863055). The phase II study of cisplatin-pemetrexed with or without 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 arginino-succinate synthase 1–deficient mesothelioma (the ATOMIC trial and NCT02709512), mesothelin-targeted agents (SS1P, anetumab ravtasine, and LMB-100), tazemetostat in BRCA1 associated protein 1-deficient

Table 5. Selected Ongoing Combination Immunotherapy Trials

Agents	Phase	NCT No.	Target	Setting	Planned No.	Primary End Point
Ipilimumab-nivolumab vs. platinum-pemetrexed	III	02899299	PD-1 + CTLA4 inhibitors vs. chemotherapy	Frontline	600	OS
Durvalumab + cisplatin-pemetrexed (PrE0505)	II	02899195	PD-L1 inhibitor + chemotherapy	Frontline	55	OS
Pembrolizumab + cisplatin-pemetrexed vs. cisplatin-pemetrexed vs. pemetrexed alone (Canadian Cancer Trials Group)	II	02784171	PD-1 inhibitor + chemotherapy	Frontline	126	PFS
ONCOS-102 + cisplatin-pemetrexed (Spain)	Ib/II	02879669	Immune-priming GM-CSF coding oncolytic adenovirus + chemo	Frontline	30	Safety, toxicity
Tremelumumab-durvalumab (Italy NIBIT-MESO-1)	II	02588131	PD-L1 + CTLA4 inhibitors	0 or 1 prior therapy	40	ORR (immune related)
Pembrolizumab vs. gemcitabine or vinorelabine (PROMISE-meso ETOP)	III	02991482	PD-1 inhibitor vs. chemo	Second line	142	PFS
Nivolumab vs. nivolumab-Ipilimumab (IFCT MAPS2)	II	02716272	PD-1 vs. PD-1 + CTLA4 inhibitor	1 or 2 prior therapies	125	Disease control rate
Ipilimumab + nivolumab (INITIATE, NKI Netherlands)	II	03048474	CTLA 4 and PD1 with translational reaserch biopsies	1 or 2 prior therapies	33	Disease control rate
Pembrolizumab + nintedanib (PEMBIB, Gustave Roussy)	Ib	02856425	PD-1 and VEGFR, PDGFR, FGFR inhibitor	At least 1 prior therapy	18	Safety, toxicity
Atezolizumab (basket trial)	II	02458638	PD-L1 inhibitor	At least 1 prior therapy	725	Disease control rate
CART-meso (University of Pennsylvania)	I	02159716	Autologous T cells transduced with antimesothelin immunoreceptor	At least 1 prior therapy	19	Safety, toxicity
Autologous redirected RNA Meso-CIR T cells (University of Pennsylvania)	I	01355965	Autologous T cells transfected with anti-mesothelin mRNA	Any	18	Safety, toxicity
Autologous T cells to target mesothelin (MSKCC)	I	02414269	Mesothelin-targeted T-cell infusions iCasp9M28z	Any	24	Safety, toxicity
Defactinib + pembrolizumab mesothelioma cohort (United Kingdom)	I/IIA	02758587	FAK and PD-1 inhibitor	Any	59	Safety, toxicity
Atezolizumab + bevacizumab (MDACC)	II	Pending	PD-L1 inibitor + VEGF inhibitor	Any	20	Safety, toxicity
Atezolizumab (basket trial)	II	02458638	PD-L1 inhibitor	1 prior therapy	725	Disease control rate
Durvalumab vs. tremelimumab + durvalumab	II	02592551	PD-1 inhibitor vs. PD-1 + CTLA4 inhibitor	Neoadjuvant	20	Biomarker modification
S1619 cisplatin-pemetrexed-atezolizumab (SWOG)	II	pending	PD-L1 inhibitor + chemotherapy	Neoadjuvant	24	Safety, feasibility
Pembrolizumab	Pilot	02707666	PD-1 inhibitor	Neoadjuvant	15	Safety, feasibility
Pembrolizumab (MDACC)	I	02959463	PD-1 inhibitor	Adjuvant with RT	24	Safety, feasibility

NCT No., ClinicalTrials.gov identifier; PD-1, programmed cell death 1; CTLA4, cytotoxic T-lymphocte associted protein 4 gene; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; MSKCC, Memorial Sloan Kettering Cancer Center; FAK, focal adhesion kinase; MDACC, M. D. Anderson Cancer Center; RT, radiotherapy.

mesothelioma (NCT02860286), trabectedin (the ATREUS trial and NCT02194231), 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

Section Authors: Natasha Leighl, MD, MMSc, Ronan J. Kelly, MD, MBA

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 such as the U.S. FDA and European Medicines Agency focus on efficacy and safety of novel interventions, approving new treatments that yield statistically better outcomes. Other bodies such as the National Institute for Health Care Excellence (United Kingdom) and pan-Canadian Oncology Drug Review focus on value, including cost and clinical relevance of these improved outcomes. By contrast, the U.S. Centers for Medicare and Medicaid Services does 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 when making funding recommendations.

However, there is growing recognition that value in cancer care is important to patients and clinicians. Several international bodies, including the American Society of Clinical Oncology and European Society for Medical Oncology, have developed standardized value frameworks to help determine the value of treatments, incorporating the magnitude of clinical benefit, toxicity, and QOL gain without aggregating these measures as a formal cost-effectiveness analysis.[247–249] For example, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale uses a structured approach to rank treatments by using a four-point scale based on relative and absolute survival gain, toxicity rates, QOL, and use of intermediate end points such as PFS.[247]

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, including multiplex genomic testing,[250] novel targeted kinase inhibitors[251] and checkpoint inhibitors, are above traditional willingness-to-pay thresholds.[252–254] Each jurisdiction must determine its own willingness to pay 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,[255] implementing strategies to ensure affordable access to treatment has never been more important for patients with lung cancer and their families.

Specific Future Perspectives

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The past year led to significant progress for new lung cancer therapies 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 SCLC. Furthermore, much focus has so far been on single-drug development, which has been very encouraging for certain subgroups of patients; in the vast majority of patients, however, combination therapy may be required to convert treatment intent to 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 owing to the inherent genomic complexity, which is 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 determining which combination of drugs will best treat resistant tumors or prevent the emergence of resistance.

Although pharmaceutical companies are still pursuing many phase II or III combination studies that assess molecular targeted therapies or immunotherapy in combination with chemotherapy, or in combination with each other, study designs remain largely empirical and 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, has led to breakthrough therapeutic advances for patients with NSCLC and provides a platform for future therapeutic developments. Better preclinical models need to be developed to study tumor-environment interactions and potential intervention opportunities. Although PD-L1 IHC assessment is used today for PD-L1 and/or 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 quantitation of the "value" of each new therapy. Although 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 need to be explored. It remains crucial to foster future research in lung cancer prevention, early detection, and screening. Although most of the excitement regarding new therapies today focuses on patients with advanced disease, the odds for making lung cancer a curable disease are favored by moving these advances toward early-stage disease. New biomarkers, most likely blood-based assays, to complement the lung cancer screening process are strongly needed 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 for patients with lung cancer and research appears to be bright, much work remains to be done.

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