Update in Lung Cancer 2014

Avrum Spira¹, Balazs Halmos², and Charles A. Powell³

¹Division of Computational Biomedicine, Boston University School of Medicine, Boston, Massachusetts; ²Department of Medicine, Columbia University Medical Center, New York, New York; and ³Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

ORCID IDs: 0000-0003-1467-0489 (A.S.); 0000-0001-7548-8360 (B.H.); 0000-0003-3509-891X (C.A.P.).

Abstract

In the past 2 years, lung cancer research and clinical care have advanced significantly. Advancements in the field have improved outcomes and promise to lead to further reductions in deaths from lung cancer, the leading cause of cancer death worldwide. These advances include identification of new molecular targets for personalized targeted therapy, validation of molecular signatures

of lung cancer risk in smokers, progress in lung tumor immunotherapy, and implementation of population-based lung cancer screening with chest computed tomography in the United States. In this review, we highlight recent research in these areas and challenges for the future.

Keywords: lung cancer; chest computed tomography screening; targeted therapy; lung immunotherapy; biomarkers

Lung cancer remains the leading cause of cancer death in the United States and in the world, with 221,200 cases and 158,040 deaths expected in the United States in 2015 (1). The incidence and mortality rates of lung cancer have declined in parallel with reduction of smoking prevalence. Concurrently, advances in early detection technologies and in the application of genomics to targeted therapeutic development promise further reductions in lung cancer deaths. In this review of advances in lung cancer over the past 2 years, we highlight the contributions to the field in epidemiology and biology as well as in early detection, immunotherapy, and targeted therapeutics, areas that offer high promise for further reductions in lung cancer mortality.

Epidemiology

The role of environmental and occupational exposures in lung cancer continues to be

prominent. Markowitz and colleagues from the team of late Dr. Irving Selikoff, a leader in mesothelioma epidemiology and public health, confirmed Dr. Selikoff's prior findings that asbestos exposure and asbestosis increase the risk of lung cancer (2). The risk of lung cancer mortality among nonsmoking asbestos-exposed insulation workers was increased 3.6-fold. Confirming the link between chronic lung disease and lung cancer, the risk of lung cancer mortality in nonsmokers with parenchymal asbestosis was additively increased over the risk of asbestos exposure alone (2). Pairon and colleagues reported that pleural plaques detected on chest computed tomography (CT) in asbestos-exposed men was associated with increased risk of lung cancer mortality, after adjustment for smoking status and asbestos exposure (3). Taken together, asbestos exposure history and radiologic correlates of asbestosis and pleural plaques are independently associated with increased lung cancer risk.

Raaschou-Nielsen and colleagues extended the evidence in support of the role of long-term exposure to ambient air pollution as a risk factor for lung cancer (4, 5). The authors conducted a metaanalysis from studies of 17 cohorts and were able to adjust for smoking and other potential confounders. The risk for lung cancer was significantly associated with exposure to particulate matter less than 10 μm (PM_{10}) (hazard ratio [HR], 1.22; 95% confidence interval, 1.03–1.45) and was associated with $\text{PM}_{2.5}$ exposure (HR, 1.18; 95% confidence interval, 0.96–1.46), the latter of which was also reported in a recent study from the American Cancer Society Cancer Prevention Study II cohort (6). Villeneuve and colleagues showed a similar effect of exposure to volatile organic hydrocarbons that are closely tied to traffic and industry sources (7). Taken together, these studies demonstrate the importance of global public health initiatives to reduce exposure to cigarette smoke, asbestos, and ambient

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Correspondence and requests for reprints should be addressed to Charles A. Powell, M.D., Chief, Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1232, New York, NY 10032. E-mail: charles.powell@mssm.edu

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air pollution, all of which are important lung carcinogens.

The role of preexisting chronic respiratory disease in mediating lung cancer risk was examined in a large international SYNERGY study of 12,739 cases and 14,945 control subjects (8). Chronic bronchitis and emphysema were positively associated with lung cancer risk, as was shown in previous studies. Pneumonia was also positively associated with risk, but only with incidence within 2 years of cancer diagnosis, suggesting that this finding was attributable to misdiagnosis or ascertainment bias. There was no association of lung cancer risk with asthma or tuberculosis.

Lung Cancer Screening

The National Lung Screening Trial (NLST), the largest randomized controlled lung cancer screening trial ever performed, showed a 20% relative decrease in lung cancer mortality and a 7% decrease in overall mortality in high-risk individuals who were screened with low-dose chest CT scan versus those screened with chest radiograph (9). The NLST initial prevalence screening examination findings were reported in 2013 (10). Important findings in the chest CT screening arm included the positive finding rate of 27.3% and cancer prevalence rate of 1.1%, with sensitivity and specificity of 93.8 and 73.4%, respectively. These results are consistent with previously published data from observational or smaller randomized controlled trials of screening but differ from those reported by Horeweg and colleagues from the NELSON (Nederlands Leuvens Longkanker Screenings Onderzoek) trial (11). The NELSON trial randomized 15,822 participants to screening versus observation. Importantly, the criteria for a positive finding were more stringent: noncalcified nodule with volume greater than 500 mm³ (approximately 9.8 mm in diameter) or volume doubling time less than 400 days. The positive finding rate was 6.5%, with a cancer prevalence rate of 0.9% after the first round of screening and 2.6% after three rounds. Similar to NLST, there was a suggestion that the benefit from screening was greater in women than in men. We await publication of the NELSON control group results to determine the impact of the protocol on lung cancer

mortality and to confirm the sex differences in benefit.

Although promising, the experience to date suggests that screening efficacy will be enhanced by refining the screening population to target those at highest risk and by standardization and implementation of multidisciplinary management protocols (12, 13). Kovalchik and colleagues examined the impact of risk on screening efficacy in NLST participants using a risk prediction model that incorporated age, body mass index, family history of lung cancer, smoking history, and emphysema diagnosis (14). Sixty percent of the participants at highest risk for lung cancer death accounted for 88% of the screening-positive lung cancer deaths, and 20% of participants at lowest risk accounted for only 1% of the prevented lung cancer deaths. These results support prospective validation of risk modeling, such as those developed by Tammemägi and colleagues (15) to assess lung cancer risk and by McWilliams and colleagues (16) to assess risk of malignancy in screen-detected nodules, to enhance the efficacy and cost-effectiveness of lung cancer screening.

After publication of the United States Preventive Services Task Force recommendation for lung cancer screening in high-risk individuals aged 55 to 74 years (17), coverage for low-dose chest CT screening in eligible individuals enrolled in commercial health plans will be available in the United States in 2015. The fate of patients covered by Medicare was unclear after the Medicare Evidence Development and Coverage Advisory Committee voted against coverage of lung cancer screening (18). Concerns raised by the committee and by stakeholders, including the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) (19, 20), were reviewed and addressed in the Final Coverage Decision issued by the Centers for Medicare and Medicaid Services, which recommended lung cancer screening for high-risk individuals within screening programs that met strict eligibility criteria and were committed to reporting data in a national registry (21). Key components of the coverage decision include: (1) Eligibility is restricted to healthy current or former smokers aged 55 to 77 years with 30 pack-years of exposure and with smoke exposure within 15 years; (2) For the initial low-dose CT, there must be a written order from a physician or

licensed provider during a lung cancer screening counseling and shared decision-making visit that uses decision aids such as the ATS's Decision Aid: For Lung Cancer Screening with Computerized Tomography (22); (3) Scanning center eligibility is restricted to centers with radiologists who have experience reading chest CT studies and with capability to provide low-dose CT with dose of less than or equal to 3.0 mGy; (3) Centers are required to collect and submit demographic and imaging data to a Centers for Medicare and Medicaid Services-approved registry. We expect that widespread implementation of lung cancer screening in 2015 will usher in a new era focused on early detection and nodule management. We hope that the guideline development process will help ensure strict program compliance with eligibility, imaging procedures, systematic nodule classification, and evaluation protocols and with reporting of registry data. Monitoring and oversight from regulatory agencies and professional societies representing the disciplines of pulmonary medicine, radiology, thoracic surgery, and oncology will be required for appropriate data analysis and to drive protocol modifications in response to the evaluation of process measures and patient outcomes.

The expected frequency of lung nodule detection (20–60% of high-risk individuals) and the fact that the large majority of these lung nodules are benign (up to 96%) make the management of indeterminate pulmonary nodules challenging (23) and suggest a role for biomarkers and other decision aids to improve discrimination of malignant from benign nodules (i.e., diagnostic markers) as well as to identify those at highest risk for lung cancer who might benefit from CT surveillance (i.e., screening markers). Patz and colleagues showed that serum biomarkers have potential as an additional tool to aid in the management of pulmonary nodules (24). Integration of nodule size with serum levels of α_1 -antitrypsin, carcinoembryonic antigen, and squamous cell carcinoma antigen had sensitivity of 88% and negative predictive value of 87% for determining lung cancer. Li and colleagues (25) used multiple reaction monitoring mass spectrometry to discover a 13-protein marker in serum for distinguishing benign versus malignant nodules in a retrospective study. Using a more sensitive SOMAscan technology for measuring serum proteins,

Mehan and colleagues (26) identified in heavy smokers a seven-protein signature that could distinguish non-small cell lung cancer (NSCLC) cases from those with benign nodules. Shen and colleagues (27) demonstrated the potential for sputum microRNA to distinguish patients with lung cancer from smokers without lung cancer. In one of the larger studies to date, Sozzi and colleagues (28) refined and validated a plasma-based microRNA (miRNA) signature for lung cancer screening in the randomized Multicenter Italian Lung Detection (MILD) trial. Mathé and colleagues (29) identified several metabolomics profiles in urine that could distinguish patients with cancer from population control subjects. Although these classifiers are promising, multicenter prospective trials are needed in which the biomarkers are validated in the clinical setting in which they would be used and demonstrate clinical usefulness in patient management.

Recently, Silvestri and colleagues (30) have taken this next translational step by prospectively validating a bronchial genomic biomarker for lung cancer detection. In two multicenter trials (Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer [AEGIS] 1 and 2), the authors have demonstrated that a gene-expression classifier measured in epithelial cells collected from the normal-appearing mainstem bronchus can serve as a sensitive biomarker for diagnosing lung cancer among smokers undergoing bronchoscopy for suspect disease ($n = 639$). The gene-expression classifier and bronchoscopy combined had a sensitivity of 97%, independent of lesion size and location. Importantly, among the subset with intermediate pretest risk of disease ($n = 101$) and those with indeterminate pulmonary nodules ($n = 77$), the negative predictive value of the biomarker was greater than 90%, potentially reducing unnecessary invasive biopsies in patients without lung cancer.

Field Carcinogenesis

Studies of the field of cancerization in lung cancer, including the AEGIS trials detailed above, hold the potential to provide insights into the molecular pathogenesis of lung cancer and directly impact clinical care of those at risk for lung cancer by providing

novel strategies for early detection and targeted chemoprevention. Beyond the study by Silvestri and colleagues (30), a number of key advances have recently been made in our understanding of the “field” of molecular alterations that occurs throughout the airway epithelium exposed to tobacco smoke. Kadara and colleagues provided novel insight into the spatial and temporal characteristics of the transcriptomic alterations found within this field of injury in smokers post lung cancer resection (31). They identified candidate genes that change dynamically over time within the field, including increased expression of phosphorylated AKT and extracellular signal-regulated kinase ERK1/2. A large number of genes were found to change in a gradient-like manner throughout the spatial mapping, although findings were limited by the lack of a control group (smokers without lung cancer) and airway samples collected before tumor resection.

The response of the basal cells, a progenitor cell population lining the airway, to cigarette smoke was explored by Shaykhiev and colleagues (32). They found genes that characterize human embryonic stem cells were selectively induced in the airway basal stem/progenitor cell population of healthy smokers. Furthermore, they identified a subset of these genes whose overexpression in lung adenocarcinoma associated with more aggressive disease. Although these studies were limited to profiling of cultured basal cells as opposed to *in vivo* profiling of these cells, the authors conclude that smoking-induced reprogramming of airway basal cells toward the hESC-like phenotype might represent an early event in the development of aggressive lung carcinomas.

To address the nature of the field of molecular changes found within the airway of smokers with lung cancer, Kadara and colleagues (33) profiled gene expression in the tumor, normal lung tissue, and epithelium that lines the small airways adjacent to the tumor from a cohort of smokers undergoing resection of NSCLC ($n = 20$). They identified a large set of genes that were differentially expressed in both the tumor and adjacent small airway epithelium as compared with the normal lung tissue. Importantly, they found that these genes were enriched within a gene expression signature that can distinguish the large airways of smokers with lung

cancer versus those with benign disease of the chest (34). Their findings suggest that the transcriptomic “field of injury” observed in the proximal airway epithelium reflects, at least in part, the gene-expression changes found within the tumor itself and the local “field of injury” immediately adjacent to the tumor.

Perdomo and colleagues (35) extended studies of the airway transcriptome in lung cancer via characterization of the microRNA alterations in the “field.” Using microRNA-seq, they identified and characterized a novel miRNA, miR4423, as being almost exclusively expressed in the airway epithelium; its expression is reduced both in lung tumors and in the proximal airway epithelium of smokers with lung cancer. Importantly, they found that expression of miR-4423 modulates bronchial epithelial cell differentiation *in vitro* and that overexpression of this miRNA in a number of NSCLC cell lines reduces anchorage-independent growth *in vitro* and reduced the size of tumor formation in a xenograft model. These data support the notion that miRNA may serve as regulators of the gene-expression alterations that characterize field carcinogenesis and may thus serve a novel detection biomarkers as well as chemoprevention targets.

Beyond advancing our insights into the molecular events occurring in the cytological normal epithelium throughout the airway of smokers with lung cancer, recent studies have also begun to shed light on the genomic alterations that characterize premalignant lesions found within this field. Nakachi and colleagues (36) used single-nucleotide polymorphism arrays to characterize novel chromosomal alterations found within premalignant lesions. Among their findings, losses of two putative tumor suppressors, *RNF20* (ring finger protein 20) and *SSBP2* (single-stranded DNA binding protein 2), and an amplification of a potential oncogene, *RASGRP3* (RAS guanyl releasing protein 3), were observed. Importantly, their study suggests that there are somatic chromosomal alterations seen throughout the field and in premalignant lesions of smokers at risk.

Ooi and colleagues (37) extended this paradigm by performing RNA-seq on laser-microdissected epithelium from squamous cell cancer, premalignant lesions, and normal basal cells all matched within the

same patient. The unique study design enabled the authors to identify transcriptomic pathways altered with initiation and progression of squamous cell cancer within individual patients, including increased expression of glucose transporter protein type 1 (*GLUT1/SLC2A1*), carcinoembryonic antigen-related cell adhesion molecule 5 (*CEACAM5*), and polypyrimidine tract binding protein 3 (*PTBP3*), and increased activation of MYC (v-myc avian myelocytomatosis viral oncogene homolog) via nuclear translocation. Although the study was limited by the relatively small cross-sectional study design, it represents a new approach for identifying the earliest molecular events associated with lung carcinogenesis within the field, which potentially can serve as both early detection biomarkers and novel targets for chemoprevention.

Lung Cancer Biology

Lung cancer science continued to provide new insights into tumor biology with notable impact in the understanding of new therapeutic targets, epigenetic regulation, and the role of the tumor microenvironment in tumor progression and regression (38). Cardarella and Johnson reviewed the impact of genomic changes on the treatment of lung adenocarcinoma and squamous cell carcinoma (Figure 1) (39). Ongoing research has demonstrated that NSCLC can be further defined at the pathological level (40) and at the molecular level by the identification and characterization of oncogenic drivers that occur in genes critical to cellular proliferation and survival (41). These advances have prompted investigators to systematically characterize NSCLCs for these oncogenic drivers and treat with appropriate targeted therapies (42). The implementation of personalized lung cancer therapy raises practical challenges; foremost is the need to obtain adequate tumor material for routine pathology diagnosis and molecular testing at time of diagnostic sampling. Ultimately, close communication between the clinical care team, testing laboratory, and pathologist is needed to ensure that specimens for molecular testing meet the laboratory's requirements for tumor content and quality.

Figure 1. Targetable and/or potentially targetable genetic changes in (A) adenocarcinoma and (B) squamous cell carcinomas of the lung. *Gene amplification. ALK = anaplastic lymphoma kinase; DDR2 = discoidin domain receptor tyrosine kinase 2; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; MEK = mitogen-activated protein kinase; MET = mesenchymal-epithelial transition factor; PDGFRA = platelet-derived growth factor receptor α ; PIK3CA = phosphatidylinositol 3-kinase, catalytic, α polypeptide. Reprinted by permission from Reference 39.

New Therapeutic Targets

Advancement of bioinformatics approaches to integrate data from multiple throughput profiling technologies has produced important new insights. These integrative analyses have identified lymphocyte-specific

protein tyrosine kinase (LCK) activation as important step in Kirsten rat sarcoma viral oncogene homolog (KRAS) NSCLC signaling cascade (43), of deoxythymidylate kinase as a therapeutic target in Lkb1-deficient mouse lung tumors (44), and of

tricyclic antidepressants as inhibitors of small cell lung cancer (45). Lung cancer oncogenes involving fusions of anaplastic lymphoma kinase (ALK), *ROS1*, *RET*, fibroblast growth factor receptor (FGFR) 1, FGFR2, and FGFR3 have shown promise as therapeutic targets. Vaishnavi and colleagues used targeted next-generation DNA sequencing of lung adenocarcinoma tumors without known genetic alterations to identify a novel gene fusion involving the kinase domain of the neurotrophic tyrosine kinase receptor, type 1 (*NRTK1*) gene in 2 of 36 specimens (46). Functional validation demonstrated fusions were associated with constitutive kinase activation that could be inhibited pharmacologically, thus increasing the number of key fusion events that will be important in lung cancer diagnostics and therapy. Oncogenic *KRAS* tumors remain a particularly difficult subset of tumors to treat with existing therapies. Molina-Arcas and colleagues (47) examined a panel of drugs targeting known *Kras* effectors to identify a strategy of combined mitogen-activated protein kinase kinase (MEK)/insulin growth factor receptor 1 (IGFR1) inhibition as a potent strategy *in vitro* and in two murine models of *Kras*-driven lung cancer. These studies and others from Sunaga and colleagues that show a role for Epireregulin inhibition in *Kras*-induced tumors (48) provide promise for improved outcomes in this difficult-to-treat cancer.

Tumor Microenvironment

The tumor microenvironment is a complex system composed of stromal fibroblasts, macrophages, lymphocytes, other bone marrow-derived cells, and extracellular matrix that, in a reciprocal fashion, can contribute to tumor regression or progression. The importance of the tumor microenvironment is demonstrated by recent studies showing the impact of the activated T cell immune checkpoint receptor PD-1, which can interact with tumor cell ligand PD-L1 (49). Other components of the immune system that contribute to tumor progression include tertiary lymphoid structures characterized by clusters of mature dendritic cells and T cells surrounded by B-cell follicles (50) and tumor-associated neutrophils. Eruslanov and colleagues reported that tumor-associated neutrophils compose up to 25% of cells acquired from resected lung

tumors and that these cells promote T-cell responses in early-stage lung cancers (51). Using an advanced lung cancer model with pleural effusion, Lin and colleagues showed that immune CD3⁺CD8⁻ T-cell subsets promote effusion development by enhancing pleural vascular permeability (52).

Lung tumor states of dormancy and progression are modulated by cell signaling interactions between tumor cells and matrix components that can involve phosphatidylinositol-3-kinase (53–55), lipid rafts (56), and matrix metalloproteinase-19 (57). Queisser and colleagues reported on the adaptation of tumor cells to hypoxia, which is found at the center of rapidly growing tumors (58). Tumor survival in hypoxic states was promoted by hypoxia inducible factor induction of heme-oxidized IRP2 ubiquitin ligase 1 (HOIL-1L), which targeted degradation of tumor suppressor protein kinase C zeta. This suggests a potential therapeutic target role for preventing HOIL-1L activation in lung cancer.

The early stage in tumor progression to a state of invasiveness and metastasis is characterized by epithelial dysregulation and instability that drive loss of cellular adhesion and increased cell mobility and proliferation. In many cases, signaling pathways important in lung development, such as transforming growth factor β (TGF- β) (59), are critical for mediating these processes. Chen and colleagues reported that β -catenin degradation in lung tumors was mediated by a novel tumor suppressor Shisa3 (60). In squamous cell carcinoma, hedgehog signaling was shown to regulate development of a stem-like phenotype in the context of coamplification of the oncogenes protein kinase Ci (*PKCI*) and SRY (sex-determining region Y)-box 2 (*SOX2*) (61).

Aiolos, a lymphocyte lineage restricted transcription factor, is frequently expressed in lung cancers and functions through lymphocyte mimicry to epigenetically drive loss of cell–cell adhesion and anchorage independence (62). This example of tumor cell cooption of hematopoietic cell signaling mechanisms offers promise for further discoveries to explain mechanisms of lung tumorigenesis.

Tumor Epigenetics

Kumar and colleagues reported that high-mobility group AT-hook 2 (*Hmga2*) operates in lung cancer as a competing endogenous RNA to promote lung cancer

progression via TGF β 1 signaling through overexpressed *Tgfb β 3* (63). This study raises the possibility of other yet-to-be-identified protein coding genes with tumor progression functions in lung carcinoma. miRNAs are a family of short endogenous noncoding RNAs that harbor critical functions in the initiation and progression of a variety of malignancies. Recent research is advancing understanding mechanisms of miRNA function in lung carcinogenesis. For example, Peng and colleagues reported that miR-486 loss as detected in a screen of repressed miRNAs in early-stage lung cancer was important for regulating insulin growth factor signaling-mediated tumor progression (64). Lin and colleagues identified an intronic microRNA, miR-135b, that targeted components in the developmentally important Hippo pathway to promote lung cancer invasion and metastasis (65).

Diagnosis and Staging of Lung Cancer

In an official ATS/European Respiratory Society Statement on The Role of the Pulmonologist in the Diagnosis and Management of Lung Cancer, Gaga and colleagues emphasize the key role of the pulmonologist in the prompt and complete diagnosis and staging of lung cancer (66). The statement recommends that all pulmonologists should be familiar with advances in molecular testing and that multidisciplinary lung cancer tumor boards should be in operation in every center that routinely cares for patients with lung cancer. Guidelines for the diagnosis and staging of lung cancer are provided in the third edition of the ACCP Evidence-Based Clinical Practice Guidelines (67, 68). The importance of accurate histological diagnosis and molecular testing in lung cancer emphasized in the 2011 International Association for the Study of Lung Cancer/ATS/European Respiratory Society classification system (40) is reflected in the changes in clinical practice and in the introduction of new terminology to describe subclasses. Hung and colleagues prospectively examined the prognostic and predictive effect of the classification system in 573 resected lung adenocarcinoma tumors (69). Risk of recurrence was significantly higher in tumors with

predominant micropapillary or solid components.

Endobronchial ultrasonography (EBUS)- and endoscopic ultrasonography (EUS)-guided needle aspiration biopsies of mediastinal and hilar lymph nodes, with real-time images provided by a convex probe, have been shown to be cost effective compared with surgical mediastinoscopy and have replaced it in numerous clinical settings (70, 71). Cornwell and colleagues compared EBUS-transbronchial needle aspiration (TBNA) to staging without EBUS-TBNA in patients believed to be N0 on positron emission tomography-CT before thoracotomy in a prospectively maintained thoracic surgery database in a veteran population (72). They reported a nontherapeutic surgical resection rate in patients found to have N2 disease of 10.8% in the EBUS group and 12.5% in the positron emission tomography-CT only group. These results confirm that the benefits of EBUS-TBNA are extended to the veteran population. Moonim and colleagues demonstrated the role of EBUS-TBNA in other malignancies, such as lymphoma (73). Using a structured pathway for diagnostic testing that included rapid on-site evaluation of aspirates with preparation of cell blocks and specimens for flow cytometry, they showed sensitivity and specificity of 89 and 97%, respectively, for the diagnosis of mediastinal lymphoma.

NSCLC Early-Stage Management

The third edition of the ACCP Guidelines indicates that surgical resection by lobectomy remains the preferred approach to the treatment of stage I and II NSCLC (74). For patients treated with surgery, outcomes are better when the surgery is performed in hospitals with high procedural volume, as defined by more than 150 surgical resections per year (75). Alternatives to surgical resection by lobectomy include sublobar resection and stereotactic ablative radiotherapy (SABR), both of which are being actively studied. Shirvani and colleagues (76) used the SEER (Surveillance, Epidemiology, and End Results)-Medicare linked database to determinate the outcome of more than 9,000 patients with early-stage lung cancer who underwent treatment with lobectomy, sublobar resection, and SABR from January

2003 to December 2009. At 3 years, unadjusted mortality was lowest for lobectomy (25%), followed by sublobar resection (35%) and SABR (45%). Propensity score-matched analysis of well-matched cohorts demonstrated a worst overall and lung-specific survival for sublobar resection versus lobectomy, but similar overall survival for the SABR versus lobectomy cohorts, suggesting that SABR may be a good option among patients with advanced age and multiple comorbidities. Port and colleagues (77) reviewed a database of 164 patients to compare those who underwent a wedge resection, a wedge plus brachytherapy, or SABR for clinical stage IA NSCLC from 2001 to 2012. Patients with clinical stage IA NSCLC treated by SABR appear to have higher overall disease recurrence than those treated by wedge resection, but there was no significant difference in disease-free survival. Since Martini and colleagues' article in 1995 (78), there are new data available from prospective randomized trials to compare lobectomy versus sublobar resection in the modern era, but there are no prospective data comparing SABR to surgery. Taken together, the available data suggest that all three methods are appropriate in selected patients, with selection determined by patient comorbidities and by tumor stage and biology.

NSCLC: Advanced Disease

Maintenance Therapy

The results of several very large phase 3 studies have been published over the last year about the usefulness of maintenance therapy after front-line platinum-based doublet chemotherapy in patients with advanced nonsquamous NSCLC. Final overall survival results of the PARAMOUNT (Phase 3, Double-Blind, Placebo-controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer) study (79) continue to confirm a significant benefit to maintenance pemetrexed (overall survival, 13.9 vs. 11.0 mo compared with placebo; HR = 0.78; $P = 0.0195$). The AVAPERL (Study of Avastin [Bevacizumab] with or without Pemetrexed as Maintenance Therapy after Avastin in

First Line) study compared maintenance bevacizumab alone versus pemetrexed/bevacizumab in patients who achieved a response or stable disease to four cycles of induction cisplatin/pemetrexed/bevacizumab therapy and demonstrated a progression-free survival (PFS) benefit to the combination arm (7.4 vs. 3.7 mo; HR = 0.48; $P < 0.001$) (80). However, in the absence of a pemetrexed-alone arm, the actual usefulness of maintenance bevacizumab cannot be ascertained from this study. Similarly, the massive PointBreak study comparing the ECOG4599 regimen of carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab versus carboplatin/pemetrexed followed by maintenance pemetrexed failed to bring clarity to this field, as the two arms performed identically as to overall survival (81). An exploratory analysis suggested that in patients who were able to tolerate maintenance therapy toxicities, PFS was longer in patients receiving pemetrexed/bevacizumab versus bevacizumab alone. Taken together, these three studies confirm benefit for maintenance therapy with pemetrexed, but it remains unclear whether bevacizumab provides equivalent or additive benefit.

Antiangiogenic Therapy

The LUME-Lung1 phase 3, double-blind, randomized study compared standard second-line chemotherapy, docetaxel plus the multi-angiokinase inhibitor, nintedanib (BIBF-1120) versus placebo in 1,314 patients with advanced NSCLC (49% adenocarcinoma and 40% squamous cell histology) progressing after front-line chemotherapy (82). Although the primary endpoint of PFS prolongation was met with a PFS of 3.4 versus 2.7 months with nintedanib versus placebo (HR = 0.79, $P = 0.0019$), overall survival was not statistically significant for the overall population (10.1 vs. 9.1 mo; HR = 0.94, $P = 0.27$).

REVEL, another important phase 3 study, demonstrated efficacy of addition of the human anti-vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab versus placebo to standard docetaxel chemotherapy in the second-line treatment of patients with stage IV NSCLC (25% squamous) after platinum-based doublet chemotherapy (83). In this study of 1,253 randomized patients, median overall survival was significantly but modestly prolonged with

the addition of ramucirumab (10.5 vs. 9.1 mo; HR = 0.86; $P = 0.023$) and median PFS was also prolonged by 1.5 months. Response rates were also improved: 23 versus 14% in the control arm. Benefits appeared similar in the squamous cell subtype. Toxicities overall appeared manageable, with an increased frequency of hematological side effects and hypertension with ramucirumab but no increase in pulmonary hemorrhage. These results led to U.S. Food and Drug Administration (FDA) approval of ramucirumab in this setting.

Specific Molecular Subtypes

Epidermal Growth Factor Receptor–mutated Disease

It is well established now that up-front epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy supersedes the efficacy of chemotherapy and has become standard of care. A combined analysis of studies of the irreversible EGFR inhibitor, afatinib versus chemotherapy demonstrated a significant overall survival benefit (which previously has been elusive in phase 3 studies of EGFR TKIs vs. chemotherapy) in particular in patients with exon 19 mutations (84). Another interesting study (85) reported results of a randomized phase 2 study of erlotinib versus erlotinib and bevacizumab in patients with advanced, EGFR-mutated NSCLC where a significant prolongation of PFS was noted in the combination arm (16 vs. 9.7 mo), and this will be further investigated in a phase 3 study.

Acquired resistance to first-line EGFR TKI therapy remains a significant problem, and a number of exciting developments have taken place in this field. Based on mouse studies focused on the T790M resistance mutation, it has been speculated that the combination of the irreversible EGFR inhibitor afatinib and the anti-EGFR monoclonal antibody cetuximab could synergize better than single-agent therapy (7% response rate noted for afatinib alone). Indeed, in the large phase IB study of Janjigian and colleagues, the combination of afatinib/cetuximab was effective, with an objective response rate of 29% (not different for T790M-positive or T790M-negative patients) and a PFS of 4.7 months (86). However, significant gastrointestinal and skin toxicities preclude wider

adoption of this regimen in general practice. An even more exciting area of development has been that of T790M-targeted third-generation EGFR inhibitors that selectively inhibit mutated EGFR and lack significant inhibition of the wild-type receptor. Multiple compounds are under active development, with two lead compounds, CO-1686 and AZD9291, already having demonstrated excellent activity in the acquired resistance setting (87, 88). Recent updates confirm outstanding activity and excellent tolerance of AZD9291, with a 51% overall response rate reported in a cohort of 253 patients, with response rates of 61% and PFS of 9.6 months in confirmed T790M-positive patients with RR of 21% and PFS of 2.8 months in T790M wild-type patients (89). Similarly, updated results of the expanded phase I/II studies of CO-1686 (rociletinib) in 130 patients show a response rate of 59% in T790M-positive and 29% in T790M-negative subjects, with hyperglycemia noted as the only dose-limiting adverse event (90). Both of these compounds are being rapidly advanced in phase III studies, including studies in comparison with other EGFR TKIs in the front-line setting; both received “breakthrough status” by the FDA and might indeed transform the management of EGFR-mutated lung adenocarcinoma. On the other hand, the randomized phase 3 IMPRESS (IRESSA Treatment beyond Progression in Addition to Chemotherapy versus Chemotherapy Alone) study demonstrated negative results as to any appreciable benefits of continuation of first-line EGFR TKI therapy on progression in addition to conventional doublet chemotherapy versus doublet chemotherapy alone (91).

ALK

Good news continues for the subset of patients with ALK-positive lung adenocarcinoma, as several second-generation ALK inhibitors, most notably ceritinib and alectinib have demonstrated excellent activity both up front as well as in the acquired resistance setting. Their central nervous system (CNS) penetration also is significant, as many relapses on the first-generation ALK inhibitor crizotinib occur in the CNS. In an expanded phase I/II study of 130 patients, the overall response rate to ceritinib was 58% (90). In a dose-finding study of alectinib in crizotinib-

refractory or -intolerant patients, the objective response rate was 54%, and of 21 patients with CNS disease, the response rate was noted to be a highly encouraging 52% (93). As a result of these promising data, ceritinib has recently gained FDA approval, and alectinib has been approved in Japan. First-line studies comparing these agents with crizotinib are being initiated.

MET

Mesenchymal–epithelial transition factor (MET) tyrosine kinase overexpression, amplification, and point mutations have been identified in NSCLC. MET amplification is a potential and relatively common acquired resistance mechanism to EGFR-targeted therapy in EGFR-mutated lung adenocarcinomas. Despite promising initial data from randomized phase II studies, two large phase III studies of MET antagonists, such as the small molecule inhibitor tivantinib and the anti-MET antibody METMab, have failed to meet primary endpoints in combination with erlotinib therapy (94, 95). Although the tivantinib study was not a biomarker-driven trial, the METMab study selected patients based on MET expression as determined by immunohistochemistry (IHC). One concern about the failure of these two drugs might be flaws in study design or in selection of the appropriate biomarker. A small but intriguing study presented at the American Society of Clinical Oncology 2014 meeting does suggest that MET fluorescence *in situ* hybridization might be a more biologically relevant biomarker than IHC, because MET fluorescence *in situ* hybridization highly amplified patients had a high response rate to the MET/ALK inhibitor crizotinib in a single-agent treatment study (96).

Other Molecular Subtypes

Exciting results have been presented for rare lung cancer subtypes, such as ROS-mutated and B-Raf-mutated lung cancers in single-arm studies of the ROS inhibitor crizotinib and the B-Raf inhibitor dabrafenib, respectively, showing impressive responses in subsets of such patients (97, 98). Given the lack of feasibility for randomized studies for such small subsets, these studies effectively establish the clinical validity of such targeted agents.

Squamous Cell Lung Cancer

In patients with advanced squamous cell lung cancer, the randomized SQUIRE study of standard chemotherapy (cisplatin/gemcitabine) with the anti-EGFR monoclonal antibody necitumumab versus placebo showed a modest but significant increase in overall survival (11.5 vs. 9.9 mo) (99). This is similar to the benefits noted with the similar anti-EGFR monoclonal antibody cetuximab in this setting.

Small Cell Lung Cancer

The year 2014 remained a year of disappointing results for small cell lung cancer (SCLC). JCOG0202 demonstrated that irinotecan/cisplatin showed no advantages over cisplatin/etoposide for patients with limited-stage SCLC (100), whereas JCOG 0509 found the promising topoisomerase II inhibitor amrubicin inferior in combination with cisplatin as compared with etoposide/cisplatin (101). Also, a key American Society of Clinical Oncology presentation of a Japanese phase 3 study now casts doubt on the utility of prophylactic cranial irradiation in patients with extensive-stage SCLC, as in this study the prophylactic cranial irradiation arm had inferior survival

outcomes despite a reduction in CNS metastases (102), whereas a European phase III study demonstrated clinical benefit for consolidation thoracic radiotherapy in the treatment of extensive-stage SCLC (103).

Immunotherapy

Results of the massive randomized double-blind phase 3 START study focusing on the utility of the MUC1 antigen-specific vaccine tecemotide (L-BLP25) in 1,513 patients with unresectable stage III NSCLC after completion of chemoradiation were published (104) and demonstrate no significant difference in overall survival, the primary endpoint, with a median overall survival of 25.6 months with tecemotide versus 22.3 months with placebo. Study therapy was overall well tolerated, and, intriguingly, a significant survival difference was noted in patients who received concurrent therapy (30.8 vs. 20.6 mo) as opposed to patients who received sequential therapy (19.4 vs. 24.6 mo); as a result, a follow-up study focusing now on subjects receiving concurrent chemoradiation is being launched. The even larger randomized, double-blind MAGRIT study investigating the utility of recMAGE-A3 vaccine therapy versus

placebo in the treatment of resected MAGE-A3–positive NSCLC showed similarly disappointing negative results (105).

On the other hand, exciting positive news continues to emanate from trials of immune checkpoint inhibitor therapy, with a number of studies demonstrating clear-cut and at times durable activity and good overall safety profile of a number of anti-PD1 and anti-PD-L1 targeting agents (106–108). There is emerging evidence that PD-L1 positivity, as determined by IHC, is an effective biomarker that can define a subset of tumors with a higher chance of response to this class of agents. Results of the pivotal KEYNOTE-001 study confirm good tolerance and significant activity of the anti-PD-1 antibody pembrolizumab in advanced NSCLC, with an overall objective response rate of 19.4% and PFS of 3.7 months. Using a cut-off of 50% tumor cell IHC expression of PD-L1, prospective analysis showed that PD-L1–positive tumors had a significantly increased response rate of 45.2% and PFS of 6.3 months (109). Clearly, immune checkpoint inhibitor therapy will transform the routine management of patients with NSCLC. ■

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