Update in Lung Cancer and Mesothelioma 2012

Charles A. Powell[1], Balazs Halmos[2], and Serge P. Nana-Sinkam[3]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Division of Hematology and Oncology, Columbia University Medical Center, New York, New York; and [3]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University, Columbus, Ohio

Lung cancer remains the number one cause of cancer-related death in the United States among both men and women. It is estimated that in 2013, there will be more than 200,000 new diagnoses of lung cancer and nearly 160,000 deaths (1). Despite the discovery and application of targeted therapies, the overall survival (OS) remains poor, with an overall 5-year survival approximating 16%. In addition, there are a growing number of cases among former smokers and never smokers. However, based on research advances in 2012, there is enthusiasm that improvements in early detection, coupled with tobacco cessation and the application of novel genetic and genomics technologies, will lead to improved outcomes.

EPIDEMIOLOGY

Although more than 85% of patients diagnosed with lung cancer will have smoked at some point in their lives, only 15 to 20% of smokers will develop lung cancer, thus suggesting the involvement of additional risk factors. Studies examining the roles of various exposures, including asbestos, welding, arsenic, and concomitant lung diseases, such as chronic obstructive pulmonary disease (COPD), tuberculosis, and pneumonia, as risk factors independent of tobacco consumption are ongoing (2, 3). A recent large epidemiological study in more than 2,000 incident cases of lung cancer cases and control subjects identified a 36% increase in lung cancer risk among welders and flame cutters. Interestingly, welding fumes were an independent risk factor for lung cancer (4).

Disparities

A recent examination of multiple registries confirmed that African Americans have the highest incidence of lung cancer (73/100,000) (5) and have a decreased OS and lower rates of surgical resection. Factors contributing to the disparities in lung cancer include inequities in access to health care, differing perceptions regarding early detection, smoking cessation and treatment, and variation in susceptibilities to the effects of cigarette smoke (6, 7). Conversely, the incidence rates for lung cancer among Hispanic men are much lower, and OS is better than in non-Hispanic whites. The explanations for these differences include a combination of decreased smoking rates among Hispanics, potential genetic variants (8), and histological distribution. Saeed and colleagues conducted a systematic analysis of the SEER database and determined that Hispanics had a higher rate of less aggressive histological subtypes of lung cancer (adenocarcinoma *in situ* and lepidic predominant adenocarcinoma) (9). Investigation of these areas should help to narrow the lung cancer outcomes gap that exists between ethnic groups.

LUNG CANCER SCREENING

In 2011, the National Lung Screening Trial randomized 50,000 current and former smokers to demonstrate a 20% lung cancer survival and 7% OS advantage in high-risk patients screened with three annual screening computed tomography (CT) scans (10). For successful widespread implementation, several issues need to be addressed: (*1*) discrimination of false-positive benign nodules from malignant nodules (11, 12), (*2*) use of biomarkers of disease risk to potentially increase the positive predictive value of the examination (13), (*3*) compliance with guidelines for nodule evaluation and assessment of radiation risk, and (*4*) cost-effectiveness.

Ost and Gould propose a Bayesian evidence-based algorithm to guide evaluation and management of pulmonary nodules (14). To complement predictions based on imaging features, Patz and colleagues established a serum marker assay to measure carcinoembryonic antigen, alpha-1 antitrypsin, and squamous cell carcinoma (SCC) antigen (15) and demonstrated 80% sensitivity and 89% specificity in a logistic regression model.

Several researchers have focused on tools to assess interval change in nodules, while acknowledging the complexities of applying these approaches to nodules that are solid, nonsolid or part-solid (16). Wilson and colleagues, for the Pittsburgh Lung Screening Study, reported that prevalent tumors had significantly slower doubling time than incident cancers, which is consistent with survival differences between these tumor types (17). A limitation of this study was that only 43% of cancers were amenable to doubling time analysis. Henschke and colleagues examined nodules from the International Early Lung Cancer Action Program (I-ELCAP) screening cohort and showed that volume doubling time in subsolid nodules was significantly longer than in solid nodules, with similar growth-rate characteristics between lung cancers found in screened patients and those discovered in the absence of screening (18). These findings suggest that the biology of subsolid nodules is more indolent compared with solid nodules and that tumors detected by screening are representative of those detected by conventional means. Naidich and colleagues from the Fleischner Society have developed evidence-based recommendations focused on the management of nonsolid and part-solid nodules (19) that complement the 2005 solid nodule recommendations (20). Among the major recommendations are that solitary pure ground-glass nodules measuring 5 mm or less do not require follow-up imaging and that solitary part-solid ground-glass nodules, especially those with a solid component of greater than 5mm, should be considered malignant until proven otherwise.

The potential benefits of lung cancer CT screening extend to detection of common comorbid conditions, such as COPD (21) and coronary artery disease, in patients who are longtime smokers. Sverzellati and colleagues, for the Multicentric Italian Lung Detection (MILD) trial (22), and Jacobs and colleagues (23) showed that coronary artery calcium scores in a lung cancer

(*Received in original form April 15, 2013; accepted in final form June 1, 2013*)

Supported by National Institutes of Health grant 1R01CA163772 (C.A.P.).

Correspondence and requests for reprints should be addressed to Charles A. Powell, M.D., Chief, Division of Pulmonary, Critical Care, and Sleep Medicine, Mount Sinai Medical Center, One Gustave Levy Place, Box 1232, New York, NY 10029. E-mail: charles.powell@mssm.edu

Am J Respir Crit Care Med Vol 188, Iss. 2, pp 157–166, Jul 15, 2013

DOI: 10.1164/rccm.201304-0716UP
Internet address: www.atsjournals.org

screening cohort were independently associated with all-cause mortality and cardiovascular events. These reports suggest that adding coronary artery calcium scoring to lung cancer screening could benefit high-risk patients with respect to disease detection and primary prevention of cardiovascular events.

To implement CT screening in a rational, cost-effective manner, there are ongoing efforts to review existing knowledge and to develop standardized protocols and management strategies (24). These issues are addressed by Bach and colleagues in a systematic review by an expert panel representing the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network (25). The recommendations, which were endorsed by the American Thoracic Society, call for annual CT screening for current or former smokers aged 55 to 74 years with at least 30 pack-years of smoking history who continue to smoke or have quit within the past 15 years. The screening should be offered only in settings that can deliver comprehensive lung cancer care, and it should be accompanied by detailed counseling that includes a complete description of potential benefits and harms. The National Comprehensive Cancer Network (26) and the American Association for Thoracic Surgery (27, 28) published similar guidelines that recommended slightly different eligibility criteria for screening participants.

LUNG CANCER BIOLOGY

Field Carcinogenesis

Because of tobacco smoke carcinogen exposure, the bronchial epithelium of smokers is subject to field cancerization that is characterized by alterations of airway cell mRNA and miRNA expression and by DNA copy number, mutation, and epigenetic alterations. Advances in the understanding of field cancerization have been recently reviewed (29, 30). The impact of the airway microbiota on airway epithelial alterations and lung cancer is an emerging area of science. Laroumagne and colleagues examined cultures acquired by bronchoscopy from 210 consecutive patients with lung cancer (31). Pathogens were found in 48% of patients, with increased prevalence in patients with COPD. With implementation of 16s ribosomal and metagenomic sequencing, it is anticipated that lung microbiome research will show that changes in lung flora play an important role in progression of field carcinogenesis and malignant transformation.

Microarray gene expression studies demonstrate that there are both reversible and irreversible smoke-induced changes that occur in the lung. Using several bronchial epithelial cell gene expression data sets obtained from smokers and nonsmokers, Beane and colleagues generated signaling pathways, such as SIRT1, that are implicated as drivers of lung cancer (32). Bossé and colleagues examined gene expression in noninvolved lung tissue among 853 patients with lung cancer (33). In three independent sets, 599 probe sets (558 up-regulated and 41 down-regulated) consistently distinguished lung tissue from current versus never smokers. Interestingly, among the probe sets up-regulated in smokers, the majority returned to never-smoker expression levels within 25 years of smoking cessation, and 20 remained up-regulated.

Lung Development Pathways

Existing paradigms suggest that lung carcinomas arise from pluripotent stem and/or progenitor cells capable of differentiation into one or several histologic cell types. These paradigms suggest that lung tumor cell ontology is determined by the consequences of gene transcriptional activation and/or repression events that recapitulate embryonic lung development. Li and Linnoila examined the role of the Achaete-Scute homolog–1 (Ascl1), which is a basic helix-loop-helix transcription factor that has been shown to be critical for the development of pulmonary neuroendocrine cells (34). In an *in vivo* genetic fate-mapping study, after naphthalene injury, Ascl1+ cells contributed to regenerating Clara cells preferentially over neuroendocrine cells. These data suggest a potential role for Ascl1+ lineage cell as a progenitor cell for lung adenocarcinoma. Using a similar approach, Xu and colleagues traced K-Ras–positive cells and observed that adenocarcinomas only arose in alveoli that were positive for markers specific for type 2 cells, thus showing that type II cells are a cell of origin for K-Ras–induced adenocarcinoma (35).

Tumor Microenvironment

The tumor microenvironment's role is increasingly recognized in lung cancer development and progression (36). The tumor stroma is a complex system composed of fibroblasts (cancer-associated fibroblasts), macrophages (tumor-associated macrophages), other immune cells, vasculature, and extracellular matrix. Ben and colleagues identified a functional single-nucleotide polymorphism (SNP) T+25C on chromosome 8p22 that regulates expression of the macrophage class A scavenger receptor (SR-A) and was associated with lung cancer risk (37). The tumor suppressive function of macrophage SR-A was demonstrated in an SR-A null mouse model. Antón and colleagues showed that binding of microenvironment-derived activated protein C to tumor endothelial protein C receptor activated Akt and extracellular signal–regulated kinase (ERK), decreased apoptosis, and increased tumor metastatic activity (38). Other research identified microenvironment-related pathways important for lung tumor growth and progression. These pathways included Rab27a (39), SLC1A5 (40), and vascular endothelial growth factor receptor (VEGFR)-2/epidermal growth factor receptor (EGFR) (41). In a recent perspective, Stathopoulos and Kalomenidis note and review the importance of tumor–host interactions in the formation of malignant pleural effusions (42). They acknowledge that articles such as that of Ye and colleagues showing a role for IL-9–producing $CD4^+$ T cells in malignant pleural effusion (43) may be broadly applicable to cancer biology.

Several researchers have elucidated mechanisms by which the immune system can promote or repress lung tumor growth (44). Feng and colleagues examined $CD11b^+CD14^+$ monocytic myeloid-derived suppressor cells (MDSCs) in the peripheral blood of patients with advanced non-small cell lung cancer (NSCLC) (45). They observed an increased frequency of MDSCs cells in patients with cancer versus control subjects and that high $S110A9^+$MDSC levels were associated with poor response to chemotherapy, suggesting that S100A9 is a marker of enhanced immune suppression. Using the oncogenic K-ras transgenic adenocarcinoma mouse model, Smith and colleagues examined the role of the immunoregulatory tumor immune evasion enzyme indoleamine 2,3-dioxygenase (IDO) in lung cancer and in breast carcinoma–derived lung metastasis (46). They found that IDO deficiency attenuated IL-6 induction, impaired MDSC function, and decreased lung tumor burden and prolonged survival. These studies support a key role for IDO in establishing a protumorigenic environment in the lung for primary tumor and metastatic tumor growth. Using immunohistochemical analysis of a large cohort of human tumors, Suzuki and colleagues examined the expression of several immune-related proteins in early-stage lung adenocarcinoma (47). They reported that stromal forkhead box P3 (FoxP3) regulatory T cells were associated with a protumorigenic environment and that chemokine expression of IL-12RBeta 2 and IL-7R were associated with antitumor and protumor outcomes, respectively. Taken together, these studies highlight future

areas of research into diagnostics and therapeutics directed toward the lung tumor microenvironment.

Epithelial-to-Mesenchymal Transition

Tumor cell metastasis requires that epithelial cells acquire mesenchymal cell properties, such as loss of cell–cell adhesion, invasiveness, vascular intravasation and extravasation, establishment of a metastatic niche, and angiogenesis (48). This process of epithelial-to-mesenchymal transition (EMT), reviewed by Gao and colleagues (49), has been the focus of several important articles that have established roles for several signaling pathways, such as Akt/GSK3Beta (50), MEK-ERK (51), Fas (52), and Par6 (TGFBR2 interacting partner, MCB) (53). Recent articles have addressed key questions related to EMT research: (*1*) Which pathways of EMT demonstrated *in vitro* can be confirmed *in vivo* models (54)? and (*2*) Is there evidence for an EMT reciprocal pathway of mesenchymal to epithelial transition (MET) that is required for the establishment of metastatic tumor properties (49, 55)? To address the first question, Stallings-Mann and colleagues generated a transgenic mouse model of expression of Rac1b or matrix metalloproteinase-3 (MMP-3) in Clara cell secretory expressing cells causing lung fibrosis, adenoma, adenocarcinoma, and acquisition of EMT morphology *in vivo* (56). The notion that these effects were associated with MMP3-induced EMT was supported by dual fluorescence labeling of cells that showed coexpression of hemagglutinin (HA)-tagged MMP3 transgene in vimentin-expressing cells. The oncogenic role of Rac1b in lung adenocarcinoma was confirmed by Zhou and colleagues, who showed elevated expression of Rac1b in human lung adenocarcinomas and that, *in vivo*, Rac1b cooperated with oncogenic K-Ras to accelerate tumor growth (57). To address the second question, Tsai and colleagues used an inducible transgenic model to show that activation of the EMT-inducing transcription factor Twist 1 promoted EMT in primary squamous cell tumors and that turning off Twist1 in distant sites allowed redifferentiation and proliferation of metastatic tumors (58). This reversion of EMT or MET was also demonstrated by Ocaña and colleagues (59). Overexpression of the paired-related homeobox transcription factor Prrx1 induced EMT in cells and in primary tumors; however, lung metastatic foci failed to form when PRRX-1–expressing cells were injected into tail veins. The formation of metastasis *in vivo* required loss of PRRX-1, which was shown to induce differentiation or MET *in vitro*. Although these articles used extrathoracic malignancy models, it is probable that primary tumor EMT and metastatic tumor MET is similarly required for lung carcinogenesis.

LUNG CANCER GENETICS, GENOMICS

Application of high-throughput sequencing technologies has identified novel mutations, such as loss of a novel tumor suppressor CSMD3, as the second most common mutated gene in a cohort of patients with NSCLC (60). The mutational complexity of lung cancer has been demonstrated in the recent seminal article from the Cancer Genome Atlas Research Network (TCGA). Sequencing analysis of 178 SCCs identified more than 300 unique exonic mutations and copy number alterations and 165 genomic rearrangements (61). Somatic mutations in TP53 were a common occurrence, as were alterations in *CDKN2A/RB1*, *NFE2L2/KEAP1/CUL3*, *PI3K/AKT*, and *SOX2/TP63/NOTCH1* pathways. In addition, these studies indicate that gene fusions, such as KIF5B-RET and ROS1/GOPC, are also functional biomarkers (62). Using a NanoString-based approach in mutation-negative adenocarcinoma, Suehara and colleagues identified two novel tyrosine kinase fusions (RET and ROS1/GOPC), each of which is being pursued in clinical trials of RET and ROS-targeting agents (62).

Genomewide Association Studies

Numerous genomewide association studies (GWAS) have been conducted in lung cancer to identify distinct chromosomal loci associated with lung cancer risk. Perhaps the best-studied regions are located at chromosome 15q25.1, which harbors subunits for the nicotinic acetylcholine receptor that are associated with tobacco dependence and lung cancer risk (63, 64). A limitation of several of these GWAS that has been addressed recently is the restriction primarily to white men. Notably, Walsh and colleagues showed in a large multicenter case control study that polymorphisms in three chromosomal regions (5p15.33, 6p21.33, and 15q25.1) were associated with lung cancer risk in African Americans (65). SNPs with select chromosomal loci were associated with specific histological subtypes, with 5p15.33 associated with adenocarcinoma and 6p21.33 with SCC.

GWAS hve also been applied to sequence variants associated with prognosis. In a cohort of 348 patients with advanced-stage lung cancer, Lee and colleagues identified 17 SNPs near *EGF*, *NALCN*, *CDH8*, *SLC35D2*, *NCOA2*, *THSD7B*, *DLST*, *ANKS1A*, and *FAM154A* that were associated with clinical outcome (66). In a study of never smokers with lung cancer, Pu and colleagues identified of SNPs in five inflammatory genes (*CD74*, *CD38*, *SYK*, *BMP8A*, and *IL17RA*) that correlated with survival (67).

Epigenetic Studies

Leng and colleagues conducted a nested case control study focused on the evaluation of methylation status of 31 genes identified in the sputum of high-risk smokers (68). Methylation in a seven-gene panel in two independent cohorts had a sensitivity and specificity of 71 and 77%, respectively, in distinguishing patients with early-stage lung cancer from control subjects. In a cohort of 467 patients with stage I or II NSCLC undergoing either surgery alone or combined with chemotherapy, Wagner and colleagues identified 26 methylation gene SNPs associated with recurrence in patients undergoing surgery alone and 25 SNPs associated with recurrence in the surgery plus adjuvant chemotherapy cohort (69).

MicroRNAs

MicroRNAs (miRNAs) have emerged as viable biomarkers for the diagnosis, prognosis, and therapeutic response in cancer (70). Lu and colleagues used miRNA profiling to generate a signature that correlated with outcome in early-stage lung cancer (71). MiRNAs are also proving useful as biomarkers in cases in which minimal diagnostic tissue is available. For example, Huang and colleagues recently demonstrated that two miRNA expression panels could distinguish small cell lung cancer (SCLC) from NSCLC and SCC from adenocarcinoma in both formalin-fixed paraffin–embedded tissues and bronchial brushings (72). Another rapidly developing field is the application of miRNAs to therapeutics. For example, tumor suppressive miRNAs, including Let-7 and miR-34, have been successfully delivered *in vivo* to abrogate lung tumor growth (73, 74).

Proteomics

In a study to identify protein signatures "common" to lung cancer subtypes, Kikuchi and colleagues applied a shotgun proteomic approach to identify proteins in pools derived from tissue samples from adenocarcinoma and SCC and from normal tissues

(75). The investigators identified a potential role in lung carcinogenesis for up-regulation of members of the p21-activated (PAK) family. Noninvasive proteomic signatures have also been shown to have potential to augment algorithms to distinguish malignant from benign CT-detected abnormalities in high-risk patients. Pecot and colleagues showed that integration of a serum proteomic signature with CT imaging features and clinical parameters could increase diagnostic accuracy (76).

STAGING AND PROGNOSIS

Despite recent updates to the lung cancer staging system, investigators recognize the presence of inter- and intrapatient heterogeneity within histologically similar lung cancers. Thus, an area of active research is the pursuit of biological and imaging biomarkers of prognosis that can augment conventional staging approaches. Several studies have suggested that positron emission tomography (PET) imaging intensity, as determined by standardized uptake value (SUV) or metabolic tumor volume, may function as a biomarker of nodal involvement and prognosis (77, 78). Others have shown molecular signatures can predict prognosis among similarly staged cases. Kratz and colleagues identified a panel of 14 genes (including *WNT3A*, *CDKAP1*, *ERBB3*, and *IL1*) by quantitative reverse transcriptase–polymerase chain reaction in tumor tissues that stratified early-stage, postsurgical patients into low, intermediate, and high-risk survival groups (79). They were able to test and validate this assay in three separate cohorts comprising a total of nearly 1,800 patients. Further validation in a prospective cohort will be required to determine which "high-risk" signature patients may benefit from adjuvant therapy.

In the current era of lung cancer, therapeutic decisions are frequently driven by results of molecular testing; thus, more information is required from diagnostic specimens. As featured in a recent review by Bulman and colleagues, careful attention to specimen acquisition and specimen processing allows endobronchial ultrasound (EBUS) to produce specimens that are sufficient for diagnosis, staging, and molecular testing (80). Navani and colleagues recently examined cytology obtained by EBUS in 774 patients and achieved NSCLC diagnostic sensitivity of 88% (95% confidence interval, 86–91%) and a 90% success rate for EGFR testing (81). Taken together, both EBUS and endoscopic ultrasound should be considered first-line approaches to diagnosis and staging in lung cancer.

TREATMENT OF LOCALIZED DISEASE

Robotic Lung Resection

Robotic lung resection heralds another significant development in minimally invasive surgery. Compared with video-assisted thoracoscopic surgery (VATS) lung resection, Louie and colleagues reported no difference in immediate postoperative clinical outcomes but noted that quality of life measures favored robotic surgery (82). Park and colleagues reported that 5-year survival was comparable to VATS and thoracotomy (83). Although the initial reports are encouraging (84), further studies requiring long-term follow-up are awaited to fully evaluate robotic segmentectomy and to establish its oncologic efficacy in the lung.

Limited Resection and Lymph Node Dissection

Van Schil and colleagues reviewed the surgical implications of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society adenocarcinoma classification (85), with emphasis on the evolving views of extent of resection and extent of lymph node dissection required for less-invasive subtypes of adenocarcinoma (86). Kim and colleagues note that the use of nonanatomic, or wedge, resection has increased between 2000 and 2007, particularly in patients with older age, T1a tumors, and COPD (87). Donahue and colleagues showed that patient-related factors, such as active smoking, diffusion capacity of lung for carbon monoxide less than 69%, tumor size greater than 2 cm, N2 disease, and advanced histologic grade, were associated with decreased survival after segmentectomy by univariate analysis, but that only tumor size greater than 2 cm was significant in a multivariate model (88). In patients with stage IA disease undergoing anatomic segmentectomy, lymphatic invasion was an independent predictor for recurrence (89). Retrospective studies in patients with stage IA disease showed no significant differences in recurrence, disease-free survival, or OS for segmentectomy versus lobectomy (via VATS or open thoracotomy) (90–95). For patients with stage IB or more advanced disease, recurrence-free survival is decreased after segmentectomy versus lobectomy (91, 96).

Nodal metastases are seen in nearly 20% of lung adenocarcinomas less than 2 cm in size and in 5% of lung adenocarcinomas less than 1 cm in size (86), and pathologic nodal involvement is more frequent in patients with pure solid tumors compared with those with ground-glass opacities, particularly those with high PET SUV (SUVmax) (97). Recent research has examined the role of limited or lobe-specific nodal sampling versus complete lymph node dissection. In a retrospective study of the Society of Thoracic Surgeons database, Cerfolio and colleagues showed a higher incidence of pathologic N2 disease after dissection compared with sampling (98), and Boffa and colleagues showed a lower rate of N1 upstaging with VATS versus thoracotomy approach but no difference in N2 upstaging (99). With regard to patient selection, Tsutani and colleagues reported that clinical factors in patients with stage IA disease, such as solid tumor size less than 0.8 cm and SUVmax on F18 fludeoxyglucose-PET less than 1.5, to be significantly associated with pathologic node-negative disease and longer disease-free survival (100). Taken together, these reports suggest that limited mediastinal lymph node sampling may be sufficient for patients with favorable prognostic features.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT), previously used for small peripheral lesions, is increasingly being explored for larger central lesions (101). In a cohort of 676 patients undergoing radiotherapy, Senthi and colleagues reported that most recurrences were distant (66%) and occurred early (median recurrence time, 9.6 mo), whereas isolated locoregional recurrence was less frequent and occurred later (102). In early-stage lung cancer, outcomes after SBRT appear similar to surgical resection despite a patient population with greater comorbidities and higher perioperative risk, but a defined follow-up strategy and further examination in prospective trials are essential (103). SBRT and sublobar resection are being prospectively compared in an ongoing phase III randomized study by the American College of Surgeons Oncology Group and Radiation Therapy Oncology Group (104).

CHEMOTHERAPY

Locally Advanced Lung Cancer

Final results of the randomized, phase III CHEST study of 270 patients with stages IB to IIIA NSCLC demonstrate a significant survival benefit for preoperative cisplatinum/gemcitabine chemotherapy followed by surgery versus surgery alone (105). Despite the study being terminated prematurely when adjuvant chemotherapy became standard of care during the conduct of this study, a statistically significant benefit emerged both in progression-free survival (PFS) (hazard ratio [HR] = 0.70) and OS (HR = 0.63) in favor of

neoadjuvant chemotherapy. This benefit seemed to be restricted to the stages IIB/IIIA subgroup.

In a pivotal multicenter, randomized, phase 3 trial for elderly patients with unresectable stage III NSCLC, the Japan Clinical Oncology Group study group recruited 200 patients aged 71 to 89 years (106). Patients received either concurrent chemoradiation with low-dose carboplatin or radiotherapy alone. The primary endpoint of median OS was 22.4 months for concurrent chemoradiation and 16.9 months for radiotherapy alone (HR = 0.68), and PFS also was better in the concurrent arm. Concurrent chemoradiation, as expected, significantly increased toxicities over radiotherapy alone; however, there was no difference in pneumonitis and esophagitis rates, and febrile neutropenia rates were low. Taken together, this study shows a significant survival advantage of chemoradiation over radiotherapy alone for carefully selected older patients with unresectable stage III NSCLC.

Advanced NSCLC—First-Line Therapy

Lilenbaum and colleagues presented data of an important phase III study in patients with advanced NSCLC and poor performance status—a group with historically extremely poor outcomes and undefined standard of care (107). They randomized patients to single-agent pemetrexed versus carboplatin/pemetrexed. A substantial benefit was noted in the doublet chemotherapy group, with a higher response rate (RR) (24 vs. 10.5%,) and improved PFS (5.9 vs. 3.0 mo) and OS (9.1 vs. 5.6 mo). Toxicity appeared to be acceptable, and the benefit of doublet therapy was maintained in the elderly subset as well.

One of the significant negative studies published in the past year was the randomized phase III Tarceva or Chemotherapy for the Treatment of Advanced Non Small Cell Lung Cancer (TORCH) study comparing first-line erlotinib followed by cisplatinum/gemcitabine chemotherapy, with the inverse sequence in molecularly unselected patients with advanced NSCLC (108). Early termination of the study was necessitated due to the inferior outcome of the patients on the erlotinib followed by chemotherapy arm (8.7 vs. 11.6 mo OS, HR = 1.24 favoring the standard arm). Only 5% of the tumors harbored an EGFR gene mutation, thus explaining the very poor primary PFS of 2.2 months on front-line erlotinib. The results of this study strongly reinforce that no chemotherapy-eligible patient should be offered front-line EGFR tyrosine kinase inhibitor therapy without EGFR mutation testing.

Advanced NSCLC—Maintenance Therapy

Data from two important, randomized phase III studies were reported this year on the value of maintenance therapy in advanced nonsquamous NSCLC. The Paramount study compared maintenance pemetrexed versus best supportive care after four cycles of induction chemotherapy with cisplatin/pemetrexed in patients with responding or stable disease on induction chemotherapy (continuation maintenance strategy) (109). This study showed improved PFS as well as OS (13.9 vs. 11.0 mo) with the maintenance pemetrexed strategy, and maintenance therapy had a manageable safety profile, further cementing the role of maintenance therapy in the management of advanced nonsquamous NSCLC.

The large, randomized, phase III PointBreak study compared two widely used approaches for the front-line therapy of advanced nonsquamous NSCLC: (*1*) carboplatinum/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab, and (*2*) carboplatinum/paclitaxel/bevacizumab followed by maintenance bevacizumab (four cycles of induction chemotherapy in each arm) (110). A total of 1,259 patients were enrolled and 939 patients were randomized, with 590 patients receiving maintenance therapy. Although PFS was slightly better in the pemetrexed arm, OS was identical. As expected, the regimens had differing toxicity patterns but overall were well tolerated. In essence, this study failed to identify a "superior" regimen for unselected patients with nonsquamous NSCLC but provides ample data to support both regimens as effective and well tolerated.

TARGETED THERAPEUTICS

K-ras Mutant Lung Adenocarcinoma

Despite decades of intense pharmacological and clinical research, targeting oncogenic k-ras has not shown success. Oncogenic k-ras signals via the Raf-MEK-ERK pathway, and therefore MEK inhibitors might provide a potential strategy for Ras-mutant tumors. Selumetinib is an orally available, potent, and selective inhibitor of the MEK1/MEK2 kinases, which had failed to show activity in patients with lung cancer in single-agent studies. After *in vitro* studies suggested synergy with docetaxel, Jänne and colleagues pursued a randomized, double-blind phase II study of docetaxel/placebo compared with docetaxel/selumetinib (75 mg orally twice a day) in 87 previously treated patients with K-ras mutant NSCLC with no crossover allowed (111). Outcomes in the docetaxel plus selumetinib arm were significantly better, with an overall RR of 36% (vs. 0%), PFS of 5.3 (vs. 2.1) months, and OS of 9.4 (vs. 5.2) months. These promising outcome data were counterbalanced by an increase in adverse events, most prominently grade 3 to 4 neutropenia (67 vs. 55%) and febrile neutropenia (18 vs. 0%), as well as a higher rate of gastrointestinal side effects. Although the benefit appears short lived compared with the robust and durable responses seen with EGFR and ALK-directed therapy for genotype-defined tumors, pivotal phase III studies of this combination are eagerly awaited.

EGFR-mutated Lung Adenocarcinoma

Rosell and colleagues reported findings of the important European Randomized Trial of Tarceva vs. Chemotherapy (EURTAC) study comparing first-line erlotinib with standard front-line chemotherapy in 174 patients with advanced lung adenocarcinomas harboring exon 19 or L858R EGFR gene mutations (112). In line with data from EGFR-mutation–focused Asian studies principally using gefitinib, they showed a significant benefit to front-line erlotinib with a significantly prolonged PFS (9.7 vs. 5.2 mo, HR = 0.37) and improved RR (64 vs. 18%) accompanied by significantly less toxicity. Patients with exon 19 deletions seemed to have somewhat better outcomes on erlotinib than patients with L858R mutations.

The phase III LUX-Lung 3 study compared the irreversible EGFR/ErbB2 inhibitor afatinib with cisplatin/pemetrexed chemotherapy (up to six cycles) in the first-line setting in patients with EGFR-mutated NSCLC (345 patients, 2:1 randomization) (113). Afatinib therapy demonstrated significantly superior RR (56.1 vs. 22.6%) as well as PFS (11.1 vs. 6.9 mo), and afatinib was better tolerated. How afatinib compares with erlotinib in the front-line setting is unclear, but it certainly appears to have substantial activity in EGFR-mutant lung cancer. Results of head-to-head comparisons with reversible EGFR inhibitors will be required for the understanding of the optimal sequencing of agents.

ALK-translocated Lung Adenocarcinoma

The randomized phase III PROFILE 1007 study compared the ALK inhibitor crizotinib at 250 mg orally twice daily with cisplatinum/pemetrexed chemotherapy in 347 patients with ALK-translocation-positive, advanced NSCLC (114). As expected, a very significant prolongation of PFS was noted (7.7 vs. 3.0 mo in favor of crizotinib); overall RR also strongly favored crizotinib (64

vs. 20%), and quality of life was better in the crizotinib arm. At this point, OS results are premature, but due to crossover to crizotinib, an OS benefit might not be detectable.

ROS Translocations

Recently, chromosomal translocations affecting the tyrosine kinase ROS1 have been described in approximately 1% of lung adenocarcinomas, mainly in younger, never-smoking patients (115). These alterations are mutually exclusive with other dominant oncogenic events. As ROS1 is a tyrosine kinase inhibited effectively by crizotinib, ongoing studies of crizotinib were logically expanded to include ROS1-translocated patients, and the results of the key PROFILE 1001 demonstrate a response rate of 57.1% in the initial cohort of 15 ROS1-translocation–positive patients (116). These results appear very similar to what is seen with crizotinib in ALK-positive patients. Due to the small number of ROS-positive patients, large, randomized studies are not expected to get completed; thus, crizotinib *de facto* is becoming a treatment of choice for patients with ROS translocation.

Acquired Resistance to Targeted Therapeutics

The success of EGFR- and ALK-targeted therapies is tempered by the uniform development of acquired resistance. This key clinical problem in EGFR-mutated tumors is caused in about one-half of the patients by the EGFR T790M mutation and in others by MET amplification, EMT transition, and by histological transformation to small cell carcinoma. Several recent studies report new mechanisms and treatment approaches for acquired resistance mechanisms against EGFR-targeted therapeutics. Takezawa and colleagues report on ErbB2 activation as a potential acquired resistance mechanism. They tested the combination of an irreversible HER inhibitor, afatinib, and the anti-EGFR antibody cetuximab, showing activity in a mouse model, then a very promising 40% response rate in a phase II human study in erlotinib-refractory patients (117). Through elegant studies, the authors demonstrate that the reason afatinib/cetuximab but not erlotinib/cetuximab can be successful in such cases is related to the anti-ErbB2 activity of afatinib. Indeed, the authors find that ErbB2 is amplified and active in 12% of the cases with acquired resistance. Zhang and colleagues identified the activation of the tumor-associated macrophage family tyrosine kinase AXL as another example of oncogene dependence switch similar to the case of MET amplification (118). A study of matched human samples from baseline and after the development of erlotinib resistance identified AXL up-regulation in about 20% of cases. Although the mechanism of AXL overexpression remains ill defined, some observations do suggest that it might be mediated in part by the EMT mechanism.

Similarly, significant data have emerged as to the range of molecular mechanisms playing a role in the development of resistance against crizotinib in patients with ALK-positive lung adenocarcinoma. Katayama and colleagues reported findings of secondary mutations in the tyrosine kinase domain of ALK in about one-third of the patients, including the previously reported L1196 mutation that is analogous to the gatekeeper T790M mutation of EGFR (119). Doebele and colleagues similarly found secondary ALK mutations in about one-third of patients, whereas other mechanisms of resistance were ALK gene copy gains, K-ras mutations, and EGFR bypass activation, such as through an EGFR L858R (120). Last, a recent interesting preclinical study suggested that suppression of signaling governed by MED12, a component of the MEDIATOR transcriptional complex, can lead to resistance against a multitude of cancer drugs, including EGR and ALK inhibitors, through the resultant activation of TGF-betaR signaling (121).

Studies are ongoing to assess novel ALK inhibitors with varying sensitivity against these secondary mutations as well as to evaluate combination strategies. Indeed, one of the most exciting reports at the 2012 American Society of Clinical Oncology meeting related to the second-generation ALK inhibitor LDK378, showing a striking 67% RR in a phase I dose escalation study in patients with crizotinib-resistant ALK-positive lung adenocarcinoma (122). The management of acquired resistance requires molecular examination of biopsies at the time of progression. In practice, this should become the standard of care so as to allow proper assessment of the molecular and histological traits of the tumor and to guide patients toward unique biomarker-driven clinical studies or tailored chemotherapy (e.g., if small cell transformation is noted).

Immunotherapy

Several recent studies have reported promising clinical activity by blocking key immune checkpoints. Ipilimumab targets the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) pathway, which is required for the priming phase of T-cell response within lymph nodes. In a randomized, double-blind, multicenter phase II study, Lynch and colleagues assigned 204 patients with previously untreated, advanced NSCLC to three regimens: (*1*) placebo (placebo plus paclitaxel 175 mg/m^2 and carboplatin AUC 6), (*2*) concurrent ipilimumab (four doses of ipilimumab 10 mg/kg plus paclitaxel and carboplatin → two doses of placebo plus paclitaxel and carboplatin), and (*3*) phased ipilimumab (two doses of placebo plus paclitaxel and carboplatin → four doses of ipilimumab plus paclitaxel and carboplatin) (123). Tumor response was measured by immune-related response criteria (irPFS, primary endpoint) and modified World Health Organization (mWHO-PFS) criteria. The study showed significantly prolonged irPFS and improved mWHO-PFS with phased ipilimumab regimen in comparison to chemotherapy alone. On the other hand, there was only a trend toward improved irPFS with concurrent ipilimumab versus control. The immune-related best overall RR was 18, 21, and 32% for control, concurrent ipilimumab, and phased ipilimumab, respectively. Ipilimumab-containing regimens had higher rates of grade 3 and 4 adverse events versus control subjects (control, 6% vs. concurrent ipilimumab, 20% vs. phased ipilimumab, 15%).

BMS-936558 is a fully human IgG4 monoclonal antibody against programmed death 1 (PD-1) receptor. The interaction of PD-1 on activated T cells with its major ligand in solid tumors, PD-L1, blocks the effector phase of T-cell response within the tumor microenvironment. Topalian and colleagues evaluated the safety profile and antitumor activity of BMS-936558 in 296 patients with advanced solid tumors (124). There were 122 patients with advanced NSCLC enrolled, and the majority of them were heavily pretreated. The cumulative RR was 18% in 122 patients with NSCLC with several durable responses and a striking 33% RR in squamous NSCLC, suggestive of histologic dependence. The objective response rates were 36% in patients with PD-L1–positive tumors versus 0% in patients with PD-L1–negative tumors, suggestive of PD-L1 expression as a logical and promising biomarker for patient selection. Brahmer and colleagues reported the safety and activity of BMS-936559, an anti–PD-L1 antibody (125). In patients with advanced NSCLC, the objective RR was around 10% overall and 16% at doses of 10 mg/kg. No squamous histology predominance was noted in this study. These studies demonstrate significant promise for immunotherapeutic approaches in the treatment of NSCLC.

MESOTHELIOMA

Asbestos causes mesothelioma, and it is also associated with increased risk of lung cancer. In an interesting study, McCormack and colleagues examined asbestos exposure cohorts to estimate the asbestos-related lung cancer burden (126). They reported that all types of asbestos fibers cause twice as many lung cancer deaths as mesothelioma deaths, except for crocidolite. These data are concerning, because the countries with high asbestos use (e.g., Russia and China) also have very high smoking rates in men. Early detection of mesothelioma among asbestos-exposed individuals remains an unmet need for this disease, with median survival of 12 months, despite the availability of the serum biomarker mesothelin (127). Pass and colleagues reported that plasma fibulin-3 levels could distinguish patients with mesothelioma from matched healthy persons with asbestos exposure and that it could help to distinguish mesothelioma pleural effusions from other effusions (128). Once prospectively validated, this biomarker could significantly aid clinical decision making.

The optimal surgical treatment of early-stage mesothelioma remains controversial. Extrapleural pneumonectomy was the former standard approach that involved *en bloc* resection of the entire pleura, lung, diaphragm, and pericardium. The high mortality and morbidity of this operation has shifted enthusiasm toward pleurectomy/decortication, which involves resection of all gross tumor without removing the lung (129). Local disease recurrence is common after both procedures but is more frequent after pleurectomy/decortication. Rosenzweig and colleagues implemented a technique to treat the intact lung of patients with malignant pleural mesothelioma with pleural intensity-modulated radiotherapy (130). For patients treated with surgery, the median survival was 26 months, with a 20% rate of acute grade 3 or worse toxicity, thus suggesting that this adjuvant approach is feasible and promising.

Several topics of this review are subjects of evidence-based reviews and recommendations within the American College of Chest Physicians Evidence-based Clinical Practice Guidelines for the Diagnosis and Management of Lung Cancer, 3rd edition (131).

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Julie A. Linek, M.D., for editorial and content contributions.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
2. Martinez VD, Vucic EA, Lam S, Lam WL. Arsenic and lung cancer in never-smokers: lessons from Chile. *Am J Respir Crit Care Med* 2012; 185:1131–1132.
3. Brenner DR, Boffetta P, Duell EJ, Bickeböller H, Rosenberger A, McCormack V, Muscat JE, Yang P, Wichmann HE, Brueske-Hohlfeld I, *et al*. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. *Am J Epidemiol* 2012;176: 573–585.
4. 't Mannetje A, Brennan P, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabiánova E, Cassidy A, Mates D, Bencko V, *et al*. Welding and lung cancer in Central and Eastern Europe and the United Kingdom. *Am J Epidemiol* 2012;175:706–714.
5. Underwood JM, Townsend JS, Tai E, Davis SP, Stewart SL, White A, Momin B, Fairley TL. Racial and regional disparities in lung cancer incidence. *Cancer* 2012;118:1910–1918.
6. Jonnalagadda S, Bergamo C, Lin JJ, Lurslurchachai L, Diefenbach M, Smith C, Nelson JE, Wisnivesky JP. Beliefs and attitudes about lung cancer screening among smokers. *Lung Cancer* 2012;77:526–531.
7. Jonnalagadda S, Lin JJ, Nelson JE, Powell CA, Salazar-Schicchi J, Berman AR, Keller SM, Smith CB, Lurslurchachai L, Halm EA, *et al*. Racial and ethnic differences in beliefs about lung cancer care. *Chest* 2012;142:1251–1258.
8. Haile RW, John EM, Levine AJ, Cortessis VK, Unger JB, Gonzales M, Ziv E, Thompson P, Spruijt-Metz D, Tucker KL, *et al*. A review of cancer in U.S. Hispanic populations. *Cancer Prev Res (Phila)* 2012;5: 150–163.
9. Saeed AM, Toonkel R, Glassberg MK, Nguyen D, Hu JJ, Zimmers TA, Robbins DJ, Koniaris LG, Lally BE. The influence of Hispanic ethnicity on nonsmall cell lung cancer histology and patient survival: an analysis of the Survival, Epidemiology, and End Results database. *Cancer* 2012;118:4495–4501.
10. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
11. Lee MC, Boroczky L, Sungur-Stasik K, Cann AD, Borczuk AC, Kawut SM, Powell CA. Computer-aided diagnosis of pulmonary nodules using a two-step approach for feature selection and classifier ensemble construction. *Artif Intell Med* 2010;50:43–53.
12. Croswell JM, Baker SG, Marcus PM, Clapp JD, Kramer BS. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. *Ann Intern Med* 2010;152:505–512, W176–180.
13. Hassanein M, Callison JC, Callaway-Lane C, Aldrich MC, Grogan EL, Massion PP. The state of molecular biomarkers for the early detection of lung cancer. *Cancer Prev Res (Phila)* 2012;5:992–1006.
14. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. *Am J Respir Crit Care Med* 2012;185:363–372.
15. Patz EF Jr, Campa MJ, Gottlin EB, Trotter PR, Herndon JE II, Kafader D, Grant RP, Eisenberg M. Biomarkers to help guide management of patients with pulmonary nodules. *Am J Respir Crit Care Med* (In press)
16. Ko JP, Berman EJ, Kaur M, Babb JS, Bomsztyk E, Greenberg AK, Naidich DP, Rusinek H. Pulmonary Nodules: growth rate assessment in patients by using serial CT and three-dimensional volumetry. *Radiology* 2012;262:662–671.
17. Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, Weissfeld J. Doubling times and CT screen–detected lung cancers in the Pittsburgh Lung Screening Study. *Am J Respir Crit Care Med* 2012; 185:85–89.
18. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, Smith JP, Libby DM, Pasmantier MW, Miettinen OS; Writing Committee for the I-ELCAP Investigators. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology* 2012;263:578–583.
19. Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, Macchiarini P, Crapo JD, Herold CJ, Austin JH, *et al*. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology* 2013; 266:304–317.
20. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EF Jr, Swensen SJ; Fleischner Society. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395–400.
21. Sekine Y, Katsura H, Koh E, Hiroshima K, Fujisawa T. Early detection of COPD is important for lung cancer surveillance. *Eur Respir J* 2012;39:1230–1240.
22. Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E, Marchianò A, La Vecchia C, De Filippo M, Kuhnigk JM, *et al*. Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. *Radiology* 2012;262:460–467.
23. Jacobs PC, Gondrie MJ, van der Graaf Y, de Koning HJ, Isgum I, van Ginneken B, Mali WP. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. *AJR Am J Roentgenol* 2012;198:505–511.
24. Arenberg D, Kazerooni EA. Setting up a lung cancer screening program. *J Natl Compr Canc Netw* 2012;10:277–285.
25. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, *et al*. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012;307: 2418–2429.
26. Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, Klippenstein D, Lackner RP, Leard L, Leung AN, *et al*. Lung cancer screening. *J Natl Compr Canc Netw* 2012;10:240–265.

27. Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, Strauss GM, *et al*. Development of the American Association for Thoracic Surgery guidelines for low-dose computed tomography scans to screen for lung cancer in North America: recommendations of the American Association for Thoracic Surgery Task Force for Lung Cancer Screening and Surveillance. *J Thorac Cardiovasc Surg* 2012;144:25–32.
28. Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, *et al*. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012;144:33–38.
29. Kadara H, Wistuba II. Field cancerization in non-small cell lung cancer: implications in disease pathogenesis. *Proc Am Thorac Soc* 2012;9:38–42.
30. Gomperts BN, Walser TC, Spira A, Dubinett SM. Enriching the molecular definition of the airway "field of cancerization": establishing new paradigms for the patient at risk for lung cancer. *Cancer Prev Res (Phila)* 2013;6:4–7.
31. Laroumagne S, Lepage B, Hermant C, Plat G, Phelippeau M, Bigay-Game L, Lozano S, Guibert N, Segonds C, Mallard V, Augustin N, Didier A, Mazieres J. Bronchial colonisation in patients with lung cancer: a prospective study. *Eur Respir J* 2012;42:220–229.
32. Beane J, Cheng L, Soldi R, Zhang X, Liu G, Anderlind C, Lenburg ME, Spira A, Bild AH. SIRT1 pathway dysregulation in the smoke-exposed airway epithelium and lung tumor tissue. *Cancer Res* 2012; 72:5702–5711.
33. Bossé Y, Postma DS, Sin DD, Lamontagne M, Couture C, Gaudreault N, Joubert P, Wong V, Elliott M, van den Berge M, *et al*. Molecular signature of smoking in human lung tissues. *Cancer Res* 2012;72: 3753–3763.
34. Li Y, Linnoila RI. Multidirectional differentiation of Achaete-Scute homologue-1-defined progenitors in lung development and injury repair. *Am J Respir Cell Mol Biol* 2012;47:768–775.
35. Xu X, Rock JR, Lu Y, Futtner C, Schwab B, Guinney J, Hogan BL, Onaitis MW. Evidence for type II cells as cells of origin of K-Ras-induced distal lung adenocarcinoma. *Proc Natl Acad Sci USA* 2012;109:4910–4915.
36. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–674.
37. Ben J, Jin G, Zhang Y, Ma B, Bai H, Chen J, Zhang H, Gong Q, Zhou X, Zhang H, *et al*. Class A scavenger receptor deficiency exacerbates lung tumorigenesis by cultivating a procarcinogenic microenvironment in humans and mice. *Am J Respir Crit Care Med* 2012;186:763–772.
38. Antón I, Molina E, Luis-Ravelo D, Zandueta C, Valencia K, Ormazabal C, Martínez-Canarias S, Perurena N, Pajares MJ, Agorreta J, *et al*. Receptor of activated protein C promotes metastasis and correlates with clinical outcome in lung adenocarcinoma. *Am J Respir Crit Care Med* 2012;186:96–105.
39. Bobrie A, Krumeich S, Reyal F, Recchi C, Moita LF, Seabra MC, Ostrowski M, Théry C. Rab27a supports exosome-dependent and -independent mechanisms that modify the tumor microenvironment and can promote tumor progression. *Cancer Res* 2012;72:4920–4930.
40. Hassanein M, Hoeksema MD, Shiota M, Qian J, Harris BK, Chen H, Clark JE, Alborn WE, Eisenberg R, Massion PP. Slc1a5 mediates glutamine transport required for lung cancer cell growth and survival. *Clinical Cancer Res* 2013;19:560–570.
41. Karoor V, Le M, Merrick D, Fagan KA, Dempsey EC, Miller YE. Alveolar hypoxia promotes murine lung tumor growth through a VEGFR-2/EGFR-dependent mechanism. *Cancer Prev Res (Phila)* 2012;5:1061–1071.
42. Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. *Am J Respir Crit Care Med* 2012;186:487–492.
43. Ye ZJ, Zhou Q, Yin W, Yuan ML, Yang WB, Xiong XZ, Zhang JC, Shi HZ. Differentiation and immune regulation of IL-9-producing CD4+ T cells in malignant pleural effusion. *Am J Respir Crit Care Med* 2012; 186:1168–1179.
44. Kerkar SP, Restifo NP. Cellular constituents of immune escape within the tumor microenvironment. *Cancer Res* 2012;72:3125–3130.
45. Feng PH, Lee KY, Chang YL, Chan YF, Kuo LW, Lin TY, Chung FT, Kuo CS, Yu CT, Lin SM, *et al*. CD14(+)S100A9(+) monocytic myeloid-derived suppressor cells and their clinical relevance in non-small cell lung cancer. *Am J Respir Crit Care Med* 2012;186:1025–1036.
46. Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, Boulden J, Sutanto-Ward E, Soler AP, Laury-Kleintop LD, *et al*. IDO is a nodal pathogenic driver of lung cancer and metastasis development. *Cancer Discov* 2012;2:722–735.
47. Suzuki K, Kadota K, Sima CS, Nitadori JI, Rusch VW, Travis WD, Sadelain M, Adusumilli PS. Clinical impact of immune microenvironment in stage I lung adenocarcinoma: tumor interleukin-12 receptor beta2 (IL-12Rbeta2), IL-7R, and stromal FoxP3/CD3 ratio are independent predictors of recurrence. *J Clin Oncol* 2012;31:490–498.
48. Toonkel RL, Borczuk AC, Powell CA. TGF-beta signaling pathway in lung adenocarcinoma invasion. *J Thorac Oncol* 2010;5:153–157.
49. Gao D, Vahdat LT, Wong S, Chang JC, Mittal V. Microenvironmental regulation of epithelial-mesenchymal transitions in cancer. *Cancer Res* 2012;72:4883–4889.
50. Chen R, Yang Q, Lee JD. BMK1 kinase suppresses epithelial-mesenchymal transition through the Akt/GSK3β signaling pathway. *Cancer Res* 2012;72:1579–1587.
51. Wang ZL, Fan ZQ, Jiang HD, Qu JM. Selective Cox-2 inhibitor celecoxib induces epithelial-mesenchymal transition in human lung cancer cells via activating MEK-ERK signaling. *Carcinogenesis* 2012;34:638–646.
52. Cai Z, Yang F, Yu L, Yu Z, Jiang L, Wang Q, Yang Y, Wang L, Cao X, Wang J. Activated t cell exosomes promote tumor invasion via Fas signaling pathway. *J Immunol* 2012;188:5954–5961.
53. Gunaratne A, Thai BL, Di Guglielmo GM. Atypical protein kinase C phosphorylates Par6 and facilitates transforming growth factor β-induced epithelial-to-mesenchymal transition. *Mol Cell Biol* 2012;33:874–886.
54. McAllister SS. Got a light? Illuminating lung cancer. *Sci Transl Med* 2012;4:142fs122.
55. Brabletz T. EMT and MET in metastasis: where are the cancer stem cells? *Cancer Cell* 2012;22:699–701.
56. Stallings-Mann ML, Waldmann J, Zhang Y, Miller E, Gauthier ML, Visscher DW, Downey GP, Radisky ES, Fields AP, Radisky DC. Matrix metalloproteinase induction of Rac1b, a key effector of lung cancer progression. *Sci Transl Med* 2012;4:142ra195.
57. Zhou C, Licciulli S, Avila JL, Cho M, Troutman S, Jiang P, Kossenkov AV, Showe LC, Liu Q, Vachani A, *et al*. The Rac1 splice form Rac1b promotes K-ras-induced lung tumorigenesis. *Oncogene* 2013;32:903–909.
58. Tsai JH, Donaher JL, Murphy DA, Chau S, Yang J. Spatiotemporal regulation of epithelial-mesenchymal transition is essential for squamous cell carcinoma metastasis. *Cancer Cell* 2012;22:725–736.
59. Ocaña OH, Córcoles R, Fabra A, Moreno-Bueno G, Acloque H, Vega S, Barrallo-Gimeno A, Cano A, Nieto MA. Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1. *Cancer Cell* 2012;22:709–724.
60. Liu P, Morrison C, Wang L, Xiong D, Vedell P, Cui P, Hua X, Ding F, Lu Y, James M, *et al*. Identification of somatic mutations in non-small cell lung carcinomas using whole-exome sequencing. *Carcinogenesis* 2012; 33:1270–1276.
61. Hammerman PS, Hayes DN, Wilkerson MD, Schultz N, Bose R, Chu A, Collisson EA, Cope L, Creighton CJ, Getz G, *et al*.; Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 2012;489:519–525.
62. Suehara Y, Arcila M, Wang L, Hasanovic A, Ang D, Ito T, Kimura Y, Drilon A, Guha U, Rusch V, *et al*. Identification of KIF5B-RET and GOPC-ROS1 fusions in lung adenocarcinomas through a comprehensive mRNA-based screen for tyrosine kinase fusions. *Clin Cancer Res* 2012;18:6599–6608.
63. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, Manolescu A, Thorleifsson G, Stefansson H, Ingason A, *et al*. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008;452:638–642.
64. Munafò MR, Timofeeva MN, Morris RW, Prieto-Merino D, Sattar N, Brennan P, Johnstone EC, Relton C, Johnson PC, Walther D, *et al*.; EPIC Study Group. Association between genetic variants on chromosome 15q25 locus and objective measures of tobacco exposure. *J Natl Cancer Inst* 2012;104:740–748.
65. Walsh KM, Gorlov IP, Hansen HM, Wu X, Spitz MR, Zhang H, Lu EY, Wenzlaff AS, Sison JD, Wei C, Lloyd SM, Chen W, Frazier ML, Seldin MF, Bierut LJ, Bracci PM, Wrensch MR, Schwartz AG, Wiencke JK, Amos CI. Fine-mapping of the 5p15.33, 6p22.1-p21.31 and 15q25.1 regions identifies functional and histology-specific lung cancer susceptibility loci in African-Americans. *Cancer Epidemiol Biomarkers Prev* 2012;22:251–260.

66. Lee Y, Yoon KA, Joo J, Lee D, Bae K, Han JY, Lee JS. Prognostic implications of genetic variants in advanced non-small cell lung cancer: a genome-wide association study. *Carcinogenesis* 2012.
67. Pu X, Ye Y, Spitz MR, Wang L, Gu J, Lippman SM, Hildebrandt MA, Hong WK, Minna JD, Roth JA, *et al*. Predictors of survival in never-smokers with non-small cell lung cancer: a large-scale, two-phase genetic study. *Clin Cancer Res* 2012;18:5983–5991.
68. Leng S, Do K, Yingling CM, Picchi MA, Wolf HJ, Kennedy TC, Feser WJ, Baron AE, Franklin WA, Brock MV, *et al*. Defining a gene promoter methylation signature in sputum for lung cancer risk assessment. *Clin Cancer Res* 2012;18:3387–3395.
69. Wagner KW, Ye Y, Lin J, Vaporciyan AA, Roth JA, Wu X. Genetic variations in epigenetic genes are predictors of recurrence in stage i or ii non-small cell lung cancer patients. *Clin Cancer Res* 2012;18: 585–592.
70. Calin GA, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer* 2006;6:857–866.
71. Lu Y, Govindan R, Wang L, Liu PY, Goodgame B, Wen W, Sezhiyan A, Pfeifer J, Li YF, Hua X, *et al*. MicroRNA profiling and prediction of recurrence/relapse-free survival in stage I lung cancer. *Carcinogenesis* 2012;33:1046–1054.
72. Huang W, Hu J, Yang DW, Fan XT, Jin Y, Hou YY, Wang JP, Yuan YF, Tan YS, Zhu XZ, *et al*. Two microRNA panels to discriminate three subtypes of lung carcinoma in bronchial brushing specimens. *Am J Respir Crit Care Med* 2012;186:1160–1167.
73. Kasinski AL, Slack FJ. miRNA-34 prevents cancer initiation and progression in a therapeutically resistant K-ras and p53-induced mouse model of lung adenocarcinoma. *Cancer Res* 2012;72:5576–5587.
74. Trang P, Wiggins JF, Daige CL, Cho C, Omotola M, Brown D, Weidhaas JB, Bader AG, Slack FJ. Systemic delivery of tumor suppressor microRNA mimics using a neutral lipid emulsion inhibits lung tumors in mice. *Mol Ther* 2011;19:1116–1122.
75. Kikuchi T, Hassanein M, Amann JM, Liu Q, Slebos RJ, Rahman SM, Kaufman JM, Zhang X, Hoeksema MD, Harris BK, *et al*. In-depth proteomic analysis of nonsmall cell lung cancer to discover molecular targets and candidate biomarkers. *Mol Cell Proteomics* 2012;11: 916–932.
76. Pecot CV, Li M, Zhang XJ, Rajanbabu R, Calitri C, Bungum A, Jett JR, Putnam JB, Callaway-Lane C, Deppen S, *et al*. Added value of a serum proteomic signature in the diagnostic evaluation of lung nodules. *Cancer Epidemiol Biomarkers Prev* 2012;21:786–792.
77. Trister AD, Pryma DA, Xanthopoulos E, Kucharczuk J, Sterman D, Rengan R. Prognostic value of primary tumor FDG uptake for occult mediastinal lymph node involvement in clinically N2/N3 node-negative non-small cell lung cancer. *Am J Clin Oncol* 2012 (In press)
78. Lee P, Bazan JG, Lavori PW, Weerasuriya DK, Quon A, Le QT, Wakelee HA, Graves EE, Loo BW. Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer. *Clin Lung Cancer* 2012;13:52–58.
79. Kratz JR, He J, Van Den Eeden SK, Zhu ZH, Gao W, Pham PT, Mulvihill MS, Ziaei F, Zhang H, Su B, *et al*. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. *Lancet* 2012;379:823–832.
80. Bulman W, Saqi A, Powell CA. Acquisition and processing of endobronchial ultrasound-guided transbronchial needle aspiration specimens in the era of targeted lung cancer chemotherapy. *Am J Respir Crit Care Med* 2012;185:606–611.
81. Navani N, Brown JM, Nankivell M, Woolhouse I, Harrison RN, Jeebun V, Munavvar M, Ng BJ, Rassl DM, Falzon M, *et al*. Suitability of endobronchial ultrasound-guided transbronchial needle aspiration specimens for subtyping and genotyping of non-small cell lung cancer: a multicenter study of 774 patients. *Am J Respir Crit Care Med* 2012; 185:1316–1322.
82. Louie BE, Farivar AS, Aye RW, Vallieres E. Early experience with robotic lung resection results in similar operative outcomes and morbidity when compared with matched video-assisted thoracoscopic surgery cases. *Ann Thorac Surg* 2012;93:1598–1604; discussion 1604–1605.
83. Park BJ, Melfi F, Mussi A, Maisonneuve P, Spaggiari L, Da Silva RK, Veronesi G. Robotic lobectomy for non-small cell lung cancer (NSCLC): long-term oncologic results. *J Thorac Cardiovasc Surg* 2012;143:383–389.
84. Pardolesi A, Park B, Petrella F, Borri A, Gasparri R, Veronesi G. Robotic anatomic segmentectomy of the lung: technical aspects and initial results. *Ann Thorac Surg* 2012;94:929–934.
85. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–285.
86. Van Schil PE, Asamura H, Rusch VW, Mitsudomi T, Tsuboi M, Brambilla E, Travis WD. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. *Eur Respir J* 2012;39:478–486.
87. Kim AW, Detterbeck FC, Boffa DJ, Decker RH, Soulos PR, Cramer LD, Gross CP. Characteristics associated with the use of nonanatomic resections among Medicare patients undergoing resections of early-stage lung cancer. *Ann Thorac Surg* 2012;94:895–901.
88. Donahue JM, Morse CR, Wigle DA, Allen MS, Nichols FC, Shen KR, Deschamps C, Cassivi SD. Oncologic efficacy of anatomic segmentectomy in stage IA lung cancer patients with T1a tumors. *Ann Thorac Surg* 2012;93:381–387; discussion 387–388.
89. Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S. Prognostic predictors in non-small cell lung cancer patients undergoing intentional segmentectomy. *Ann Thorac Surg* 2012;93:1788–1794.
90. Carr SR, Schuchert MJ, Pennathur A, Wilson DO, Siegfried JM, Luketich JD, Landreneau RJ. Impact of tumor size on outcomes after anatomic lung resection for stage 1A non-small cell lung cancer based on the current staging system. *J Thorac Cardiovasc Surg* 2012;143:390–397.
91. Schuchert MJ, Awais O, Abbas G, Horne ZD, Nason KS, Pennathur A, Souza AP, Siegfried JM, Wilson DO, Luketich JD, *et al*. Influence of age and IB status after resection of node-negative non-small cell lung cancer. *Ann Thorac Surg* 2012;93:929–935; discussion 935–936.
92. Schuchert MJ, Abbas G, Awais O, Pennathur A, Nason KS, Wilson DO, Siegfried JM, Luketich JD, Landreneau RJ. Anatomic segmentectomy for the solitary pulmonary nodule and early-stage lung cancer. *Ann Thorac Surg* 2012;93:1780–1785; discussion 1786–1787.
93. Yamashita S, Tokuishi K, Anami K, Moroga T, Miyawaki M, Chujo M, Yamamoto S, Kawahara K. Thoracoscopic segmentectomy for T1 classification of non-small cell lung cancer: a single center experience. *Eur J Cardiothorac Surg* 2012;42:83–88.
94. Zhong C, Fang W, Mao T, Yao F, Chen W, Hu D. Comparison of thoracoscopic segmentectomy and thoracoscopic lobectomy for small-sized stage IA lung cancer. *Ann Thorac Surg* 2012;94:362–367.
95. Yang CF, D'Amico TA. Thoracoscopic segmentectomy for lung cancer. *Ann Thorac Surg* 2012;94:668–681.
96. Taylor MD, Nagji AS, Bhamidipati CM, Theodosakis N, Kozower BD, Lau CL, Jones DR. Tumor recurrence after complete resection for non-small cell lung cancer. *Ann Thorac Surg* 2012;93:1813–1820; discussion 1820–1811.
97. Hattori A, Suzuki K, Matsunaga T, Fukui M, Kitamura Y, Miyasaka Y, Tsushima Y, Takamochi K, Oh S. Is limited resection appropriate for radiologically "solid" tumors in small lung cancers? *Ann Thorac Surg* 2012;94:212–215.
98. Cerfolio RJ, Bryant AS, Minnich DJ. Complete thoracic mediastinal lymphadenectomy leads to a higher rate of pathologically proven N2 disease in patients with non-small cell lung cancer. *Ann Thorac Surg* 2012;94:902–906.
99. Boffa DJ, Kosinski AS, Paul S, Mitchell JD, Onaitis M. Lymph node evaluation by open or video-assisted approaches in 11,500 anatomic lung cancer resections. *Ann Thorac Surg* 2012;94:347–353, discussion 353.
100. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, Okada M. Prediction of pathologic node-negative clinical stage IA lung adenocarcinoma for optimal candidates undergoing sublobar resection. *J Thorac Cardiovasc Surg* 2012;144:1365–1371.
101. Verstegen NE, Lagerwaard FJ, Senan S. Developments in early-stage NSCLC: advances in radiotherapy. *Ann Oncol* 2012;23 suppl 10:x46–51.
102. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; 13:802–809.

103. Puri V, Crabtree TD, Kymes S, Gregory M, Bell J, Bradley JD, Robinson C, Patterson GA, Kreisel D, Krupnick AS, *et al.* A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. *J Thorac Cardiovasc Surg* 2012;143:428–436.
104. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2012;144:S35–S38.
105. Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlowski TM, Maiorino L, Hetzel M, Leschinger M, Visseren-Grul C, *et al*. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *J Clin Oncol* 2012;30:172–178.
106. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, Sawa T, Ishikura S, Shibata T, Fukuda H, *et al.*; Japan Clinical Oncology Group Lung Cancer Study Group. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). *Lancet Oncol* 2012;13:671–678.
107. Lilenbaum R, Zukin M, Pereira JR, Barrios CH, Ribeiro RDA, Beato CAM, Nascimento YN, Murad A, Franke FA, Precivale M, *et al*. A randomized phase III trial of single-agent pemetrexed (p) versus carboplatin and pemetrexed (cp) in patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2012;30:7506.
108. Gridelli C, Ciardiello F, Gallo C, Feld R, Butts C, Gebbia V, Maione P, Morgillo F, Genestreti G, Favaretto A, *et al*. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J Clin Oncol* 2012;30:3002–3011.
109. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, *et al*. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247–255.
110. Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Hermann RC, Liu J, Guba SC, Bonomi P, Govindan R. A randomized, open-label, phase III, superiority study of pemetrexed (pem) + carboplatin (cb) + bevacizumab (bev) followed by maintenance bev versus paclitaxel (pac)+ cb+bev in patients with stage IIIB or IV non-squamous cell lung cancer (NS-NSCLC). Presented at the Chicago Multidisciplinary Symposium in Thoracic Oncology. September 6–8, 2012, Chicago, IL.
111. Jänne PA, Shaw AT, Pereira JR, Jeannin G, Vansteenkiste J, Barrios C, Franke FA, Grinsted L, Zazulina V, Smith P, *et al*. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol* 2013;14:38–47.
112. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, *et al.*; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–246.
113. Yang JC, Shih JY, Su WC, Hsia TC, Tsai CM, Ou SH, Yu CJ, Chang GC, Ho CL, Sequist LV, *et al*. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012;13:539–548.
114. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, *et al.* Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368: 2385–2394.
115. Bergethon K, Shaw AT, Ou SH, Katayama R, Lovly CM, McDonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R, *et al*. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863–870.
116. Shaw AT, Camidge DR, Clark JW, Wilner K, Tye L, Stephenson P, Varella-Garcia M, Iafrate A, Ou SI. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. Presented at the Chicago Multidisciplinary Symposium in Thoracic Oncology. September 6–8, 2012, Chicago, IL. Abstract 15.
117. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, Ohashi K, Janjigian YY, Spitzler PJ, Melnick MA, *et al.* HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. *Cancer Discov* 2012;2:922–933.
118. Zhang Z, Lee JC, Lin L, Olivas V, Au V, LaFramboise T, Abdel-Rahman M, Wang X, Levine AD, Rho JK, *et al*. Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. *Nat Genet* 2012;44:852–860.
119. Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, Jessop NA, Wain JC, Yeo AT, Benes C, *et al*. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med* 2012;4:120ra117.
120. Doebele RC, Pilling AB, Aisner DL, Kutateladze TG, Le AT, Weickhardt AJ, Kondo KL, Linderman DJ, Heasley LE, Franklin WA, *et al*. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012;18:1472–1482.
121. Huang S, Hölzel M, Knijnenburg T, Schlicker A, Roepman P, McDermott U, Garnett M, Grernrum W, Sun C, Prahallad A, *et al.* MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signaling. *Cell* 2012;151:937–950.
122. Mehra R, Camidge DR, Sharma S, Felip E, Tan DS, Vansteenkiste JF, De Pas TM, Kim DW, Santoro A, Liu G, *et al*. First-in-human phase i study of the ALK inhibitor LDK378 in advanced solid tumors. *J Clin Oncol* 2012;30:3007.
123. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Neal J, Lu H, Cuillerot JM, *et al.* Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol* 2012;30:2046–2054.
124. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–2454.
125. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, *et al*. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455–2465.
126. McCormack V, Peto J, Byrnes G, Straif K, Boffetta P. Estimating the asbestos-related lung cancer burden from mesothelioma mortality. *Br J Cancer* 2012;106:575–584.
127. Hollevoet K, Reitsma JB, Creaney J, Grigoriu BD, Robinson BW, Scherpereel A, Cristaudo A, Pass HI, Nackaerts K, Rodriguez Portal JA, *et al*. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:1541–1549.
128. Pass HI, Levin SM, Harbut MR, Melamed J, Chiriboga L, Donington J, Huflejt M, Carbone M, Chia D, Goodglick L, *et al*. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. *N Engl J Med* 2012;367:1417–1427.
129. Nakas A, von Meyenfeldt E, Lau K, Muller S, Waller D. Long-term survival after lung-sparing total pleurectomy for locally advanced (International Mesothelioma Interest Group STAGE T3-T4) non-sarcomatoid malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 2012;41:1031–1036.
130. Rosenzweig KE, Zauderer MG, Laser B, Krug LM, Yorke E, Sima CS, Rimner A, Flores R, Rusch V. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2012;83:1278–1283.
131. Detterbeck FC, Lewis SZ, Diekemper R, Addrizzo-Harris D, Alberts WM. Executive summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:7S–37S.