un}g cancer is the leading cause of cancer death in humans in the United States and in the world, causing more than 1.6 million deaths worldwide annually.1 Lung cancer mortality rates for US men and women have been declining.2 An explosion in our understanding of lung cancer biology and pathogenesis has led to marked improvements in outcomes in recent years, which is summarized in this article.

**Biology and molecular biology**

By the early 1970s, the distinct nature of small-cell lung carcinomas (SCLC)³ was established, as was the fact that SCLCs produce hormones, such as adrenocorticotropic hormone, which cause paraneoplastic syndromes.⁴ In the mid-1970s, investigators at the National Cancer Institute Veterans Affairs Medical Oncology Branch established human tumor cultures from patients to better understand the biology and pathogenesis. Much of what we know about lung cancer biology was discovered using these cell lines and their mouse xenografts.⁵ SCLC cells had chromosomal deletions in sites of tumor suppressor genes and gains in regions of dominant oncogenes such as MYC family members.⁷–⁹ Non–small-cell lung cancer (NSCLC) lines attached to plastic, whereas many SCLCs grew as floating aggregates labeled as classic types. Some SCLCs attached and were called variants.

The cell lines were adapted to serum-free media, which allowed for the study of exogenous growth factors.¹⁰ Bombesin, bradykinin, and other neuropeptides were shown to be produced and to stimulate the growth of SCLCs, and neuropeptide receptors were invariably present.¹¹–¹³ These SCLCs had neural characteristics such as CD56, which is shared with natural killer cells.¹⁴ In contrast, NSCLCs had no neuroendocrine features but frequently expressed receptors for ERB family members and could be stimulated to grow by their ligands.¹⁵,¹⁶

Recent studies identified underlying genetic changes using newer sequencing technologies. The majority of lung adenocarcinomas have mutations or translocations in molecular drivers such as KRAS, EGFR, and ALK.¹⁷ The Cancer Genome Atlas studies identified NKX2-1 (TITF1), which encodes a line-age-specific transcription factor, to be involved in most lung adenocarcinomas (and later in SCLC tumors).¹⁸ Twenty-six genes were mutated at significantly higher frequency in lung adenocarcinomas, including EBRB1, ERBB4, EPHA3, KDR, and NTRK. Somatic mutations in tumor suppressor genes such as NF1, APC, RB1, and ATM were also observed.¹⁹ Aberrations in MET, ERBB2, and RIT1 occurred in 13% of patients otherwise lacking an activated oncogene, serving as driver alterations.²⁰

Genomic studies in squamous carcinomas showed a mean of 360 exonic mutations, 165 genomic rearrangements, and 323 segments of copy number alterations per tumor.²¹ Recurrent mutations were found in 11 genes including p53 in nearly all specimens.²¹ Loss-of-function mutations
Key points

- Significantly altered pathways included NFE2L2 and KEAP1 in 34%, PIK3CA pathway genes in 47%, and CDKN2A and RB1 in 72% of patients.

- SCLCs have high mutations rates, and inactivation of TP53 and RB1 was found to be nearly universally present. Recurrent mutations were found in CREBBP, EP300, and MLL genes encoding histone modifiers.

- Recent studies on the expression of immune checkpoint proteins showed that many lung cancer cells express programmed death ligand 1 (PD-L1), which can serve as a biomarker and target for immunotherapies.

- Chest computed tomography (CT) scans are more sensitive in detecting small nodules.

- The Early Lung Cancer Action Project demonstrated that low-dose chest CT scans improved detection of small nodules and were associated with high rates of 5-year survival in screen-detected patients.

- Studies addressing these high false-positive rates using radiologic algorithms for nodule characteristics, history features, and an array of biomarkers are in progress to make screening more cost effective.

Early detection

The National Cancer Institute conducted randomized trials to determine whether quarterly sputum cytology or annual chest x-rays could detect early lung cancer and reduce lung cancer mortality. These studies failed to show a reduction in lung cancer mortality even though survival was improved because of lead time and length time bias. The randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) trial confirmed that chest x-rays did not reduce lung cancer mortality rates.

Chest computed tomography (CT) scans are more sensitive in detecting small nodules. The Early Lung Cancer Action Project demonstrated that low-dose chest CT scans improved detection of small nodules and were associated with high rates of 5-year survival in screen-detected patients. The subsequent National Lung Screening Trial (NLST) demonstrated that annual low-dose spiral chest CT scans improved surgical cure rates and reduced lung cancer mortality by 20%. This improved outcome came at the expense of additional radiation and a high rate of false-positive results leading to unnecessary biopsies and resections.

Studies addressing these high false-positive rates using radiologic algorithms for nodule characteristics, history features, and an array of biomarkers are in progress to make screening more cost effective. Studies to detect early lung cancers and discriminate benign from malignant small pulmonary nodules used various molecular and cellular analyses of sputum, blood, bronchial brushings, washings and biopsies, and exhaled breath. Markers assessed include chromosomal changes, gene expression, microRNA expression, and/or evaluation of volatile organic compounds.

Prevention

The relationship between cigarette smoking and lung cancer, established by the US Surgeon General's 1964 report, signaled a decline in cigarette smoking. The importance of early smoking cessation became quite apparent by the report of Doll and Peto, which showed that lung cancer rates were lower among those who quit at < 30 years of age than rates in continuing smokers, although higher than in never smokers. Since then, the importance of secondhand smoke was established, and it is well established that smoking cessation improves survival even in patients diagnosed with lung cancer.

In addition to an increased risk of lung cancer among smokers, patients with resected lung cancer have a high risk of second lung cancers, approaching 2% per year. Primary lung cancers occur in equal numbers in former and current smokers, and...
approximately less than 10% occur in never smokers, although the rate in never smokers has been increasing in recent years.

Lung cancers progress through sequential changes in the bronchial epithelium from metaplasia through dysplasia, carcinoma in situ, and then cancer. Prostacyclins prevented lung cancers in preclinical and animal models. Thus, we designed a chemoprevention trial using the oral prostacyclin iloprost. High-risk patients were given 6 months of iloprost or placebo and had bronchoscopies at baseline and after 6 months of therapy. At baseline, current smokers had worse dysplasia compared with former smokers, with a difference in average score of 0.9. After 6 months, former smokers receiving iloprost had significantly improved histologic scores compared with those receiving placebo. No differences were observed in continuing smokers. We are following this study with prevention studies using inhaled iloprost and a proposed immunoprevention study of a checkpoint inhibitor to include current smokers.

Pathology and staging

The International Association for the Study of Lung Cancer Pathology and Staging Committees made improvements to both the staging and pathology classifications. For example, lesions previously identified as bronchioloalveolar cancers are now separated into adenocarcinoma in situ and invasive and minimally invasive adenocarcinomas. Immunohistochemical markers such as TTF1, P63, or p40 can distinguish between poorly differentiated squamous and adenocarcinomas even in small biopsies, and neuroendocrine markers can define large-cell neuroendocrine tumors. The International Association for the Study of Lung Cancer Staging Committee collected data on hundreds of thousands of patients worldwide to revise the new eighth edition of the TNM classification, grouping patients into stages with discreet outcomes so that optimal therapy can be selected.

Surgery and radiation

Surgical advances, including video-assisted thoracoscopic surgery, have reduced postoperative pain and length of stay without compromising outcomes. Segmental or wedge resections have been used for small CT-detected nodules in less fit patients with high cure rates. More recently, the use of robotic techniques has been developed and will be compared with standard video-assisted thoracoscopic surgery procedures.

Most recurrences after surgical resection were in distant sites, leading to both adjuvant and neoadjuvant chemotherapy trials to reduce distant recurrences. Meta-analyses of both surgical adjuvant and neoadjuvant studies showed small but significant survival benefits, with hazard ratios of 0.87 translating to a 5% survival benefit at 5 years. Recent adjuvant studies added erlotinib or bevacizumab to standard chemotherapy given sequentially or concurrently, respectively. Unfortunately, both trials were negative, and erlotinib did not improve survival in patients with or without EGFR mutations. Interestingly, 5-year survival rates in the control groups exceeded 60%, compared with less than 50% in historical controls, likely as a result of stage migration.

Postoperative radiation showed a detrimental effect in early-stage disease but a small benefit in stage IIIA/N2 disease. New radiation techniques have reduced toxicity, and radiation therapy is used with triple-modality therapy in many patients with stage IIIA/N2 disease.

Newer radiation techniques have revolutionized the indications for radiotherapy. The introduction of stereotactic body radiation therapy (SBRT) to small lesions provided an alternative to surgical resection in early-stage lung cancers.
Hot Topics

**Key points**

- Stereotactic brain radiation is used routinely in the treatment of brain metastases and may prolong survival compared with whole-brain radiotherapy with far fewer adverse effects.
- Cytotoxic chemotherapy was the first treatment to improve survival for patients with advanced SCLC. High response rates were reported for many classes of agents in SCLC.
- Studies showed that the doublet combination of etoposide and platinum was as effective or more effective than more complex three-drug combinations with less toxicity, and this doublet has been the standard since the 1980s.
- A recent randomized trial showed that a regimen of once-daily fractions to 70 Gy was slightly less effective than 45 Gy in twice-daily fractions.
- Concurrent chemotherapy and radiotherapy or the early institution of radiotherapy was superior to late sequential therapy.
- Prophylactic cranial irradiation reduced the frequency of brain metastases and improved survival in both limited- and extensive-stage SCLC after induction therapy.
- Whole-brain doses are generally limited to 25 Gy to minimize subsequent CNS toxicity.

**Chemotherapy: SCLC and NSCLC**

Cytotoxic chemotherapy was the first treatment to improve survival for patients with advanced SCLC. High response rates were reported for many classes of agents in SCLC. Studies showed that the doublet combination of etoposide and platinum was as effective or more effective than more complex three-drug combinations with less toxicity, and this doublet has been the standard since the 1980s.

In limited SCLC, combined concurrent chest radiotherapy and chemotherapy were superior to either alone. Accelerated twice-daily radiotherapy was superior to once-daily therapy and shortened the treatment course. A recent randomized trial showed that a regimen of once-daily fractions to 70 Gy was slightly less effective than 45 Gy in twice-daily fractions. Concurrent chemotherapy and radiotherapy or the early institution of radiotherapy was superior to late sequential therapy. In extensive SCLC, recent studies showed benefit with chest irradiation after good responses to induction chemotherapy, but additional randomized studies are required to make this standard therapy.

Prophylactic cranial irradiation reduced the frequency of brain metastases and improved survival in both limited- and extensive-stage SCLC after induction therapy. Whole-brain doses are generally limited to 25 Gy to minimize subsequent CNS toxicity.

In NSCLC, platinum doublet chemotherapy prolonged survival compared with placebo or single-agent chemotherapy. Randomized trials comparing various platinum doublets showed no difference in outcome. No differences in chemotherapy effect by histology had been reported until differences by histology were reported in a randomized trial comparing pemetrexed plus cisplatin to gemcitabine plus cisplatin. The pemetrexed combination produced superior survival in patients with nonsquamous histology, whereas the gemcitabine combination was superior in squamous histology. Several two-drug platinum combinations have been shown to be sufficiently safe for patients with a performance status of 2 and elderly patients.

**Targeted therapy**

The first targeted therapies were antiangiogenic and anti–epidermal growth factor receptor (EGFR) antibodies that were studied without predictive biomarkers. The anti–vascular endothelial growth factor (VEGF) bevacizumab and the anti-VEGF receptor ramucirumab improved overall survival slightly when combined with chemotherapy in both the first- and second-line settings, respectively. Bevacizumab was limited to nonsquamous histology and failed to improve survival when combined with some platinum doublets. Nintedanib, an anti-VEGF receptor and multi–tyrosine kinase inhibitor (TKI), prolonged survival when combined with second-line chemotherapy but only in nonsquamous histology, although all histologies were studied.

The recognition that epidermal growth factor and EGFRs served as autocrine and paracrine growth factors led to the development of anti-EGFR antibodies such as cetuximab and necitumumab. When added to chemotherapy, these antibodies improved survival but only slightly, with hazard ratios of approximately 0.84 to 0.87. Although these trials were conducted in unselected patients, the use...
of biomarkers such as protein expression by immunohistochemistry or gene copy number by fluorescent in situ hybridization improved hazard ratios to 0.70. Additional studies to confirm the value of these agents in selected patients are indicated.

Another way to improve outcomes from chemotherapy is to use antibodies to deliver cytotoxic chemotherapy to the tumor. Although there had been little improvement in outcomes from platinum doublets in SCLC, recent studies with an antibody drug conjugate called rovalpituzumab tesirine targeting DLL3 showed high response rates in patients with SCLC who experienced treatment failure with multiple lines of chemotherapy. 100

### Molecular Therapies

The EGFR TKIs gefitinib and erlotinib produced dramatic responses in a small number of patients. 101, 102 Four randomized trials adding these agents to chemotherapy without the use of biomarkers were negative. 103–106 In 2004, several groups reported that certain EGFR mutations altered the ATP binding site such that ATP could constitutively bind and activate downstream signal pathways even in the absence of ligand. 107–109 Preclinical studies demonstrated that the most sensitive cell lines and most responding patients had these activating mutations. 110

These observations led to randomized trials comparing chemotherapy to one of three EGFR TKIs (gefitinib, erlotinib, or afatinib)111–119 (Table 1). All showed that EGFR TKIs produced higher objective response rates (ORRs), prolonged progression-free survival (PFS), reduced toxicities, and improved quality of life compared with chemotherapy. Because these trials allowed cross-over, there was little difference in overall survival. On the basis of these trials, first-line TKIs became the accepted standard for patients with activating EGFR mutations. 120–122

### Key Points

- Another way to improve outcomes from chemotherapy is to use antibodies to deliver cytotoxic chemotherapy to the tumor.
- Recent studies with an antibody drug conjugate called rovalpituzumab tesirine targeting DLL3 showed high response rates in patients with SCLC who experienced treatment failure with multiple lines of chemotherapy.
- The EGFR TKIs gefitinib and erlotinib produced dramatic responses in a small number of patients.
- Four randomized trials adding these agents to chemotherapy without the use of biomarkers were negative.

### Table 1 - Results of randomized, phase III, first-line trials of EGFR TKIs versus platinum doublet chemotherapy in EGFR-mutant patients

<table>
<thead>
<tr>
<th>First author</th>
<th>Study</th>
<th>Agent</th>
<th>No. of EGFR mutant–positive patients</th>
<th>ORR (%)</th>
<th>EGFR TKI vs. platinum doublet</th>
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</thead>
<tbody>
<tr>
<td>Mok111</td>
<td>IPASS</td>
<td>Gefitinib</td>
<td>261</td>
<td>71.2 vs. 47.3</td>
<td>9.8 vs. 6.4 vs 21.6 vs 21.9</td>
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<td>Han115</td>
<td>First-SIGNAL</td>
<td>Gefitinib</td>
<td>42</td>
<td>84.6 vs. 37.5</td>
<td>8.4 vs. 6.7 vs 27.2 vs 25.6</td>
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<td>Mitsudomi113</td>
<td>WJTOG 3405</td>
<td>Gefitinib</td>
<td>177</td>
<td>62.1 vs. 32.2</td>
<td>9.2 vs. 6.3 vs 35.5 vs 38.8</td>
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<td>Maemondo112</td>
<td>NEJSG002</td>
<td>Gefitinib</td>
<td>230</td>
<td>73.7 vs. 30.7</td>
<td>10.8 vs. 5.4 vs 30.0 vs 23.6</td>
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<tr>
<td>Inoue116</td>
<td>NEJSG002</td>
<td>Gefitinib</td>
<td>230</td>
<td>73.7 vs. 30.7</td>
<td>10.8 vs. 5.4 vs 30.0 vs 23.6</td>
</tr>
<tr>
<td>Zhou114</td>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>154</td>
<td>83 vs. 36</td>
<td>13.1 vs. 4.6 vs 22.6 vs 28.8</td>
</tr>
<tr>
<td>Rosell116</td>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>154</td>
<td>54.5 vs. 10.5</td>
<td>9.2 vs. 5.4 vs 19.3 vs 19.5</td>
</tr>
<tr>
<td>Sequist117</td>
<td>LUX-Lung 3</td>
<td>Afatinib</td>
<td>345</td>
<td>56 vs. 23</td>
<td>13.6 vs. 6.9 vs 31.6 vs 28.2</td>
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<tr>
<td>Wu119</td>
<td>LUX-Lung 6</td>
<td>Afatinib</td>
<td>364</td>
<td>67 vs. 23</td>
<td>11.0 vs. 5.6 vs 23.6 vs 23.5</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; EURTAC, European randomized trial of tarceva versus chemotherapy; First-SIGNAL, first-line single agent iredessa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung; IPASS, Iressa Pan-Asia study; LUX-Lung 3, phase III trial of afatinib vs. pemetrexed/cisplatin in locally advanced or metastatic patients; LUX-Lung 6, equivalent to LUX-Lung 3 but with gemcitabine/cisplatin chemotherapy; NEJSG002, North East Japan Gastro Study Group 002 trial; OPTIMAL, erlotinib versus standard chemotherapy in the first-line treatment of patients with advanced EGFR mutation-positive non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.
Chemotherapy studies required stopping the chemotherapy at the time of Response Evaluation Criteria in Solid Tumors (RECIST) progression because of rapid and symptomatic drug-resistant progression. Interestingly, progression on TKIs was often slow, and patients remained asymptomatic. Many of the progressions occurred in a single site that could be treated with local therapy while continuing the TKI. Continuation of the TKI with asymptomatic progression and local therapy to single-site progression extended the median PFS from approximately 10 to 11 months to 14 to 19 months.123,124

Unfortunately, these TKI therapies are not curative, and all patients eventually experience progression. The most frequent cause of progression (in approximately 50% to 60% of patients) is the development of a gatekeeper mutation in the EGFR gene at T790M.

Third-generation EGFR TKIs that bind to both the original and the T790M mutations without binding to the wild-type receptor were developed. Recent studies showed that molecular studies can detect the presence of T790M mutations in the plasma. Data on first-line use of osimertinib are limited to an expansion cohort where the ORR was 77% and median PFS was 19.3 months.

A randomized phase III trial that compares the sequence of first-generation EGFR TKI versus first-line osimertinib has completed accrual, but results have not been reported. Nevertheless, osimertinib has completed accrual, but results have not been reported. Although first-line osimertinib may produce a longer first remission, it may or may not prolong the time to the need for chemotherapy at progression. Not surprisingly, resistance to osimertinib is universal and is often a result of new gatekeeper mutations (C797S) that inhibit osimertinib binding or of activation of other pathways.131 Recently, the allostERIC EGFR TKI inhibitor EA1045 in combination with cetuximab was shown to be effective in mouse models of lung cancer driven by EGFR (L858R/T790M and L858R/T790M/C797S).132

Perhaps the key to treatment with molecular therapy in cancer is a question of how the majority of cells with the activating mutation survive in the presence of the inhibitor. Such understanding could lead to the development of upfront rational combinations. Altering the microenvironment with angiogenesis inhibition could decrease survival of persisting cells, and one small trial that added bevacizumab to erlotinib reported a longer PFS compared with erlotinib alone.133

To discover genes allowing survival after exposure to EGFR TKIs, we used a synthetic lethal short hairpin RNA silencing approach. Multiple genes in the Wnt/β-catenin pathway were identified.134 Inhibitors of this pathway, such as porcupine and tankyrase inhibitors, were synergistic with EGFR TKIs.134,135 We also studied persisting cells by conducting serial RNA sequencing analyses before and after EGFR TKI therapy. In most cell lines, there was evidence of an epithelial phenotype at the outset with high expression of E-cadherin and low expression of vimentin. Within days, E-cadherin expression was lost and vimentin expression increased, suggesting an epithelial-mesenchymal transition phenomenon. This early reprogramming suggests that combination therapy should start together. Histone deacetylase (HDAC) inhibitors prevented epithelial-mesenchymal transition and the emergence of drug-tolerant peritumor cells.136,137
Preclinical studies showed synergy between HDAC inhibitors and EGFR TKIs. A randomized phase II trial comparing the combination of entinostat and erlotinib versus erlotinib alone in patients with wild-type and mutant EGFR showed superior survival in patients with high E-cadherin expression at baseline, including EGFR-mutant patients. Several other phase I trials showed that EGFR TKIs and HDAC inhibitors can be given safely.

Other molecular driver alterations that activate and drive lung cancers include the ALK gene, which is activated by fusion to other genes on chromosome 2. This fusion gene drives growth in animal models. This observation led to the study of the ALK inhibitor crizotinib in patients with lung cancer with ALK fusions, where ORR exceeded 50%. These observations led to randomized trials comparing crizotinib with standard chemotherapy in both the first- and second-line settings, which showed longer PFS with crizotinib.

Other ALK inhibitors, including ceritinib, alectinib, brigatinib, and lorlatinib, were developed and have greater sensitivity, the ability to cross the blood-brain barrier, and different spectra of activity against gatekeeper mutations. These agents were initially studied after progression on crizotinib and showed response rates of ≥ 40% and median PFS durations of ≥ 6 months. There are fewer data on the use of these agents in the first-line setting before crizotinib. Data from a Japanese trial of first-line alectinib showed a median PFS of 27.7 months, and the median overall survival was not reached. Randomized trials comparing crizotinib in the first-line setting have been completed. One of these trials, from Japan, was reported preliminarily with an ORR of 88%.

BRAF mutations occur in 2% to 4% of patients on NSCLCs, and the majority of these are V600E mutations. BRAF inhibitors such as dabrafenib and vemurafenib have single-agent activity in approximately a third of patients with V600E activating BRAF mutations (Table 2). However, the combination of a BRAF inhibitor with a MEK inhibitor such as trametinib produced an ORR of 63% with a median PFS of 9.7 months.

HER2 mutations occur in approximately 2% of NSCLCs and also can be activated by amplification, and the two mechanisms of activation may be distinct. HER2 TKIs, such as dacomitinib, afatinib, and neratinib, did not produce high response rates (Table 2). The combination of neratinib with temsirolimus produced a higher response rate than either alone, and studies of other HER2 inhibitors such as trastuzumab and trastuzumab emtansine are indicated.

Crizotinib is a potent inhibitor of ROS1 and MET as well as ALK. Studies of crizotinib in patients with a ROS1 fusion reported ORRs of approximately 60% and a median PFS of approximately 15 months (Table 2). MET signaling is activated by amplification and by mutations in MET. The mechanism by which exon 14 splice mutations activate the pathway differs from the EGFR mutations and ALK fusions. The MET receptor is normally inactivated by c-CBL binding. Loss of the c-CBL binding site by the mutations leads to decreased receptor ubiquination and impaired receptor degradation so the receptor is always signaling. These exon 14 MET splice mutations occur in approximately 3% of patients with lung cancer, and amplification occurs in an additional 1% to 2%. Both of the MET genetic alterations seem to predict sensitivity to MET TKIs, with response rates in up to 67% of patients.

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Key points

- Molecular driver alterations that activate and drive lung cancers include the ALK gene, which is activated by fusion to other genes on chromosome 2. This fusion gene drives growth in animal models.
- ALK inhibitors, including ceritinib, alectinib, brigatinib, and lorlatinib, were developed and have greater sensitivity, the ability to cross the blood-brain barrier, and different spectra of activity against gatekeeper mutations.
- There are fewer data on the use of these agents in the first-line setting before crizotinib. Data from a Japanese trial of first-line alectinib showed a median PFS of 27.7 months, and the median overall survival was not reached.
- Randomized trials comparing crizotinib with crizotinib in the first-line setting have been completed. One of these trials, from Japan, was reported preliminarily with an ORR of 88%.
- Studies of crizotinib in patients with a ROS1 fusion reported ORRs of approximately 60% and a median PFS of approximately 15 months.
- The mechanism by which exon 14 splice mutations activate the pathway differs from the EGFR mutations and ALK fusions. The MET receptor is normally inactivated by c-CBL binding.
### TABLE 2 - Results of TKI therapy of other drivers

<table>
<thead>
<tr>
<th>Oncogenic driver, drug, and study</th>
<th>Therapy line</th>
<th>No. of patients</th>
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<th>PFS (months)</th>
<th>CNS ORR (%)</th>
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ALK, anaplastic lymphoma receptor tyrosine kinase; NR, not reported; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
The combination of a RET inhibitor with a mammalian target of rapamycin inhibitor such as everolimus produced higher response rates and longer PFS.164

Gene fusions harboring the kinase domain of the NTRK1 gene encoding a high-affinity nerve growth factor were reported in 3.3% of lung adenocarcinomas without known oncogenic drivers.175 TRK fusions are oncogenic in several cancer types, and TRK inhibitors showed preclinical and clinical activity.176,177

Because several genetic alterations drive lung cancers and because TKIs are preferred in first-line therapy, simultaneous evaluation of multiple drivers must be undertaken before institution of therapy. Advances in sequencing, including the next-generation sequencing platform, allow for the identification of multiple driver alterations in a single test. Panel testing demonstrated that molecular drivers were present in as many as 64% of the lung adenocarcinomas.17 In a large study using a panel, patients with a driver mutation who were treated with a specific TKI had a superior survival compared with patients with a driver mutation who did not receive a TKI or with patients without a driver mutation.

Immunotherapy

The newest treatment modality in lung cancer is immunotherapy using monoclonal antibodies directed at checkpoint proteins such as PD-1, PD-L1, and CTLA. The anti–PD-1 antibodies nivolumab and pembrolizumab were approved by the US Food and Drug Administration for second-line therapy of NSCLC because they were superior to docetaxel.25,26,178,179 Anti–PD-L1 antibodies such as atezolizumab and durvalumab were superior to docetaxel in the second-line setting but only in phase II studies, although phase III trials are in progress.20,180,181

These checkpoint inhibitor antibodies produced higher response rates in the first-line setting when given alone or in combination with cytotoxic chemotherapy or with a CTLA inhibitor.182–184 The results of two randomized phase III trials that compared pembrolizumab and nivolumab were recently announced. Pembrolizumab was superior to platinum doublets in patients who had tumors that were greater than 49% PD-L1 positive, whereas nivolumab was not superior to platinum doublet chemotherapy in patients with any positive level of PD-L1 expression.185,186 On the basis of these and other data, multiple randomized phase III trials are being conducted comparing both anti–PD-1 and anti–PD-L1 inhibitors in the first-line setting to the combination of the checkpoint inhibitor with chemotherapy and/or with anti-CTLA4 antibodies.

PD-L1 expression in the tumor and/or immune cells is by no means a perfect biomarker, and many studies are seeking to find superior biomarkers of response. Smoking status and total mutation burden predict benefit from checkpoint inhibitors likely because of the presence of clonal neoantigens that can be recognized by T cells.20,31

Patients with earlier stage lung cancer have more intact immune systems, and these immune therapies are likely to have higher response rates in these settings. There are trials of most of the inhibitors combined in some manner with chemotherapy and radiotherapy in patients with locally advanced NSCLC. For patients with resectable, early-stage disease, neoadjuvant trials provide a method to determine whether response rates to checkpoint inhibitors are higher than in patients with more advanced lung cancer. In addition, the neoadjuvant setting provides an outstanding setting to determine the optimal biomarkers for response. Trials of the checkpoint inhibitors in the adjuvant and neoadjuvant settings are in progress.20,180,181

Key points

- Gene fusions harboring the kinase domain of the NTRK1 gene encoding a high-affinity nerve growth factor were reported in 3.3% of lung adenocarcinomas without known oncogenic drivers.
- Advances in sequencing, including the next-generation sequencing platform, allow for the identification of multiple driver alterations in a single test.
- Panel testing demonstrated that molecular drivers were present in as many as 64% of the lung adenocarcinomas.
- The newest treatment modality in lung cancer is immunotherapy using monoclonal antibodies directed at checkpoint proteins such as PD-1, PD-L1, and CTLA.
- The anti–PD-1 antibodies nivolumab and pembrolizumab were approved by the US Food and Drug Administration for second-line therapy of NSCLC because they were superior to docetaxel.
- The results of two randomized phase III trials that compared pembrolizumab and nivolumab were recently announced.
- Pembrolizumab was superior to platinum doublets in patients who had tumors that were greater than 49% PD-L1 positive, whereas nivolumab was not superior to platinum.
In conclusion, lung cancer remains the leading cancer killer in the world. However, the pessimism surrounding the disease and the outlook for patients with the disease is no longer justified. Given the scientific discoveries over the past few decades, the recent progress in diagnosis and therapy has changed the outlook for patients. The future looks even brighter.

Hot Topics

References

34. Strauss GM, Gleason RE, Sugarbaker DJ: Screening for lung cancer re-examined: A reinterpretation of the Mayo Lung


