A Decade of Advances in Treatment for Advanced Non–Small Cell Lung Cancer

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Lung cancer continues to be the leading cause of cancer-related mortality in the United States and worldwide. An estimated 220,520 patients were diagnosed with lung cancer in the United States in 2010, with 157,300 deaths attributed to the disease. This cancer accounts for more cancer-related deaths than breast, prostate, and colorectal cancers combined. The high mortality rate is largely related to advanced stage of disease at discovery, with more than 50% of patients presenting with metastatic disease. This rate may decline in the next decade, because more early-stage lung cancers will be detected if computed tomography (CT) screening for high-risk individuals becomes widely accepted. Recently, the National Lung Screening Trial (NLST), which randomized individuals with at least a 30-pack-year smoking history to screening chest radiograph or CT, reported a 20% reduction in lung cancer mortality in those undergoing screening CT scans. The topic of lung cancer screening is discussed in more detail in the article by Midthun elsewhere in this issue.

The leading cause of lung cancer continues to be cigarette smoking; however, roughly 10% to 15% of lung cancer patients in the United States have no history of smoking. This amounts to approximately 30,000 never-smokers with lung cancer annually in the United States, more than the number of cases of multiple myeloma, chronic myelogenous leukemia, acute leukemia, sarcoma, or cancers of the brain, esophagus, stomach, liver, or cervix. National efforts continue to focus on smoking cessation; however, the percentage of current smokers in the United States has not changed since 2004, after a significant gradual decline from 1997. It is currently estimated that approximately 20% of adults in America continue to smoke. Other potential causes of lung cancer, including radon gas and asbestos, have also been the focus of national agencies, with specific recommendations concerning radon mitigation and asbestos abatement issued by the Environmental Protection Agency.

For those with lung cancer, the last 10 years have seen small but real advances in both curative intent and palliative therapies. This review will focus on systemic therapies for advanced incurable non–small cell lung cancer (NSCLC), detailing changes in practice and emerging discoveries in advanced disease. Advances in the treatment of early stage NSCLC will be discussed elsewhere.

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in this issue in an article by Paoletti and colleagues. Therapies for small cell lung cancer will be additionally reviewed in the article by Neal and colleagues.

**ADVANCES IN CHEMOTHERAPY**

**Choosing Therapy Based on Histology**

NSCLC is subclassified by histology into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma has surpassed squamous cell histology in the United States as the most common type of NSCLC, possibly related to the introduction of low-tar filter cigarettes in the 1960s, whereas large cell carcinoma continues to be rare. Up until the early 2000s, the distinction between squamous cell carcinoma and adenocarcinoma was not relevant, because treatment options for both were identical. As such, the classification of a tumor as non–small cell lung cancer not otherwise specified (NSCLC-NOS) previously sufficed, but has recently been met with consternation from medical oncologists, who are increasingly prescribing therapies based on the distinction between squamous and nonsquamous cell NSCLC histology.

**Bevacizumab**

In 2006, the United States Food and Drug Administration (FDA) approved the antiangiogenesis agent bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor (VEGF), for use in patients with advanced nonsquamous cell NSCLC. Approval came after a large phase 3 trial comparing standard first-line chemotherapy with carboplatinum and paclitaxel to identical therapy with the addition of bevacizumab demonstrated a significant improvement in median survival (MS) to 12.2 months. The 1-year survival rate was 51%, with 20% of patients surviving 2 years. The trial was restricted to patients with nonsquamous cell histology because early clinical trial data suggested an increased incidence of fatal hemoptysis in patients with squamous cell NSCLC. There is no clear explanation for this association, although one hypothesis has been that squamous cell carcinoma of the lung may be exquisitely sensitive to the effects of VEGF antagonism, with bleeding from tumor-associated blood vessels as the tumor shrinks. This association may also relate to the tendency for squamous cell carcinoma of the lung to cavitate. A retrospective analysis from the two randomized clinical trials evaluating the addition of bevacizumab to carboplatinum and paclitaxel suggested an increased incidence of significant hemoptysis with bevacizumab in those tumors that cavitated, independent of histology, although the number of events was small. Central location of lesions did not appear to be predictive of hemoptysis in these trials, but again, the small number of cases limits conclusions.

**Pemetrexed**

The other drug that is presently FDA approved based on NSCLC histology is pemetrexed (Alimta), an antifolate chemotherapy targeting multiple enzymes involved in folate metabolism, including thymidylate synthase (TS). Pemetrexed initially received approval in 2004 as second-line therapy for patients with advanced NSCLC, regardless of NSCLC histology. The approval was based on the results of a phase 3 trial comparing docetaxel, the standard second-line therapy at the time, with pemetrexed. Efficacy was similar with both regimens; however, toxicity favored pemetrexed with less neutropenia and alopecia. In 2008 this indication was modified, restricting pemetrexed to use only in patients with nonsquamous cell histology. The FDA reached this decision after reviewing subset analyses by histology in this trial and additionally from a phase 3 first-line trial with pemetrexed. The former was unplanned, and reported a small survival advantage with pemetrexed in patients with nonsquamous cell carcinoma (MS 9.3 months vs 8 months; \( P = .048 \)), whereas patients with squamous cell histology fared better with docetaxel (MS 7.4 months vs 6.2 months; \( P = .018 \)). Given the small size of the trial with an unplanned subset analysis, conclusions from this alone would not justify a change of indication. However, a preplanned subset analysis from a larger phase 3 trial comparing first-line therapy with cisplatin and pemetrexed with cisplatin and gemcitabine in 1725 patients also suggested a survival benefit by histology. Although neither regimen seemed superior overall, nonsquamous cell histology predicted for survival benefit with the pemetrexed-containing regimen (\( n = 1000 \); hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.7–0.94; \( P = .005 \)); whereas patients with squamous cell histology appeared to do better with the gemcitabine-containing regimen (\( n = 473 \); HR 1.23, 95% CI 1.0–1.51; \( P = .05 \)). This trial led to the second FDA indication of pemetrexed with cisplatin in patients with chemo-naïve advanced nonsquamous cell NSCLC. An even more compelling argument for a histology effect came from a subsequent trial evaluating maintenance pemetrexed. Patients who received 4 cycles of standard platinum-based doublet therapy for advanced NSCLC without evidence of progression were randomized in a 2:1 ratio to pemetrexed...
Biomarker studies have demonstrated that high levels of ERCC1 as measured by IHC or reverse-transcription polymerase chain reaction (RT-PCR) are associated with better prognosis after surgery for early-stage lung cancer.\textsuperscript{14,15} One explanation for this has been that enhanced ERCC1 activity may limit further molecular events in tumor cells, leading to a less aggressive phenotype. This observation is supported by a large retrospective analysis of the International Adjuvant Lung Trial (IALT), the first randomized study demonstrating a survival benefit with chemotherapy after complete resection of stage I to III NSCLC.\textsuperscript{15} Patients in the trial were randomized to receive cisplatin-based doublet chemotherapy or observation. There was a 4% absolute improvement in overall survival with chemotherapy. However, in the population of patients with ERCC1-positive tumors by IHC (n = 355), there was no benefit observed with chemotherapy. These patients overall had a better prognosis than those with ERCC1-negative tumors, with 5-year survival rates of 46% in the observation arm (n = 170) compared with 39% (n = 202), respectively (HR 0.66, 95% CI 0.49–0.90; P = .009). Whether they would have benefited from a nonplatinum chemotherapy doublet is uncertain; but the benefit of any chemotherapy would be expected to be less, considering the better overall prognosis. Conversely, those with ERCC1-negative tumors (n = 426) survived longer if given chemotherapy, with a 5-year survival rate of 47% in the treated group versus 39% in the untreated group (HR 0.65, 95% CI 0.50–0.86, P = .002).

In the metastatic setting, the potential value of ERCC1 in selecting chemotherapy has been evaluated retrospectively in several studies. A recent meta-analysis of 12 such studies reported that both response and survival in patients treated with platinum-based chemotherapy were superior in patients with low ERCC1 expression by IHC or RT-PCR.\textsuperscript{16} A total of 865 patients were included in this meta-analysis, with a response rate of 47% in ERCC1 low/negative tumors compared with 28% in ERCC1 high/positive tumors (odds ratio 0.48, 95% CI 0.35–0.64; P<.00001). MS was 74 versus 45 weeks, respectively (median ratio 0.48, 95% CI 0.47–1.01; P<.00001). Although comparison is limited in such an analysis, IHC seemed better than RT-PCR in predicting the response rate. Based on encouraging results from individual retrospective studies, the Spanish Lung Cancer Group (SLCG) conducted a prospective phase 3 trial randomizing patients with metastatic NSCLC to first-line standard chemotherapy with docetaxel and cisplatin or to a genotypic arm that selected therapy based on ERCC1 mRNA expression.\textsuperscript{17} Those with low tumor levels
received cisplatin and docetaxel, whereas patients with high tumor expression were administered docetaxel and gemcitabine. The response rate in the control arm was 39% compared with 51% in the genotypic arm (n = 346; P = .02). Additional ongoing prospective trials are listed in Table 1 and are discussed later.

**Ribonucleotide reductase M1**

The RRM1 gene encodes the regulatory subunit of ribonucleotide reductase, an enzyme that is required for DNA synthesis and repair, catalyzing the biosynthesis of deoxyribonucleosides from the corresponding ribonucleotides. Like ERCC1, expression of RRM1 has been associated with prognosis in NSCLC, with longer survival reported in patients with high expression by IHC and RT-PCR.\(^{18,19}\) RRM1 is also a molecular target of gemcitabine, an antimetabolite that has proven activity in several malignancies including NSCLC. Preclinical studies\(^{19,20}\) and retrospective analyses\(^{21–23}\) from clinical trials have in turn indicated RRM1 expression to be a strong predictor of therapeutic efficacy with gemcitabine-based chemotherapy.

The value of RRM1 as a marker for sensitivity to gemcitabine has been prospectively evaluated in a phase 2 feasibility study conducted at the Moffitt Cancer Center.\(^{24}\) A total of 53 patients with chemo-naïve advanced NSCLC were treated with doublet chemotherapy based on mRNA expression of both RRM1 and ERCC1. In patients with tumors showing high RRM1 expression by RT-PCR, gemcitabine was not given. Patients were then further divided into those with high and low expression of ERCC1; patients with high expression did not receive cisplatin. Although the purpose of the study was to assess the feasibility

**Table 1**

Selected ongoing randomized non–small cell lung cancer clinical trials prospectively evaluating predictive biomarkers for chemotherapy

<table>
<thead>
<tr>
<th>Sponsor (Location)</th>
<th>Stage</th>
<th>Phase</th>
<th>Primary End Point/Planned Number</th>
<th>Biomarker</th>
<th>Method</th>
<th>Control Arm</th>
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<td></td>
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<td>H Lee Moffitt Cancer Center (USA)</td>
<td>IIIB/IV</td>
<td>3</td>
<td>PFS 267</td>
<td>ERCC1</td>
<td>AQUA (protein)</td>
<td>GC</td>
<td>GC</td>
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<td>GD</td>
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<tr>
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<td>IIIB/IV</td>
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<td>TTP 480</td>
<td>BRCA1</td>
<td>RT-PCR (mRNA)</td>
<td>GP</td>
<td>DP</td>
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<td>RAP80</td>
<td></td>
<td>GP</td>
<td>D</td>
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<tr>
<td>Yonsei U. (Korea)</td>
<td>IIIB/IV</td>
<td>R2</td>
<td>RR 117</td>
<td>ERCC1</td>
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<td>DC</td>
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<td></td>
<td>RRM1</td>
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<td>GD</td>
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<td><strong>Postoperative (adjuvant) chemotherapy</strong></td>
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<td>II/IIIA</td>
<td>2/3</td>
<td>Feasibility 108</td>
<td>EGFR</td>
<td>Sequence (DNA mut)</td>
<td>PemP</td>
<td>Erlotinib</td>
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<td>ERCC1</td>
<td>IHC</td>
<td>PemP</td>
<td>Observation</td>
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<tr>
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<td>OS 432</td>
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<td>DP</td>
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<td>ITACA (Italy/ Germany)</td>
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<td>3</td>
<td>OS 700</td>
<td>ERCC1</td>
<td>TS</td>
<td>DP(^{a})</td>
<td>GP</td>
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**Abbreviations:** AQUA, automated quantitative analysis; BREC, BRAC1/RAP80 expression customization; C, carboplatin; D, docetaxel; G, gemcitabine; ITACA, International Tailored Chemotherapy Adjuvant; MADeIt, Molecular Analysis-Directed Individualized Therapy; NSCLC, non–small cell lung cancer; OS, overall survival; P, cisplatinum; Pem, pemetrexed; PFS, progression-free survival; R, randomized; RR, response rate; RT-PCR, reverse-transcription polymerase chain reaction; SCAT, Spanish Customized Adjuvant Treatment; TASTE, Tailored Post Surgical Therapy in Early-Stage NSCLC; TTP, time to progression; V, vinorelbine.

\(^{a}\) Investigator choice of listed chemotherapy options on control arm.
of molecularly directed therapy, with only a small number of patients treated, response and survival data were encouraging, with an overall response rate of 44%, MS of 13.3 months, and 1-year survival rate of 59%.

**Ongoing trials evaluating ERCC1/RRM1** Based on the data discussed above, a handful of randomized trials have been launched to prospectively test the predictive value of both RRM1 and ERCC1 (see Table 1). Some of these trials are being conducted in the adjuvant setting, after surgery, where two additional questions are also being considered: Is there a population of patients with stage I NSCLC who would benefit from adjuvant chemotherapy and, conversely, are there patients with node-positive disease who may not benefit from traditional adjuvant chemotherapy? To date, the role of chemotherapy in patients with node-negative NSCLC has not been established, although there is a suggestion that larger tumors, particularly those at least 4 cm in size, may benefit from chemotherapy.25 The Southwest Oncology Group is conducting a pilot study in this population, in which patients with completely resected stage I NSCLC (per AJCC 6th edition26) with T1 tumors 2 cm or larger will only receive adjuvant chemotherapy if their tumors are found to have low protein expression of ERCC1 or RRM1 (NCT00792701). This is a feasibility trial, and interpretation of results will be limited by both the prognostic and predictive value of these biomarkers. If there is a signal from this study, additional trials may randomize only patients with low expression of ERCC1 and tumors between 2 and 4 cm in size to adjuvant chemotherapy or observation, or those with high expression of ERCC1 and tumors larger than 4 cm without nodal involvement to chemotherapy or observation.

**Breast cancer 1/Receptor-associated protein 80**

BRCA1 is a tumor suppressor gene that encodes the breast cancer type 1 susceptibility protein. One of the major functions of BRCA1 is to help repair damaged DNA, in particular, correcting double-strand breaks by participating in homologous recombination, a process for which nucleotide sequences are used from a sister chromatid as a template for repair.27 BRCA1 is also thought to be involved in transcription-coupled NER.28 The importance of BRCA1 is perhaps best illustrated in women with germline BRCA1 mutations. Approximately 65% of these women will develop breast cancer by the age of 70 years, and an estimated 39% will develop ovarian cancer.25,30 BRCA-1 has also emerged as a potential predictive biomarker for chemotherapy, with decreased expression associated with cisplatin sensitivity, and increased expression predictive of benefit from antimicrotubulin agents, such as taxanes.31–34 These observations led to a phase 2 trial using BRCA1 mRNA expression to guide therapy in patients with epidermal growth factor receptor (EGFR) wild-type advanced NSCLC. A total of 123 patients were stratified to gemcitabine/cisplatin (low BRCA1), docetaxel/cisplatin (intermediate BRCA1), or docetaxel alone (high BRCA1).35 Response rates/MS were 25%/11 months (low BRCA1); 46%/9 months (intermediate BRCA1); and 42%/11 months (high BRCA1), respectively. An exploratory analysis of this study further evaluated another potential biomarker, receptor-associated protein 80 (RAP80), a nuclear protein required for the accumulation of BRCA1 to sites of DNA breaks.36–38 Eleven patients were evaluable with low expression of both BRCA1 and RAP80; although the number of patients was small, the outcome of this group was impressive, with MS not reached and time to progression of 14 months. However, the prognostic impact of these biomarkers needs to be considered, with limited data suggesting that high levels of BRCA1 are associated with a poorer prognosis in early-stage lung cancer.39 The response rate in the patients with low BRCA1/RAP80 was not provided. Based on encouraging findings from this trial, the SLCG is currently conducting a phase 3 trial comparing standard first-line chemotherapy for advanced NSCLC to customized therapy based on BRCA1 and RAP80 mRNA levels (BREC trial) (see Table 1).

**Thymidylate synthase**

TS is a key enzyme in folate metabolism, which is essential for the generation of thymidine monophosphate required for DNA synthesis and repair. TS is a major target of several chemotherapies, including pemetrexed, and is currently being evaluated as a predictive biomarker of benefit with pemetrexed in patients with nonsquamous cell NSCLC. This approach is supported by preclinical studies correlating high expression of TS with resistance to pemetrexed, and low levels with chemosensitivity to pemetrexed.40–42 High expression of TS typically seen in squamous cell NSCLC43 has been hypothesized to explain, at least partly, the lack of activity seen with pemetrexed in patients with this histologic subtype of NSCLC. The predictive power of TS expression will be tested prospectively in the EPIC trial (Elderly and Poor Performance Status Individualized Chemotherapy trial), in which patients...
with chemo-naïve advanced NSCLC will be randomized to standard therapy or individualized therapy based on mRNA levels of TS, ERCC1, and RRM1.

**MOLECULAR THERAPY**

To date, three molecular targets have been validated in the treatment of advanced NSCLC: EGFR, anaplastic lymphoma kinase (ALK), and VEGF. The benefit of bevacizumab, a monoclonal antibody to VEGF, has been discussed previously, and this section will focus on EGFR and ALK.

**Epidermal Growth Factor Receptor**

The EGFR is a transmembrane protein composed of an extracellular ligand binding domain and an intracellular tyrosine kinase (Fig. 1). Activation of this receptor by ligand binding leads to receptor dimerization and autophosphorylation of the intracellular tyrosine kinase domain. This activated receptor complex in turn initiates a cascade of intracellular signaling resulting in cellular proliferation, inhibition of apoptosis, angiogenesis, and metastasis. Because the EGFR is aberrantly expressed in 40% to 90% of NSCLCs, it became an attractive target for drug development in the 1990s.

Two oral, small-molecule EGFR tyrosine kinase inhibitors (TKI), gefitinib (Iressa) and erlotinib (Tarceva), have been developed in parallel over the last decade. Gefitinib received FDA approval first, based on two phase 2 trials reporting encouraging response rates, symptom control, and survival in previously treated patients with advanced NSCLC. However, the results of a confirmatory phase 3 trial failed to show a survival advantage with gefitinib compared with best supportive care alone, and gefitinib lost its FDA indication in 2005, with use limited to those who were already benefiting from the drug. Erlotinib fared better, with a positive phase 3 trial randomizing patients with advanced NSCLC to salvage erlotinib or best supportive care alone. MS was improved by 2 months with better quality of life, and erlotinib was FDA approved for use as second-line or third-line treatment in 2004. Recently, the FDA indication for erlotinib was

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*[Fig. 1. Epidermal growth factor receptor (EGFR) activation and inhibition.](https://doi.org/10.1038/s41416-020-0816-z)*

*The EGFR is a transmembrane protein that is activated by ligand binding (e.g., EGF or TGFα), resulting in dimerization with another EGFR (homo) or related receptor (hetero) and autophosphorylation of the EGFR intracellular tyrosine kinase domain. This activated complex in turn initiates a cascade of intracellular signaling resulting in cellular proliferation, inhibition of apoptosis, angiogenesis, and metastases. The EGFR is inhibited by both monoclonal antibodies (e.g., cetuximab) to the extracellular ligand-binding portion and small-molecule adenosine triphosphate (ATP) competitive inhibitors (e.g., erlotinib and gefitinib) of the intracellular tyrosine kinase domain. EGF, epidermal growth factor; TGFα, transforming growth factor α; Y, tyrosine residue; P, phosphate.*
expanded to include maintenance erlotinib, based on modest survival results from the SATURN trial (Sequential Tarceva in Unresectable NSCLC).50 This trial randomized patients with advanced NSCLC, whose disease did not progress after standard first-line chemotherapy, to erlotinib or observation. Progression-free survival (PFS), the primary endpoint, was 12.3 weeks with erlotinib versus 11.1 weeks in the observation arm, with an HR of 0.71 (95% CI 0.62–0.82; P < .0001). A 1-month improvement in MS was reported with an HR of 0.81 (95% CI 0.7–0.95; P = .0088).

Cetuximab, a monoclonal antibody to EGFR, has also been evaluated in a phase 3 trial in patients with advanced NSCLC (the FLEX study).51 A total of 1124 patients with chemo-naïve advanced NSCLC were randomized to standard chemotherapy or to the same therapy with cetuximab. Unlike previous trials finding no benefit when gefitinib or erlotinib was added to chemotherapy, the FLEX trial found a modest improvement in MS of 1.2 months with cetuximab (MS 11.3 months vs 10.1 months; HR 0.87, 95% CI 0.762–0.996; P = .044). The FDA is currently considering approval of this costly agent.

Predicting response to erlotinib/gefitinib
Well before erlotinib or gefitinib came to market, certain characteristics emerged as predictive of response, often dramatic and prolonged, to these agents. These included, adenocarcinoma histology, East Asian ancestry, female sex and, most importantly, no history of smoking. Considering the profound benefit seen in these patients, three separate research centers sequenced archived tumor tissue from responding patients and simultaneously discovered mutations in the tyrosine kinase domain of EGFR.52–54 Both in-frame deletions in exon 19 and a specific missense mutation in exon 21 (L858R) were reported. Since this discovery, a growing database of patients with newly diagnosed EGFR-mutant NSCLC with acquired resistance to erlotinib or gefitinib, generally within 1 year of starting treatment. Progression tends to be slow, and oncologists often choose to continue erlotinib for fear of rapid progression. This phenomenon was illustrated in a group of 10 patients with EGFR-mutant NSCLC with acquired resistance to erlotinib or gefitinib.63 After baseline CT and positron emission tomography/CT scans, erlotinib or gefitinib was held for 3 weeks, at which time imaging was repeated. The same EGFR TKI was then restarted and imaging was repeated 3 weeks later. This small study found that stopping EGFR inhibition led to an increased rate of clinical and radiographic progression, which stabilized or improved on reinitiation of drug. Another approach to such patients has been to discontinue EGFR inhibition temporarily, with rechallenge after progression of disease on salvage chemotherapy. Re-responses in this situation are not uncommon, with one explanation being that without the selection pressure from the EGFR TKI, the resistant clone will fade.64,65

Much work has been done to elucidate mechanisms of acquired resistance to erlotinib and gefitinib (Fig. 2). It is estimated that at least 50% of such tumors harbor an additional EGFR mutation, the T790M mutation in exon 20, where a bulky methionine is substituted for threonine at position 790 on exon 20.63,66–69 It was initially thought that the T790M mutation led to resistance simply by steric interference with drug binding in the adenosine triphosphate (ATP) pocket of EGFR; however, subsequent studies suggest that the introduction of this mutation leads to increased ATP affinity of the mutant EGFR receptor.70,71 Because erlotinib and gefitinib are reversible ATP competitive inhibitors, restoring the ATP affinity of the mutant EGFR decreases its vulnerability to erlotinib or gefitinib. Another mechanism of acquired resistance to EGFR TKIs is amplification of the MET oncoprotein, which is identified in approximately 20% of cases, with some overlap with the T790M mutation.72,73 Increased cell signaling through the MET kinase appears to circumvent EGFR inhibition, maintaining activation of downstream molecules. Identification of both MET amplification and the T790M EGFR mutation as mechanisms of acquired resistance to EGFR TKIs has allowed the development of clinical trials evaluating agents specifically targeting these events (Table 2). For example, a next-generation irreversible EGFR inhibitor that covalently binds to EGFR for resistance mediated by the T790M mutation, or combination therapy with an EGFR TKI and a MET inhibitor for tumors with MET amplification. Other potential mechanisms of acquired resistance are currently being investigated (eg, epithelial to mesenchymal transition, increased

Acquired resistance to EGFR TKI
Inevitably, most patients with EGFR-mutant advanced NSCLC develop resistance to gefitinib or erlotinib, generally within 1 year of starting
insulin-like growth factor receptor 1 signaling, and transformation to small-cell histology) with clinical trials being developed to exploit such mechanisms.69

**Anaplastic Lymphoma Kinase**

The ALK was originally identified in 1994 as part of a chimeric protein found in large cell anaplastic lymphomas.74,75 The fusion resulted

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**Table 2**

Selected ongoing non–small cell lung cancer clinical trials in patients with acquired resistance to EGFR TKIs

<table>
<thead>
<tr>
<th>Trial Sponsor/Identifier</th>
<th>Phase</th>
<th>Agent/Design</th>
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<td>Exelixis NCT00596648</td>
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<td>XL-184: oral multikinase inhibitor including MET, VEGFR2 plus/minus Erlotinib</td>
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<tr>
<td>Boehringer NCT01090011</td>
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<td>BIBW 2992 (Afatinib): oral irreversible inhibitor of EGFR/HER2 plus Cetuximab: monoclonal antibody to EGFR</td>
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<tr>
<td>Pfizer NCT01121575</td>
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<td>PF00299804: oral irreversible inhibitor of EGFR/HER2 plus/minus Crizotinib: oral inhibitor of MET and ALK</td>
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<td>Merrimack NCT00994123</td>
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<td>MM-121: monoclonal antibody to HER3 plus Erlotinib</td>
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<tr>
<td>Northwest U (US) NCT01259089</td>
<td>1/2</td>
<td>AUY-922: intravenous heat shock protein 90 Inhibitor plus Erlotinib</td>
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**Fig. 2.** Mechanisms of acquired resistance to geftinib/erlotinib. Two established mechanisms of acquired resistance to erlotinib and gefitinib include MET amplification and the T790M EGFR mutation. The former is found in approximately 20% of cases with such resistance, and is thought to circumvent EGFR inhibition by restoring activation of downstream molecules. T790M EGFR mutations are identified in 50% to 60% of cases, and are thought to increase ATP affinity of the mutant EGFR. Because erlotinib and gefitinib are reversible ATP competitive inhibitors, increasing the ATP affinity of the mutant EGFR decreases its vulnerability to these inhibitors. Y, tyrosine residue; P, phosphate.
from a translocation of the ALK gene on chromosome 2 to nucleophosmin (NPM) on chromosome 5, transforming cells driven by the constitutive tyrosine kinase activity of ALK. NPM-ALK rearrangements are thought to activate numerous cell-signaling pathways promoting tumorigenesis. The importance of ALK in lung cancer was only recently realized. In 2007, Japanese researchers first identified an ALK gene rearrangement in a patient with NSCLC. RT-PCR demonstrated a translocation of the echinoderm microtubule-associated protein like 4 (EML4) gene on chromosome 2 with ALK. In a relatively short period, ALK has since been validated as a target in NSCLC.

Based on encouraging activity in two patients with ALK-rearranged NSCLC in a phase 1 dose escalation trial of crizotinib, a small-molecule MET and ALK inhibitor, an expansion cohort of 82 patients with ALK-rearranged lung cancer were treated with crizotinib. A response rate of 57% was reported, with an additional 33% showing stability or regression not meeting strict criteria for response. PFS was not reached when the study results were published in 2010, with updated results at the European Society of Medical Oncology annual meeting reporting a median PFS of 9.2 months. These encouraging results have led to the term oncogene addiction, with the potential for profound tumor regression if this oncogene can be successfully inhibited. A handful of other driver mutations in NSCLC has been identified, and efforts are focusing on developing agents to target these events. The most common driver mutation in NSCLC is KRAS, and investigators continue to evaluate anti-KRAS strategies. This target has proved to be elusive, though, and several anti-KRAS agents have failed in the clinic to date. Other driver mutations include HER2, BRAF, PI3K, and MEK. Of course, most NSCLCs are not likely to depend on one molecular event, and a cocktail of targeted therapies will be required to halt the progression of these tumors at the molecular level.

**SUMMARY**

The last decade has seen small but significant advances in the treatment of advanced NSCLC cancer. A plateau in the effectiveness of chemotherapy has clearly been reached, and refinement in such therapy will require further identification and validation of predictive biomarkers. The promise of targeted therapy has been realized in small molecular cohorts of patients with NSCLC, and other such groups are emerging...
with a plethora of agents available to inhibit respective driver mutations. Routine molecular testing to assist in choosing a therapy for advanced NSCLC is now becoming standard practice. For patients without one dominant mutation characterizing their tumor, a customized approach will likely require identification of multiple pathways essential to the tumor phenotype and a cocktail of agents targeting these pathways. Ongoing advances in technology allowing rapid, sophisticated evaluation of both proteins and genes should help realize the ultimate goal of individualizing therapy for every patient diagnosed with lung cancer.

REFERENCES

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