EGFR: The Paradigm of an Oncogene-Driven Lung Cancer
Gregory J. Riely and Helena A. Yu

Abstract

Somatic, activating mutations in EGFR identify a significant minority of patients with non–small cell lung cancer (NSCLC). Although these mutations are associated with an approximately 70% response rate to some EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, and afatinib), patients develop resistance (i.e., “acquired resistance”) after a median of 9 to 12 months. In patients with clinical acquired resistance, repeat biopsy of tumors has identified a number of relevant mechanisms of resistance, but by far the most frequent event is the acquisition of EGFR T790M, a mutation in the “gatekeeper” residue that confers resistance to gefitinib, erlotinib, and afatinib. This emphasizes the critical dependence upon EGFR signaling for some tumors, a property that has been exploited therapeutically. Dual EGFR blockade using afatinib and cetuximab led to a 29% radiographic response rate. More recently, drugs that target EGFR T790M (e.g., rociletinib, AZD9291, and others) have entered clinical trials, with impressive results observed in phase I clinical trials. The development of these newer drugs, with efficacy after resistance to first-line EGFR tyrosine kinase inhibitor, has led to exploration of these strategies in multiple disease settings: at resistance, in the first line, and in adjuvant treatment of those with completely resected early-stage disease who would otherwise die of recurrent/metastatic disease. This example of translational research that identifies mechanisms of resistance to first-generation drugs, and then targets those mechanisms yielding clinical benefit, is a paradigm for how targeted therapies can be developed. *Clin Cancer Res; 21(10); 2221–6. © 2015 AACR.*

See all articles in this CCR Focus section, “Progress in Lung Cancer.”

Introduction

Drugs targeting the EGFR began initial development in the late 1990s and were hypothesized to be effective because a variety of epithelial malignancies, including non–small cell lung cancer (NSCLC; especially squamous cell lung cancer; ref. 1) overexpressed EGFR protein. The earliest molecules to reach the clinic in the 1990s and were hypothesized to be effective because a variety of clinical trials both gefitinib and erlotinib. Although the anti-EGFR antibody cetuximab did not show significant clinical activity (as a single agent or in combination with chemotherapy), in large clinical trials both gefitinib and erlotinib had single-agent activity, with response rates <10% (2–5).

This modest single-agent activity led to initial regulatory approvals for both erlotinib and gefitinib in patients with previously treated advanced NSCLC (Table 1). The FDA approval for erlotinib was based on improvement in overall survival, compared with placebo, for an unselected group of patients with previously treated lung cancer (5). Gefitinib received an accelerated approval based on the response rate in single-arm trials of pretreated patients (2, 3), contingent upon the results of subsequent randomized trials. After a randomized trial comparing gefitinib and best supportive care to best supportive care alone in patients with previously treated lung cancer (analogous to ref. 5 with erlotinib) failed to show an improvement in overall survival (6), in 2005, the U.S. label for gefitinib was changed to effectively withdraw its approval.

Despite the low frequency of overall response rates, these clinical trials provided an opportunity to observe dramatic radiographic and clinical responses in a small proportion of patients treated with erlotinib or gefitinib. Initial trials noted higher response rates for patients from Asia, those who were never smokers, and those patients with adenocarcinoma histology (2, 7). Molecular analysis of tumors from patients with radiographic responses led to the identification of somatic activating mutations in the EGFR gene that were present more frequently in patients with response to erlotinib or gefitinib (8–10). These seminal articles identified the activating characteristics of these mutations and their association with response to erlotinib and gefitinib.

Although the data about EGFR mutations and their association with response were clear, EGFR mutations occurred in just 10% to 20% of patients and in the early development of EGFR tyrosine kinase inhibitors (TKI), some investigators explored the role of other predictive biomarkers, including EGFR copy number (not frank amplification but rather increased copy number). The IPASS trial was the single trial that best clarified the predictive nature of EGFR mutations (11). This trial randomized patients with clinical factors predictive of response to EGFR TKI (East Asian patients, never smokers, patients with adenocarcinoma) to either gefitinib or paclitaxel and carboplatin. In the ensuing biomarker analysis, despite analysis of EGFR IHC, EGFR copy number, and clinical factors, the best predictor of response was EGFR mutations and any predictive effect of IHC or EGFR copy number was driven by their association with EGFR mutation. These findings led to the European approval of gefitinib as a first-line treatment for EGFR-mutant lung adenocarcinoma. Arguments have been made that a similar approval would be appropriate in the United States as well (12).
with afatinib than those with exon 19 deletion. More recently, circulating tumor DNA data from the EURTAC trial (a randomized trial of erlotinib vs. chemotherapy) demonstrated significant differences in outcomes based on EGFR genotype, with a poorer outcome for patients with \textit{EGFR} L858R (23). These data have reemphasized the notion that there may be a differential effect of EGFR TKIs for the two most common genotypes of \textit{EGFR} mutation. Although initial data supported this distinction based on findings with erlotinib and gefitinib, these more recent data extend these findings to afatinib.

**Mechanisms of Acquired Resistance to EGFR TKIs**

After initial response to EGFR TKIs, patients typically develop progression of disease after 9 to 12 months. Understanding how resistance develops in such patients remains a key question. Multiple preclinical and clinical approaches have been used to understand mechanisms of resistance to TKIs with a broad list of pathways implicated (Table 2). Initial focused sequencing analysis of biopsy specimens from patients with acquired resistance looking for secondary mutations (built upon the identification of gatekeeper mutations in the BCR-ABL fusion oncogene in patients who had become resistant to imatinib) led to the identification of \textit{EGFR} T790M as a secondary mutation in \textit{EGFR} that was associated with acquired resistance (24, 25). In the laboratory, investigators have developed cell lines and \textit{in vivo} tumor xenografts that are resistant to EGFR TKIs. Analysis of such cell lines has helped to identify such findings as MET amplification (26, 27), AXL overexpression (28), and epithelial-to-mesenchymal transition (29). Similarly, analysis of genetically engineered mouse models of \textit{EGFR}-mutant cancers (mice with inducible expression of various \textit{EGFR}s that develop lung cancers that mimic the clinical responsiveness of human tumors to EGFR TKIs) have been used, with resulting observations including upregulation of the gene for \textit{PD-L1} (30). These data implicate development of an immunosuppressive environment in tumors with resistance to EGFR TKIs. Immunotherapies currently in development may play a role in the treatment of EGFR-mutant lung cancers (31).

In multiple biopsy series that included analyses of a number of the previously reported mechanisms of resistance for the frequency of these events (though there has been little comprehensive analysis of samples for all reported mechanisms of resistance), it has become apparent that the most frequently identified mechanism of acquired resistance is the secondary mutation in \textit{EGFR} T790M, occurring in >60% of tumors (32–34). This secondary

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**Table 1.** Representative EGFR TKIs currently in use or development

<table>
<thead>
<tr>
<th>First generation (target WT EGFR)</th>
<th>Second generation (irreversible inhibitors of EGFR and HER2)</th>
<th>Third generation (EGFR mutant-specific, irreversible inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib*</td>
<td>Neratinib</td>
<td>Rociletinib (Clovis)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Afatinib*</td>
<td>AZD9291 (AstraZeneca)</td>
</tr>
<tr>
<td>Icotinib</td>
<td>Dacomitinib</td>
<td>HM6173 (Hannmi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR88 (Novartis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASP8273 (Astellas)</td>
</tr>
</tbody>
</table>

*FDA approved for treatment of lung cancer.

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**Table 2.** A partial list of mechanisms implicated in acquired resistance to EGFR TKIs

<table>
<thead>
<tr>
<th>Secondary mutations</th>
<th>Activation of alternate pathways</th>
<th>Other pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR T790M</strong></td>
<td>HER2 amplification (58)</td>
<td>Activation of PD-L1 (30)</td>
</tr>
<tr>
<td>(24, 25)</td>
<td>MET amplification (26, 27)</td>
<td>Epithelial-mesenchymal transition (29, 33, 59)</td>
</tr>
<tr>
<td><strong>EGFR T784A</strong></td>
<td>mTORC1 (60)</td>
<td>Small cell transformation (61, 62)</td>
</tr>
<tr>
<td>(40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF V600E</strong></td>
<td>AXL (64)</td>
<td></td>
</tr>
<tr>
<td>(63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NRAS mutation</strong></td>
<td>IGFR (66, 67)</td>
<td></td>
</tr>
<tr>
<td>(65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EGFR activation</strong></td>
<td>(68, 69)</td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

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mutation in EGFR is thought to alter kinase ATP affinity above that of gefitinib or erlotinib (35). The secondary mutations in EGFR emphasize the continued dependence upon EGFR signaling that is required for patients with EGFR-mutant lung cancer. Without a complete understanding of mechanisms of acquired resistance to EGFR TKIs and before development of drugs that target EGFR T790M, investigators explored a broad array of single-agent and combination therapies in the setting of acquired resistance to erlotinib, gefitinib, and afatinib with generally dismal results (reviewed in Yu and colleagues; ref. 36).

Although understanding the molecular mechanisms of acquired resistance to EGFR TKIs has been important in developing new therapies, some clinical resistance occurs in individual sites (such as isolated central nervous system (CNS) lesions as well as visceral sites). A variety of approaches have been developed to deal with resistance to EGFR TKIs clinically, before development of new therapies. Primarily, these strategies revolve around the use of local therapies. Two groups have reported interesting retrospective series that suggest that local therapies (radiation or surgery) for CNS progression or extra-CNS progression may delay the time until an additional change in therapy is required (37, 38).

**Targeting Acquired Resistance to Erlotinib and Gefitinib with Dual Blockade of EGFR**

The high frequency of EGFR T790M mutation in the acquired resistance setting (and other, less common secondary mutations such as T854A and D761Y) emphasized that continued signaling through EGFR was critical to survival of such as T854A and D761Y) emphasized that continued signaling through EGFR was critical to survival of cells (34, 39, 40). This observation led to the hypothesis that dual EGFR blockade using an EGFR tyrosine kinase coupled with an antibody to EGFR (i.e., cetuximab) could sufficiently dampen EGFR signaling (even in the context of EGFR T790M), thus leading to cancer cell apoptosis (41). Although an initial trial of erlotinib combined with cetuximab showed only modest activity and no RECIST-defined partial responses, there was significantly greater activity with the combination of afatinib and cetuximab (42, 43). After an initial dose escalation that defined the tolerability of full doses of afatinib and cetuximab in combination, a broader study of efficacy was reported (42). In this study of patients with and without EGFR T790M, but with clinically proven resistance to erlotinib or gefitinib, there was a response rate of 29% and a median progression-free survival duration of 5 months. The response rate understates the evidence of tumor shrinkage in the majority of patients treated with this combination therapy. Enthusiasm for the efficacy of this combination has led to a clinical trial that compares the efficacy and tolerability of the combination of afatinib and cetuximab to afatinib alone as initial therapy for EGFR-mutant lung cancers.

**EGFR T790M-Directed Therapies**

As the primary mechanism of acquired resistance, EGFR T790M was a clear target for drug development to address this important medical need. Moreover, a drug that preferentially targets mutant EGFR (T790M along with the activating mutations) would likely reduce WT EGFR-related adverse events often observed (including rash and diarrhea). A sea change occurred in drug development for patients with acquired resistance to first-generation EGFR TKIs with the first described compound directed at EGFR T790M, WZ4002 (44). This drug, identified by screening an irreversible kinase inhibitor library for drugs that bound EGFR T790M, was 100-fold less potent against WT EGFR and 30- to 100-fold more potent against EGFR T790M. This compound binds irreversibly to mutant EGFR at the C797 residue. Although this compound was not taken forward into clinical development, multiple other drugs with similar characteristics have begun to be studied early-phase clinical trials (see Table 1). The first reported clinical data came with rocitinib (CO-1686, Clovis Oncology; ref. 45) with clear evidence of single-agent clinical activity in patients with acquired resistance to erlotinib or gefitinib (46). Subsequently, AZD9291 (AstraZeneica; ref. 47) entered phase I clinical trials in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib, gefitinib, or afatinib (48). Both of these drugs have been explored in single-arm studies with relatively large numbers of patients. A number of other compounds have more recently entered clinical trials with early clinical data anticipated in 2015 (Table 1). AZD9291 and rociletinib, the EGFR T790M-directed drugs with the most data, have shown similar high response rates >50%, but they appear to have unique patterns of adverse events that may distinguish some members of this class of drugs. Rociletinib has a 22% rate of observed grade 3 hyperglycemia, and grade 3 QTc prolongation has been reported in 7% of patients, but the worst rash reported was grade 1 (46). AZD9291 has been reported to have grade 3 rash and diarrhea in 2% to 5% of patients (48). In early reports, there were no grade 3 events of QTc prolongation or hyperglycemia with AZD9291. These differences in adverse events may allow for preferential combination therapies with other classes of drugs.

Although AZD9291 and rociletinib have shown impressive response rates as single-agent kinase inhibitors, it is likely that clinically meaningful drug resistance will occur for this class of drugs after a relatively short time, emphasizing the importance of beginning to understand mechanisms of resistance to these drugs. Potential mechanisms of resistance to EGFR T790M-specific kinase inhibitors have been identified in preclinical work. In the initial presentation of the WZ4002 compound, Zhou and colleagues identified the C797-binding site as a potential source of resistance and went on to show that a C797S mutation would lead to a 100-fold increase in IC50 for cell lines with this mutation (44). Similarly, development of a cell line resistant to WZ4002 implicated amplification of the MAPK1 gene and upregulation of MAPK signaling as mechanisms of acquired resistance to EGFR TKI treatment (49). Importantly, treatment with a MEK inhibitor restored EGFR-TKI sensitivity in these models. Combining the EGFR T790M-specific drug with a MEK inhibitor significantly delayed the emergence of resistance in vitro, suggesting one of many rational combinations that will be explored as development of T790M-specific drugs moves forward. In addition, in a cell line that was developed to be resistant to rociletinib, elevated levels of phosphorylated AKT were observed (50). Addition of an AKT inhibitor made the cell line sensitive to rociletinib. The impressive clinical activity observed with third-generation, mutant-specific EGFR TKIs has led to a rapid move to compare these drugs with erlotinib, gefitinib, and afatinib in the first-line treatment of patients with EGFR-mutant NSCLC.

**Can EGFR TKIs Be Used to Cure Some EGFR-Mutant Lung Cancers?**

Since the identification of EGFR mutations and their association with response to EGFR TKIs in 2004, there have been intermittent calls for a targeted trial of EGFR TKIs in the adjuvant setting for
patients with early-stage EGFR-mutant lung cancer to build upon the palliative results seen in the advanced-stage setting. Although retrospective data support the use of EGFR TKIs in the adjuvant setting, with likely improved disease-free and overall survival, only modest prospective randomized data exist (51). During the same time period, investigators have demonstrated that imatinib prolongs overall survival when given as adjuvant therapy for patients with resected gastrointestinal stromal tumors (GIST; ref. 52). GIST investigators have gone on to show that 3 years of adjuvant imatinib is better than 1 year of adjuvant imatinib (53). With an annual incidence of 4,000 to 6,000 cases per year in the United States, these trials were completed in relatively short order.

Three clinical trials have been reported in which the prospective study of adjuvant EGFR TKIs was explored in patients with EGFR-mutant lung cancer, all with significant methodologic limitations. The BR.19 trial was a placebo-controlled trial of adjuvant gefitinib for patients with completely resected lung cancers that was stopped early after a trial of gefitinib in unselected patients with advanced lung cancer failed to improve overall survival (54). Although an unselected patient population was included in this trial, EGFR mutation testing was done on available specimens, and only 15 patients had EGFR-mutant lung cancer, prohibiting meaningful analysis of the results. Similarly, the RADIANT study explored the value of adjuvant erlotinib in patients with completely resected lung cancer who had overexpression or increased gene copy number of EGFR (55). Subset analysis of the small proportion of patients with EGFR-mutant lung cancer showed a disease-free survival benefit (which, due to hierarchical testing, was not deemed statistically significant), but was underpowered to detect a survival advantage. Finally, a randomized trial of adjuvant gefitinib after all patients with stage IIIA EGFR-mutant lung cancer were treated with pemetrexed and carboplatin showed improved disease-free survival, and a trend toward improved overall survival, but, with only 60 patients, the study was underpowered to show statistically significant overall survival differences (56). Fortunately, multiple ongoing randomized studies have enrolled patients with EGFR-mutant lung cancer to treatment with erlotinib or gefitinib (Table 3). In North America, the most prominent trial is the NCI-sponsored ALCHEMIST EGFR trial, which seeks to enroll 410 people with resected, stage IB–III, EGFR-mutant lung cancers previously treated with standard chemotherapy to either erlotinib or placebo (57). The investigators are seeking to show an HR of 0.67 for overall survival, its primary endpoint. Similar trials are enrolling patients in Asia. Although there are ongoing trials of erlotinib or gefitinib in the adjuvant setting and retrospective data suggest that this strategy will improve overall survival, questions remain about whether these studies use a duration of therapy that is likely to show benefit and whether the optimal drug is being used. As described above in GIST, there is evidence that 3 years of imatinib is better than 1 year. Similarly, in women with estrogen receptor–expressing breast cancers, adjuvant hormonal therapy is now recommended for 10 years for some patients. The early impressive clinical data for patients with the EGFR inhibitors that target EGFR T790M (i.e., rociletinib and AZD9291), in conjunction with a suggestion of better tolerability (lower rates of grade 3 rash and grade 3 diarrhea), would seem to make them better candidates for testing in the adjuvant setting. With these caveats, it is likely that optimization of duration of therapy and identification of the right drug can be accomplished and that of EGFR TKIs may cure some patients with early-stage resected EGFR-mutant lung cancers who might otherwise die from recurrent or metastatic disease.

Disclosure of Potential Conflicts of Interest

G.J. Riely is a consultant/advisory board member for ARIAD Pharmaceuticals and Novartis. H.A. Yu reports receiving commercial research grants from Astellas Pharma, AstraZeneca, Clovis Oncology, and Incyte, and is a consultant/advisory board member for Clovis Oncology. No other potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.A. Yu

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.A. Yu

Writing, review, and/or revision of the manuscript: G.J. Riely, H.A. Yu

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.A. Yu

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Table 3. Ongoing adjuvant EGFR TKI trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>EGFR TKI</th>
<th>Comparison arm</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0140214</td>
<td>Erlotinib × 2 y</td>
<td>Cisplatin/vinorelbine for 4 cycles</td>
<td>Stage III, EGFR mutations in exon 19 or 21</td>
</tr>
<tr>
<td>NCT01405079</td>
<td>Gefitinib × 2 y</td>
<td>Cisplatin/vinorelbine for 4 cycles</td>
<td>Stage II–III, EGFR exon 19 deletion or L858R</td>
</tr>
<tr>
<td>NCT01683175</td>
<td>Erlotinib × 2 y</td>
<td>Cisplatin/vinorelbine for 4 cycles</td>
<td>Stage II, EGFR exon 19 deletion or L858R</td>
</tr>
<tr>
<td>NCT02525240</td>
<td>Gefitinib × 2 y</td>
<td>Placebo</td>
<td>Stage III, EGFR exon 19 deletion or L858R</td>
</tr>
<tr>
<td>NCT01746251</td>
<td>Afatinib × 2 y</td>
<td>Afatinib × 3 mo</td>
<td>Stage I–III, EGFR mutation, prior chemotherapy</td>
</tr>
<tr>
<td>NCT01929200</td>
<td>Gefitinib × 2 y</td>
<td>Icotinib × 1 year</td>
<td>Stage II–III, EGFR mutation in exon 19 or 21</td>
</tr>
<tr>
<td>NCT01996098</td>
<td>Chemotherapy followed by</td>
<td>Chemotherapy alone</td>
<td>Stage II–III, EGFR mutation in exon 19 or 21</td>
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<tr>
<td>NCT02194738</td>
<td>Icotinib × 2 y</td>
<td>Icotinib × 1 year</td>
<td>Stage II–III, EGFR mutation in exon 19 or 21</td>
</tr>
<tr>
<td>NCT02264210</td>
<td>Erlotinib × 2 y</td>
<td>Placebo</td>
<td>Stage IB–III, EGFR mutation</td>
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<tr>
<td>WJOG6410L</td>
<td>Gefitinib × 2 y</td>
<td>Cisplatin/vinorelbine</td>
<td>Stage II, EGFR exon 19 deletion or L858R</td>
</tr>
</tbody>
</table>

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