Managing Acquired Resistance in *EGFR*-Mutated Non–Small Cell Lung Cancer

Patrick M. Forde, MD, and David S. Ettinger, MD

The authors are affiliated with the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. Dr Forde is an assistant professor of oncology and Dr Ettinger is a professor of oncology.

Corresponding author:
Patrick M. Forde, MBBCh, MRCP UK, MRCPI
Assistant Professor of Oncology
Sidney Kimmel Cancer Center
Johns Hopkins Medicine
Bunting-Blaustein CRB 1, Rm G92
1650 Orleans St
Baltimore, MD 21287
Phone: 410-502-7159
E-mail: pforde1@jhmi.edu

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Abstract: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) deliver high response rates with relatively modest toxicity in patients with advanced *EGFR*-mutated non–small cell lung cancer. Despite this, nearly all tumors eventually develop resistance to first-line therapy. At present, the only standard treatment option for patients with acquired resistance is cytotoxic chemotherapy. In this article, we review the latest research into methods of targeting acquired resistance to EGFR TKI therapy, including third-generation EGFR TKIs that target the T790M resistance mutation and other novel agents in development.

Background

Activating mutations in exons 18 to 21 of the epidermal growth factor receptor *(EGFR)* gene occur in approximately 10% to 15% of white patients and 24% to 51% of Asian patients with lung adenocarcinoma.[1,2,3] In non–small cell lung cancer (NSCLC), mutations in *EGFR* are frequently mutually exclusive with other activating tumor mutations and act as a driver for growth and metastasis of the cancer. EGFR tyrosine kinase inhibitors (TKIs) are oral drugs that selectively bind the tyrosine kinase region of the intracellular domain of EGFR and inhibit signal transduction. The EGFR TKI afatinib (Gilotrif, Boehringer Ingelheim) was approved by the US Food and Drug Administration (FDA) in 2013 for the first-line treatment of metastatic NSCLC[4] harboring mutations in exon 19 or 21. Prior to the recognition that *EGFR* mutations sensitize tumors to EGFR TKIs, erlotinib (Tarceva, Genentech/Astellas) was approved by the FDA in 2004 as maintenance therapy after initial chemotherapy for unselected metastatic NSCLC and also as second- or subsequent-line therapy for unselected metastatic NSCLC.[5] The objective response rate (ORR) to first-line afatinib treatment of NSCLC harboring mutations in *EGFR* ranges from 56% to 67%, with a median progression-free survival (PFS) of approximately 11 months in 2 large phase 3 studies.[6,7] Similarly, the ORR to first-line erlotinib in

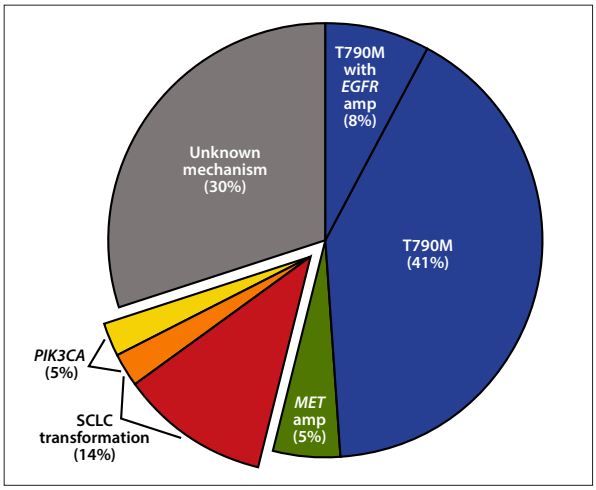

Figure. The frequency of observed drug resistance mechanisms. The pie chart depicts the prevalence of observed mechanisms of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in 37 patients with non–small cell lung cancer (NSCLC) biopsied at the time that resistance was acquired. Specimens from before and after treatment were compared, and only acquired mechanisms of resistance are depicted. The blue wedge represents resistant cancers that developed the *EGFR* T790M resistance mutation, including a subset that developed concomitant *EGFR* amplification. The green wedge represents cancers that developed *MET* amplification, and the red wedge represents cancers that underwent transformation to SCLC. The yellow wedge represents cancers that developed *PIK3CA* mutations, and the orange wedge represents one patient who had both SCLC transformation and acquisition of a *PIK3CA* mutation.

amp, amplification; EGFR, epidermal growth factor receptor; SCLC, small cell lung cancer.

Adapted from Sequist LV et al. *Sci Transl Med.* 2011;3(75):75ra26. Republished with permission from the AAAS.[11]

EGFR-mutated NSCLC has ranged from 58% to 83% in 2 first-line phase 3 studies, with median PFS ranging from 9.4 to 13.1 months.[8,9] Despite promising initial responses, virtually all patients with *EGFR*-mutated lung cancer eventually experience disease progression on EGFR TKI therapy. This has led to intense interest in strategies to treat acquired resistance to EGFR TKIs.

Resistance of *EGFR*-mutated NSCLC to first-generation EGFR TKI therapy occurs through several different cellular alterations (see the figure). These include development of secondary mutations in *EGFR* (including the T790M mutation in up to 68% of cases), *MET* amplification, *PIK3CA* mutation, *BRAF* mutation, or *HER2* amplification.[10-14] Transformation of NSCLC to small cell histology after EGFR TKI therapy, with persistence of the initial *EGFR* mutation, also has been reported.[11] These tumors may be sensitive to standard small cell–type regimens, such as platinum etoposide.

This article will review potential methods of targeting these resistance pathways, including recent early-phase clinical trials in the area.

The Role of EGFR TKIs in First-Line Chemotherapy

Given that the overwhelming majority of sensitizing *EGFR* mutations in NSCLC occur in nonsquamous tumors, for most patients standard therapy after a first-line EGFR TKI will include platinum and pemetrexed (Alimta, Lilly), or alternatively, carboplatin/paclitaxel and bevacizumab (Avastin, Genentech). Recent data suggest that there may not be a significant benefit to continuing an EGFR TKI when commencing chemotherapy. IMPRESS (A Study of IRESSA Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone) randomly assigned 265 patients—with disease progression on first-line gefitinib within 28 days of randomization defined by Response Evaluation Criteria In Solid Tumors (RECIST)—to cisplatin/pemetrexed plus either gefitinib or placebo.[15] There was no significant difference in ORR or PFS between the 2 arms and, although OS data are not yet mature, the investigators reported that there may be a trend toward inferior survival in the arm combining chemotherapy with gefitinib (survival from time of randomization, 14.8 months for the chemotherapy/gefitinib arm vs 17.2 months for the chemotherapy/placebo arm).

Although several studies are ongoing to further investigate the role of continued anti-EGFR TKIs (NCT01928160, NCT02064491), it is not currently recommended to continue EGFR TKIs with erlotinib or gefitinib past RECIST progression after chemotherapy has commenced.

Switching to Afatinib After Progression on Erlotinib or Gefitinib

Afatinib is an irreversible inhibitor of the human epidermal growth factor receptor (HER) family, including HER1, HER2, and HER4. Upregulation of HER2 is 1 possible mechanism of resistance to first-line EGFR TKI therapy. The LUX-Lung 1 trial enrolled 585 patients with *EGFR*-mutated NSCLC who had progressive disease after at least 12 weeks of EGFR TKI therapy (erlotinib, gefitinib, or both) and 1 or 2 prior lines of chemotherapy.[16] Patients were randomly assigned in a 2:1 ratio to afatinib or placebo. The primary endpoint of the study was overall survival (OS). This study failed to demonstrate an improvement in OS for afatinib (the median OS was 10.8 months for afatinib vs 12 months for placebo, P=.74). The median PFS was longer with afatinib (3.3 months for

afatinib vs 1.1 months for placebo, *P*<.0001). Although half of patients who received afatinib had some shrinkage in their tumors, the RECIST ORR to afatinib was only 7%. Toxicities reported with afatinib included grade 3 diarrhea in 17% of patients and grade 3 rash in 14%.

In a smaller study of single-agent afatinib (50 mg/day orally) conducted in Japan, 45 of 62 patients enrolled had activating mutations in *EGFR* and 82% of patients had acquired resistance to erlotinib or gefitinib therapy. In this study, 8.2% of patients had an objective response.[17]

Based on the results of these studies, switching therapy to single-agent afatinib is not recommended for patients with *EGFR*-mutated NSCLC refractory to erlotinib or gefitinib.

Combination Therapy With Afatinib and Cetuximab

In a phase 1/2 study, 126 patients with *EGFR*-mutated NSCLC and acquired resistance to erlotinib or gefitinib received combination therapy with afatinib (40 mg/day orally) and cetuximab (Erbitux, Bristol-Myers Squibb/Lilly) (500 mg/m^2 every 2 weeks intravenously).[18] All patients enrolled in the phase 2 component of the study had received erlotinib or gefitinib with a median duration of treatment of 1 year. A total of 79% of patients had been treated with cytotoxic chemotherapy in addition to erlotinib or gefitinib, and 52% had received 2 or more lines of prior chemotherapy. The T790M resistance mutation was found in 57% of 124 patients in whom testing was performed. Deletions in exon 19 of *EGFR* were present in the tumors of 62% of patients, whereas 33% of patients had L858R mutations in exon 21.

Among the 126 patients who received the combination of afatinib and cetuximab, the ORR was 29%, and 18% of patients had tumor shrinkage of at least 50%. The ORR was not significantly different between T790M-positive (32%) and T790M-negative (25%) tumors (*P*=.341). The median duration of response to afatinib and cetuximab was 5.7 months (range, 1.8-24.4). The median PFS for all patients was 4.7 months (95% CI, 4.3-6.4).

Grade 3 and 4 treatment-related adverse events were reported in 44% and 2% of patients, respectively. The most common of these were grade 3 rash (20%) and grade 3 diarrhea (6%). Two patients died because of treatment-related adverse events (pneumonitis and dyspnea). Although 13% of patients discontinued therapy owing to toxicity, it should be noted that 64% of patients did not require a dose reduction.

At present, combination therapy with afatinib and cetuximab is not approved by the FDA for the treatment of *EGFR*-mutated NSCLC. Although the reported response rate in this phase 1/2 study is promising, mature PFS and OS data from a randomized study are required before this combination can be routinely recommended, particularly given the concern for overlapping dermatologic and gastrointestinal toxicity between the agents. We consider platinum doublet chemotherapy to be standard therapy for patients who have progressed after first-line first-generation EGFR TKIs if the patient is not eligible for clinical trial participation. In the setting of resistance to both first-generation EGFR TKI therapy and chemotherapy, and in the absence of clinical trial options, the use of the afatinib/cetuximab combination—where available—may be discussed with individual patients with preserved Eastern Cooperative Oncology Group (ECOG) performance status who wish to pursue further systemic therapy.

Third-Generation EGFR TKIs

AZD9291

The third-generation EGFR TKI AZD9291 irreversibly inhibits T790M (the most frequent mutation that leads to resistance to first-generation EGFR TKIs), as well as the mutations in exon 19 and 21 of EGFR that are most often present in untreated *EGFR*-mutated NSCLC.[19] Third-generation EGFR TKIs spare wild-type *EGFR*, thus reducing the incidence of dermatologic toxicity. AZD9291 was investigated in a phase 1 dose-escalation study at doses of 20 to 240 mg per day orally in patients with *EGFR*-mutated NSCLC and acquired resistance to EGFR TKIs; a dose expansion cohort at the recommended phase 2 dose was also enrolled.[20] The dose-escalation phase of the study enrolled 31 patients, and the expansion phase enrolled 201 patients. The ORR among all patients was 53% (95% CI, 46%-60%), including an ORR of 64% (95% CI, 55%-73%) in T790M-positive patients and 22% (95% CI, 12%-36%) in T790M-negative patients. The most frequent side effects were rash, diarrhea, nausea, and pruritis; however, no dose-limiting toxicities were reported. Of note, hyperglycemia is rare with AZD9291, occurring in only 3 patients on this study. Grade 3 or 4 toxicities occurred in 24% of patients; however, this led to dose reduction in only 2% of patients and discontinuation in 4%. Based on efficacy and tolerability, 80 mg daily has been chosen as the phase 2/3 dose of AZD9291. Several large studies of AZD9291 in *EGFR*-mutated NSCLC are ongoing, including a phase 2, single arm, open-label study (NCT02094261) in second-line T790M-positive patients and a phase 3 study vs platinum/pemetrexed chemotherapy in second-line T790M-positive patients (NCT0215198). In the first-line setting, AZD9291 is being compared with erlotinib or gefitinib in previously untreated patients with *EGFR*-mutated advanced NSCLC in an international phase 3 trial (NCT02296125). Also ongoing is a phase 1 study

combining AZD9291 with several novel therapeutics, including selumetinib (a MEK inhibitor), MEDI4736 (a programmed death ligand 1 antibody), and AZD6094 (a MET inhibitor) (NCT02143466).

Rociletinib (CO-1686)

Rociletinib is an irreversible inhibitor of the T790M resistance mutations, as well as the exon 19 and 21 mutations commonly present in untreated *EGFR*-mutated NSCLC. Like AZD9291, rociletinib also spares wild-type *EGFR*.[21] Among 72 patients enrolled in an initial dose-finding study, the ORR was 58% among patients with the T790M resistance mutation. Common toxicities included hyperglycemia (grade 3 in 22%), nausea, and diarrhea.[22] In a subsequent report of 27 T790M patients resistant to first-generation EGFR TKIs who received rociletinib at the recommended phase 2 dose (625 mg twice a day orally), the ORR was 67% and the median PFS was 10.4 months.[23] Among 11 patients without the T790M mutation, four had an objective response. In the second-line setting, a phase 2 trial of rociletinib (625 mg twice a day) is ongoing (NCT02147990). A first-line study (nonselective for T790M) comparing rociletinib vs erlotinib is also underway (NCT02186301).

HM61713

HM61713 is also an irreversible inhibitor of T790M and common activating *EGFR* mutations. Among 83 patients with *EGFR*-mutated NSCLC resistant to first-generation EGFR TKIs enrolled in a phase 1 study, the ORR in 48 patients with tumors harboring the T790M resistance mutation was 29.2%. Most adverse events were grades 1 and 2, including skin exfoliation and diarrhea.[24]

ASP8273

ASP8273 also targets T790M and common exon 19 and exon 21 *EGFR* mutations. In a phase 1 dose-escalation/dose expansion study that has enrolled 31 patients to date, 7 out of 9 patients pretreated with gefitinib or erlotinib and harboring the T790M mutation had an objective response.[25] Adverse events included nausea and diarrhea. In contrast to AZD9291 and rociletinib, hyperglycemia has not yet been reported with this agent.

Targeting Amplification of *MET*

Tumor *MET* amplification occurs in 5% of patients with acquired resistance to EGFR TKI therapy.[26] In a phase 2 study of the addition of cabozantinib (Cometriq, Exelixis) (which targets MET/RET/vascular endothelial growth factor receptor [VEGFR]) to erlotinib in patients with *EGFR*-mutated NSCLC and resistance to first-line EGFR TKIs, the ORR among 35 patients enrolled was 9%.[27] Similarly, the addition of the MET inhibitor INC280 to gefitinib in patients with acquired resistance to a first-line EGFR TKI delivered a 15% unconfirmed response rate in 41 patients.[28] In a phase 1 study of the ALK/MET inhibitor crizotinib (Xalkori, Pfizer) in combination with the pan-HER inhibitor dacomitinib, a single objective response was reported from 35 patients enrolled who were resistant to first-generation EGFR TKI therapy. In addition, 19 patients had stable disease as best response.[29] Of note, perhaps owing to the relative infrequent finding of *MET* amplification as a resistance mechanism, only 2 patients on this study had *MET* amplification reported on prestudy tumor biopsies.

PIKCA Mutations

Approximately 5% of EGFR TKI–resistant tumors have developed mutations in *PIK3CA*.[11] Given this information, several studies are ongoing that target the PI3K pathway as a mechanism to overcome EGFR TKI resistance. In a phase 2 study, the AKT inhibitor MK-2206 had a 9% ORR in patients with *EGFR* mutations and acquired resistance to an EGFR TKI.[30] Ongoing studies include combining erlotinib with the PI3K inhibitor BKM120 (NCT01487265), and a study of combined mammalian target of rapamycin (mTOR)/EGFR inhibition (NCT00993499).

HER2 Amplification

Amplification of *HER2* occurs in 12% of *EGFR*-mutated lung cancers with acquired resistance to EGFR TKI therapy.[14] The combination of afatinib (which is a dual HER2/EGFR inhibitor) and cetuximab has delivered an ORR of 30% in patients with acquired resistance to an EGFR TKI.[18] This combination is currently being investigated in a large cooperative group trial in the first-line setting, with the goal of delaying the emergence of acquired resistance.

Conclusion

Despite the initial high rate of response of *EGFR*-mutated NSCLC to erlotinib or gefitinib, acquired resistance occurs in almost all patients. Currently, the standard therapy for these patients is to switch to platinum doublet chemotherapy. The combination of afatinib and cetuximab has delivered a promising response rate in patients with *EGFR*-mutated NSCLC that is resistant to first-line EGFR TKI therapy. Several third-generation TKIs specific for the T790M resistance mutation are delivering high response rates that may be durable in some cases. Targeting the 50% of acquired resistance in tumors that is

not mediated through T790M remains challenging, and approaches that combine pathway inhibition with novel strategies such as immunotherapy may be most likely to yield benefit.

Disclosures

Dr Ettinger is a consultant for Ariad Pharmaceuticals, Boehringer Ingelheim, Eisai, Golden Biotech, Helsinn Therapeutics, Eli Lilly, Genentech, Sandoz, BMS, and EMD Serono. Dr Forde has no disclosures to report.

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