

First-line treatment of EGFR-mutant non-small-cell lung cancer: the role of erlotinib and other tyrosine kinase inhibitors

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Abstract: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) were initially established as second- or third-line treatment of advanced non-small-cell lung cancer (NSCLC). Subsequent studies, including IPASS, OPTIMAL, and EURTAC, have demonstrated that these TKIs are effective first-line therapeutic options in patients with tumors harboring activating mutations in the *EGFR* gene. The TKIs are better tolerated than conventional chemotherapy, with frequent yet mild side effects such as rash and diarrhea, and rarely interstitial lung disease. Because most patients on TKIs develop resistance due to a variety of mechanisms, the use of TKIs in the acquired-resistance setting and in the setting of earlier-staged cancers is being extensively studied. Here we review the major trials leading to the established use of EGFR TKIs in NSCLC, followed by discussion of recently completed and ongoing trials using the next-generation EGFR inhibitor afatinib.

Keywords: epidermal growth factor receptor, non-small-cell lung cancer, tyrosine kinase inhibitor, epidermal growth factor receptor mutation

Introduction

Lung cancer remains the leading cause of cancer-related deaths in the United States, estimated to be responsible for over 160,000 deaths in 2012,¹ and worldwide lung cancer causes 1.3 million deaths per year.² Non-small-cell lung cancer (NSCLC) comprises about 85% of all lung cancers.¹ While treatment advances have been made over the last 20 years, the prognosis for patients with advanced NSCLC remains poor. The recommended first-line therapy of a platinum-based doublet for advanced NSCLC has a response rate of only approximately 20% and a median overall survival (OS) of 8–10 months.³ The addition of bevacizumab to a platinum-based chemotherapy doublet increases the median OS to slightly over 12 months.⁴ The second-line chemotherapeutic agents of docetaxel and pemetrexed have response rates of only 8%–9% with progression-free survival of less than 3 months.⁵

Given the absence of a durable response to treatment for advanced NSCLC, targeted therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were greeted with much excitement in the middle of the last decade. The TKIs erlotinib and gefitinib went on to gain conditional approval as second- and third-line therapies in unselected patients with NSCLC, but only erlotinib secured continued approval for use in the United States. In this paper, we review the role of erlotinib and other EGFR TKIs in the treatment of NSCLC, focusing on more recent data on the efficacy of these drugs in the first-line setting. We also review the side effects of the TKIs and the challenges associated with treatment, such as acquired resistance.

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Epidermal growth factor receptor as the target

Studies from the late 1990s and early 2000s have shown that overexpression of the EGFR, which is involved in a signal-transduction network central to many cellular processes, is commonly seen in NSCLC.^{6,7} Therefore, EGFR became the target of new drugs in the 1990s. Gefitinib, developed by AstraZeneca, and erlotinib, developed by OSI Pharmaceuticals, were two small-molecule EGFR TKIs that inhibit the binding of adenosine triphosphate (ATP) and prevent downstream signaling. In the phase II IDEAL 1 trial, gefitinib as second- or third-line therapy for advanced NSCLC had tumor response rates around 18% and symptom improvements in more than two-thirds of patients.⁸ In another phase II trial, gefitinib, as third-line therapy for advanced NSCLC, was associated with partial radiographic responses in 12% of patients receiving 250 mg daily and 9% of patients receiving 500 mg daily. Almost all patients with radiographic responses reported improved symptoms.⁹ The initial clinical data on erlotinib were also exciting, with a phase II study showing that erlotinib had a response rate of about 12% in previously treated NSCLC patients.¹⁰ Interestingly, this study revealed that EGFR protein-staining intensity by immunohistochemistry was not predictive of survival on the drug but that there was a correlation between the presence of a rash and survival. These early results prompted further studies to examine whether gefitinib and erlotinib could prolong survival.

The landmark BR.21 trial, published in 2005, showed that erlotinib improved length of life. In this study, patients with stage IIIB or IV NSCLC who had received one or two prior chemotherapy regimens were randomized to erlotinib 150 mg daily or placebo. The response rate was 8.9% for erlotinib and less than 1% for placebo. OS for the erlotinib group was 6.7 months compared with 4.7 months in the placebo group, and erlotinib was approved by the US Food and Drug Administration (FDA) as a result.¹¹ A similar study for gefitinib as second- or third-line treatment for patients with locally advanced or metastatic NSCLC, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial, failed to demonstrate a survival advantage for gefitinib over best supportive care, leading to a restriction of the FDA approval for gefitinib to patients who had previously achieved clinical benefit. One potential explanation is that the patients included in this trial had very poor prognosis compared to those in the BR.21 trial. Interestingly, in the ISEL trial, gefitinib was associated with better median survival in the prespecified subgroups of never smokers (8.9 months versus 6.1 months)

and Asians (9.5 months versus 5.5 months).¹² These subgroup differences, together with the observation that a few individual patients achieved extraordinary tumor responses, motivated researchers to investigate the molecular basis of response to EGFR TKI therapy.

Surprisingly, a number of groups reported simultaneously that these responses correlated strongly with somatic mutations in the *EGFR* gene within the tumors. Researchers at Massachusetts General Hospital found that there were somatic mutations in the tyrosine kinase domain of *EGFR* in eight of the nine patients who responded to gefitinib, while these mutations were absent in all of the seven patients with no response.¹³ Their colleagues at the Dana-Farber Cancer Institute also found *EGFR* mutations in gefitinib responders and no *EGFR* mutations in nonresponders.¹⁴ In adenocarcinoma tumor samples from never smokers, a Memorial Sloan-Kettering group similarly identified *EGFR* mutations that were associated with sensitivity to gefitinib and erlotinib.¹⁵ These *EGFR* mutations activate the EGFR signaling pathway that promotes survival, and commonly include exon 19 deletions or the L858R point mutation on exon 21. It is thought that lung adenocarcinomas that have these “driver” *EGFR* mutations are “oncogene-addicted” to the EGFR pathway; hence their sensitivity to EGFR tyrosine kinase inhibition.^{14,16–18} A meta-analysis showed that activating *EGFR* mutations were associated with a 67% response rate, time to progression of 11.8 months, and OS of 23.9 months.¹⁹

EGFR TKIs in the first-line setting

Studies have identified *EGFR* mutations to be present in about 15% of NSCLC in the Western population and approximately 50% in the Asian population.^{20–23} The two most common mutations, accounting for 90%, are exon 19 deletions (50%) and L858R point mutations (40%), with a variety of other mutations such as exon 20 insertions, G719X, L861Q, and de novo T790M comprising the remainder.²⁰ Other characteristics associated with the presence of *EGFR*-mutation status are no or light history of smoking, female sex, and adenocarcinoma histology.^{20,21,24} Interestingly, there was no observed benefit for the EGFR TKIs when added to first-line chemotherapy in unselected NSCLC patients,^{25–28} and mutation status was never determined for the majority of patients in these studies. However, those patients who were never smokers generally appeared to have a survival benefit with these TKIs. Based on this observation, subsequent studies attempted to examine the efficacy of EGFR TKIs as first-line therapy in selected patients, either clinically by smoking status or molecularly by *EGFR*-mutation status.

The Iressa Pan-Asia Study (IPASS) randomized 1217 previously untreated, never-smoker or former light-smoker patients with advanced pulmonary adenocarcinoma to gefitinib or carboplatin plus paclitaxel. At 12 months, the rate of progression-free survival (PFS) with gefitinib was 25%, while that with carboplatin plus paclitaxel was 7%. About one-third of the patients had known *EGFR*-mutation status, and of these about 60% were positive for *EGFR* mutations. Among those with activating *EGFR* mutations, PFS was longer in the gefitinib group (hazard ratio for progression, 0.48; 95% confidence interval, 0.36–0.64; $P < 0.001$). Among those with wild-type *EGFR*, PFS was shorter in the gefitinib group compared to the carboplatin–paclitaxel group (hazard ratio for progression, 2.85; 95% confidence interval, 2.05–3.98; $P < 0.001$). OS, however, was not statistically different between gefitinib and chemotherapy.^{22,23}

Another phase III study examining the role of EGFR TKIs as first-line therapy is the First-SIGNAL trial, in which 313 Korean never smokers with advanced lung adenocarcinoma were randomized to gefitinib or cisplatin and gemcitabine. Similar to the IPASS study, PFS was superior for gefitinib, but OS was similar in both groups. PFS was 16.7% at 1 year in the gefitinib group, compared to 2.8% at 1 year for the chemotherapy group. The median OS of the gefitinib group was 22.3 months versus 22.9 months for the chemotherapy group. However, about 75% of patients on the chemotherapy arm eventually crossed over to gefitinib, diluting any difference in OS between the two groups.²⁹

In the US, the phase II CALGB 30406 study randomized 181 never smokers or former light smokers or patients with *EGFR*-mutant tumors to erlotinib or erlotinib plus carboplatin and paclitaxel as first-line treatment. PFS was similar in both groups: 5.0 months for erlotinib versus 6.6 months for erlotinib plus chemotherapy ($P = 0.1988$). The difference in OS was not statistically significant in the two arms: 24.6 months for erlotinib monotherapy versus 19.8 months for erlotinib plus chemotherapy. Not surprisingly, the subgroup of patients with activating *EGFR* mutations had the greatest benefit from treatment in both arms. In the erlotinib monotherapy group, OS was 31.3 months for mutant *EGFR* compared to 18.1 months for wild-type *EGFR*. Similarly in the erlotinib–chemotherapy group, OS was 38.1 months for mutant *EGFR* versus 14.4 months for wild-type *EGFR*. However, within the *EGFR*-mutant subpopulation, there was no difference in response rate, PFS, or OS between the two treatment arms.³⁰

A number of other Asian trials selected only patients with *EGFR* mutations and compared EGFR TKIs

with chemotherapy. The West Japan Thoracic Oncology Group 3405 trial randomized 177 treatment-naïve patients with stage IIIB or IV *EGFR*-mutant NSCLC to gefitinib or cisplatin plus docetaxel. The gefitinib group had a mean PFS of 9.2 months versus 6.3 months for the chemotherapy group.³¹ Updated OS rates were reported at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO): a median 36 months for gefitinib versus 39 months for cisplatin and docetaxel, with the difference not statistically significant.³² The similar OS rates were likely due to the high crossover rate (91%) from the chemotherapy arm to the gefitinib arm. The North-East Japan Study Group similarly randomized 230 treatment-naïve patients with stage IV *EGFR*-mutant NSCLC to gefitinib or carboplatin–paclitaxel. The median PFS for gefitinib was higher: 10.8 months versus 5.4 months in the chemotherapy group.³³

The OPTIMAL trial from China was the first to use erlotinib to demonstrate a similar PFS benefit for first-line TKI compared with carboplatin–gemcitabine – 13.1 months versus 4.6 months – in patients with activating *EGFR* mutations.³⁴ The recently reported OS was similar in both arms.³⁵

The benefit of TKIs as first-line therapy in *EGFR*-mutant adenocarcinoma in Asian patients has recently been duplicated in European patients. In the EURTAC trial, 174 patients who had *EGFR* mutations and who had never received chemotherapy for metastatic disease were randomized to either erlotinib or a platinum-based doublet. The chemotherapy regimens were a platinum agent (cisplatin or carboplatin) plus a second drug (docetaxel or gemcitabine). The median PFS was 9.7 months in the erlotinib group versus 5.2 months in the chemotherapy group.^{36,37} Median OS did not differ significantly between the two groups: 19.3 months for erlotinib and 19.5 months for chemotherapy.

These pivotal trials examining erlotinib or gefitinib as first-line therapy are summarized in Table 1. As a result of these studies of TKIs in the first-line setting for NSCLC patients with *EGFR* mutations, the European Medicines Agency has expanded the label of erlotinib to include first-line therapy for patients with advanced *EGFR*-mutant NSCLC.³⁸ In the US, the National Comprehensive Cancer Network has similar recommendations for erlotinib in its guidelines for NSCLC, but FDA approval has not yet been granted for this indication.³⁹ Barriers to the use of first-line EGFR TKIs for patients include the availability of rapid tumor testing, with turnaround times often ranging from 1 to 4 weeks, and the availability of adequate tumor tissue from the initial diagnostic sample sometimes lacking. This can lead to the difficult dilemma of repeat biopsy versus

Table 1 Selected phase III and randomized phase II studies involving EGFR tyrosine kinase inhibitors as first-line treatment in advanced pulmonary adenocarcinoma

Study	Patient population	Treatments	Median OS (in months)		Median PFS (in months)		
			All	Activating EGFR mutations	All	WT EGFR	Activating EGFR mutations
IPASS ^{22,23}	Asian never smokers or former light smokers	Gefitinib vs carboplatin/paclitaxel	18.8 vs 17.4; HR = 0.90 (95% CI: 0.79–1.02); P = 0.109	21.6 vs 21.9; HR = 1.00 (95% CI: 0.76–1.33); P = 0.990	5.7 vs 5.8; HR = 0.74 (95% CI: 0.65–0.85)	11.2 vs 12.7; HR = 1.18 (95% CI: 0.86–1.63); P = 0.309	HR = 0.48 (95% CI: 0.36–0.64)
First-SIGNAL ²⁹	Asian never smokers	Gefitinib vs cisplatin/gemcitabine	22.3 vs 22.9; HR = 0.932 (95% CI: 0.716–1.213); P = 0.604	27.2 vs 25.6; HR = 1.043 (95% CI: 0.498–2.182)	5.8 vs 6.4; HR = 1.198 (95% CI: 0.944–1.520); P = 0.138	18.4 vs 21.9; HR = 1.000 (95% CI: 0.523–1.911)	8.0 vs 6.3; HR = 0.544 (95% CI: 0.269–1.100); P = 0.086
CALGB 30406 ³⁰	Mostly Caucasian never smokers or former light smokers or patients with activating EGFR mutations	Erlotinib vs erlotinib/cisplatin/paclitaxel	24.6 (95% CI: 18.4–33.8) vs 19.8 (95% CI: 14.4–27.8)	31.3 (95% CI: 23.8–NA) vs 38.1 (95% CI: 19.6–NA)	5.0 (95% CI: 2.9–7.0) vs 6.6 (95% CI: 5.4–8.2)	18.1 (95% CI: 9.5–27.8) vs 14.4 (95% CI: 8.7–20.2)	2.6 (95% CI: 1.4–3.9) vs 4.8 (95% CI: 2.8–5.6)
WJTOG3405 ^{31,32}	Japanese patients with exon 19 del or L858R EGFR mutations	Gefitinib vs cisplatin/docetaxel	36 (95% CI: 26.3–NA) vs 39 (95% CI: 31.2–NA); HR = 1.185 (95% CI: 0.767–1.829)	30.5 vs 23.6; P = 0.31	9.2 (95% CI: 8.0–13.9) vs 6.3 (95% CI: 5.8–7.8); HR = 0.489 (95% CI: 0.336–0.710); P < 0.0001		
NEJSG ³³	Japanese patients with activating EGFR mutations	Gefitinib vs carboplatin/paclitaxel	Absolute median OS not reported; HR = 1.065; P = 0.6849		10.8 vs 5.4; HR = 0.30 (95% CI: 0.22–0.41); P < 0.0001		
CTONG 0802 (OPTIMAL) ^{34,35}	Chinese patients with activating EGFR mutations	Erlotinib vs carboplatin/gemcitabine	19.3 (95% CI: 14.7–26.8) vs 19.5 (95% CI: 16.1–NA); HR 1.04 (95% CI: 0.65–1.68); P = 0.87		13.1 (95% CI: 10.58–16.53) vs 4.6 (95% CI: 4.21–5.42); HR = 0.16 (95% CI: 0.10–0.26); P < 0.0001		
EURTAC ³⁶	European patients with activating EGFR mutations	Erlotinib vs platinum-based doublet	Ongoing		9.7 (95% CI: 8.4–12.3) vs 5.2 (95% CI: 4.4–5.8); HR = 0.37 (95% CI: 0.25–0.54); P < 0.0001		
LUX-Lung 3 ⁶⁷	European and Asian patients with activating EGFR mutations	Afatinib vs cisplatin/pemetrexed	Ongoing		11.1 vs 6.9; HR = 0.58 (95% CI: 0.43–0.78); P = 0.0004		

Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; WT, wild-type; NA, not available.

“empiric” treatment with chemotherapy or even an EGFR TKI, despite the inferior efficacy in *EGFR*-wild-type patients, and the treatment decision often depends on the clinician’s estimation of the likelihood of an *EGFR* mutation.

Side effects and quality of life on EGFR TKI treatment

In the previously mentioned studies in this review, erlotinib and gefitinib have been shown to have more tolerable side effects than conventional chemotherapy. In the recent EURTAC trial, for example, the rate of neutropenia was zero in the erlotinib group compared to 22% in the chemotherapy group. Six percent of the patients on erlotinib had severe adverse events compared to 20% on chemotherapy.³⁶

Rash is the most common side effect of the EGFR TKIs. The BR.21 trial reported that about 76% of patients on erlotinib developed any rash and about 9% had a grade 3 rash.¹¹ In the EURTAC trial, 13% of patients on erlotinib had grade 3 or 4 rash. In the IPASS study, about 66% of patients on erlotinib had a rash. The presence of the TKI-associated rash has been shown to correlate with response to the TKIs and/or overall survival.^{40,41} However, the burden of this dermatologic adverse drug reaction is not insignificant. Diarrhea is the second most common side effect: the BR.21 trial also reported that 55% of patients on erlotinib had diarrhea, compared to 19% of patients on placebo, and in the IPASS study, 47% of patients on erlotinib developed diarrhea, though the majority were grade 1 or 2. A much less frequent yet potentially lethal side effect of the EGFR TKIs is pulmonary toxicity, usually manifested as interstitial lung disease (ILD)/interstitial pneumonitis. Japanese researchers found that the observed incidence rate of ILD over 12 weeks was 4% for gefitinib versus 2.1% for chemotherapy.⁴² In the ISEL trial, however, the frequency of ILD symptoms reported by patients on gefitinib was similar to that in the placebo group.¹² Across an international group of patients treated in the phase IV erlotinib study, ILD was reported in only 0.1% of patients.⁴³ However, the incidence might have been underestimated because of the difficulty of distinguishing ILD symptoms from progressing disease.

The early phase II studies on gefitinib and erlotinib showed that a significant percentage of patients on these TKIs reported improved symptoms, often associated with objective tumor response.^{9,10} In the IPASS study, significantly more patients receiving gefitinib than those receiving carboplatin–paclitaxel had a clinically relevant improvement in quality of life as per the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire. Not surprisingly,

this benefit of gefitinib is restricted to patients with *EGFR*-mutant adenocarcinoma.²²

The EGFR TKIs have also been found to have tolerable toxicity profile in elderly patients. A Japanese study examined 71 patients at least 70 years old who received gefitinib as first-line therapy for advanced NSCLC. There was no difference in the rate of toxicities in the elderly patients compared to younger patients.⁴⁴

Resistance to erlotinib

Although the response rate to EGFR TKI is approximately 80% in *EGFR*-mutant patients, PFS is only about 1 year, as most patients eventually develop acquired resistance to the TKIs.⁴⁵ The two main mechanisms of acquired resistance include the secondary mutation T790M and *MET* amplification.

In 2005, researchers identified the T790M gatekeeper mutation, where threonine is replaced by methionine at position 790 in the *EGFR* gene, in biopsies from patients whose lung cancer had progressed after having initially responded to an EGFR TKI.^{46,47} In vitro studies show that T790M confers resistance to gefitinib,^{46,48} possibly by increasing EGFR’s affinity for ATP, thus decreasing the binding of the ATP-competitive TKI.⁴⁹

While T790M is found in about half of patients with acquired resistance to erlotinib and gefitinib, the other mechanism of resistance – *MET* amplification – makes up about 5%–10% of these patients. There is a significant overlap of these two mechanisms, as about half of the patients with *MET* amplification also had the T790M mutation.^{50,51} It is theorized that *MET* activates an AKT-mediated signaling pathway that bypasses the inhibited EGFR, a process dubbed “bypass track activation.” In vitro inhibition of *MET* restores sensitivity to EGFR TKIs.⁵⁰ *MET* amplification and T790M are not the only known mechanisms of acquired resistance to EGFR TKIs. Other secondary mutations implicated in conferring resistance include D761Y,⁵² T854A,⁵³ and L747S.⁵⁴ These mutations might change the conformation of EGFR, decreasing binding affinity to the TKIs.⁵⁴ *EGFR* amplification and mutations in the *PIK3CA* gene have also been found in tumor biopsies of patients with EGFR-TKI-resistant lung cancer.⁵⁵ And surprisingly, some TKI-resistant tumors have been found to have transformed from NSCLC to small-cell lung cancer, or have undergone an epithelial–mesenchymal transition which may similarly confer histological resistance through unclear mechanisms.⁵⁵

Currently, the best management of patients with acquired resistance to EGFR TKIs remains unclear.

While chemotherapy is the only approved systemic treatment in this setting, researchers continue to examine the role of TKIs, with their generally more tolerable side effects, in this palliative setting. Switching between erlotinib and gefitinib is rarely successful. Only about 20%–30% patients who developed resistance to gefitinib had disease control with erlotinib.^{45,56} However, after intervening therapies and/or a TKI-free period, it is reasonable to consider an EGFR TKI retreatment. There exists evidence that the genetic mechanisms of acquired resistance can be lost in the absence of selective pressure from TKIs.⁵⁵ At the 2012 ASCO Annual Meeting, it was reported that in a series of 19 patients who developed resistance to erlotinib or gefitinib received one to four intervening chemotherapy regimens, then were re-treated with a TKI; four patients (21%) progressed, while 14 (74%) had stable disease for at least 1 month, with median PFS of 4.4 months.⁵⁷ In another small series of ten patients, re-treating with erlotinib led to an improvement in symptoms and a modest decrease in fluorodeoxyglucose positron emission tomography uptake of the tumors.⁵⁸ Even continuing TKI despite acquired resistance is a palliative treatment option that can be considered. In a case series of 19 patients who had disease progression by RECIST but were relatively asymptomatic, erlotinib was continued, and these patients had a median post-progression of disease survival of 29 months.⁵⁹ Even when systemic chemotherapy is started to treat TKI-resistant tumors, the concurrent use of TKIs might lead to a better response rate than chemotherapy alone. Goldberg and colleagues reviewed 78 patients who developed resistance on TKIs, 34 of whom subsequently received chemotherapy plus erlotinib and 44 received chemotherapy alone. The response rate for chemotherapy plus erlotinib was 41% versus 18% for chemotherapy alone, although there was no statistically significant difference in PFS or OS.⁶⁰

However, a more effective strategy to overcome acquired resistance to the first-generation EGFR TKIs is to use one of the several second-generation TKIs currently in clinical trials. While other next-generation TKIs are also in clinical trials and have been reviewed elsewhere,^{61,62} one frontrunner is afatinib (BIBW2992), an irreversible ErbB family inhibitor that has been shown to suppress the kinase activity of wild-type and activated EGFR, including erlotinib-resistant isoforms. Afatinib suppresses transformation in isogenic cell-based assays, inhibits survival of cancer cell lines and induces tumor regression in xenograft and transgenic lung cancer models carrying the L858R-T790M construct.⁶³

The most exciting clinical trial of afatinib in the acquired-resistance setting is a phase Ib study in the US and

The Netherlands. Patients who had progressed on erlotinib or gefitinib were given afatinib and cetuximab, a monoclonal antibody against EGFR. Approximately 94% of patients, regardless of T790M mutation status, had a partial response or stable disease.⁶⁴ Afatinib monotherapy has also been tested in several clinical trials. The LUX-Lung 1 trial compared afatinib versus placebo in patients with advanced, metastatic NSCLC after failure of erlotinib/ gefitinib and one or two lines of chemotherapy. The median PFS in the afatinib was 3.3 months versus 1.1 months ($P < 0.0001$), with no difference in overall survival.⁶⁵ The LUX-Lung 2 phase 2 clinical trial narrowed the study population to patients with *EGFR* mutations at stage IIIB or IV who had zero or one previous chemotherapy regimen. Sixty percent of the 129 patients, 61 of whom had the afatinib as a first-line treatment, had an objective response: two complete responses and 77 partial responses.⁶⁶ To further examine the efficacy of afatinib in never-treated patients, the phase III LUX-Lung 3 trial was conducted, with results recently announced at the ASCO 2012 Annual Meeting. A total of 345 untreated patients with advanced adenocarcinoma with activating *EGFR* mutations were randomized in a 2:1 ratio to afatinib versus cisplatin and pemetrexed. Patients receiving afatinib had a statistically significant superior median PFS of 11.1 months versus 6.9 months for the chemotherapy group. Afatinib resulted in significant side effects, however. Up to 95% of patients on afatinib experienced diarrhea – 14.4% had grade 3 diarrhea – and 62% of patients experienced rash. Nevertheless, patients on afatinib reported better quality of life, measured by EORTC QLQ C-30, compared to those on cisplatin and pemetrexed.⁶⁷ Given the promising results of this pivotal trial, afatinib is now being compared head-to-head with gefitinib as first-line treatment in patients with stage IIIB or IV lung adenocarcinoma with *EGFR* activating mutations (NCT01466660).

Conclusion

The discovery of TKIs of EGFR as effective therapy, both as first and subsequent lines of therapy, ushered in the era of personalized medicine in lung cancer management. Instead of palliative cytotoxic chemotherapy, patients with activating *EGFR* mutations now have the option of taking an oral antineoplastic pill with relatively tolerable side effects and a longer life expectancy. However, acquired resistance to these TKIs remains a challenging problem. Several next-generation EGFR TKIs are in development that might overcome resistance to first-generation TKIs or provide alternative options in the first-line setting. These targeted therapeutic agents may

one day transform advanced lung cancer from a terminal disease with only months of expected survival into a chronic illness to be managed over years.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.
3. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346(2):92–98.
4. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542–2550.
5. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22(9):1589–1597.
6. Rusch V, Klimstra D, Venkatraman E, Pisters PW, Langenfeld J, Dmitrovsky E. Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor alpha is frequent in resectable non-small cell lung cancer but does not predict tumor progression. *Clin Cancer Res*. 1997;3(4):515–522.
7. Brabender J, Danenberg KD, Metzger R, et al. Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival. *Clin Cancer Res*. 2001;7(7):1850–1855.
8. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL 1 Trial) [corrected]. *J Clin Oncol*. 2003;21(12):2237–2246.
9. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA*. 2003;290(16):2149–2158.
10. Pérez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol*. 2004;22(16):3238–3247.
11. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123–132.
12. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005;366(9496):1527–1537.
13. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129–2139.
14. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497–1500.
15. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA*. 2004;101(36):13306–13311.
16. Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. *Cancer Cell*. 2006;9(6):485–495.
17. Politi K, Zakowski MF, Fan PD, Schonfeld EA, Pao W, Varmus HE. Lung adenocarcinomas induced in mice by mutant EGF receptors found in human lung cancers respond to a tyrosine kinase inhibitor or to down-regulation of the receptors. *Genes Dev*. 2006;20(11):1496–1510.
18. Sequist LV, Bell DW, Lynch TJ, Haber DA. Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. *J Clin Oncol*. 2007;25(5):587–595.
19. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res*. 2009;15(16):5267–5273.
20. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009;361(10):958–967.
21. D’Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J Clin Oncol*. 2011;29(15):2066–2070.
22. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947–957.
23. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29(21):2866–2874.
24. Pham D, Kris MG, Riely GJ, et al. Use of cigarette-smoking history to estimate the likelihood of mutations in epidermal growth factor receptor gene exons 19 and 21 in lung adenocarcinomas. *J Clin Oncol*. 2006;24(11):1700–1704.
25. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 1. *J Clin Oncol*. 2004;22(5):777–784.
26. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 2. *J Clin Oncol*. 2004;22(5):785–794.
27. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2005;23(25):5892–5899.
28. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol*. 2007;25(12):1545–1552.
29. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30(10):1122–1128.
30. Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 Trial. *J Clin Oncol*. 2012;30(17):2063–2069.
31. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121–128.
32. Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol*. 2012;30 Suppl:abstr 7521.
33. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380–2388.

34. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.
35. Zhou C, Wu YL, Chen G, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2012;30 Suppl:abstr 7520.
36. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EORTC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239–246.
37. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: interim results of the European Erlotinib Versus Chemotherapy (EORTC) phase III randomized trial. *J Clin Oncol*. 2011;29 Suppl:abstr 7503.
38. European Medicines Agency. Tarceva: EPAR product information. London: European Medicines Agency; 2011.
39. National Comprehensive Cancer Network. NCCN guidelines: non-small cell lung cancer. Fort Washington: National Comprehensive Cancer Network; 2012.
40. Pérez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol*. 2005;23(22):5235–5246.
41. Wacker B, Nagrani T, Weinberg J, et al. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. *Clin Cancer Res*. 2007;13(13):3913–3921.
42. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med*. 2008;177(12):1348–1357.
43. Reck M, van Zandwijk N, Gridelli C, et al. Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. *J Thorac Oncol*. 2010;5(10):1616–1622.
44. Narumi S, Inoue A, Morikawa N, et al. First-line gefitinib for elderly patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR mutations: a combined analysis of NEJ studies. *J Clin Oncol*. 2012;30 Suppl:abstr 7563.
45. Costa DB, Nguyen KS, Cho BC, et al. Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. *Clin Cancer Res*. 2008;14(21):7060–7067.
46. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352(8):786–792.
47. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2(3):e73.
48. Kobayashi S, Ji H, Yuza Y, et al. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. *Cancer Res*. 2005;65(16):7096–7101.
49. Yun C-H, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008;105(6):2070–2075.
50. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316(5827):1039–1043.
51. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci U S A*. 2007;104(52):20932–20937.
52. Balak MN, Gong Y, Riely GJ, et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin Cancer Res*. 2006;12(21):6494–6501.
53. Bean J, Riely GJ, Balak M, et al. Acquired resistance to epidermal growth factor receptor kinase inhibitors associated with a novel T854A mutation in a patient with EGFR-mutant lung adenocarcinoma. *Clin Cancer Res*. 2008;14(22):7519–7525.
54. Costa DB, Halmos B, Kumar A, et al. BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. *PLoS Med*. 2007;4(10):1669–1679; discussion 1680.
55. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26.
56. Vasile E, Tibaldi C, Falcone A. Is erlotinib really active after failure of gefitinib in advanced non-small-cell lung cancer patients? *Ann Oncol*. 2009;20(4):790–791.
57. Heon S, Nishino M, Goldberg SB, et al. Response to EGFR tyrosine kinase inhibitor (TKI) retreatment after a drug-free interval in EGFR-mutant advanced non-small cell lung cancer (NSCLC) with acquired resistance. *J Clin Oncol*. 2012;30 Suppl:abstr 7525.
58. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res*. 2007;13(17):5150–5155.
59. Oxnard GR, Lo P, Jackman DM, et al. Delay of chemotherapy through use of post-progression erlotinib in patients with EGFR-mutant lung cancer. *J Clin Oncol*. 2012;30 Suppl:abstr 7547.
60. Goldberg SB, Oxnard GR, Digumarthy S, et al. Chemotherapy with erlotinib or chemotherapy alone in advanced NSCLC with acquired resistance to EGFR tyrosine kinase inhibitors (TKI). *J Clin Oncol*. 2012;30 Suppl:abstr 7524.
61. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. *Clin Lung Cancer*. 2009;10(4):281–289.
62. Soria JC, Mok TS, Cappuzzo F, Jänne PA. EGFR-mutated oncogene-addicted non-small cell lung cancer: current trends and future prospects. *Cancer Treat Rev*. 2011;38(5):416–430.
63. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008;27(34):4702–4711.
64. Horn L, Groen HJM, Smit EF, et al. Activity and tolerability of combined EGFR targeting with afatinib (BIBW 2992) and cetuximab in T790M+ non-small cell lung cancer patients. In: *Proceedings of the 14th World Conference on Lung Cancer*; July 3–7, 2011; Amsterdam, Netherlands. New York: Millennium Medical Publishing, Inc; 2011.
65. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol*. 2012;13(5):528–538.
66. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol*. 2012;13(5):539–548.
67. Yang JC, Schuler MH, Yamamoto N, et al. LUX-Lung 3: a randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. *J Clin Oncol*. 2012; 30 Suppl:abstr LBA7500.

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