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, and worldwide lung cancer causes 1.3 million deaths per year. Non-small-cell lung cancer (NSCLC) comprises about 85% of all lung cancers. 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. The addition of bevacizumab to a platinum-based chemotherapy doublet increases the median OS to slightly over 12 months. 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.

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.
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. 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 I 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. 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. 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. 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 IIB 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. 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). 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. Their colleagues at the Dana-Farber Cancer Institute also found EGFR mutations in gefitinib responders and no EGFR mutations in nonresponders. 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. 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. 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.

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. 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. Other characteristics associated with the presence of EGFR-mutation status are no or light history of smoking, female sex, and adenocarcinoma histology. Interestingly, there was no observed benefit for the EGFR TKIs when added to first-line chemotherapy in unselected NSCLC patients, 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.

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.

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.

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 IIB 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. 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. 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.

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. The recently reported OS was similar in both arms.

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. 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. 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. 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>
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<td><strong>IPASS</strong>&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>Asian never smokers or former light smokers</td>
<td>Gefitinib vs carboplatin/paclitaxel</td>
<td>18.8 vs 17.4; HR = 0.90 (95% CI: 0.79–1.02);</td>
<td>11.1 vs 12.7; HR = 1.18 (95% CI: 0.86–1.63);</td>
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<td>P = 0.109</td>
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<td><strong>First-SIGNAL</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Asian never smokers</td>
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<td>18.4 vs 21.9; HR = 1.00 (95% CI: 0.944–1.520);</td>
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<td>P = 0.604</td>
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<td><strong>CALGB 30406</strong>&lt;sup&gt;30&lt;/sup&gt;</td>
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<td>HR = 1.185 (95% CI: 0.767–1.829);</td>
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<td>30.5 vs 23.6;</td>
<td>10.8 vs 5.4; HR = 0.30 (95% CI: 0.22–0.41);</td>
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<td>P = 0.31</td>
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<td>13.1 (95% CI: 10.58–16.53) vs 4.6 (95% CI: 4.21–5.42);</td>
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<td>HR = 1.065;</td>
<td>HR = 0.16 (95% CI: 0.10–0.26);</td>
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<td><strong>EURTAC</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>European patients with activating EGFR mutations</td>
<td>Erlotinib vs platinum-based doublet</td>
<td>19.3 (95% CI: 14.7–26.8) vs 19.5 (95% CI: 16.1–NA);</td>
<td>9.7 (95% CI: 8.4–12.3) vs 5.2 (95% CI: 4.4–5.8);</td>
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<td>HR = 1.04 (95% CI: 0.65–1.68);</td>
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<td>P = 0.87</td>
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<td><strong>LUX-Lung 3</strong>&lt;sup&gt;37&lt;/sup&gt;</td>
<td>European and Asian patients with activating EGFR mutations</td>
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<td>11.1 vs 6.9; HR = 0.58 (95% CI: 0.43–0.78);</td>
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**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.

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. 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. 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. In the ISEL trial, however, the frequency of ILD symptoms reported by patients on gefitinib was similar to that in the placebo group. Across an international group of patients treated in the phase IV erlotinib study, ILD was reported in only 0.1% of patients. 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. 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.

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.

**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. 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. In vitro studies show that T790M confers resistance to gefitinib, possibly by increasing EGFR’s affinity for ATP, thus decreasing the binding of the ATP-competitive TKI.

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. 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. 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 and T854A and L747S. These mutations might change the conformation of EGFR, decreasing binding affinity to the TKIs. EGFR amplification and mutations in the PIK3CA gene have also been found in tumor biopsies of patients with EGFR-TKI-resistant lung cancer. 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.

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.\textsuperscript{45,58} However, after intervening therapies and/or a TKI-free period, it is reasonable to consider an EGFR TKI retreat. There exists evidence that the genetic mechanisms of acquired resistance can be lost in the absence of selective pressure from TKIs.\textsuperscript{59} 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.\textsuperscript{37} 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.\textsuperscript{39} 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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