The use of EGFR tyrosine kinase inhibitors in non-small-cell lung cancer (NSCLC)

Introduction

Patients with non-small-cell lung cancer (NSCLC) represent a heterogeneous population, making disease management challenging; however, increased understanding of the molecular pathogenesis of the disease has paved the way for new treatments using molecularly targeted anti-cancer agents. Currently, the most established target is the epidermal growth factor receptor (EGFR), a member of the ErbB kinase family of structurally related receptor tyrosine kinases. In humans, the ErbB family consists of EGFR (HER1, ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3) and HER4 (ErbB4). ErbB proteins play a number of key roles in the regulation of cellular proliferation, and their dysregulation has been identified in a variety of cancers. For example, somatic mutations of EGFR have been reported in approximately 50% of Asian patients and 10–15% of Caucasian patients with lung adenocarcinoma, with the most common mutations being exon 19 deletions (Del19) and an L858R point mutation (L858R). Importantly, in a phenomenon known as ‘oncogene addiction’, tumors bearing EGFR mutations have been observed to become dependent on EGFR signaling pathways for their survival and growth.
Four EGFR tyrosine kinase inhibitors (TKIs; erlotinib, gefitinib, afatinib and osimertinib) are currently available for the management of NSCLC, while others are in development. Of the available TKIs, erlotinib, gefitinib and afatinib are the first-line standard of care in patients with EGFR mutation-positive NSCLC, as supported by robust phase III data. Erlotinib and gefitinib were the earliest small-molecule inhibitors to be approved for NSCLC and are generally referred to as first-generation EGFR TKIs. These agents block receptor tyrosine kinase activity by reversibly binding at or near the adenosine triphosphate binding site on the intracellular kinase domain. Afatinib is a second-generation ErbB family blocker, which irreversibly blocks signaling from all relevant homo- and heterodimers of the ErbB family of receptors. Other second-generation EGFR TKIs, such as dacomitinib, are currently in development.

Despite the proven activity of EGFR TKIs in a first-line treatment setting, patients inevitably develop acquired resistance. The most common resistance mechanism, identified in at least 50–70% of tumors, proceeds through accumulation of the so-called ‘gatekeeper’ T790M mutation in exon 20 of EGFR. Osimertinib is a third-generation EGFR TKI with low selectivity for wild-type EGFR and high potency toward T790M. In the phase I/II AURA trial and subsequent phase III AURA 3 trial, osimertinib demonstrated striking efficacy, with response rates of approximately 60–70%, in patients with acquired resistance to erlotinib, gefitinib or afatinib and T790M-positive tumors, and is approved in this setting. Of note, only 7% of patients treated with osimertinib in AURA 3 were previously treated with afatinib. Osimertinib also showed promising results in a first-line setting; in an expansion cohort of AURA, an objective response rate (ORR) of 77% was achieved, with progression-free survival (PFS) of 19.3+ months, as well as manageable tolerability. On the basis of these findings, first-line osimertinib was recently assessed against gefitinib or erlotinib (but not afatinib) in the phase III FLAURA trial [ClinicalTrials.gov identifier: NCT02296125]. FLAURA achieved its primary endpoint of PFS; osimertinib was associated with a striking improvement of ~9 months in median PFS versus first-generation EGFR TKIs, thus positioning it as a first-line treatment option. However, mechanisms of resistance to osimertinib and treatment options following acquired resistance remain uncertain. Other third-generation EGFR TKIs currently in development include olmutinib (approved in South Korea), ASP8273, nazartinib, PF-06747775, avitinib and HS-10296.

With the currently approved EGFR TKIs, and the potential approval of additional agents in the future, it is important to understand the similarities and differences between these agents in order to determine the most appropriate intervention for each patient. It is also essential that mechanisms of resistance are understood so that the sequence of therapy can be tailored to the molecular evolution of the tumor. This article reviews the available clinical data in this regard, and discusses key considerations when assessing optimal sequential therapy with EGFR TKIs for the treatment of EGFR mutation-positive NSCLC.

Clinical trial data supporting the first-line use of EGFR TKIs in EGFR mutation-positive NSCLC

Phase III clinical trials versus chemotherapy
The use of first-line EGFR TKIs versus chemotherapy for patients with advanced EGFR mutation-positive NSCLC is supported by robust efficacy and tolerability data from numerous phase III trials, including the gefitinib trials, First-SIGNAL (subgroup analysis), IPASS (subgroup analysis), WJTOG3405, and NEJ002; the erlotinib trials, OPTIMAL, EURTAC, and ENSURE; and the afatinib trials, LUX-Lung 3 and LUX-Lung 6. Together, these trials unequivocally demonstrated that EGFR TKIs improve PFS versus platinum-based chemotherapy, with a median PFS of 9.2–11.1 months reported with EGFR TKIs across the trials compared with 4.6–6.9 months with platinum doublets.

As well as demonstrating efficacy benefits, EGFR TKIs were generally tolerable. Although they were associated with a class-related safety profile with characteristic adverse events (AEs), including gastrointestinal (e.g. diarrhea, stomatitis) and cutaneous (e.g. rash/acute) events, they were better tolerated than chemotherapy. Furthermore, AEs with EGFR TKIs were generally manageable, and led to treatment discontinuation in just 6–8%, 1–13% and 7–16% of patients treated with afatinib, erlotinib and gefitinib, respectively.

Despite the wealth of clinical trial data available, it is difficult to use the results from these studies
to judge which EGFR TKI might be most suitable for a particular patient because of the inherent difficulties of cross-trial comparisons. However, notwithstanding these limitations, it is noteworthy that afatinib, but not gefitinib or erlotinib, has demonstrated OS benefit in phase III trials. Patients with Del19-positive tumors treated with afatinib experienced significantly longer OS than those treated with chemotherapy [LUX-Lung 3, median 33.3 months with afatinib versus 21.1 months with chemotherapy (p = 0.0015); LUX-Lung 6, median 31.4 months versus 18.4 months with chemotherapy (p = 0.023)]. As the crossover rates from chemotherapy to afatinib in LUX-Lung 3 (74%) and LUX-Lung 6 (54%) were generally similar to the crossover rates in the erlotinib and gefitinib trials (74% on average), it is possible that the OS benefit with afatinib reflects potential efficacy advantages in targeting the entire ErbB family rather than just EGFR, although this requires confirmation in an appropriately powered randomized trial.

The recent exploratory phase IIb LUX-Lung 7 trial, which compared first-line afatinib and gefitinib, demonstrated a trend toward improved OS with afatinib versus gefitinib in both Del19 and L858R patient subgroups, although the trial was not powered to detect an OS difference. This trial is discussed further in the next section.

**Head-to-head trials of EGFR TKIs**

Until recently there has been a paucity of head-to-head trials that directly compared different TKIs in a first-line setting. Recent randomized clinical trials, however, have suggested that first- and second-generation TKIs are not interchangeable, although there does not appear to be any significant difference between first-generation EGFR TKIs. Likewise, recent data from the phase III FLAURA trial demonstrate that first-line osimertinib is superior to first-generation EGFR TKIs (but not necessarily second-generation TKIs). A number of other head-to-head trials are ongoing.

**Afinitinib versus gefitinib: LUX-Lung 7.** The phase IIb LUX-Lung 7 trial compared afatinib versus gefitinib in treatment-naive patients with EGFR mutation-positive (Del19 or L858R) NSCLC. The trial was exploratory in nature and no formal hypothesis was specified. Three clinically relevant coprimary endpoints were chosen: PFS by independent central review, OS and time to treatment failure (TTF; defined as time from randomization to treatment discontinuation for any reason including disease progression, treatment toxicity or death), with the latter endpoint chosen to reflect real-world clinical practice and treatment guidelines. In this trial, PFS and TTF were significantly longer with afatinib than with gefitinib [PFS median 11.0 months versus 10.9 months; hazard ratio (HR) 0.73, p = 0.017; Figure 1(a); TTF median 13.7 months versus 11.5 months; HR 0.73, p = 0.0073]. The longer PFS observed with afatinib compared to gefitinib was supported by the clinically relevant observation that the PFS curves clearly separate after the median, and a log-rank test, which does not compare median PFS but rather compares PFS across the entire Kaplan–Meier curve, showed significant differences between the overall curves. This distinction, and PFS advantage with afatinib over gefitinib, was exemplified by exploring the proportion of patients with a PFS event between the two treatments at different time-points; at 12 months [47.4% (95% CI 39.2–55.2) versus 41.3% (95% CI 33.0–49.5)], 18 months [27.3% (95% CI 20.2–34.9) versus 15.2% (95% CI 9.3–22.5)] and 24 months [17.6% (95% CI 11.7–24.6) versus 7.6% (95% CI 3.5–13.8)]. ORRs were observed in 70% of patients in the afatinib arm versus 56% in the gefitinib arm (p = 0.0083). Furthermore, although the trial was not powered to detect a difference in OS, there was a trend toward improved OS with afatinib versus gefitinib, although the findings were not statistically significant (median OS 27.9 months versus 24.5 months; HR 0.86; p = 0.2580). Extensive use of post-progression therapy is believed to have contributed to the lack of significant OS benefit in this study. It should also be noted that efficacy benefits with afatinib were consistent regardless of age, race, Eastern Cooperative Oncology Group (ECOG) performance status, and EGFR mutation type (Del19 and L858R).

Overall, the frequency and severity of all-cause AEs in the LUX-Lung 7 trial were similar in both arms and were consistent with previous studies. The most frequent drug-related grade ≥3 AEs in the afatinib arm were diarrhea (13%), rash or acne (9%) and fatigue (6%); in the gefitinib arm, the most frequent drug-related grade ≥3 AEs were elevated ALT/AST (9%) and rash/acne (3%). Four patients (3%) on gefitinib reported interstitial lung disease compared with no patients on afatinib. There was no difference in the frequency of discontinuations due to AEs (6% in
**Figure 1.** PFS in recent head-to-head trials: (a) Lux-Lung 7, (b) ARCHER 1050 and (c) FLAURA.

(a) Park K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase IIb, open-label, randomised controlled trial. *Lancet Oncol* 2016; 17(5): 577–589, with permission from Elsevier.

(b) Wu YL, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase III trial. *Lancet Oncol* 2017; pii: S1470-2045(17)30608-3.

(c) Soria JC, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2017. DOI: 10.1056/NEJMoa1713137.

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
each arm).³³ Low rates of treatment discontinuation were largely attributable to dose adjustments, facilitated by the availability of several dose strengths of afatinib. As with LUX-Lung 3 and LUX-Lung 6,³⁵ recent post-hoc analysis indicated that dose reductions effectively mitigated treatment-related AEs without compromising PFS benefits with afatinib.³⁶

**Gefitinib versus erlotinib: CTONG0901 and WJOG 5108L.** Few clinically relevant differences between gefitinib and erlotinib have been observed in clinical trials comparing the two agents.³⁷,³⁸ In the recent CTONG0901 trial, which compared the efficacy and safety of gefitinib and erlotinib in 256 patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC in any line, there was no significant difference in PFS (median 13.0 months versus 10.4 months, *p* = 0.108), ORR (56.3% versus 52.3%, *p* = 0.530) or OS (median 22.9 months versus 20.1 months, *p* = 0.250).³⁸

Similarly, in the recent WJOG 5108L trial, no significant difference in efficacy was found between erlotinib and gefitinib in patients with *EGFR* mutation-positive NSCLC, albeit in a second-line setting.³⁷ Together, these trials indicate that the first-generation *EGFR* TKIs provide similar efficacy, with some differences in tolerability in patients with *EGFR* mutation-positive NSCLC.

**Dacomitinib versus gefitinib: ARCHER 1050.** The phase III ARCHER 1050 trial compared first-line dacomitinib versus gefitinib in Asian or European (Spain, Italy, Poland) patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC. Dacomitinib significantly improved the primary endpoint of PFS (independent review) versus gefitinib [median 14.7 months versus 9.2 months; HR 0.59 (95% CI 0.47–0.74); *p* < 0.0001; Figure 1(b)]. Median duration of response was also significantly longer (14.8 months versus 8.3 months; *p* < 0.0001) with dacomitinib versus gefitinib, while ORR was comparable between treatment arms (74.9% versus 71.6%).³⁹ OS data are not currently available. The most frequent AEs with dacomitinib were diarrhea, skin rash and stomatitis. Similar improvements in most patient-reported measures of key disease-associated symptoms were reported in both treatment groups, but there was a significant increase in patient-reported symptoms of diarrhea and sore mouth with dacomitinib versus gefitinib, likely attributable to dacomitinib-related AEs. Dacomitinib dose reduction was required in 66.1% of patients.³⁹

It should be noted that, in contrast to LUX-Lung 7, the ARCHER 1050 trial excluded patients with brain metastases, and the studied population was relatively young (59% of patients were aged <65 years) and predominantly (77%) Asian.³⁹ Nevertheless, results from ARCHER 1050 support the evidence obtained from LUX-Lung 7 suggesting that second-generation TKIs confer efficacy benefits over first-generation agents.

**Osimertinib versus erlotinib/gefitinib: FLAURA.** The third-generation *EGFR* TKI, osimertinib, has recently been assessed versus gefitinib or erlotinib in the global phase III FLAURA trial in patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC.²⁵ In accordance with highly encouraging data from phase I expansion cohorts,²⁴ osimertinib significantly improved PFS versus gefitinib/erlotinib [median 18.9 months versus 10.2 months; HR 0.46 (95% CI 0.37–0.74); *p* < 0.0001; Figure 1(c)].²⁵ OS data are currently immature. The most frequent AEs with osimertinib were diarrhea (58%; grade ≥3: 2%) and dry skin (32%; grade ≥3: <1%). AEs led to the discontinuation of osimertinib in 13% of patients. These data support the use of osimertinib as a first-line treatment option in patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC. It is important to note, however, that because second-generation *EGFR* TKIs were not included in the comparator arm, it is not possible to draw conclusions regarding potential benefits of osimertinib over afatinib or dacomitinib in this setting.

**Resistance mechanisms to EGFR TKIs**

The striking efficacy of osimertinib as a second-line treatment option in patients with T790M-positive tumors,²¹,²³ as well as its recently demonstrated efficacy in the first-line setting, raises questions regarding the optimal sequence of therapy and adds a level of complexity with respect to the choice of initial treatment in patients with *EGFR* mutation-positive NSCLC. Indeed, the availability of multiple *EGFR* TKIs, including the emergence of osimertinib, underpins the importance of assessing mechanisms of resistance in individual patients so that the treatment sequence is optimized according to the molecular evolution of tumors.

It is clear that the accrual of T790M is the most predominant mechanism of resistance to erlotinib, gefitinib and afatinib.¹⁹,²⁰,⁴⁰–⁴³ Moreover, recent evidence indicates that the percentage of
patients whose tumors develop T790M is remarkably similar, regardless of which first-line EGFR TKI they receive prior to osimertinib. Data from the phase II extension period of the AURA study, which assessed osimertinib following erlotinib, gefitinib or afatinib, demonstrated a T790M accrual rate of 68% for afatinib and erlotinib and 69% for gefitinib at the point of acquired resistance to first-line therapy. This suggests that a good proportion of patients treated with these agents in the first-line setting could potentially go on to benefit from treatment with osimertinib.

A number of T790M-independent mechanisms of resistance have been identified in patients treated with erlotinib/gefitinib, including MET gene amplification leading to aberrant signaling mediated by ErbB3, PI3KCA gene mutations, HER2 gene amplification and small-cell histologic transformation. Some of these pathways are inhibited by afatinib and dacomitinib. Accordingly, it is possible that the superior PFS observed with afatinib and dacomitinib over gefitinib reflect their wider inhibitory profile, which may delay or even completely suppress acquired resistance.

In contrast to first- and second-generation EGFR TKIs, resistance mechanisms to osimertinib have not been clearly elucidated and appear to be quite heterogeneous, varying from patient to patient. Few clinical studies have assessed resistance mechanisms to osimertinib, and those studies that have been undertaken have been restricted to small patient cohorts or case studies. However, there is evidence to suggest that one mechanism of resistance to osimertinib may be the acquisition of tertiary EGFR mutations. In a study by Thress and colleagues, an EGFR C797S mutation was detected in 6 of 15 patients with osimertinib-resistant T790M-positive tumors. Another tertiary resistance mutation, EGFR L718Q, was identified in a case study of a patient with acquired resistance to osimertinib. Other resistance mechanisms that have been identified in case studies include HER2 or MET amplification, small-cell transformation and acquisition of a mutation in the BRAF gene. Despite progress in identifying resistance mechanisms (albeit in a small number of patients), the cause of resistance to osimertinib in many cases remains unknown. Interestingly, in the Thress and colleagues study, of the nine patients without C797S, four had lost the EGFR T790M mutation at the point of resistance, while five patients retained T790M. Clearly, a number of other resistance mechanisms, possibly independent of EGFR, remain to be identified. Due to this lack of clarity regarding resistance mechanisms, possible therapy options following the failure of osimertinib are not clear.

Given the apparent heterogeneity of resistance and the involvement of intracellular pathways other than EGFR in some osimertinib-resistant tumors (e.g. BRAF mutations, MET or HER2 amplification), osimertinib-based combination strategies may be effective and are an active area of investigation. For example, ongoing clinical trials are assessing a range of novel combination regimens incorporating agents that target EGFR, VEGFR, MET/MEK and PD1/PD-L1. However, at present the development of treatment options post-osimertinib remains an area of unmet clinical need. Overall, therefore, despite possibly offering superior PFS as first-line treatment versus first-generation EGFR TKIs, a sequential strategy starting with osimertinib may not prove to be as effective as first-, or second-generation EGFR TKIs followed by osimertinib. This will need to be assessed in a prospective clinical trial.

**Comparison of sequential regimens in patients with EGFR mutation-positive NSCLC**

At present, few data comparing sequential regimens in patients with EGFR mutation-positive NSCLC are available. However, a recent post-hoc analysis of the LUX-Lung 7 study was undertaken in order to compare outcomes in patients who received a third-generation EGFR TKI post-progression. For patients treated with afatinib, 20 received a third-generation EGFR TKI (including 15 who received osimertinib) and for patients treated with gefitinib, 23 received a third-generation EGFR TKI (including 17 who received osimertinib). The median OS with afatinib versus gefitinib in patients with EGFR mutation-positive NSCLC was 90% were reported. Although based on a small number of patients, these findings suggest that sequential therapy with afatinib/gefitinib followed by a third-generation EGFR TKI can be effective, and indicates that, in some patients at least, EGFR mutation-positive NSCLC could potentially become a chronic disease with effective sequential treatment.
Further clinical scrutiny with prospective clinical trials is needed. For example, it would be particularly interesting to undertake a prospective three-arm study that compares investigator choice of afatinib/dacomitinib or erlotinib/gefitinib followed by osimertinib versus first-line osimertinib (Figure 2). A key endpoint of such a study would be OS. At present, OS data from FLAURA (median OS not reached in either arm) are too immature to be interpretable, especially considering the likely confounding effects of crossover from the erlotinib/gefitinib arm to osimertinib. Detailed analysis of the molecular features of tumors as they become resistant to first-line EGFR TKIs will be a fundamental aspect of future clinical studies and could be facilitated by the ongoing development of liquid biopsy methodologies to circumvent the requirement for repeated tumor biopsies.47

**Figure 2.** Possible sequential regimens with EGFR TKIs in patients with EGFR mutation-positive NSCLC. First-line osimertinib provides PFS benefit over first-generation EGFR TKIs. Second-line treatment options following osimertinib are currently uncertain because resistance mechanisms are heterogeneous. At least 50% of patients treated with first-line afatinib are likely to accrue the T790M mutation and could therefore benefit from second-line osimertinib. Overall, therefore, a sequential regimen of first- or second-generation EGFR TKIs followed by osimertinib could be a treatment option in this setting.12,13,23,25,33,39

**Possible EGFR TKI-based treatment options in patients with T790M-negative tumors**

Of course, the sequential regimens described above are only applicable to patients who accrue the T790M resistance mutation following first-line
therapy. The optimal treatment of patients who develop resistance to EGFR TKIs via mechanisms independent of T790M are unclear. At present, outside of clinical trials, platinum-based chemotherapy represents the main treatment option for these patients.\textsuperscript{55} Given the biological heterogeneity of T790M-independent resistance mechanisms, targeted therapy options are currently limited in this setting. It was hoped that second-generation TKIs, with their broad inhibitory profiles, could be effective in patients with acquired resistance to erlotinib or gefitinib. However, clinical trial data have demonstrated that afatinib monotherapy following acquired resistance to erlotinib or gefitinib has limited efficacy.\textsuperscript{56,57} On the other hand, afatinib-based combinations have shown promise in this setting.\textsuperscript{58} For example, the efficacy of afatinib plus cetuximab was investigated in a recent phase Ib study in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib \( (n = 126) \).\textsuperscript{59} In this study, an ORR of 29\% was observed, with similar ORR findings regardless of T790M status (32\% and 25\% in T790M-positive and negative tumors, respectively).

Another strategy worth pursuing could be the combination of afatinib with paclitaxel. In the phase III LUX-Lung 5 trial, afatinib plus paclitaxel was evaluated \textit{versus} chemotherapy alone in patients acquiring resistance to erlotinib/gefitinib and, thereafter, afatinib monotherapy.\textsuperscript{57} PFS (median 5.6 months \textit{versus} 2.8 months, HR 0.60; \( p = 0.003 \)) and ORR (32.1\% \textit{versus} 13.2\%; \( p = 0.005 \)) were significantly improved with afatinib plus paclitaxel \textit{versus} chemotherapy alone, although no difference was observed in OS.

Other potential treatment strategies to treat T790M-negative tumors that are currently being investigated include the concept of EGFR TKI rechallenge or the combination of EGFR TKIs with immunotherapeutic agents or compounds that target other intracellular pathways such as \( MET, MEK, \) or PI3K.\textsuperscript{55} In this respect, some early-phase clinical trials have shown promising activity of novel treatment regimens in T790M-negative patients. For example, combination of osimertinib with MEDI4736 (PD-L1 antibody), savolitinib (\( MET \) inhibitor), or selumetinib (a \( MEK \) \(1/2 \) inhibitor) has shown clinical activity in this setting, albeit in a small number of patients.\textsuperscript{60} Further data from larger phase III trials are required. At this stage, effective treatment strategies, including sequential regimens, have not been defined in T790M-negative patients; thus, this represents an area of considerable unmet medical need.

**Summary and conclusion**

Although several EGFR TKIs are available for the treatment of \textit{EGFR} mutation-positive NSCLC, the development of acquired resistance is inevitable.\textsuperscript{20,43} It is therefore beneficial to consider the optimal sequence of EGFR TKIs in order to maximize their clinical benefit.

Currently gefitinib, erlotinib and afatinib are approved for first-line use in NSCLC based on robust phase III data. The recent LUX-Lung 7 trial showed that afatinib improved PFS, TTF and ORR \textit{versus} gefitinib in treatment-naïve patients with \textit{EGFR} mutation-positive NSCLC. While the tolerability profile was different with afatinib, the rate of treatment discontinuations due to AEws was the same in both arms. These data, along with the more recent ARCHER 1050 trial (dacomitinib \textit{versus} gefitinib), demonstrated that second-generation EGFR TKIs confer efficacy benefits over first-generation EGFR TKIs. Results from the recent phase III FLAURA study also showed efficacy benefits with first-line osimertinib \textit{versus} first-generation TKIs (gefitinib or erlotinib). Therefore, the optimal first-line treatment of choice for individual patients should be carefully considered, especially when assessing how best to utilize third-generation EGFR TKIs, such as osimertinib, in treatment regimens.

Further analysis of LUX-Lung 7 indicated that patients treated with afatinib or gefitinib followed by third-generation EGFR TKIs (including osimertinib) achieved striking OS benefit, thus supporting the idea of sequential therapy (with third-generation EGFR TKIs such as osimertinib held back for second-line use) as a reasonable treatment strategy. This is particularly pertinent when considering recent data indicating that approximately 50–70\% of patients with acquired resistance to afatinib, erlotinib or gefitinib have T790M-positive tumors.

The debate about sequence of therapy will be intensified by the outcomes of the FLAURA trial. Given the striking PFS improvement with osimertinib over first-generation EGFR TKIs (second-generation TKIs were not included in the comparator arm), and its favorable tolerability profile, many physicians will be prompted to prescribe osimertinib as first-line treatment. Consequently,
further analysis of resistance mechanisms to osimertinib, and rational therapeutic options following treatment failure, will be a major research priority. Ultimately, given the lack of treatment options following acquired resistance to osimertinib at the moment, sequential therapy with first- or second-generation TKIs followed by osimertinib may provide survival benefit over the use of first-line osimertinib. This possibility requires further clinical assessment. Another unmet medical need is the development of sequential treatment options for patients with T790M-negative tumors. Therefore, it is clear that more clinical trials are required to delineate the most appropriate sequential therapy in patients with $EGFR$ mutation-positive NSCLC.

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