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Turning *EGFR* mutation-positive non-small-cell lung cancer into a chronic disease: optimal sequential therapy with EGFR tyrosine kinase inhibitors

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Abstract: Four epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib, afatinib and osimertinib, are currently available for the management of *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), with others in development. Although tumors are exquisitely sensitive to these agents, acquired resistance is inevitable. Furthermore, emerging data indicate that first- (erlotinib and gefitinib), second- (afatinib) and third-generation (osimertinib) EGFR TKIs differ in terms of efficacy and tolerability profiles. Therefore, there is a strong imperative to optimize the sequence of TKIs in order to maximize their clinical benefit. Osimertinib has demonstrated striking efficacy as a second-line treatment option in patients with T790M-positive tumors, and also confers efficacy and tolerability advantages over first-generation TKIs in the first-line setting. However, while accrual of T790M is the most predominant mechanism of resistance to erlotinib, gefitinib and afatinib, resistance mechanisms to osimertinib have not been clearly elucidated, meaning that possible therapy options after osimertinib failure are not clear. At present, few data comparing sequential regimens in patients with *EGFR* mutation-positive NSCLC are available and prospective clinical trials are required. This article reviews the similarities and differences between EGFR TKIs, and discusses key considerations when assessing optimal sequential therapy with these agents for the treatment of *EGFR* mutation-positive NSCLC.

Keywords: acquired resistance, EGFR mutations, EGFR TKI, NSCLC, T790M

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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 anticancer agents.[1] Currently, the most established target is the epidermal growth factor receptor (EGFR),[1] 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).[2]

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.[2] For example, somatic mutations of *EGFR* have been reported in approximately 50% of Asian patients and 10–15% of Caucasian patients with lung adenocarcinoma,[3] with the most common mutations in these populations being exon 19 deletions (Del19) and an L858R point mutation (L858R).[4] 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.[5,6]

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Four EGFR tyrosine kinase inhibitors (TKIs; erlotinib, gefitinib, afatinib and osimertinib) are currently available for the management of NSCLC, while others are in development.[7] 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.[8–15] 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.[16] Afatinib is a second-generation ErbB family blocker, which irreversibly blocks signaling from all relevant homo- and heterodimers of the ErbB family of receptors.[17] Other second-generation EGFR TKIs, such as dacomitinib, are currently in development.[7]

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*.[18–21] 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.[21–23] Of note, only 7% of patients treated with osimertinib in AURA 3 were previously treated with afatinib.[23] 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.[24] 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].[25] 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,[25] 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.[7]

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[8–10,26–29]; the erlotinib trials, OPTIMAL, EURTAC, and ENSURE[11,14,15]; and the afatinib trials, LUX-Lung 3 and LUX-Lung 6.[12,13] 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/acne) events, they were better tolerated than chemotherapy.[9–15] Furthermore, AEs with EGFR TKIs were generally manageable, and led to treatment discontinuation in just 6–8%,[12,13] 1–13%[11,14,15] and 7–16%[9,10] 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 ($p = 0.023$)].[30] 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),[31] 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.[32]

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.

Afatinib versus *gefitinib: LUX-Lung 7.* The phase IIb LUX-Lung 7 trial compared afatinib *versus* gefitinib in treatment-naïve patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC.[33] 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.[33] 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)].[33] 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; $p = 0.2580$).[32] Extensive use of post-progression therapy is believed to have contributed to the lack of significant OS benefit in this study.[34] 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

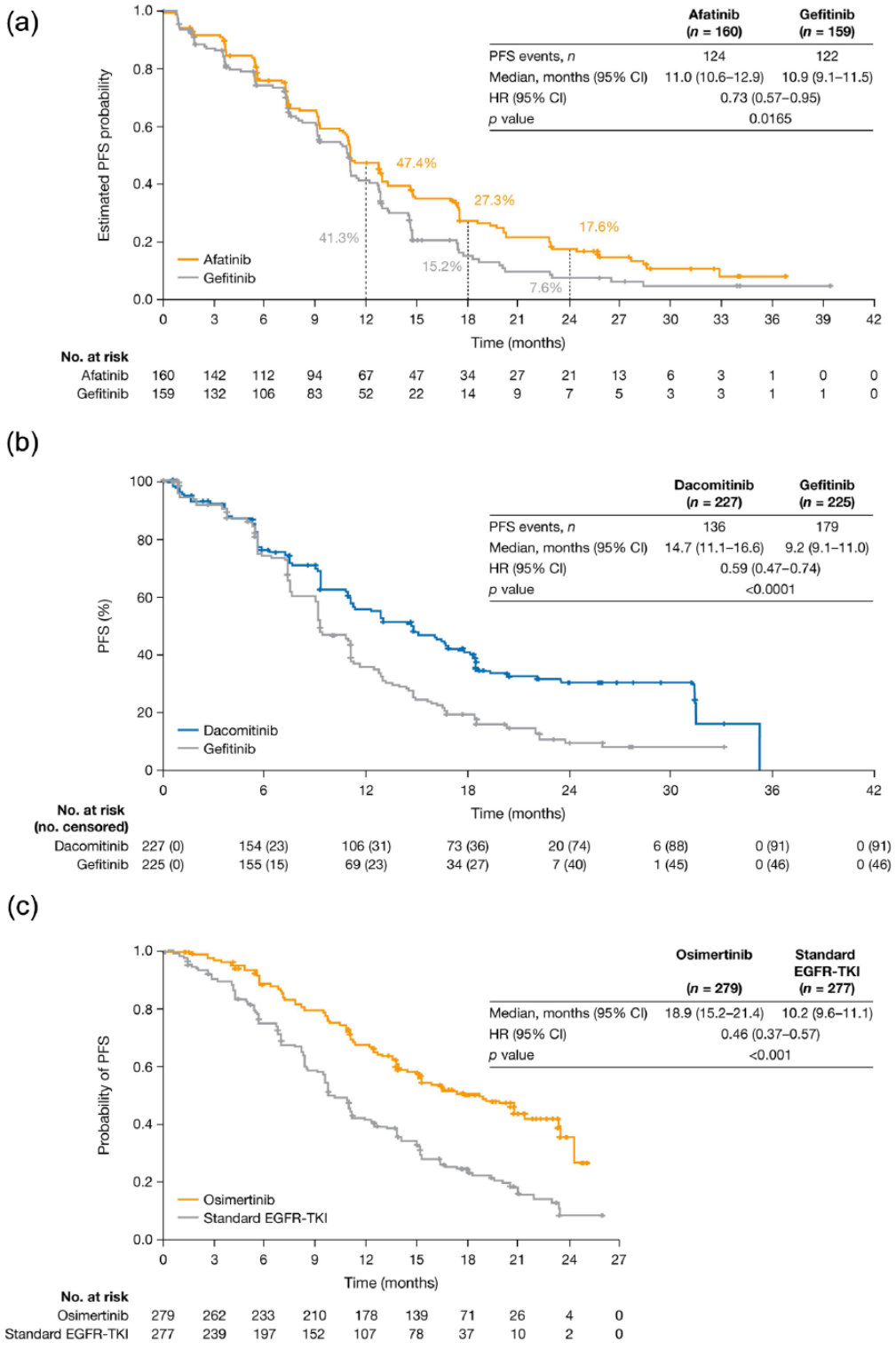

Figure 1. PFS in recent head-to-head trials: (a) Lux-Lung 7, (b) ARCHER 1050 and (c) FLAURA.
(a) Park K, *et al*. Afatinib *versus* gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase IIb, open-label, randomised controlled trial. *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 0.37–0.57); $p < 0.001$; Figure 1(c)].[25] OS data are currently immature. The most frequent AEs of any causality in the osimertinib group were rash or acne (58%; grade ⩾3: 1%), diarrhea (58%; grade ⩾3: 2%) and dry skin (36%; 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.[21] 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.[20,41,43–45] 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.[46,47] 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.[48–52] 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.[52] Another tertiary resistance mutation, EGFR L718Q, was identified in a case study of a patient with acquired resistance to osimertinib.[48] Other resistance mechanisms that have been identified in case studies include *HER2* or *MET* amplification,[51] small-cell transformation[53] and acquisition of a mutation in the *BRAF* gene.[49] 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.[46] 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 who received a third-generation EGFR TKI post-progression was 'not evaluable' *versus* 46.0 months (HR 0.51; 95% CI 0.17–1.52; $p = 0.22$). In patients receiving first-line afatinib followed by a subsequent third-generation EGFR TKI, 3-year OS rates ⩾90% were reported.[32,54]

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.

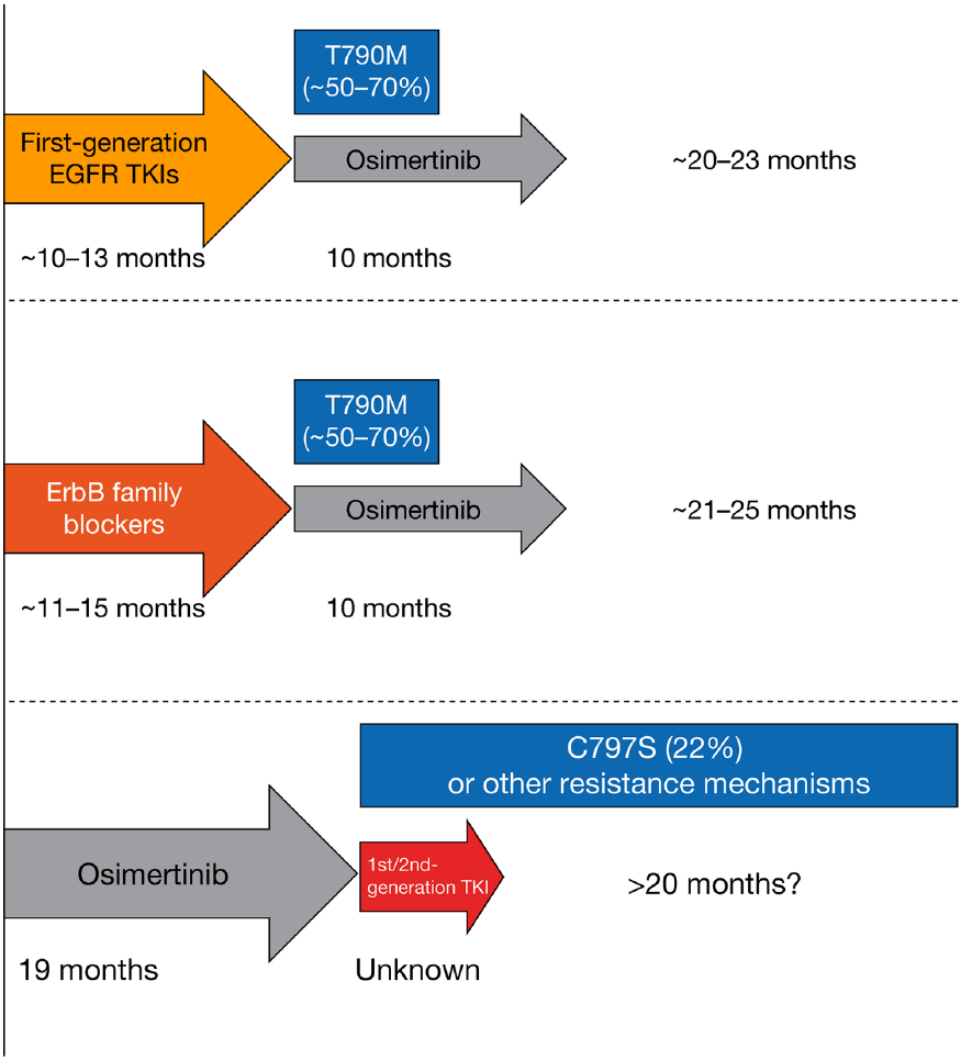

Figure 2. Possible sequential regimens with EGFR TKIs in patients with *EGFR* mutation-positive NSCLC. First-line osimertinib provides PFS benefit over first-generation EGFR TKIs. Second-line treatment options following osimertinib are currently uncertain because resistance mechanisms are heterogeneous. It is possible that second-line treatment with a first- or second-generation EGFR TKI may be beneficial in some patients, although the margin of benefit is currently unclear and has been speculated on in this figure. Approximately 50–70% of patients treated with a first- or second-generation EGFR TKI in the first line 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.[8,9,11–15,20,21,23,25,33,38,39,42,43,61–63]

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]

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.[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.[56,57] On the other hand, afatinib-based combinations have shown promise in this setting.[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).[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 *versus* chemotherapy alone in patients acquiring resistance to erlotinib/gefitinib and, thereafter, afatinib monotherapy.[57] PFS (median 5.6 months *versus* 2.8 months, HR 0.60; p = 0.003) and ORR (32.1% *versus* 13.2%; p = 0.005) were significantly improved with afatinib plus paclitaxel *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.[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.[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 *EGFR* mutation-positive NSCLC, the development of acquired resistance is inevitable.[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 *versus* gefitinib in treatment-naïve patients with *EGFR* mutation-positive NSCLC. While the tolerability profile was different with afatinib, the rate of treatment discontinuations due to AEs was the same in both arms. These data, along with the more recent ARCHER 1050 trial (dacomitinib *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 *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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Conflict of interest statement

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References

1. Zer A and Leighl N. Promising targets and current clinical trials in metastatic non-squamous NSCLC. *Front Oncol* 2014; 4: 329.
2. Roskoski R Jr. The ErbB/HER family of protein-tyrosine kinases and cancer. *Pharmacol Res* 2014; 79: 34–74.
3. Chan BA and Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res* 2015; 4: 36–54.
4. Reguart N and Remon J. Common EGFR-mutated subgroups (Del19/L858R) in advanced non-small-cell lung cancer: chasing better outcomes with tyrosine-kinase inhibitors. *Future Oncol* 2015; 11: 1245–1257.
5. Engelman JA and Janne PA. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *Clin Cancer Res* 2008; 14: 2895–2899.
6. Torti D and Trusolino L. Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils. *EMBO Mol Med* 2011; 3: 623–636.
7. Sullivan I and Planchard D. Next-generation EGFR tyrosine kinase inhibitors for treating EGFR-mutant lung cancer beyond first line. *Front Med (Lausanne)* 2016; 3: 76.
8. 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: 2380–2388.
9. 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: 121–128.
10. Mok TS, Wu YL, Thongprasert S, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361: 947–957.
11. 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 (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239–246.
12. Sequist LV, Yang JC, Yamamoto N, *et al.* Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31: 3327–3334.
13. Wu YL, Zhou C, Hu CP, *et al.* Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 213–222.
14. Wu YL, Zhou C, Liam CK, *et al.* First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; 26: 1883–1889.
15. Zhou C, Wu YL, 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: 735–742.

16. Marshall J. Clinical implications of the mechanism of epidermal growth factor receptor inhibitors. *Cancer* 2006; 107: 1207–1218.
17. Hirsh V. Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Curr Oncol* 2011; 18: 126–138.
18. Arcila ME, Oxnard GR, Nafa K, *et al*. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin Cancer Res* 2011; 17: 1169–1180.
19. 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: e73.
20. 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: 75ra26.
21. Yang JC, Ahn MJ, Kim DW, *et al*. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol* 2017; 35: 1288–1296.
22. Janne PA, Yang JC, Kim DW, *et al*. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015; 372: 1689–1699.
23. Mok TS, Wu YL, Ahn MJ, *et al*. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017; 376: 629–640.
24. Ramalingam S, Yang JCH, Lee CK, *et al*. Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts. *J Thorac Oncol* 2016; 11(Suppl. 4): S152.
25. Soria JC, Ohe Y, Vansteenkiste J, *et al*. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; 378: 113–115.
26. 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: 2866–2874.
27. 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: 1122–1128.
28. Inoue A, Kobayashi K, Maemondo M, *et al*. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; 24: 54–59.
29. Yoshioka H, Mitsudomi T, Morita S, *et al*. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol* 2014; 32: 5S (suppl; abstr 8117).
30. Yang JC, Wu YL, Schuler M, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; 16: 141–151.
31. Lee CK, Davies L, Wu YL, *et al*. Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: individual patient data meta-analysis of overall survival. *J Natl Cancer Inst* 2017; 109. DOI: 10.1093/jnci/djw279.
32. Paz-Ares L, Tan EH, O'Byrne K, *et al*. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. *Ann Oncol* 2017; 28: 270–277.
33. Park K, Tan EH, O'Byrne 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 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016; 17: 577–589.
34. Park K. Afatinib for patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer: clinical implications of the LUX-Lung 7 study. *Ann Transl Med* 2016; 4: 476.
35. Yang JC, Sequist LV, Zhou C, *et al*. Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials. *Ann Oncol* 2016; 27: 2103–2110.
36. Hirsh V, Yang CH, Tan EH, *et al*. First-line afatinib (A) vs gefitinib (G) for patients (pts) with

EGFR mutation positive (EGFRm+) NSCLC (LUX-Lung 7): patient-reported outcomes (PROs) and impact of dose modifications on efficacy and adverse events (AEs). *J Clin Oncol* 2016; 34: (suppl; abstr 9046).

37. Urata Y, Katakami N, Morita S, *et al*. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. *J Clin Oncol* 2016; 34: 3248–3257.
38. Yang JJ, Zhou Q, Yan HH, *et al*. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. *Br J Cancer* 2017; 116: 568–574.
39. Wu YL, Cheng Y, Zhou X, *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 3 trial. *Lancet Oncol* 2017; 18: 1454–1466.
40. Campo M, Gerber D, Gainor JF, *et al*. Acquired resistance to first-line afatinib and the challenges of prearranged progression biopsies. *J Thorac Oncol* 2016; 11: 2022–2026.
41. 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: 786–792.
42. Wu SG, Liu YN, Tsai MF, *et al*. The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. *Oncotarget* 2016; 7: 12404–12413.
43. Yu HA, Arcila ME, Rekhtman N, *et al*. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013; 19: 2240–2247.
44. 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: 6494–6501.
45. Engelman JA, Zejnullahu K, Mitsudomi T, *et al*. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007; 316: 1039–1043.
46. Minari R, Bordi P and Tiseo M. Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors in T790M-positive non-small cell lung cancer: review on emerged mechanisms of resistance. *Transl Lung Cancer Res* 2016; 5: 695–708.
47. Sun JM and Park K. Can we define the optimal sequence of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of epidermal growth factor receptor-mutant nonsmall cell lung cancer? *Curr Opin Oncol* 2017; 29: 89–96.
48. Bersanelli M, Minari R, Bordi P, *et al*. L718Q mutation as new mechanism of acquired resistance to AZD9291 in EGFR-mutated NSCLC. *J Thorac Oncol* 2016; 11: e121–e123.
49. Ho CC, Liao WY, Lin CA, *et al*. Acquired BRAF V600E mutation as resistant mechanism after treatment with osimertinib. *J Thorac Oncol* 2017; 12: 567–572.
50. Kim TM, Song A, Kim DW, *et al*. Mechanisms of acquired resistance to AZD9291: a mutation-selective, irreversible EGFR inhibitor. *J Thorac Oncol* 2015; 10: 1736–1744.
51. Planchard D, Loriot Y, Andre F, *et al*. EGFR-independent mechanisms of acquired resistance to AZD9291 in EGFR T790M-positive NSCLC patients. *Ann Oncol* 2015; 26: 2073–2078.
52. Thress KS, Paweletz CP, Felip E, *et al*. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med* 2015; 21: 560–562.
53. Li L, Wang H, Li C, *et al*. Transformation to small-cell carcinoma as an acquired resistance mechanism to AZD9291: a case report. *Oncotarget* 2017; 8: 18609–18614.
54. Corral J, Park K, Yang JCH, *et al*. Afatinib versus gefitinib in patients with EGFR mutation-positive (EGFRm+) NSCLC: updated overall survival data from the phase IIb trial LUX-Lung 7. *Ann Oncol* 2017; 28(Suppl. 2): ii28–ii51.
55. Corallo S, D'Argento E, Strippoli A, *et al*. Treatment options for EGFR T790M-negative EGFR tyrosine kinase inhibitor-resistant non-small cell lung cancer. *Target Oncol* 2017; 12: 153–161.
56. 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: 528–538.
57. Schuler M, Yang JC, Park K, *et al*. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III

randomized LUX-Lung 5 trial. *Ann Oncol* 2016; 27: 417–423.

58. Bennouna J and Moreno Vera SR. Afatinib-based combination regimens for the treatment of solid tumors: rationale, emerging strategies and recent progress. *Future Oncol* 2016; 12: 355–372.

59. Janjigian YY, Smit EF, Groen HJ, *et al*. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov* 2014; 4: 1036–1045.

60. Oxnard GR, Ramalingam SS, Ahn MJ, *et al*. Preliminary results of TATTON, a multi-arm phase Ib trial of AZD9291 combined with MEDI4736, AZD6094 or selumetinib in EGFR-mutant lung cancer. *J Clin Oncol* 2015; 33(Suppl. 15): (suppl; abstr 2509).

61. Ramalingam SS, Yang JC, Lee CK, *et al.* Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2017: JCO2017747576.

62. 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: 528–538.

63. Mitsudomi T, Ahn M-J, Bazhenova L, *et al.* Overall survival in patients with EGFR T790M-positive advanced non-small cell lung cancer treated with osimertinib: results from two Phase II studies. *Ann Oncol* 2017; 28 (Suppl. 5): 482.