Optimizing outcomes in *EGFR* mutation-positive NSCLC: which tyrosine kinase inhibitor and when?

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Despite the efficacy of standard-of-care *EGFR* tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib and afatinib, in *EGFR* mutation-positive non-small-cell lung cancer, resistance develops, most commonly due to the T790M mutation. Osimertinib showed clinical activity in the treatment of T790M-positive disease following progression on a first-line TKI, and is approved in this setting. Recently, osimertinib improved efficacy versus first-generation TKIs (erlotinib and gefitinib) in the first-line setting. Multiple factors can influence first-line treatment decisions, including subsequent therapy options, presence of brain metastases and tolerability, all of which should be considered in the long-term treatment plan. Further research into treatment sequencing is also needed, to optimize outcomes in *EGFR* mutation-positive non-small-cell lung cancer.

First draft submitted: 17 November 2017; Accepted for publication: 15 December 2017; Published online: 16 January 2018

Keywords: afatinib • dacomitinib • *EGFR* • erlotinib • gefitinib • non-small-cell lung cancer • osimertinib • resistance • treatment sequencing • T790M

Somatic mutations of the *EGFR* gene are found in up to 50% of Asian patients and 10–15% of Caucasian patients with lung adenocarcinoma [1]. Tumors with these mutations become dependent on *EGFR* signaling, enabling molecularly targeted inhibition of this pathway with tyrosine kinase inhibitors (TKIs) to be used as treatment [2]. Erlotinib and gefitinib were the first *EGFR* TKIs developed; they reversibly and competitively inhibit the tyrosine kinase domain of *EGFR* (Figure 1) [3]. Known as the first-generation *EGFR* TKIs, they rapidly became standard of care first-line treatment for *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), and molecular testing for *EGFR* mutations in patients with lung adenocarcinoma is now recommended as part of baseline workup [4]. The hypothesis that broader inhibition of the *EGFR* family could improve outcomes led to the development of second-generation ERBB family blockers, afatinib and dacomitinib. These agents irreversibly bind to *EGFR*, ERBB2 and ERBB4 and block transphosphorylation of ERBB3 to inhibit all ERBB family signaling (Figure 1) [5]. Currently, erlotinib, gefitinib and afatinib are standard of care for the first-line treatment of *EGFR* mutation-positive NSCLC [4].

Despite their proven efficacy, resistance to these treatments inevitably develops. The most common mechanism of resistance is acquisition of another *EGFR* mutation, *EGFR* T790M (around 50–70% of cases) [6,7]. The most recent additions to the *EGFR* TKI family – the third-generation *EGFR* TKIs – add to the targeting of *EGFR*-activating mutations, with specific activity on *EGFR* T790M (Figure 1). One such agent, osimertinib, demonstrated striking efficacy in patients with *EGFR* T790M-positive disease that had progressed on a first- or second-generation *EGFR* TKI and is approved in this setting [7–9]. These data highlight the importance of molecular testing throughout treatment to understand tumor evolution and enable the use of targeted therapies.

Most recently, osimertinib has been assessed as a first-line treatment for *EGFR* mutation-positive NSCLC compared with a first-generation *EGFR* TKI (erlotinib or gefitinib), demonstrating a significant improvement in median progression-free survival (PFS), and thus positioning it as another potential first-line treatment option [10]. Consequently, physicians now have a number of options available and need to consider how best to use these

Figure 1. Overview of activity range of first-, second- and third-generation EGFR tyrosine kinase inhibitors.
TKI: Tyrosine kinase inhibitor.

agents to provide the best chance of long-term survival, while also considering the impact on quality of life, which is of particular importance to patients with advanced cancer. Based on the molecular evolution of lung tumors, sequencing of EGFR TKIs may be key to obtaining the best outcome. In this review, we consider the data supporting the use of the available EGFR TKIs and key considerations for selection of first-line treatment.

First- & second-generation EGFR TKIs

The first-generation EGFR TKIs, erlotinib and gefitinib, demonstrated superior efficacy to platinum-based chemotherapy in several Phase III trials (OPTIMAL [11], EURTAC [12] and ENSURE [13] for erlotinib, and IPASS [subgroup of *EGFR* mutation-positive NSCLC] [14], WJTOG3405 [15] and NEJ002 [16] for gefitinib [Table 1]). In these trials, erlotinib and gefitinib were associated with median PFS of 9.2–13.1 months compared with 4.6–6.3 months among patients receiving platinum-based chemotherapy. However, none of the trials were able to show an overall survival (OS) improvement with the first-generation TKIs, which was thought to be related to crossover from chemotherapy to an EGFR TKI upon progression [13,17–20]. Overall, the EGFR TKIs were tolerable, with key adverse events (AEs) including class-related gastrointestinal and skin toxicities (discussed in further detail later).

The second-generation ERBB family blocker, afatinib, has also demonstrated significantly improved PFS versus platinum-based chemotherapy in patients with *EGFR* mutation-positive NSCLC in two large, randomized Phase III trials (Table 1). In LUX-Lung 3, in patients with common mutations (Del19/L858R), median PFS was 13.6 months for afatinib versus 6.9 months with cisplatin–pemetrexed [25]. These results were confirmed in the LUX-Lung 6 trial, which was conducted in Asia [27]. Subgroup analysis showed that the results were consistent irrespective of age, gender and race. While PFS generally favored afatinib irrespective of mutation type, benefit was most pronounced among those with Del19-positive disease (Table 1) [25,27]. This has also been observed for the first-generation EGFR TKIs [31,32]. LUX-Lung 3 and 6 both also included prespecified analyses of patient-reported outcomes, whereby afatinib was associated with longer time to deterioration and improvements in lung cancer-related symptoms, such as cough, dyspnea and pain [25,27,33]. Moreover, in contrast with the first-generation EGFR TKIs, afatinib was associated with an OS benefit in both of these trials. Among patients with Del19-positive NSCLC, median OS was significantly longer in patients receiving afatinib than those receiving chemotherapy (LUX-Lung 3: median, 33.3 vs

Table 1. Key prospective randomized clinical trials of first-, second- and third-generation *EGFR* tyrosine kinase inhibitors in patients with previously untreated *EGFR* mutation-positive non-small-cell lung cancer.

EGFR TKI generation	Study	Treatment arms	Median PFS, months (HR [95% CI]) versus comparator		Median OS, months (HR [95% CI]) versus comparator		Response rate (%)	Median duration of response, months (95% CI)	Ref.
			Common mutations	Del19	L858R	Common mutations	Del19	L858R	
First	ENSURE ¹	Erlotinib, n = 110	11.0 (0.34 [0.22–0.51])	11.1 (0.20 [0.11–0.37])	8.3 (0.57 [0.31–1.05])	26.3 (0.91 [0.63–1.31])	26.7 (0.79 [0.48–1.30])	25.3 (1.05 [0.60–1.84])	[13]
		Gemcitabine + cisplatin, n = 107							
	EURTAC ¹	Erlotinib, n = 86 Platinum-based chemotherapy, n = 87	9.7 (0.37 [0.25–0.54])	11.0 (0.30 [0.18–0.50])	8.4 (0.55 [0.29–1.02])	22.9 (0.92 [0.63–1.35])	NR (0.94 [0.57–1.54])	NR (0.99 [0.56–1.76])	[12,21]
	OPTIMAL ¹	Erlotinib, n = 82	13.1 (0.16 [0.10–0.26])	15.3 (0.13 [0.07–0.25])	12.5 (0.26 [0.14–0.49])	22.8 (1.19 [0.83–1.71])	27.0 (1.52 [0.91–2.52])	21.5 (0.92 [0.55–1.54])	[11,20]
		Platinum-based chemotherapy, n = 72							
	IPASS	Gefitinib, n = 132	9.5 (0.48 [0.36–0.64]) [‡]	11.0 (0.38 [0.26–0.56])	9.2 (0.55 [0.35–0.87])	NR (1.00 [0.76–1.33])	27.2 (0.79 [0.54–1.15])	18.7 (1.44 [0.90–2.30])	[14,17,22]
		Carboplatin + paclitaxel, n = 129							
	NEJ-002 ¹	Gefitinib, n = 114	10.8 (0.32 [0.24–0.44]) [§]	11.5 (NR [NR–NR])	10.8 (NR [NR–NR])	27.7 (0.89 [0.63–1.24])	29.3 (NR [NR–NR])	28.4 (NR [NR–NR])	[16,18,23]
		Carboplatin + paclitaxel, n = 114							
Second	WJTOG3405	Gefitinib, n = 86	8.4 (0.33 [0.21–0.54])	NR (NR [NR–NR])	NR (NR [NR–NR])	34.8 (1.25 [0.88–1.78])	35.2 (NR [NR–NR])	32.2 (NR [NR–NR])	[15,24]
		Cisplatin + docetaxel, n = 114							
	LUX-Lung 3 [¶]	Afatinib, n = 230	13.6 (0.47 [0.34–0.65])	13.7 (0.47 [0.34–0.65])	10.8 (0.73 [0.46–1.17])	31.6 (0.78 [0.58–1.06])	33.3 (0.54 [0.36–0.79])	27.6 (1.30 [0.80–2.11])	[25,26]
	LUX-Lung 6 [¶]	Pemetrexed + cisplatin, n = 115							[26,27]
		Afatinib, n = 242	13.7 (0.25 [0.18–0.35])	13.7 (0.20 [0.13–0.33])	9.6 (0.32 [0.19–0.52])	23.6 (0.83 [0.62–1.09])	31.4 (0.64 [0.44–0.94])	19.6 (1.22 [0.81–1.83])	
	LUX-Lung 7 [¶]	Gemcitabine + cisplatin, n = 122							[28,29]
		Afatinib, n = 160	11.0 (0.73 [0.57–0.95])	12.7 (0.76 [0.55–1.06])	10.9 (0.79 [0.48–1.06])	27.9 (0.86 [0.66–1.12])	30.7 (0.83 [0.58–1.17])	25.0 (0.91 [0.62–1.36])	
	ARCHER-1050 [¶]	Gefitinib, n = 159							[30]
		Dacomitinib, n = 227	14.7 (0.59 [0.47–0.74])	16.5 (0.55 [0.41–0.75])	12.3 (0.63 [0.44–0.88])	NR	NR	NR	
Third	FLAURA ¹	Gefitinib, n = 225							[10]
		Osimertinib, n = 279	18.9 (0.46 [0.37–0.57])	21.4 (0.43 [0.32–0.56])	14.4 (0.51 [0.36–0.71])	NR	NR	NR	

†PFS by investigator assessment.

‡Analysis included ten patients with uncommon *EGFR* mutations.§Analysis included seven patients with uncommon *EGFR* mutations.

¶PFS by independent assessment.

#Interquartile range.

HR: Hazard ratio; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor.

21.1 months, $p = 0.0015$; LUX-Lung 6: median, 31.4 vs 18.4 months, $p = 0.023$ [Table 1]) [26]. It was hypothesized that the observed OS benefit may be related to broad inhibition of the ERBB family by afatinib compared with reversible inhibition of EGFR only by first-generation EGFR TKIs. In addition, given the availability of first-generation TKIs at the time those trials were conducted, a significant proportion of patients did receive additional lines of TKIs after the study treatment, which may have impacted OS.

However, until recently, there were no head-to-head trials comparing first- and second-generation EGFR TKIs to substantiate the hypothesis that second-generation EGFR TKIs were more effective. The exploratory Phase IIB LUX-Lung 7 trial, which compared first-line afatinib with gefitinib in *EGFR* mutation-positive (Del19 or L858R) NSCLC, was the first prospective, randomized trial to compare first- and second-generation TKIs [28]. Patients received treatment until disease progression, or beyond if deemed beneficial by the investigator. Given the exploratory nature of the trial, no formal hypothesis was specified. Three coprimary end points were selected: PFS by independent central review, OS and time to treatment failure (TTF). TTF, which was defined as the time from randomization until treatment discontinuation for any reason, including progression, AEs or death, was included to reflect clinical practice where many patients receive treatment beyond radiological progression in the absence of clinical deterioration. In LUX-Lung 7, afatinib significantly prolonged PFS (median, 11.0 vs 10.9 months; hazard ratio [HR]: 0.73; $p = 0.017$) and TTF (median, 13.7 vs 11.5 months; HR: 0.73; $p = 0.0073$) versus gefitinib. A significantly higher proportion of patients achieved an objective response with afatinib (70%) versus gefitinib (56%; Table 1) [28]. Median OS was not significantly different between treatment arms (27.9 months with afatinib vs 24.5 months with gefitinib; HR: 0.86; $p = 0.2580$). However, LUX-Lung 7 was not powered for OS, as the sample size was based on controlling the width of the CI for the HR of PFS [29]. As in LUX-Lung 3 and LUX-Lung 6, the efficacy findings were generally consistent across patient subgroups of gender, age and ethnicity. Furthermore, the efficacy benefits of afatinib over gefitinib were not affected by *EGFR* mutation type [28,29].

More recently, another second-generation EGFR TKI, dacomitinib, has been assessed in the first-line setting versus gefitinib in the Phase III ARCHER 1050 trial [34]. This study enrolled patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC, but excluded patients with brain metastases. Dacomitinib significantly prolonged PFS compared with gefitinib (14.7 vs 9.2 months; HR: 0.59; $p < 0.0001$; Table 1). While the proportion of patients who achieved an objective response was similar between the two groups (75% in the dacomitinib group and 70% in the gefitinib group), duration of response was longer with dacomitinib than gefitinib (HR: 0.55; $p < 0.0001$). OS data were not mature at the time of data cutoff. Although cross trial comparisons of LUX-Lung 7 and ARCHER 1050 should be cautioned, especially given differences among patient populations, the cumulative evidence suggests that second-generation EGFR TKIs may be more effective than first-generation EGFR TKIs.

Third-generation EGFR TKIs in patients with acquired resistance

Despite the efficacy of first- and second-generation EGFR TKIs, resistance inevitably develops, usually within 10–14 months after starting treatment. The predominant mechanism of resistance appears to be acquisition of *EGFR* T790M, occurring in 50–70% of patients [6,7]. The third-generation EGFR TKIs were developed to target this mechanism, showing high potency for T790M and *EGFR* TKI-sensitizing mutations, although the pharmacological potency for the common Del19/L858R mutations is lower with osimertinib than second-generation EGFR TKIs [35,36]. A number of third-generation TKIs are in development, but osimertinib is the only agent approved in Europe and the USA for treatment of advanced *EGFR* T790M mutation-positive NSCLC, based on impressive data from the Phase I/II AURA, Phase II AURA2 and Phase III AURA3 studies. AURA enrolled patients with advanced NSCLC that had progressed after treatment with EGFR TKIs. In the Phase I part, the response rate for osimertinib was 61%, with a median PFS of 9.6 months among patients who had centrally confirmed *EGFR* T790M [8]. These results were confirmed in the Phase II AURA extension, in patients with EGFR TKI-pretreated *EGFR* T790M-positive disease, where the response rate was reported as 62% and median PFS was 12.3 months [7]. Similarly, in the AURA2 study in patients who had progression on previous EGFR TKI therapy, the response rate was 70% [37]. Pooled OS analysis from AURA2 and the AURA extension showed median OS of 26.8 months from initiation of osimertinib in patients with T790M-positive NSCLC that had progressed after a first- or second-line EGFR TKI [38]. Osimertinib was subsequently assessed in the randomized Phase III AURA3 trial in patients with T790M-positive advanced NSCLC who had disease progression after first-line EGFR TKI therapy. Patients were randomized to osimertinib or platinum-based therapy plus pemetrexed. Osimertinib significantly prolonged investigator-assessed PFS versus chemotherapy (10.1 vs 4.4 months; HR: 0.30; 95% CI:

Figure 2. Testing algorithms for detection of T790M. Conventional paradigm (A) and an alternate proposal with the incorporation of plasma-based assays (B).

FFPE: Formalin-fixed, paraffin-embedded; TKI: Tyrosine kinase inhibitor.

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0.23–0.41; $p < 0.001$) and was associated with a significantly higher response rate (71 vs 31%; odds ratio [OR]: 5.39; 95% CI: 3.47–8.48; $p < 0.001$). OS data have not been reported [9].

With the emergence of third-generation EGFR TKIs, this is the first time a biopsy at progression has been needed to guide subsequent therapy. However, biopsy may not always be feasible due to accessibility, and even if it is, the procedure is not without risk. In addition, scheduling the biopsy and performing testing can ultimately delay subsequent therapy. Biopsies are also associated with a failure rate of 5–10%, despite availability of sufficient tissue, and they may not reflect differences in tumors across sites [39]. As a result, there is increased interest in noninvasive genotyping by analysis of cell-free plasma DNA. A *post hoc* analysis of AURA showed that sensitivity of plasma genotyping for *EGFR* T790M was 70% in patients who were T790M-positive on central tumor genotyping [40]. Moreover, outcomes were similar in patients with T790M-positive disease that was detected in plasma or based on tumor biopsy [40]. Some patients had positive T790M on tissue but not on liquid biopsy, related to the lower sensitivity of plasma analyses. Interestingly, some patients had positive T790M on liquid biopsies that was not observed in the tumor tissue, a situation which may reflect spatial heterogeneity, with possible impact on the efficacy of osimertinib. As such, the authors suggested that plasma genotyping could be performed as an initial step to detect T790M mutations, and that patients who were T790M-positive by plasma could proceed with third-generation TKI therapy without biopsy; however, those with T790M-negative results in plasma should have a tumor biopsy to confirm T790M-negativity/positivity and determine subsequent therapy (Figure 2). Further analysis of methods for detection of *EGFR* mutations (Del19, L858R and T790M) in plasma was performed using data from the AURA3 trial, which enrolled only patients with confirmed T790M mutations [41]. Three plasma assays – allele-specific PCR, droplet digital PCR and next-generation sequencing – were used, with droplet digital PCR and next-generation sequencing showing higher sensitivity for detection of T790M compared with allele-specific-PCR [41].

Third-generation EGFR TKIs as first-line treatment

Osimertinib has recently been evaluated in a first-line setting in the randomized Phase III trial, FLAURA [10]. In this study, patients with common (Del19/L858R) *EGFR* mutations were randomized to osimertinib or a first-generation EGFR TKI, whereby the specific EGFR TKI (erlotinib or gefitinib) was chosen by the site as the sole comparator prior to site initiation. The primary end point – PFS by investigator assessment – was significantly improved in the osimertinib arm versus the erlotinib/gefitinib arm (median, 18.9 vs 10.2 months; HR: 0.46; 95% CI: 0.37–0.57; $p < 0.0001$; Table 1). PFS benefit was consistent across subgroups, including race, age, gender and presence of stable CNS metastases at baseline. The response rate was similar between treatment arms (80% with osimertinib and 76% with erlotinib/gefitinib; OR: 1.28; 95% CI: 0.85–1.93; $p = 0.2335$). However, median duration of response was 17.2 months with osimertinib versus 8.5 months with erlotinib/gefitinib. At data cutoff, OS data were immature (25%). Importantly, censoring of OS started at 15 months, which is when crossover from erlotinib/gefitinib to osimertinib may start to have an impact [10]; as such, the OS results are awaited with interest. Similar to the results from AURA and AURA3, plasma testing for *EGFR* mutations within the FLAURA trial showed good concordance with tissue testing, supporting the use of plasma testing in clinical practice to identify patients suitable for treatment [42].

While FLAURA supports that osimertinib is more effective than erlotinib/gefitinib, the results should be considered further in light of several limitations. First, despite being the only approved second-generation EGFR TKI, afatinib was not included as a comparator. In light of emerging differences between first- and second-generation EGFR TKIs observed in LUX-Lung 7 and ARCHER 1050, this precludes any evaluation of clinical benefit for osimertinib over a second-generation EGFR TKI. Additionally, as well as the OS data from FLAURA (and AURA3 for the sequencing strategy), we await further details on efficacy by TKI comparator (erlotinib or gefitinib) and information on subsequent therapies. Based on current standard practice, most patients with *EGFR* mutation-positive NSCLC receive a first- or second-generation TKI in the first-line until disease progression. Will results from FLAURA change this treatment paradigm? While it would appear likely that osimertinib will become a first-line treatment option for *EGFR* mutation-positive NSCLC, the optimal first-line choice remains complex. In the next section, we consider some of the key arguments that have emerged following presentation of the FLAURA data.

Factors influencing first-line treatment choice: mechanisms of resistance & subsequent therapy options

With the availability of multiple agents for *EGFR* mutation-positive NSCLC, treatment needs to be considered in terms of a long-term plan to maximize survival. Thus, the sequence of treatment and consideration of the molecular status of the tumor is of key importance. In the Phase III trials of first-generation EGFR TKIs, rates of subsequent therapy were generally high (around 60–70%) [17,18,20]. With regard to the second-generation EGFR TKIs, detailed analysis of the LUX-Lung 3, 6 and 7 trials showed that 71% of patients received a further line of treatment following discontinuation of afatinib, with 28% of patients receiving four lines of subsequent treatment [43]. Subsequent therapy after afatinib predominantly consisted of platinum-based chemotherapy, with others including single-agent chemotherapy, first-generation EGFR TKI monotherapy, chemotherapy combination therapies and third-generation EGFR TKIs, thus suggesting a range of potential treatment options post-afatinib that may impact survival of patients. Furthermore, subsequent treatment duration was similar irrespective of *EGFR* mutational subgroup (Del19/L858R) [43].

As previously discussed, acquisition of an *EGFR* T790M mutation is the predominant mechanism of resistance for first- and second-generation TKIs. For patients with T790M-positive NSCLC who have progressed on an EGFR TKI, osimertinib is now a clear treatment of choice based on data from AURA and AURA3. Due to lack of availability of third-generation EGFR TKIs and the fact that T790M testing was not mandated at the time the LUX-Lung 3, 6 and 7 trials were conducted, only a minority of patients ($n = 37$) received osimertinib, primarily in the third- or later-line setting [43]. Analysis of these patients has to be interpreted with caution, based on small sample size and the possibility of sample enrichment; for instance, the median duration of treatment with first-line treatment in these patients was notably long at 21.9 months. Nevertheless, exploratory hypothesis-generating analysis of time on osimertinib and OS in patients starting on afatinib who received subsequent osimertinib in any line was highly encouraging. Median time on osimertinib in any treatment line was 20.2 months, and median follow-up for osimertinib-treated patients was greater than 4 years. At this time, median OS had not yet been reached [43]. In the current treatment landscape, it is likely that many patients will be eligible for, and able to receive

osimertinib after front-line first- and second-generation *EGFR* TKIs, with achievement of prolonged OS. However, those data obviously correspond to a focus on patients who ultimately received multiple lines of treatment, and not the whole intent-to-treat population enrolled in those trials.

Of course, we should also consider that patients who receive first- or second-generation *EGFR* TKIs in first-line can develop resistance based on mechanisms other than T790M acquisition. Other identified mechanisms of acquired resistance include small-cell histologic transformation, *MET* amplification and *HER2* amplification [44]. However, treatment of T790M-negative disease is an area of unmet medical need and, currently, platinum-doublet chemotherapy is the principal treatment option for patients with T790M-negative disease after first- or second-generation *EGFR* TKIs. In some cases, continuation of the first-line *EGFR* TKI, potentially with local therapy for asymptomatic or loco-regional progression may be feasible. Additionally, the combination of afatinib with the *EGFR*-targeting monoclonal antibody, cetuximab, was associated with a response rate of 25% and median PFS of 4.6 months in patients with *EGFR* TKI-resistant T790M-negative NSCLC [45]. Other options currently under investigation include immuno-oncology agents, such as nivolumab, and novel targeted agents, potentially as combination therapy (e.g., osimertinib plus savolitinib [a *MET* inhibitor] or selumetinib [a MEK1/2 inhibitor]) [46]. Phase II data with the erlotinib and bevacizumab combination are also available [47,48].

The results from FLAURA pose a challenge for treating physicians. It may seem intuitive to start with an agent that provides improved PFS versus first-generation *EGFR* TKIs, albeit without any evidence versus second-generation TKIs. However, OS data are immature and, as such, it may be premature to alter standard treatment based on these results. This becomes even more relevant when we consider the potential treatment options post-osimertinib. Resistance mechanisms for osimertinib are currently not well understood and appear to be heterogeneous. Most information available is based on small cohort analyses. For example, in the cohort of treatment-naïve patients in AURA, osimertinib resistance mechanisms were evaluated in 19 patients [49]. Potential resistance mechanisms were identified in nine patients, and included *MET*, *EGFR* and *KRAS* amplification, *KRAS* or *PIK3CA* mutations and *EGFR* C797S mutation. However, resistance mechanisms could not be identified in the remaining ten patients. Another analysis of 23 patients with acquired resistance to osimertinib identified *MET* amplification and *EGFR* C797S mutations as the predominant mechanisms of resistance [50]. Other reported mechanisms include small-cell transformation [51–53], *EGFR* L781Q mutation [54], *ERBB2* amplification [55] and *BRAF* mutations [56]. Preclinical studies have also identified potential resistance mechanisms. For example, cells that are resistant to osimertinib appear to have enhanced levels of phosphorylated MEK and may be particularly sensitive to combined *EGFR* and MEK inhibition [57,58]. The identification of heterogeneous resistance mechanisms to osimertinib has prompted the initiation of several early-phase clinical trials [59]. The ongoing Phase IB TATTON trial (NCT02143466) is assessing the combination of osimertinib with the MEK1/2 inhibitor, selumetinib, the immune checkpoint inhibitor, durvalumab, or the *MET* inhibitor, savolitinib, in patients with *EGFR* mutation-positive NSCLC who have progressed on an *EGFR* TKI. Other Phase I studies are assessing the combination of osimertinib with the VEGFR2 antibody, ramucirumab, or the *EGFR* antibody, necitumumab, in patients with T790M-positive NSCLC (NCT02789345) and the combination of osimertinib with navitoclax, a BCL-2 family inhibitor (NCT02520778).

The types of mutations observed with osimertinib have important implications for potential subsequent therapies. For example, C797S mutations can occur *in cis* (on the same allele) or *in trans* (on a different allele) with T790M [60] or indeed can occur without T790M (loss of T790M mutation) [61]. For those that occur *in trans*, combination therapy of first-generation *EGFR* TKIs with third-generation *EGFR* TKIs may be feasible [62]. However, C797S mutations *in cis* with T790M are likely to be resistant to first- and second-generation *EGFR* TKIs, precluding their use post-osimertinib. Patients with tumors with *ERBB2* or *MET* amplification may be suitable for investigational compounds that target these pathways. However, outside of suitable clinical trials and for unknown driver mutations, the likely second-line treatment after osimertinib will be chemotherapy. In AURA3, subsequent therapy was received in 24% of patients in the osimertinib group compared with 71% of the chemotherapy group [9]. In the AURA Phase II expansion cohort, 41% of patients were treated after progression on osimertinib [7]. While it must be acknowledged that osimertinib was being evaluated in a second-line setting in these trials, these data might indicate limited treatment options after osimertinib.

As such, the overall sequence of first- or second-generation TKIs followed by osimertinib may offer improved survival outcomes versus osimertinib in first-line; OS data from AURA3 and FLAURA will be of interest to analyze treatment sequences further (Figure 3). On the other hand, holding back osimertinib for second-line use will mean that a proportion of patients with *EGFR* mutation-positive NSCLC will never receive osimertinib and its associated efficacy and tolerability benefits. Nevertheless, given the predominance of T790M-driven resistance (50–70% [6,7]

Figure 3. Potential treatment sequences in *EGFR* mutation-positive non-small-cell lung cancer after first-line *EGFR* tyrosine kinase inhibitor.

OS: Overall survival; TKI: Tyrosine kinase inhibitor.

of patients) and high uptake of postprogression therapy, around 50% of patients could ultimately receive sequential *EGFR* TKIs. Ultimately, prospective clinical trials assessing sequential treatment with first- or second-generation TKIs followed by osimertinib versus osimertinib followed by appropriate second-line treatment are required. The European Organisation for Research and Treatment of Cancer APPLE study is currently ongoing with this aim (NCT02856893), integrating the use of cell-free DNA analyses.

Factors influencing first-line treatment choice: brain metastases

Patients with *EGFR* mutation-positive NSCLC appear to be particularly prone to the development of brain metastases [63]. Thus, efficacy and safety of *EGFR* TKIs in patients with *EGFR* mutation-positive NSCLC and brain metastases is of high importance. Preclinical studies suggest that osimertinib is able to cross the blood–brain barrier [64]. Moreover, in FLAURA, osimertinib significantly prolonged PFS compared with erlotinib/gefitinib in patients with asymptomatic brain metastases (HR: 0.47; 95% CI: 0.30–0.74); this difference was a similar magnitude to that in patients without brain metastases (HR: 0.46; 95% CI: 0.36–0.59). *De novo* CNS progression events were also lower with osimertinib than erlotinib/gefitinib (6 vs 15%) [10].

Several prospective studies have indicated that the first-generation TKIs, erlotinib and gefitinib, have clinical activity in patients with NSCLC and brain metastases, although there are limited data regarding direct intracranial activity [65,66]. These findings are consistent with observations that erlotinib and gefitinib can permeate the blood–brain barrier, albeit inefficiently [67–71]. In an effort to increase drug concentrations in the brain, several studies have assessed high-dose regimens of gefitinib or erlotinib in patients with *EGFR* mutation-positive NSCLC and brain metastases [67,69]. A number of retrospective studies have assessed the combination of first-generation *EGFR* TKIs with whole-brain radiation therapy (WBRT), which is thought to increase permeability of the blood–brain barrier [72–74]. These studies indicate that concomitant WBRT may enhance the intracranial activity of first-generation TKIs.

The second-generation inhibitor, afatinib, has demonstrated efficacy in patients with stable brain metastases at baseline. Analysis of the LUX-Lung 3 and 6 trials showed that afatinib improved PFS versus chemotherapy in patients with asymptomatic brain metastases (HR: 0.50; 95% CI: 0.27–0.95). Afatinib also delayed CNS

progression compared with chemotherapy, and for most patients with baseline brain metastases, the brain was not the site of first disease progression [75]. Furthermore, an additional competing risk analysis in afatinib-treated patients with baseline brain metastases showed that the cumulative incidence of CNS progression was lower than that of non-CNS progression (31 vs 52%; Figure 4). Risk of *de novo* CNS progression with afatinib was also very low (observed in only 6% of patients receiving afatinib in LUX-Lung 3 and 6). Non-CNS progression for patients without baseline brain metastases was 78% [BOEHRINGER INGELHEIM, DATA ON FILE].

Overall, both afatinib and osimertinib have demonstrated activity in patients with asymptomatic brain metastases at standard therapeutic doses, while there are also limited data showing activity of erlotinib and gefitinib in patients with brain metastases, especially as high-dose regimens or in combination with WBRT. Further data on the impact of these agents on brain metastases are required, as well as long-term outcomes (including impact of subsequent therapy), to help determine which agent is the most appropriate first-line option for these patients.

Factors influencing first-line treatment choice: tolerability profile

EGFR TKIs are associated with a predictable, class-related AE profile, based on their mode of action. Inhibition of wild-type EGFR results in characteristic gastrointestinal (e.g., diarrhea) and skin (e.g., rash) AEs, although there are some differences in the AE profile between different EGFR TKIs. For example, in LUX-Lung 7, the most common drug-related grade 3/4 AEs with afatinib were diarrhea (13%), rash or acne (9%) and fatigue (6%), while elevated liver enzymes (9%) and rash or acne (3%) were the most common drug-related grade 3/4 AEs with gefitinib [28]. Treatment discontinuations due to treatment-related AEs were equally low in both treatment groups (6.3%). This is partly due to the well-defined dose adjustment protocol for management of afatinib-associated AEs. *Post hoc* analysis from LUX-Lung 3, 6 and 7 showed that dose adjustment resulted in a reduction in the frequency and severity of AEs, as would be expected. Importantly, however, this did not impact on efficacy: median PFS was similar in patients who received a dose reduction within the first 6 months of treatment and those who remained on the 40-mg dose (or 50 mg) [76,77].

Osimertinib and other third-generation EGFR TKIs were designed to be EGFR wild-type sparing in an effort to improve tolerability. The overall incidence of treatment-related AEs in FLAURA was similar between osimertinib and gefitinib (91 and 92%, respectively), but with a lower incidence of grade ≥ 3 treatment-related AEs for osimertinib (18 vs 28%). The most common grade 3/4 treatment-related AEs with osimertinib were decreased appetite (3%) and diarrhea (2%) [10,78]. Information on discontinuations due to treatment-related AEs in FLAURA are not available yet; however, the discontinuation rate due to any AE was 13% in the osimertinib group and 18% in the erlotinib/gefitinib group [10].

Overall, osimertinib has a favorable safety profile. However, it should be considered that the most likely second-line treatment after osimertinib will be chemotherapy. The tolerability profile of chemotherapy can be extremely challenging for patients, especially in later-line treatment, with a detrimental impact on patient quality of life. In contrast, the majority of patients receiving a first- or second-generation EGFR TKI will likely be able to receive osimertinib in second-line, thus prolonging their chemotherapy-free period. Given that EGFR TKIs are generally better tolerated than chemotherapy, sequential use of EGFR TKIs may offer improved tolerability and quality of life in the longer term. Again, data from AURA3 and FLAURA are awaited.

One final consideration is the potential for drug–drug interactions. Gefitinib and erlotinib undergo extensive hepatic metabolism via CYP450 enzymes; additionally, erlotinib is a potent inhibitor of CYP1A1 and a moderate inhibitor of CYP3A4 and CYP2C8 [79]. Osimertinib is metabolized by CYP3A4 and CYP3A5, may inhibit breast cancer resistance protein and may induce CYP3A4, CYP1A2 and CYP2C [80,81]. In contrast, afatinib undergoes minimal hepatic metabolism and is not a substrate for CYP-dependent enzymes [79]. This would suggest that afatinib has a low potential for drug–drug interactions, which is an important factor in patients with advanced NSCLC, many of whom may have additional co-morbidities and are likely to be receiving multiple medications.

Conclusion

Gefitinib, erlotinib and afatinib are approved for the first-line treatment of *EGFR* mutation-positive NSCLC. Emerging evidence suggests that second-generation inhibitors may be more effective than first-generation TKIs. Following disease progression on these agents, osimertinib, a third-generation EGFR TKI, has shown considerable efficacy in patients with T790M-positive disease, and is approved in this setting. For patients with T790M-negative disease, options are more limited, and chemotherapy is the current principal treatment. Recent data from FLAURA showed that osimertinib had superior PFS to first-generation TKIs in the first-line setting, positioning osimertinib

Figure 4. Competing risk analysis for progression in afatinib-treated patients. Risk of progression in patients with baseline brain metastases (LUX-Lung 3 and 6; [A]) and those without baseline brain metastases (LUX-Lung 3, 6 and 7; [B]). PD: Progressive disease.

Figure 5. Evidence to evaluate when choosing the sequence in patients with *EGFR* mutation-positive non-small-cell lung cancer.

TKI: Tyrosine kinase inhibitor.

as another first-line choice. While, given the results from FLAURA, it may seem intuitive to use osimertinib in the first-line, it is important to consider the long-term treatment plan. Currently, subsequent treatment options for osimertinib are not clearly defined, and mature OS data are not available. Extent of OS from FLAURA will be of great interest, as we cannot extrapolate from the sum of median PFS in individual trials. In LUX-Lung 3, 6 and 7, afatinib was associated with median OS of around 30 months in patients with NSCLC and common (Del19/L858R) mutations, despite few patients receiving a subsequent T790M inhibitor (due to availability) [26,82]. In some cases, it may also be appropriate for patients to receive treatment beyond progression (as seen in LUX-Lung 7 and AURA3). In addition, use of local therapies with continued *EGFR* TKI treatment, for oligoprogression or focal progression, may provide long-term disease control for some patients [83].

Although there is a lack of data-assessing sequential treatment with *EGFR* TKIs, initial hypothesis-generating data show that sequential afatinib followed by osimertinib confers encouraging survival outcomes in *post hoc* analysis (median OS not yet reached after a median follow-up of >4 years) for the subset of patients treated with the sequence. Overall, further research is needed to determine the most appropriate sequential therapy to optimize clinical benefit in patients with *EGFR* mutation-positive NSCLC. An illustrated summary of this section can be found in Figure 5.

Future perspective

Over the next 5–10 years, it is likely that research will focus on outcomes and tolerability of different sequences, for example, first- or second-generation TKIs followed by a third-generation TKI, or a third-generation TKI followed by appropriate treatment. This will enable us to determine the optimal treatment sequence to prolong patient survival, while maintaining quality of life. Additional research on mechanisms of resistance and suitable post-treatment options for the third-generation TKI, osimertinib, will be of great interest, particularly if it is possible to target specific mutations and thus enable personalized medicine. There is rationale for novel combination regimens in the post-osimertinib setting and the results of ongoing early-phase trials are eagerly awaited. Treatment options for patients with T790M-negative disease following progression on an *EGFR* TKI are also likely to evolve, given the unmet medical need in this patient population. Further assessment of currently available *EGFR* TKIs for patients with brain metastases could help to define the optimal treatment for these patients, along with novel agents that can effectively penetrate the blood–brain barrier.

Supplementary data

A video abstract and transcript are available as an accompaniment to this paper. To view the supplementary transcript for this please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2017-0636.

Financial & competing interests disclosure

N Girard has acted as a consultant and received financial assistance for travel from AstraZeneca, Hoffman LaRoche, Boehringer Ingelheim and Pfizer. The author has also received academic grants from AstraZeneca, Hoffman LaRoche, Boehringer Ingelheim and Pfizer. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by C Allinson of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the preparation of this article.

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Executive summary

First- & second-generation EGFR tyrosine kinase inhibitors

- The first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib and afatinib, have demonstrated robust efficacy for the first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), and are approved in this indication.
- Recent data suggest that second-generation ERBB family blockers, afatinib and dacomitinib, have improved efficacy compared with first-generation EGFR TKIs, erlotinib and gefitinib.

Third-generation EGFR TKIs in patients with acquired resistance

- Despite the evidence observed in the first-line setting with first- and second-generation TKIs, resistance develops, predominantly due to acquisition of the *EGFR* T790M mutation.
- The third-generation EGFR TKIs show high potency for T790M mutations. Osimertinib significantly prolonged progression-free survival versus chemotherapy in patients with T790M-positive NSCLC who had disease progression after first-line EGFR TKI therapy, and is approved in this setting.

Third-generation EGFR TKIs as first-line treatment

- Recently, osimertinib has demonstrated improved progression-free survival versus the first-generation EGFR TKIs in the first-line setting.

Factors influencing first-line treatment choice: mechanisms of resistance & subsequent therapy

- For patients who receive a first- or second-generation EGFR TKI and experience resistance due to a T790M mutation (around 50–70% of cases), osimertinib is a clear treatment of choice.
- For patients who receive a first- or second-generation EGFR TKI and experience resistance due to another mechanism, chemotherapy is the principal treatment; options, including afatinib in combination with cetuximab or immuno-oncology agents in combination with novel targeted agents, are under investigation.
- Resistance mechanisms for osimertinib appear heterogeneous, with *MET* amplification, small-cell transformation and *EGFR* C797S mutation identified as the main mechanisms. The likely current second-line treatment option post-osimertinib will be chemotherapy, although investigational agents within clinical trials may be suitable for particular mutations.
- Further information on the overall sequence of first- or second-generation TKIs followed by osimertinib versus osimertinib in first-line are required.

Factors influencing first-line treatment choice: brain metastases

- Osimertinib and afatinib have both demonstrated activity in patients with brain metastases in prospective randomized trials, while evidence for erlotinib and gefitinib is more limited.
- Further information on long-term outcomes of patients with brain metastases is required to determine the best first-line treatment option.

Factors influencing first-line treatment choice: tolerability profile

- EGFR TKIs have a predictable, class-related adverse event (AE) profile, although there are some differences between different EGFR TKIs.
- Afatinib has a well-defined dose adjustment protocol for management of treatment-related AEs, which does not impact on efficacy.
- Osimertinib, which is EGFR wild-type sparing, has a favorable safety profile, with a lower incidence of grade ≥ 3 treatment-related AEs than gefitinib.
- The tolerability of the overall treatment sequence should also be considered.

Conclusion

- Erlotinib, gefitinib and afatinib are approved for the first-line treatment of *EGFR* mutation-positive NSCLC, and recent data have also positioned osimertinib as a potential first-line treatment option.
- Selecting the optimal first-line treatment requires consideration of patient factors, subsequent therapy options for long-term treatment and the tolerability profile of the overall treatment sequence.

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