Afatinib in the first-line treatment of epidermal-growth-factor-receptor mutation-positive non-small cell lung cancer: a review of the clinical evidence

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***Abstract*:** First-line afatinib significantly improved progression-free survival, patient-reported outcomes, and quality of life compared with chemotherapy regimens in patients with advanced epidermal-growth-factor-receptor (*EGFR*) mutation-positive non-small cell lung cancer, based on results of the LUX-Lung 3 and LUX-Lung 6 trials. When the analysis of these trials was restricted to patients with common *EGFR* mutations only (exon 19 deletions and L858R), the advantage over chemotherapy was even more pronounced. A significant overall survival advantage was firstly demonstrated *versus* chemotherapy in patients with non-small cell lung cancer-harboring *EGFR* exon 19 deletion (del19) mutations. First-line afatinib was also effective in patients with certain uncommon *EGFR* mutation and patients with central nervous system metastasis. So far, these data are not sufficient to conclude that afatinib is better than first-generation EGFR inhibitors. In addition, the toxicity profile of afatinib was somewhat worse than that observed with either erlotinib or gefitinib. In the absence of direct comparisons, for each patient the choice among the available EGFR inhibitors should take into account all the clinically relevant endpoints, including disease control, survival prolongation, tolerability, and quality of life.

Keywords: afatinib, *EGFR* mutation, first-generation EGFR-TKI, non-small cell lung cancer

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) are recognized as standard first-line therapies for non-small cell lung cancer (NSCLC) patients with activating epidermal growth factor receptor mutations (*EGFR* mutations) [Azzoli *et al.* 2011]. Findings from six pivotal randomized phase III studies done in this genetically selected subset of patients with lung cancer have shown better progression-free survival (PFS) and responses with gefitinib or erlotinib than with platinum-based chemotherapy [Mok *et al.* 2009; Maemondo *et al.* 2010; Mitsudomi *et al.* 2010; Zhou *et al.* 2011; Han *et al.* 2012; Rosell *et al.* 2012]. However, there were no differences in overall survival (OS) between EGFR-TKIs and chemotherapy in these studies, most likely because of the high proportion of crossover from chemotherapy to EGFR-TKIs observed after study completion and the strong response to EGFR-TKIs in the salvage setting. Moreover, all patients inevitably develop acquired resistance to these agents, primarily due to secondary *EGFR*-T790M mutations, molecular aberrations affecting other signaling pathways, or transformation to small-cell histology [Sequist *et al.* 2011; Yu *et al.* 2013]. Next-generation tyrosine kinase inhibitors (TKIs) (including afatinib as second-generation inhibitor and T790M-mutant-selective third-generation inhibitors) have been developed in order to improve survival benefits and possibly overcome acquired resistance to EGFR-TKIs.

Afatinib, a second-generation irreversible TKI that inhibits signaling from all homodimers and heterodimers formed by ErbB receptor-family

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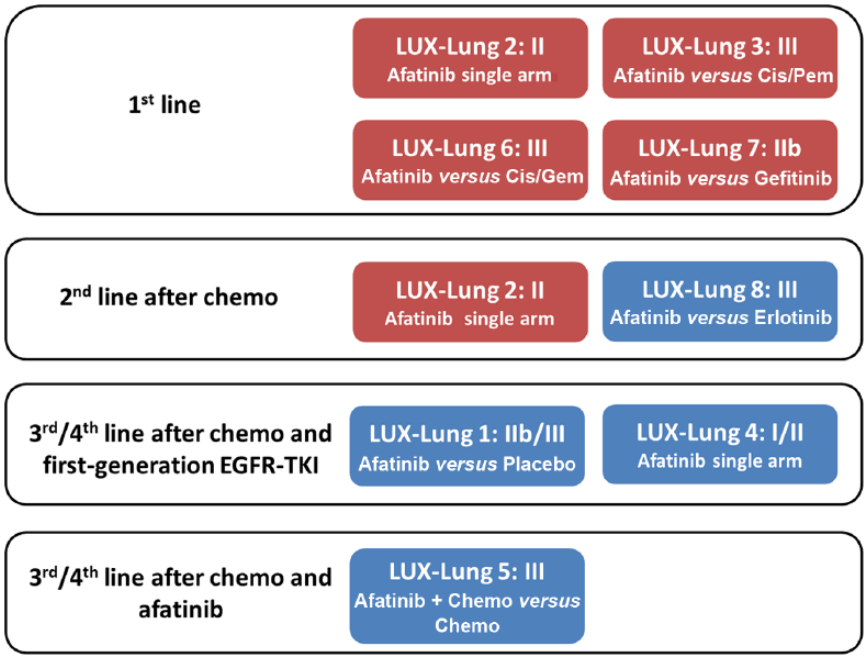

Figure 1. Summary box of LUX-Lung trials with afatinib in non-small cell lung cancers.
Red box: clinical trials in *EGFR* mutation-positive patients; Blue box: clinical trials in unselected patients
Cis, cisplatin; Pem, pemetrexed; Gem, gemcitabine; Chemo: chemotherapy.

members (including EGFR, ErbB2, ErbB3, and ErbB4), has shown potent preclinical antitumor activity in both EGFR-TKI-naïve and -resistant cultured cells and xenograft models, providing biological rationale for the evaluation of afatinib in clinical trials [Li *et al.* 2008; Solca *et al.* 2012]. The implication was that this agent might work better in the long run and actually provide therapeutic salvage for patients whose tumors had progressed during treatment with first-line EGFR-TKIs. An intense program of clinical research (the LUX-Lung program, Figure 1) was developed in several categories of NSCLC patients (*EGFR*-mutated and wild-type tumors, reversible EGFR-TKIs-naïve or -resistant patients, and adenocarcinoma and squamous cell carcinoma histology). There was great hope that afatinib would be highly effective for patients with acquired resistance when it was developed. Nevertheless, it turned out to be rather disappointing in these patients, probably as a result of dose limitations from toxicity caused by inhibiting wild-type EGFR simultaneously [Miller *et al.* 2012]. Thus, afatinib cannot inhibit T790M mutation (the most common mechanisms of EGFR-TKI-acquired resistance) at tolerable doses in humans. The first global approval of afatinib was granted by the US FDA on 12 July 2013 for the first-line treatment of *EGFR*-mutation-positive metastatic NSCLC, supported by the results of LUX-Lung 3 (LL3) [Sequist *et al.* 2013]. After that, a lot of countries including Europe, Japan and Taiwan, have approved the use of afatinib in treatment-naïve or EGFR-TKI-naïve NSCLC. This article mainly focuses on data of afatinib in first-line treatment of *EGFR*-mutation-positive NSCLC. The use of afatinib in other indications is beyond the scope of this review.

Afatinib *versus* chemotherapy in the first-line treatment of epidermal-growth-factor receptor common mutation-positive non-small cell lung cancer

Progression-free survival benefit

The LL3 (345 patients recruited globally) and LUX-Lung 6 (LL6) (364 patients recruited in Asia) trials were the largest randomized, phase III trials ever to be undertaken in treatment-naïve patients with *EGFR*-mutation-positive advanced NSCLC [Sequist *et al.* 2013; Wu *et al.* 2014]. Patients were randomly assigned, with a 2:1 ratio, to receive afatinib 40 mg daily or up to six cycles of standard-of-care platinum-based chemotherapy every 21 days (cisplatin/pemetrexed in LL3 and cisplatin/gemcitabine in LL6). Mutation-positive patients were stratified by mutation type [exon 19 deletion (del19), L858R, or other] and race (Asian

Table 1. Progression-free survival and overall survival benefit from LUX-Lung 3 and LUX-Lung 6 trials.

	n	Median PFS (months)	HR for PFS (95% CI)	Median OS (months)	HR for OS (95% CI)
LUX-Lung 3					
Del19	170	13.7	0.28 (0.18–0.44)	33.3 *versus* 21.1	0.54 (0.36–0.79)
L858R	138	11.0	0.73 (0.46–1.16)	27.6 *versus* 40.3	1.30 (0.80–2.11)
Del19+L858R	308	13.6 *versus* 6.9	0.47 (0.34–0.65)	31.6 *versus* 28.2	0.78 (0.58–1.06)
LUX–Lung 6					
Del19	186	13.7	0.20 (0.13–0.32)	31.4 *versus* 18.4	0.64 (0.44–0.94)
L858R	138	9.6	0.32 (0.19–0.54)	19.6 *versus* 24.3	1.22 (0.81–1.83)
Del19+L858R	324	11.0 *versus* 5.6	0.25 (0.18–0.35)	23.6 *versus* 23.5	0.83 (0.62–1.09)

EGFR-TKI *versus* chemotherapy.
PFS, progression-free survival; HR, hazard ratio; OS, overall survival; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CI, confidence interval.

or non-Asian). Both trials met their primary endpoints of PFS by independent blinded review. Afatinib significantly prolonged median PFS *versus* chemotherapy in both LL3 [11.1 *versus* 6.9 months; hazard ratio (HR) = 0.58; 95% CI, 0.43 to 0.78; $p < 0.001$] and LL6 (11.0 *versus* 5.6 months; HR = 0.28; 95% CI, 0.20 to 0.39; $p < 0.0001$). Significantly higher response rates were observed with afatinib compared with chemotherapy, 56% *versus* 23% and 67% *versus* 23% in LL3 and LL6, respectively, according to independent assessments. When the analysis was restricted to patients with common *EGFR* mutations only (del19s and L858R), the advantage over chemotherapy was even more pronounced **(Table 1)**. Median PFS in LL3 patients with *EGFR* common mutations was 13.6 months for afatinib and 6.9 months for chemotherapy (HR = 0.47; 95% CI, 0.34 to 0.65; $p = 0.001$). Overall, these results had confirmed the efficacy of afatinib in selected patients for *EGFR* mutations, and overlapped the previous trials with reversible EGFR-TKIs, as erlotinib and gefitinib in the first-line setting [Mok *et al.* 2009; Maemondo *et al.* 2010; Mitsudomi *et al.* 2010; Zhou *et al.* 2011; Han *et al.* 2012; Rosell *et al.* 2012; Wu *et al.* 2015].

Overall survival benefit

Moreover, a trend towards OS benefit was observed in a prespecified analysis of median OS in patients with common mutations (LL3, 31.6 *versus* 28.2 months; HR = 0.78, 95% CI, 0.58 to 1.06; $p = 0.11$; LL6, 23.6 *versus* 23.5 months; HR = 0.83, 95% CI, 0.62 to 1.09; $p = 0.18$), whereas in the overall dataset (all *EGFR* mutations), no significant difference was observed between the two arms (LL3, 28.2 *versus* 28.2 months; HR = 0.88, 95% CI, 0.66 to 1.17; $p = 0.39$; LL6, 23.1 *versus* 23.5 months; HR = 0.93; 95% CI, 0.72 to 1.22; $p = 0.61$) **[Yang *et al.* 2015c]**. As a subgroup analysis of a secondary endpoint (both LL3 and LL6 had PFS as the primary endpoint), patients who had the *EGFR*-del19 mutation and received afatinib had a median OS duration that was prolonged by 1 year compared with patients who received chemotherapy (LL3: HR = 0.54; 95% CI, 0.6 to 0.79; $p = 0.0015$; LL6: HR = 0.64; 95% CI, 0.44 to 0.94; $p = 0.023$). By contrast, no significant differences in OS were found by treatment group for patients with *EGFR*-L858R-positive tumors in either LL3 (HR = 1.30; 95% CI, 0.80 to 2.11; $p = 0.29$) or LL6 (HR = 1.22; 95% CI, 0.81 to 1.83; $p = 0.34$).

In the pooled analysis of these two randomized trials, afatinib had significantly improved OS compared with chemotherapy among patients with tumors harboring common *EGFR* mutations (HR = 0.81; 95% CI, 0.66 to 0.99; $p = 0.037$) [Yang *et al.* 2015c]. Consistent with individual study findings, subgroup analyses suggested that the OS benefit of afatinib was driven mainly by patients with lung adenocarcinoma harboring the *EGFR*-del19 mutation (HR = 0.59; 95% CI, 0.45 to 0.77; $p = 0.0001$), whereas in patients with L858R-positive tumors there was no difference between treatment arms (HR = 1.25; 95% CI, 0.92 to 1.71; $p = 0.16$). As emphasized by the investigators, the impressive advantage in OS reported in patients with lung adenocarcinoma harboring del19 mutations strongly suggested that the 19 deletions and L858R mutation represent

two distinct subclasses of NSCLC, and should be studied separately in future trials.

Furthermore, although most patients in LL3 and the entire population of LL6 were Asian, a significant OS improvement with afatinib in the del19 subgroup was also noted in the smaller subpopulation of non-Asian patients in LL3 (33.6 *versus* 20.0 months; HR = 0.45; 95% CI, 0.21 to 0.95; $p = 0.03$). In the Chinese subgroup of LL6, median OS was 31.6 *versus* 16.3 months (HR = 0.61; 95% CI, 0.41 to 0.91; $p = 0.015$) in 19 deletions [Wu *et al.* 2014]. There was argument that there was less crossover to TKI in the chemotherapy arms therefore these arms were underperforming. However, in the LL3 subgroup analysis of Japanese patients, where there was 100% crossover, results showed afatinib was still associated with significantly improved OS in those with del19 mutations (46.9 *versus* 31.5 months; HR = 0.34; 95% CI, 0.13 to 0.87; $p = 0.018$) [Kato *et al.* 2015]. These subgroup data supported the concept that the OS benefit with afatinib over chemotherapy in patients with del19 mutation was a real phenomenon, independent of ethnicity.

Symptom and quality-of-life improvement

Patient-reported outcomes (PROs) are clinically meaningful treatment outcomes that are directly assessed by patients and reflect their disease-related symptoms, functional activity and health-related quality of life (QoL). In clinical trials for patients with advanced cancer such as NSCLC, the validity of PFS as a relevant primary endpoint requires not only rigorous and objective assessment of tumor progression but also a parallel benefit in PROs [Fallowfield and Fleissig, 2012; Damm *et al.* 2013]. Both LL3 and LL6 fully integrated comprehensive PRO evaluation into outcome analyses, demonstrating improvements in lung cancer-related symptoms and QoL, and a longer time to deterioration of these PROs [Yang *et al.* 2013; Geater *et al.* 2015]. Compared with chemotherapy, afatinib led to a significant delay in the time-to-deterioration for cough and dyspnea. The adverse-event (AE) profiles of both treatments were also reflected in the PRO symptom analysis, with worsening nausea, vomiting, and fatigue on the chemotherapy arm, and worsening diarrhea, dysphagia, and sore mouth on afatinib. Finally, and perhaps most importantly, afatinib was associated with significantly better mean scores in the longitudinal analysis of health status and QoL that captured patients' perception of treatment that likely accounted for changes in both disease symptoms and treatment-related AEs during the study period.

As the latest two front-line studies comparing EGFR blockade with standard chemotherapy in patients with the *EGFR* mutation, LL3 and LL6 are distinguished by a number of factors. First of all, this is the first time that an OS benefit has been demonstrated in patients with tumors that contain the *EGFR*-del19 mutations but no such benefit was observed in patients with L858R-positive tumors. Besides, the PFS exceeding 13 months achieved with afatinib in those with common mutations appears superior in the context of previous studies with erlotinib and gefitinib. Secondly, both studies enrolled well over 300 patients to meet the regulatory requirements of different regions, making it far more robust and thereby tightening the CIs around the benefits already noted in similar studies. Of note, pemetrexed and cisplatin, the control arm in LL3, was considered a state-of-the-art chemotherapy regimen according to data from Scagliotti and colleagues [Scagliotti *et al.* 2008].

Afatinib *versus* first-generation epidermal-growth-factor-receptor-tyrosine-kinase inhibitor in the first-line treatment of epidermal-growth-factor-receptor-mutation-positive non-small cell lung cancer

Efficacy

A total of nine phase III randomized controlled trials (RCTs) of advanced NSCLC patients with either 19 or 21 exon alteration receiving first-line EGFR-TKIs were published [Mok *et al.* 2009; Maemondo *et al.* 2010; Mitsudomi *et al.* 2010; Zhou *et al.* 2011; Han *et al.* 2012; Rosell *et al.* 2012; Sequist *et al.* 2013; Wu *et al.* 2014; Wu *et al.* 2015]. In each of these studies, significant improvements in PFS and response were reported with EGFR TKI therapy *versus* chemotherapy. None of the drugs demonstrated an OS benefit *versus* chemotherapy in the overall population or in *EGFR*-del19 or L858R-mutation subgroups, with the notable exception of afatinib [Lee *et al.* 2013; Yang *et al.* 2015c]. Possible explanation for the impressive advantage in OS might lie in mechanistic differences between the irreversible ERBB-family blocker afatinib and first-generation reversible EGFR-TKIs. Data derived from

indirect meta-analyses showed no statistically significant differences between afatinib and erlotinib or gefitinib in terms of PFS, but some numerical differences were observed, particularly in patients with common *EGFR* mutations [Popat *et al.* 2014]. The estimated HR (95% CI) for afatinib compared with gefitinib was 0.70 (0.40 to 1.16) and compared with erlotinib was 0.86 (0.50 to 1.50) in the total population, along with 0.60 (0.34 to 0.99) and 0.73 (0.42 to 1.24), respectively, in common mutants. The estimated probability of afatinib being the best treatment with regard to PFS in the total population was 70% *versus* 27% for erlotinib, 3% for gefitinib and 0% for chemotherapy. OS findings were not significantly different between treatments. Particularly, OS data for both afatinib trials were immature at the point of data cutoff for this analysis. According to another recently published meta-analysis, the pool HR for PFS was 0.24 in the del19 subgroup and 0.48 in the exon 21 L858R substitution subgroup. Compared with chemotherapy, treatment with EGFR-TKIs demonstrated 50% greater benefit in del19s than in exon 21 L858R mutations [Lee *et al.* 2015]. Increasing evidence demonstrates that they have different prognostic and predictive roles and are hence considerable as a stratification factor in clinical trials [Zhang *et al.* 2014; Lee *et al.* 2015; Yang *et al.* 2015c]. In the subgroup with del19s, the pooled HR for PFS was 0.24 (0.17 to 0.33) with afatinib and 0.25 (0.20 to 0.31) with first-generation EGFR-TKIs [Lee *et al.* 2015], prompting a similar effect among various EGFR inhibitors. The CTONG0901 study compared erlotinib *versus* gefitinib in patients with *EGFR* exon 19 or 21 mutations. There was no significant difference in either PFS (13.0 *versus* 10.4 months, $p = 0.100$) or OS (22.9 *versus* 20.1 months, $p = 0.210$) [Yang *et al.* 2015d].

The indirect retrospective comparison across completed studies of afatinib *versus* gefitinib/erlotinib did not seem to be convincing enough because of the differences in the chemotherapy comparator arms used, the populations evaluated, the ratio of del19s *versus* L858R mutations *versus* other mutations and nonsmokers *versus* smokers. LUX-Lung 7 (LL7) was the first prospective global randomized trial evaluating two EGFR-directed therapies in patients with *EGFR*-mutant NSCLC [Park *et al.* 2015]. The primary endpoint of PFS was met by 11.0 months *versus* 10.9 months (HR = 0.73; 95% CI, 0.57 to 0.95; $p = 0.017$). Afatinib treatment was associated with a significant improvement in response rate (70% *versus* 56%, $p = 0.008$) and time to treatment failure (13.7 months *versus* 11.5 months; HR = 0.73; 95% CI, 0.58 to 0.92; $p = 0.007$). The improvement in efficacy was observed in both del19 and L858R populations. OS data were immature.

Toxicity profile

Given the unequal affinity for the kinase domain of EGFR, the toxicological properties of these EGFR-TKIs may differ from each other when observed in *EGFR*-mutant tumors. Thus, the toxicity data of afatinib in LL3 and LL6 [Sequist *et al.* 2013; Wu *et al.* 2014], erlotinib in OPTIMAL, EURTAC and ENSURE [Zhou *et al.* 2011; Rosell *et al.* 2012; Wu *et al.* 2015], and gefitinib in NEJ002 and WJTOG3405 [Maemondo *et al.* 2010; Mitsudomi *et al.* 2010] is summarized in Figure 1. The most common treatment-related adverse events, rash and diarrhea, were more frequent with afatinib therapy than with erlotinib or gefitinib therapy. Dose reduction due to afatinib occurred in more than 40% of patients. However, there was no reduction of efficacy for those who were dose reduced *versus* ones who had no dose reduction (11.3 months *versus* 11.0 months, respectively) [Yang *et al.* 2015a]. Treatment with gefitinib was associated with a higher frequency of severe (grade $\geqslant$ 3) hepatotoxicity compared with erlotinib or afatinib. Frequency of interstitial lung disease (ILD) with a minimum of grade 3 was low for both first-generation and second-generation EGFR-TKIs. Treatment-related AEs with a minimum of grade 3 occurred in 42% of patients receiving afatinib, 33% of patients receiving erlotinib and 41% of patients receiving gefitinib. The direct comparison between afatinib and gefitinib was made in LL7, and the results were consistent with previous experience [Park *et al.* 2015].

Efficacy of afatinib in patients harboring uncommon epidermal-growth-factor-receptor mutations or with brain metastases

Uncommon *EGFR* mutations are defined as any mutation other than del19 or Leu858Arg, and account for approximately 10% of all mutation-positive NSCLC. The clinical data available regarding the activity of first-generation EGFR-TKIs in these tumors are inconclusive, anecdotal, and mostly retrospective [Asahina *et al.* 2006; De Pas *et al.* 2011; Wu *et al.* 2011; Watanabe *et al.*

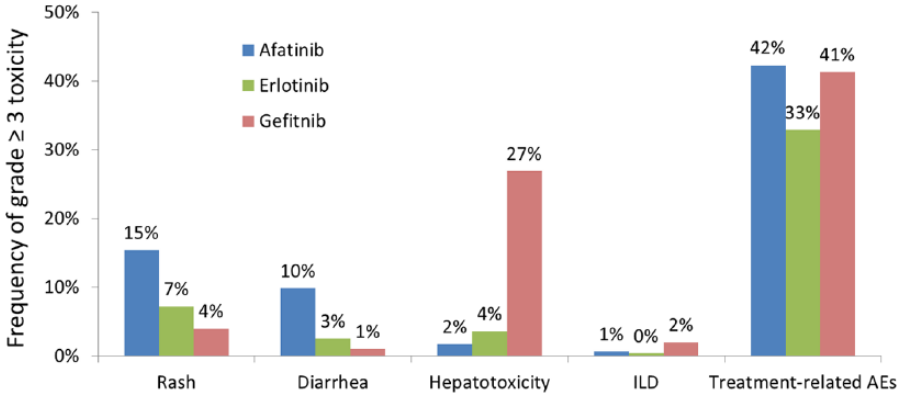

Figure 2. The frequency of grade ⩾ 3 adverse events including rash, diarrhea, hepatotoxicity and interstitial lung disease.
ILD, interstitial lung disease, AEs, adverse events.

2014]. Since preclinical data suggested that afatinib could irreversibly inhibit all ERBB family receptor tyrosine kinases, it was thought that this agent could be effective for patients with uncommon mutations, especially for patients with tumors that had the T790M mutation [Solca *et al.* 2012].

Therefore, a *post-hoc* analysis was conducted to assess the activity of afatinib in patients with uncommon *EGFR* mutations in the LUX-Lung clinical trials programme, with data from the non-randomized phase II LUX-Lung 2 (LL2) study and the phase III randomized LL3 and LL6 trials [Yang *et al.* 2015b]. Of the total 600 patients given afatinib across the three trials, 75 (12%) patients had uncommon *EGFR* mutations. The investigators divided these patients into three cohorts: point mutations and duplications in exons 18–21 (group 1), *de novo* T790M mutation in exon 20 (group 2), or exon 20 insertions (group 3). The best response to afatinib (Objective Response Rate (ORR) = 71.1%; 95% CI, 54.1 to 84.6) was noted in group 1, especially in patients with G719X, L861G, and S768I that were the three most frequently reported types of uncommon *EGFR* mutations, suggesting that this group of uncommon mutations can be categorized as sensitive *EGFR* mutations and supporting the use of afatinib in these patients (**Table 2**). However, patients had an objective response of less than 15% in groups 2 and 3, with a median PFS of 2.9 months and 2.7 months, respectively. Comparison between the 75 patients who received afatinib and the 25 patients who received chemotherapy was restricted due to the small size of the cohort and molecular heterogeneity within the genetic subgroups. The combination modality with afatinib plus cetuximab was explored in patients with the T790M mutation, although in the resistance setting [Janjigian, *et al.* 2014]. The efficacy was mild but the toxicity was quite serious. T790M mutant-selective inhibitors such as ADZ9291 are being tested in the first-line setting and may be the preferred treatment option for patients with *de novo* T790M mutation. It was imperative to assess uncommon *EGFR* mutations independently or appropriately grouped, but not as a whole group.

In preclinical studies, afatinib demonstrated high potency of kinase inhibition with the median inhibitory concentration lower than that of first-generation EGFR-TKIs gefitinib or erlotinib [Solca *et al.* 2012]. This suggested that afatinib would penetrate into the central nervous system (CNS) with concentrations high enough to treat CNS metastases effectively. In LL3, 35 patients with stable brain metastases (asymptomatic, stable $>$ 4 weeks with no treatment required) at baseline were included [Schuler *et al.* 2013]. Within the brain metastases group (afatinib: n = 20, pemetrexed/cisplatin: n = 15), median PFS by independent review was 11.1 months in the afatinib arm and 5.4 months in chemotherapy (HR = 0.52; 95% CI, 0.22 to 1.23; p = 0.13). Objective response in patients with brain metastases was 70% (afatinib) *versus* 20% (pemetrexed/cisplatin), odds ratio = 11.0, p = 0.007. By investigator review, progressive disease in the brain was observed for 4.2% (7/167) and 3.7% (3/82) of patients without brain metastases at baseline for afatinib and pemetrexed/cisplatin, respectively. The median (range) time to intracranial

Table 2. Response to afatinib or chemotherapy in patients with epidermal-growth-factor-receptor (*EGFR*) uncommon mutations.

	Mutations	*n*	Objective response (95% CI)	Median PFS (95% CI, months)	Median OS (95% CI, months)
Group 1	L861G, G719X, S768I, etc.	38	71.1% (54.1–84.6)	10.7 (5.6–14.7)	19.4 (16.4–26.9)
Group 2	*De novo* T790M	14	14.3% (1.8–42.8)	2.9 (1.2–8.3)	14.9 (8.1–24.9)
Group 3	Exon 20 insertions	23	8.7% (1.1–28.0)	2.7 (1.8–4.2)	9.2 (4.1–14.2)
Chemotherapy	All uncommon *EGFR* mutations	25	24.0% (9.4–45.1)	8.2 (5.2–10.8)	30.2 (13.0–42.3)

CI, confidence interval; EGFR, epidermal growth factor receptor.

progression in this small group was 11.6 (1.3–20.2) months with afatinib and 5.5 (2.6–8.2) months with pemetrexed/cisplatin.

Conclusion

Afatinib is the first agent to demonstrate improvement in both PFS and OS *versus* standard-of-care platinum-doublet chemotherapy in a molecularly defined population of patients with NSCLC when used in the first-line setting. Maximal survival benefit is seen in patients with advanced NSCLC and the del19 mutant. Particularly in light of the OS advantage afatinib could take the place of gefitinib or erlotinib and be considered the preferred first-line therapy for patients with *EGFR*-del19 mutations. Further strategy development of EGFR-TKIs to enhance antitumor activity, particularly for tumors with exon 21 L858R mutations remains important. LL7 has confirmed the efficacy benefit of irreversible ERBB blockade with afatinib over reversible EGFR inhibition with gefitinib in treatment of *EGFR*-mutant NSCLCs, although the toxicity profile of afatinib is somewhat worse than that observed with first-generation TKIs.

To date, four molecules have been approved for the first-line treatment of *EGFR*-mutated lung cancer. Gefitinib and erlotinib are available in almost all countries. Afatinib has been approved by the US FDA and by the European Medicines Agency, and icotinib has been approved only in China. The concern of how to choose from a group of agents that share a similar mechanism may be quite crucial. For each patient, the choice among the available EGFR inhibitors should take into account all the clinically relevant endpoints, including disease control, survival prolongation, tolerability, and QoL.

The therapeutic landscape is still evolving. Other, more active, third-generation EGFR-TKIs with specific activity at T790M mutation, such as AZD9291 and CO-1686, seem to have a better efficacy and toxicity profile in early clinical trials as monotherapy, and the results are very encouraging in patients with advanced NSCLC who develop resistance to EGFR-TKI with secondary T790M mutation. Preclinical data suggest that AZD9291 could be highly effective as well in the front-line setting, and a clinical trial testing this agent in TKI-naïve patients is underway. Whether the use of AZD9291 in the first-line setting will extend the survival benefit for patients compared with erlotinib, gefitinib, or afatinib remains to be determined clinically. Besides, potential combined modality therapies are being developed to maximize the duration of disease control and further improve long-term outcomes.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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