First-line afatinib for the treatment of *EGFR* mutation-positive non-small-cell lung cancer in the 'real-world' clinical setting

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Abstract: Afatinib is an ErbB family blocker that is approved for the treatment of epidermal growth factor receptor (*EGFR)* mutation-positive non-small-cell lung cancer (NSCLC). Pivotal randomized clinical studies demonstrated that afatinib significantly prolonged progression-free survival compared with platinum-based chemotherapy (LUX-Lung 3, LUX-Lung 6), and with gefitinib (LUX-Lung 7), with manageable side effects. However, these results were derived from controlled studies conducted in selected patients and are not necessarily representative of real-world use of afatinib. To gain a broader understanding of the effectiveness and safety of first-line afatinib, we have undertaken a literature review of real-world studies that have assessed its use in a variety of patient populations. We focused on patients with uncommon *EGFR* mutations, brain metastases, or those of advanced age, as these patients are often excluded from clinical studies but are regularly seen in routine clinical practice. The available real-world studies suggest that afatinib has clinical activity, and is tolerable, in diverse patient populations in an everyday clinical practice setting. Moreover, consistent with LUX-Lung 7, several real-world comparative studies indicate that afatinib might confer better efficacy than first-generation EGFR tyrosine kinase inhibitors. Tolerability-guided dose adjustment, undertaken in 21–68% of patients in clinical practice, did not appear to reduce the efficacy of afatinib. Taken together, these findings provide further support for the use of afatinib as a treatment option in patients with *EGFR* mutation-positive NSCLC.

Keywords: afatinib, brain metastases, EGFR tyrosine kinase inhibitors, NSCLC, real-world, uncommon mutations

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the first-line treatment of choice for patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). Today, in many countries, physicians have a choice of three generations of approved EGFR TKIs for the first-line treatment of *EGFR* mutation-positive NSCLC: the first-generation reversible EGFR TKIs erlotinib, gefitinib (and icotinib in China); the second-generation ErbB family blockers afatinib and dacomitinib; and the third-generation EGFR-wild-type sparing, irreversible EGFR inhibitor osimertinib. All of these agents have been associated with significant progression-free survival (PFS) benefit *versus* standard care in prospective phase III trials; in these studies median PFS assessed by independent review was typically 9.7–13.1 months with erlotinib,[1–3] 9.2–10.8 months with gefitinib,[4–6] 11.2 months with icotinib,[7] 11.0–13.6 months with afatinib,[8,9] 14.7 months with dacomitinib,[10] and 17.7 months with osimertinib,[11] in patients with tumors harboring common *EGFR* mutations (Del19 or L858R). As well as impressive efficacy, EGFR TKIs have a better tolerability profile than traditional platinum-doublet chemotherapy. Adverse events (AEs) are predictable, manageable with supportive care measures and/or tolerability-guided dose reductions,[12,13] and rarely lead

to permanent drug discontinuation (typically ⩽10% of patients).[1–9,11]

The availability of three generations of EGFR TKIs for the treatment of *EGFR* mutation-positive NSCLC raises the ongoing question of which EGFR TKI, or sequence of EGFR TKIs, offers the best option for an individual patient? Recent prospective head-to-head trials have demonstrated that afatinib (LUX-Lung 7), dacomitinib (ARCHER-1050), and osimertinib (FLAURA) are associated with superior PFS *versus* first-generation EGFR TKIs in patients with *EGFR* mutation-positive (Del19/L858R) NSCLC.[10,11,14] These trials were undertaken in similar, but not identical, patient populations. ARCHER-1050, for example, excluded patients with brain metastases. The results of these studies indicated that later-generation EGFR TKIs are probably preferable to first-generation EGFR TKIs as first-line treatment of choice. Notably, however, no prospective data are available that have directly compared second- and third-generation EGFR TKIs.

Regardless of which EGFR TKI is chosen, resistance to first-line treatment is inevitable,[15,16] so availability of subsequent treatment options is an important consideration. The most common resistance mechanism to first- and second-generation EGFR TKIs, observed in around 50–70% of cases, is the clonal expansion of tumor cells harboring the gatekeeper T790M resistance mutation in exon 20 of *EGFR*.[17–20] The T790M mutation is highly sensitive to osimertinib, which is approved in this setting following failure of erlotinib, gefitinib, or afatinib.[20–22] In contrast to first- and second-generation EGFR TKIs, a predominant resistance mechanism to osimertinib has not been defined.[23–26] In a recent analysis of 91 patients from FLAURA, the most common mechanisms of resistance to first-line osimertinib were MET amplification (15%) and the emergence of the tertiary *EGFR* mutation, C797S (7%).[26] No putative mechanisms of resistance could be identified in >60% of patients. Consequently, targeted treatment options following failure of osimertinib are yet to be defined. Thus, the optimal sequencing of EGFR TKIs in patients with *EGFR* mutation-positive NSCLC is currently unclear, and is a matter for debate. At present, no prospective studies have assessed overall survival (OS) following different sequences of EGFR TKIs. However, second-generation ErbB family blockers appear to confer an OS advantage over first-generation *EGFR* TKIs in a first-line setting. In exploratory analysis of ARCHER-1050, dacomitinib improved OS *versus* gefitinib (median 34.1 *versus* 26.8 months; hazard ratio (HR) 0.76 [95% confidence interval (CI) 0.58–0.99], $p = 0.044$).[27] Twenty-two patients treated with dacomitinib received a subsequent third-generation EGFR TKI; median OS in these patients was 36.7 months. In LUX-Lung 7, there was a trend towards OS improvement with afatinib *versus* gefitinib in the overall dataset (median 27.9 *versus* 24.5 months; HR 0.86 [95% CI 0.66–1.12]) and in patients with Del19 mutations (median 30.7 *versus* 26.7 months; HR 0.83 [95% CI 0.58–1.17]).[28] Twenty patients received a third-generation EGFR TKI following osimertinib; median OS in these patients was not reached and the 3-year survival rate was ~90%.[28] At the time of writing, mature OS data following first- or second-line treatment with osimertinib in the FLAURA and AURA3 studies, respectively, are currently unavailable but are eagerly awaited. It is hoped that OS and/or PFS-2 data from these two studies will provide valuable insights into the optimal use of osimertinib, either as front-line treatment or as sequential therapy following first-line EGFR TKI failure.

Clearly, clinical trial data help inform treatment decisions for patients with *EGFR* mutation-positive NSCLC. However, when considering treatment choices in real-world clinical practice, it is important to remember that randomized controlled trials are designed to assess the efficacy and safety of study drugs under well-defined conditions and in selected patient populations.[29] In addition, the design features of clinical trials, such as strict stopping/discontinuation criteria based on Response Evaluation Criteria In Solid Tumors (RECIST) parameters, may not reflect real-world clinical practice. For example, many patients may continue treatment beyond radiological progression. Therefore, it is important to complement randomized controlled data with real-world studies that include patients whose profiles might otherwise preclude their participation in randomized controlled trials, such as a high comorbidity burden, poor performance status, poor prognostic features, or poor compliance to medication.[29,30] Other features specifically prompting exclusion from clinical studies of EGFR TKIs include uncommon *EGFR* mutations, brain metastases, or advanced age. Real-world data could also provide additional information regarding outcomes in patients who received sequential EGFR TKI treatment.

The importance of real-world data is being increasingly recognized by regulatory bodies,

including the US Food and Drug Administration, as a repository of important information for monitoring the safety of approved agents, and to support approval decisions of new agents.[29,31] Furthermore, for the reasons outlined above, it is becoming increasingly acknowledged that documented evidence of efficacy and safety of anticancer agents within the constraints of clinical trials may not be reflected in real-world practice. For example, recent empirical analysis, undertaken for the ASCO Value Framework, demonstrated that real-world data in oncology tend to show inferior efficacy than prospective trials, especially when surrogate endpoints such as PFS have been used.[32] For lung cancer, the analysis estimated that randomized controlled trials overestimate real-world outcomes by an average of 18% for PFS and 6% for OS. It is especially important, therefore, that real-world studies are undertaken in patients with *EGFR* mutation-positive NSCLC to assess the performance of different TKIs in 'real' populations, and help guide the selection of optimal treatment for each individual.

Here, we have undertaken a literature review of real-world studies that have assessed afatinib in a first-line treatment setting in patients with *EGFR* mutation-positive NSCLC. We searched PubMed and the abstract databases of major oncology meetings (American Society of Clinical Oncology, European Society for Medical Oncology, and World Conference of Lung Cancer) with the following search terms: ('afatinib' or 'EGFR TKI') and ('retrospective' or 'real-world' or 'expanded-access' or 'single-center' or 'elderly' or 'brain metastases' or 'uncommon *EGFR* mutation'). We report the efficacy of afatinib in the diverse populations seen in clinical practice, including patients with uncommon mutations, patients with brain metastases, and elderly patients. We describe the tolerability of afatinib, and the effectiveness of tolerability-guided dose reduction on AEs and outcomes in the real-world. In addition, information about mechanisms of resistance to afatinib are reviewed, and the implications for subsequent therapy are considered.

Real-world efficacy of first-line afatinib in *EGFR* mutation-positive NSCLC

Comparative efficacy of afatinib and first-generation TKIs

Real-world studies generally indicate that afatinib has similar or improved efficacy compared with first-generation EGFR-TKIs across a broad range of patients treated in diverse clinical practice settings (Table 1). Three single-center analyses have recently been undertaken in Taiwan. In an analysis of 448 patients treated with first-line afatinib ($n = 81$), erlotinib ($n = 63$), or gefitinib ($n = 304$) at the Chang-Gung Memorial Hospital, Taoyuan City, PFS was longer with afatinib (median not reached) than gefitinib (11.4 months, $p < 0.001$; Figure 1) but not erlotinib (median not reached).[33] In a subgroup analysis, PFS was significantly improved with afatinib compared with gefitinib ($p = 0.001$) in patients harboring a Del19 mutation. In patients with the activating L858R *EGFR* mutation, afatinib significantly improved PFS *versus* both erlotinib and gefitinib ($p = 0.02$).[33] The patient population was more diverse than typically observed in randomized trials; for example, 20% of patients had baseline brain metastases and 18% of patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of >1. Nevertheless, multivariate analysis demonstrated that afatinib reduced the risk of progression *versus* gefitinib in all patient subgroups except ECOG PS >1; there was a trend towards improved PFS in patients with baseline brain metastases.

In a retrospective single-center study of 422 patients treated with first-line EGFR TKIs at the China Medical University Hospital, Taichung, PFS was significantly longer with afatinib *versus* gefitinib (median 12.2 *versus* 9.8 months; HR 0.72 [95% CI 0.54–0.97], $p = 0.035$).[34] A trend towards longer PFS with afatinib compared with erlotinib (HR 0.87 [95% CI 0.62–1.20]) did not reach statistical significance. PFS with afatinib, gefitinib, and erlotinib was similar in patients with Del19 mutations or L858R. In the third Taiwanese real-world study, undertaken at the National Taiwan University Hospital, there was no significant difference in PFS or OS between patients treated with afatinib ($n = 99$), gefitinib ($n = 134$), or erlotinib ($n = 68$; Table 1).[35]

In an analysis of 467 patients treated with first-line EGFR TKIs at the Samsung Medical Center in South Korea, afatinib ($n = 165$) conferred longer PFS than gefitinib ($n = 230$), or erlotinib ($n = 72$).[37] Median PFS was 19.1, 13.7, and 14.0 months, respectively (Figure 2). Multivariate analysis, which adjusted data according to important clinical characteristics such as *EGFR* mutation type, ECOG PS, age, and gender, demonstrated that the PFS benefit conferred by

Table 1. Summary of real-world, comparative studies of afatinib and first-generation EGFR TKIs in *EGFR* mutation-positive NSCLC.

Location and patients (*n*)	Efficacy outcome	Afatinib	Comparator	*p* value	Study
Taiwan Overall: afatinib (104); gefitinib (195); erlotinib (123)	PFS, months	12.2	Gefitinib, 9.8 Erlotinib, 11.4	0.035 0.38	Tu et al.[34]
Uncommon mutations: afatinib (23); gefitinib (14); erlotinib (12)	PFS, uncommon mutations, months	19.7	Gefitinib, 7.0 Erlotinib, 7.0	0.506	
Brain metastases: afatinib (22); gefitinib (34); erlotinib (17)	PFS, brain metastases, months	9.9	Gefitinib, 8.9 Erlotinib, 7.2	0.367	
Taiwan Overall: afatinib (81); gefitinib (304); erlotinib (63) Brain metastases: afatinib (17); gefitinib (60); erlotinib (11) No patients with uncommon mutations	PFS, months	Not Reached	Gefitinib, 11.4 Erlotinib, Not Reached	<0.001	Kuan et al.[33]
Taiwan Overall: afatinib (99); gefitinib (134); erlotinib (68) Brain metastases: afatinib (31); gefitinib (11); erlotinib (38) Uncommon mutations: afatinib (17); gefitinib (10); erlotinib (4)	PFS, months	12.4	Gefitinib, 12.4 Erlotinib, 14.4	0.67	Lin et al.[35]
	OS, months	37.0	Gefitinib, Not Reached Erlotinib, 33.6	0.81	
Japan Overall: afatinib (215); gefitinib (726); erlotinib (413)	OS, months	38.6	30.9	0.0031 unadjusted <0.0001 adjusted by IPTW	Ito et al.[36]
South Korea Overall: afatinib (165); gefitinib (230); erlotinib (72)	PFS, months	19.1	Gefitinib, 13.7 Erlotinib, 14.0	0.001	Kim et al.[37,38]
Uncommon mutations: afatinib (14); gefitinib (12); erlotinib (5)	PFS, uncommon mutations, months	Not reached Afatinib only, 15.7	Gefitinib, 5.0 Erlotinib, 6.1	0.06 0.21	
Brain metastases: afatinib (71); gefitinib (NR); erlotinib (NR)	PFS, brain metastases, months	Afatinib + WBRT, 11.5 Afatinib + GKS, 15.6			
Taiwan Uncommon mutations: afatinib (24); gefitinib/erlotinib (32) Brain metastases not reported	PFS, months	11.0*	Gefitinib/erlotinib, 3.6	0.03	Shen et al.[39]
	ORR, %	63	Gefitinib/erlotinib, 50	0.35	

Table 1. (Continued)

Location and patients (*n*)	Efficacy outcome	Afatinib	Comparator	*p* value	Study
Czech Republic Overall: afatinib (102); gefitinib (138); erlotinib (47)	PFS, months	14.9	Gefitinib, 9.1 Erlotinib, 6.7	0.015	Skřičková et al.[40]
Uncommon mutations: afatinib (14); gefitinib (22); erlotinib (11) Brain metastases not reported	OS, months	28.9	Gefitinib, 18.5 Erlotinib, 19.2	0.046	
Japan Overall: afatinib (28); gefitinib (83); erlotinib (36) Uncommon mutations and brain metastases not reported	TTF, months	13.1	Gefitinib, 9.2 Erlotinib, 9.8	0.123 0.795	Fujiwara et al.[41]

*Excluded patients with *EGFR* exon 20 insertions.
EGFR, epidermal growth factor receptor; IPTW, inverse probability treatment weighting; NR, not reported; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine-kinase inhibitor; TTF, time to treatment failure; WBRT, whole-brain radiation therapy.

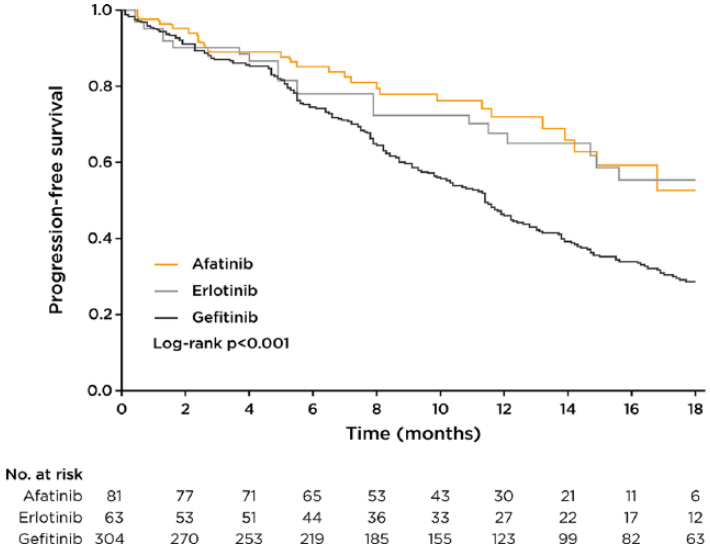

Figure 1. Progression-free survival in patients receiving gefitinib, erlotinib, or afatinib in a real-world study of 448 patients with *EGFR* mutation-positive (L858R or del19) non-small-cell lung cancer (NSCLC). (Reproduced with permission from Kuan et al.[33]; https://creativecommons.org/licenses/by/3.0/.)

afatinib was significantly better than that seen with gefitinib or erlotinib (HR 0.46 [95% CI 0.34–0.63], $p < 0.001$).

An analysis of the records of 147 Japanese patients with *EGFR* mutation-positive NSCLC demonstrated that time to treatment failure (TTF) with afatinib (13.1 months) was longer than that observed among patients who received gefitinib (9.2 months), or erlotinib (9.8 months).[41] Median OS with afatinib had not been reached at the time of reporting, and was 27.3 and 29.3 months for gefitinib and erlotinib, respectively. An analysis of data for 287 patients collected from the TULUNG clinical registry in the Czech Republic demonstrated numerically longer PFS (median 14.9, 9.1, and 6.7 months; $p = 0.015$) and OS (median 28.9, 18.5, and 19.2 months; $p = 0.046$) with afatinib over gefitinib and erlotinib, respectively.[40] It should be noted, however, that patients receiving

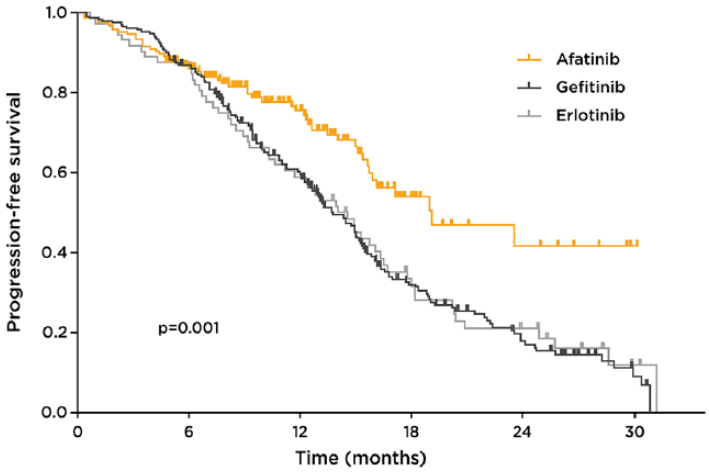

Figure 2. Progression-free survival following first-line afatinib, gefitinib, or erlotinib in 467 patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). (Reproduced with permission from Kim et al.[37])

afatinib had better PS than those receiving other EGFR TKIs, with no patients in the afatinib group having ECOG PS of >1. Another recent analysis of 500 patients treated at the British Columbia Cancer Agency demonstrated that second-generation EGFR TKIs were associated with improved OS compared with first-generation EGFR TKIs (median 43 *versus* 23 months; HR 0.6 [95% CI 0.4–0.8], $p < 0.01$).[42] Similar OS outcomes were observed in patients with Del19 mutations (median 43 *versus* 25 months; HR 0.6 [95% CI 0.4–0.9], $p = 0.04$) or the L858R mutation (median 43 *versus* 20 months; HR 0.5 [95% CI 0.3–1.0], $p = 0.05$). Notably, the patient population analyzed was considerably more diverse than would be expected in a clinical trial; 47% of patients had brain metastases and 30% had ECOG PS of >1.

More recently, a comparative analysis of OS using propensity score methodology was undertaken in 1,354 patients who received erlotinib/gefitinib ($n = 1,139$) or afatinib ($n = 215$) between January 2008 and August 2017 across 11 institutions in Japan.[36] There was a trend towards improved OS with afatinib (median 38.6 months) *versus* first-generation TKIs (median 30.9 months). The trend remained apparent even after adjustment by propensity scoring (HR 0.78, $p < 0.0001$ adjusted by inverse probability treatment weighting; HR 0.75, $p = 0.0629$ adjusted by matching). Subgroup analysis demonstrated significant OS advantage with afatinib *versus* both gefitinib and erlotinib in patients with a Del19 mutation.

Although these retrospective studies do not substitute for prospective data, taken together, they do appear to suggest that afatinib may be associated with more favorable outcomes than first-generation TKIs in a real-world setting, thus supporting the findings of LUX-Lung 7.[14] Median OS, PFS, and TTF achieved with afatinib in real-world studies appear to be at least similar, and in many cases better, than observed with the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 studies.

Activity in patients with uncommon EGFR mutations

At present, limited prospective data are available regarding the relative activity of EGFR TKIs against uncommon *EGFR* mutations. This reflects the fact that most randomized trials were restricted to patients with common mutations (Del19 and L858R). However, this is an increasingly important issue, because improvements in mutation screening techniques have demonstrated that uncommon mutations, such as exon 20 insertions, point mutations in exon 18 (e.g. E709X, G719X), exon 20 (e.g. S768I, *de novo* T790M), exon 21 (e.g. L861Q), or compound mutations (tumors which harbor more than one mutation) are more prevalent than previously thought and occur in up to a quarter of cases of *EGFR* mutation-positive NSCLC.[43,44]

To the best of the authors' knowledge, the only available randomized clinical trial data on uncommon mutations comprises *post hoc* subanalyses of

the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials, which permitted enrolment of patients with uncommon mutations,[45] and *post hoc* analysis of the NEJ-002 trial that compared gefitinib to carboplatin/paclitaxel.[46] The analysis of the LUX-Lung trials indicated that afatinib had clinical activity against uncommon point mutations or duplications in exons 18–21, including G719X, S768I, and L861Q, but had limited activity against exon 20 insertions or the *de novo* T790M mutation.[45] In contrast, *post hoc* subanalysis of NEJ-002 indicated that uncommon *EGFR* mutations (G719X, L861Q) are insensitive to gefitinib.[46] These data appear to reflect recent preclinical findings which have shown that second-generation ErbB family blockers, including afatinib, have a broader activity profile across uncommon *EGFR* mutations, including compound mutations, compared with first- and third-generation EGFR TKIs.[47,48]

A number of real-world studies have indicated that afatinib has similar activity against certain uncommon mutations as it has against tumors harboring common mutations, and may confer superior outcomes to first-generation TKIs in this setting. For example, in a Taiwanese real-world study of 56 patients with uncommon mutations (not including patients with exon 20 insertions), afatinib conferred longer PFS than first-generation EGFR TKIs (median 11.0 *versus* 3.6 months; adjusted HR 0.49, $p = 0.04$; Table 1).[39] In patients with G719X, S768I, or L861Q mutations, both ORR (70% *versus* 57%; $p = 0.68$) and PFS (median 18.3 *versus* 2.6 months; $p = 0.12$) were numerically higher with afatinib *versus* gefitinib/erlotinib. In another Taiwanese study, PFS in patients with uncommon *EGFR* mutations was longer with afatinib ($n = 23$) than with either gefitinib ($n = 14$) or erlotinib ($n = 12$) (19.7, 7.0, and 7.0 months, respectively) although the difference was not statistically significant ($p = 0.506$).[34] A recent phase IIIb study assessed the efficacy and safety of first-line afatinib in a broad population ($n = 479$) of Asian patients with *EGFR* mutation-positive NSCLC.[49,50] Sixty-seven (14.0%) patients in this study had uncommon *EGFR* mutations. Of note, there was no significant difference in PFS between these patients and those with common *EGFR* mutations (median 12.6 *versus* 9.1 months).[50] In a retrospective analysis of 31 patients with uncommon *EGFR* mutations undertaken in South Korea, PFS was longer in patients receiving afatinib than gefitinib or erlotinib but did not reach significance owing to the small sample size (median not reached, 5.0 and 6.1 months; respectively; $p = 0.06$).[37] Finally, in a Japanese analysis, afatinib conferred higher ORR than first-generation EGFR TKIs in patients with single or compound G719X mutations (~80% *versus* 35–56%).[51]

These real-world observations are consistent with clinical trial data, and support the current indication for afatinib in patients harboring uncommon nonresistant *EGFR* mutations. It must be noted, however, that real-world data, such as the subanalysis of the three LUX-Lung studies,[44] indicate that exon 20 insertion mutations may be insensitive to afatinib.

Activity in patients with brain metastases

As with uncommon *EGFR* mutations, limited prospective data are available regarding the efficacy of EGFR TKIs against brain metastases. However, this is an important consideration because brain metastases affect more than 25% of patients with NSCLC during the course of their disease.[52] Moreover, metastatic spread to the brain appears to be more common in patients with NSCLC harboring *EGFR* mutations than in cases with *EGFR* wild-type tumors.[53] Although first-generation EGFR TKIs can cross the blood–brain barrier, it is unlikely that pharmacologically relevant concentrations could be achieved in the brain using standard dosing schedules, although some small clinical studies have demonstrated promising results with pulsed-dose regimens of erlotinib or gefitinib, or when these agents are combined with radiotherapy.[54–56] In contrast, preclinical and clinical evidence indicates that second- and third-generation EGFR TKIs can effectively penetrate the blood–brain barrier, and could therefore represent viable treatment options for central nervous system (CNS) lesions.[57–59] Indeed, subanalyses of the LUX-Lung 3/6 and FLAURA trials have demonstrated that afatinib and osimertinib are active in patients with baseline brain metastases and may protect against CNS spread of the disease.[15,60,61] Although these studies are encouraging, they are based on small numbers of patients and do not include patients with active brain metastases. It is important, therefore, to assess activity in patients with CNS metastases in a real-world clinical setting.

Whereas the presence of brain metastases at baseline can be indicative of poor prognosis in patients with *EGFR* mutation-positive NSCLC,[62,63] available real-world data indicate that afatinib may be active in this patient subgroup. For example, a Taiwanese cohort ($n = 259$) of patients with

EGFR mutation-positive NSCLC treated with first-line afatinib included 82 patients with brain metastases at baseline.[64] The incidence of CNS progression was higher in these patients compared with those without baseline brain metastases, and OS was shorter (median 33.8 months and not reached, respectively; $p = 0.005$). Nevertheless, response rate to afatinib was similar in the two groups (63.4% and 72.3%, respectively). In another retrospective single-center study undertaken in Taiwan ($n = 422$), 34, 17, and 22 patients with baseline brain metastases were treated with first-line gefitinib, erlotinib, and afatinib, respectively. There was no significant difference in PFS in the three groups (median 8.9, 7.2, and 9.9 months, respectively; $p = 0.367$; Table 1).[34] Response rate was not reported. In a study of 165 patients at the Samsung Medical Center in South Korea, 71 (43%) had baseline brain metastases. PFS was not significantly different between patients who did not have brain metastases, those who had brain metastases treated with afatinib alone, and those who also received whole-brain radiotherapy or gamma knife surgery (median not reached, and 15.7, 11.5, and 15.6 months, respectively; $p = 0.21$; Table 1).[38] The brain metastases response rate in patients receiving afatinib only was 76%, demonstrating a high level of intracranial activity in this study.

In a retrospective analysis of 125 patients treated with first-line afatinib at the National Cancer Centre Singapore, 42 (34%) had brain metastases.[65] PFS was similar in patients with or without brain metastases treated with 40 mg afatinib (median 13.3 and 15.0 months). In another retrospective study, undertaken in Taiwan, an ORR of 82% and a complete cranial response rate of 64% were observed in a cohort of 11 patients with *EGFR* mutation-positive NSCLC and brain metastases.[66] Promising tumor responses were also reported with afatinib in 3 of 11 patients (ORR 27%) with NSCLC with leptomeningeal carcinomatosis enrolled in a Japanese, prospective multicenter study.[57] Two of the three responses were in patients with uncommon *EGFR* mutations. In this study, afatinib levels were measured in plasma and cerebrospinal fluid (CSF) on the eighth day of afatinib treatment (40 mg/day). The mean ± standard deviation (SD) concentration in plasma and CSF was 233 ± 195 nM and 3.2 ± 2.0 nM, respectively. The CNS penetration rate was 2.5 ± 2.9%, indicating that afatinib penetrated the blood–brain barrier. In a recent phase IIIb study of Asian patients with *EGFR* mutation-positive NSCLC treated with first-line afatinib ($n = 397$), 92 had brain metastases at baseline. There was no significant difference in PFS between these patients and those without brain metastases (median 10.9 *versus* 12.4 months, respectively; $p = 0.018$).[49]

Overall, real-world studies support clinical trial findings that patients with brain metastases gain similar benefit from afatinib as those without.[14,60]

Activity in elderly patients

Given that ~60% and ~30% of patients with NSCLC are >65 years old and >75 years old at diagnosis, respectively, it is important to consider the efficacy and safety of treatment options in this patient subgroup.[67] Treatment decisions can be further complicated by the fact that elderly patients tend to have poorer ECOG PS, more comorbidities, and receive more co-medications than their younger counterparts. Further complicating matters, there is no universally recognized definition of what constitutes an elderly patient.

Subanalysis of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 studies indicates that afatinib is effective in elderly patients with no new or unexpected safety signals.[67] Overall, there were slightly more grade ⩾3 AEs, regardless of treatment, compared with younger patients. Nevertheless, the rate of treatment discontinuations owing to treatment-related AEs ranged from 9% to 16% across studies, indicating that AEs were generally manageable in elderly patients. However, as clinical trials tend to exclude patients with poor performance status or certain comorbidities (e.g. cardiovascular problems) they are not representative of the elderly population in real-world clinical practice. It is important, therefore, to assess the efficacy and tolerability of afatinib in elderly patients in a real-world setting.

Until recently, very few data were available regarding the activity of afatinib in elderly patients in the real world. There is some evidence that patient age influences treatment decisions in real-world clinical practice. In South Korea, for example, gefitinib appeared to be prescribed preferentially to afatinib and erlotinib in older patients.[37] There was no evidence, however, that afatinib was less effective in elderly patients in this study; univariate analysis

of PFS according to age (<60 years; ⩾60 years) showed that age did not predict PFS. In the international, noninterventional RealGiDo study, which included 228 patients across 13 countries and assessed the impact of afatinib dose modifications on efficacy and safety in a real-world setting, the effectiveness of first-line treatment with afatinib seemed to be similar regardless of age.[68] In patients aged <75 years *versus* ⩾75 years, median TTF was 17.8 *versus* 24.9 months and median TTP was 20.5 *versus* 25.7 months.[68] In a Taiwanese cohort study, multivariate analysis demonstrated that afatinib (n = 29) conferred superior PFS to gefitinib (n = 150) in patients aged ⩾65 years old (HR 0.47 [95% CI 0.23–0.96]).[33] Together, these data indicate that afatinib may be active in elderly patients with *EGFR* mutation-positive NSCLC, though more data are required.

Real-world safety and tolerability of first-line afatinib in *EGFR* mutation-positive NSCLC

Most frequent AEs

AEs observed with afatinib in real-world practice, as in clinical studies, have been predominantly gastrointestinal or dermatological in nature (Table 2). The most common AEs in real-world studies were dermatological events (31–85%), diarrhea (23–65%), paronychia (29–44%), and stomatitis/mucositis (30–34%).[8,9,14] The frequency of grade 3–4 AEs were variable across real-world studies, presumably reflecting the heterogeneity of patients included in the analyses, but the overall tolerability profile was generally similar to clinical trial findings; grade 3–4 diarrhea and rash/acne were reported in 5–14% and 9–16% of patients enrolled in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7.[8,9,14]

AEs necessitated dose reduction for 21–68% patients across real-world studies,[37,69,70] However, few patients discontinued treatment (⩽5%),[42,69] suggesting that AEs could be managed effectively in everyday clinical practice.

The impact of tolerability-guided dose adjustment on clinical outcomes

Given widespread use of tolerability-guided dose adjustment protocols with afatinib, it is important to assess the impact of dose reduction on clinical efficacy. Several real-world analyses have explored the impact of tolerability-guided dose reduction on clinical outcomes such as tumor response, PFS and TTF (Table 3). In an analysis from Taiwan, response rates (72.2 *versus* 71.6%; p = 0.8028) and TTF were no different for patients who received <40 mg afatinib (n = 67), following dose reduction or a lower starting dose, than those who received 40 mg (n = 79).[71] TTF was 13.3 *versus* 15.5 months (p = 0.227). Furthermore, subgroup analysis indicated that dose reduction did not influence TTF in patients harboring either Del19 or L858R mutations.

Similarly, afatinib doses of <40 mg during the first 6 months of treatment had no influence on clinical outcomes in a cohort of patients treated at the National Taiwan University Hospital[64]; median PFS (13.2 and 12.5 months; p = 0.865) and median OS (36.7 months and not reached; p = 0.992) were similar in patients who received 40 mg and <40 mg, and control of brain metastasis was similar between the two groups. An analysis from the Kaohsiung Medical University, Taiwan, in which dose groups were defined by starting dose, also found similar response rates (76 *versus* 95%; p = 0.0862) and PFS (15.4 *versus* 14.6 months; p = 0.8418) in patients receiving 30 and 40 mg afatinib, respectively.[70] Similarly, dose reduction was found to have no effect on PFS (16.1 *versus* 10.3 months for 30 *versus* 40 mg afatinib, respectively; p = 0.923; Figure 3) among a subset of afatinib-treated patients (n = 104) included in a retrospective analysis in Taiwan.[34] Median PFS of 12.4 and 23.5 months, respectively, were reported for patients receiving 40 mg (n = 53) *versus* reduced dose (30 or 20 mg; n = 112) afatinib at the Samsung Medical Center in South Korea.[37] In a recent phase IIIb study of Asian patients with *EGFR* mutation-positive NSCLC treated with first-line afatinib (n = 397), 119 had a dose reduction. Whereas dose reduction appeared to reduce the incidence of grade ⩾3 AEs (diarrhea prior to/after dose reduction: 27/4%; rash/acne: 24/11%; stomatitis: 11/5%) PFS was not compromised. Median PFS in patients who received a dose reduction within the first 6 months was 14.1 months compared with 11.3 months in patients who remained on the starting dose (p = 0.041).[49]

Findings from a study undertaken at the National Cancer Centre in Singapore suggest that patients with, but not without, brain metastases who start on standard 40 mg afatinib may have better outcomes than those who start on a reduced dose of 30 mg.[65] Among a subset of 40 patients with brain metastases, those who started on 40 mg afatinib

Table 2. Adverse events reported in real-world studies of afatinib in *EGFR* mutation-positive NSCLC.

Study location	Patients (*n*)	Most common adverse events (%)		Study
		Any grade	Higher grade	
South Korea	165	Rash/acne (48%) Stomatitis (30%) Paronychia (29%) Diarrhea (23%)	Grade 3–4 Rash/acne (2%) Paronychia (2%) Diarrhea (3%)	Kim et al.[37]
Singapore	125	Rash (66%) Paronychia (44%) Diarrhea (39%)	Grade 3: Rash (<1%) Paronychia (<1%) Diarrhea (4%)	Tan et al.[65]
Taiwan	140	NR	Grade ⩾2: Skin lesions (71%) Diarrhea (23%)	Liang et al.[69]
Taiwan	48	Rash/acne (85%) Dry skin (71%) Diarrhea (65%)	Grade ⩾2: Diarrhea (6%) Stomatitis (4%) Rash/acne (17%)	Yang et al.[70]
Czech Republic	102	Overall: 39% Skin and subcutaneous tissue disorders (31%) Gastrointestinal disorders (25%)	NR	Skřičková et al.[40]

EGFR, epidermal growth factor receptor; NR, not reported; NSCLC, non-small-cell lung cancer.

had longer PFS than those on 30 mg (13.3 *versus* 5.3 months; $p = 0.04$). In patients without brain metastases ($n = 79$), median PFS with 30 mg afatinib had not been reached, and was 15 months with 40 mg afatinib. However, this was not a randomized study, thus a selection bias for patients on 30 mg cannot be ruled out.

A recent noninterventional observational study, undertaken across 29 sites in 13 countries (the Real-GiDo study) assessed outcomes in 228 patients treated with first-line afatinib. In this study, median TTF was 18.7 months and time to progression (TTP) was 20.8 months.[68] Seventy-one (31.1%) of 228 patients received a starting dose of ⩽30 mg, predominantly due to the patient's condition, 155 (68.0%) received 40 mg and two received 50 mg.[68] Of patients who started on 40 mg, 104 (67.1%) had a dose reduction, of which 90 (86.5%) occurred within the first 6 months of treatment. Overall, afatinib was associated with fewer treatment-related grade ⩾3 AEs (24.6 *versus* 48.9%) and serious treatment-related AEs (6.6 *versus* 14.0%) than observed in LUX-Lung 3. Most patients (>60%) received medications to manage diarrhea and/or skin AEs. Of note, dose reduction did not appear to impact efficacy; median TTF (19.4, 17.7, and 19.5 months) and TTP (25.9, 20.0, 29.0 months) were similar in patients who started on ⩽30 mg, reduced to <40 mg, or remained on ⩾40 mg afatinib, respectively.

Together these real-world data suggest that afatinib dose reduction may not adversely impact on efficacy, and support observations from the LUX-Lung 3 and LUX-Lung 6 trials.[13] These findings are further supported by a recent phase II trial that assessed low-dose, first-line afatinib (20 mg/day starting dose with the option, if tolerated, to escalate in 10 mg increments to a maximum of 50 mg/day) in 46 patients with *EGFR* mutation-positive NSCLC.[72] Median PFS was 15.2 months, with grade ⩾3 AEs in 26% of patients; 46% of patients escalated to 30 mg/day and 22% escalated to 40 mg/day. Overall, therefore, real-world and clinical trial data highlight the possibility of tailoring afatinib dose based on individual patient characteristics and AEs to potentially optimize outcomes.

Table 3. Summary of real-world studies exploring the impact of afatinib dose reduction on efficacy and tolerability.

Study location	Patients (*n*)	Efficacy outcome	Afatinib 40 mg	Afatinib reduced to <40 mg	*p* value	Study
Korea	165	PFS, months	12.4	23.5	NA	Kim et al.[37]
Singapore	79	PFS, months –BM	15	Not reached	NA	Tan et al.[65]
	40	PFS, months +BM	13.3	5.3	0.04	
Taiwan	140	PFS, months	12.0	11.0	<0.05	Liang et al.[69]
Taiwan	48	PFS, months	14.6	15.4	0.8418	Yang et al.[70]
		DCR, %	100	100	0.1486	
Taiwan	146	Response rate, %	72	72	0.8028	Liu et al.[71]
		TTF, months	13.3	15.5	0.227	
Taiwan	98	PFS, months	10.3	16.1	0.923	Tu et al.[34]
Global	228	TTF, months	19.5*	17.7	0.543	Halmos et al.[68]
		TTP, months	29.0*	20.0	0.392	

*⩾40 mg.
BM, brain metastases; DCR, disease control rate; NA, not available; PFS, progression-free survival; TTF, time to treatment failure.

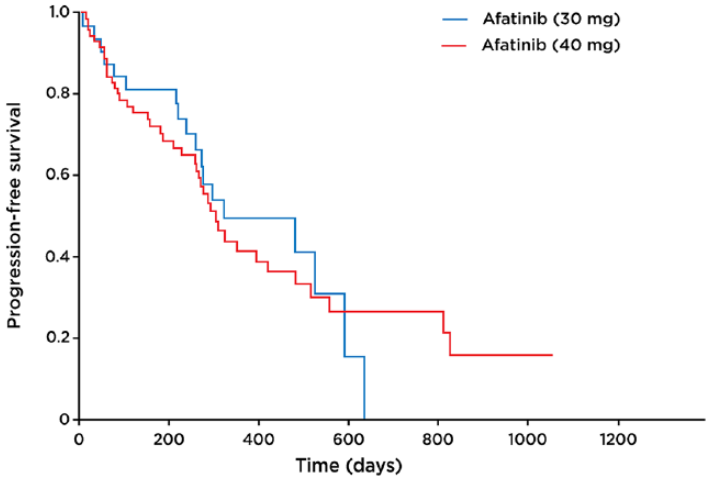

Figure 3. Progression-free survival in patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) who received first-line afatinib at doses of 30 mg or 40 mg. (Reproduced with permission from Tu et al.[34]; https://creativecommons.org/licenses/by/3.0/.)

Mechanisms of acquired resistance to EGFR TKIs in real-world studies

In addition to exploring efficacy and safety in various patient populations, real-world studies provide valuable data on resistance mechanisms to different EGFR TKIs, and insight into the implications of these mechanisms for sequential treatment. Various studies have found a similar

rate of acquisition of the T790M mutation after afatinib to those reported with erlotinib or gefitinib, indicating that T790M is also the predominant mechanism of acquired resistance to afatinib. For example, in the phase I/II AURA trial, the T790M rate in 36 patients treated with afatinib was 68%.[20]

Real-world studies also indicate that T790M is the predominant mechanism of resistance to afatinib. In a single-center study in Austria, prevalence of *EGFR* T790M was assessed in 67 predominantly Caucasian patients, who progressed after initially achieving disease control with afatinib.[73] In total, 73% of patients acquired T790M after treatment with afatinib. Acquisition of T790M did not appear to be associated with any particular baseline characteristics. All patients who acquired T790M subsequently received osimertinib with an ORR of 76%. These favorable outcomes with osimertinib subsequent to afatinib are consistent with a retrospective analysis of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials, in which median time on osimertinib treatment was 20.2 months and OS had not been reached after more than 4 years follow-up.[74] Moreover, a recent real-world study indicates that favorable outcomes are possible in patients treated with sequential osimertinib after first-line afatinib. In this analysis of 204 patients, overall median time on treatment was 27.6 months. Certain patient populations, such as Asians (46.7 months) and those with an *EGFR* Del19 mutation (30.3 months) demonstrated particularly prolonged time on treatment.[75] Analysis of OS of these patients is currently immature.

Other studies have indicated that T790M is the predominant mechanism of acquired resistance to afatinib. For example, in a Japanese study, 43% of 37 patients acquired T790M after first-line afatinib.[76] The investigators found no association between acquisition of T790M and baseline characteristics of age or performance status. In a Taiwanese study, 48% of 42 patients who were rebiopsied after afatinib failure had acquired T790M; 64% of patients with Del19 and 45% of those with *L858R* mutations.[77] Acquisition of T790M was not associated with age, gender, or smoking status. In another Taiwanese study of 28 afatinib-treated patients, T790M was identified in 32% of patients.[69]

The prevalence of acquired T790M resistance among patients receiving afatinib in real-world studies and clinical trials suggests that many patients could benefit from a second-line T790M-targeted therapy, such as osimertinib, with high response rates and prolonged treatment durations achieved with the afatinib–osimertinib sequence.[75]

Conclusions/key points

In general, real-world studies suggest that afatinib is effective in diverse patient populations in everyday clinical practice, following local policy or practice. Findings reported for clinical activity measures, such as PFS, TTF, and ORR, in real-world studies which included patients with brain metastases and uncommon *EGFR* mutations were similar to those in clinical trials.

Consistent with LUX-Lung 7,[14] some real-world comparisons indicate that afatinib confers better efficacy over first-generation EGFR TKIs.[33,37] thus providing further evidence that first- and second-generation EGFR TKIs are not interchangeable. Moreover, available evidence indicates that afatinib is superior over first-generation EGFR TKIs in patients with common and uncommon *EGFR* mutations.

The tolerability profile of afatinib in real-world studies was as expected, with gastrointestinal and cutaneous AEs predominant. Available evidence indicates that AEs can be managed with supportive care and/or tolerability-guided dose reduction such that the rate of treatment discontinuation is generally low. Dose reduction does not appear to compromise clinical efficacy of afatinib.

In the real-world, T790M is the predominant mechanism of acquired resistance to afatinib, suggesting that many patients treated with first-line afatinib could benefit from second-line treatment with osimertinib.

Overall, the real-world clinical data presented herein supplement findings of clinical trials and support the use of first-line afatinib as a treatment option in patients with *EGFR* mutation-positive NSCLC.

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