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REVIEW

Afatinib as First-Line Treatment in Asian Patients with *EGFR* Mutation-Positive NSCLC: A Narrative Review of Real-World Evidence

Shun Lu · Jin-Yuan Shih · Tae-Won Jang · Chong-Kin Liam · Yongfeng Yu

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ABSTRACT

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are a standard of care in the first-line treatment of patients with *EGFR* mutation-positive metastatic non-small-cell lung cancer (NSCLC). *EGFR* mutations are relatively common in Asian patients with NSCLC, and there is an increasing number of studies supporting the effectiveness of the second-generation TKI afatinib in routine clinical practice in Asia. This article reviews these real-world studies investigating afatinib as first-line treatment for *EGFR* mutation-positive NSCLC in Asian patients. Evidence from real-world studies with afatinib in this patient population supports findings from randomized controlled trials (RCTs) showing that afatinib is associated with more favorable outcomes compared with the first-generation EGFR TKIs. The effectiveness of afatinib has also been shown in real-world studies in Asian patients with poor prognostic factors, who are often under-represented or excluded from RCTs, such as those with uncommon *EGFR* mutations, brain metastases, or poor performance status, and elderly patients. The tolerability profile of afatinib in the real-world setting reflects that seen in RCTs, with no new safety signals reported in real-world studies in Asian patients with *EGFR* mutation-positive NSCLC. Dose-modification strategies also seem to be effective in the real world, with results of the RealGido study, which included 44% Asian patients, confirming findings from prospective clinical trials showing that tolerability-guided afatinib dose modifications can reduce the incidence of adverse events without adversely affecting clinical outcomes. While further research, including clinical trial data, is needed, real-world data have also demonstrated the feasibility of sequential afatinib followed by the third-generation TKI osimertinib in T790M-positive *EGFR* mutation-positive patients, which showed longer overall survival. Together, these real-world results demonstrate the real-world clinical effectiveness of afatinib as first-line treatment for patients with *EGFR* mutation-positive NSCLC.

S. Lu (✉) · Y. Yu
Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiaotong University, 159 Tianzhou Road, Shanghai 200030, China
e-mail: shunlu@sjtu.edu.cn

J.-Y. Shih
Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

T.-W. Jang
Department of Internal Medicine, Kosin University Gospel Hospital, Busan, South Korea

C.-K. Liam
Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

PLAIN LANGUAGE SUMMARY

Some patients with non-small-cell lung cancer (NSCLC) have a mutation in the *EGFR* gene, whose normal function is to regulate cell division. The proportion of NSCLC patients with these *EGFR* mutations is particularly high in Asian populations. Treatment of patients with *EGFR* mutation-positive NSCLC has changed markedly in recent years following the development of drugs called EGFR tyrosine kinase inhibitors (TKIs). Several EGFR TKIs have been developed, and clinical trial data have shown that the second-generation TKI afatinib and the third-generation TKI osimertinib are more effective than the first-generation TKIs erlotinib and gefitinib. However, these clinical trials, known as randomized controlled trials (RCTs), are highly selective, and many patients, such as elderly patients or those in poor health and/or with underlying diseases, are excluded. Consequently, less is known about how well TKIs work in these patients. Therefore, other less-selective studies, known as observational or 'real-world' studies, are used to provide information on the safety and effectiveness of EGFR TKIs across all patient groups seen in the clinic, not just those included in RCTs. In this article, we review the real-world evidence for the TKI afatinib as a treatment for Asian patients with *EGFR* mutation-positive NSCLC. Evidence from these real-world studies confirms that afatinib is more effective than erlotinib and gefitinib in real-world patients in Asia. Importantly, the efficacy and safety of afatinib is seen in groups of Asian patients often excluded from clinical trials including the elderly, those with brain metastases, and frail patients or those with other underlying diseases. Importantly, the safety profile of afatinib was similar to that seen in RCTs, and no additional side effects were identified in real-world patients. Also, importantly, real-world studies show that side effects can be effectively controlled by reducing the dose of afatinib. Real-world studies have also been used to demonstrate the feasibility and effectiveness of the sequential use of EGFR TKIs, particularly in Asian patients.

Keywords: Afatinib; Asian patients; Epidermal growth factor receptor; Non-small-cell lung cancer; Real-world evidence; Tyrosine kinase inhibitor

Key Summary Points
Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are the standard of care for patients with EGFR mutation-positive non-small-cell lung cancer.
Less is known about the effectiveness of EGFR TKIs in patients often excluded from randomized controlled trials.
Observational data can demonstrate clinical effectiveness in these real-world patients.
Real-world evidence demonstrates the effectiveness of afatinib in Asian patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14141273.

INTRODUCTION

The prevalence of epidermal growth factor receptor (*EGFR*) mutations in patients with non-small-cell lung cancer (NSCLC) is relatively high in Asian populations compared with non-Asian populations [1–4]. For example, in a large, global meta-analysis of 456 studies, while the overall pooled prevalence for *EGFR* mutations

was 32.3%, the prevalence was only 14.1% in Europe but 50.2% in China [2]. Further, a study in south-west China reported a prevalence of 48.7% [5].

First-line use of EGFR tyrosine kinase inhibitors (TKIs) is a standard of care in *EGFR* mutation-positive metastatic NSCLC, both globally and in Asia [6–8]. Three generations of EGFR TKIs are available for the treatment of *EGFR* mutation-positive NSCLC, including the first-generation EGFR TKIs erlotinib and gefitinib (and icotinib in China), the second-generation ErbB family blockers afatinib and dacomitinib, and the third-generation EGFR TKIs osimertinib, as well as, for second-line therapy in South Korea, olmutinib, and in China, almonertinib. Except for olmutinib and almonertinib, all these EGFR TKIs have demonstrated significant improvements in progression-free survival (PFS) compared with the previous standard-of-care, platinum-based chemotherapy, in Phase 3 trials in patients with *EGFR* mutation-positive NSCLC [9–19]. Second- and third-generation TKIs have also demonstrated superior outcomes versus the first-generation TKIs, erlotinib and gefitinib [16, 17, 20, 21]. However, no prospective head-to-head studies have yet compared second- and third-generation agents.

While randomized controlled trials (RCTs) are clearly necessary to demonstrate treatment efficacy and safety, their 'external validity' or generalizability to broader patient populations seen in routine clinical practice may be limited. For example, RCTs generally have strict inclusion and exclusion criteria, as well as design features such as discontinuation criteria based on Response Evaluation Criteria In Solid Tumors (RECIST) assessments that may not reflect clinical practice where patients often continue treatment beyond radiological progression. It is therefore important to complement data from clinical trials with evidence from observational studies that reflect real-world clinical practice and include patient populations who would typically not be included in a clinical trial, such as elderly patients and those with poor performance status or other less favorable prognostic factors (e.g., uncommon *EGFR* mutations, brain metastases, comorbidities) [22–24]. As such, there is increasing recognition of the value of real-world evidence, including by, for example, the US Food and Drug Administration and the American Society of Clinical Oncology (ASCO) [22, 24, 25], as well as regulatory bodies in Asian countries [26].

There is an increasing number of studies supporting the safety and effectiveness of afatinib in real-world patient populations, particularly in Asian patients. This is in contrast to other second- and third-generation EGFR TKIs, such as dacomitinib and osimertinib [27], for which substantially less real-world evidence is available, possibly due, at least in part, to their more recent regulatory approvals. As the vast majority of real-world evidence in Asian patients with *EGFR* mutation-positive NSCLC is for afatinib, we therefore performed a literature review of real-world studies that have assessed afatinib as first-line treatment for *EGFR* mutation-positive NSCLC in Asian patients. We searched PubMed and EMBASE (up to 10 January 2020) and the most recent abstract databases of major oncology meetings [ASCO, European Society for Medical Oncology (ESMO), ESMO Asia, and World Conference on Lung Cancer] with the following search terms: ('afatinib' or 'EGFR TKI') and ('Asian') and ('retrospective' or 'real-world' or 'expanded-access' or 'single-center' or 'elderly' or 'brain metastases' or 'uncommon *EGFR* mutation'). For this narrative review, articles identified from the database searches were selected based on their potential relevance to the topic of this review, focusing on clinical outcomes with afatinib in the diverse Asian populations seen in real-world clinical practice. Reference lists of the selected articles were also checked for additional potentially contributory references. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Table 1 Real-world studies conducted in Asia comparing afatinib with first-generation EGFR TKIs in *EGFR* mutation-positive NSCLC: summary of results for the overall study population

Study	Treatment	Patients (*n*)	Clinical outcome (months)	*p* value[a]
Japan				
Fujiwara et al. [28]	Afatinib	28	TTF: 13.1	
	Gefitinib	83	TTF: 9.2	0.123
	Erlotinib	36	TTF: 9.8	0.795
Ito et al. [29]	Afatinib	215	OS: 38.6	0.0031[b]
	Gefitinib	726	OS (gefitinib and erlotinib combined): 30.9	
	Erlotinib	413		
South Korea				
Kim et al. [30]	Afatinib	165	PFS: 19.1	0.001
	Gefitinib	230	PFS: 13.7	
	Erlotinib	72	PFS: 14.0	
Taiwan				
Kuan et al. [31]	Afatinib	81	PFS: not reached	
	Gefitinib	304	PFS: 11.4	< 0.001
	Erlotinib	63	PFS: not reached	
Lin et al. [32]	Afatinib	99	PFS: 12.4	0.67
	Gefitinib	134	PFS: 12.4	
	Erlotinib	68	PFS: 14.4	
Su et al. [33]	Afatinib	99	PFS: 16.1	< 0.001
	Gefitinib	534	PFS: 11.5	
	Erlotinib	220	PFS: 11.7	
Tu et al. [34]	Afatinib	104	PFS: 12.2	
	Gefitinib	195	PFS: 9.8	0.035
	Erlotinib	123	PFS: 11.4	0.38

EGFR epidermal growth factor receptor, *IPTW* inverse probability treatment weighting, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PFS* progression-free survival, *TKIs* tyrosine kinase inhibitors, *TTF* time to treatment failure

[a] Afatinib versus comparator(s)

[b] Unadjusted p value = 0.0031; $p < 0.0001$ when adjusted by IPTW

REAL-WORLD EVIDENCE FOR THE EFFECTIVENESS OF AFATINIB

Effectiveness in General, Asian Real-World NSCLC Populations

Evidence from real-world studies on the effectiveness of afatinib among Asian patients supports the prospective clinical trial data on the efficacy of afatinib in patients with *EGFR* mutation-positive NSCLC. As seen in RCTs, real-world evidence indicates that afatinib is associated with more favorable outcomes versus the first-generation EGFR TKIs in real-world Asian patient populations (Table 1).

Several real-world studies conducted in Asian countries have compared clinical outcomes with afatinib versus first-generation EGFR TKIs in *EGFR* mutation-positive NSCLC, including studies conducted in Japan [28, 29], South Korea [30], and Taiwan [31–34] (Table 1). Key clinical outcomes [PFS, overall survival (OS), time to treatment failure (TTF)] were numerically, and, in many cases, significantly, greater with afatinib than with gefitinib and/or erlotinib across these comparative studies [28–31, 33, 34]. For example, in the South Korean study, median PFS was 19.1 months with afatinib compared with 13.7 and 14.0 months with gefitinib and erlotinib, respectively ($p = 0.001$ for both comparisons) [30]. One exception was a study conducted in Taiwan, in which median PFS of 12.4, 12.4, and 12.6 months were reported for afatinib, gefitinib, and erlotinib, respectively ($p = 0.67$) [32].

This evidence is supported by results from various other non-comparative real-world studies with afatinib in Asian patients with *EGFR* mutation-positive NSCLC. In an analysis of 85 patients in Malaysia, afatinib was also an effective first-line treatment for patients with *EGFR* mutation-positive NSCLC, with an objective response rate (ORR) of 76.5%, disease control rate of 95.3%, and median PFS of 14.2 months [95% confidence interval (CI) 11.85–16.55] [35]. In an analysis of 140 patients in Taiwan, the ORR with first-line afatinib was 67.2% and median PFS was 11.8 months [36]. In an analysis of 76 patients in Japan who received afatinib in the first-line setting, median PFS was 17.8 months (95% CI 13.7–21.5) [37]. As might be expected, median PFS was substantially longer in the first-line than the second-line setting: median PFS was 8.0 months (95% CI 4.9–9.5 months) in 52 patients who received afatinib after failure of a first-generation EGFR TKI [37]. Similarly, a Chinese study included 39 patients treated in the first-line setting and 21 patients who received afatinib as second- or later-line therapy. As first-line therapy, afatinib was associated with a median PFS of 12.3 months (95% CI 7.6–17.0) in the overall population and 15.6 months (95% CI 9.5–21.8) in patients with the common mutations Del19 or L858R. Median PFS in the first-line setting among patients treated with an initial dose of afatinib 40 mg/day ($n = 29$) or 30 mg/day ($n = 10$) was 14.5 (95% CI 9.4–19.7) and 5.2 months (95% CI 0.8–9.6), respectively ($p = 0.101$), whereas, second- or later-line treatment with afatinib at these starting doses was associated with median PFS of 3.0 ($n = 12$, 95% CI 1.3–4.8) and 5.0 ($n = 9$, 95% CI 2.5–7.5) months, respectively ($p = 0.375$) [27, 38]. Similar outcomes were reported in another real-world study in China; in 88 patients who received first-line afatinib, median PFS was 14.2 months [39].

Interestingly, and in contrast to evidence suggesting that RCTs tend to overestimate outcomes in lung cancer by 18% versus real-world studies [25], clinical outcomes with afatinib in some real-world studies in Asian patients appeared to be better than those seen in afatinib RCTs. For example, PFS in real-world studies conducted in South Korea [30] and in Japan [37] demonstrated a median PFS of 19.1 and 17.8 months, respectively, with first-line afatinib, whereas median PFS ranged from 11.0 to 13.7 months with afatinib in the LUX-Lung 3, 6, and 7 RCTs [18–20].

Also noteworthy are findings from the global real-world GioTag study, in which TTF and OS were longer in Asian patients than in the overall global study population of *EGFR* mutation-positive NSCLC patients who received sequential treatment with afatinib followed by osimertinib after the development of the

Table 2 Real-world studies conducted in Asia comparing afatinib with first-generation EGFR TKIs or other relevant treatments in *EGFR* mutation-positive NSCLC: summary of results for subgroups with uncommon *EGFR* mutations and brain metastases at baseline

Study	Treatment	Patients (*n*)	Clinical outcome (months)	*p* value[a]
Subgroup with uncommon EGFR mutations[b]				
South Korea				
Kim et al. [30]	Afatinib	14	PFS: not reached	0.06
	Gefitinib	12	PFS: 5.0	
	Erlotinib	5	PFS: 6.1	
Taiwan				
Lin et al. [32]	Afatinib	17	OS: 38.6	0.81
	Gefitinib	10	OS: not reached	
	Erlotinib	4	OS: 33.6	
Shen et al. [44]	Afatinib	24	PFS: 11.0[c]	0.03
	Gefitinib	32 (combined)	PFS: 3.6 (combined)	
	Erlotinib			
Tu et al. [34]	Afatinib	23	PFS: 19.7	0.506
	Gefitinib	14	PFS: 7.0	
	Erlotinib	12	PFS: 7.0	
Yang et al. [74]	Afatinib	17	PFS: 5.5	0.3025
	Gefitinib	31	PFS: 6.2	
	Erlotinib	9	PFS: 9.0	
Subgroup with brain metastases at baseline				
South Korea				
Kim et al.[d] [30]	Afatinib only	71 (combined)	PFS: 15.7	0.21
	Afatinib + WBRT		PFS: 11.5	
	Afatinib + GKS		PFS: 15.6	
Taiwan				
Kuan et al. [31]	Afatinib	17	PFS	HR: 0.42 (95% CI 0.16–1.05)[e]
	Gefitinib	60		
	Erlotinib	11		
Su et al. [54]	Afatinib	NR[f]	PFS: 8.2	0.34
	Gefitinib		PFS: 10.5	
	Erlotinib		PFS: 10.4	

Table 2 continued

Study	Treatment	Patients (*n*)	Clinical outcome (months)	*p* value[a]
Tu et al. [34]	Afatinib	22	PFS: 9.9	0.367
	Gefitinib	34	PFS: 8.9	
	Erlotinib	17	PFS: 7.2	

CI confidence interval, *EGFR* epidermal growth factor receptor, *GKS* gamma knife surgery, *HR* hazard ratio, *NR* not reported, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PFS* progression-free survival, *TKIs* tyrosine kinase inhibitors, *WBRT* whole brain radiotherapy

[a] Afatinib versus comparator(s)

[b] *EGFR* mutations other than Del19 or L858R

[c] Excluded patients with *EGFR* exon 20 insertions

[d] Data for gefitinib and erlotinib not reported

[e] HR for afatinib versus gefitinib

[f] Overall, 115, 116, and 75 patients received afatinib, gefitinib, and erlotinib, respectively; however, the number of patients with brain metastases at baseline was not reported

T790M mutation [40–42]. Median TTF was 37.1 months (90% CI 28.1–40.3) in the Asian subgroup ($n = 50$) compared with 27.7 months (90% CI 26.7–29.9) in the overall population ($n = 204$), while median OS was 44.8 months (90% CI 37.0–57.8) in Asian patients and 37.6 months (90% CI 35.5–41.3) in the overall population [42]. Similarly, in a subgroup analysis of 169 GioTag patients, who received an afatinib starting dose of 40 mg/day, median TTF was 27.6 months (90% CI 26.3–31.3) overall but 46.7 months (90% CI 28.4–not reached) in Asian patients [43].

Effectiveness in Real-World Populations Often Excluded from Clinical Trials

Patients with poor prognostic factors, such as those with uncommon *EGFR* mutations, baseline brain metastases, elderly patients, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, are often excluded from RCTs. Hence, there are limited prospective, clinical trial data with afatinib for such patients, and real-world studies are particularly valuable. This section focuses on real-world studies in Asian patients with these poor prognostic factors, and Table 2 provides an overview of studies comparing afatinib with first-generation EGFR TKIs in two of these subgroups, i.e., patients with uncommon *EGFR* mutations and those with brain metastases.

Patients with Uncommon Mutations

Several real-world studies conducted in Asia have indicated that afatinib has similar activity against certain uncommon mutations as it has against tumors harboring common mutations, and may confer superior outcomes compared with first-generation EGFR TKIs in this setting (Table 2). In a retrospective analysis of 56 patients with uncommon *EGFR* mutations in Taiwan who were treated with EGFR TKIs, ORRs were 62.5% with afatinib compared with 50% for gefitinib or erlotinib ($p = 0.35$) [44]. Median PFS in the respective treatment groups was 11.0 versus 3.6 months ($p = 0.03$) after exclusion of 5 patients with exon 20 insertions, which are generally considered resistant to EGFR TKIs. In patients with G719X, S7681, or L861Q mutations, median PFS was 18.3 months with afatinib compared with 2.6 months with first-generation EGFR TKIs ($p = 0.012$). A similar retrospective analysis of 49 patients with uncommon *EGFR* mutations in Taiwan demonstrated a median PFS of 19.7 months with afatinib compared with a median PFS of 7.0 months for both gefitinib and erlotinib, although the difference was not significant

($p = 0.506$) [34]. In contrast, a retrospective analysis of 57 Taiwanese patients with uncommon *EGFR* mutations found no significant differences in median PFS (5.5, 6.2, 9.0 months, $p = 0.3025$) or OS (20.5, 16.1, 12.1 months, $p = 0.9116$) between patients treated with first-line afatinib, gefitinib, or erlotinib, respectively [45]. Another comparative analysis from Taiwan in 31 patients harboring uncommon *EGFR* mutations found no significant differences between these three EGFR TKIs in OS [32]. Also in Taiwan, a small retrospective analysis of 7 patients with L747P or L747S substitutions in exon 19 reported that 5 patients who received afatinib had an ORR of 80% and median PFS of 12.0 months, whereas there were no responses in the two patients who received gefitinib/erlotinib and median PFS was 0.9 months [46]. Further, a South Korean analysis of 467 patients with a median follow-up of 17.7 months showed that, in the subgroup of 31 patients with uncommon *EGFR* mutations, afatinib recipients had a much longer median PFS (not reached) than patients treated with gefitinib (5.0 months) or erlotinib (6.1 months), although the difference did not achieve statistical significance ($p = 0.06$) as the sample size was small [30].

In a real-world analysis of 85 patients who received afatinib in Malaysia, only 6 patients (7.1%) had uncommon or complex mutations, and median PFS in this small subgroup was generally similar to that in patients harboring Exon 21 L858R point mutations but shorter than that for patients with exon 19 deletion (9.0 vs. 8.7 vs. 16.0 months) [35]. Also of interest, in an analysis of a broad population of 479 Asian patients who were treated with afatinib, including 67 patients with uncommon *EGFR* mutations, median PFS was 12.6 months in the subgroup with uncommon mutations compared with 9.1 months for those with common mutations, but the difference was not significant [47]. Although this was a prospective Phase 3b trial, it was conducted in a setting similar to real-world practice. A pooled analysis of data from this Phase 3b Asian study and a German non-interventional study also showed that afatinib was active against uncommon *EGFR* mutations, including L861Q, S7681, or G719X [48], further adding to the evidence supporting the real-world effectiveness of afatinib in patients with uncommon *EGFR* mutations.

Patients with Brain Metastases

Preclinical and clinical trial evidence indicates that afatinib has activity in patients with baseline brain metastases and may protect against CNS spread of the disease [49–52]. However, these studies are limited by small numbers of patients and do not include patients with active brain metastases. Therefore, it is also important to consider real-world data with afatinib in *EGFR* mutation-positive NSCLC patients with brain metastases. Table 2 provides an overview of studies comparing afatinib with first-generation EGFR TKIs in Asian patients with brain metastases at baseline.

Although the global real-world GioTag study did not compare the activity of afatinib specifically in Asian patients with or without brain metastases at baseline, it did compare its activity in patients with or without brain metastases [40, 42]. With respect to the latter, median TTF with sequential afatinib and osimertinib was 22.2 months (90% CI 16.8–29.9) for patients with brain metastases at baseline compared with 28.1 months (90% CI 27.0–30.3) for those without.

In a Taiwanese study, 82 of 259 afatinib-treated patients with *EGFR* mutation-positive NSCLC had brain metastases at baseline [53]. Although median OS was shorter among patients with versus those without brain metastases (33.8 months vs. not reached, $p = 0.005$), ORR was generally similar (63.4% vs. 72.3%). In a comparative study of 422 patients with *EGFR* mutation-positive NSCLC in Taiwan, findings of a subgroup analysis in 49 patients with brain metastases at baseline showed a median PFS of 9.9 months with afatinib, 8.9 months with gefitinib, and 7.2 months with erlotinib, although the difference was not significant (Table 2) [34]. A similar analysis conducted in Taiwan also showed no significant difference in PFS ($p = 0.34$) or OS ($p = 0.46$) among patients with brain metastases receiving first-line afatinib, gefitinib, or erlotinib [54]. A

comparative real-world analysis of 88 Taiwanese patients with brain metastases at baseline showed a trend towards a reduction in risk among patients treated with afatinib compared with gefitinib [31] (Table 2). Other real-world data from Taiwan in a small patient population ($n = 11$) showed that afatinib was associated with an ORR of 82% and a complete cranial response rate of 64% [55].

The results of a study conducted in Singapore, in which 42 of 125 patients with *EGFR* mutation-positive NSCLC patients had brain metastases at baseline, showed that median PFS was similar between patients with brain metastases who started on afatinib 40 mg/day and afatinib-treated patients without brain metastases (13.3 vs. 15.0 months, hazard ratio [HR] 0.79, 95% CI 0.34–1.80) [56]. Analysis of data from a cohort of 85 afatinib recipients in Malaysia, which included 25 patients with brain metastases at baseline, also showed no significant difference in median PFS between those with and those without brain metastases (13.5 vs. 14.3 months, HR 0.67, 95% CI 0.34–1.27, $p = 0.209$ for univariate analysis) [35]. Furthermore, a study conducted in South Korea ($n = 165$), in which 43% of patients ($n = 71$) had brain metastases at baseline, found no significant differences in median PFS between patients with brain metastases who were treated with afatinib alone, afatinib plus whole brain radiotherapy, or afatinib plus gamma knife surgery (Table 2) [57]. Regular MRI imaging showed that patients treated with afatinib alone had a brain metastases response rate of 76%, indicating a high level of intracranial activity.

Elderly Patients

Despite the fact that patients diagnosed with *EGFR* mutation-positive NSCLC are generally elderly (≥ 65 years of age) [58], these patients are often under-represented in RCTs; therefore, real-world data on the effectiveness of afatinib in this patient population are of particular value. In the real-world, global GioTag study with sequential afatinib and osimertinib (~ 25% Asian patients), TTF was similar in patients aged < 65 years and those aged ≥ 65 years [28.7 months (90% CI 26.8–30.0) vs. 27.3 months (90% CI 20.4–31.3)] [40, 42].

Similar findings were reported in another real-world global study (RealGiDo) with afatinib in *EGFR* mutation-positive NSCLC, which included a total of 228 patients (43.9% Asian) [59]. In this analysis, median TTF and time to progression (TTP) were consistent in patients aged < 75 years and those aged ≥ 75 years [median TTF was 17.8 vs. 24.9 months ($p = 0.51$), respectively, and median TTP was 20.5 vs. 25.7 months ($p = 0.24$), respectively]; importantly, age had no effect on the afatinib safety profile. In a retrospective analysis of 448 Taiwanese patients with *EGFR* mutation-positive NSCLC patients treated with afatinib or first-generation EGFR TKIs, afatinib was associated with significantly longer PFS than gefitinib in subgroups aged < 65 years (HR 0.52, 95% CI 0.30–0.88) and ≥ 65 years (HR 0.47, 95% CI 0.23–0.96) [31]. Together, these data indicate that advanced age should not preclude use of afatinib.

Patients with ECOG PS ≥ 2

Patients with ECOG PS ≥ 2 generally have a less favorable prognosis than those with ECOG PS of 0 or 1, and are often excluded from RCTs, limiting the available evidence of treatment efficacy in these patients. Real-world data from the global GioTag and RealGiDo studies (both of which included a significant proportion of Asian patients) provide some insight into the effectiveness of afatinib in patients with *EGFR* mutation-positive NSCLC and poor performance status.

In the GioTag study with sequential afatinib and osimertinib, TTF was longer in patients with ECOG PS ≤ 1 ($n = 152$) than in those with ECOG PS ≥ 2 ($n = 31$) [30.0 months (90% CI 28.1–31.7) vs. 22.2 months (90% CI 16.0–26.5)] [40, 42]. Similarly, in the RealGiDo study, both median TTF and median TTP were significantly longer in patients with ECOG ≤ 1 than in those with ECOG PS ≥ 2 (20.0 vs. 11.3 months and 22.4 vs. 12.2 months, respectively; p values not reported) [59]. In contrast, in a cohort of 85

afatinib-treated patients in Malaysia, median PFS was numerically longer among those with ECOG PS ≥ 2 than in patients with ECOG PS ≤ 1 (15.9 vs. 13.8 months) (HR 0.86, 95% CI 0.39–1.90, $p = 0.703$) [35]. These data suggest that afatinib provides real-world clinical benefit in patients with ECOG PS ≥ 2.

REAL-WORLD EVIDENCE FOR THE TOLERABILITY AND SAFETY OF AFATINIB

Based on data from RCTs, the tolerability profile of EGFR TKIs is predictable and usually manageable with supportive care and/or dose reductions [60, 61]. Typically $\leq 10\%$ of patients in Phase 3 clinical trials discontinued therapy because of adverse events [9–12, 14–19]. Encouragingly, discontinuation rates appear consistent in real-world clinical practice. Among 541 patients with *EGFR* mutation-positive NSCLC who received afatinib in an observational study in Asia, treatment-related adverse events leading to discontinuation of afatinib occurred in 3.1% of patients [62]. In a study in South Korea, 6.1% of 165 patients who received first-line afatinib discontinued treatment due to adverse events [30]. These values are consistent with those reported in the RCTs of afatinib [18–20]. The tolerability profile of afatinib in the real-world setting also reflects that seen in prospective clinical trials, and no new safety signals have been reported in real-world studies in Asian patients with *EGFR* mutation-positive NSCLC. As seen in RCTs, the most frequently reported adverse events in the real-world setting in Asian patients were primarily gastrointestinal and dermatologic. For example, in a large ($n = 467$), comparative analysis conducted in South Korea, rash/acne, stomatitis, paronychia, diarrhea, dry skin, and pruritus were the most frequently reported adverse events with afatinib, gefitinib, and erlotinib [30]. Most adverse events were grade 1 or 2, whereas grade 3 or 4 adverse events were uncommon but more frequently reported with afatinib than the first-generation EGFR TKIs.

REAL-WORLD PRESCRIBING PRACTICES FOR AFATINIB

Tolerability-Guided Dose Modification

Well-designed prospective clinical trials with afatinib in *EGFR* mutation-positive patients with NSCLC have shown that tolerability-guided dose modification can reduce the incidence of adverse events without adversely impacting efficacy [18–20]. Results from the real-world RealGido study confirmed this in a broad patient population that included a large proportion of Asian patients (44%) [59]. In the overall study population of 228 patients, 31% received a modified afatinib dose of ≤ 30 mg/day. Most dose reductions occurred within the first 6 months of treatment and were related to adverse events. Importantly, clinical efficacy (TTP or TTF) among patients who received a modified starting dose of afatinib was similar to that for the overall real-world population [59].

Results from the RealGido study are supported by those from an analysis of 140 patients in Taiwan, in which there was no significant difference in clinical outcomes (response, PFS, and adverse events) between patients who received afatinib 40 mg/day and those who received afatinib < 40 mg/day in the first 6 months [36]. While these data support the clinical trial evidence, and demonstrate that tolerability-guided dose reductions do not impact efficacy, a retrospective study in 245 patients in Taiwan suggested that reducing the afatinib dose to < 20 mg/day may be associated with poorer outcomes [32].

Sequencing

Regardless of which EGFR TKI is used in the first-line setting, the development of resistance is inevitable, making the choice of subsequent treatments an important consideration [63, 64]. Optimal treatment sequencing of EGFR TKIs is an area of ongoing discussion, with clonal evolution of tumors being an increasingly important consideration [65].

The T790M mutation is the most common resistance mechanism to first- and second-generation EGFR TKIs, reported in ~ 50% of Asian patients after first-line afatinib therapy, with C797S, *BRAF* V600E, and MET amplifications also detected but at much lower prevalences [66, 67]. However, resistance mechanisms and targeted treatment options after first-line osimertinib therapy are not well defined [68–71]. Consequently, optimal treatment sequencing of EGFR TKIs is an area of active discussion [63, 72], with some studies assessing the benefit of using first- or second-generation EGFR TKIs as first-line therapy, reserving osimertinib as second-line therapy. Indeed, this discussion may be particularly relevant to Asian populations following the limited OS benefit seen in this subgroup with first-line osimertinib in the Phase 3 FLAURA trial, in which osimertinib was no more effective than first-generation EGFR TKIs (HR 1.00, 95% CI 0.75–1.32 for OS) [21].

In this regard, findings of the real-world GioTag study with sequential afatinib and osimertinib are noteworthy. The GioTag study demonstrated encouraging TTF and OS results, particularly in Asian patients with *EGFR* mutation-positive NSCLC [42]. These data are also supported by those from a retrospective Japanese study that demonstrated better outcomes when osimertinib was administered after afatinib versus after gefitinib/erlotinib [73]. The study included 111 patients with the T790M mutation treated with osimertinib, and showed that ORR was 82.9% for the sequence of afatinib followed by osimertinib compared with 53.9% for first-generation EGFR TKI followed by osimertinib ($p = 0.0065$). Follow-up is ongoing, but available data indicate a numerically longer PFS for the afatinib-treated patients (15.7 vs. 8.9 months, $p = 0.195$).

CONCLUSION

This review highlights the wealth of real-world evidence supporting the effectiveness and tolerability of afatinib in Asian patients with *EGFR* mutation-positive NSCLC. Data on the effectiveness of afatinib in routine clinical practice complement results of well-designed prospective clinical trials demonstrating the efficacy of afatinib in Asian patients, and point towards more favorable outcomes with afatinib versus first-generation EGFR TKIs in real-world patient populations. Moreover, various subgroup analyses with afatinib in the real-world setting demonstrated effectiveness in patients often under-represented in or excluded from prospective clinical trials, such as those with uncommon *EGFR* mutations, brain metastases at baseline, elderly patients, and those with ECOG PS $\geq$ 2.

In general, tolerability data from real-world studies in Asian patients reflect those reported in prospective clinical trials with afatinib. In addition, findings of the real-world RealGido study, which included 44% Asian patients, confirmed that prospective clinical trial data showing tolerability-guided afatinib dose modifications can reduce the incidence of adverse events without adversely affecting clinical outcomes.

An area of ongoing discussion and a need for further research is that of optimal treatment sequences for patients with *EGFR* mutation-positive NSCLC. Interestingly, the global real-world GioTag study, in which Asian patients represented about one-quarter of the study population, showed encouraging results for the overall study population, and TTF was significantly longer in Asian than in non-Asian patients treated with sequential afatinib and osimertinib. Together, and in contrast to the limited real-world data available for some other EGFR TKIs [27], this wealth of real-world evidence supports the use of afatinib as a first-line therapy in Asian patients with *EGFR* mutation-positive NSCLC.

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