Afatinib for the first-line treatment of *EGFR* mutation-positive NSCLC in China: a review of clinical data

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Mutations in the *EGFR* gene are particularly prevalent among Chinese patients with non-small-cell lung carcinoma. Six *EGFR* tyrosine kinase inhibitors are approved for the first-line treatment of *EGFR* mutation-positive non-small-cell lung carcinoma in China, which poses questions about which agent is most suitable for a particular patient. In this article, we review available clinical trial and real-world data with afatinib in Chinese patients. We assess its efficacy and safety in key patient subgroups such as those with uncommon mutations or brain metastases. We also consider possible subsequent therapies following afatinib. Encouragingly, available data suggest that sequential afatinib and osimertinib confer prolonged overall time to failure of almost 4 years in Asian patients, and represents a viable option in this setting.

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In China, lung cancer is the most common malignancy, accounting for 18% of new diagnoses in 2018 [1]. It is also the leading cause of cancer mortality, taking the lives of over 690,000 people in 2018. Of the lung cancer subtypes, non-small-cell lung cancer (NSCLC) is the most common, and is generally diagnosed at an advanced stage [2]. In recent years, investigation into the molecular basis of NSCLC has led to the identification of a number of targetable molecular aberrations, including mutations in the genes encoding the *EGFR* and anaplastic lymphoma kinase [3].

Mutations in *EGFR* are highly prevalent in Chinese patients with NSCLC, being detected in 35–50% of individuals [4–9]. In contrast, *EGFR* mutations are found in around 14% of European and 24% of North and South American NSCLC patients [10]. In Chinese populations, *EGFR* mutations are most commonly detected in women, nonsmokers and patients with NSCLC of adenocarcinoma histology [4,6,7]. Some geographical variations in incidence rates have been reported, with higher rates of around 46–49% reported in northern and South-West China [5,7]; conversely, lower detection rates (~35%) were reported in the Yunnan province of South-West China [4].

As has been observed worldwide, two subtypes of *EGFR* mutation are detected in the majority of Chinese patients: the point mutation L858R, and deletions in exon 19 (Del19) [5,7]. Del19 mutations are generally more common than the L858R mutation [4,5,11,12]. The uncommon mutations, G719X, L861Q and S768I, have also been detected in Chinese populations, together accounting for approximately 6% of *EGFR* mutations in one study in South-West China [7], and 4% in a population in North China [5]. In a study of 5363 Chinese lung cancer patients, uncommon mutations were seen in 12% of patients with *EGFR* mutations. The most frequent uncommon mutations were exon 20 insertions and G719X, and were detected in 31 and 21% of patients with uncommon mutations, respectively [13].

Currently, the treatment of *EGFR* mutation-positive (*EGFR*m+) NSCLC in China generally follows the guidelines issued by the Chinese Society of Clinical Oncology (CSCO) [14]. In a joint initiative, the European Society of Medical Oncology (ESMO) and CSCO recently published pan-Asian-adapted clinical practice guidelines for managing patients with metastatic NSCLC [15]. These guidelines are largely similar to those issued by the CSCO, and include a range of recommendations for the first-line treatment of *EGFR*m+ NSCLC. In both guidelines,

the recommended first-line therapy for patients with advanced *EGFR*mut+ NSCLC is an *EGFR* tyrosine kinase inhibitor (TKI) [14,15].

Six *EGFR* TKIs are currently approved in China for the first-line treatment of *EGFR*mut+ NSCLC: the reversible first-generation *EGFR* TKIs, erlotinib, gefitinib and icotinib, which was developed in China [16]; the irreversible ErbB-family blockers, afatinib and dacomitinib; and the third-generation irreversible, wild-type-sparing *EGFR* TKI, osimertinib [15]. Erlotinib, gefitinib, afatinib and icotinib have all demonstrated improvements in progression-free survival (PFS) versus chemotherapy in Phase III trials of patients with treatment-naïve *EGFR*mut+ NSCLC [11,17–24]. In subsequent comparative studies, second- and third-generation *EGFR* TKIs were shown to confer significantly longer PFS versus first-generation *EGFR* TKIs [25–28]. Of note, in the recent Phase III FLAURA trial, osimertinib demonstrated significantly improved overall survival (OS) compared with gefitinib or erlotinib [29]. Furthermore, in an exploratory analysis, dacomitinib, demonstrated improved OS, as well as PFS, versus gefitinib [27,28]. In the global Phase IIb LUX-Lung 7 study (discussed in detail below), afatinib showed a trend toward improved OS, and significantly improved PFS, versus gefitinib [25,30]. While these studies clearly demonstrate the superiority of second- and third-generation TKIs versus first-generation *EGFR* TKIs, no head-to-head trials have compared outcomes between second- and third-generation TKIs.

As afatinib has been approved in China for only a short time (~2 years) at the time of writing, experience with afatinib in routine clinical practice in China is currently limited. To facilitate a broader understanding of the use of afatinib in our country, we summarize available data on the efficacy and tolerability of afatinib, and the impact of dose adjustments, in Chinese patients. This information is especially relevant given the high prevalence of *EGFR* mutations among NSCLC patients in China. In addition, we provide a general comparison of the efficacy and safety of the *EGFR* TKIs in Chinese patients.

Afatinib in Chinese patients: clinical data

Efficacy

Afatinib has undergone a comprehensive clinical development program, including several Phase III studies involving large numbers of Chinese patients. Two pivotal Phase III studies comparing afatinib with platinum-based chemotherapy in patients with advanced *EGFR*mut+ NSCLC (including uncommon *EGFR* mutations) have been conducted: LUX-Lung 3 and LUX-Lung 6. Although no LUX-Lung 3 trial sites were located in mainland China, 72% of patients were East Asian, drawn from sites in Taiwan, Hong Kong, Thailand, South Korea and Japan [22]. LUX-Lung 6 was conducted in China, Thailand and South Korea, with almost 90% of afatinib-treated patients from China [23,31].

Afatinib significantly improved PFS versus platinum-based chemotherapy in the overall populations of both Phase III studies [22,23], and in 327 Chinese patients treated in LUX-Lung 6 (Table 1 & Figure 1A) [31]. In LUX-Lung 6, Chinese patients with Del19 appeared to derive a slightly greater PFS benefit from afatinib than did those with L858R (hazard ratio [HR]: 0.21 and 0.33, respectively; Figure 1B) [31]. In a preplanned analysis in patients with Del19 mutations, afatinib significantly prolonged OS versus chemotherapy in the overall populations and in Chinese patients (Table 1 & Figure 2) [31,32]. Afatinib was also associated with significantly higher response rates versus chemotherapy, in both the overall and Chinese populations in LUX-Lung 6 [23,31]. In Chinese patients, the objective response rate (ORR) with afatinib was 67% compared with 24% in chemotherapy-treated patients ($p < 0.0001$); further, the disease control rate (DCR) was significantly higher (92 vs 77%; $p = 0.0003$) and median duration of response longer (9.7 vs 4.2 months) with afatinib (Table 1) [31]. Of note, the ORR with afatinib was significantly higher than with platinum chemotherapy in all mutation subgroups examined (L858R, Del19 and others) and was particularly pronounced in Del19-positive patients (ORR: 78 vs 27%; odds ratio: 9.17 [95% CI: 4.37–19.26]; $p < 0.0001$) [31].

LUX-Lung 7 confirmed the efficacy of first-line afatinib in patients from a range of countries and ethnic backgrounds [25,30]. Of 319 randomized patients, just over half were Asian; of these, 48 (15% of all patients) were from China. PFS was significantly longer with afatinib compared with gefitinib in the overall population (HR: 0.73 [95% CI: 0.57–0.95]; $p = 0.017$; Table 1), with no significant differences between Asian and non-Asian patients ($p_{\text{interaction}} = 0.88$) and similar HRs in the two groups (Asian 0.76 [95% CI: 0.54–1.06]; non-Asian 0.72 [95% CI: 0.49–1.06]) [25]. In addition, time-to-treatment failure was significantly longer with afatinib than gefitinib (HR: 0.73 [95% CI: 0.58–0.92]; $p = 0.007$), with similar findings in Asians (13.2 vs 11.4 months) and non-Asians (14.1 vs 11.5 months) [25]. A trend toward improved OS with afatinib versus gefitinib was observed in the overall LUX-Lung 7 population (HR: 0.86 [95% CI: 0.66–1.12]) with no interaction between Asians and non-Asians

Table 1. Overview of Phase IIb/III studies of afatinib in patients with advanced *EGFR* mutation-positive NSCLC in which a large proportion of patients were enrolled at sites in China.

	LUX-Lung 6				LUX-Lung-7		1200.66
	All patients		Chinese patients		All patients		All patients [†]
	Afatinib	Gemcitabine + cisplatin	Afatinib	Gemcitabine + cisplatin	Afatinib	Gefitinib	Afatinib
Number of patients (n)	242	122	217	110	160	159	541
Patient baseline characteristics							
Ethnicity/country of origin (%)	Chinese: 90 SE Asian: 6 South Korean: 5	Chinese: 90 SE Asian: 8 South Korean: 2	China: 100	China: 100	Asian: 59 White: 30 Other: 11 [‡]	Asian: 55 White: 34 Other: 11 [‡]	China: 76 Hong Kong: 5 India: 9 Singapore: 4 Taiwan: 6
Male (%)	36	32	37	34	43	33	47
Median age (years; range)	58 (49–65)	58 (49–62)	58 (30–78)	58 (27–75)	63 (30–86)	63 (32–89)	59 (27–82)
Never smokers (%)	75	81	73	84	66	67	69
Tumor histology (%)							
– Adenocarcinoma	100	100	100	100	99	99	96
– Mixed/other	0	0	0	0	1	1	2
– Squamous cell carcinoma	0	0	0	0	0	0	2
ECOG PS (%)							
– 0	20	34	20	36	32	30	18
– 1	80	66	80	64	68	70	80
– 2	0	0	0	0	0	0	2
<i>EGFR</i> mutation type (%)							
– L858R	38	38	38 [§]	38	42	42	40
– Del19	51	51	51	50	58	58	48
– L858R + Del19	NR	NR	NR	NR	0	1	0
– Uncommon	11	12	11	12	NR	NR	12
Brain metastases at screening (%)	NR	NR	NR	NR	16	15	19
Efficacy							
Median PFS (months)	11.0	5.6	11.0	5.6	11.0	10.9	12.1
Median OS (months)	23.1	23.5	23.1	23.2	27.9	24.5	NR
– L858R	19.6	24.3	18.7	24.5	25.0	21.2	
– Del19	31.4	18.4	31.6	16.3	30.7	26.4	
Response							
– ORR (%)	67	23	67	24	72.5	56.0	NR
– DCR (%)	93	76	92	77	91.3	87.4	NR
– Median DOR (months)	9.7	4.3	9.7	4.2	10.1	8.4	NR
Safety							
Patients with grade ≥3 AE (%)	36	60	36	57	57	54	45
Patients undergoing dose reductions (%)	28	NR	34	61 [¶]	42	2	29
Patients requiring treatment discontinuation due to TRAE (%)	6	40	6	42	6	6	3
Most common grade ≥3 TRAEs (%)							
– Rash/acne	15	0	16	0	9	3	9
– Diarrhea	5	0	6	0	13	1	11
– Fatigue	<1	<1	0	0	6	0	NR
– Stomatitis/mucositis	5	0	6	0	4	0	4
– Neutropenia	<1	27	<1	28	<1	0	NR
– Vomiting	1	19	<1	19	0	<1	NR
– Leucopenia	<1	15	<1	17	NR	NR	NR
– Paronychia	0	0	NR	NR	2	<1	3

Percentages may not sum to 100 due to rounding.

[†]All patients were TKI-naïve; 60% were treatment naïve.[‡]Includes 17 patients in each arm who were from France, where ethnic details could not be captured by law.[§]Includes four patients with both L858R and Del19 mutations.[¶]39% received all courses without interruption.

Data taken from [23,25,30–33].

AE: Adverse event; DCR: Disease control rate; DOR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; NR: Not reported; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; SE: South-east; TKI: Tyrosine kinase inhibitors.

Figure 1. Progression-free survival in Chinese patients treated with afatinib or gemcitabine plus cisplatin in the LUX-Lung 6 study (independent review). (A) Kaplan–Meier curves; (B) forest plot of patient subgroups. Cis: Cisplatin; ECOG: Eastern Cooperative Oncology Group; Gem: Gemcitabine; HR: Hazard ratio; PFS: Progression-free survival. Reproduced from [31], with permission from Dove Medical Press Ltd.

Figure 2. Overall survival in Chinese patients treated with afatinib compared with gemcitabine plus cisplatin in the LUX-Lung 6 study (independent review). (A) Overall population (median: 23.1 vs 23.2 months; $p = 0.78$); (B) patients with Del19 mutations (median: 31.6 vs 16.3 months; $p = 0.015$); (C) patients with the L858R mutation (median: 18.7 vs 24.5; $p = 0.22$).

Cis: Cisplatin; Gem: Gemcitabine; HR: Hazard ratio; OS: Overall survival.

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[$p_{\text{interaction}} = 0.44$]; the HR was 0.95 [0.67–1.33] and 0.78 [95% CI: 0.52–1.17], respectively [30]. In the overall population, ORR, DCR and duration of response were all numerically higher with afatinib than gefitinib (Table 1); the difference in ORR between the arms was statistically significant ($p = 0.0083$) [25]. No comparisons for these end points have been made between Asian and non-Asian patients.

Results from a large, single-arm Phase IIIb study of afatinib in *EGFR* TKI-naïve patients (study 1200.66; ClinicalTrials.gov: NCT01953913) provide further evidence of the efficacy of afatinib in Asian patients [33]. In total, 541 patients treated at 34 sites in China, Hong Kong, India, Singapore and Taiwan were included in the analysis; of these patients, more than three-quarters (76.2%) were enrolled at sites in China. Afatinib demonstrated encouraging time to symptomatic progression (TTSP; median: 14.0 months [95% CI: 12.9–15.9]) and PFS (median: 12.1 months [95% CI: 11.0–13.6]) in patients with common and uncommon *EGFR* mutations. Median TTSP was longer than median PFS, which suggests that afatinib treatment may be continued beyond progression, reflecting real-world clinical practice and treatment guidelines [15,34,35].

Real-world data support the findings of prospective studies. While few studies in Chinese patients have been published, a recent analysis of 60 patients treated with afatinib (30% with uncommon *EGFR* mutations and 40% with baseline brain metastases), showed median PFS of 12.3 months in patients receiving first-line afatinib [36]. A

number of other real-world studies conducted in Taiwan also corroborate findings from clinical trials [37–40]; median PFS with afatinib was around 12 months in NSCLC patients with common *EGFR* mutations (L858R/Del19), and 11 to almost 20 months in patients with uncommon mutations [39,41].

Long-term response to afatinib

Data from the LUX-Lung 3, 6 and 7 studies indicate that afatinib is associated with long-term response of 3 years or longer in a proportion of patients [42]. In LUX-Lung 6, 10% of afatinib-treated patients were long-term responders (treated with afatinib for ≥ 3 years), with a median treatment duration of 56 months (range: 37–68 months). Baseline characteristics of the long-term responders were generally consistent with the overall patient populations, though there was a higher proportion of women and patients with Del19 mutations. Many long-term responders had tolerability-guided dose adjustments, with some patients successfully undergoing prolonged treatment at doses as low as 20 mg.

Afatinib in patients with brain metastases

Treatment with afatinib has been shown to confer clinical benefit in patients with brain metastases and may even slow central nervous system (CNS) progression compared with conventional chemotherapy. In LUX-Lung 6, median PFS in patients with baseline brain metastases was 8.2 months with afatinib compared with 4.7 months with gemcitabine and cisplatin (HR: 0.47 [95% CI: 0.18–1.21]; $p = 0.11$) [43]. Furthermore, median time to CNS progression was longer with afatinib (15.2 months) than with chemotherapy (7.3 months). Patients in the 1200.66 study with brain metastases at baseline had slightly shorter median PFS (10.9 months) than those without baseline brain metastases (12.4 months), but still derived substantial benefit from afatinib [44].

In a Korean real-world study, 22 of 29 patients (76%) with evaluable follow-up brain magnetic resonance imaging for nonirradiated brain metastatic lesions had a significant response to first-line afatinib [45]. Further, a Taiwanese retrospective analysis of 28 patients with lung adenocarcinoma, who were treated with first-line afatinib or whole brain radiotherapy followed by afatinib maintenance, reported ORR rates of 82 versus 88%, respectively [46]. The complete response rate for intracranial lesions was notably higher in patients receiving afatinib monotherapy compared with whole brain radiotherapy plus afatinib maintenance (64 vs 18%; $p = 0.02$).

Tolerability

In the LUX-Lung trials, afatinib demonstrated a predictable safety profile, with adverse events (AEs) largely related to its mechanism of action, and generally consistent with the AEs reported for other *EGFR* TKIs (Table 1) [22,23,25,31,47,48]. Afatinib-related AEs were primarily gastrointestinal and dermatologic; the most frequently observed drug-related AEs in LUX-Lung 3, 6 and 7 were diarrhea, rash/acne and stomatitis/mucositis (Table 1). In the overall populations of LUX-Lung 3 and 6, afatinib had a better tolerability profile than chemotherapy, with markedly lower rates of hematologic toxicity [22,23]. In the sub-analysis of Chinese patients in LUX-Lung 6, similar proportions of patients experienced grade ≥ 3 treatment-related AEs in the afatinib and chemotherapy groups (36% in each), but substantially more patients in the chemotherapy arm experienced grade 4 treatment-related AEs (21 vs 1% with afatinib) [31]. In LUX-Lung 7, afatinib was associated with a higher incidence of grade ≥ 3 treatment-related AEs, particularly diarrhea and rash, compared with gefitinib. However, elevated liver enzymes and interstitial lung disease were more common with gefitinib [25]. The safety profile of afatinib appeared to be similar between the overall population and the Chinese sub-population of LUX-Lung 6, with rash/acne, diarrhea and stomatitis/mucositis the most frequent treatment-related AEs (Table 1) [23,31]. Consistent with global studies of afatinib, diarrhea, rash/acne and stomatitis were also the most frequently reported grade ≥ 3 afatinib-related AEs in the 1200.66 real-world study [33].

Impact of tolerability-guided dose adjustment

Afatinib is available in multiple dose strength formulations. Specific recommendations for tolerability-guided dose adjustment have been developed, and studies suggest that these do not negatively impact on efficacy in Asian populations [33,49]. In the 1200.66 study, around a quarter of patients had at least one dose reduction which effectively managed treatment-related AEs, including diarrhea and rash, such that treatment discontinuations were uncommon ($< 10\%$). Neither PFS nor TTSP were affected by dose reduction during the first 6 months of treatment. PFS and TTSP in patients who did not undergo dose reduction were 11.3 and 14.7 months, respectively, compared with 14.1 and 17.7 months in patients who underwent dose reduction [49].

Similar PFS outcomes with or without dose reductions were also reported for LUX-Lung 6 [50], LUX-Lung 7 [51], a Taiwanese real-world analysis [40] and a global real-world study in which 44% of patients were Asian [52]. In LUX-Lung 6, no significant difference in PFS was seen in patients who underwent afatinib dose reduction during the first 6 months of treatment compared with those who did not (median: 12.3 vs 11.0 months; HR 1.00 [95% CI: 0.69–1.46]; $p = 0.982$; Figure 3A) [50]. Sixty-seven patients (28%) treated with afatinib required dose reductions due to treatment-related AEs (Table 1), of whom 54 (81%) experienced grade ≥ 3 treatment-related AEs. After dose reduction, only 12% of patients had grade ≥ 3 treatment-related AEs (Figure 3B) [50]. In LUX-Lung 7, there was no difference in the frequency of discontinuations due to treatment-related AEs between afatinib and gefitinib (6% in each arm; Table 1), but there were more dose reductions due to AEs in patients receiving afatinib (42 vs 2%), likely due to the well-defined dose adjustment protocol for afatinib and the fact that gefitinib is only available in one dose formulation [25]. As with LUX-Lung 6, there was no significant difference in PFS in patients who did or did not undergo dose reduction within the first 6 months (median: 12.8 vs 11.0 months; HR 1.34 [95% CI: 0.90–2.00]; $p = 0.144$) [51]. In the Taiwanese real-world study, patients receiving afatinib doses of 40 mg during the first 6 months of treatment had a median PFS of 12.0 months, compared with 11.0 months in patients who received < 40 mg (HR: 0.84 [95% CI: 0.53–1.31]; $p > 0.05$) [40].

The effectiveness of tolerability-guided dose reduction of afatinib for the management of AEs reflect its pharmacokinetic characteristics. Afatinib shows moderate-to-high interpatient variability in exposure [53]. Key covariates of increased exposure include lower bodyweight, female sex and age [53]. AEs tend to be more common in patients with higher initial plasma concentrations [50]. Dose reduction reduces excessive plasma concentrations, thereby mitigating treatment-related AEs [50]. While dose reduction does not appear to impact efficacy, it is important not to adapt starting dose based on clinical characteristics because there are no prospective data to support a < 40 mg starting dose and under-dosing may be a possibility.

Patient-reported outcomes

Assessment of patient-reported outcomes (PROs) is an important complement to efficacy and tolerability data and can help provide a broader picture of the impact of treatment at an individual patient level. For example, PRO data can provide evidence on whether AEs associated with targeted therapy impact quality of life. In LUX-Lung 6, global health status/quality of life (measured using the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Core Questionnaire C30 [QLQ-C30]) was improved with afatinib compared with chemotherapy, including in an exploratory analysis of patients with common *EGFR* mutations (Del19 and/or L858R) [31,54,55]. In Chinese patients treated in LUX-Lung 6, significantly greater proportions of patients in the afatinib group had improvements in cough, dyspnea and pain than in the gemcitabine/cisplatin group; time to deterioration of cough, dyspnea and pain were also delayed with afatinib [31].

Although better PFS and OS outcomes with afatinib relative to chemotherapy have been seen in patients with Del19 mutations than in those with L858R [23,31], PRO data from the overall LUX-Lung 6 population suggest that, for cough and dyspnea, afatinib confers similar benefit in patients with Del19 and L858R [55]. Similar improvements in health-related quality of life, as assessed by the EuroQol 5 dimensions questionnaire (EQ-5D) and the EuroQol Visual Analog Scale (EQ-VAS), were observed with afatinib and gefitinib in LUX-Lung 7; notably, quality of life was not affected by dose reductions during the first 6 months of treatment in patients treated with afatinib [51,56].

Mechanisms of acquired resistance to afatinib & subsequent therapy

Despite the impressive initial efficacy of afatinib and other *EGFR* TKIs in *EGFR* + NSCLC, resistance to treatment eventually develops in most patients. In general, resistance mechanisms to first-generation *EGFR* TKIs have been more comprehensively studied than resistance mechanisms to afatinib. The predominant resistance mechanism to the first-generation *EGFR* TKIs is the T790M mutation in *EGFR* [57], which is detected in approximately 50–70% of patients overall and is more prevalent in patients with Del19-positive tumors than L858R-positive tumors [58–60]. A number of studies indicate that the T790M emergence rate is similar in patients treated with afatinib as it is with patients treated with gefitinib/erlotinib, ranging from 40 to 73% [37,58,61–64]. Few data, however, are available regarding the T790M acquisition rate in Chinese NSCLC patients. Additional mechanisms of resistance to *EGFR* TKIs have largely been identified based on studies of erlotinib and gefitinib and include *MET* amplification (5–20%), transformation to small cell lung cancer ($\sim 10\%$), epithelial mesenchymal transition (EMT; 1–2%), mutations in *PI3K* (2–3%), *BRAF* ($\sim 1\%$) or *KRAS* ($\sim 1\%$) and other secondary mutations in *EGFR* ($\sim 1\%$) [65,66]. Up to 10–15% of patients who become resistant to first-generation *EGFR* TKIs demonstrated amplification of

Figure 3. Impact of dose reduction on progression-free survival and adverse events in patients receiving afatinib in the LUX-Lung 6 study. (A) PFS in patients who had dose reductions within the first 6 months, and those who remained on afatinib ≥ 40 mg once daily; **(B)** most common treatment-related adverse events pre- and post-afatinib dose reduction.

HR: Hazard ratio; PFS: Progression-free survival.
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HER2 [65,66]. However, it is unlikely *HER2* amplification is a major mechanism of resistance to afatinib given that it is an ErbB family blocker. Emerging evidence indicates that many (up to 46%) of *EGFR* TKI-resistant tumors demonstrate co-occurring mechanisms of resistance based on next-generation sequencing of blood-derived cell-free tumor DNA [66–69]. Again, these studies have predominantly been based on studies of erlotinib or gefitinib. Further data are required to elucidate mechanisms of resistance to afatinib.

In patients with T790M-positive disease following progression on a first-line *EGFR* TKI, treatment with second-line osimertinib, which is approved in this setting, produces high response rates and prolonged PFS (median: ~10–12 months) [58,70]. Data from retrospective analyses suggest that the use of osimertinib in patients with T790M-positive disease progressing after first-line afatinib can result in promising clinical outcomes in patients with *EGFR* + NSCLC [61,71]. In a global, observational, study (GioTag) of 204 patients treated with sequential afatinib and osimertinib, overall time on treatment was over 2 years (median: 27.6 months) [71]. Time on treatment was particularly striking in Asian patients (nearly 4 years) and patients with tumors harboring *EGFR* Del19 mutations. A recent updated analysis of GioTag demonstrated median OS of 41.3 months overall (90% CI: 36.8–46.3) and 45.7 months (90% CI: 45.3–51.5) in those with Del19-positive tumors [72]. OS in Asian patients was immature. In a post-hoc analysis of data from 37 patients in LUX-Lung 3, 6 and 7 who discontinued afatinib and received subsequent osimertinib, of whom 54% were Asian, median time on osimertinib in any treatment line was 20.2 months (95% CI: 12.8–31.5), and median OS had not been reached at the time of analysis [73]. In ten patients who received consecutive afatinib and osimertinib, median PFS-2 (the time from initiation of afatinib to the last day of osimertinib therapy) was 53.3 months. Together, these findings illustrate that sequential use of *EGFR* TKIs can lead to prolonged periods of chemotherapy-free treatment in patients with *EGFR* + NSCLC. Moreover, recent findings suggest that outcomes may be particularly favorable if second- and third-generation TKIs are used sequentially. In a Japanese retrospective analysis, ORR with osimertinib was higher in patients with *EGFR* + NSCLC who had previously received afatinib than those who had previously received a first-generation *EGFR* TKI (83 vs 54%; $p = 0.007$), as was DCR (91 vs 71%; $p = 0.03$) [74]. Further, median PFS with osimertinib was numerically longer in afatinib-treated patients than in those treated with a first-generation *EGFR* TKI (15.6 vs 8.9 months; $p = 0.20$).

A possible shortcoming of sequential *EGFR* TKI therapy is that it is only applicable to patients who develop T790M-dependent acquired resistance to first-line therapy. Currently, subsequent therapies for patients who receive first-line afatinib and progress due to a T790M-independent mechanism are limited, with platinum-doublet chemotherapy being the principal treatment option in these patients [14]. However, in LUX-Lung 3, 6 and 7 studies, there was a high uptake of subsequent therapies (71%; 64% in Chinese patients) following progression on or after first-line afatinib, indicating that clinicians and patients are motivated to continue treating *EGFR* TKI-resistant disease even without targeted therapy [73]. Moreover, recent data suggest that targeting alternative signaling pathways, either as monotherapy or in combination with chemotherapy, an *EGFR* TKI or an immune checkpoint inhibitor may be applicable for some patients, including those with T790M-independent resistance to first-line *EGFR* TKIs [75,76]. Potential treatment options in development for T790M-negative tumors have recently been reviewed in detail elsewhere [76]. In brief, a number of targeted agents could be considered for patients with T790M-negative tumors following failure of afatinib, depending on whether a specific resistance mechanism is identified. For example, in the case of *MET* amplification a clinical trial with a selective *MET* inhibitor, such as capmatinib, tepotinib or savolitinib could be considered [76]. Alternatively, simultaneous targeting of *EGFR* and *MET* with a bi-specific antibody is another potential approach for the treatment of disease that has relapsed following prior *EGFR* TKI therapy [77]. In patients with AXL activation (associated with EMT) several AXL blockers are in clinical development, including DS-1205c, bemcentinib (BGB324) and duberminib (TP-0903) [76]. Also in the case of *BRAF* or *PI3K* mutations, clinical trials with *MEK* inhibitors (e.g., selumetinib) or *mTOR* inhibitors (e.g., sapanisertib), respectively, may be appropriate [76].

Immune checkpoint inhibitors could play a role post afatinib. For example, in a sub-analysis of the triple-arm, Phase III IMpower study in patients with *EGFR* + disease, addition of the anti-programmed death ligand-1 (PD-L1) antibody, atezolizumab, to bevacizumab plus chemotherapy significantly improved OS (median: not evaluable vs 17.5 months; HR: 0.31 [95% CI: 0.11–0.83]), and PFS (median: 10.3 vs 6.1 months; HR: 0.41 [95% CI: 0.23–0.75]) versus bevacizumab plus chemotherapy alone [75]. The combination was associated with a treatment-related grade ≥ 3 AE rate of 57%. However, the combination of an *EGFR* TKI with an immune checkpoint PD-(L)1 blocker could potentially lead to severe immune-related AEs. For example, the Phase IB TATTON trial (second-line osimertinib plus durvalumab) was terminated due to a high incidence of interstitial

lung disease [78]. On the other hand, while few data are currently available in NSCLC, a Phase II study of afatinib and pembrolizumab in patients with head and neck cancer indicated that this combination may be feasible, with no recorded cases of pneumonitis [79]. Sequential regimens of an EGFR TKI followed by a PD-(L)1 blocker do not appear to be associated with immune-related AEs in patients with *EGFR* mutation-positive NSCLC [80].

In summary, in patients with *EGFR* mutation-positive NSCLC treated with first-line afatinib, second-line osimertinib appears to be a promising approach in patients with T790M-mediated resistance. With respect to T790M-independent mechanisms of resistance to afatinib, and potential second-line treatment approaches, more data are required.

Afatinib compared with other EGFR TKIs in Chinese patients

Current CSCO clinical guidelines do not provide specific recommendations regarding the preferred first-line EGFR TKI, leaving the decision to individual clinicians. Many factors may be considered when choosing a first-line treatment, including the type of *EGFR* mutation, whether brain metastases are present, the patient's preference, age and performance status, the efficacy and safety profile of each agent and its impact on PROs, subsequent treatment options and the cost of therapy. Table 2 summarizes prospective clinical trial data assessing the efficacy and safety of EGFR TKIs in Chinese patients (or in broader Asian populations that include Chinese patients, if China-specific data were not available). While it is not possible to directly compare independent clinical trials, these studies may provide some insight into the relative efficacy and safety profiles of the EGFR TKIs in Chinese patients.

Median PFS was largely similar in each study, ranging from 9.8 to 17.8 months (Table 2). The longest PFS was observed with osimertinib. Sub-analyses of the FLAURA trial in Asian patients (14% of whom were Chinese) demonstrated a significant improvement in PFS versus gefitinib or erlotinib (HR: 0.54 [95% CI: 0.41–0.72] [82]), although the magnitude of the effect was less than observed in non-Asian patients (HR: 0.34) [26]. In a further sub-analysis, significant PFS benefit was also observed in Chinese patients (median: 17.8 vs 9.8 months; HR: 0.56 [95% CI: 0.37–0.85]) [83]. In the only head-to-head trial undertaken exclusively in Chinese patients, CTONG 0901, there was no difference in PFS between erlotinib and gefitinib (HR: 0.81 [95% CI: 0.62–1.05] [81]).

Median OS across studies ranged from 20.1 to 37.1 months. Again, median OS was highest with osimertinib. However, interestingly, unlike the overall FLAURA dataset [26], there was no evidence of an OS benefit with osimertinib versus gefitinib/erlotinib in Asian patients (HR: 1.00 [95% CI: 0.75–1.32]) [29]. There was also no evidence of OS benefit between afatinib and gefitinib in Asian patients (HR: 0.95 [95% CI: 0.67–1.33]) [30] or between erlotinib and gefitinib in Chinese patients (HR: 0.84 [95% CI: 0.63–1.13]) [81]. Based on OS, therefore, it is unclear which first-line EGFR TKI may be most effective in Chinese, or Asian, patients. Of note, as osimertinib has only recently become available, few patients in any of the listed trials would have received second-line osimertinib following failure of another EGFR TKI. Given encouraging clinical activity observed in GioTag, and other studies (discussed previously), it is possible that sequential EGFR TKI regimens could confer prolonged OS (in patients with T790M-mediated acquired resistance) compared with what has been observed to date. This possibility requires prospective evaluation in clinical trials.

When considering the optimal use of EGFR TKIs in patients with EGFRm+ NSCLC, in China and elsewhere, it is also important to assess recent progress regarding EGFR-TKI-based combination strategies. Several novel combinations, such as erlotinib plus ramucirumab [84], gefitinib plus pemetrexed-carboplatin [85,86] and erlotinib plus bevacizumab [87], have demonstrated promising outcomes with significant PFS benefit and, in some cases [85,86], OS benefit observed in randomized trials. In one trial, the latter combination conferred OS of over 50 months [86]. These findings indicate that novel combinations of existing drugs may be able to achieve similar or better outcomes than single targeted agents in EGFRm+ NSCLC.

It is important to consider tolerability profiles when deciding upon first-line treatment in individual patients. As discussed, while EGFR TKIs have overlapping, class-based tolerability profiles, available data indicate that there are qualitative and quantitative differences in the frequency of grade AEs with different TKIs. Although afatinib was associated with a relatively high incidence of grade ≥ 3 rash/acne, diarrhea and stomatitis in clinical trials and real-world studies, certain other grade ≥ 3 AEs may be more prevalent with first-generation EGFR TKIs (e.g., elevated AST/ALT). Furthermore, while osimertinib has a generally favorable tolerability profile, as it spares wild-type EGFR, certain grade ≥ 3 AEs occurred that appeared to be less prevalent with other EGFR TKIs (e.g., prolonged QT interval).

Table 2. Comparison of prospective clinical trial data on EGFR tyrosine kinase inhibitors in Chinese patients (or Asian patients if Chinese-specific data unavailable) with *EGFR* mutation-positive non-small-cell lung cancer.

EGFR TKI	Trial	n	Median PFS (months)	Median OS (months)	ORR (%)	Most common grade ≥ 3 AEs (%) [†]	Ref.
Afatinib [‡]	LUX-Lung 6	193 [§]	11.0 [§]	23.6 [§]	69 [§]	Any: 36 Rash/acne: 16 Stomatitis: 6 Diarrhea: 6	[31]
	LUX-Lung 7 [¶]	94 [#]	11.0 ^{††}	27.9 ^{††}	NR	Any: 31 Diarrhea: 13 Rash/acne: 9 Fatigue: 6	[25,30]
Erlotinib	ENSURE	110	11.0	26.3	63	Any: 44 Rash: 6	[18]
	OPTIMAL	83	13.1	22.8	82	Any: 17 Increased ALT: 4 Rash: 2	[11]
	CTONG 0901 ^{‡‡}	128	13.0	22.9	56	Any: 5 Rash: 2 Increased bilirubin: 2	[81]
Gefitinib	CTONG 0901 ^{‡‡}	128	10.4	20.1	52	Any: 2	[81]
	LUX-Lung 7 [¶]	88 [#]	11.0	24.5	NR	Any: 18 Increased ALT/AST: 8 Rash/acne: 3 ILD: 2	[25,30]
Erlotinib or gefitinib	FLAURA ^{§§,¶}	160 [#]	11.0	35.8	75	Any: 48 Increased AST: 6 Diarrhea: 3 Decreased appetite: 3	[29,82]
	FLAURA (Chinese only) ^{¶¶}	65	9.8	NR	75	Any: 23 Increased ALT: 6	[83]
Osimertinib	FLAURA ^{§§,¶}	162 [#]	16.5	37.1	80	Any: 40 Decreased appetite: 3 Prolonged QT: 3	[29,82]
	FLAURA (Chinese only) ^{¶¶}	71	17.8	NR	83	Any: 49 Decreased neutrophil count: 6 Decreased WBC/lymphocyte count: 4/4 Prolonged QT: 4 Elevated AST: 4	[83]
Icotinib	CONVINCE	148	11.2	30.5	NR	Rash: 15 Diarrhea: 7	[24]

[†]Top three AEs listed (if over 1% frequency).[‡]Treatment-related AEs reported in LUX-Lung 6 and 7; treatment-emergent AEs reported for other trials.[§]Patients with common EGFR mutations.[¶]There was a trend toward improved PFS with afatinib vs gefitinib in Asian patients in LUX-Lung 7 (HR: 0.76; 95% CI: 0.54–1.06); there was no significant difference in OS (HR: 0.94; 95% CI: 0.67–1.33).[#]Asian patients.^{††}Data on file.^{‡‡}No significant difference in PFS (HR: 0.81; 95% CI: 0.62–1.05) or OS (HR: 0.84; 95% CI: 0.63–1.13) between erlotinib and gefitinib in CTONG 0901.^{§§}There was a significant improvement in PFS with osimertinib vs gefitinib/erlotinib in Asian patients in FLAURA (HR: 0.54; 95% CI: 0.41–0.72); there was no significant difference in OS (HR: 1.00; 95% CI: 0.75–1.32).^{¶¶}There was a significant improvement in PFS with osimertinib vs gefitinib/erlotinib in Chinese patients in FLAURA (HR: 0.56; 95% CI: 0.37–0.85).

AE: Adverse event; HR: Hazard ratio; ILD: Interstitial lung disease; NR: Not reached; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; WBC: White blood cell.

Conclusion & future perspective

Afatinib is an effective first-line treatment option in Chinese patients with *EGFR* ⁺ NSCLC. Its safety profile is predictable, with drug-related AEs being manageable with supportive care and tolerability-guided dose adjustments. Such dose adjustments do not appear to compromise the efficacy of afatinib, but rather, may help to facilitate long-term continuation of active treatment. While second- and third-generation EGFR TKIs are both superior to first-generation TKIs, no prospective data are available comparing second- and third-generation EGFR TKIs in China or, indeed, in any population. Therefore, it remains unclear what the optimal treatment should be. On one hand, osimertinib is an attractive first-line treatment option in Chinese patients based on the FLAURA data. However, resistance to osimertinib is mediated by a diverse range of mechanisms [88], and currently no targeted

agents are available that specifically address these resistance mechanisms. Consequently, an alternative sequencing strategy, where osimertinib is reserved for second-line use following failure of afatinib, warrants consideration in Chinese patients with *EGFR*m+ NSCLC as 50–70% of these patients will develop T790M-mediated resistance. Data from GioTag, showing a combined time on treatment of nearly 4 years in Asian patients [71], highlight the potential of this strategy, which warrants further investigation in patients with T790M-positive tumors. Also, combination strategies are of potential interest for example second- or third-generation *EGFR* TKIs combined with anti-angiogenic agents or low toxicity chemotherapy. Furthermore, more data are required to assess how *EGFR* mutation subtype, and concurrent genetic alterations, influence the response to different treatment regimens.

Increased availability of effective treatments for *EGFR* mutation-positive NSCLC highlight the importance of rebiopsy (tissue and/or blood) and NGS at the point of tumor progression to inform subsequent treatment decisions. Treatment options for patients with T790M-independent mechanisms of resistance remain an unmet medical need. However, ongoing clinical development programs with agents including MET, MEK and mTOR inhibitors, and novel combination strategies including immune checkpoint inhibitors, will hopefully identify individualized therapeutic strategies depending on the precise molecular signature of tumors following acquired resistance to afatinib.

In the absence of strong comparative data, further study is required to determine the most appropriate sequencing of *EGFR* TKIs that will maximize clinical benefit. The ongoing European APPLE study comparing first-line osimertinib with first-line gefitinib followed by osimertinib at progression may provide some insight into this issue [89], but similar studies should be undertaken in Asia. In addition, further research into patient-specific factors that may influence response to specific targeted therapies is needed. Additional investigation is also needed to establish suitable treatment options for patients who progress on first-line osimertinib treatment.

As the majority of patients with *EGFR*m+ NSCLC go on to receive second or later lines of therapy, maximizing the clinical benefits associated with each treatment line is essential, so that patients are able to live extended lives while maintaining quality of life.

Executive summary

Background

- Mutations in *EGFR* are highly prevalent in Chinese patients with NSCLC, being detected in 35–50% of individuals.
- Currently, the treatment of *EGFR* mutation-positive (*EGFR*m+) NSCLC in China generally follows the guidelines issued by the Chinese Society of Clinical Oncology (CSCO).
- Six *EGFR* tyrosine kinase inhibitor (TKIs) are currently approved in China for the first-line treatment of *EGFR*m+ NSCLC: erlotinib; gefitinib; icotinib; afatinib; dacomitinib and osimertinib.
- This article summarizes available clinical trial and real-world data on the efficacy and tolerability of afatinib, and the impact of dose adjustments, in Chinese patients. In addition, we provide a general comparison of the efficacy and safety of the *EGFR* TKIs in Chinese patients.

Afatinib in Chinese patients: clinical data

Efficacy

- In the Phase III LUX-Lung 6 trial (almost 90% Chinese patients), afatinib significantly improved progression-free survival (PFS) versus platinum-based chemotherapy. Afatinib significantly prolonged OS versus chemotherapy in patients with Del19-positive tumors. Similar findings were observed in a sub-analysis of Chinese patients. Approximately 10% of afatinib-treated patients were long-term responders (treated with afatinib for ≥ 3 years).
- In the Phase IIb LUX-Lung 7 trial (>50% Asian patients; 15% Chinese patients), afatinib significantly improved PFS and time-to-treatment failure versus gefitinib, with no significant differences between Asian and non-Asian patients.
- In a large, single-arm Phase IIIb study of afatinib in *EGFR* TKI-naïve patients (1200.66; >75% Chinese patients), afatinib conferred encouraging time to symptomatic progression and PFS in patients with both common and uncommon *EGFR* mutations.
- Few real-world studies of afatinib in Chinese patients have been published, but available data corroborate findings from clinical trials.
- Sub-analyses of LUX-Lung 6 and 1200.66 indicate that afatinib confers clinical benefit in Chinese patients with brain metastases and may slow CNS progression compared with conventional chemotherapy.

Tolerability

- Consistent with global studies, the most frequent treatment-related adverse events (AEs) in Chinese patients treated with afatinib in LUX-Lung 6 and 1200.66 were diarrhea, rash/acne and stomatitis.
- Based on available data, tolerability-guided dose reductions reduced the frequency and severity of AEs without impacting on efficacy in Chinese patients.

- In Chinese patients treated in LUX-Lung 6, significantly greater proportions of patients in the afatinib group had improvements in cough, dyspnea and pain than in the chemotherapy group; time to deterioration of cough, dyspnea and pain were also delayed with afatinib.

Mechanisms of acquired resistance to afatinib & subsequent therapy

- The predominant resistance mechanism to the first- and second-generation EGFR TKIs is the T790M mutation in *EGFR*, which is detected in approximately 50–70% of patients.
- Data from retrospective analyses suggest that the use of osimertinib in patients with T790M-positive disease progressing after first-line afatinib can result in promising clinical outcomes in patients with *EGFR*⁺ NSCLC.
- In a global, observational, study (GioTag) of 204 patients treated with sequential afatinib and osimertinib, median time-to-treatment failure was over 2 years (near 4 years in Asian patients) and median OS was 41.3 months.
- Currently, subsequent therapies for patients who receive first-line afatinib and progress due to a T790M-independent mechanism are limited, with platinum-doublet chemotherapy being the principal treatment option in these patients.

Afatinib compared with other EGFR TKIs in Chinese patients

- Current CSCO guidelines do not provide specific recommendations regarding the preferred first-line EGFR TKI, leaving the decision to individual clinicians.
- In prospective clinical trials, median PFS achieved with different EGFR TKIs in Chinese patients ranged from 9.8 to 17.8 months.
- The longest PFS was observed with osimertinib in the Phase III FLAURA trial, although the magnitude of benefit over gefitinib/erlotinib appeared to be greater in non-Asian than Asian patients.
- Median OS across studies ranged from 20.1 to 37.1 months. No EGFR TKI has shown a significant OS benefit over another EGFR TKI in Asian or Chinese patients.
- Little prospective data are available assessing clinical outcomes in patients received second-line osimertinib following failure of another EGFR TKI.
- Novel combinations of existing drugs (e.g., an EGFR TKI plus chemotherapy) may be able to achieve similar or better outcomes than single targeted agents in *EGFR*⁺ NSCLC.
- Although EGFR TKIs have overlapping, class-based tolerability profiles, available data indicate that there are qualitative and quantitative differences in the frequency of grade AEs with different, for example, afatinib was associated with a relatively high incidence of grade ≥ 3 rash/acne, diarrhea and stomatitis.
- Osimertinib has a generally favorable tolerability profile, as it spares wild-type EGFR. Nevertheless, certain grade ≥ 3 AEs appeared to be less prevalent with other EGFR TKIs (e.g., prolonged QT interval).

Conclusion & future perspective

- Afatinib is an effective and tolerable first-line treatment option in Chinese patients with *EGFR*⁺ NSCLC.
- No prospective data are available comparing second- and third-generation EGFR TKIs in China or, indeed, in any population.
- Osimertinib is an attractive first-line treatment option in Chinese patients based on the FLAURA data. However, as treatment options are limited following failure of osimertinib, it may be better to withhold it for second-line use in patients who develop T790M-mediated resistance.
- In the absence of strong comparative data, further study is required to determine the most appropriate sequencing of EGFR TKIs that will maximize clinical benefit in China.

Author contributions

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

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