



# A Phase IIIb Open-Label, Single-Arm Study of Afatinib in EGFR TKI-Naïve Patients with *EGFRm+* NSCLC: Final Analysis, with a Focus on Patients Enrolled at Sites in China

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## Abstract

**Background** Afatinib has been shown as a suitable option for the treatment of epidermal growth factor receptor mutation-positive (*EGFRm+*) non-small-cell lung cancer (NSCLC) in randomized controlled trials. However, patients treated in real-world clinical practice, including elderly patients, and those with brain metastases or poor Eastern Cooperative Oncology Group (ECOG) performance statuses, are often excluded from these studies.

**Objective** To report the final results, with a particular focus on patients enrolled in China, from a prospective phase IIIb, “near real-world” study of afatinib in tyrosine kinase inhibitor (TKI)-naïve Asian patients with *EGFRm+* NSCLC.

**Patients and Methods** NCT01953913 was conducted at 34 centers across Asia. Entry criteria were broad to reflect real-world settings. Patients received afatinib 40 mg/day until tumor progression, lack of clinical benefit, or poor tolerability. Assessments included safety, time to symptomatic progression (TTSP), and progression-free survival (PFS).

**Results** 541 patients were treated, of whom 412 were enrolled in China. Dose reductions were implemented in 28.7% of patients overall, and 17.7% of patients from China. Safety findings were consistent with phase III studies of afatinib. Median TTSP in all patients was 14.0 months (95% CI 12.9–15.9), and median PFS was 12.1 months (95% CI 11.0–13.6). Median TTSP (13.8 months, 95% CI 12.7–16.1) and PFS (11.4 months, 95% CI 10.9–13.7) were similar in patients from China to the overall population. Among patients from China who had dose reductions, TTSP was numerically longer than in those who did not (16.4 vs. 13.8 months;  $P = 0.0703$ ), while PFS was significantly longer (13.9 vs. 11.1 months;  $P = 0.0275$ ). Among patients from China with brain metastases, TTSP was numerically shorter than in those without (11.0 vs. 14.4 months;  $P = 0.0869$ ), whereas PFS was significantly shorter (9.2 vs. 12.9 months;  $P = 0.0075$ ).

**Conclusions** Safety data for afatinib when used in a “near real-world” setting in patients with *EGFRm+* NSCLC was consistent with the known safety profile of afatinib. Supporting efficacy data of afatinib were provided in all patients, and in those enrolled in China. Tolerability-guided afatinib dose reduction allowed patients to remain on treatment and continue to experience clinical benefit.

**Trial Registration Number and Date of Registration** NCT01953913 (1 October 2013).

## 1 Introduction

The development of targeted epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) resulted in improved efficacy versus chemotherapy in patients with *EGFR* mutation-positive (*EGFRm+*) non-small-cell lung cancer (NSCLC) [1–7], and these agents are recommended

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### Key Points

In this prospective, phase IIIb, “near real-world” study, Asian patients with EGFR TKI-naïve *EGFR*m+ NSCLC were treated with afatinib.

Results were consistent with previously reported data for afatinib in this patient population, and no new safety signals were identified.

Additionally, patients who had afatinib dose reductions were able to stay on treatment.

first-line treatment options for patients with advanced *EGFR*m+ NSCLC [8–10].

*EGFR* mutations are particularly common among eastern Asian populations with NSCLC [11–14]. The second-generation TKI afatinib, an irreversible ErbB-family blocker, provides broader inhibition relative to first-generation TKIs, which may delay the development of acquired resistance [15]. In contrast to other EGFR TKIs, afatinib blocks signaling via all hetero- and homo-dimers formed by ErbB1 (EGFR), but also ErbB2 (human epidermal growth factor receptor 2 (HER2)), ErbB3 (HER3), and ErbB4 (HER4) [16, 17].

In the phase III LUX-Lung 3 and LUX-Lung 6 trials in treatment-naïve patients with advanced *EGFR*m+ NSCLC, afatinib significantly improved progression-free survival (PFS) compared with platinum doublet therapy [6, 7]. In the phase IIb LUX-Lung 7 study, also conducted in treatment-naïve patients with advanced *EGFR*m+ NSCLC, afatinib improved PFS as well as objective response rate (ORR) and time to treatment failure (TTF) compared with gefitinib [18]. Across these LUX-Lung trials, afatinib had a predictable and manageable safety profile, and few patients discontinued treatment because of adverse events (AEs) [6, 7, 18]. The clinical activity of afatinib has been shown in patients with brain metastases [19–21]; this is in contrast to dacomitinib, as patients with brain metastases were excluded from the phase III ARCHER 1050 trial [22].

As randomized controlled trials often have strict inclusion and exclusion criteria, performing trials that are more reflective of real-world clinical practice is crucial. Therefore, the aim of this study was to provide “near real-world” data on the safety and efficacy of afatinib in TKI-naïve Asian patients with locally advanced or metastatic *EGFR*m+ NSCLC. Interim results of the trial have been presented [23], and here we present final results for the overall population with a particular focus on data from the large subgroup of patients enrolled at study sites in China.

## 2 Materials and Methods

### 2.1 Study Design and Patient Population

This phase IIIb, multicenter, open-label, single-arm trial focused on the safety, tolerability, and efficacy of afatinib in a broad population of TKI-naïve Asian patients with locally advanced or metastatic *EGFR*m+ NSCLC (NCT01953913).

The primary safety endpoint was the number of patients with serious AEs (SAEs) and the secondary safety endpoint was the number of patients with AEs assessed by the treating physician as related to afatinib [i.e., treatment-related AEs (TRAEs)]. Various other safety endpoints were also evaluated. Although there were no primary or key secondary efficacy endpoints in the trial, time to symptomatic progression (TTSP) and PFS were selected to reflect real-world clinical practice and current treatment guidelines. These parameters were evaluated in the overall population and in the subgroup of patients in China. Tumor response (i.e., ORR) was also evaluated.

The study was conducted at 34 centers in China, Hong Kong, India, Singapore, and Taiwan. Inclusion and exclusion criteria were relatively broad to reflect a real-world setting. Inclusion criteria included age  $\geq 18$  years (up to age 75 years in India only), with locally advanced or metastatic *EGFR*m+ NSCLC, and Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2. Exclusion criteria included: previous use of EGFR TKI therapy; use of any anti-cancer medication  $< 2$  weeks, radiotherapy  $< 4$  weeks (except for palliative treatment), and major surgery  $< 4$  weeks prior to starting afatinib; history or presence of cardiovascular abnormalities; and symptomatic brain metastases.

The initial dosage regimen of afatinib was 40 mg orally once daily, which was continued until tumor progression, lack of clinical benefit, or poor tolerability. Afatinib could be continued beyond radiologic progression for as long as the clinical investigator deemed that the patient was benefiting from treatment.

Treatment interruptions and dose reductions with afatinib could be implemented when necessary for the management of TRAEs, as follows: any drug-related grade  $\geq 3$  AE; grade  $\geq 2$  diarrhea persisting for  $\geq 48$  h despite adequate treatment; reduced renal function (grade  $\geq 2$ ), as measured by serum creatinine, proteinuria or  $> 50\%$  reduction in glomerular filtration rate versus baseline. In cases where treatment interruption was required, afatinib was suspended until AE severity recovered to grade  $\leq 1$ , or to baseline severity. If recovery was achieved within 6 weeks, afatinib was resumed at a lower dose (decreased by 10 mg/day decrements to a minimum of 20 mg/day); if the patients could not tolerate 20 mg/day, permanent discontinuation of afatinib was to be considered. Afatinib dose could not be increased after a dose reduction.

## 2.2 Assessments and Statistical Analyses

The incidences and intensities of AEs, including SAEs, were monitored on a regular basis, including a daily record of diarrhea status. AE severity was classified according to the Common Terminology Criteria for Adverse Events v3.0, and the relationship of AEs to the study drug was determined by the investigators. TTSP was defined as the time from the date of the first dose of afatinib to the date of first documented clinically significant symptomatic progression necessitating a change in or discontinuation of cancer therapy. PFS was defined as the time from the date of the first dose of afatinib to the date of first documented radiologic and/or symptomatic progression according to the investigator's assessment or death, whichever came first. Both TTSP and PFS were assessed by the investigators. Radiologic assessments of tumors were conducted at the discretion of investigators, as per local standards. Patients with missing data were censored at the date of first administration.

Kaplan–Meier estimates and 95% confidence intervals (CIs) for the median of the survival distribution were calculated for TTSP and PFS using Greenwood's standard error estimate. A post hoc analysis of efficacy outcomes (TTSP and PFS) was conducted for various subgroups including by age, ECOG PS, common/uncommon *EGFR* mutations, presence/absence of brain metastasis at baseline, and afatinib dose adjustment during the first 6 months of treatment.

## 3 Results

### 3.1 Patients, Treatment Exposure, and Dose Reductions

#### 3.1.1 Overall Population

Of the 577 patients enrolled in the trial, 541 entered the study and were treated with afatinib (Fig. 1). Thus, demographic data for the overall population are based on these 541 patients who received the study drug. Recruitment of patients was between October 2013 and May 2017 and stopped once the recruitment goal was met. Baseline characteristics were generally representative of patients with *EGFR*m+ advanced NSCLC (Table 1).

The median duration of afatinib treatment was 12.9 months (386.0 days), with a range from 0.2 to 53.2 months (5 to 1596 days). Most patients ( $n = 300$ ; 55.5%) received afatinib as first-line therapy. Afatinib dose reductions from 40 mg/day to 30 mg/day were performed in 155 patients (28.7%), and 36 (6.7%) of these patients had their dose reduced further to 20 mg/day. The median duration of

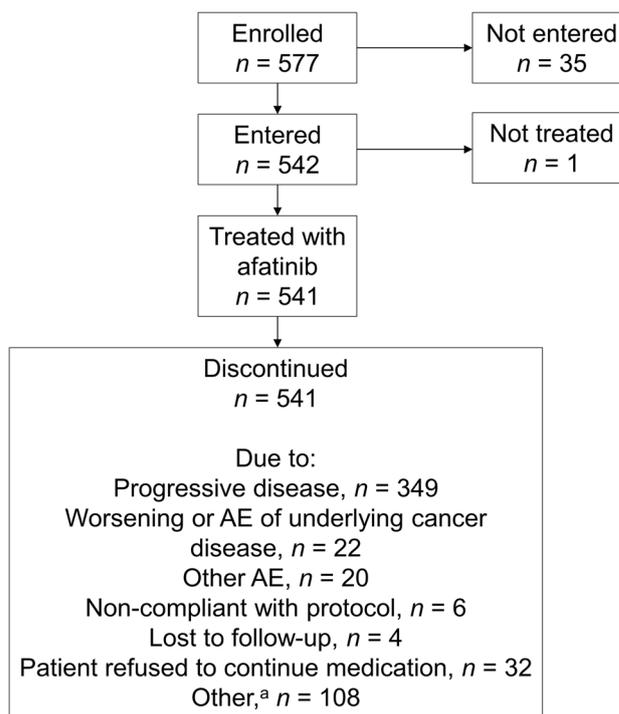


Fig. 1 Disposition diagram. <sup>a</sup>Includes patients who switched to commercial drug. AE adverse event

treatment with afatinib 40, 30, and 20 mg/day was 253.0, 265.0, and 225.5 days, respectively.

#### 3.1.2 Subgroup of Patients Enrolled in China

From the overall population of 541 patients, 412 (76.2%) were enrolled at 12 sites in China (Table 1). In general, patient demographics and afatinib treatment patterns were similar between the patients enrolled in China and the overall population. Median age was 59.0 years (range 32–81), 54.4% were female, and 67.7% of patients had never smoked. Common *EGFR* mutations (Del19 and L858R), with or without uncommon *EGFR* mutations, were harbored by 87.4% of patients; uncommon *EGFR* mutations only were reported in 12.6% of patients. ECOG PS score was 0 or 1 in 99% of patients, and 20.4% of patients had brain metastases.

The median duration of afatinib treatment in patients enrolled in China with afatinib 40, 30, and 20 mg/day was 277, 266, and 229 days, respectively. Afatinib dose reductions from 40 mg/day to 30 mg/day occurred in 73 patients (17.7%), and 19 (4.6%) of these patients had their dose reduced further to 20 mg/day. The median time to first dose reduction was 56 days (range 12–1273).

**Table 1** Baseline demographic and clinical characteristics of the overall population and subgroup of patients enrolled at sites in China

| Parameter                                       | Overall population (N = 541) | Subgroup enrolled at sites in China (n = 412) |
|---|------------------------------|---|
| Age, n (%)                                      |                              |   |
| Years, median (range)                           | 59.0 (27–82)                 | 59.0 (32–81)                                  |
| ≥ 65 years, n (%)                               | 147 (27.2)                   | 105 (25.5)                                    |
| < 65 years, n (%)                               | 394 (72.8)                   | 307 (74.5)                                    |
| Female, n (%)                                   | 286 (52.9)                   | 224 (54.4)                                    |
| Country, n (%)                                  |                              |   |
| China   | 412 (76.2)                   | 412 (100)                                     |
| Hong Kong                                       | 25 (4.6)                     |   |
| India   | 50 (9.2)                     |   |
| Singapore                                       | 24 (4.4)                     |   |
| Taiwan  | 30 (5.5)                     |   |
| Smoking status, n (%)                           |                              |   |
| Current smoker                                  | 29 (5.4)                     | 23 (5.6)                                      |
| Ex-smoker                                       | 137 (25.3)                   | 110 (26.7)                                    |
| Never smoked                                    | 375 (69.3)                   | 279 (67.7)                                    |
| Tumor histology, n (%)                          |                              |   |
| Adenocarcinoma                                  | 517 (95.6)                   | 399 (96.8)                                    |
| Squamous cell carcinoma                         | 12 (2.2)                     | 11 (2.7)                                      |
| Other   | 12 (2.2)                     | 2 (0.5)                                       |
| EGFR mutation, n (%) <sup>a</sup>               |                              |   |
| Common, with or without uncommon <sup>b</sup>   | 477 (88.2)                   | 360 (87.4)                                    |
| Uncommon only <sup>c</sup>                      | 64 (11.8)                    | 52 (12.6)                                     |
| Del19   | 261 (48.2)                   | 178 (43.2)                                    |
| L858R   | 219 (40.5)                   | 184 (44.7)                                    |
| Exon 20 insertion                               | 30 (5.6)                     | 26 (6.3)                                      |
| L861Q   | 31 (5.7)                     | 29 (7.0)                                      |
| G719X   | 25 (4.6)                     | 23 (5.6)                                      |
| S768I   | 11 (2.0)                     | 10 (2.4)                                      |
| T790M   | 6 (1.1)                      | 6 (1.5)                                       |
| Other   | 7 (1.3)                      | 2 (0.5)                                       |
| ECOG PS score, n (%)                            |                              |   |
| 0   | 99 (18.3)                    | 62 (15.0)                                     |
| 1   | 431 (79.7)                   | 346 (84.0)                                    |
| 2   | 11 (2.0)                     | 4 (1.0)                                       |
| Brain metastases, n (%)                         | 103 (19.0)                   | 84 (20.4)                                     |
| Therapy line of afatinib, n (%)                 |                              |   |
| First   | 300 (55.5)                   | 243 (59.0)                                    |
| Second  | 158 (29.2)                   | 123 (29.9)                                    |
| Third or later                                  | 53 (9.8)                     | 46 (11.2)                                     |
| Prior anti-cancer therapies, n (%) <sup>d</sup> | 281 (51.9)                   | 213 (51.7)                                    |
| Surgery   | 122 (22.6)                   | 100 (24.3)                                    |
| Radiotherapy                                    | 64 (11.8)                    | 39 (9.5)                                      |
| Other   | 215 (39.7)                   | 172 (41.7)                                    |
| Chemotherapy                                    | 211 (39.0)                   | 171 (41.5)                                    |

ECOG PS Eastern Cooperative Oncology Group performance status, EGFR epidermal growth factor receptor

<sup>a</sup>Patients can appear in more than one mutation category

<sup>b</sup>Patients with EGFR mutation categories: Del19 and/or L858R, and with or without uncommon EGFR mutation

<sup>c</sup>Patients with mutation categories other than Del19 and/or L858R

<sup>d</sup>Patients may have more than one prior therapy recorded

### 3.2 Safety and Tolerability

#### 3.2.1 Overall Population

Almost all patients (98.7%) treated with afatinib experienced an AE, although most (54.2%) were grade 1 or 2. Similarly, almost all patients (97.6%) had a TRAE. The three most common AEs were diarrhea (90.2% of patients), rash/acne (77.1%), and stomatitis (58.8%). These were also the three most common any grade/grade  $\geq 3$  TRAEs (diarrhea: 89.6%/10.9%; rash/acne: 76.5%/8.7%; stomatitis: 58.4%/4.3%; Fig. 2a).

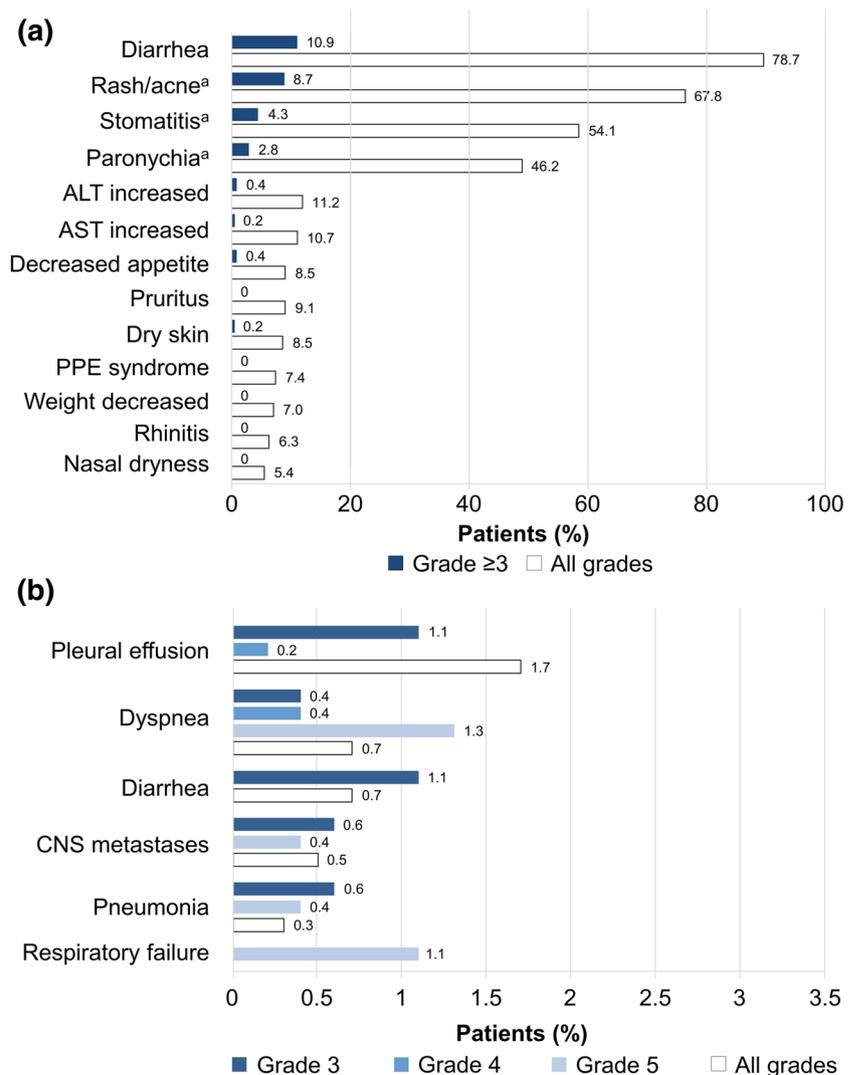
A total of 154 patients (28.5%) experienced an AE leading to a reduction in afatinib dose. The most frequent AEs resulting in a dose reduction were diarrhea (11.1% of patients) and rash/acne (9.6%). Overall, 47 patients (8.7%) experienced AEs leading to treatment discontinuation, although TRAEs leading to treatment discontinuation were reported in only 17 patients (3.1%).

Overall, 164 patients (30.3%) had SAEs, including 58 (10.7%), 24 (4.4%), and 46 (8.5%) patients with SAEs of grade 3, 4, and 5 (fatal), respectively. The most frequently reported SAEs included pleural effusion, dyspnea, and diarrhea (Fig. 2b). Although 46 patients had AEs with fatal outcomes, a number of the deaths could be attributed to disease progression, and only three cases (0.6%) were assessed by investigators as drug related; these deaths were attributed to decreased appetite, dyspnea, and respiratory failure.

#### 3.2.2 Subgroup of Patients Enrolled in China

In general, safety and tolerability data for the patients enrolled in China were similar to data reported for the overall population. The proportion of patients enrolled in China treated with afatinib who experienced any AE was 99.3%, although most were grade 1 or 2 (61.7%). As was the case in the overall population, almost all patients enrolled in China (97.8%) had a TRAE. Similarly, the most frequent TRAEs

**Fig. 2 a** Most frequently reported treatment-related adverse events (TRAEs) of any grade and grade  $\geq 3$  intensity; **b** SAEs reported in the overall population. <sup>a</sup>Grouped terms. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CNS* central nervous system, *PPE* palmar-plantar erythrodysesthesia, *SAEs* serious adverse events



**Table 2** Most frequently reported treatment-related adverse events (TRAEs)<sup>a</sup> in patients enrolled in China before and after tolerability-guided dose reductions

| TRAE                       | Before dose reduction |           | After dose reduction |           |
|----------------------------|-----------------------|-----------|----------------------|-----------|
|                            | Grade $\geq 3$        | Any grade | Grade $\geq 3$       | Any grade |
| Diarrhea, %                | 26.0                  | 95.5      | 3.9                  | 51.3      |
| Rash/acne, % <sup>b</sup>  | 23.4                  | 70.1      | 10.4                 | 58.4      |
| Stomatitis, % <sup>b</sup> | 13.0                  | 64.3      | 4.5                  | 43.5      |
| Paronychia, % <sup>b</sup> | 7.8                   | 39.0      | 3.3                  | 43.5      |
| Decreased appetite, %      | 0.6                   | 11.7      | 1.3                  | 11.0      |

<sup>a</sup>TRAEs (any grade) reported in >10% of patients prior to dose reduction

<sup>b</sup>Grouped term

grade  $\geq 3$  were diarrhea (8.0%), rash/acne (6.8%), stomatitis (3.2%), and paronychia (1.9%).

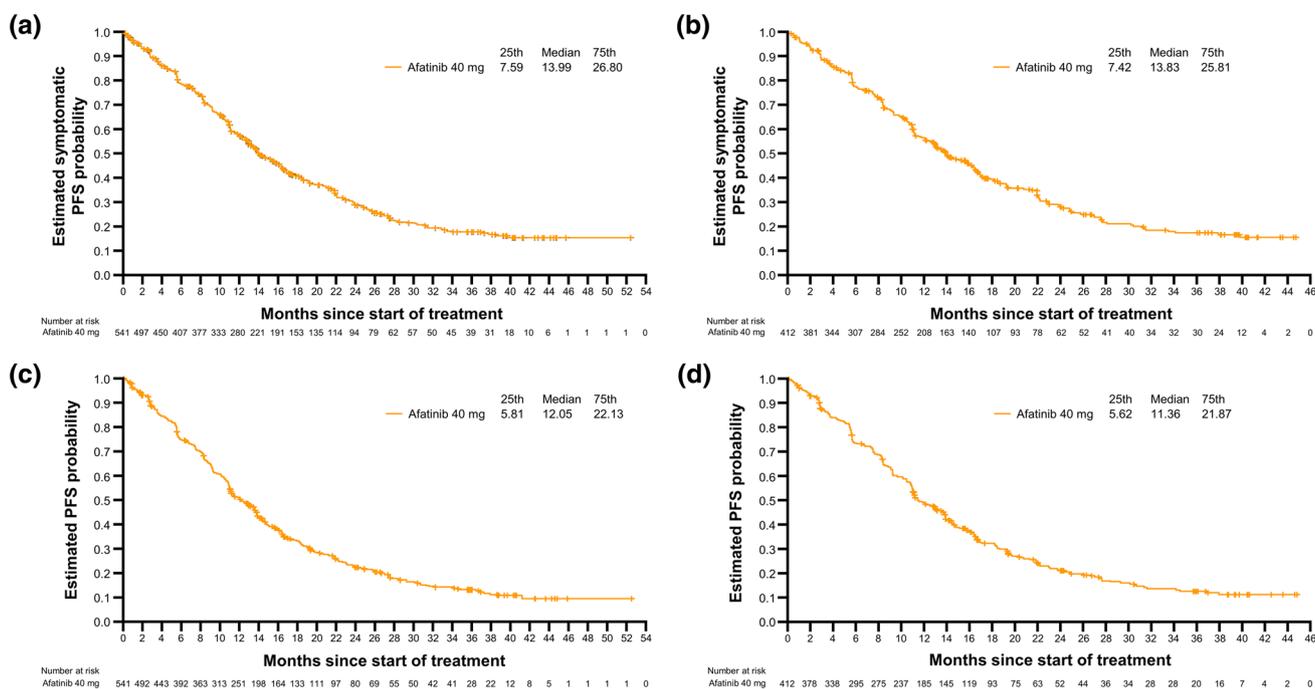
SAEs were reported in 104 patients (25.2%) enrolled in China, including 34 (8.3%), 19 (4.6%), and 28 (6.8%) with SAEs of grade 3, 4, and 5, respectively. The most frequently reported SAEs included dyspnea, pleural effusion, and respiratory failure. Among this subgroup, 92 patients (22.3%) experienced an AE leading to dose reduction, most commonly diarrhea (9.2%) and rash (7.5%). Any grade TRAEs, and grade  $\geq 3$  TRAEs in particular, were dramatically reduced by afatinib dose reduction (Table 2). Only

11 patients (2.7%) had a drug-related AE leading to treatment discontinuation. Paronychia, anemia, and rash were the reasons for treatment discontinuation in two patients each (0.5%); other AEs leading to discontinuation were reported in only one patient each. A total of 19 patients (4.6%) were deemed to have a drug-related SAE; ten, three, and three patients had grade 3, 4, and 5 drug-related SAEs, respectively. Of the patients enrolled in China, 28 had AEs leading to death, although only three cases were assessed by investigators as drug related; these deaths were attributed to decreased appetite, dyspnea, and respiratory failure.

### 3.3 Time to Symptomatic Progression (TTSP), Progression-Free Survival (PFS), Objective Response Rate (ORR), and Post Hoc Subgroup Analyses

#### 3.3.1 Overall Population

The overall population of 541 patients included those with previous chemotherapy treatment, uncommon mutations, and brain metastases. A total of 371 patients (68.6%) had clinically meaningful symptomatic progression during the study period, and the median TTSP was 14.0 months (95% CI 12.9–15.9; Fig. 3). A total of 416 patients (76.9%) progressed or died during the study, and the median PFS was 12.1 months (95% CI 11.0–13.6; Fig. 3).



**Fig. 3** Kaplan–Meier curves for **a** TTSP in the overall population; **b** TTSP in patients enrolled in China; **c** PFS in the overall population; and **d** PFS in patients enrolled in China. PFS progression-free survival, TTSP time to symptomatic progression

The ORR for the overall population was 59.1% (95% CI 54.9–63.3). A total of 13 patients (2.4%) achieved a complete response and 307 patients (56.7%) had a partial response. The median duration of objective response was 12.2 months (95% CI 11.1–13.5). Results of the post hoc subgroup analyses for TTSP and PFS are presented in Table 3. Both TTSP and PFS were numerically longer in patients with common versus uncommon *EGFR* mutations, in elderly ( $\geq 65$  years of age) versus younger ( $< 65$  years of age) patients, in patients with an ECOG PS of 0 versus 1, in patients without versus those with brain metastases at baseline, and in patients with afatinib dose reductions from 40 mg in the first 6 months versus those without dose reductions.

### 3.3.2 Subgroup of Patients Enrolled in China

Results of the post hoc subgroup analyses for TTSP and PFS in patients enrolled in China are presented in Table 3. The median TTSP was 13.8 months (95% CI 12.7–16.1; Fig. 3), which was nearly the same as the median TTSP of 14.0 months reported in the overall population. Similar to the overall population, median TTSP in patients enrolled in China was numerically longer in patients with common versus uncommon *EGFR* mutations (14.3 vs. 9.2 months) and among elderly versus patients aged  $< 65$  years old (16.1 vs. 13.5 months). Median TTSP was similar among patients with ECOG PS of 0 or 1 (14.3 vs. 13.8 months). PFS results in patients enrolled in China were comparable to those in the overall population; 310 patients (75.2%) progressed or died during the study, and the median PFS was 11.4 months (95% CI 10.9–13.7).

A total of 92 of the patients enrolled in China had their afatinib dose reduced (22.3%), 66 of whom had reductions during the first 6 months of treatment. TTSP in patients who had a dose reduction in the first 6 months of treatment was 16.4 months compared with 13.8 months in patients who did not have a dose reduction (hazard ratio (HR) 1.38; 95% CI 0.97–1.96;  $P = 0.0703$ ) (Electronic Supplementary Material (ESM), Fig. S1). PFS in patients who had a dose reduction was significantly longer at 13.9 months compared with 11.1 months in patients who did not have a dose reduction (HR 1.46; 95% CI 1.04–2.04;  $P = 0.0275$ ) (ESM, Fig. S1).

Among the 84 patients enrolled in China with brain metastases at baseline, TTSP was 11.0 months compared with 14.4 months in those without brain metastases (HR 1.29; 95% CI 0.96–1.73;  $P = 0.0869$ ; ESM, Fig. S1). PFS was significantly shorter in patients with brain metastases compared with those without (9.2 vs. 12.9 months; HR 1.45; 95% CI 1.10–1.90;  $P = 0.0075$ ; ESM, Fig. S1).

## 4 Discussion

Results of this prospective “near real-world” study conducted in several Asian countries were consistent with previously reported data for afatinib in TKI-naïve patients with locally advanced or metastatic *EGFR*m+ NSCLC and did not identify any new safety signals. Evaluating drugs in real-world settings is important because naturalistic studies can generate data relevant to a broad range of patients, as is typically seen in clinical practice.

Although the baseline demographics and clinical characteristics of this study group were more diverse to emulate a real-world setting, safety data were generally consistent with those from the randomized LUX-Lung 3, 6, and 7 trials with afatinib; the most frequently reported TRAEs (diarrhea, rash/acne, stomatitis) are recognized AEs of afatinib and EGFR TKIs [6, 7, 18].

Although the overall rate of afatinib dose reduction in the current study was similar to that in the LUX-Lung 6 study [7], it was lower than that reported in LUX-Lung 3 and 7 [6, 18], which may reflect differences in study populations and/or management of AEs such as diarrhea. There was a low rate of discontinuation due to TRAEs in the current study (as well as in the LUX-Lung 3, 6, and 7 trials), which suggests that TRAEs with afatinib may be managed by dose reduction while maintaining therapeutic efficacy. This was also observed in the subgroup of patients enrolled in China, in which the number and severity of TRAEs after dose reduction was dramatically reduced. In addition, TTSP was longer, but not significantly, and PFS was significantly longer in patients who had their dose reduced compared with those who did not. This supports previous findings from the LUX-Lung 3 and 6 trials, which found no negative effect of dose reduction on PFS [18], and shows that timely dose reduction can allow patients to remain on therapy for longer, while continuing to derive clinical benefit.

Findings of a global, non-interventional, real-world study (RealGiDo) with afatinib provide support to these findings, in that the use of dose reductions reduced the intensity and frequency of AEs, but did not compromise clinical effectiveness [24]. Other studies have evaluated afatinib in routine clinical practice, showing similar tolerability profiles and safety findings to those observed in the current study [25–27].

Median PFS in the overall population in the current study was approximately 12 months and median TTSP was approximately 14 months. These findings suggest that afatinib treatment may be continued beyond disease progression. Similarly, in LUX-Lung 7, in which 35% of patients received afatinib beyond radiologic progression, median TTF was almost 3 months longer than median PFS (13.7 vs. 11.0 months) [18].

**Table 3** Post hoc analysis of time to symptomatic progression (TTSP) and progression-free survival (PFS) for specified subgroups in overall population and Chinese centers

|                              | Overall population      |                          |
|------------------------------|-------------------------|--------------------------|
|                              | Subgroup                |                          |
| <i>EGFR</i> mutation type    | Common                  | Uncommon only            |
| <i>N</i>                     | 477                     | 64                       |
| Median TTSP, months (95% CI) | 14.42 (13.40–16.39)     | 9.23 (6.01–20.66)        |
| Median PFS, months (95% CI)  | 12.68 (11.10–13.83)     | 9.06 (5.58–12.94)        |
| Afatinib dose adjustment     | 40 mg in first 6 months | <40 mg in first 6 months |
| <i>N</i>                     | 421                     | 120                      |
| Median TTSP, months (95% CI) | 13.83 (12.51–15.67)     | 16.12 (12.94–23.02)      |
| Median PFS, months (95% CI)  | 11.33 (10.90–13.53)     | 13.86 (10.90–16.52)      |
| Baseline brain metastasis    | With                    | Without                  |
| <i>N</i>                     | 103                     | 438                      |
| Median TTSP, months (95% CI) | 12.78 (10.08–15.63)     | 14.42 (13.14–16.52)      |
| Median PFS, months (95% CI)  | 10.08 (8.31–12.05)      | 12.94 (11.30–14.09)      |
| Age                          | <65 years               | ≥65 years                |
| <i>N</i>                     | 394                     | 147                      |
| Median TTSP, months (95% CI) | 13.63 (12.22–15.27)     | 17.01 (13.69–21.71)      |
| Median PFS, months (95% CI)  | 11.53 (10.87–13.56)     | 13.56 (11.07–15.67)      |
| ECOG PS                      | ECOG 0                  | ECOG 1                   |
| <i>N</i>                     | 99                      | 431                      |
| Median TTSP, months (95% CI) | 16.42 (13.04–21.87)     | 13.76 (12.22–15.63)      |
| Median PFS, months (95% CI)  | 14.84 (12.25–19.31)     | 11.33 (10.87–13.04)      |
|                              | Chinese centers         |                          |
|                              | Subgroup                |                          |
| <i>EGFR</i> mutation type    | Common                  | Uncommon only            |
| <i>N</i>                     | 360                     | 52                       |
| Median TTSP, months (95% CI) | 14.32 (12.91–16.42)     | 9.23 (5.68–20.66)        |
| Median PFS, months (95% CI)  | 12.02 (10.94–13.83)     | 9.06 (5.58–16.58)        |
| Afatinib dose adjustment     | 40 mg in first 6 months | <40 mg in first 6 months |
| <i>N</i>                     | 346                     | 66                       |
| Median TTSP, months (95% CI) | 13.76 (11.30–16.09)     | 16.39 (12.91–27.59)      |
| Median PFS, months (95% CI)  | 11.10 (10.77–12.97)     | 13.86 (10.94–19.31)      |
| Baseline brain metastasis    | With                    | Without                  |
| <i>N</i>                     | 84                      | 328                      |
| Median TTSP, months (95% CI) | 11.03 (9.03–15.63)      | 14.35 (12.91–16.58)      |
| Median PFS, months (95% CI)  | 9.20 (7.45–11.07)       | 12.94 (11.10–14.42)      |
| Age                          | <65 years               | ≥65 years                |
| <i>N</i>                     | 307                     | 105                      |
| Median TTSP, months (95% CI) | 13.53 (11.53–15.93)     | 16.09 (12.68–22.00)      |
| Median PFS, months (95% CI)  | 11.33 (10.64–13.56)     | 12.97 (10.90–15.70)      |
| ECOG PS                      | ECOG 0                  | ECOG 1                   |
| <i>N</i>                     | 62                      | 346                      |
| Median TTSP, months (95% CI) | 14.32 (8.31–19.21)      | 13.79 (12.02–15.93)      |
| Median PFS, months (95% CI)  | 13.56 (8.31–19.21)      | 11.33 (10.90–13.56)      |

CI confidence interval, ECOG PS Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor

Around three-quarters of the overall population were enrolled in centers in China, and subgroup analyses showed similar results for these patients compared with the overall population. The median PFS here (11.4 months) was similar to PFS values observed in two other studies enrolling Chinese patients (12.3 and 14.2 months, respectively) [28, 29]. Studies recruiting patients from Taiwan also had similar PFS values (11.8, 12.4, and 12.2 months, respectively) [30–32]. However, patients in this study had lower median PFS than that reported in a retrospective real-world study of patients in Korea (15.1 months) [33].

TTSP and PFS were shorter, the latter significantly so, in patients enrolled in China with baseline brain metastases compared with those without. This may be expected, as these patients are likely to be more unwell than patients without brain metastases, and has been observed previously in the LUX-Lung 3 and 6 studies [19]. However, it should be noted that patients with brain metastases in this analysis and in the LUX-Lung studies still gained substantial clinical benefits from afatinib treatment, and in the LUX-Lung studies this benefit was greater than that observed with platinum-based chemotherapy [19].

The use of osimertinib as a first-line treatment option in patients with *EGFR*m+ (Del19 or L858R) NSCLC is now established, based on results showing improved efficacy versus first-generation EGFR TKIs in the Phase III FLAURA trial [34]. Notably, however, OS results were not shown to be statistically significant in Asian patients receiving osimertinib versus those receiving first-generation EGFR TKIs [35]. Afatinib also remains an important treatment choice in patients with uncommon *EGFR* mutations (accounting for around 10% of *EGFR* mutations) [36], showing improved efficacy versus first-generation EGFR TKIs [37]. In a large database study of afatinib treatment in this patient group, median TTF was 10.8 months and ORR was 60.0% in those with “major” uncommon mutations (G719X, L861Q, and S768I) [38]. Interestingly, results from a Japanese retrospective cohort study showed a statistically significant survival advantage in patients with *EGFR* L858R mutations without brain metastases who were treated with afatinib versus osimertinib [39].

Most patients in this study received afatinib as first-line therapy (55.5%). First-line treatment with afatinib expands the number of available options for patients, often meaning that chemotherapy can be postponed until later lines. Results from the global real-world GioTag study demonstrated that sequential treatment with afatinib followed by osimertinib was associated with encouraging outcomes in patients with *EGFR*m+ NSCLC, particularly in Del19-positive patients and Asian patients [40]. Resistance mechanisms to osimertinib are highly heterogeneous [41], and thus there are currently no approved targeted treatment options following progression on the drug. Delaying osimertinib use to second-line

treatment, after first-line afatinib treatment, may therefore maximize the length of time on targeted treatment.

The lack of a comparator treatment arm is a notable limitation of the current study. Furthermore, the subgroup analyses of TTSP and PFS, including in patients enrolled in China, were conducted post hoc, with the inherent disadvantages of this type of analysis. It may be seen as a limitation that over 75% of the patients were from one country, and, thus, the subgroup analysis of patients from China closely reflected the overall analysis. However, it is also useful to gain information on this large patient group from the world’s most populous country.

## 5 Conclusions

Safety data for afatinib, when used in a “near real-world” setting in TKI-naïve Asian patients with locally advanced or metastatic NSCLC harboring *EGFR* mutations, were consistent with previously reported data and did not identify any new safety signals in either the overall population or the large subgroup of patients from China. For most patients, AEs were manageable and did not require discontinuation of afatinib. The study also provides supporting efficacy data with afatinib in this setting, including “near real-world” data on efficacy in a large population of Chinese patients.

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## Declarations

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**Conflicts of interest** Y-LW reports receiving honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Hengrui, Merck Sharp & Dohme, Pfizer, Roche, Sanofi; and receiving grants or funds from AstraZeneca, BMS, and Pfizer. KCL declares receiving honoraria (outside the submitted work) from Pfizer, AstraZeneca, Eli Lilly, Roche. YT is employed by Boehringer Ingelheim (China) Investment Co., Ltd. ZX is employed by Boehringer Ingelheim (China) Investment Co., Ltd. AC was employed by Boehringer Ingelheim International GmbH. DC-LH was employed by Boehringer Ingelheim Taiwan Limited and is currently employed with Merck Sharp & Dohme (I.A.) LLC, Taiwan Branch. All the remaining authors declare no potential conflicts of interest.

**Ethics approval** At each participating center, the study was approved by the Institutional Review Board or Independent Ethics Committee, and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. All patients provided written informed consent.

**Consent for publication** All patients provided written informed consent.

**Availability of data and material** To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (see <https://www.mystudywindow.com/msw/datasharing>). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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