

Prospective Observational Real-World Study of Afatinib as First-Line Treatment in Patients with Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) in China

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Purpose: Approximately 38% of Chinese patients with non-small cell lung cancer (NSCLC) exhibit a mutation in the epidermal growth factor receptor (EGFR) gene. Afatinib, which targets the EGFR, is approved for first-line treatment in advanced *EGFR* mutation-positive NSCLC worldwide. The aim of this prospective, observational and non-interventional real-world study was to examine the effectiveness and safety of first line afatinib in Chinese patients, newly diagnosed with *EGFR* mutation-positive NSCLC.

Patients and Methods: Patients were enrolled at 10 sites in China from May 2020 to December 2021 and followed-up from May 2020 to December 2023. Adult patients (aged ≥ 18 years) were treated with oral afatinib 30 mg or 40 mg once daily. The primary outcome was time on treatment (TOT). Secondary outcomes were overall survival (OS), overall response rate (ORR) and safety.

Results: A total of 72 patients were enrolled and treated with afatinib. Most were male (54.2%), Chinese (98.6%), never smokers (63.9%), and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 (98.6%) and patients had a mean (SD) age of 62.2 (9.6) years. Median TOT overall was 14.4 months and was prolonged in younger (aged < 65 years) vs older (aged ≥ 65 years) age groups, common vs uncommon baseline *EGFR* mutations, and higher afatinib starting dose (40 mg vs 30 mg). Median OS was not reached; the median follow-up time of the study was 25.1 months. ORR was 62.7% overall and was higher in common vs uncommon baseline *EGFR* mutations, higher afatinib starting dose, and with vs without brain metastases. The two most common treatment-emergent adverse events were diarrhea and rash. No new safety concerns were found.

Conclusion: This study provides real-world evidence of the effectiveness and safety of afatinib as first-line therapy for Chinese patients with *EGFR* mutation-positive advanced NSCLC.

Keywords: NSCLC, *EGFR* mutation-positive, afatinib, real-world evidence

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases which is the most frequently diagnosed of all cancers and the leading cause of cancer mortality, globally.^{1,2} Lung cancer is also the leading cause of cancer death in China, accounting for 715,000 lung cancer-related deaths in 2020. In the same year, there were an estimated 820,000 new lung cancer diagnoses in China.³ At diagnosis, approximately two-thirds of lung cancer patients are at an advanced, inoperable stage. Therefore, there has been considerable effort in developing new drugs to address the unmet medical needs of patients with lung cancer.⁴

Nearly one-third (32.3%) of patients with NSCLC exhibit a mutation in the epidermal growth factor receptor (EGFR) gene. The prevalence of *EGFR* mutation in NSCLC is higher in Asian than Western countries.^{5–7} A recent meta-analysis estimated the prevalence of *EGFR* mutation in Asian and European NSCLC patients to be 49.1% and 12.8%, respectively.⁷ Similar to other Asian countries, China has a high prevalence of *EGFR* mutation (38.4%) in NSCLC patients, compared with 14.1% in those from European populations reported by another meta-analysis.⁶ Overall, the prevalence of *EGFR* mutation in NSCLC is higher in females, non-smokers (compared with past or current smokers) and patients with adenocarcinoma.⁶

Approved drugs for lung cancer in China and the US targeting the EGFR include erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib.^{4,8,9} Afatinib is an orally administered irreversible inhibitor of the ErbB family of tyrosine kinases structurally related to the EGFR.¹⁰

The LUX-Lung randomized controlled trials (RCTs) have demonstrated the efficacy and safety of afatinib in treating *EGFR* mutation-positive NSCLC patients. The benefit of afatinib over platinum-doublet chemotherapy was shown in the LUX-Lung 3 and 6 Phase III trials by significantly prolonging progression-free survival (PFS) and improving symptom control and quality of life.^{11–13} A *post-hoc* subgroup analysis of Chinese patients (n = 237) in the LUX-Lung 6 trial supports results obtained in the overall LUX-Lung 6 Southeast Asia population.¹⁴ In the LUX-Lung 7 phase 2B, open-label, RCT first-line afatinib significantly improved PFS and time to treatment failure in treatment-naïve patients with *EGFR*-mutated NSCLC compared with gefitinib.¹⁵ Analysis of overall survival (OS) data from two randomized, Phase 3 trials (LUX-Lung 3 and LUX-Lung 6) showed that afatinib improved OS in patients with an exon 19 deletion *EGFR* mutation, but not in the whole patient population.¹⁶

Results from phase IIb, open-label, single-arm trials^{17–20} and real-world studies^{21–28} have supported the efficacy/effectiveness of first-line afatinib for *EGFR* mutation-positive NSCLC that was shown in the LUX-Lung studies. Chinese real-world studies have shown the benefit of afatinib for: advanced lung adenocarcinoma patients with TKI-sensitive *EGFR* mutations,²¹ TKI-naïve advanced NSCLC patients with *EGFR* mutations,²² and in advanced NSCLC patients with uncommon *EGFR* mutations.²⁸

Currently, there are limited real-world data available for treatment-naïve, Chinese patients with advanced *EGFR*-mutant NSCLC treated with first-line afatinib and there is a need for more information to aid clinical decision-making. In an effort to expand the evidence base, the aim of this prospective, observational and non-interventional real-world study was to examine the effectiveness and safety of first-line afatinib in Chinese patients, newly diagnosed with *EGFR* mutation-positive NSCLC.

Materials and Methods

Study Design

This prospective, observational and non-interventional real-world study of first-line afatinib in newly diagnosed, *EGFR* mutation-positive NSCLC patients was conducted at 10 sites in China (NCT04206787). Patients were enrolled from May 2020 to December 2021 and followed-up from May 2020 to December 2023. Data were collected at baseline and during each follow-up period.

Patients were treated with oral afatinib 30 mg or 40 mg once daily, as indicated in the approved label of afatinib for first-line therapy of NSCLC.

This study was conducted in line with the principles of the Declaration of Helsinki. The Ethical Committee of all the sites that participated in this study approved this study (Leading Site: The First Affiliated Hospital, Zhejiang University School of Medicine, No. 2019–348). All patients provided written informed consent as per local regulatory requirements.

Inclusion and Exclusion Criteria

Patients aged ≥ 18 years and diagnosed with stage III or IV locally advanced or metastatic *EGFR* mutation-positive NSCLC and initiating afatinib first-line treatment were included in the study. All patients provided written informed consent as per local regulatory requirements.

Main exclusion criteria were: patients who had received previous systemic therapy for NSCLC (previous adjuvant or neo-adjuvant therapies were permitted), patients with symptomatic brain metastases at the start of afatinib treatment (patients with previously treated brain metastases were eligible provided they were asymptomatic for at least 4 weeks on stable medication), patients concurrently participating in an interventional oncology clinical trial within the previous 30 days prior to, or during first-line treatment with afatinib.

Primary and Secondary Outcomes

The primary outcome was time on treatment (TOT) which was defined as the period from the start to the end of afatinib treatment. Secondary outcomes were overall survival (OS), overall response rate (ORR) according to RECIST version 1.1, and safety – adverse events (AEs), serious AEs (SAEs), and adverse drug reactions (ADRs). Treatment-emergent adverse events (TEAEs) were classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 26.1 and graded using CTCAE version 5.0.

An additional outcome was the incidence of resistance mechanisms to afatinib, notably the *EGFR* T790M mutation which is the most common mutation for acquired resistance to *EGFR* inhibitors.²⁹ If available, genetic testing was conducted using next generation sequencing or polymerase chain reaction.

Statistical Analysis

Continuous variables were summarized by mean, median, range and standard deviation (SD) of categorical data by frequency and percentage (%). Patients who were lost to follow-up or withdrew before the end of study were censored at the time of last known contact.

TOT and OS were analyzed using the Kaplan–Meier method with 90% confidence intervals estimated by the Brookmeyer–Crowley method, while the Clopper–Pearson method was used to estimate the ORR with 95% confidence intervals.

All statistical analyses were conducted using SAS statistical software (version 9.4).

Results

A total of 72 patients were enrolled and all were treated with afatinib. The majority of patients (45 [62.5%] patients) started afatinib at 40 mg, while the remaining 27 (37.5%) patients started afatinib at 30 mg. A total of 22 (30.6%) patients had afatinib dose modification: 14 patients experienced 1 dose modification, 5 patients experienced 2 dose modifications, and 3 patients experienced >2 dose modifications.

Demographic and patient baseline characteristics are shown in Table 1. Most patients were male (54.2%), Chinese (98.6%) and with a mean (SD) age of 62.2 (9.6) years. Most were never smokers (63.9%), and had an ECOG performance status score of 0–1 (98.6%).

The mean (SD) time since the first diagnosis was 1.73 (8.81) months. Histologically, 71 patients (98.6%) had predominantly adenocarcinoma, 1 patient (1.4%) had predominantly squama cell carcinoma, and no patients presented with large cell/undifferentiated carcinoma. The majority of patients were classified as stage IVA (44 patients [61.1%]) and IVB (16 patients [22.2%]). At the start of afatinib treatment, 60 (83.3%) patients had distant metastasis, the most common being in the lung (28 patients [38.9%]) and lymph nodes (22 patients [30.6%]); 12 patients (16.7%) had brain metastasis.

The *EGFR* mutation status of patients at baseline is shown in Table 2. Common *EGFR* mutations were exon 19 deletion (55.6%) followed by L858R (29.2%).

The median follow-up time of the study was 25.1 months.

Table 1 Patient Demographics and Clinical Characteristics (N =72)

Sex, male/female, n (%)	39 (54.2)/33 (45.8)
Ethnicity, n (%)	
Chinese	71 (98.6)
Other	1 (1.4)
Age (years), mean (SD)	62.2 (9.6)
Age category, n (%)	
<65 years	39 (54.2)
≥65 years	33 (45.8)
Body mass index (kg/m ²), mean (SD) †	23.04 (3.44)
Smoking status, n (%) ‡	
Never smoked	46 (63.9)
Ex-smoker	18 (25.0)
Current smoker	7 (9.7)
Baseline ECOG performance status score, n (%) †	
0	16 (22.2)
1	50 (69.4)
2	1 (1.4)

Notes: † n = 67; ‡ n = 71 (Smoking status was defined according to "Cigarette smoking among adults—United States, 1992, and changes in the definition of current cigarette smoking". *MMWR Morb Mortal Wkly Rep.* 1994; 43 (19): 342–346).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2 EGFR Mutation Status in Treated Patients (N = 72)

	n (%)
EGFR mutation category*	
Exon 19 deletions	40 (55.6)
L858R	21 (29.2)
Exon 20 insertions	3 (4.2)
L861Q	7 (9.7)
G719S, G719A, G719C	5 (6.9)
Common EGFR mutations (exon 19 and/or L858R)	59 (81.9)
Uncommon EGFR mutations	
Excluding common EGFR mutations (exon 19 and/or L858R)	13 (18.1)
Excluding common EGFR mutations (exon 19 and/or L858R), EGFR exon 20 insertions and T790M mutations	10 (13.9)

Notes: * >1 EGFR mutations were detected in 4 (5.6%) patients.

Abbreviation: EGFR, epidermal growth factor receptor.

A total of 46 patients (63.9%) discontinued the study. Reasons for discontinuation were death (n = 25; 34.7%), withdrawal of consent (n = 9; 12.5%), lost to follow-up (n = 9; 12.5%), investigator decision (n = 1; 1.4%), and other (n = 2; 2.8%).

Effectiveness

The Kaplan-Meier plot for the primary outcome, TOT with afatinib, is shown in [Figure 1](#). The median TOT was 14.4 months (90% confidence interval [CI], 11.3–18.1).

Subgroup analysis results displayed in [Supplementary Table 1](#) show that median TOT was prolonged in younger (aged <65 years) vs older (aged ≥65 years) age groups (15.9 vs 11.8 months), common vs uncommon baseline *EGFR* mutations (14.9 vs 7.5 months), and higher afatinib starting dose (40 mg vs 30 mg: 15.0 vs 10.2 months).

The Kaplan-Meier plot for the secondary outcome, OS with afatinib, is shown in [Figure 2](#). Median OS was not reached (90% CI, 28.32 – not reached).

Best overall response and objective response rates (ORR) are shown in [Table 3](#). The ORR was 62.7%, and attributable to partial responses (n = 42).

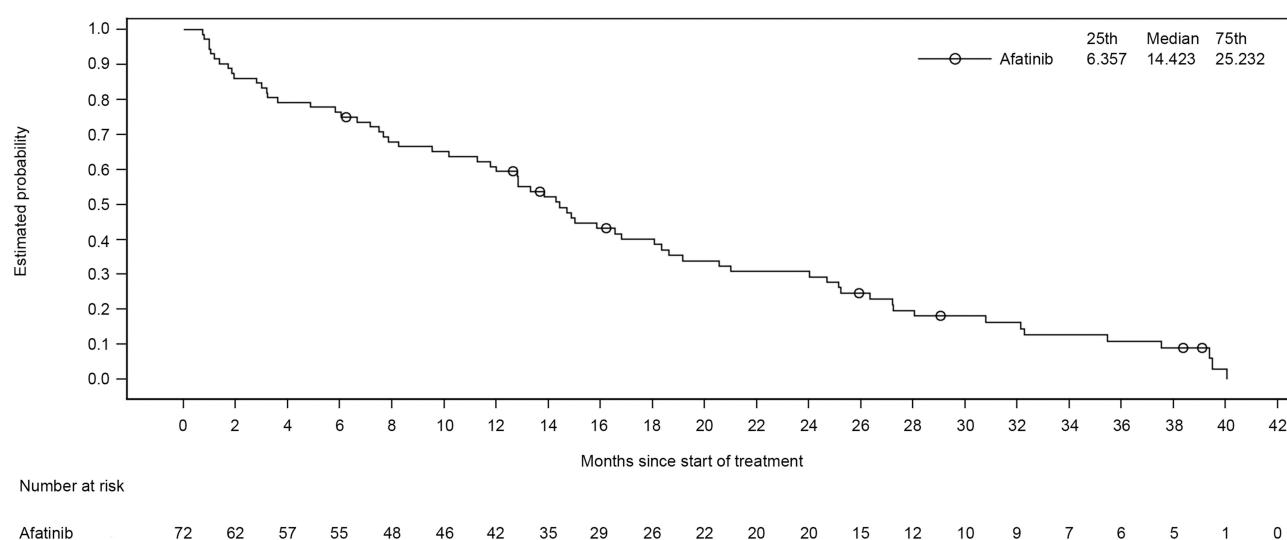


Figure 1 Kaplan-Meier plot of time on treatment (TOT) with Afatinib (N = 72).

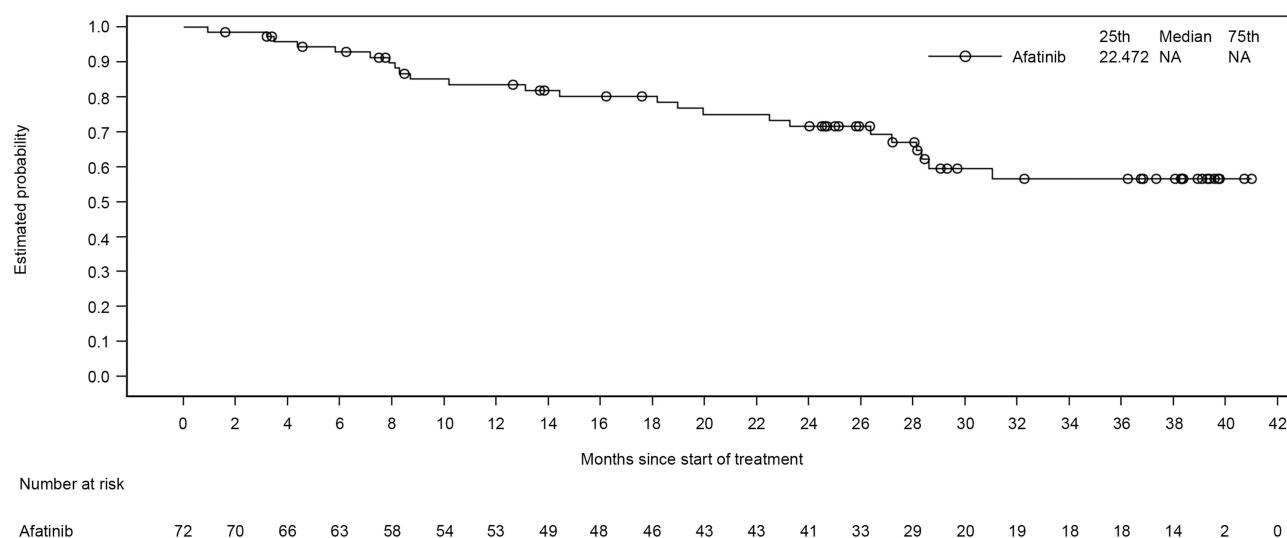


Figure 2 Kaplan-Meier plot of overall survival (OS) with Afatinib (N = 72).

Table 3 Best Overall Response and Objective Response Rate

Best Overall Response (BOR), n (%) †	
Complete response (CR)	0
Partial response (PR)	42 (62.7)
Stable disease (SD)	12 (17.9)
Progressive disease (PD)	7 (10.4)
Not evaluable	6 (9.0)
Objective response rate (ORR) (95% CI) ‡	62.7% (50.01–74.20)

Notes: †n = 67 (100%); ‡ORR was defined as the percentage of patients with a best overall response of CR or PR. 95% CI was calculated by the Clopper-Pearson exact method.

Abbreviation: CI, confidence interval.

Subgroup analysis results for ORR are shown in ([Supplementary Table 2](#)). ORR was higher in common vs uncommon baseline *EGFR* mutations (65.5% vs 50.0%), higher afatinib starting dose (67.4% vs 54.2%), and with vs without brain metastases (75.0% vs 60.0%).

Of 15 patients undergoing mutation testing for acquired resistance after ending afatinib treatment, 4 (26.7%) were positive for the *EGFR* T790M mutation. The majority of patients (n = 11; 73.3%) were negative for the T790M mutation: these included patients with unknown T790M status but who were positive for another *EGFR* mutation for acquired resistance.

Safety

A total of 68 patients (94.4%) reported AEs and 63 patients (87.5%) experienced AEs which were assessed as related to afatinib treatment. SAEs occurred in 12 patients (16.7%), including 2 patients (2.8%) with SAEs assessed as related to afatinib treatment. AEs leading to withdrawal of afatinib treatment and death were reported in 5 patients (6.9%) and 4 patients (5.6%), respectively ([Table 4](#)).

The most frequently reported TEAEs by SOC were gastrointestinal disorders (n = 58, 80.6% of patients), skin and subcutaneous tissue disorders (n = 41, 56.9%), and infections and infestations (n = 23, 31.9%).

The most frequently reported TEAEs by PT were diarrhea (n = 53, 73.6%), rash (n = 36, 50.0%), and mouth ulceration (n = 34, 47.2%) ([Table 5](#)).

The severity of most reported TEAEs was CTCAE Grades 1 to 3. Grade 4 and 5 TEAEs were each reported in 2 patients (2.8%), respectively. The Grade 4 TEAEs by PT were pneumonia, respiratory failure, and nausea. Only nausea was assessed as related to afatinib treatment with an outcome of recovered/resolved. The Grade 5 TEAEs by PT were

Table 4 Overview of Adverse Events (AEs; N = 72)

Category	n (%)
Overall AEs	68 (94.4)
Drug-related AEs	63 (87.5)
Serious AEs	12 (16.7)
Serious drug-related AEs	2 (2.8)
AEs leading to withdrawal of afatinib treatment	5 (6.9)
AEs leading to death	4 (5.6)

Table 5 Treatment-Emergent Adverse Events (TEAEs) Occurring in >5% of Patients (N = 72)

System Organ Class Preferred Term	n (%)
TEAEs occurring in >5% of patients	65 (90.3)
Gastrointestinal disorders	58 (80.6)
Diarrhoea	53 (73.6)
Mouth ulceration	34 (47.2)
Nausea	4 (5.6)
Vomiting	4 (5.6)
Skin and subcutaneous tissue disorders	41 (56.9)
Rash	36 (50.0)
Palmar-plantar erythrodysesthesia syndrome	7 (9.7)
Infections and infestations	23 (31.9)
Paronychia	23 (31.9)
Metabolism and nutrition disorders	12 (16.7)
Hypokalaemia	7 (9.7)
Decreased appetite	5 (6.9)
Investigations	8 (11.1)
Alanine aminotransferase increased	7 (9.7)
Aspartate aminotransferase increased	6 (8.3)
Blood and lymphatic system disorders	7 (9.7)
Anaemia	7 (9.7)
Hepatobiliary disorders	6 (8.3)
Hepatic function abnormal	6 (8.3)
Respiratory, thoracic, and mediastinal disorders	5 (6.9)
Cough	5 (6.9)
General disorders and administration site conditions	4 (5.6)
Pyrexia	4 (5.6)
Nervous system disorders	4 (5.6)
Headache	4 (5.6)

rectal cancer and death, each reported by 1 patient, with none of the Grade 5 events being assessed as related to afatinib treatment.

Discussion

The results of this real-world study demonstrated encouraging TOT outcomes in Chinese patients with *EGFR* mutation-positive advanced NSCLC who received afatinib as first-line treatment. Patients were mostly male, never smokers with an ECOG performance status score of 0–1 and had a mean age of 62 years. No new safety findings were observed.

Median TOT overall was 14.4 months and was prolonged in younger age groups (aged <65 years), common baseline *EGFR* mutations, and higher afatinib starting dose (40 mg). Although median OS was not reached, the median follow-up time of the study was 25.1 months. ORR was 62.7% overall and was higher in common baseline *EGFR* mutations, higher afatinib starting dose, and with brain metastases.

Results of this real-world study are comparable with previous clinical trials of first-line afatinib in patients with *EGFR* mutation-positive stage IIIB/IV NSCLC. Median PFS for afatinib in the LUX-Lung 3, 6 and 7 clinical trials was 11.1, 11.0 and 11.0 months, respectively.^{11,13,15} However, TOT assessed in this study does not represent PFS, as patients may receive treatment beyond disease progression or discontinue treatment for reasons other than progression. Median OS in the LUX-Lung 3 and LUX-Lung 6 trials for patients treated with afatinib was 28.2 and 23.1 months, respectively.¹⁶

Previous real-world studies have shown the benefit of afatinib in Chinese patients with NSCLC. In the open-label phase IIIB “near real-world” study of afatinib in *EGFR* TKI-naïve Asian patients with metastatic *EGFR* mutation-positive NSCLC, median time to symptomatic progression (TTSP) was 14.0 months in the overall population and 13.8 months in patients enrolled in China. Among patients from China with brain metastases, median TTSP was shorter than in patients without brain metastases (11.0 vs 14.4 months, not significant), and was prolonged in patients with common *versus* uncommon *EGFR* mutations (14.3 vs 9.2 months).¹⁹ In the current study, median TOT was also prolonged in common vs uncommon *EGFR* mutations (14.9 vs 7.5 months) and comparable for patients with vs without baseline brain metastasis (14.7 vs 14.4 months). Both of these studies reflect the effectiveness of afatinib in Chinese patients including subgroups with brain metastases or common *EGFR* mutations.

A retrospective study of 60 Chinese patients with advanced lung adenocarcinoma and sensitive *EGFR* mutations of whom 39 received first-line treatment with afatinib reported an ORR of 56.4% and a disease control rate (DCR) of 97.4%. Median PFS was 12.3 months. No significant differences were found in median PFS between patients stratified based on the afatinib starting dose (40 mg vs 30 mg).²¹ These subgroup results contrast with differences in TOT presented in the current study for the subgroup analysis that compared an afatinib starting dose of 40 mg vs 30 mg, but caution is needed when comparing outcomes from different studies because TOT and PFS are not strictly comparable.

A prospective real-world study in China of 88 TKI-naïve patients with advanced NSCLC and *EGFR* mutations treated with afatinib 40 mg reported a median PFS of 14.2 months, while median TTSP was 16.3 months, the ORR was 54.5%, and the DCR was 92.0%.²² In comparison, in patients treated with 40 mg afatinib in the present study, median TOT was 15.9 months and the ORR was 67.4%.

There are some data regarding the sensitivity of tumors with uncommon *EGFR* mutations to *EGFR* inhibitors. In our study, for the 10 patients with uncommon *EGFR* mutations (excluding *EGFR* exon 20 insertions and T790M mutations), the median TOT was 10.7 months, and the ORR was 50%, indicating the activity of afatinib in this subgroup of patients. A combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6, showed that afatinib was active in advanced NSCLC tumors harboring the most frequently reported uncommon *EGFR* mutations (particularly Gly719Xaa, Leu861Gln, and Ser768Ile).³⁰ Categorized by uncommon mutation type, median PFS was 10.7 months (group 1: point mutations or duplications in exons 18–21), 2.9 months (group 2: de novo T790M mutations in exon 20 alone or in combination with other mutations), and 2.7 months (group 3: exon 20 insertions).³⁰

Finally, a retrospective Chinese study of advanced NSCLC patients with uncommon *EGFR* mutations treated with first-line afatinib (n = 51) reported a median PFS of 16.6 months and an ORR of 56.7%,²⁸ which is comparable to the ORR attained in patients with uncommon *EGFR* mutations (50.0%) in the current study.

The two most frequently reported TEAEs the current study were diarrhea and rash which were also the two most common TEAEs in a combined analysis²⁰ of three phase IIIB studies of afatinib in patients with *EGFR* TKI-naïve NSCLC.^{17–19}

Limitations of this non-interventional, observational study include disadvantages of real-world studies such as lack of randomization with a potential bias in patient selection, and missing data (eg from patients lost to follow-up).³¹ Strenuous efforts were made to include data from all enrolled patients, and all were followed-up until an OS event was recorded. In addition, the limited study sample size, with data collected from 10 sites in China, may be prone to selection bias which may have had an impact on the assessment of study outcomes.

Conclusions

This study provides additional, supportive real-world evidence of the effectiveness and safety of afatinib as first-line therapy for Chinese patients with *EGFR*-mutation-positive advanced NSCLC. In addition, the TOT outcome provides an encouraging signal to show how afatinib was used as first-line treatment in the real-world setting in the Chinese population.

Data Sharing Statement

Datasets generated during and/or analyzed during the current study are available upon request via the link <https://trials.boehringer-ingelheim.com/>.

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Author Contributions

Jianying Zhou and Yongsheng Wang are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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