



## Afatinib in locally advanced/metastatic NSCLC harboring common *EGFR* mutations, after chemotherapy: a Phase IV study

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**Aim:** The current study evaluated the efficacy and tolerability of second-line afatinib in patients with *EGFR* mutation-positive (*EGFRm+*) non-small-cell lung cancer (NSCLC) following chemotherapy. **Patients & methods:** In this open-label, single-arm Phase IV study, patients with *EGFRm+* (Del19/L858R) NSCLC who had progressed following platinum-based chemotherapy received afatinib (starting dose 40 mg/day). The primary end point was confirmed objective response. **Results:** 60 patients received afatinib for a median duration of 11.5 months. 50% of patients had a confirmed objective response, of median duration 13.8 months. Median progression-free survival was 10.9 months. The most common treatment-related adverse events were diarrhea (72%), rash (28%) and paronychia (23%). **Conclusion:** Our data support the use of afatinib (40 mg/day) as an effective and well-tolerated second-line treatment in *EGFRm+* NSCLC.

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**Keywords:** afatinib • *EGFR* • second line

The oral, irreversible ErbB family blocker afatinib is approved in the USA and the EU for first-line treatment of *EGFR* mutation-positive (*EGFRm+*) locally advanced or metastatic non-small-cell lung cancer (NSCLC), the recommended dose being 40 mg/day [1–4]. In the EU, afatinib is also approved as a second-line treatment option for *EGFR* tyrosine kinase inhibitor (TKI)-naïve patients with *EGFRm+* NSCLC that has progressed on or after platinum-based chemotherapy [2]. Approval of first-line afatinib was based on the results of two large, randomized, Phase III studies (LUX-Lung 3 and LUX-Lung 6) and was further supported by results of the Phase IIb LUX-Lung 7 study. In patients with *EGFRm+* NSCLC, these studies showed superior efficacy and patient-reported outcomes with first-line afatinib compared with standard platinum-doublet chemotherapy (LUX-Lung 3 and LUX-Lung 6) and the reversible first-generation *EGFR* TKI gefitinib (LUX-Lung 7) [5–7]. In addition, the LUX-Lung 2 study provided data to support the use of second-line afatinib in patients with *EGFRm+* NSCLC progressing following first-line chemotherapy [8]. LUX-Lung 2 included patients with lung adenocarcinoma who had received no more than one round of chemotherapy and had mutations in exons 18–21 of the *EGFR* gene. Afatinib was

administered as second-line therapy to 68 patients, 61 of whom received a dose of 50 mg/day and seven of whom received 40 mg/day [8]. A total of 39 of 68 (57%) patients had a confirmed objective response (OR) [8]. Median progression-free survival (PFS) by independent review was 8.0 months and median overall survival was 23.3 months [8].

While the benefits of first-line afatinib have been shown, chemotherapy is still commonly used as first-line therapy. Consequently, use of afatinib as second-line therapy remains common in patients with *EGFR*<sup>m+</sup> NSCLC. The current single-arm, open-label Phase IV trial was designed to assess the efficacy and safety of afatinib 40 mg/day as second-line therapy in *EGFR* TKI-naïve patients with advanced/metastatic NSCLC and common *EGFR* mutations (Del19 and/or L858R) who had progressed following first-line platinum-based chemotherapy.

## Materials & methods

### Study design & patients

This multicenter, open-label, single-arm Phase IV study was performed across 24 sites in seven countries (Egypt, Malaysia, Philippines, Poland, Romania, Serbia and Thailand). Eligible patients were aged 18 years or older, and had an Eastern Cooperative Oncology Group performance status of 0 or 1, a pathologically confirmed diagnosis of stage IIIB or IV adenocarcinoma of the lung (American Joint Committee on Cancer version 6), measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [9], radiologically confirmed progression or recurrence of disease during or following first-line therapy with a platinum-based chemotherapy regimen, and documented presence of a common *EGFR* mutation (L858R and/or Del19), with no other known *EGFR* mutations. Patients had to have recovered from any previous therapy-related toxicity to grade 1 or less, or grade 2 or less for alopecia and stable sensory neuropathy, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0) [10], and to have a life expectancy of at least 3 months. Patients were excluded if they had previously received: more than one line of prior therapy, not counting radiotherapy, radiosensitizers and/or intrapleural administration of anticancer agents; less than three cycles of platinum-based chemotherapy due to toxicity and/or intolerance of treatment; any *EGFR*-targeting TKI or antibody; chemotherapy, biological therapy or investigational agents within 3 weeks of the start of trial treatment; hormonal therapy within 2 weeks; radiotherapy within 4 weeks (except for palliative radiation to target organs other than the chest, which was allowed up to 2 weeks prior to the trial, and single-dose palliative treatment for symptomatic metastasis [to be discussed with the sponsor before enrollment in the study]); or major surgery within 4 weeks of starting trial treatment, or surgery scheduled during the projected course of the trial.

The study protocol was designed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable regional requirements. All patients provided written informed consent to participate in the trial.

### Procedures

Eligible patients received afatinib 40 mg orally once daily. If patients had any drug-related adverse events (AEs) grade  $\geq 3$ , or grade 2 diarrhea for more than 2 days, and/or a rash for more than 7 days, then the study treatment was interrupted until recovery to grade 1 or less, following which, the dose was reduced. Reductions in dose to 30 mg/day and then to 20 mg/day were allowed; if a patient could not tolerate 20 mg/day, afatinib was permanently discontinued. Dose increases were not permitted. Patients were treated with afatinib until disease progression or discontinuation for other reasons. However, patients who had obtained clinical benefit (as judged by the investigator and based on a careful clinical assessment) could continue on afatinib beyond radiological progression.

Assessment of *EGFR* mutations was based on an existing analysis, conducted locally, or if this was not available, was performed locally on a tumor biopsy using a validated technique, or sent to the central laboratory for analysis. Tumors were assessed by CT scan or MRI every 8 weeks until week 56, and then every 12 weeks until documented progression or discontinuation of treatment. Safety laboratory assessments (urine analysis, biochemistry and hematology) were done locally at screening, on the first visit of each treatment cycle, and at the end of treatment.

### Outcomes

The primary end point was confirmed objective tumor response (OR), defined as complete response (CR) or partial response (PR) (response outcomes were assessed by investigators according to RECIST version 1.1) [9]. Secondary end points were PFS, defined as the time from treatment start to disease progression or death, and disease control,

Table 1. Patient disposition.

Characteristic	Afatinib 40 mg/day	
	n	(%)
Enrolled	70	
Not entered	10	
Entered	60	(100.0)
Not treated	0	
Treated	60	(100.0)
Patients discontinued from afatinib <sup>†</sup>	60	(100.0)
Reasons for discontinuation:		–
– Progressive disease according to RECIST	24	(40.0)
– Clinical signs and symptoms of progression	2	(3.3)
Adverse events <sup>‡</sup>	12	(20.0)
Noncompliant with protocol	1	(1.7)
Lost to follow-up	0	(0.0)
Refused to continue afatinib	1	(1.7)
Other <sup>†</sup>	20	(33.3)

<sup>†</sup>Due to trial completion, all patients are reported as having discontinued afatinib. However, 20 patients, marked as 'other', were still continuing to derive benefit from second-line afatinib and therefore continued to receive afatinib outside of the clinical trial, in accordance with the drug label.

<sup>‡</sup>Four other patients discontinued treatment due to AEs, but were reclassified as having symptoms of disease progression, rather than AEs, and so are not listed here.

AE: Adverse event; RECIST: Response Evaluation Criteria In Solid Tumors.

defined as CR, PR or stable disease (SD) [9]. The safety and tolerability of afatinib was assessed on the basis of the incidence and intensity of AEs, graded according to CTCAE version 3.0 [10].

### Statistical analysis

Efficacy and safety were evaluated in a descriptive manner and no formal statistical hypothesis tests were used. The treated dataset (encompassing all patients who were documented to have taken at least one dose of afatinib) was used for efficacy and safety analyses, calculation of demographic data, and assessment of exposure. The proportions of patients with an OR and with disease control were calculated; 95% CIs were calculated using the Clopper–Pearson formula. For patients with an OR, the time to response and duration of response were determined using Kaplan–Meier analysis; for patients with disease control, the duration of disease control was also calculated using Kaplan–Meier analysis. For assessment of PFS, patients without disease progression who were still on afatinib at database lock were censored. Median PFS was calculated using Kaplan–Meier analysis. For safety analyses, exposure was assessed according to the duration of treatment. All AE analyses were descriptive and based on the number of patients with AEs.

In the Phase II LUX-Lung 2 study [8], a confirmed investigator-assessed PR rate of 60% was reported among the 68 patients receiving second-line afatinib. In the current study, with 60 patients and a predicted response rate of 60%, the 95% CI of the response rate was anticipated to be 47–72% based on the Clopper–Pearson exact method. Thus, a sample size of 60 patients was considered to provide reasonable precision for estimation of the response rate.

This study is registered with ClinicalTrials.gov (NCT02208843).

### Results

Between 9 October 2014 and 13 June 2017, 70 patients were enrolled across 24 sites (Egypt, three sites; Malaysia, one site; Philippines, three sites; Poland, four sites; Romania, five sites; Serbia, four sites; Thailand, four sites). Of these, 60 patients received at least one dose of afatinib 40 mg/day (Table 1). Baseline characteristics for these patients are shown in Table 2. Briefly, 27 (45%) patients were male, most were white (41 patients [68%]), and the mean age was 59.9 years. All patients had EGFRm+ NSCLC, having either an L858R mutation (20 patients [33%]) or a Del19 mutation only (38 patients [63%]), or both mutations simultaneously (two patients [3%]). Almost all patients (57 patients [95%]) had stage IV NSCLC at screening, and all patients had received prior chemotherapy. The mean time from first diagnosis was 12.8 months (range 2–192 months; median 8.4 months). Nine patients

Table 2. Baseline demographic and clinical characteristics.

Characteristic	Afatinib 40 mg/day (N = 60)
Sex, n (%):	
– Female	33 (55.0)
– Male	27 (45.0)
Race, n (%):	
– Asian	19 (31.7)
– White	41 (68.3)
– Black or African American	0 (0.0)
– Age in years, mean (standard deviation)	59.9 (9.8)
Smoking status, n (%):	
– Never smoked	35 (58.3)
– Ex-smoker	20 (33.3)
– Currently smokes	5 (8.3)
Baseline ECOG performance score, n (%):	
– 0	10 (16.7)
– 1	50 (83.3)
EGFR mutation category, n (%):	
– L858R only	20 (33.3)
– Del19 only	38 (63.3)
– L858R and Del19	2 (3.3)
– Time since first diagnosis (months), mean (standard deviation; range)	12.8 (24.5; 2–192)
Clinical stage at screening, n (%):	
– IIIB	3 (5.0)
– IV	57 (95.0)
– Any metastases at screening, n (%)	60 (100.0)
Location of metastatic sites, n (%)	
– Adrenal glands	13 (21.7)
– Bone	23 (38.3)
– Brain	9 (15.0)
– Liver	10 (16.7)
– Lung ipsilateral	29 (48.3)
– Lung contralateral	27 (45.0)
– Pleural effusion	22 (36.7)
– Other	26 (43.3)
Prior therapies, n (%):	
– Chemotherapy	60 (100%)
– Surgery	17 (28.3%)
– Radiotherapy <sup>†</sup>	18 (30.0%)

<sup>†</sup>Palliative radiotherapy targeting organs other than the chest were allowed up to 2 weeks prior to trial treatment, and single-dose palliative treatment for symptomatic metastasis above this allowance could be allowed following discussion with the sponsor prior to enrollment.  
ECOG: Eastern Cooperative Oncology Group.

(15%) had brain metastases at screening, seven of whom had received whole brain irradiation (WBRT), one patient had undergone stereotactic radiation, and one had no brain radiotherapy.

All patients received afatinib at a starting dose of 40 mg/day. Overall, 52 (87%) patients were treated for at least 90 days, and the median duration of treatment was 11.5 months. On completion of the study, 38 patients had discontinued afatinib due to disease progression or AEs. One patient had discontinued treatment by choice and one patient had been discontinued due to noncompliance with the study protocol. Twenty patients were continuing to derive benefit from second-line afatinib, and therefore continued treatment with afatinib outside of the trial, in accordance with the drug label (Table 1). Two patients with baseline brain metastases (one of whom had previously

**Table 3. Best confirmed treatment response.<sup>†</sup>**

Characteristic	Afatinib 40 mg/day (N = 60)		
	n	(%)	95% CI <sup>‡</sup>
Confirmed disease control <sup>§</sup>	50	(83.3)	71.5–91.7
Confirmed objective tumor response	30	(50.0)	36.8–63.2
Complete response	1	(1.7)	0.0–8.9
Partial response	29	(48.3)	35.2–61.6
Stable disease	20	(33.3)	21.7–46.7
Progressive disease	6	(10.0)	3.8–20.5
Nonevaluable <sup>¶</sup>	4	(6.7)	1.8–16.2

<sup>†</sup> According to RECIST version 1.1 and based on investigator assessment.  
<sup>‡</sup> Clopper–Pearson method.  
<sup>§</sup> Defined as complete response, partial response and stable disease.  
<sup>¶</sup> Patients classified as nonevaluable were exposed to study drug for up to 4 weeks, but did not have a visit to check tumor response, due to death prior to the scheduled visit.  
RECIST: Response Evaluation Criteria In Solid Tumors.

**Table 4. Safety and tolerability findings.**

Number of patients, n (%)	
Patients with any AE	57 (95.0)
Patients with afatinib-related <sup>†</sup> AEs	55 (91.7)
Patients with AEs leading to afatinib dose reduction	25 (41.7)
Patients with AEs leading to afatinib discontinuation <sup>‡</sup>	12 (20.0)
Patients with other significant AEs (according to ICH E3 <sup>§</sup> )	25 (41.7)
Patients with serious AEs <sup>¶</sup>	21 (35.0)
Patients with AEs by highest CTCAE grade	
– Grades 1 or 2	32 (53.3)
– Grades $\geq 3$	25 (41.7)

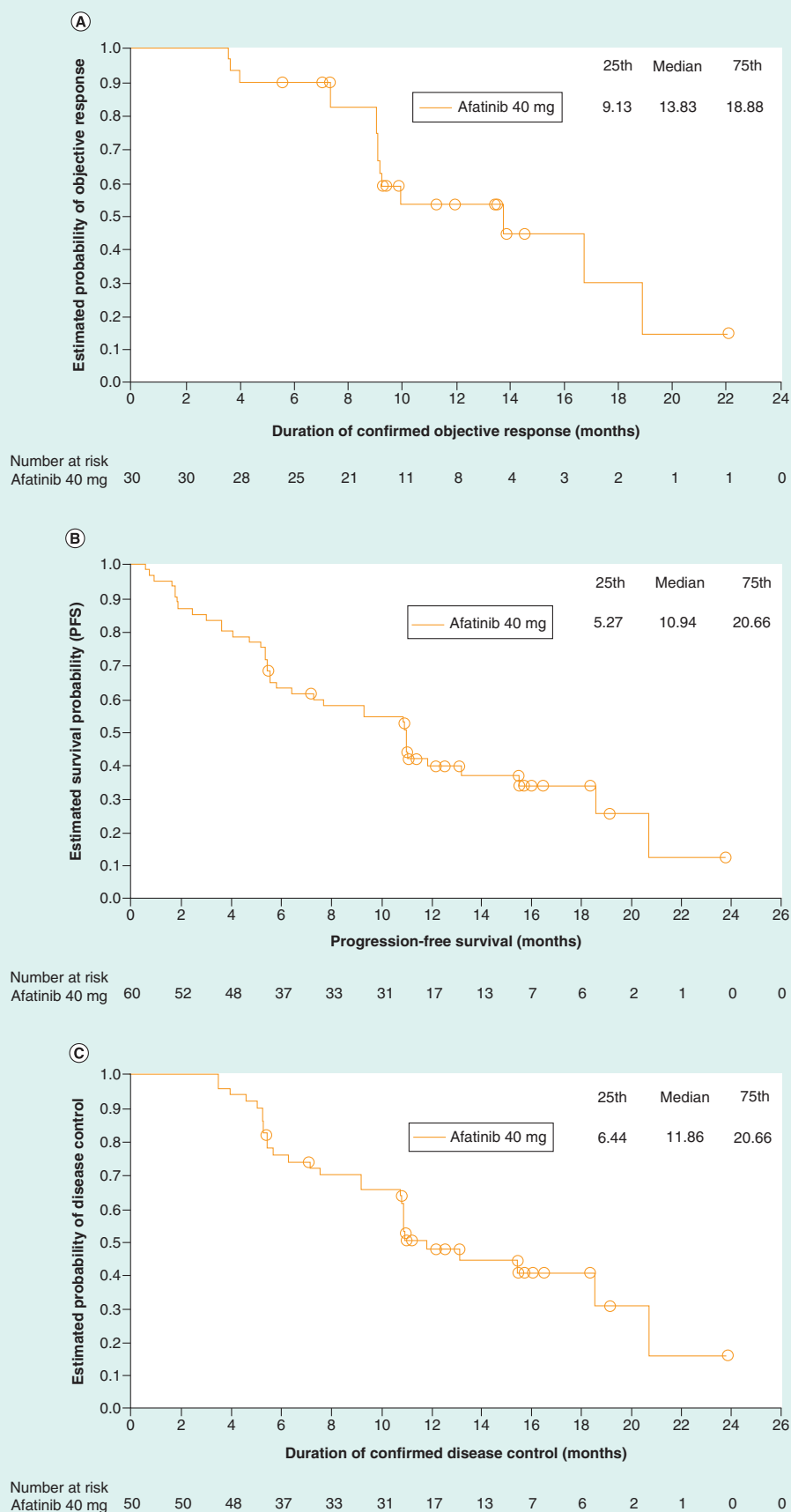
<sup>†</sup> As defined by the investigator.  
<sup>‡</sup> Four additional patients discontinued treatment due to AEs, but were reclassified as having symptoms of disease progression, rather than AEs, so are not listed here.  
<sup>§</sup> Guideline from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on the structure and content of clinical study reports.  
<sup>¶</sup> Patients could be counted in more than one category of serious AE.  
AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events.

received WBRT) remained on treatment for 12 months (without evidence of disease progression in the brain) and then switched to commercially available afatinib.

The primary study end point of confirmed OR (as assessed by the investigators) was achieved by 30 patients (50%), with one patient (2%) achieving a confirmed CR and 29 (48%) a confirmed PR (Table 3). The median duration of response was 13.8 months (95% CI: 9.16–18.88; Figure 1A). Six of nine patients with brain metastases at baseline (67%) achieved a confirmed PR, two (22%) had stable disease, and one (11%) had progressive disease. Only one patient developed a new brain lesion following 8 weeks of afatinib exposure, although this was asymptomatic and did not lead to treatment discontinuation. This patient had a history of brain metastases and had previously received WBRT; they continued to receive treatment following disease progression until death (~5 months from the start of treatment). Among the 51 patients with no history of brain metastases, four patients developed new brain lesions, 131, 240, 299 and 632 days following the start of treatment.

Regarding the secondary efficacy end points of PFS and disease control, 39 patients (65%) had an event contributing to the PFS analysis (i.e., disease progression as determined by investigator assessment or death); median PFS was 10.9 months (95% CI: 6.4–13.2; Figure 1B). Fifty patients (83%) showed confirmed disease control, with a median duration of disease control of 11.9 months (95% CI: 10.8–20.7; Figure 1C).

Ninety-five percent of patients had at least one AE during the study (Table 4). A total of 32 patients (53%) had AEs of grade 1 or 2, while 25 (42%) experienced AEs grade  $\geq 3$ . More than 90% of patients (92%) had at least one AE deemed by the investigator to be related to treatment (Table 4). The most commonly occurring drug-related



**Figure 1. Kaplan–Meier analysis of key study end points.** Kaplan–Meier curves of (A) duration of objective response, (B) PFS, and (C) disease control, all based on investigator assessment. PFS: Progression-free survival.

Table 5. Afatinib-related AEs with an incidence of at least 10%.

MedDRA preferred term, n (%)	All Grades <sup>†</sup>	Grade 3	Grade 4
Overall drug-related AEs	55 (91.7)	12 (20.0)	3 (5.0)
Diarrhea	43 (71.7)	6 (10.0)	0
Rash/acne <sup>‡</sup>	35 (58.3)	2 (3.4)	0
Rash	17 (28.3)	1 (1.7)	0
Dermatitis acneiform	10 (16.7)	0	0
Dermatitis	6 (10.0)	1 (1.7)	0
Paronychia <sup>‡</sup>	16 (26.7)	0	0
Paronychia	14 (23.3)	0	0
Mucosal inflammation	11 (18.3)	4 (6.7)	0
Fatigue	9 (15.0)	1 (1.7)	0
Anemia	8 (13.3)	1 (1.7)	0
Hypokalemia	8 (13.3)	2 (3.3)	1 (1.7)
Nausea	8 (13.3)	0	0

<sup>†</sup> AEs with grades 1, 2, 3, 4, 5; there were no grade 5 AEs in the study.

<sup>‡</sup> Grouped terms; these include additional AEs that are not listed due to <10% incidence of the preferred terms.

AE: Adverse event; MedDRA: Medical dictionary for regulatory activity.

AEs (any grade) were diarrhea (72%), rash (28%), paronychia (23%), mucosal inflammation (18%) and dermatitis acneiform (17%; Table 5). Serious AEs occurred in 21 (35%) of patients (Table 4); most of these were considered to be serious because the patient had to be hospitalized (14 patients [23%]). Seven patients (12%) had serious AEs that were considered to be drug-related by the investigator, with diarrhea being the most common of these (four patients [7%]).

In total, 25 patients (42%) required a reduction in the dose of afatinib to 30 mg/day (Table 4); six patients (10%) required a further reduction to 20 mg/day. The median duration of treatment was 169 days for patients taking afatinib 40 mg/day, 212 days for 30 mg/day, and 135 days for 20 mg/day. Twenty per cent of patients had AEs that led to permanent discontinuation of afatinib (Table 4). The most commonly occurring AEs leading to afatinib dose reduction were diarrhea (six patients [10%]), rash (four patients [7%]), and dermatitis and mucosal inflammation (three patients [5%] each).

Eleven patients (18%) died during the treatment period, but no deaths were attributed to afatinib treatment. Nine of the 11 patients died due to disease progression, while the other two patients had pre-existing risk factors and died from a cerebrovascular accident and a myocardial infarction, respectively.

## Discussion

The current findings confirm the efficacy of 40 mg/day afatinib as second-line therapy for TKI-naive patients with EGFRm+ NSCLC, after failure of first-line chemotherapy. Half of the patients had a confirmed OR, and the median duration of response exceeded 1 year. In addition, more than 80% of patients had confirmed disease control, with a median duration of 12 months. Median PFS was 11 months.

These results are consistent with those of a previous trial of second-line afatinib (the Phase II LUX-Lung 2 trial) in which the OR rate with afatinib (starting dose 40/50 mg/day) was 57%, median PFS was 8 months, and median overall survival was 23 months [8]. The benefits of afatinib that we observed are also similar to previously reported outcomes with first-line afatinib. The LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7 trials demonstrated favorable outcomes with regard to PFS (11–14 months), time-to-treatment failure (14 months, LUX-Lung 7 only), OR rate (56–70%) and disease control (90 and 93%, LUX-Lung 3 and LUX-Lung 6) [5–7,11].

Nine of the patients enrolled in this study (15%) had brain metastases at baseline, and good control of the brain metastases was achieved in eight of them. Only one patient had developed a new metastatic brain lesion by the time that systemic progression was detected; the brain lesion was asymptomatic and did not lead to discontinuation of treatment. In addition, most patients with baseline brain metastases achieved disease control; six (67%) had a confirmed PR, two (22%) had stable disease, and one (11%) had disease progression. Five of these patients (55%) remained on treatment for more than 12 months. While the data available do not allow a comparison of central nervous system (CNS) versus non-CNS progression in patients with baseline brain metastases, our results are similar



to those from LUX-Lung 3, 6 and 7, all of which allowed enrollment of patients with baseline brain metastases; these trials also demonstrated improvements with afatinib in patients with brain metastases [7,12,13]. In addition, competing risk analyses for patients with baseline brain metastases in LUX-Lung 3 and 6 showed that, during treatment with afatinib, the risk of CNS progression was lower than the risk of non-CNS progression [14]. Overall, results from multiple studies consistently show beneficial effects of afatinib in patients with brain metastases.

No new safety signals were identified; the safety profile of afatinib was similar to that identified in previous large trials of EGFR TKIs [5–8,15–24]. Despite the high incidence of AEs, there were relatively few discontinuations due to AEs; this suggests that clinicians successfully managed these events, with dose reductions due to AEs undertaken in approximately 40% of patients. Dose reductions did not compromise the total duration of exposure to afatinib.

Potential barriers to the use of EGFR TKIs are present in many countries, which may result in the second-line rather than first-line use of these agents. Barriers include the cost of mutation testing, the availability of samples for testing, and the time required to obtain the results and mutation analysis (usually at least 2 weeks) [25,26]. Further, in some low- and middle-income countries, patients may not be able to easily access molecular testing and first-line targeted therapies due to restrictions in government funding and/or policies. For example, in Egypt in 2018, only out-of-pocket payers and those with national and international private insurance coverage (approximately 10% of patients) were able to access first-line EGFR TKIs and other biology-driven therapies such as bevacizumab and immune checkpoint inhibitors [27]. A further 35–40% of patients were able to access EGFR TKIs, but only as second-line therapy. In Malaysia, Thailand and The Philippines, first-line EGFR TKI treatment is generally not reimbursed by the government, making this treatment unattainable for all but wealthier patients. Patients who cannot afford to pay for EGFR TKIs receive first-line chemotherapy, and as a result, do not undergo routine *EGFR* testing at diagnosis. Testing is generally recommended when the patient progresses on first-line chemotherapy; this testing is either paid for by the patient or sponsored by a pharmaceutical company, and is generally only conducted in the largest cities. For patients with confirmed *EGFRm+* disease, subsequent EGFR TKI treatment may be paid for by patients, the Charity Sweepstakes Office (The Philippines), or in the case of individuals employed in the government sector, the government.

Even in wealthier countries where EGFR TKIs are approved and reimbursed for the first-line treatment of patients with *EGFRm+* NSCLC, some physicians continue to administer first-line chemotherapy [28]. This may be initiated without waiting for the results of mutation testing, such as when a patient presents in poor health, in order to prevent further deterioration, or when the preference of the physician/patient at diagnosis is to initiate treatment immediately, in order to halt disease progression. Our results suggest that, in patients with *EGFRm+* NSCLC who have progressed on or following chemotherapy, treatment with afatinib can provide significant improvements in outcomes. This supports the use of afatinib as a second-line treatment option after progression on/failure of chemotherapy. Our findings are also of relevance to the smaller group of patients who start chemotherapy and subsequently switch to afatinib treatment, and suggest that prior treatment does not impact on outcomes with afatinib. Together with previous studies of first-/second-line afatinib, these findings highlight the benefits of this treatment option in patients with *EGFRm+* NSCLC, regardless of prior chemotherapy treatment.

## Conclusion

In conclusion, our findings provide further support for the use of afatinib 40 mg/day as second-line therapy in EGFR TKI-naïve patients with *EGFRm+* (Del19/L858R) NSCLC. These results confirm those of LUX-Lung 2, and suggest that the recommended dose of afatinib (40 mg/day) provides effective treatment for patients with *EGFRm+* NSCLC in the first- or second-line setting, and irrespective of prior chemotherapy exposure.

## Author contributions

S Thongprasert and A Cseh contributed toward study conception and design. All authors contributed toward data collection, analysis and interpretation. All authors contributed toward writing and revision of the manuscript, are fully responsible for all content and editorial decisions, and have approved the final version.

## Financial & competing interests disclosure

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#### Data sharing statement

The authors certify that this manuscript reports original clinical trial data. Clinical trial registration number: NCT 02208843. The datasets generated and analyzed during the study are available from Sumitra Thongprasert on reasonable request.

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#### Ethical conduct of research

The study protocol was designed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice and applicable regional requirements. All patients provided written informed consent to participate in the trial. Clinicaltrials.gov NCT02208843.

#### Summary points

- The 40 mg/day afatinib dose was assessed in *EGFR* mutation-positive non-small-cell lung cancer patients progressing on chemotherapy.
- A total of 60 patients received at least one dose of afatinib 40 mg/day.
- Most patients (87%) were treated with afatinib for at least 90 days, and median duration of treatment was 11.5 months.
- Objective response was achieved by 50% of patients; median duration of response was 13.8 months.
- A total of 83% of patients had disease control, with median duration 11.9 months.
- Good control of brain metastases was achieved by eight/nine patients with baseline brain metastases.
- Median progression-free survival was 10.9 months.
- Most common drug-related adverse events were diarrhea, rash and paronychia.
- Our data support the use of second-line afatinib in patients with *EGFR* mutation-positive non-small-cell lung cancer.

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