Hong Kong J Radiol. 2022;25:184-91 | https://doi.org/10.12809/hkjr2217459

ORIGINAL ARTICLE

First-line Afatinib in Epidermal Growth Factor Receptor–mutant Metastatic Non-small Cell Lung Cancer: a Clinical Retrospective Study

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ABSTRACT

Background: *We sought to analyse epidermal growth factor receptor mutated (EGFR-MT) metastatic non-small cell lung cancer (NSCLC) patients treated with afatinib as first-line therapy in a clinical setting. The outcomes of cases, especially those harbouring rare mutations, were reviewed.*

Methods: *A single-centre retrospective study of 85 patients with NSCLC treated with first-line afatinib was performed. Demographics, clinical data, and treatment information were used to assess the effects of age, mutation types (common/uncommon), Eastern Cooperative Oncology Group performance status (ECOG PS), presence of brain metastasis, and other factors on progression-free survival (PFS) and overall survival (OS).*

Results: *Median age was 63 years. ECOG PS ≥2 was present in 10.6% of cases. A total of 11.8% of all cases had brain metastasis at first presentation and 41.2% had uncommon mutations. The median PFS was 14.9 months; the median OS was 33.9 months. 91.8% of patients experienced treatment-related adverse effects. Dose reductions were required for 30.6% of cases. Patients with major uncommon mutations had PFS of similar lengths to those with common mutations. Age, presence of brain metastasis, ECOG PS of ≥2 and presence of exon 20 insertions correlated negatively with PFS and OS.*

Conclusions: *Afatinib is an effective first-line treatment for patients with EGFR-MT NSCLC. The drug is well tolerated, with good response rates across a broad spectrum of patients. Given its high efficacy in major uncommon mutations, it should be considered as first-line treatment in this subset.*

Key Words: *Afatinib; Carcinoma, non-small-cell lung; ErbB receptors; Mutation; Progression-free survival*

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Submitted: 25 Aug 2021; Accepted: 15 Dec 2021.

Contributors: DYLC and KSL designed the study. DYLC acquired and analysed the data. DYLC, THS and KSL drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: All authors have disclosed no conflicts of interest.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: This study was approved by the University of Hong Kong / Hospital Authority Hong Kong West Cluster Institutional Review Board (Ref UW 21604) and was carried out in accordance with the Declaration of Helsinki.

中文摘要

阿法替尼一線治療表皮生長因子受體突變轉移性非小細胞肺癌：臨床回顧性研究

周一樂、蘇子謙、梁國全、謝佩楹、劉健生

背景：分析臨床使用阿法替尼作為表皮生長因子受體突變（EGFR-MT）轉移性非小細胞肺癌（NSCLC）患者的一線治療方案並檢視治療結果，尤其是帶有罕見突變的病例。

方法：對85例接受阿法替尼一線治療NSCLC的病例進行單中心回顧性研究。應用人口統計學、臨床數據和治療信息評估年齡、突變類型（常見／不常見）、ECOG體能狀態（ECOG PS）、是否有腦轉移及其他因素對疾病無惡化存活期（PFS）和總存活期（OS）的影響。

結果：年齡中位數為63歲。10.6%病例的ECOG PS得分≥2。11.8%病例在首次診斷時發現腦轉移，41.2%病例有罕見突變。PFS中位數為14.9個月；OS中位數為33.9個月。91.8%病例有與治療相關的不良反應。30.6%病例需要減少劑量。具有主要罕見突變患者的PFS與具有常見突變的患者類似。年齡、是否存在腦轉移、ECOG PS得分≥2以及是否存在20外顯子插入突變與PFS和OS呈負相關。

結論：阿法替尼是對EGFR-MT NSCLC患者有效的一線治療方案。該藥物的耐受性和緩解率均良好。鑑於其在主要罕見突變中的高效性，阿法替尼可被視為對這類患者的一線治療方案。

INTRODUCTION

Patients with non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor mutation (EGFR-MT) are currently treated with tyrosine kinase inhibitors (TKIs).[1] Activating mutations in the EGFR gene causes aberrant EGFR signalling, which sensitises tumours to targeted TKI treatment. The Food and Drug Administration has currently approved five TKIs, with gefitinib and erlotinib being first-generation, afatinib and dacomitinib in the second generation, and osimertinib in the third generation.[2]

Afatinib is an irreversible blocker of the ErbB family of receptors (inhibiting signalling via heterodimers and homodimers formed by $ErbB_1$ (EGFR), $ErbB_2$ (human epidermal growth factor receptor 2 [HER_2]), $ErbB_3$ (HER_3), and $ErbB_4$ (HER_4).[3] Randomised controlled trials (RCTs) have shown that afatinib significantly improved progression-free survival (PFS) compared with standard chemotherapy.[4,5] Adverse events (AEs) were tolerable with few treatment discontinuations.

Post-hoc analysis of the LUX-Lung trials[6] found afatinib had significant activity against certain uncommon mutations, including G719X, L861Q, and S768I. Preclinical data showed that afatinib was less effective against tumours with exon 20 insertions, or de novo T790M mutations alone or in combination with other mutations.

There are not as much prospective clinical data on other EGFR TKIs targeting uncommon mutations. As a result, afatinib is the TKI of choice in the first-line setting for more than 80 countries to treat patients with NSCLC with EGFR-MT.

Clinical trials typically have strict inclusion criteria, and certain patient subgroups are frequently excluded, such as elderly patients, patients with brain metastases, or with an Eastern Cooperative Oncology Group (ECOG) performance status ≥2. Given the lack of prospective data in these patients, the goal of this study was to analyse the available data of EGFR-MT patients treated with afatinib in an environment similar to daily clinical practice, and to examine and compare outcomes of individuals with uncommon mutations.

METHODS

Cases of patients aged ≥18 years with histologically

proven metastatic NSCLC that were treated with first-line afatinib from 1 January 2015 to 30 June 2021 at Queen Mary Hospital Hong Kong were retrospectively reviewed. Median follow-up time was 23 months. The data cut-off was on 31 July 2021. Those that had received prior anticancer treatment or had primary tumours other than in the lung were excluded. Cases were categorised into four key groups: tumours harbouring major uncommon point mutations (G719X, L861Q, and S768I); exon 20 insertions; other uncommon mutations; and common mutations (exon 19 deletion, exon 21 L858R). Cases with brain metastasis and poor performance status were not excluded.

The primary objective was to evaluate the safety and efficacy of afatinib in these groups. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Efficacy endpoints included: PFS (time from first afatinib administration to date of progression or to date of death, whichever came first) and overall survival (OS) [time from diagnosis to date of death]. 'Progression' was defined as a worsening radiological appearance as per standard of care at the participating institution via Response Evaluation Criteria in Solid Tumours (RECIST) or by clinical symptomatic progression. Computed tomography (CT) and magnetic resonance imaging were used for patients that underwent baseline brain imaging assessment. Reassessment imaging was arranged every 3 to 6 months using CT or positron emission tomography/CT when feasible. Objective response rates (ORRs) were judged by the authors based on available imaging information via RECIST criteria. *EGFR* mutations were detected using real-time polymerase chain reactions.

Patients received afatinib at starting doses of 40 mg, 30 mg, or 20 mg once daily based on perceived tolerance to treatment by the clinician. Treatment was continued until disease progression, poor tolerability, or other reasons requiring withdrawal. Treatment-related adverse events (TRAEs) were managed using tolerance-guided dose modifications. When TRAEs reversed to Grade 1 or back to baseline, treatments could be resumed at a lower dose (in 10 mg decrements). If patients could not tolerate 20 mg afatinib daily or if TRAEs did not return to Grade 1 or to baseline within 6 weeks, treatment was discontinued. The optimum dose of afatinib was defined as the final dose that a patient received without need for further decrements due to TRAEs.

Statistical Analysis

Data were analysed using SPSS (Windows version 23.0; IBM Corp., Armonk [NY], United States). Kaplan–Meier estimates were used for median OS (mOS) and median PFS (mPFS). Univariable and multivariable analyses for prognostic factors of PFS and OS were performed by Cox proportional hazard models. A p value of <0.05 was considered statistically significant. All cases were included in safety and efficacy analyses. Exploratory subgroup analysis was conducted post hoc and descriptive statistics are presented.

RESULTS

A total of 85 patients (median age 63 years, range 37-90) were treated with afatinib within the listed period (Table 1). Within the dataset, 50 (58.8%) patients had common mutations, whereas 35 (41.2%) patients were harbouring uncommon mutations. Two patients with L858R mutations had de novo T790M mutations. Major uncommon point mutations such as G719X, L861Q and S768I were the most frequent group, accounting for 68.6% of all uncommon mutations.

Efficacy

Progression-free Survival and Overall Survival

The mPFS was 14.9 months (95% confidence interval [CI]=10.7-19.0), with 63 cases having progressed at the time of analysis. The mPFS according to clinical and treatment characteristics are shown in Tables 2 and 3. On both univariable and multivariable analyses, cases with the exon L858R point mutation had significantly shorter mPFS compared with those with the exon 19 deletion (5.3 months vs. 16.4 months; HR=2.34, 95% CI=1.01-5.62; $p = 0.048$) [Figure 1]. Patients aged ≥65 years (12.0 months vs. 16.8 months; HR=1.49, 95% CI=1.02-2.48; $p = 0.034$) had worse mPFS than those of younger age (Figure 2). Patients with ECOG performance status 2-3 (2.7 months vs. 16.4 months; HR=7.28, 95% CI=3.23-16.42; $p < 0.001$) had a worse mPFS than those with better ECOG performance status (Figure 3).

Final OS data was largely congruent with PFS findings. mOS was 33.9 months (95% CI=20.6-47.2) for all cases. Cases with exon L858R point mutation had significantly shorter mOS compared with cases with the exon 19 deletion (11.3 months vs. 45.2 months; HR=2.51, 95% CI=1.03-6.08; $p = 0.042$).

Safety and Dosage

TRAEs were common among patients, with up to 91.8%

Table 1. Baseline demographics and disease characteristics of patients with NSCLC treated with first-line afatinib (n = 85).

	Patients
Sex	
Female	41 (48.2%)
Male	44 (51.8%)
Median age, range, y	63 (37-90)
≥65	37 (43.5%)
≥75	12 (14.1%)
Smoking status	
Never smoked	60 (70.6%)
Ex-smoker	15 (17.6%)
Current smoker	7 (8.24%)
Unknown	3 (3.5%)
Histological classification	
Adenocarcinoma	76 (89.4%)
Squamous cell carcinoma	2 (2.4%)
Undifferentiated carcinoma	7 (8.2%)
EGFR mutation	
Common	
L858R in exon 21	9 (10.6%)
Exon 19 deletion	41 (48.2%)
Uncommon	
Major uncommon point mutations	24 (28.2%)
G719A in exon 18	3 (3.5%)
G719A in exon 18 and R776C in exon 20	1 (1.2%)
G719A in exon 18 and L861Q in exon 21	1 (1.2%)
G719A in exon 18 and S768I in exon 20	1 (1.2%)
G719A and E709K in exon 18	1 (1.2%)
G719C and G709V in exon 18	2 (2.4%)
G719D in exon 18 and S768I in exon 20	1 (1.2%)
G719R in exon 18 and S768I in exon 20	2 (2.4%)
G719S in exon 18 and L861Q in exon 21	1 (1.2%)
G719X in exon 18	1 (1.2%)
L861Q in exon 21	5 (5.9%)
L861Q and I706T in exon 21	1 (1.2%)
S768I and G719C in exon 20	1 (1.2%)
S768I in exon 20 and L858R in exon 21	2 (2.4%)
S768I and V769L in exon 20	1 (1.2%)
Exon 20 insertion	5 (5.9%)
Other mutations	6 (7.1%)
Exon 18 3 nucleotide deletion	1 (1.2%)
L833V, H835L in exon 21	1 (1.2%)
L838V in exon 21	1 (1.2%)
L838V, L858R in exon 21	1 (1.2%)
R831H in exon 21	1 (1.2%)
V834L, L858R in exon 21	1 (1.2%)
Baseline ECOG performance status	
0	10 (11.8%)
1	66 (77.6%)
2	7 (8.2%)
3	2 (2.4%)
Baseline brain metastases	10 (11.8%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
* Data are shown as No. (%), unless otherwise specified.

of all patients experiencing some form of TRAE (Table 4). Dose adjustments were required for patients, with up to 54 (63.5%) patients requiring dose reductions. In total, 11.8% of all patients had dose increments. No TRAEs resulted in death.

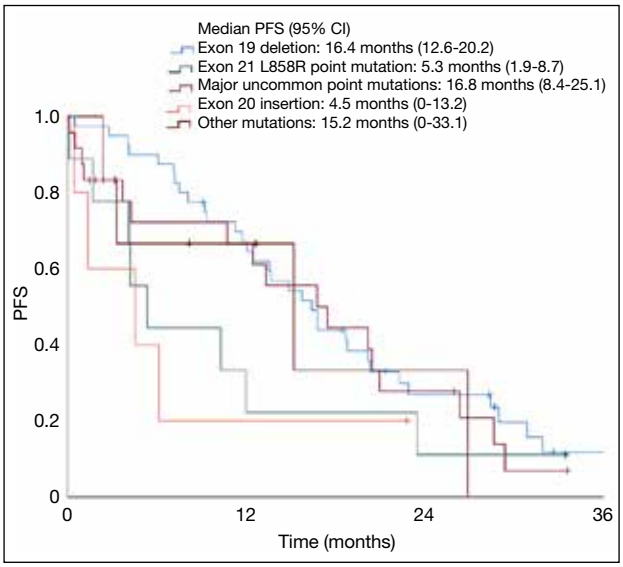

Figure 1. PFS according to type of *EGFR* mutation.
Abbreviations: 95% CI = 95% confidence interval; PFS = progression-free survival.

Most cases started with afatinib 40 mg daily (54.1%), followed by 30 mg daily (36.5%) and 20 mg daily (9.4%). Initial starting dose was maintained for 49 (57.6%) patients (Table 5). Dose reductions were largely due to AEs from treatment whereas dose increments were due to initially perceived poor tolerance to treatment. The optimum dose for most cases was 30 mg daily and most cases with brain metastasis on diagnosis often had surgery or radiotherapy in conjunction with afatinib treatment.

Objective Response Rate and Resistance

Overall, 38 of 85 cases (44.7%) had an objective response, including one (1.2%) complete response and 37 (43.5%) partial responses. In all, 27 (31.8%) cases had stable disease. Disease control rate was 76.5%.

Sixty-three cases eventually developed progressive disease on afatinib. Forty-eight were retested for T790M mutations, with 39 undergoing plasma EGFR testing and nine with tissue sample testing. Fourteen (29.2%) cases developed exon 20 T790M mutations. All cases that developed T790M mutations had adenocarcinoma exclusively. For cases that had common mutations, 19 received osimertinib as second-line treatment and nine others received chemotherapy. Within the uncommon mutation group, four cases received osimertinib, eight received chemotherapy, and one continued second-line treatment with mobocertinib.

Table 2. Univariable analyses and multivariable analyses for progression-free survival.*

	No. of patients (n = 85)	Median PFS, mo (95% CI)	1-year PFS	Univariable analysis		Multivariable analysis	
				HR (95% CI)	p Value	HR (95% CI)	p Value
Age							
<65 y	48 (56.5%)	16.8 (12.5-21.0)	66.0%	Reference		Reference	
>65 y	37 (43.5%)	12.0 (8.4-15.5)	48.7%	1.78 (1.08-2.87)	0.024	1.49 (1.02-2.48)	0.034
Gender							
Female	41 (48.2%)	13.6 (8.6-18.7)	60.8%	Reference			
Male	44 (51.8%)	14.8 (9.2-20.5)	56.4%	1.17 (0.71-1.93)	0.534	1.17 (0.69-2.00)	0.560
ECOG							
0-1	76 (89.4%)	16.4 (16.2-20.2)	63.3%	Reference		Reference	
2-3	9 (10.6%)	2.7 (0-6.2)	13.9%	7.28 (3.23-16.42)	<0.001	7.28 (3.23-16.42)	<0.001
EGFR mutation types							
Exon 19 deletion	41 (48.2%)	16.4 (12.6-20.2)	67.2%	Reference		Reference	
L858R in exon 21	9 (10.6%)	5.3 (1.9-8.7)	22.2%	2.89 (1.24-6.72)	0.014	2.34 (1.01-5.62)	0.048
Major uncommon point mutations	24 (28.2%)	16.8 (8.4-25.1)	66.7%	1.19 (0.66-2.14)	0.564	0.89 (0.53-1.89)	0.318
Exon 20 insertion	5 (5.9%)	4.5 (0-13.2)	20.0%	2.42 (0.85-6.92)	0.099	1.79 (0.88-4.68)	0.395
Other mutations	6 (7.1%)	15.2 (0-33.1)	66.7%	1.34 (0.47-3.82)	0.581	0.92 (0.31-2.72)	0.874
Brain metastasis screening†							
No	47 (55.3%)	15.2 (10.1-20.3)	60.6%	0.74 (0.32-1.70)	0.473	0.71 (0.35-1.51)	0.397
Yes	9 (10.6%)	13.6 (0-35.7)	55.6%	Reference		Reference	
Afatinib dose adjustment							
Dose maintained	49 (57.6%)	12.0 (5.7-18.2)	51.6%	Reference		Reference	
Dose increased	10 (11.8%)	20.2 (10.7-29.7)	74.1%	0.52 (0.22-1.22)	0.134	0.58 (0.24-1.38)	0.216
Dose reduced	26 (30.6%)	16.8 (13.8-19.8)	65.2%	0.66 (3.38-1.16)	0.148	0.64 (0.36-1.11)	0.111
Afatinib optimum dose							
40 mg daily	31 (36.5%)	20.2 (10.1-30.2)	58.6%	Reference		Reference	
30 mg daily	40 (47.1%)	15.2 (11.8-18.6)	61.4%	1.01 (0.59-1.72)	0.986	1.41 (0.43-3.03)	0.790
20 mg daily	14 (16.5%)	6.07 (0-18.7)	46.6%	1.48 (0.70-3.12)	0.300	1.44 (0.75-2.81)	0.272

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival.
* Data are shown as No. (%), unless otherwise specified.
† Fifty-five patients had baseline brain imaging.

DISCUSSION

This study was a retrospective review of a single-centre experience of cases of metastatic NSCLC EGFR-MT treated with first-line afatinib. Case demographics and population subsets are comparable to other reported studies with EGFR TKIs being used in daily clinical practice.[7] Typically underrepresented subgroups such as the elderly people, cases with brain metastasis, cases with uncommon mutations, and those with ECOG performance status ≥2 were also included in this review. A majority of cases harboured exon 19 deletions and up to 41.2% of all cases were harbouring uncommon mutations. This is likely due to selection bias whereby clinicians were influenced by the mOS results of the LUX-Lung 3 and 6 trials, which favoured afatinib over chemotherapy in the first-line setting,[8] and a tendency to prescribe afatinib for patients harbouring uncommon mutations as well.

The mPFS in this review was consistent with other clinical studies (mPFS 11.8-11.9 months) and the LUX Lung trials (mPFS 11.0-11.1 months).[8,9] Other studies, such as that of Kim et al,[10] have found a substantially longer mPFS of 19.1 months using first-line afatinib, which could be partly due to the fact that only ECOG performance status 0-2 cases were involved.

Our results also showed that cases with the exon 19 deletion had a significantly longer mPFS compared with those that had exon 21 L858R mutations. Although Kim et al[10] and Liang et al[9] have highlighted similar outcomes where cases with exon 19 deletions had longer mPFS and improved ORR compared to those having exon 21 L858R mutations, two out of the nine patients that had L858R mutations in our subgroup also harboured de novo T790M, which may have skewed results unfavourably.

Cases with unfavourable clinical characteristics, such as poor ECOG performance status or advanced age showed

Table 3. Univariable analyses and multivariable analyses for overall survival.*

	No. of patients (n = 85)	Median OS, mo (95% CI)	1-year PFS	Univariable analysis		Multivariable analysis	
				HR (95% CI)	p Value	HR (95% CI)	p Value
Age							
<65 y	48 (56.5%)	45.2 (32.9-57.6)	89.1%	Reference		Reference	
>65 y	37 (43.5%)	22.9 (14.0-31.9)	67.5%	2.23 (1.11-4.46)	0.003	2.13 (1.15-3.94)	0.016
Gender							
Female	41 (48.2%)	36.2 (27.0-45.5)	82.4%	Reference			
Male	44 (51.8%)	25.9 (17.1-34.8)	77.1%	1.63 (0.78-3.41)	0.281	1.47 (0.71-3.12)	0.294
ECOG							
0-1	76 (89.4%)	38.1 (25.8-50.4)	85.1%	Reference		Reference	
2-3	9 (10.6%)	4.8 (0-10.8)	33.3%	7.53 (2.67-21.23)	<0.001	7.38 (2.95-18.42)	<0.001
EGFR mutation types							
Exon 19 deletion	41 (48.2%)	45.2 (27.7-62.8)	90.2%	Reference		Reference	
L858R in exon 21	9 (10.6%)	11.3 (5.9-16.6)	44.4%	2.89 (1.24-6.72)	0.014	2.51 (1.03-6.08)	0.042
Major uncommon point mutations	24 (28.2%)	38.1 (17.3-58.9)	78.7%	1.67 (0.80-3.52)	0.174	0.86 (0.30-1.77)	0.488
Exon 20 insertion	5 (5.9%)	10.4 (0.4-28.5)	40.0%	2.51 (0.74-8.56)	0.141	1.40 (0.37-5.30)	0.617
Other mutations	6 (7.1%)	29.2 (9.8-31.8)	83.3%	2.18 (0.63-7.50)	0.219	1.34 (0.37-4.92)	0.654
Brain metastasis screening†							
No	47 (55.3%)	36.2 (25.7-46.8)	82.3%	0.53 (0.21-1.62)	0.111	0.57 (0.24-1.33)	0.188
Yes	9 (10.6%)	14.0 (0-32.1)	60.0%	Reference		Reference	
Afatinib dose adjustment							
Dose maintained	49 (57.6%)	25.9 (5.1-46.7)	75.8%	Reference		Reference	
Dose increased	10 (11.8%)	NR	85.4%	0.45 (0.10-1.96)	0.285	1.18 (0.54-2.56)	0.239
Dose reduced	26 (30.6%)	29.2 (19.1-39.3)	84.0%	1.02 (0.52-2.01)	0.958	1.75 (0.69-4.47)	0.685
Afatinib optimum dose							
40 mg daily	31 (36.5%)	44.5 (14.8-61.9)	83.9%	Reference		Reference	
30 mg daily	40 (47.1%)	44.6 (25.2-47.3)	84.9%	0.92 (0.92-1.80)	0.811	1.30 (0.57-3.00)	0.535
20 mg daily	14 (16.5%)	23.3 (0-31.9)	53.8%	2.61 (1.15-5.91)	0.022	2.16 (0.68-6.84)	0.190

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reached; OS = overall survival.

* Data are shown as No. (%), unless otherwise specified.

† Fifty-five patients had baseline brain imaging.

decreased mPFS compared to those without, reaching statistical significance on univariable and multivariable analysis. Cases with brain metastasis on screening, however, did not show significantly worse mPFS, contrary to the findings of Tan et al.[11]

Afatinib was demonstrated to be effective in cases with major uncommon point mutations (G719X, L861Q and S768I) with a response rate and mPFS comparable to those with common *EGFR* mutations. This is consistent with findings from Passaro et al[12] and Yang et al,[13] implying that afatinib may be a suitable choice of treatment for patients harbouring these mutations. The Food and Drug Administration has recently expanded the front-line indication for afatinib to cover NSCLC with these three *EGFR* mutations. In contrast, exon 20 insertions had a much shorter mPFS. Recently approved treatments, including amivantamab and mobocertinib have shown promise in early-phase clinical studies for exon 20 insertions and could play a role in this subgroup of patients in the future.[14,15]

This study showed a much lower incidence of grade >3 AEs due to afatinib compared with an incidence of 36.0% to 57.0% reported by RCTs.[4,5] This is likely due to the lower starting doses given within this patient group. Early dose reductions in patients before developing grade 3 AEs in daily practice would also explain these findings. Of note, the incidence of the acquired T790M mutation was lower than the rates reported in several studies (32.1%-47.6%).[10,16] This could possibly be due to the fact that not all cases progressing on afatinib were retested for T790M. Another reason could be that certain cases that had uncommon mutations were already resistant to afatinib, and therefore did not develop resistance via T790M mutations.

In-vitro analysis of *EGFR* mutations, including

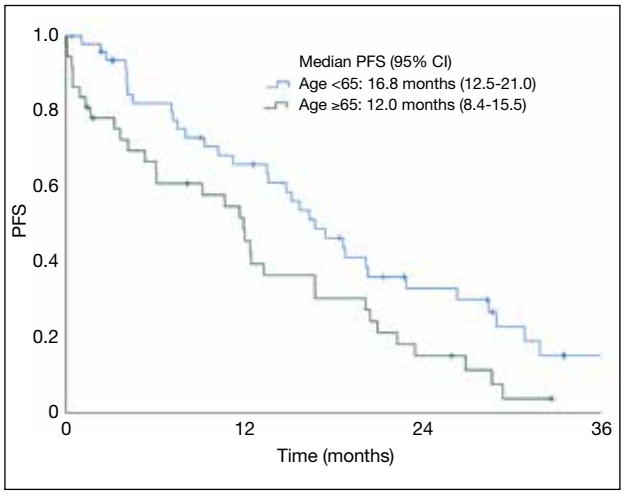

Figure 2. PFS according to age.
Abbreviations: 95% CI = 95% confidence interval; PFS = progression-free survival.

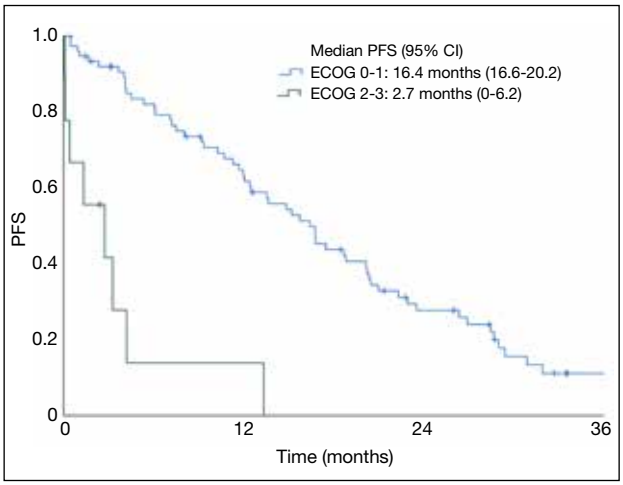

Figure 3. PFS according to ECOG performance status.
Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival.

Table 4. Overall summary of TRAEs (n = 85).*

TRAE	Patients			
Any TRAE		78 (91.8%)		
TRAEs leading to dose reduction		26 (30.6%)		
Most common TRAEs (occurring in ≥10% of cases)	All Grades	Grade 1	Grade 2	Grade 3
Diarrhoea	67 (78.8%)	48 (56.5%)	13 (15.3%)	6 (7.1%)
Skin rash	59 (69.4%)	42 (49.4%)	13 (15.3%)	4 (4.7%)
Mucositis	37 (43.5%)	33 (38.8%)	3 (3.5%)	1 (1.2%)
Paronychia	29 (34.1%)	27 (31.8%)	2 (2.4%)	0
Dry skin	23 (27.1%)	23 (27.1%)	0	0
HFS	15 (17.6%)	7 (8.2%)	8 (9.4%)	0
Stomatitis	8 (9.4%)	5 (5.9%)	3 (3.5%)	0
Abnormal liver function	4 (4.7%)	4 (4.7%)	0	0

Abbreviation: HFS = hand-foot syndrome; TRAEs = treatment-related adverse effects.
* Data are shown as No. (%).

Table 5. Afatinib starting dose, dose adjustment, and optimal dose and treatment of baseline brain metastases (n = 85).

Treatment pattern and outcome	Patients
Afatinib starting dose	
40 mg once daily	46 (54.1%)
30 mg once daily	31 (36.5%)
20 mg once daily	8 (9.4%)
Afatinib dose adjustment	
Starting dose maintained	49 (57.6%)
Dose increased	10 (11.8%)
Dose reduced	26 (30.6%)
Afatinib optimum dose	
40 mg daily	31 (36.5%)
30 mg daily	40 (47.1%)
20 mg daily	14 (16.5%)
Brain metastasis treatment	
No brain metastasis	75 (88.2%)
Afatinib alone	2 (2.4%)
Afatinib with surgery or radiotherapy	8 (9.4%)

* Data are shown as No. (%).

uncommon and compound mutations against different EGFR TKIs, showed that afatinib had activity against almost all mutations tested and was more potent than erlotinib and gefitinib. When compared with osimertinib, afatinib also demonstrated a greater spectrum of efficacy against uncommon *EGFR* mutations, while it was less effective against T790M, as expected.[17] Clinical data, however, are limited. Recent literature demonstrated favourable activity with manageable toxicity in patients with NSCLC harbouring uncommon *EGFR* mutations treated with first-line osimertinib. A phase II study by Cho et al[18] demonstrated an ORR and PFS of 53% and 8.2 months, respectively, for patients with G719X mutations. For afatinib, an ORR of 77.8% and a PFS of 13.8 months were reported by Yang et al.[6] Although cross-trial comparisons should be done with caution, osimertinib showed a response rate in cases with G719X

mutations that was comparable to that of other EGFR TKIs.[6]

Numerous factors need to be considered when choosing a therapy, including central nervous system activity, toxicities, and types of *EGFR* mutations. Clinical efficacy of EGFR TKIs in patients with uncommon mutations should be assessed prospectively, due to the small number and heterogeneity of patients studied thus far.

Clinical analyses of afatinib that include patient characteristics such as poor ECOG performance status, brain metastasis, old age, and uncommon mutations are limited. This study is one of the few retrospective reviews that examined a population similar to that encountered in daily clinical practice. The results of our study provide additional data on these subgroups, especially in patients with uncommon mutations.

A few limitations should be noted. Given their retrospective nature, data may be prone to bias during measurement. Because radiological assessments were performed at different radiology centres, with potentially different methodologies, response rates and progression were not solely measured based on RECIST criteria. Caution is therefore needed when comparing with published data. As there may have been inadequate follow-up duration for patients, a fair amount of data regarding patients' PFS and OS were censored. The number of patients with exon 21 L858R was also relatively small compared to exon 19 mutations, with exploratory subgroup analysis performed, limiting the strength of conclusions.

In summary, afatinib is an effective first-line treatment for patients with EGFR-MT NSCLC. The drug is generally well-tolerated and response rates and PFS are consistent with previous RCTs and other clinical analyses. Given its high efficacy in major uncommon point mutations, it should be considered as first-line treatment for patients harbouring these mutations.

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