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ORIGINAL RESEARCH ARTICLE

Afatinib in Untreated Stage IIIB/IV Lung Adenocarcinoma with Major Uncommon Epidermal Growth Factor Receptor (EGFR) Mutations (G719X/L861Q/S768I): A Multicenter Observational Study in Taiwan

Ping-Chih Hsu[1,2] · Suey-Haur Lee[3] · Li-Chung Chiu[1,2] · Chung-Shu Lee[1,4] · Chiao-En Wu[2,5] · Scott Chih-Hsi Kuo[1,2] · Jia-Shiuan Ju[1] · Allen Chung-Cheng Huang[1] · Shih-Hong Li[1] · Ho-Wen Ko[1,2] · Cheng-Ta Yang[1,6,7] · Chin-Chou Wang[2,3,4]

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Abstract

Background Real-world clinical experience with afatinib as a treatment for advanced lung adenocarcinoma harboring uncommon epidermal growth factor receptor (EGFR) mutations (G719X, L861Q and S768I) has rarely been reported.

Objective We aimed to perform a retrospective multicenter study to analyze afatinib therapy in untreated advanced lung adenocarcinoma harboring uncommon EGFR mutations.

Patients and Methods Between May 2014 and June 2021, the data of 90 stage IIIB/IV lung adenocarcinoma patients with uncommon EGFR mutations (G719X/L861Q/S768I) treated with first-line afatinib from the cancer center database of Linkou, Tucheng, and Kaohsiung Chang Gung Memorial Hospitals were retrospectively retrieved and analyzed.

Results Afatinib had an objective response rate (ORR) of 63.3% and a disease control rate (DCR) of 86.7%. The median progression-free survival (PFS) with first-line afatinib therapy was 17.3 months (95% confidence interval (CI), 12.07–22.53), and the median overall survival (OS) was 28.5 months (95% CI, 20.22–36.77) in all study patients. In the multivariate analysis, poor performance (Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2) and brain and liver metastases were independent predictors of unfavorable PFS. The G719X mutation (alone+compound) was an independent predictor of favorable PFS (hazard ratio (HR) = 0.578; 95% CI, 0.355−0.941; $P = 0.027$). Most afatinib-related adverse events (AEs) were limited to grades 1 and 2 and were manageable.

✉ Chin-Chou Wang
ccwang5202@yahoo.com.tw

1 Division of Thoracic Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan 33305, Taiwan

2 Department of Medicine, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

3 Division of Pulmonary and Critical Care Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City 83301, Taiwan

4 Department of Thoracic Medicine, New Taipei Municipal TuCheng Hospital, New Taipei 23652, Taiwan

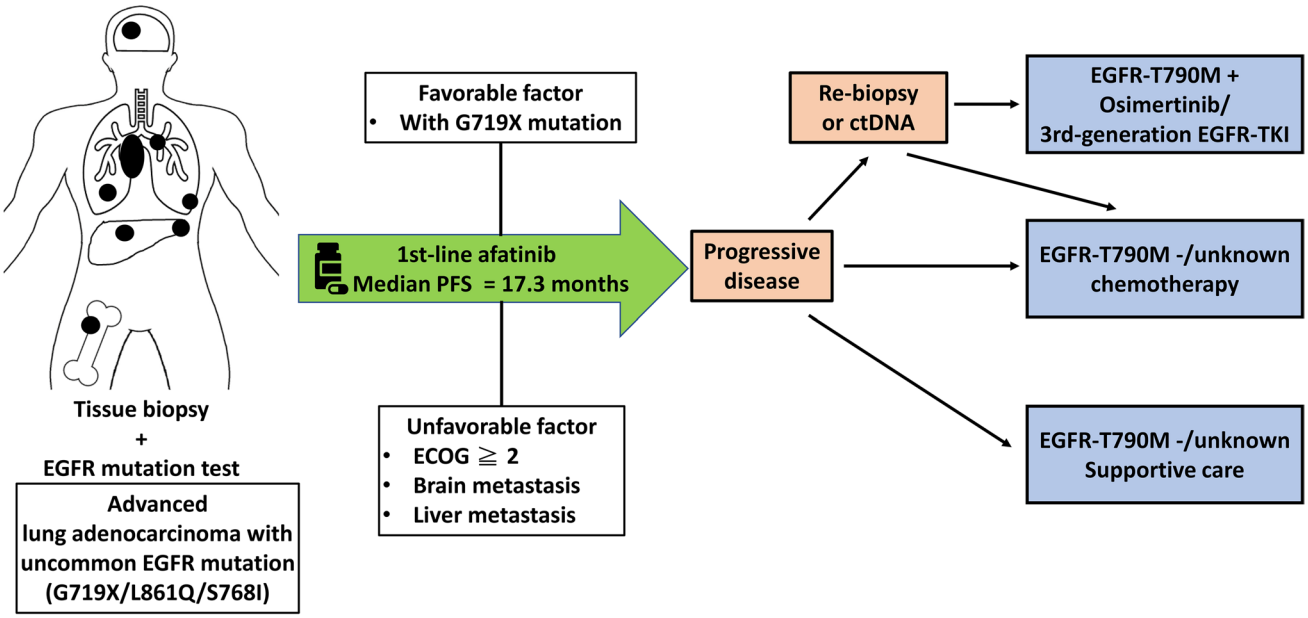
5 Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan 33305, Taiwan

6 Department of Internal Medicine, Taoyuan Chang Gung Memorial Hospital, Taoyuan 33378, Taiwan

7 Department of Respiratory Therapy, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

Conclusions First-line afatinib therapy is effective and safe for advanced lung adenocarcinoma harboring uncommon EGFR mutations. The G719X mutation was an independent factor associated with a favorable outcome. Poor performance (ECOG PS ≥ 2), brain metastasis, and liver metastasis were predictive factors of shorter PFS with first-line afatinib therapy.

Graphical Abstract



Key Points

We demonstrated that afatinib has a promising objective response rate (ORR) and median progression-free survival (PFS) in Eastern Asian patients with advanced lung adenocarcinoma with major uncommon EGFR mutations, and that the efficacy is more prominent in patients with the G719X mutation.

In this study, we identified favorable and unfavorable clinical factors associated with PFS, the secondary T790M mutation rate after resistance to afatinib and subsequent treatment information for this patient group.

Future studies may focus on afatinib-based therapy combined with other therapies, such as antiangiogenic agents (e.g., bevacizumab or ramucirumab) in patients with unfavorable clinical factors, including brain and liver metastasis.

1 Introduction

The epidermal growth factor receptor (EGFR) signaling pathway plays a crucial role in promoting the pathogenesis of human non-small-cell lung cancer (NSCLC) [1, 2]. The EGFR protein consists of an extracellular ligand-binding receptor, a transmembrane domain, and an intracellular tyrosine kinase domain. When mutations occur in exons 18–21, which encode the tyrosine kinase domain, the kinase activity of EGFR increases and activates downstream pro-survival signaling pathways in NSCLC [1–3]. EGFR mutations are the most frequent oncogenic driver mutations in East Asian lung adenocarcinoma patients (ranging from 45 to 55%) [3, 4]. First- to third-generation EGFR-tyrosine kinase inhibitors (TKIs) have been developed and various pivotal clinical trials have shown promising efficacy of these TKIs in treating patients with advanced and unresectable NSCLC harboring EGFR mutations, with a 60−80% objective response rate (ORR) and

9- to 19-month progression-free survival (PFS) [5–12]. The L858R mutation in exon 21 and an exon 19 deletion mutation account for most EGFR mutations in NSCLC (approximately 90%), and such cases respond to EGFR-TKI therapies [5–13]. Other uncommon EGFR mutations (5−7% of EGFR mutations), including Gly719Xaa (G719X) in exon 18, Ser768Ile (S768I) in exon 20 and Leu861Gln (L861Q) in exon 21, can occur in NSCLC, and these cases respond to EGFR-TKI therapies [13, 14].

The second-generation EGFR-TKI afatinib has the characteristic of irreversible covalent binding to the tyrosine kinase domain of ErbB1 (EGFR), ErbB2 and ErbB4 receptors, and exerts a pan-ErbB receptor blockade effect [8–10, 14]. Afatinib has been shown to significantly improve the ORR and PFS as a first-line therapy in advanced EGFR-mutated NSCLC compared with conventional chemotherapy in phase III clinical trials (LUX-Lung 3, 6). Afatinib has been approved as a first-line therapy for advanced NSCLC harboring EGFR mutations according to the results of previous clinical trials and is widely used in clinical practice [8–10, 14, 15].

A previous study reported that the ORR and PFS with first-generation EGFR-TKI (gefitinib and erlotinib) therapy in advanced NSCLC patients with uncommon mutations (G719X/L861Q/S768I) were significantly inferior to those in patients with common mutations (exon 19 deletion and L858R mutation) [16]. In three previous prospective studies (LUX-Lung 2, 3 and 6 trials), NSCLC patients harboring uncommon EGFR mutations were recruited to explore the efficacy of afatinib therapy [8, 9, 17]. Although the three clinical trials showed that afatinib was effective for the treatment of NSCLC patients harboring uncommon mutations, the numbers of patients were low in all three trials. The study subjects with uncommon mutations in the three trials were very heterogeneous, and some patients with rare mutations, such as T790M and exon 20 insertion mutations that do not respond to afatinib, were recruited [8, 9, 17].

Afatinib has been suggested as a preferred first-line therapy for advanced NSCLC patients with G719X, L861Q or S768I mutations, but real-world clinical data on such patients are limited. In this study, we performed a

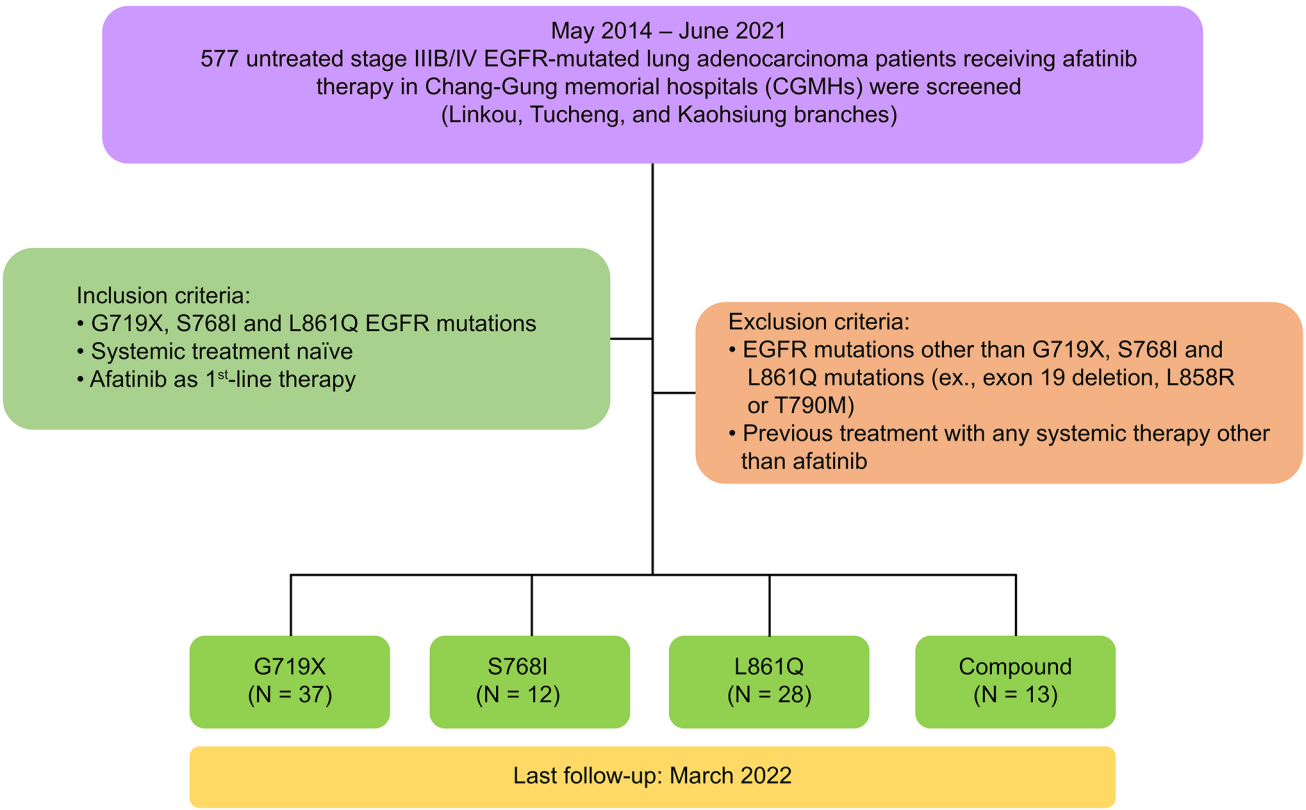


Fig. 1 The inclusion and exclusion criteria for study patients

retrospective clinical analysis of advanced NSCLC patients harboring uncommon mutations (G719X/L861Q/S768I) who received afatinib as first-line therapy.

2 Methods

2.1 Patients, Treatment and Follow-Up

The study patients were retrospectively screened using the cancer center databases of Linkou, Tucheng and Kaohsiung Chang Gung Memorial Hospitals (CGMHs). Between May 2014 and June 2021, 577 patients with histologically diagnosed stage IIIB/IV EGFR-mutated lung adenocarcinoma who received first-line afatinib therapy were screened, and 90 study subjects were finally included in the analysis. The inclusion criteria for the study subjects were as follows: (1) the presence of G719X, L861Q or S768I mutations; (2) no previous systemic treatment (no targeted therapy, chemotherapy, or immunotherapy prior to afatinib); and (3) afatinib therapy as first-line treatment. Patients were excluded for the following reasons: (1) the presence of EGFR mutations other than G719X, L861Q and S768I mutations, such as exon 19 deletion, L858R or T790M mutations, and (2) previous systemic therapy prior to afatinib. The screening and inclusion of study subjects are summarized in Fig. 1.

All patients in this study underwent computed tomography (CT) with contrast medium enhancement, fluorodeoxyglucose (FDG)-positron emission tomography (PET), and brain magnetic resonance imaging (MRI) to determine the baseline stage at initial diagnosis. All study patients received follow-up CT scans every 3–4 months during the course of afatinib therapy to assess the treatment response. Other additional imaging examinations, including sonograms, FDG-PET scans or MRI, during the follow-up period were performed by the order of clinical physicians to facilitate determination of disease status as needed.

The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to assess treatment response, and responses were determined to be a complete response (CR) or a partial response (PR). Stable disease (SD) and progressive disease (PD) were defined as nonresponses. The PFS duration was defined as the time from the date of the first afatinib dose to the date of the first images revealing PD or death. Overall survival (OS) was measured from the date afatinib treatment was initiated to the date of death. If patients were still being treated with afatinib and survived through the last follow-up time point (31 March 2022), PFS and OS were censored at the last clinical visit date. The National Cancer Institute Common Terminology Criteria were used to assess and grade treatment-related adverse events (AEs).

Table 1 Baseline demographic information of all patients

Total	$N = 90$ (%)
Sex	
Male	61 (67.8%)
Female	29 (32.2%)
Age, years (mean ± SD)	67.4 ± 11.2
ECOG PS	
0–1	67 (74.4%)
≥ 2	23 (25.6%)
Smoking status	
Nonsmoker	78 (86.7%)
Former/current smoker	12 (13.3%)
Histology	
Adenocarcinoma	90 (100%)
Stage	
IIIB	4 (4.4%)
IV	86 (95.6%)
EGFR mutation	
G719X alone	37 (41.1%)
S768I alone	12 (13.3%)
L861Q alone	28 (31.1%)
Compound mutations	13 (14.5%)
G719X + S768I	5 (5.6%)
G719X + L861Q	5 (5.6%)
S768I + L861Q	3 (3.3%)
Brain metastasis	30 (33.3%)
Bone metastasis	37 (41.1%)
Liver metastasis	10 (11.1%)
Starting dose of afatinib	
40 mg	60 (66.7%)
30 mg	30 (33.3%)
Dose de-escalation (40 mg − > 30 mg)	24 (26.7%)
Local radiation during afatinib therapy	
Brain	25 (27.8%)
Bone	12 (13.3%)

SD standard deviation, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *EGFR* epidermal growth factor receptor

EGFR mutations, including primary or secondary mutations with resistance to first-line afatinib therapy, were assayed by direct sequencing or amplified refractory mutation system–Scorpion (ARMS/S) assays.

2.2 Statistical Analysis

The demographic and treatment information of the study patients are presented as quantitative variables. The age of the study patients is presented as the mean ± standard deviation (SD). Cox regression with univariate and multivariate analyses was performed to analyze PFS according

to different clinical variables. The statistical significance of continuous variable comparisons between two study groups was assessed by the Mann-Whitney test. Categorical variables were compared between two study groups using chi-square and Fisher's exact tests. Kaplan-Meier survival curves were generated to compare the PFS and OS between the study groups. Two-sided P values less than 0.05 were defined as statistically significant. IBM SPSS Statistics version 22.0 (SPSS Corp., Chicago, IL, USA) was used to perform the statistical analysis. PFS and OS survival curves were generated using GraphPad Prism (Version 5.0; GraphPad Software, San Diego, CA, USA).

Table 2 Efficacy of first-line afatinib therapy (total $N = 90$)

	N (%)
Complete response (CR)	0
Partial response (PR)	57 (63.3%)
Stable disease (SD)	21 (23.3%)
Progressive disease (PD)	12 (13.3%)
Objective response rate (ORR)	63.3%
Disease control rate (DCR)	86.7%
Median PFS (months) (All)	17.3 (95% CI, 12.07–22.53)
Median OS (months) (All)	28.5 (95% CI, 20.22–36.77)
Median PFS with different EGFR mutations (months)	
G719X alone	24.9 (95% CI, 12.17–32.63)
S768I alone	12.3 (95% CI, 9.70–14.90)
L861Q alone	15.6 (95% CI, 5.80–18.97)
Compound mutation	13.1 (95% CI, 7.23–22.53)

PFS progression-free survival, *EGFR* epidermal growth factor receptor

3 Results

3.1 Baseline Demographic and Treatment Information of the Study Patients

The baseline demographic and treatment information of the study patients is summarized in Table 1. The histological diagnosis of all 90 patients included in this study was adenocarcinoma (100%). Of the EGFR mutations in the

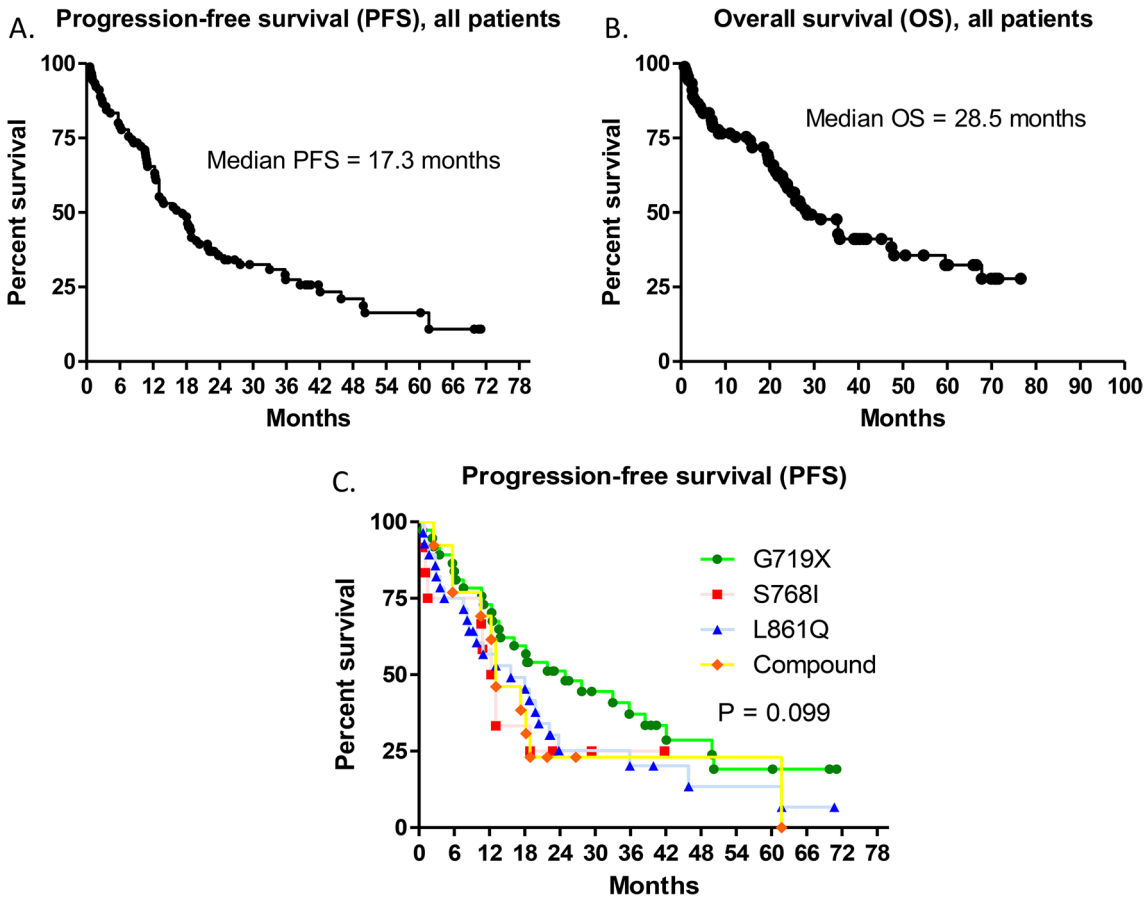


Fig. 2 The efficacy of first-line aftinib treatment in this study. **A** The median progression-free survival (PFS) with first-line afatinib in all study patients. **B** The median overall survival (OS) with first-line afatinib in all studies. **C** The median PFS of first-line afatinib in patients with different uncommon EGFR mutations

90 patients, 37 (41.1%) involved G719X alone, 12 (13.3%) involved S768I alone, 28 (31.1%) involved L861Q alone, and the remaining 13 (14.5%) were compound mutations. Of the 13 patients with compound mutations, five had G719X combined with S768I, five had G719X combined with L861Q, and the other three had S768I combined with L861Q. Sixty (66.7%) patients were treated with afatinib at a starting dose of 40 mg, and 24 (26.7%) patients had dose de-escalation.

Sixty-nine (76.7%) patients in this study had progressive disease following first-line afatinib therapy, and the subsequent treatment information is shown in Supplementary Table S1 (Online Supplementary Material (OSM)). In all, 29 patients underwent tissue rebiopsy or ctDNA testing for secondary T790M mutations after progressive disease following first-line afatinib treatment; the positive rate of T790M mutation was 27.6%. All patients with a T790M mutation received third-generation EGFR-TKIs, either osimertinib or some other drug, in clinical trials. The patients were divided into the G719X mutation group (34 (37.8%)) and the group without the G719X mutation (35 (38.9%)) for analysis. No significant difference was found in tissue rebiopsy, circulating tumor (ct)-DNA after secondary T790M tests, or the secondary T790M mutation rate between the two groups. One patient without the G719X mutation had a secondary T790M mutation and received the third-generation EGFR-TKI almonertinib (HS-10296) in a clinical trial. More patients in the G719X mutation group than in the group without the G719X mutation received second-line platinum-based doublet chemotherapy ($P = 0.0356$).

3.2 Efficacy of Afatinib Therapy

Of the 90 patients who received first-line afatinib treatment, 57 (63.3%) achieved PR, 21 (23.3%) had SD, and 12 (13.3%) had PD. The ORR and disease control rate (DCR) were 63.3% and 86.7%, respectively (Table 2).

The median PFS was 17.3 months (95% confidence interval (CI), 12.07–22.53; Fig. 2A), and the median OS was 28.5

Table 3 Cox regression of predictive factors associated with progression-free survival (PFS) after afatinib treatment

Variables	Patients *N* (%)	Median PFS (months)	Univariate analysis *p* value HR (95% CI)	Multivariate analysis	
				HR (95% CI)	*p* value
Age					
< 60 years	21	17.3	0.134		
≥ 60 years	69	18.4	0.662 (0.383−1.143)		
Gender					
Male	29	13.6	0.655		
Female	61	18.0	0.812 (0.488−1.351)		
ECOG PS					
0–1	67	21.9	< 0.001	0.133 (0.071−0.247)	< 0.001
≥ 2	23	5.7	0.181 (0.102−0.318)		
Smoking status					
Nonsmoker	78	17.3	0.574		
Former/current smoker	12	13.6	0.817 (0.402−1.662)		
EGFR mutations (with or without G719X)					
With G719X mutation	47	18.2	0.081	0.578 (0.355−0.941)	0.027
Without G719X mutation	43	13.1	0.654 (0.407−1.053)		
Metastatic sites					
Brain					
With brain metastasis	30	10.9	0.001	2.659 (1.540−4.608)	< 0.001
Without brain metastasis	60	18.9	2.435 (1.477−4.012)		
Bone					
With bone metastasis	37	13.1	0.038		
Without bone metastasis	53	18.9	1.658 (1.029−2.670)		
Liver					
With liver metastasis	10	9.8	0.006	2.202 (1.047−4.629)	0.037
Without liver metastasis	80	18.4	2.647 (1.330−5.272)		

PFS progression-free survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *HR* hazard ratio, *EGFR* epidermal growth factor receptor, *CI* confidence interval

Table 4 Comparison of characteristics between patients with and without G719X mutation

Variables	With G719X Total $N = 47$	Without G719X Total $N = 43$	P value
Sex			
Male	17	12	0.402
Female	30	31	
Age, years (mean ± SD)	67.3 ± 12.3	67.6 ± 9.9	0.697
ECOG PS			
0–1	35	32	0.996
≥ 2	12	11	
Smoking status			
Nonsmoker	40	38	0.649
Former/current smoker	7	5	
Stage			
IIIB	3	1	0.618
IV	44	42	
Brain metastasis	14	16	0.456
Bone metastasis	15	22	0.064
Liver metastasis	5	5	0.881

SD standard deviation, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

months (95% CI, 20.22–36.77; Fig. 2B) for all patients in this study. The median PFS among patients with different uncommon EGFR mutations who were treated with afatinib was analyzed, and the median PFS times were 24.9 months (95% CI, 12.17–32.63), 12.3 months (95% CI, 9.70–14.90), 15.6 months (95% CI, 5.80–18.97), and 13.1 months (95% CI, 7.23–22.53) for patients with the G719X mutation alone, the S768I mutation alone, the L861Q mutation alone, and compound mutations, respectively ($P = 0.099$ log-rank test, Fig. 2C). No statistical significance was recorded in the comparisons of PFS among different uncommon EGFR mutation groups.

3.3 Analysis of Predictive Factors Associated with Progression-Free Survival (PFS)

The median PFS according to different variables was analyzed using Cox regression, and the results are shown in Table 3. In the univariate analysis, baseline characteristics including poor performance (Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2) and brain, bone and liver metastases were significantly associated with shorter PFS. In the multivariate analysis, ECOG PS ≥ 2 and brain and liver metastases were independent predictors of unfavorable PFS. However, presence of the G719X mutation (alone + compound) was an independent predictor of favorable PFS (hazard ratio (HR) = 0.578; 95% CI, 0.355-0.941; $P = 0.027$).

Patients were divided into those with G719X mutations and those without G719X mutations to compare clinical variables, and no significant differences in clinical factors were noted between the two groups. More patients in the non-G719X mutation group than in the G719X mutation group had bone metastasis, but this difference was not statistically significant (Table 4).

3.4 Comparisons of PFS and Overall Survival (OS) Based on the Status of G719X Mutation and Brain Metastasis

The G719X mutation and brain metastasis were identified as independent predictive factors associated with PFS after first-line afatinib therapy; therefore, we performed a survival analysis of PFS with first-line afatinib therapy and OS based on these two factors. Patients with the G719X mutation tended to have a longer median PFS (18.2 vs. 13.1 months, $P = 0.069$) and median OS (47.4 vs. 23.0 months, $P = 0.051$) than those without the G719X mutation, but this difference was not statistically significant (Fig. 3A, C). Patients without brain metastasis had a significantly longer median PFS (18.9 vs. 10.9 months, $P < 0.001$) and median OS than those with brain metastasis.

3.5 First-Line Afatinib Treatment-Related Adverse Events (AEs)

First-line afatinib treatment-related AEs are summarized in Table 5. Among the 90 patients in this study, the most frequent AE was skin rash and acne (92.2%), followed by diarrhea (81.1%), paronychia (73.1%), and stomatitis (43.3%). Grade 3 AEs primarily included skin toxicity (11.1%) and diarrhea (10.0%). All grade 3 skin toxicities were controlled by reducing the afatinib dose and consulting with a dermatologist. All grade 3 diarrhea was controlled by reducing the afatinib dose, temporally interrupting afatinib therapy, and increasing the loperamide dose. One patient in this study experienced grade 3 fever that was managed by temporal interruption of afatinib therapy and hospitalization with intravenous administration of antibiotics. Fever did not return after afatinib treatment was resumed. Overall, the safety of afatinib in advanced lung adenocarcinoma patients with uncommon mutations is acceptable, and related AEs are manageable.

4 Discussion

The results of our study provide important information for clinical practice regarding afatinib therapy in patients with advanced lung adenocarcinoma harboring uncommon EGFR mutations (G719X/L861Q/S768I). We demonstrated that

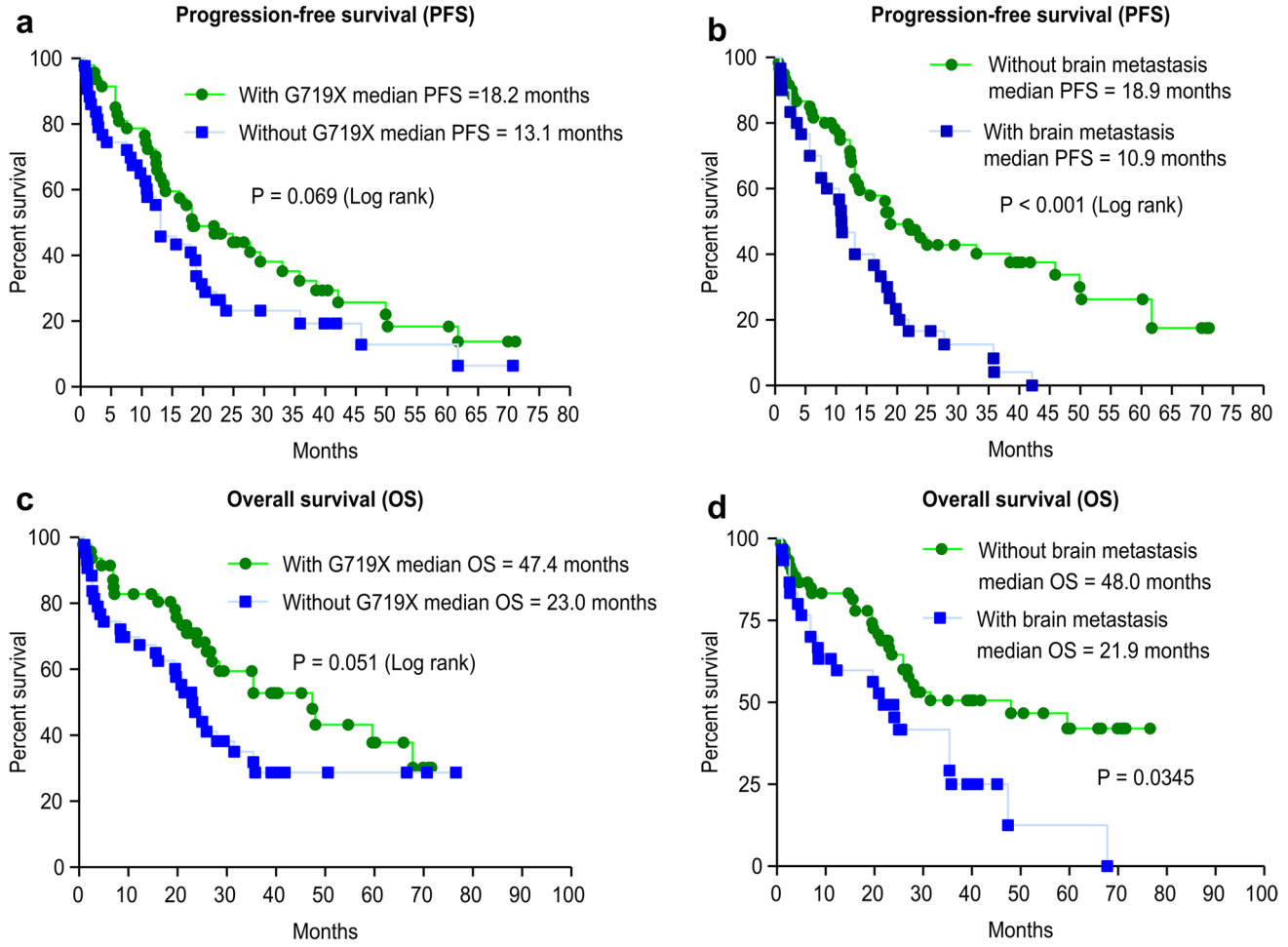


Fig. 3 Analysis of progression-free survival (PFS) and overall survival (OS) by Kaplan-Meier survival curves based on G719X mutation and brain metastasis status. **A** Comparison of the median PFS between patients with and without the G719X mutation (HR = 0.660; 95% CI, 0.407–1.072; $P = 0.069$). **B** Comparison of the median PFS between patients with and without brain metastasis (HR = 0.286; 95% CI, 1.62–5.04; $P < 0.001$). **C** Comparison of the median OS between patients with and without the G719X mutation (HR = 0.571; 95% CI, 0.326–1.002; $P = 0.051$). **D** Comparison of the median OS between patients with and without brain metastasis (HR = 2.90; 95% CI, 1.224–4.177; $P = 0.201$)

Table 5 Treatment-related adverse events (AEs) associated with afatinib treatment

Adverse events (AEs)	All, $n = 90$	Grades 1–2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Skin rash/acne	83 (92.2%)	73 (81.1%)	10 (11.1%)	0
Paronychia	65 (72.2%)	64 (66.7%)	1 (1.1%)	0
Diarrhea	73 (81.1%)	64 (66.7%)	9 (10.0%)	0
Stomatitis	39 (43.3%)	38 (42.2%)	1 (1.1%)	0
Nausea or vomiting	20 (22.2%)	18 (20.0%)	2 (2.2%)	0
Increased liver transaminases	7 (7.8%)	7 (7.8%)	0	0
Fever	1 (1.1%)	0	1 (1.1%)	0

first-line afatinib had an ORR of 63.3% and resulted in a PFS of 17.3 months. We found that ECOG PS ≥ 2 and brain and liver metastases were independent factors associated with unfavorable PFS, while the G719X mutation was independently associated with better PFS. The safety of afatinib was acceptable, and most AEs were manageable in this study.

A previous study by Chiu et al. showed that patients with advanced lung adenocarcinoma harboring uncommon mutations (G719X/L861Q/S768I) responded to first-generation EGFR-TKIs, including gefitinib and erlotinib, and that the ORR and PFS with first-generation EGFR-TKI therapy were 41.6% and 7.7 months, respectively [16]. In the subgroup analysis of LUX-Lung serial clinical trials (LUX-Lung 2, 3 and 6 trials), afatinib was shown to be active in patients with G719X, L861Q, and S768I mutations (ORR of 50−100% and PFS of 8−15 months). In the same analysis, patients with T790M and exon 20 insertion mutations were shown to be less responsive to afatinib therapy [18]. Taken together, the second-generation EGFR-TKI afatinib has been suggested to be more effective than the first-generation EGFR-TKIs gefitinib and erlotinib for the treatment of advanced NSCLC with uncommon EGFR mutations (G719X/L861Q/S768I). However, Yang et al. reported high heterogeneity within the uncommon EGFR mutation subgroup in LUX-Lung serial clinical trials, and further research is needed to verify this hypothesis [18]. The third-generation EGFR-TKI osimertinib was approved for the treatment of T790M-mutated NSCLC based on the results of the AURA trial, which was conducted later than the LUX-Lung series [19, 20]. Although new drugs, including mobocertinib and amivantamab, have been approved for the treatment of advanced NSCLC with exon 20 insertion mutations, more studies are needed to explore the efficacy of both drugs [21].

Two previous studies conducted by Yang et al. established the G719X, L861Q and S768I mutations as major uncommon mutations and demonstrated that afatinib treatment resulted in an ORR of approximately 60% and a time to treatment failure (TTF) of 10−12 months in patients with major uncommon mutations [22, 23]. Two other previous studies showed that first-line afatinib had an ORR of 50% and a TTF of 13.2−20.3 months in NSCLC patients with major uncommon mutations [24, 25]. The results of our study are compatible with those of the four previous studies. Although the patient number included in the two studies by Yang et al. was larger than that in our study, our study provided more clinical information, such as performance status and metastatic sites, in patients with major uncommon mutations. The four previous studies also did not provide clinical information related to resistance to first-line afatinib therapy, such as the presence of secondary T790M mutations and treatments following first-line afatinib. In our study, patients with the G719X mutation had the longest PFS with first-line afatinib therapy, whereas those with the S768I mutation had the longest TTF in the two previous studies by Yang et al., while the L861Q mutation resulted in the longest TTF in the study by Li et al. [22–24]. These differences may need to be verified in future studies.

Previous studies have shown that patients with EGFR-mutated NSCLC with baseline liver and brain metastases had shorter PFS after EGFR-TKI therapy and unfavorable outcomes [15, 24, 26–28]. Our study identified that patients with liver metastasis had shorter PFS than those without liver metastasis, which is consistent with findings in the study by Li et al. [24]. In the study by Li et al., patients with baseline brain metastasis tended to have a shorter TTF with afatinib therapy, but the differences between that study and our study were not statistically significant. The number of patients with baseline brain metastasis in the study by Li et al. was much smaller than that in our study (12 and 30, respectively), and the small number of patients may be the reason why statistical significance was not achieved.

The results of this study showed that patients with the G719X mutation had better outcomes than patients with major uncommon mutations, which suggests that afatinib therapy alone can be a standard first-line treatment for advanced NSCLC harboring the G719X mutation in the absence of concern about tolerance or other contraindications. The patients with the G719X mutation in this study tended to have longer OS than those without the G719X mutation. A previous study reported that advances in systemic therapy subsequent to first-line therapy improved OS in advanced NSCLC patients [29]. In addition, previous studies have shown that administration of subsequent chemotherapy after acquired resistance to front-line EGFR-TKIs in EGFR-mutated NSCLC contributes to an improvement in OS [30, 31]. Our data showed that significantly more patients in the G719X mutation group received subsequent platinum-based doublet chemotherapy than those in the group without the G719X mutation. Taken together, these results revealed that patients with the G719X mutation tended to have longer OS than those without the G719X mutation. Bevacizumab is an antiangiogenic agent that targets vascular endothelial growth factor (VEGF) and has been widely used in the treatment of advanced nonsquamous cell carcinoma. According to previous studies, when given in combination with EGFR-TKIs, including afatinib and erlotinib, bevacizumab has been shown to synergize with those EGFR-TKIs [32–34]. In addition, bevacizumab combined with EGFR-TKIs was shown to improve brain metastasis control and to reduce the occurrence of brain metastasis progression in patients with metastatic EGFR-mutated NSCLC [32–34]. Therefore, bevacizumab combined with afatinib can be considered a therapeutic strategy for major uncommon EGFR-mutated lung adenocarcinoma in patients without the G719X mutation or in those with baseline brain and liver metastases.

A secondary EGFR-T790M point mutation accounts for most of the mechanism of acquired resistance to first-line afatinib therapy in patients with common EGFR-mutated NSCLC who receive first-line afatinib therapy (ranging from 30% to 50%) [35, 36]. Although the use of liquid biopsy or tissue rebiopsy has been suggested for the detection of

secondary T790M mutation after resistance to first-/second-generation EGFR-TKIs in clinical practice [37, 38], less than half of patients who experience progressive disease following first-line afatinib in this study underwent tissue rebiopsy or ctDNA testing for secondary EGFR-T790M mutations. Previous studies have shown that liquid biopsy has a 30% false-negative rate and that a tissue biopsy is necessary to determine the presence or absence of secondary T790M mutations [37, 39]. In addition, liquid biopsy was performed in patients with primary common EGFR mutations (exon 19 deletion and L858R) but not in those with uncommon mutations [38, 39]. The cost of liquid biopsy is also not covered by national reimbursement in Taiwan [39, 40]. In previous studies, some patients did not receive tissue rebiopsy because of patient apprehension, unapproachable tumor sites and economic concerns [39]. The third-generation EGFR-TKI osimertinib was approved by the US Food and Drug Administration (FDA) in November 2015 and has been covered by national reimbursement in Taiwan since April 2020 [39, 40]. The patients included in this study were treated at any time from May 2014 to June 2021. Taken together, these findings may explain why less than half of the patients in this study underwent tissue rebiopsy or ctDNA testing for secondary EGFR-T790M mutations. To our knowledge, we are the first to show data for secondary EGFR-T790M mutations in advanced lung adenocarcinoma patients harboring uncommon EGFR mutations who acquired resistance to first-line afatinib therapy. In this study, the secondary EGFR-T790M mutation rate was 27.6%, which is slightly lower than that in the common EGFR mutation population reported in previous studies [23, 36].

Based on the results of this study, tissue rebiopsy or ctDNA testing for secondary EGFR-T790M mutations is recommended for advanced lung adenocarcinoma patients harboring major uncommon EGFR mutations because a proportion of patients could receive subsequent osimertinib therapy. Osimertinib is currently the preferred therapy for advanced EGFR-mutated patients with secondary EGFR-T790M mutations after they acquire resistance to first-line first- and second-generation EGFR-TKIs [19, 20].

The efficacy of osimertinib for the treatment of NSCLC harboring uncommon EGFR mutations was investigated in 3 recent studies, and osimertinib was shown to result in an ORR of 45−60% and a median PFS of 8−12 months in TKI-naïve patients [41–43]. The numbers of patients with major uncommon mutations in the three studies were limited (32 in Cho et al., 45 in Pizzutilo et al. and 30 in Bar et al.), and, therefore, more studies are needed to verify the efficacy of osimertinib in advanced NSCLC patients with major uncommon mutations [41–43]. In a recent study (UNICORN study), no S768I-mutated NSCLC patient was included in the study [43]. In our study, the secondary T790M test (liquid and tissue rebiopsies) rate was limited and was in agreement with previous real-world studies [23, 36, 44], and moreover, the proportion of patients who did not receive subsequent osimertinib was also in line with our findings. The limited secondary T790M test rates may suggest that osimertinib should be administered as a front-line therapy rather than as a subsequent treatment with first-/second-generation EGFR-TKIs in patients with EGFR-mutated NSCLC. Compared with the three previous studies (KCSG-LU15-09, ARTICUNO and UNICORN studies) [41–43], the results of our study (ORR of 63.3% and median PFS of 17.3 months) suggest that the efficacy of afatinib is not inferior to that of osimertinib when used as a first-line therapy for advanced NSCLC patients with major uncommon mutations. Currently, no subsequent targeted therapy for EGFR-mutated NSCLC patients with resistance to osimertinib is effective because of the complex acquired resistance mechanism, including small-cell lung cancer (SCLC) transformation and other genetic alterations [45, 46]. Therefore, afatinib is one of the optimal first-line therapies for advanced NSCLC with major uncommon mutations.

Afatinib treatment-related side effects were recorded in this study, and the toxicity profile is similar to profiles in previous clinical trials [9, 10, 18]. Skin toxicity, diarrhea, paronychia, and stomatitis were the most common AEs induced by afatinib. Dose de-escalation was recorded in 24 patients (26.7%) in this study. A previous study suggested that afatinib dose adjustments are acceptable in clinical practice and do not affect the efficacy of afatinib in advanced EGFR-mutated NSCLC patients [47].

Some limitations of this study should be clarified. The study population included only East Asian individuals, and thus, future studies are needed to verify the efficacy of afatinib for advanced lung adenocarcinoma patients harboring major uncommon mutations in other ethnic groups. Another second-generation EGFR-TKI, dacomitinib, has been approved as a first-line treatment of advanced NSCLC with common EGFR mutations due to its promising efficacy, as shown in pivotal clinical trials [11]. The results of this study are not applicable to dacominitinib used to treat advanced lung adenocarcinoma patients with major uncommon mutations. In addition, the primary EGFR mutations in this study were detected by polymerase chain reaction (PCR)-based single gene sequencing and not by next-generation sequencing (NGS), which can detect more known and unknown genetic alterations. Some genetic mutations, such as those in MET and TP53, concurrently appear in EGFR-mutated NSCLC and negatively alter the efficacy of EGFR-TKI therapy and survival [44, 48, 49]. We did not find other unknown concurrent genetic alterations that affect the efficacy of afatinib therapy.

5 Conclusion

Afatinib is an effective and safe therapy for untreated advanced lung adenocarcinoma harboring uncommon EGFR mutations (G719X/L861Q/S768I), and its efficacy is more prominent in patients with the G719X mutation. Baseline brain and liver metastases were associated with shorter PFS after first-line afatinib therapy, and additional combination therapy can be considered for these patients.

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Declarations

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Conflict of interest All authors in this work declare no conflicts of interest.

Ethics approval This retrospective research was approved by the institutional review board (IRB) (no. 202201170B0) of Chang Gung Medical Foundation. The IRB of the Chang-Gung Medical Foundation granted a waiver of informed consent given the retrospective nature of this study. All study procedures were implemented in accordance with the Declaration of Helsinki. No identifiable information of the study subjects, such as personal IDs and birthdays, was presented in this paper.

Availability of data and materials The datasets generated and analyzed during this study are not publicly available because of local regulations regarding medical confidentiality.

Authorship and author contributions All authors of this paper meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and have approved the final manuscript.

Conception and design of the study: PCH and CCW; writing of the manuscript: SHL and PCH; acquisition of the study data (information of the study patients): PCH, SHL, LCC, CSL, CEW, SCHK, JSJ, ACCH, SHL, HWK, CTY, and CCW; analysis and interpretation of the data: PCH, SHL, LCC, CSL, CEW, ACCH, SCHK; validation of the data: PCH, LCC, and CCW; supervision of study work (review and revision of the study): PCH, CTY, and CCW; administrative and funding support: PCH and CCW.

Code availability Not applicable.

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