ORIGINAL RESEARCH ARTICLE

The Difference in Clinical Outcomes Between Osimertinib and Afatinib for First-Line Treatment in Patients with Advanced and Recurrent *EGFR*-Mutant Non-Small Cell Lung Cancer in Taiwan

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Abstract

Background Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors are the standard first-line treatment for patients with advanced and recurrent *EGFR*-positive non-small cell lung cancer.

Objective The main objective of the present study was to compare the clinical efficacies between osimertinib and afatinib as first-line treatment in patients with *EGFR*-mutant non-small cell lung cancer.

Methods We retrospectively analyzed patients with advanced and recurrent non-small cell lung cancer who harbored an exon 19 deletion or an exon 21 L858R mutation and were being given either osimertinib or afatinib as first-line treatment from January 2018 to December 2020.

Results A total of 128 patients were selected for this study. The osimertinib group included 47 patients, while 81 patients received afatinib. The median follow-up time was 20.1 months in the osimertinib group and 22.7 months in the afatinib group. The median progression-free survival was 18.8 months and 13.1 months in the osimertinib and afatinib groups, respectively (hazard ratio 0.75 [95% confidence interval 0.48–1.18]). The median overall survival was not reached in the osimertinib group and was 41.7 months in the afatinib group (hazard ratio 0.79 [95% confidence interval 0.36–1.72]). In patients without brain metastasis, the median progression-free survival was 17.9 months and 17.2 months in the osimertinib and afatinib groups, respectively (hazard ratio 1.02 [95% confidence interval 0.56–1.85]). In patients with brain metastasis at baseline, the median progression-free survival was 22.1 months in the osimertinib group, and 10.9 months in the afatinib group (adjusted hazard ratio 0.45 [95% confidence interval 0.21–0.96]).

Conclusions Our research demonstrates that there was no strong evidence showing that patients taking osimertinib as first-line treatment experienced longer median progression-free survival and overall survival than patients treated with afatinib. However, there was a statistical significance revealing that osimertinib provided better median progression-free survival than afatinib in patients with brain metastasis at baseline.

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retrospective studies have also confirmed the results taken from clinical trials that showed that patients with advanced or recurrent *EGFR*-mutant NSCLC receiving second-generation EGFR-TKIs experienced better median PFS than those treated with first-generation EGFR-TKIs [10–12]. Furthermore, the FLAURA study proved that patients with treatment-naïve advanced NSCLC with *EGFR* mutations receiving the third-generation EGFR-TKI osimertinib experienced significantly better median PFS and OS than those treated with gefitinib and erlotinib [13, 14].

The FLAURA study provides truly promising data for treatment with first-line EGFR-TKIs. However, the GioTag study also showed a good median time on treatment and OS in patients with *EGFR*-mutant NSCLC undergoing sequential afatinib and osimertinib treatment [15]. Therefore, the difference in the clinical outcomes between second-generation and third-generation EGFR-TKIs for first-line treatment has become an important issue. Although clinical trials for comparing the efficacy of second-generation and third-generation EGFR-TKIs are ongoing (NCT04413201, jRCTs031190221), some retrospective studies have been published that demonstrate that there was no significant difference in either median PFS or time to discontinuation of TKI treatment between afatinib and osimertinib [16, 17]. However, the median follow-up time was not equal between the two groups in these studies, and the study population was relatively small in one of the two studies. Thus, we conducted the present study in order to compare the clinical outcomes between osimertinib and afatinib for patients with advanced and recurrent NSCLC with *EGFR* mutation within the Taiwanese population.

Key Points

Patients with advanced epidermal growth factor receptor mutant non-small cell lung cancer undergoing osimertinib treatment did not experience significantly longer median progression-free survival and overall survival than those being treated with afatinib.

In patients with non-small cell lung cancer with brain metastasis, patients receiving osimertinib experienced statistically better median progression-free survival than those taking afatinib.

There was no difference regarding median progression-free survival in patients without brain metastasis between the osimertinib and afatinib groups.

1 Introduction

Currently, the treatment strategy for patients with advanced non-small cell lung cancer (NSCLC) is personalized and depends on the results of molecular biological tests. Previous studies have shown that patients with lung adenocarcinoma with an actionable oncogenic driver mutation who are receiving matched targeted therapy will experience longer overall survival (OS) [1]. In Asia, approximately 50–60% of patients with lung adenocarcinoma harbor epidermal growth factor receptor (EGFR) mutations [2, 3]. Fortunately, previous clinical trials have demonstrated that patients with advanced NSCLC with a sensitizing *EGFR* mutation who were undergoing first-generation and second-generation EGFR-tyrosine kinase inhibitor (TKI) treatment experienced better progression-free survival (PFS), while exhibiting fewer adverse effects than those patients receiving platinum-based chemotherapy [4–6]. At present, EGFR-TKIs are the standard first-line treatment for patients with advanced *EGFR*-positive NSCLC.

Recently, certain clinical trials have been conducted to compare the clinical efficacies between different generation EGFR-TKIs. The LUX-Lung 7 study, a phase IIB trial, demonstrated that patients with advanced *EGFR*-mutant NSCLC receiving afatinib, a second-generation EGFR-TKI as first-line treatment, experienced longer median PFS than those receiving gefitinib, a first-generation EGFR-TKI [7]. The ARCHER-1050 study, a phase III trial, showed that dacomitinib, a second-generation EGFR-TKI, provided longer median PFS and OS than gefitinib in patients with treatment-naive *EGFR*-mutated NSCLC without the occurrence of any central nervous system metastasis [8, 9]. Real-world

2 Material and Methods

2.1 Study Design and Patients

This study was a retrospective, single-center, observational study performed at Taichung Veterans General Hospital in Taiwan. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan, with written informed consent documents for genetic testing and clinical data records obtained from all patients (No. CF12019).

Patients diagnosed with lung cancer between January 2018 and December 2020 were included in the study. All patients were required to fulfill the following inclusion criteria: a diagnosis of histologically and cytologically confirmed NSCLC, recurrence or stage IV lung cancer according to the 8th edition of the American Joint Committee for Cancer staging system [18], harboring a *EGFR* exon 19 deletion or exon 21 L858R point mutation, and receiving first-line treatment involving either osimertinib or afatinib. Patients

were excluded if they had *EGFR* mutations other than the exon 19 deletion or the exon 21 L858R point mutation, were taking EGFR-TKIs other than osimertinib and afatinib, or had undergone combined treatment with either chemotherapy or anti-angiogenesis agents. Computed tomography of the chest of each patient was performed every 3 months in order to qualify for National Health Insurance reimbursement. Treatment response to osimertinib and afatinib was evaluated through the Response Evaluation Criteria in Solid Tumors (Version 1.1) [19].

Each patient's demographic and clinical data, including age, sex, smoking status, Eastern Cooperative Oncology Group Performance Status (ECOG PS), clinical stage, status of brain metastasis at baseline, subtype of *EGFR* mutation at baseline, best response to EGFR-TKIs, and the PFS and OS of osimertinib and afatinib, were all recorded for analysis. We defined PFS as the time period from the first dose of EGFR-TKI to either progression or death, while the definition of OS was determined as the time period from the first dose of EGFR-TKI to death.

2.2 *EGFR* Mutation Test

EGFR mutation status in tumor tissue was tested by either the cobas® EGFR Mutation Test version 2 (Roche Molecular Systems, Pleasanton, CA, USA) or matrix-assisted laser desorption ionization-time of flight mass spectrometry. The method for matrix-assisted laser desorption ionization-time of flight mass spectrometry was based upon our previous studies [3, 20–22]. The detection procedure was performed according to the user's manual of the MassARRAY® System (Cat. No. 10411, SEQUENIM, San Diego, CA, USA acquired by Agena Bioscience, http://agenabio.com/, San Diego, CA, USA in 2014). Extracted DNA was used to perform serial biochemical reactions, including 40 cycles of PCR; SAP (Shrimp Alkaline Phosphatase) treatment and 200 cycles of signal nucleotide extension reaction by using the iPLEX Pro® reagent kit containing Sequenase, iPLEX Pro® reaction mixture, and home-designed probes. After the SpectroClean Resin clean-up, samples were loaded onto the matrix of the SpectroCHIP by Nanodispenser (Matrix) and then analyzed using the Bruker Autoflex matrix-assisted laser desorption ionization-time of flight mass spectrometry. Data were collected and analyzed by MassARRAYTyper (Version 4) software (Agena Bioscience).

2.3 Statistical Analyses

We used the Fisher's exact test to assess the differences in patient characteristics and demographic data between the osimertinib and afatinib groups. Survival curves for PFS and OS were estimated through the Kaplan–Meier method. The Cox proportional hazard model was used to evaluate the
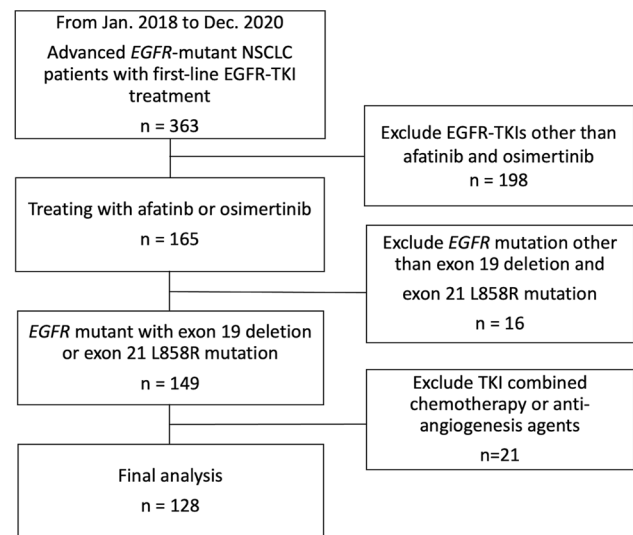
Fig. 1 Flowchart of patient collection. *EGFR* epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *TKI* tyrosine kinase inhibitor

univariate and multivariate analyses for survival times of PFS and OS. All statistical tests were done with SPSS 23.0 (SPSS Inc., Chicago, IL, USA) software. Two-tailed tests and p values < 0.05 for significance were used.

3 Results

3.1 Clinical and Demographic Baseline Characteristics of Patients Treated with Osimertinib or Afatinib as First-Line Treatment

A total of patients with 128 stage IV and recurrent NSCLC who had been treated with either osimertinib or afatinib as first-line treatment were included in our analysis. The osimertinib group included 47 patients, while 81 patients received afatinib. The flowchart of patient collection is demonstrated in Fig. 1. In the osimertinib group, 21 (44.7%) patients were aged ≥ 65 years, while in the afatinib group, 32 (39.5%) patients were aged ≥ 65 years. In the osimertinib group, 15 (31.9%) patients were male, while in the afatinib group, 40 (49.4%) patients were male. Most patients were nonsmokers in both groups, [33 (70.2%) in the osimertinib group, 52 (64.2%) in the afatinib group]. In the osimertinib group, 43 (91.5%) had an ECOG PS of 0–1, while in the afatinib group, 73 (90.1%) patients had an ECOG PS of 0–1. The majority of patients were stage IV in both the osimertinib and afatinib groups (83% vs 81.5%). Twenty-one (44.7%) patients with osimertinib as first-line treatment had brain metastasis at baseline, with 28 (34.6%) patients in the afatinib group experiencing the same. Regarding baseline

EGFR mutation status, 26 (55.3%) patients harbored the exon 19 deletion in the osimertinib group, while similarly 35 (43.2%) patients did as well in the afatinib group. Based on the Fisher's exact test, no significant differences were found between the osimertinib and afatinib groups regarding age, sex, smoking status, ECOG PS, clinical stage, brain metastasis at baseline, or baseline *EGFR* mutation status. The detailed information surrounding patient characteristics is shown in Table 1.

3.2 Clinical Efficacy of Patients with Osimertinib or Afatinib as First-Line Treatment

The date of the end of the follow-up was 22 December, 2021. The median follow-up time was 20.1 months in the osimertinib group and 22.7 months in the afatinib group. In the osimertinib group, the overall objective response rate (ORR) and disease control rate (DCR) was 66.0% and 85.1%, respectively. Amongst patients undergoing afatinib treatment, the ORR and DCR was 60.5% and 92.6%, respectively. The median PFS was 18.8 months (95% confidence interval [CI] 12.3–24.0) in the osimertinib group (*n* = 47)

and 13.1 months (95% CI 7.7–18.5) in the afatinib group (*n* = 81) [log rank, *p* = 0.208; hazard ratio (HR) 0.45 (95% CI 0.21–0.96)] (Fig. 2A). The median OS was not reached in the osimertinib group but was 41.7 months (95% CI 29.7–53.7) in the afatinib group [log rank, *p* = 0.552; HR 0.79 (95% CI 0.36–1.72)] (Fig. 2B). Regarding the subtype of *EGFR* mutation at baseline, in patients with the exon 19 deletion, the median PFS was 31.0 months (95% CI 15.1–46.9) in the osimertinib group (*n* = 26) and 17.2 months (95% CI 9.2–25.2) in the afatinib group (*n* = 35) [log rank, *p* = 0.284; HR 0.68 (95% CI 0.33–1.39)] (Fig. 3A). Amongst those with the exon 21 L858R point mutation, the median PFS was 17.4 months (95% CI 6.4–28.4) in the osimertinib group (*n* = 21) and 10.2 months (95% CI 8.5–11.9) in the afatinib group (*n* = 46) [log rank, *p* = 0.593; HR 0.85 (95% CI 0.48–1.53)] (Fig. 3B).

3.3 Clinical Efficacy of Osimertinib and Afatinib in Patients Without Brain Metastasis at Baseline

A total of 79 patients did not have brain metastasis at baseline. The median PFS was 17.9 months (95% CI 15.1–20.7)

**Table 1** Clinical characteristics and demographic data

Characteristics	EGFR-TKI		
	Afatinib, *n* (%)	Osimertinib, *n* (%)	*p* value[a]
Age, years			0.582
≥ 65	32 (39.5)	21 (44.7)	
< 65	49 (60.5)	26 (55.3)	
Sex, *n* (%)			0.065
Male	40 (49.4)	15 (31.9)	
Female	41 (50.6)	32 (68.1)	
Smoking status, *n* (%)			0.562
Non-smokers	52 (64.2)	33 (70.2)	
Former or current-smokers	29 (35.8)	14 (29.8)	
ECOG PS, *n* (%)			1
0–1	73 (90.1)	43 (91.5)	
2–3	8 (9.9)	4 (8.5)	
Stage, *n* (%)			0.223
Post-operation recurrence	15 (18.5)	8 (17.0)	
Stage 4A	21 (25.9)	19 (40.4)	
Stage 4B	45 (55.6)	20 (42.6)	
Brain metastasis at baseline, *n* (%)			0.265
Yes	28 (34.6)	21 (44.7)	
No	53 (65.4)	26 (55.3)	
Baseline *EGFR* mutation status, *n* (%)			0.229
Exon 19 deletions	35 (43.2)	26 (55.3)	
Exon 21 L858R	46 (56.8)	21 (44.7)	

EGFR epidermal growth factor receptor, *ECOG PS* Eastern Cooperative Oncology Group performance status, *TKI* tyrosine kinase inhibitor

[a]By Fisher's exact test
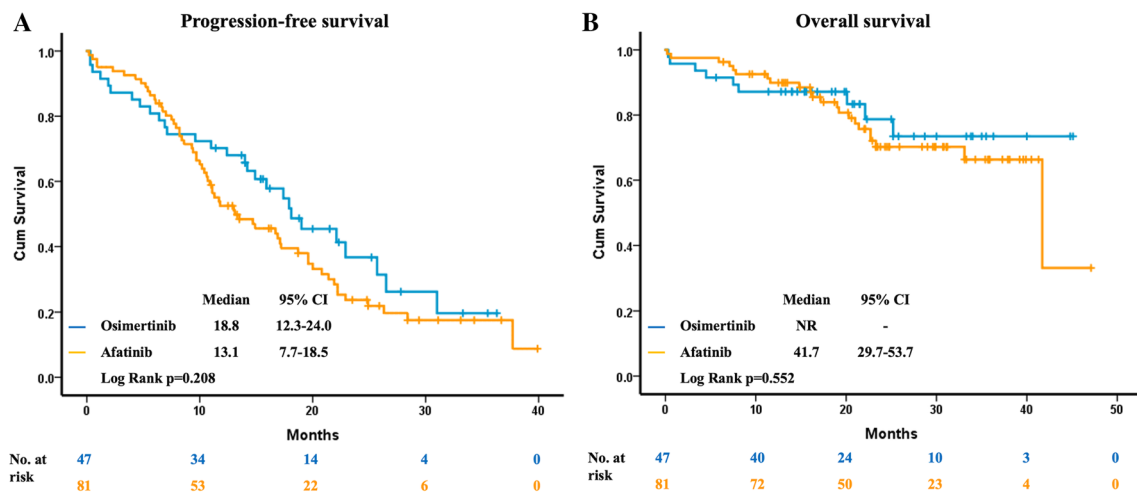
Fig. 2 Survival curve of patients with osimertinib and afatinib as first-line treatment. **A** Progression-free survival. **B** Overall survival. *CI* confidence interval, *Cum survival* cumulative survival, *NR* not reached
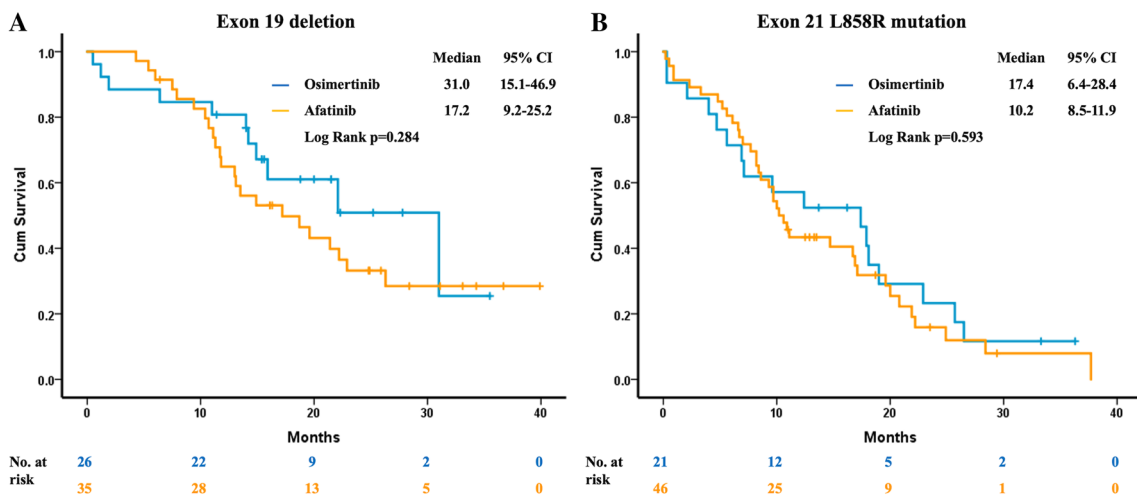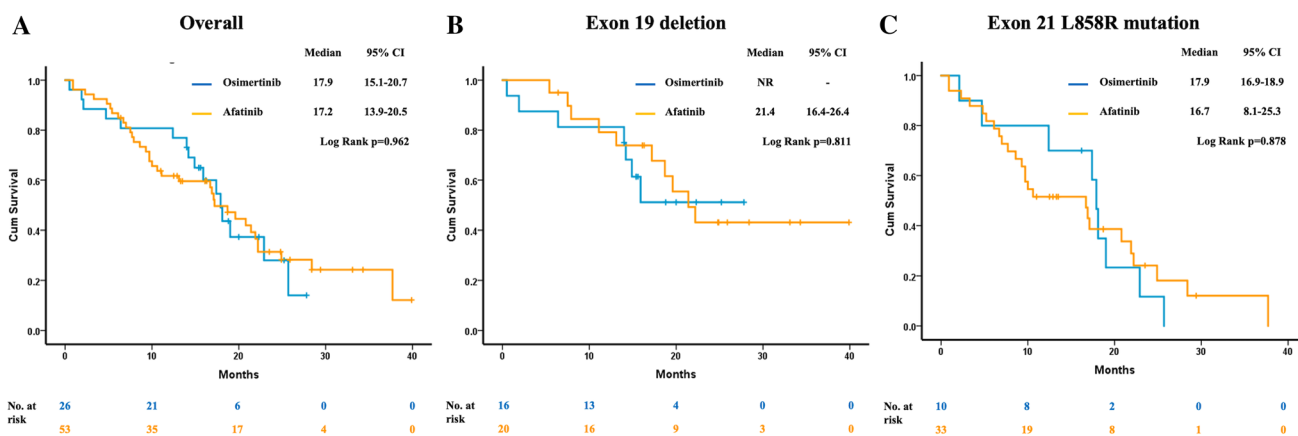

Fig. 3 Progression-free survival of osimertinib and afatinib in patients with different subtypes of epidermal growth factor receptor mutation. **A** Exon 19 deletion. **B** Exon 21 L858R point mutation. *CI* confidence interval, *Cum survival* cumulative survival

in the osimertinib group and 17.2 months (95% CI 13.9–20.5) [*n* = 26] in the afatinib group (*n* = 53) [log rank, *p* = 0.962; HR 1.02 (95% CI 0.56–1.85)] (Fig. 4A). During the follow-up period, four patients (15.4%) in the osimertinib group and 12 (22.6%) in the afatinib group experienced a new development of brain metastasis. Amongst patients with the exon 19 deletion, the median PFS was not reached in the osimertinib group (*n* = 16) but was 21.4 months (95% CI 16.4–26.4) in the afatinib group (*n* = 20) [log rank, *p* = 0.811; HR 1.13 (95% CI 0.42–3.00)] (Fig. 4B). In patients harboring the exon 21 L858R point mutation, the median PFS was 17.9 months (95% CI 16.9–18.9) in the osimertinib group (*n* = 10) and 16.7 months (95% CI 8.1–25.1) in the afatinib group (*n* = 33) [log rank, *p* = 0.878; HR 1.06 (95% CI 0.49–2.31)] (Fig. 4C).

3.4 Clinical Efficacy of Osimertinib and Afatinib in Patients with Brain Metastasis at Baseline

A total of 49 patients had brain metastasis at baseline. The median PFS was 22.1 months (95% CI 2.1–42.1) in the osimertinib group (*n* = 21) and 10.9 months (95% CI 9.7–12.1) in the afatinib group (*n* = 28) [log rank, *p* = 0.045] (Fig. 5A). The multivariate analysis showed that osimertinib provided statistically significantly longer PFS than afatinib in patients with brain metastasis [HR 0.45 (95% CI 0.21–0.96), *p* = 0.038]. Concerning different subtypes of *EGFR* mutation, in patients having the exon 19 deletion, the median PFS was 31.0 months (95% CI 14.7–47.3) in the osimertinib group (*n* = 10) and 11.8 months (95% CI 9.7–13.9) in the afatinib group (*n* = 15) [log rank, *p* = 0.088;

Fig. 4 Progression-free survival of osimertinib and afatinib in patients without brain metastasis. **A** Overall population. **B** Patients with exon 19 deletion. **C** Patients with exon 21 L858R point mutation. *CI* confidence interval, *Cum survival* cumulative survival, *NR* not reached
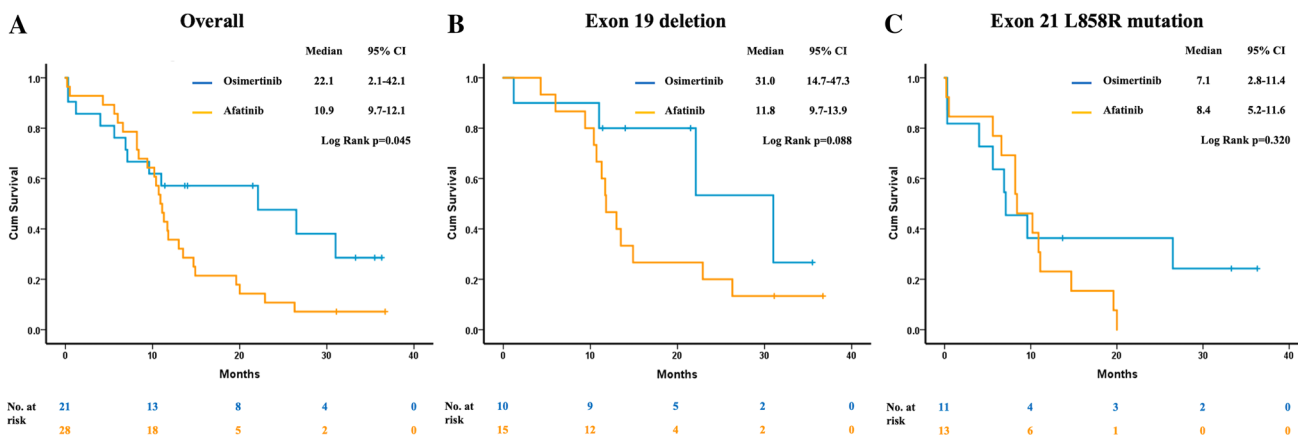
Fig. 5 Progression-free survival of osimertinib and afatinib in patients with brain metastasis. **A** Overall population. **B** Patients with exon 19 deletion. **C** Patients with exon 21 L858R point mutation. *CI* confidence interval, *Cum survival* cumulative survival

HR 0.39 (95% CI 0.13–1.20)] (Fig. 5B). Amongst patients harboring the exon 21 L858R point mutation, the median PFS was 7.1 months (95% CI 2.8–11.4) in the osimertinib group (*n* = 11) and 8.4 months (95% CI 5.2–11.6) in the afatinib group (*n* = 13) [log rank, *p* = 0.320; HR 0.63 (95% CI 0.25–1.60)] (Fig. 5C).

3.5 Univariate and Multivariate Analyses for PFS and OS

The univariate analysis revealed that patients with stage IVB disease (*n* = 65) had a worse PFS than patients with recurrence disease (*n* = 23), with an HR of 2.50 (95% CI 1.33–4.72; *p* = 0.005). Patients harboring the exon 19 deletion (*n* = 61) experienced a statistically lower risk of progressive disease than patients with the exon 21 L858R point mutation (*n* = 67), with an HR of 0.49 (95% CI 0.32–0.75; *p* = 0.001). The multivariate analysis confirmed both of the above results. Additionally, there was no strong evidence to

present that patients receiving osimertinib as first-line treatment had better PFS than patients taking afatinib with an HR of 0.75 (95% CI 0.48–1.18; *p* = 0.211) (Table 2).

Regarding OS, when compared with patients with recurrent disease, patients with stage IVB disease had a higher risk of death at a HR of 12.06 (95% CI 1.58–91.97; *p* = 0.016), with the multivariate analysis proving this result [HR 14.14 (95% CI 1.77–113.16); *p* = 0.013]. No statistical difference was found in any other factors, including age, sex, smoking status, ECOG PS, status of brain metastasis at baseline, subtype of *EGFR* mutation, or type of EGFR-TKI used (Table 3).

3.6 Subsequent Treatment After Progressive Disease to Afatinib and Osimertinib

Up until the end date of the follow-up period, 62 patients (76.5%) experienced progressive disease during afatinib treatment. Amongst them, 44 patients (44/62, 70.1%)

Table 2 Univariate and multivariate analyses of progression-free survival

Characteristics	HR (95% CI)[a]	p value	Adjusted HR (95% CI)[a]	p value
Age (years)				
< 65	Reference			
≥ 65	1.10 (0.72–1.67)	0.657		
Sex				
Female	Reference			
Male	1.03 (0.68–1.58)	0.883		
Smoking status				
C/FS	Reference			
NS	1.24 (0.80–1.94)	0.343		
ECOG PS				
2–3	Reference			
0–1	1.56 (0.68–3.59)	0.291		
Stage				
Recurrence	Reference			
Stage IVA	1.61 (0.81–3.20)	0.172		
Stage IVB	2.50 (1.33–4.72)	0.005	2.46 (1.26–4.82)	0.008
Brain metastasis at baseline				
Yes	Reference			
No	0.72 (0.47–1.10)	0.124		
Baseline *EGFR* mutation status				
Exon 21 L858R mutation	Reference			
Exon 19 deletion	0.49 (0.32–0.75)	0.001	0.45 (0.28–0.71)	0.001
EGFR-TKI				
Afatinib	Reference			
Osimertinib	0.75 (0.48–1.18)	0.211		

CI confidence interval, *C/FS* current/former-smokers, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *HR* hazard ratio, *NS* non-smoker, *TKI* tyrosine kinase inhibitor

[a]By Cox proportional hazard model

underwent re-biopsy, while 16 patients (16/44, 36.4%) harbored the Threonine 790 Methionine (T790M) mutation. Thirty-six patients (36/66, 58.1%) with or without T790M had received osimertinib after progressive disease occurred during afatinib treatment. Four patients (4/62, 6.5%) did not receive systemic therapy after afatinib treatment. In the osimertinib group, 28 patients (59.6%) experienced progressive disease during the follow-up period. Five patients (5/28, 17.9%) did not receive any systemic therapy after osimertinib treatment. The detailed information of sequential treatment is demonstrated in Table 4.

4 Discussion

The present research is the first study to investigate the difference in clinical efficacies between osimertinib and afatinib in a Taiwanese population. Our data have demonstrated that osimertinib as a first-line treatment established a trend showing a longer median PFS than afatinib in patients with advanced and recurrent NSCLC harboring the *EGFR* mutation in real-world practice. However, these results did not reach statistical significance. In a subgroup analysis, there was no difference regarding median PFS in patients without brain metastasis between the osimertinib and afatinib groups. Patients with brain metastasis receiving osimertinib as the first-line treatment experienced statistically better median PFS than those taking afatinib.

Afatinib, a second-generation EGFR-TKI, can interrupt the signal of the pan-Erb B family of receptors irreversibly [23]. The 50% inhibitory concentration of afatinib is lower than the 50% inhibitory concentration of first-generation EGFR-TKIs, including gefitinib and erlotinib, against *EGFR*-mutant cell lines in an in vitro study [24]. The clinical trial LUX-Lung 7 proved that patients with treatment-naive *EGFR*-mutant NSCLC undergoing afatinib treatment experienced longer median PFS than patients being treated with gefitinib [11.0 vs 10.9 months, HR 0.74 (95% CI 0.57–0.95), $p = 0.0178$] [7]. A prospective, phase IIIb, single-arm study of afatinib demonstrated that its clinical efficacies were

Table 3 Univariate and multivariate analyses of overall survival

Characteristics	HR (95% CI)[a]	p value	Adjusted HR (95% CI)[a]	p value
Age (years)				
< 65	Reference			
≥ 65	0.95 (0.46–1.98)	0.899		
Sex				
Female	Reference			
Male	1.18 (0.58–2.41)	0.653		
Smoking status				
C/FS	Reference			
NS	1.15 (0.54–2.47)	0.72		
ECOG PS				
2–3	Reference			
0–1	0.89 (0.27–2.94)	0.851		
Stage				
Recurrence	Reference			
Stage IVA	6.59 (0.79–54.83)	0.081	6.60 (0.80–54.71)	0.081
Stage IVB	12.06 (1.58–91.97)	0.016	14.14 (1.77–113.16)	0.013
Brain metastasis at baseline				
Yes	Reference			
No	0.61 (0.30–1.26)	0.182		
Baseline *EGFR* mutation status				
Exon 21 L858R mutation	Reference			
Exon 19 deletion	0.68 (0.33–1.41)	0.299		
EGFR-TKI				
Afatinib	Reference			
Osimertinib	0.79 (0.36–1.72)	0.553		

CI confidence interval, *C/FS* current/former-smokers, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *HR* hazard ratio, *NS* non-smoker, *TKI* tyrosine kinase inhibitor

[a]By Cox proportional hazard model

consistent with the results from clinical trials with a median PFS of 11.4 months in a population studied in China [25]. Huang et al. confirmed the phenomenon that afatinib reduced the risk of progression when compared with first-generation EGFR-TKIs [HR 0.73 (95% CI 0.57–0.94); $p =0.017$] in real-world practice [11]. Furthermore, real-world data from Poland and Canada also presented that afatinib provided a more favorable OS than first-generation EGFR TKIs [26, 27].

Osimertinib, a third-generation, irreversible, selective EGFR-TKI was developed to be active against the T790M mutation, a resistance mechanism of first-generation and second-generation EGFR-TKIs. Preclinical data have revealed that osimertinib could block signaling pathways and cellular growth in both cell lines through sensitizing the *EGFR* mutation and druggable *EGFR* mutation combined with T790M in vitro [24]. AURA 3, a phase III trial, demonstrated that osimertinib provided significantly better median PFS than standard platinum-based chemotherapy in patients with advanced NSCLC harboring the T790M mutation after

having acquired resistance to first-generation and second-generation EGFR-TKI treatment [10.1 vs 4.4 months, HR 0.30 (95% CI 0.23–0.41); $p < 0.001$] [28]. Our previous real-world data confirmed the clinical benefits of osimertinib in patients with T790M, where the median PFS and OS was 10.1 and 30.2 months, respectively [10]. In the FLAURA study, patients with treatment-naïve $EGFR^+$ NSCLC undergoing osimertinib treatment experienced longer median PFS than patients being treated with gefitinib and erlotinib [18.9 vs 10.2 months, HR 0.46 (95% CI 0.37–0.57); $p < 0.001$] [13]. Furthermore, osimertinib reduced the risk of death when compared with the control group [38.6 vs 31.8 months, HR 0.80 (95.05% CI 0.64–1.00); $p = 0.046$] [14].

Although osimertinib has become the preferred standard first-line treatment in patients with advanced NSCLC with a sensitizing *EGFR* mutation, sequential treatment with first-generation and second-generation TKIs followed by osimertinib have also provided attractive results. In the GioTag study, the median time on treatment with afatinib and sequential osimertinib was 27.7 months, with the median

Table 4 Information regarding sequential treatment

Sequential treatment	N (%)
Afatinib	62 (100)
Osimertinib	28 (45.2)
Pemetrexed	5 (8.1)
Platinum + pemetrexed	15 (24.2)
Platinum + pemetrexed + bevacizumab	2 (3.2)
Platinum + pemetrexed + bevacizumab + atezolizumab	1 (1.6)
Platinum + paclitaxel	1 (1.6)
Platinum + paclitaxel + bevacizumab	1 (1.6)
Platinum + paclitaxel + pembrolizumab	1 (1.6)
Platinum + etoposide	2 (3.2)
Gemcitabine	1 (1.6)
No sequential treatment	5 (8.1)
Osimertinib	28 (100)
Pemetrexed	3 (10.7)
Platinum + pemetrexed	8 (28.5)
Platinum + pemetrexed + bevacizumab	4 (14.3)
Platinum + pemetrexed + bevacizumab + atezolizumab	1 (3.6)
Platinum + etoposide	2 (7.1)
Gefitinib + capmatinib	1 (3.6)
Gemcitabine	1 (3.6)
TS-1	1 (3.6)
No sequential treatment	7 (25.0)

OS being 37.6 months in patients harboring T790M after afatinib treatment [15]. Our previous study also demonstrated that the median PFS1 (PFS of gefitinib, erlotinib, or afatinib) plus PFS2 (PFS of osimertinib) was 27.5 months, while the median OS from first-line EGFR-TKI was 61.3 months amongst the 151 patients who had T790M and had received osimertinib as a subsequent treatment after experiencing resistance to first-generation and second-generation EGFR-TKIs [10]. Additionally, a subgroup analysis of the FLAURA study displayed that there was no OS benefit for patients taking osimertinib when comparing them to those being treated with first-generation TKIs in an Asian population [14]. In a FLAURA China study, although first-line osimertinib treatment provided a statistically significant median PFS benefit vs gefitinib and erlotinib [17.8 vs 9.8 months, HR 0.56 (95% CI 0.37–0.85)], there was no strong evidence to prove that osimertinib reduced the risk of death when compared with the control group in patients with advanced Chinese NSCLC with the *EGFR* mutation [33.1 vs 25.7 months, HR 0.85 (95% CI 0.56–1.29)] [29]. Therefore, whether first-line osimertinib treatment truly prolongs OS in an Asian population still remains uncertain. Furthermore, the comparison of clinical benefits between osimertinib and afatinib for patients with treatment-naïve *EGFR*-mutant NSCLC has become an important and concerning issue as well.

To clarify the difference in clinical efficacies between osimertinib and afatinib, the Heat on Beat study, a randomized phase II trial, was designed in Japan for comparing OS between afatinib and osimertinib groups in patients with treatment-naïve advanced or recurrent NSCLC with the *EGFR* mutation, with the results still pending [30]. Another randomized phase IV trial, AFAMOSI, was conducted in order to investigate the clinical benefits and safety of sequential afatinib and osimertinib treatment as compared to only osimertinib, as a first-line regimen in patients with EGFR(+)/T790M(−) non-squamous NSCLC (NCT04413201) [31].

Although clinical trials remain ongoing, few real-world data discussing this topic have been published. CJLSG1903, a retrospective multicenter study, enrolled patients from 15 hospitals in Japan who were being treated with either osimertinib or afatinib as a first-line therapy [16]. This study demonstrated that osimertinib did not significantly prolong the median time to discontinuation of TKIs [20.5 vs 18.6 months, HR 1.15 (95% CI 0.93–1.41); $p = 0.204$], time to treatment failure [20.5 vs 16.0 months, HR 0.92 (95% CI 0.76–1.13); $p = 0.443$], or PFS [20.5 vs 16.5 months, HR 1.02 (95% CI 0.81–1.28), $p = 0.864$], when compared with afatinib. Moreover, it presented that osimertinib had a statistically significantly higher risk of death when compared with afatinib [25.1 vs 36.2 months, HR 1.47 (95% CI 1.07–2.02); $p = 0.018$]. However, the median follow-up time was not equal in the afatinib and osimertinib groups (26.2 vs 9.4 months). The event rate was 73.5% in the afatinib group, but only 29.4% in the osimertinib group. Therefore, we should interpret these results cautiously. In another real-world retrospective study, Mitsuya et al. reported that there were no significant differences in both median PFS [not reached vs 23 months, HR 0.932 (95% CI 0.379–2.287); $p = 0.877$] and OS [33 vs 36 months, HR 2.917 (95% CI 0.780–10.905); $p = 0.112$] to be found between the osimertinib and afatinib groups in patients with advanced or recurrent *EGFR*-mutated NSCLC [17]. However, this study only enrolled 49 patients for analysis, and the median follow-up time was not the same. Our present study has demonstrated that patients receiving osimertinib ($n = 47$) as a first-line treatment did not experience statistically prolonged PFS [18.8 vs 13.1 months, HR 0.75 (95% CI 0.48–1.18); $p = 0.211$] or OS [not reached vs. 41.7 months, HR 0.79 (95% CI 0.36–1.72); $p = 0.553$], when compared to those treated with afatinib ($n = 81$). Although the HRs of both PFS and OS are in favor of osimertinib as a first-line treatment, the results did not reach statistical significance. This condition may be a result of the small number of patients we enrolled for analysis. In our study, the median follow-up time was 20.1 months in the osimertinib group and 22.7 months in the afatinib group without any statistical difference being evident ($p = 0.413$). Additionally, the event rates of PFS and OS were

relatively close in the two groups (osimertinib vs afatinib; PFS 59.6% vs 75.3%; OS 19.1% vs 27.2%). Therefore, we believe that our findings are more powerful than those seen in other studies.

Regarding the status of brain metastasis at baseline, CJLSG1903 showed that osimertinib provided a trend towards a longer median PFS (HR 0.60; $p = 0.062$), as well as time to discontinuation of TKI (HR 0.66; $p = 0.0103$), than afatinib did in patients with brain metastasis [16]. The findings from the present study are consistent with the above results. Amongst patients with brain metastasis in our research study, patients in the osimertinib group ($n = 21$) experienced significantly superior median PFS than patients in the afatinib group ($n = 28$) [22.1 vs. 10.9 months, HR 0.45 (95% CI 0.21–0.96); $p = 0.038$]. Alternatively, there were no differences in median PFS between the osimertinib ($n = 26$) and afatinib ($n = 53$) groups in patients without brain metastasis [17.9 vs 17.2 months; HR 1.02 (95% CI 0.56–1.85); $p = 0.962$]. In preclinical data, osimertinib also demonstrated significantly better brain penetration than first-generation and second-generation EGFR-TKIs through in vitro and in vivo models [32, 33]. According to the preclinical data and clinical results, osimertinib as first-line therapy may be a favorable choice in patients with *EGFR*-mutant NSCLC with brain metastasis. Otherwise, a subgroup analysis from our study involving an exon 19 deletion with brain metastasis ($n = 25$), an exon 19 deletion without brain metastasis ($n = 36$), an L858R mutation with brain metastasis ($n = 24$), and an L858R mutation without brain metastasis ($n = 43$) did not reveal a difference in median PFS between the two groups. However, the population in each subgroup was too small, making it difficult to draw conclusions from these data.

Finally, in the present study, we demonstrated through univariate and multivariate analyses that patients with stage IVB disease experienced significantly worse PFS and OS than patients with recurrent disease. However, patients without brain metastasis did not have significantly better PFS and OS than patients with brain metastasis. Actually, there was still a trend to imply the phenomenon with an HR of 0.72 (95% CI 0.47–1.10) and an HR of 0.61 (95% CI 0.30–1.26), respectively. Additionally, it seems that patients with ECOG PS 0–1 did not experience longer PFS and OS than patients with ECOG PS 2–3. These results may have been caused by the extremely unequal patient numbers (116 patients in the PS 0–1 group vs 12 in the PS 2–3 group).

Although our research was the first study in Taiwan to compare the difference in clinical efficacy between osimertinib and afatinib in patients with advanced and recurrent *EGFR*-mutant NSCLC, there were still some limitations that should be acknowledged. First, the present research was a single-center retrospective study, thus more bias would therefore be present when compared with other studies that are prospectively designed. Second, only Taiwanese

individuals were eligible for analysis. Therefore, our findings may not be generalizable to other ethnic populations. Third, because of the fact that the enrolled population was relatively small, we should interpret the data from the subgroup analysis cautiously. Fourth, the follow-up time was not long enough, thus it is difficult to discuss OS-related issues. Fifth, 25% of patients in the osimertinib group and 8.1% of patients in the afatinib group did not receive sequential treatment after progressive disease to first-line EGFR-TKI therapy. The condition might influence the results of OS. Finally, because previous trials had displayed the adverse events of each drug clearly, we did not emphasize this topic [7, 13].

5 Conclusions

Our findings shed light on the differences in clinical efficacies between patients receiving osimertinib and afatinib as first-line treatment in treatment-naïve advanced and recurrent NSCLC with the *EGFR* mutation. Our research has demonstrated that there was no significant difference in median PFS and OS between the osimertinib and afatinib groups. However, osimertinib provided statistically longer median PFS than afatinib in patients with brain metastasis. Nevertheless, we believe further results from additional clinical trials for the purpose of confirming our findings are still required.

Declarations

original draft was performed by Yen-Hsiang Huang, Kuo-Hsuan Hsu, Jeng-Sen Tseng, and Kun-Chieh Chen. Tsung-Ying Yang, Kang-Yi Su, Sung-Liang Yu, Jeremy J.W. Chen, and Gee-Chen Chang revised the manuscript critically for important intellectual content.

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