Original Article

Osimertinib *vs.* afatinib as first-line treatment for patients with metastatic non-small cell lung cancer with an *EGFR* exon 19 deletion or exon 21 L858R mutation

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Background: The optimal treatment sequencing for patients with metastatic epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC) remains a subject of debate. In the United States, osimertinib is the preferred *EGFR* tyrosine kinase inhibitor (TKI) in the first-line setting. However, small retrospective studies suggest that alternative *EGFR* TKI sequencing strategies may produce similar outcomes. This study aimed to compare the outcomes of patients with metastatic NSCLC harboring an *EGFR* exon 19 deletion or exon 21 L858R mutation treated with osimertinib *vs.* afatinib as first-line therapy.

Methods: This retrospective, single-institution study examined 86 patients with metastatic *EGFR*-mutant NSCLC treated with either afatinib (n=15) or osimertinib (n=71) in the first-line setting. The primary outcome was progression-free survival (PFS), and secondary endpoints included time on *EGFR* TKI, overall survival (OS), and the incidence of adverse events (AEs).

Results: There was no difference in the PFS (median: 27.9 *vs.* 29.0 months, P=0.75), OS (P=0.18), and the median time on first-line *EGFR* TKI (23.9 *vs.* 15.2 months, P=0.10) between the afatinib and osimertinib groups, respectively. The number of AEs was also similar between the two treatment groups (P=0.17).

Conclusions: In this real-world retrospective study, there were no differences in PFS or OS between patients treated with afatinib or osimertinib in the first-line setting. These findings should be further investigated in larger prospective studies.

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Keywords: Epidermal growth factor receptor mutations (*EGFR* mutations); non-small cell lung cancer (NSCLC); *EGFR* tyrosine kinase inhibitor (*EGFR* TKI); osimertinib; afatinib

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Introduction

Lung cancer is one of the most common solid malignancies and is the number one cause of cancer-related deaths in the United States (US) (1). Activating mutations in the gene which encodes the epidermal growth factor receptor (*EGFR*) tyrosine kinase are present in approximately 15% of Caucasian and almost 50% of Asian patients with advanced non-small cell lung cancer (NSCLC) (2). Deletions in exon 19 and point mutations L858R in exon 21 make up 85–90% of all *EGFR* mutations. These mutations are referred to as sensitizing *EGFR* mutations and provide the opportunity for targeted therapy with tyrosine kinase inhibitors (TKIs) (3,4). However, despite all advances in target therapy, the 5-year survival for *EGFR*-mutant advanced NSCLC remains low at approximately 24% (5).

There are currently three generations of *EGFR* TKIs utilized in clinical practice in the US. First-generation TKIs include gefitinib and erlotinib, which are both reversible inhibitors of mutant and wild-type *EGFR* (3). Efficacy and tolerability of these agents have been compared in numerous phase III trials in which both gefitinib and erlotinib improved outcomes compared with chemotherapy (6,7). The second-generation *EGFR* TKIs, afatinib and dacomitinib, are irreversible inhibitors of wild-type and mutant *EGFR*. In clinical trials, both afatinib and dacomitinib demonstrated improvements in progression-free survival (PFS) and overall survival (OS) compared to standard cytotoxic systemic therapy (8,9). OS benefit from afatinib in LUX-Lung 3 and LUX-Lung 6 was observed in patients with *EGFR* exon 19 deletions but not in with exon 21 L858R mutations (9). When compared to first-generation gefitinib, both second-generation TKIs had a statistically significant improvement in PFS but only dacomitinib showed prolonged OS (8). Osimertinib is the only third-generation *EGFR* TKI currently clinically available in the US. It selectively inhibits *EGFR*-sensitizing and *EGFR* T790M resistance mutations while exhibiting lower activity against wild-type *EGFR*. This characteristic minimizes off-target toxicities, reducing adverse effects compared to earlier generations TKIs (4). Results from the first-line FLAURA trial demonstrated superior PFS and OS in patients treated with osimertinib compared to the first-generation TKIs, gefitinib or erlotinib (4,10).

While the superiority of second- and third-generation over first-generation *EGFR* TKIs is well-established, it is unclear whether second- and third-generation *EGFR* TKIs lead to similar outcomes or if one drug class is superior to the other (3,4,8). In this single-institution, retrospective study, we aimed to compare the efficacy of osimertinib to afatinib in the first-line setting for patients with metastatic NSCLC harboring an *EGFR* exon 19 deletion or exon 21 L858R mutation. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-686/rc).

Highlight box

Key findings

- In this retrospective study, there were no differences in progression-free survival (PFS) or overall survival (OS) between patients treated with afatinib or osimertinib in the first-line setting.

What is known and what is new?

- There are currently three generations of epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) utilized in clinical practice in the United States. Results from the first-line FLAURA trial demonstrated superior PFS and OS in patients treated with osimertinib compared to the first-generation TKIs.
- It has not been established whether second- and third-generation *EGFR* TKIs lead to similar outcomes or if one drug class is superior to the other.

What is the implication, and what should change now?

- With limited guidance addressing optimal sequencing of *EGFR* TKIs, this study provides positive real-world data that suggests afatinib may provide similar outcomes to osimertinib. Further investigation with larger prospective studies are needed to confirm our findings.

Methods

Study design and participants

This is a retrospective, single-institution study of patients

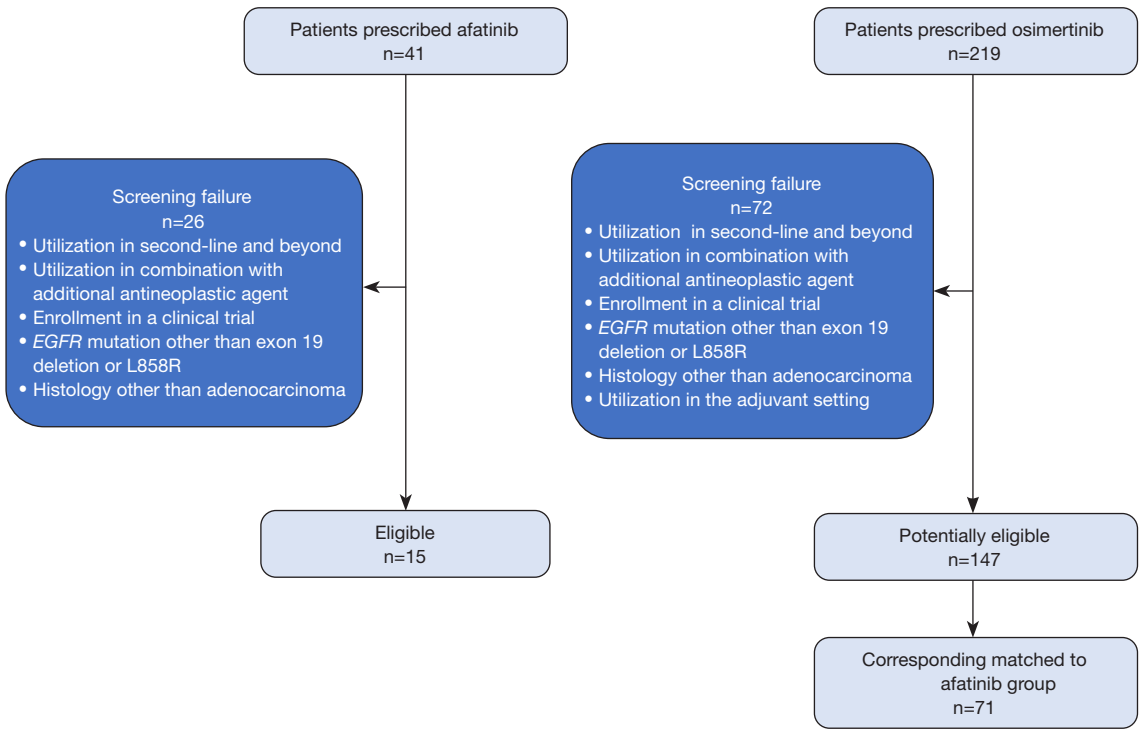

Figure 1 CONSORT diagram. *EGFR*, epidermal growth factor receptor.

with metastatic NSCLC with a sensitizing *EGFR* mutation who were treated with either osimertinib or afatinib in the first-line setting at the H. Lee Moffitt Cancer Center and Research Institute between January 1, 2013 and April 30, 2021. Eligible patients were aged ≥18 years, had a diagnosis of stage IV NSCLC with a common *EGFR* mutation (exon 19 deletion or L858R mutation), and received single-agent osimertinib or afatinib in the first-line metastatic setting as standard of care. Exclusion criteria included enrollment in a clinical trial or receipt of any antineoplastic agents other than osimertinib or afatinib in the first-line metastatic setting. Data on patient demographics, tumor characteristics, treatment, toxicities, and survival outcomes were collected. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the University of South Florida (MCC 21723; IRB No. 003669) and individual consent for this retrospective analysis was waived.

A report was run of all patients who were prescribed afatinib or osimertinib through the H. Lee Moffitt Cancer Center & Research Institute specialty pharmacy between January 1, 2013 and April 30, 2021. The generated list of 41 patients who have been prescribed afatinib was assessed for eligibility, and 15 patients met the criteria. A generated list of 219 patients prescribed osimertinib produced 147 that met eligibility criteria. In an effort to account for confounders, the 147 eligible patients in the osimertinib group were matched to the 15 patients from the afatinib group based on age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lung cancer histology, type of *EGFR* mutation, smoking history, and baseline presence of central nervous system (CNS) metastasis (*Figure 1*).

Statistical analysis

The primary endpoint of this study was PFS defined as the time from date of diagnosis to date of documented progression, as determined by imaging and the patient's treating physician, or death. Secondary endpoints included time on *EGFR* TKI defined as time from initiation of TKI therapy to date of discontinuation of TKI for any reason [i.e., adverse event (AE), disease progression, or death], OS defined as the length of time from the date of histological diagnosis to date of death from any cause, and the incidence of AEs. If progression or death had not occurred prior to the time of data cutoff or if a patient was lost to follow-up,

the date of the last contact was utilized. Difference in PFS and OS between the afatinib and osimertinib groups was assessed using Kaplan-Meier (KM) method and log-rank test. A matched study design was employed in selecting patients in the osimertinib group based on corresponding patients in the afatinib group. The matching was based on age, gender, ECOG PS score, baseline presence of CNS metastasis, smoking history, NSCLC histology, and type of *EGFR* mutation (exon 19 del *vs.* L858R). Patient and clinical characteristics were summarized using descriptive statistics including median and range for continuous measures. Categorical measures included proportions and frequencies. The association between continuous variables and treatment types were evaluated using Kruskal-Wallis tests and the associations with categorical variables were evaluated using Chi-squared tests or Fisher's exact tests when the expected frequencies is less than five in some cells. Time-to-event for OS was calculated from date of diagnosis to date of death for patients that died and date of last contact for censored patients. For the KM plot of time on TKI and treatment group, time on TKI (months) was dichotomized using median value for each treatment group. Univariate Cox regression was performed to examine associations between the covariates and PFS as well as OS. Statistical analysis was performed using R version 4.1.1 (2021-08-10).

Results

Patients characteristics

A total of 86 patients were included in the study, 15 in the afatinib group and 71 in the osimertinib group. Baseline characteristics were similar between the two groups. The majority of the patients were female (67% in afatinib, 76% in osimertinib), White (60% in afatinib, 72% in osimertinib), and non-Hispanic (73% in afatinib, 85% in osimertinib). As previously stated, the groups were matched based on age, gender, ECOG PS, histology, type of *EGFR* mutation, smoking history, and baseline presence of CNS metastasis. Most patients had an exon 19 deletion (93% and 73%, afatinib *vs.* osimertinib, respectively). The median age at initiation of TKI therapy was 63 years in the afatinib group and 68 in the osimertinib group, the median ECOG PS in both groups was 1, all patients had adenocarcinoma, and most patients were never smokers. Baseline CNS metastases were present in 33% of patients in the afatinib group and 28% in the osimertinib group (*Table 1*).

Outcomes

With a median follow-up of 56 *vs.* 22 months for patients treated with afatinib and osimertinib, respectively, there were no differences in PFS and OS. The median PFS was 27.9 months [95% confidence interval (CI), 19.2 to not estimable (NE)] in the afatinib group and 29.0 months (95% CI, 20.2 to NE) in the osimertinib group (P=0.75) (*Figure 2*, Table S1). The median OS was NE for both groups (95% CI, 64.2 to NE and 27.2 to NE, afatinib *vs.* osimertinib, respectively, P=0.18) (*Figure 3*, Table S1). The mutational status (exon 19 deletion *vs.* exon 21 L858R) did not independently impact PFS or OS (*Table 2*, Table S2). The median time on TKI was 23.9 months (range, 0.4 to 75.4 months) for patients treated with afatinib *vs.* 15.2 months (range, 0.8 to 47.7 months) for patients treated with osimertinib; however, this difference was not statistically significant (P=0.10) (Table S1). An *EGFR* T790M mutation was confirmed via *EGFR* pyrosequencing in tumor tissue or liquid biopsy in blood plasma with Guardant 360® (target hybrid capture-based next-generation sequencing) or Biodesix [droplet digital polymerase chain reaction (PCR)] in 78% (7/9) of the patients who progressed on afatinib. Osimertinib was selected as a second-line therapy in six of these seven patients. Additionally, three other patients were treated with osimertinib in the second-line setting after afatinib either due to AEs secondary to afatinib or due to physician's choice upon progression even in the absence of a T790M mutation. There were no differences in the incidence (7% *vs.* 14%, afatinib *vs.* osimertinib group, respectively, P=0.68) or location of new metastatic lesions between the two groups (P=0.636) (*Table 3*). Four patients developed CNS metastasis while on therapy, and all were in the osimertinib group. Patients that were on TKI for a longer period (time on TKI ≥ median time on TKI) had longer PFS and OS.

AEs

Toxicities were not formally graded due to the retrospective nature of the study. The majority of patients in both the afatinib and osimertinib groups experienced AEs. There was no difference in the number of AEs between the two groups (P=0.17). The most common AE in both groups was diarrhea (60% in the afatinib group *vs.* 38% in the osimertinib group) followed by rash in the afatinib group and fatigue in the osimertinib group. A summary of the

Table 1 Summary of baseline characteristics by treatment type

Characteristics	Afatinib (n=15)	Osimertinib (n=71)	P
Age (years)			
Median (range)	62.9 (47.2–83.2)	67.6 (32.4–89.7)	0.498
<65 years, n [%]	9 [60]	30 [42]	0.333
Sex, n [%]			0.518
Male	5 [33]	17 [24]	
Race, n [%]			0.149
Asian	1 [7]	8 [11]	
Black	0 [0]	5 [7]	
Other	4 [27]	6 [8]	
Unknown	1 [7]	1 [1]	
White	9 [60]	51 [72]	
Ethnicity, n [%]			0.388
Hispanic	1 [7]	3 [4]	
Non-Hispanic	11 [73]	60 [85]	
Unknown	3 [20]	8 [11]	
Smoking status, n [%]			0.899
Never	8 [53]	42 [59]	
Ever	7 [47]	29 [41]	
ECOG PS score, n [%]			1.000
0	2 [13]	11 [15]	
1	12 [80]	53 [75]	
2	1 [7]	7 [10]	
Histology, n [%]			1.00
Adenocarcinoma	15 [100]	71 [100]	
Baseline CNS metastasis, n [%]			0.757
No	10 [67]	51 [72]	
Yes	5 [33]	20 [28]	
Mutation, n [%]			0.175
Exon 19 deletion	14 [93]	52 [73]	
Exon 21	1 [7]	19 [27]	

ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system.

AEs is reported in *Table 4*. More patients required dose reductions in the afatinib group (64% *vs.* 19%, afatinib *vs.* osimertinib, respectively, P=0.002). In the afatinib group, 14 patients experienced AEs, and 14% (2/14) of those had treatment held. In the osimertinib group, 53 patients experienced AEs, but only 4% of those (2/53) had treatment held. The differences in treatment hold were not statistically significant (P=0.195). There was no difference in the rate of discontinuation as the result of AEs between the afatinib and osimertinib groups (7% *vs.*

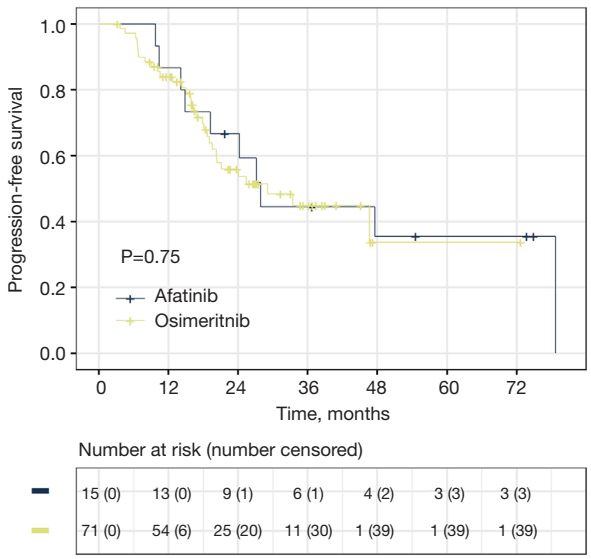

Figure 2 Progression-free survival.

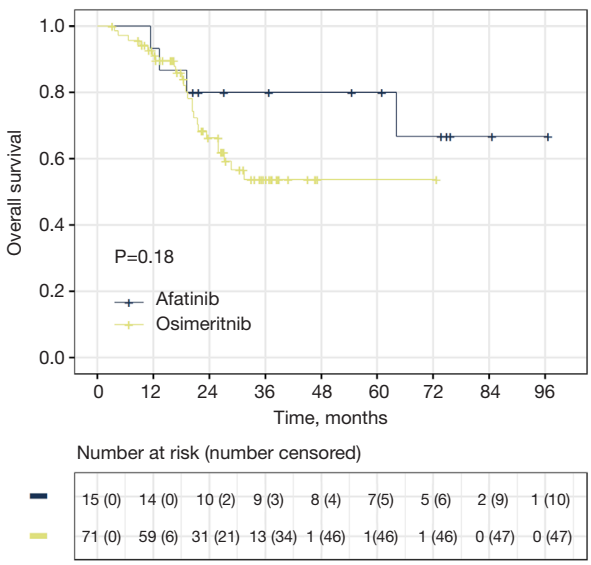

Figure 3 Overall survival.

3%, P=0.442) (*Table 5*). There were no deaths in either group that were attributed to *EGFR* TKI therapy.

Discussion

Despite advancements in the treatment of patients with *EGFR*-mutant NSCLC, there are limited data addressing the optimal sequencing of *EGFR* TKIs. Osimertinib has been recommended as the preferred first-line treatment in the US due to its toxicity profile and efficacy; however, in this retrospective study, there were no statistical differences in PFS or OS in patients with *EGFR*-mutant NSCLC treated with osimertinib *vs.* afatinib in the first-line setting. Also, patients in the afatinib group were on first-line *EGFR* TKI therapy nearly 9 months longer than the ones in the osimertinib group. However, the latter was not statistically significant and could be related to the longer follow-up time of patients treated with afatinib, the small number of patients in the afatinib group, or possibly because the vast majority of patients treated with afatinib had an exon 19 deletion in which afatinib has found to be more effective in compared to the exon 21 L858R mutation (9). The extended follow-up time in the afatinib group can potentially be explained by the earlier date of approval and treatment start date in the afatinib group starting years prior to osimertinib and that four of the fifteen patients treated with afatinib were still on therapy at time of data cut off. Although there was no difference in the number of

Table 2 Outcomes

Endpoint	Afatinib (n=15)	Osimeritnib (n=71)	P
PFS (months)	27.9	29.0	0.75
OS (months)	NE	NE	0.18
Time on first-line TKI (months)	23.9	15.2	0.10

PFS, progression-free survival; OS, overall survival; NE, not estimable; TKI, tyrosine kinase inhibitor.

Table 3 Pattern of metastasis at the time of disease progression in the first-line setting

Metastases	Afatinib (n=15)	Osimertinib (n=71)	P
New metastases, n [%]			0.68
Yes	1 [7]	10 [14]	
No	14 [93]	61 [86]	
Location of new metastasis, n [%]			0.636
Brain	0 [0]	4 [40]	
Calvarium	0 [0]	1 [10]	
Liver	1 [100]	2 [20]	
Lung	0 [0]	2 [20]	
Pancreas	0 [0]	1 [10]	

Table 4 AEs secondary to *EGFR* TKI in the first-line setting

AEs	Afatinib (n=15)	Osimertinib (n=71)	P
Any grade	14 [93]	53 [75]	0.17
Diarrhea	9 [60]	27 [38]	–
Rash	3 [20]	5 [7]	–
Fatigue	–	6 [8]	–
Mouth sore	–	4 [6]	–
Paronychia	2 [13]	1 [1]	–
Thrombocytopenia	–	2 [3]	–
Aphthous ulcer	–	1 [1]	–
Cardiotoxicity	–	1 [1]	–
Cough	–	1 [1]	–
Decreased appetite	–	1 [1]	–
Dry skin	–	1 [1]	–
Myositis	–	1 [1]	–
Nail changes	–	1 [1]	–
Weight loss	–	1 [1]	–

Data are presented as n [%]. AE, adverse event; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Table 5 Summary of therapy changes among patients that experienced AEs due to *EGFR* TKI in the first-line setting

Therapy changes	Afatinib (n=14)	Osimeritnib (n=53)	P
Led to discontinuation, n [%]			0.511
No	13 [93]	51 [96]	
Yes	1 [7]	2 [4]	
Dose reduction, n [%]			0.002
No	5 [36]	43 [81]	
Yes	9 [64]	10 [19]	
Dose held, n [%]			0.190
No	12 [86]	51 [96]	
Yes	2 [14]	2 [4]	

AE, adverse event; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

AEs between the two groups, patients treated with afatinib required more dose reductions. However, very few patients in both groups needed to have treatment discontinued due to AEs, showcasing the safe profile of both drugs.

In the LUX-Lung 7 trial, afatinib was found to have improved PFS, time to treatment failure, and overall response rate compared to gefitinib, but did not meet statistical significance in OS (3). In contrast, significant survival benefit with osimertinib was observed in the FLAURA trial when compared to the first-generation *EGFR* TKIs erlotinib and gefitinib (4). Patients treated with osimertinib had a 54% lower risk of disease progression and a 20% lower risk of death (11). Although osimertinib and afatinib were never compared head-to-head, the available prospective data demonstrates a clear OS benefit with osimertinib over first-generation *EGFR* TKI, which was not seen with afatinib in the LUX-Lung 7 trial. This finding suggests that osimertinib may be a more efficacious drug. However, in our small retrospective study, we did not identify differences in outcomes between patients treated with afatinib and osimertinib.

Sequential treatment with afatinib followed by osimertinib was assessed in the retrospective GioTag study (12). Overall median time to treatment failure after afatinib followed by osimertinib was 28.1 months. Specifically looking at the osimertinib treatment period, the time to treatment failure was 15.6 months. The authors of this study noted that time to treatment failure with second-line osimertinib did not appear to be impacted by prior afatinib therapy (12). This finding is consistent with a small patient subset from our study in which six patients experienced prolonged time on TKI therapy when treated with afatinib followed by osimertinib. The National Comprehensive Cancer Network NSCLC panel recommends osimertinib as the preferred first-line *EGFR* TKI over afatinib (2). However, in line with our findings in a US-based population, a large retrospective study conducted in 15 institutions in Japan, also did not find differences in PFS in patients treated with osimertinib and afatinib in the first-line setting (13). However, in the former study, the authors reported longer OS in Asian patients treated with afatinib, which is distinct from our results in a predominantly White population.

Approximately 50% of patients treated with a first- or second-generation *EGFR* TKI will develop an *EGFR* T790M resistance mutation (14,15). In our study, 80% of patients that had disease progression on afatinib developed an *EGFR* T790M mutation, and, in contrast with previous data, all but one patient were subsequently treated with osimertinib (4,16-18). Previous real-world studies suggest that ~30% of the patients will be eligible for second-line therapy with a *EGFR* TKI, which has been theorized to be

due to the rapid progressive nature of the disease leaving patients unable to proceed with subsequent therapy (16-18). This is much lower than what we report in our study. Possible explanations could be higher rates of genomic testing at the time of disease progression at a high-volume academic center such as ours or possibly due to the small number of patients included in the afatinib group in this study. Further, the *EGFR* sequencing strategy applied to six patients in the present study is in line with the recommended guidelines and a previously reported large, global prospective study of sequential afatinib followed by osimertinib in patients with an acquired *EGFR* T790M (UpSwinG study, NCT04179890) (2,19). In the latter, time to treatment failure was 22.7 months and OS was 36.5 months. The UpSwinG study results demonstrate positive outcomes in survival and time to treatment failure utilizing this specific *EGFR* TKI sequencing (19). Although we noted higher rates of *EGFR* T790M acquired mutation as well as higher rates of sequential osimertinib therapy than previously reported (4,16,18,20-27), in our study only a small patient subset developed an *EGFR* T790M mutation during afatinib treatment (n=7), therefore we do not have power to determine differences in PFS with second-line treatment strategies (PFS2).

The median number of AEs did not differ based on the treatment group. The most common AE in both groups were diarrhea followed by rash in the afatinib group, which is consistent with previously reported findings (3,4,9,28). The rate of AEs in both groups was lower than that reported in landmark trials with *EGFR* TKIs (3,4,9). In our study, diarrhea was reported in 60% of the patients in the afatinib group, whereas in the LUX-Lung 3 and LUX-Lung 7 studies, diarrhea was reported in over 90% of the patients (3,9). Comparatively, in our study, diarrhea was reported in 38% of the patients in the osimertinib group, whereas in the FLAURA trial, diarrhea was reported 58% of the patients (4). We believe the AE incidence differences found between our study and the *EGFR* TKI landmark trials is a byproduct of the retrospective nature of this study and possibly due to effective pre-therapy counseling of patients in a tertiary referral cancer center where patients are trained in the early identification and mitigation of AEs. Further, the accuracy in capturing the rate of AEs in a retrospective study is contingent on patient reporting and comprehensive documentation, which has inconsistencies.

In the RealGiDO study (29,30), an observational real-world study on afatinib, 67.1% of patients underwent dose reductions, while only 8.7% of the patients treated with osimertinib in the FLOWER trial needed dose reductions (30). In line with previous studies (3,9), we identified significantly more dose reductions in the afatinib group compared to the osimertinib group (64% *vs.* 19%, respectively, P=0.002) which could indicate a greater impact on quality of life in the afatinib group compared to the osimertinib group. Although several patients needed dose reductions, the rate of treatment discontinuation due to AEs was low for both treatment groups (7% *vs.* 3%, afatinib *vs.* osimertinib, respectively). Our findings are similar to the ones from the LUX-Lung 3, LUX-Lung 7, and RealGiDO studies, which reported afatinib discontinuation rates between 6–8%, and the FLOWER study with an osimertinib discontinuation rate of 7% (3,4,9,29,30). Also, in our study, we did not find any differences in dose delays between the two groups.

There are several limitations to this study. This is a single-center study with a small sample size of patients treated with afatinib. Therefore, to control for selection bias, the osimertinib group was matched to the afatinib group by age, gender, ECOG PS, histology, *EGFR* mutation type, smoking history, and baseline presence of CNS metastasis. Also, only 7% of patients in the afatinib group had an *EGFR* L858R mutation compared to 27% of patients in the osimertinib group. Historically, *EGFR* L858R mutations are associated with worse prognosis, which may impact outcomes and make it challenging to interpret subgroup analysis. Further, patients in the afatinib group had a longer follow-up, which may also skew the outcomes data. Also, in a retrospective study, there is an inherent risk of inaccurate or incomplete documentation. Adherence could not be accounted for due to lack of consistent documentation. Data on second-line and subsequent therapy was not collected, so we are unable to conclude which *EGFR* sequencing strategy may be superior as this was not analyzed. AEs' reporting and recording in the electronic medical record may not reflect real-world experience. Also, AEs were not graded according to CTCAE criteria and reporting of progression was based on imaging and treating physician documentation rather than RECIST criteria (31,32).

Conclusions

In conclusion, we did not find differences in PFS and OS in patients with *EGFR*-mutant NSCLC treated with osimertinib *vs.* afatinib in the first-line setting. Although the median time on first-line *EGFR* TKI was numerically longer for patients treated with afatinib, this finding was

not statistically significant, and could be a result of the small sample size and longer follow-up time for this patient group. Furthermore, both groups experience similar AE rates. Future studies are needed to confirm our findings, but our results suggest that treatment with afatinib results in similar outcomes to treatment with osimertinib.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-686/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the University of South Florida (MCC 21723; IRB No. 003669) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Outcomes

Endpoint	Afatinib (n=15)	Osimertinib (n=71)	P
PFS (months)	27.9 (19.2, NE)	29.0 (20.2, NE)	0.75
OS (months)	NE (64.2, NE)	NE (27.2, NE)	0.18
Time on first-line TKI (months)	23.9 [0.4, 75.4]	15.2 [0.8, 47.7]	0.10

Data are presented as median (95% CI) or median [range]. PFS, progression-free survival; NE, not estimable; OS, overall survival; TKI, tyrosine kinase inhibitor; CI, confidence interval.

Table S2 PFS and OS stratified by mutational status

Endpoint	Exon 19 deletion (n=66)	Exon 21 L858R (n=20)	P
PFS (months)	27.1 (19.5, NE)	26.6 (25.4, NE)	0.35
OS (months)	64.2 (27.2, NE)	NE	0.26

Data are presented as median (95% CI). PFS, progression-free survival; OS, overall survival; NE, not estimable; CI, confidence interval.

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