Original Article

Osimertinib versus comparator first-generation epidermal growth factor receptor tyrosine kinase inhibitors as first-line treatment in patients with advanced *EGFR*-mutated non-small cell lung cancer: a Chinese, multicenter, real-world cohort study

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Background: In the phase 3 FLAURA trial, osimertinib was compared with first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as a first-line treatment for *EGFR*-mutant non-small cell lung cancer (NSCLC). Osimertinib showed longer progression-free survival (PFS), overall survival (OS), and a similar safety profile. However, more studies demonstrating the effectiveness and safety of osimertinib as a first-line strategy are needed in real-world populations.

Methods: We enrolled 1,556 patients with *EGFR*-mutated stage IIIc–IV NSCLC from the CAPTRA-Lung database. All patients received either osimertinib (n=202) or a first-generation EGFR-TKI (n=1,354) as their initial treatment. To adjust for differences in baseline characteristics between two groups, 1:2 propensity score matching (PSM) was performed. Propensity scores included gender, age, Eastern Cooperative Oncology Group performance status score, smoking history, family history of tumor, pathology, *EGFR* mutations, and central nervous system (CNS) metastases. The standardized mean differences (SMD) before and after PSM were calculated to examine the balance of covariate distributions between two groups.

Results: After PSM, 202 patients receiving osimertinib and 404 patients receiving first-generation EGFR-TKIs were finally identified. SMD of each matched variable is less than 0.10. The median PFS was 19.4 months [95% confidence interval (CI): 14.3–24.4] in the osimertinib arm and 10.9 months (95% CI: 9.3–12.5) in the comparator arm [hazard ratio (HR) for progression, 0.47; 95% CI: 0.38–0.59; P<0.001). The median OS was 40.5 months (95% CI: 27.1–54.0) *vs.* 34.3 months (95% CI: 30.6–38.0) in two groups, respectively (HR for death, 0.76; 95% CI: 0.58–1.00; P=0.045). The incidence of grade 3 adverse events (AEs) between the two groups was 1% and 4.2%, respectively. No grade 4 AEs and treatment-related deaths were reported in both groups.

Conclusions: In real-world settings, osimertinib demonstrates longer PFS and OS, with a similar safety profile to that of comparator EGFR-TKIs when used as a first-line strategy in NSCLC patients.

Keywords: Osimertinib; comparator epidermal growth factor receptor tyrosine kinase inhibitor (comparator EGFR-TKI); propensity score matching (PSM); real-world study

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Introduction

Lung cancer is a major global health concern, responsible for the highest number of cancer-related deaths worldwide (1). The majority of lung cancer cases (more than 85%) fall under the category of non-small cell lung cancer (NSCLC). Among the various driver genes in NSCLC, epidermal growth factor receptor (*EGFR*) mutation is the most significant, and the detection of *EGFR* mutations is crucial for the determination of personalized targeted therapy. The most common sensitizing driver mutations in NSCLC patients are exon 19 deletions and L858R substitutions within exon 21. These mutations have a higher prevalence in Asian patients (around 50%) compared to Caucasian patients (approximately 10%) (2,3).

Numerous global clinical trials involving patients with *EGFR*-mutated advanced NSCLC have demonstrated the safety and efficacy of first- or second-generation tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, icotinib, or afatinib, in the first-line setting. These TKIs have been shown to extend median progression-free survival (mPFS) to approximately 10 months compared to chemotherapy (4-11). Several guidelines recommend EGFR-TKIs as the standard first-line treatment for advanced NSCLC patients with a sensitive *EGFR* mutation (12,13).

Despite the progression-free survival (PFS) advantage, there is no significant overall survival (OS) improvement for patients receiving first-generation EGFR-TKIs. Furthermore, patients may develop acquired resistance to first-generation TKIs, with a predominant mechanism being exon 20 T790M, after an average of 10–14 months. Osimertinib was firstly developed as a 2nd-line agent for patients with this acquired resistance. Fortunately, further studies showed that osimertinib also had positive effects as a first-line strategy for patients with advanced *EGFR*-mutant NSCLC, including exon 19 deletion and exon 21 L858R

substitution (14,15). Besides, FLAURA trial demonstrated a considerably prolonged OS for patients in the osimertinib group compared to those in the reference group (38.6 *vs.* 31.8 months; P=0.046) (16). Additional study results from Asian and Chinese populations confirmed the effectiveness and safety of osimertinib as a first-line therapy for patients with advanced *EGFR*-mutated NSCLC (17-19). Based on the results of clinical trials, osimertinib was approved as a first-line treatment for patients with *EGFR*-mutant advanced NSCLC by the Food and Drug Administration (FDA) (20).

However, although multiple studies demonstrated the PFS benefits associated with first-line osimertinib compared with first-generation EGFR-TKIs, whether first-line osimertinib produced an OS benefit yielded varying results in different studies (16-22). Furthermore, the sample sizes of current real-world studies were relatively small. Therefore, we conducted a retrospective study using the data extracted from a real-world, multicenter, prospective observational cohort in China to assess the effectiveness and safety of osimertinib as a first-line strategy for patients with *EGFR*-mutated stage IIIc–IV NSCLC, compared against first-generation EGFR-TKIs. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-577/rc).

Highlight box

Key findings

- This multicenter, real-world study revealed that progression-free survival (PFS) and overall survival (OS) for *EGFR* mutant non-small cell lung cancer (NSCLC) patients receiving osimertinib as first-line therapy were 19.4 and 40.5 months, respectively, both significantly longer than those receiving first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Besides, osimertinib demonstrated a similar safety profile to comparator EGFR-TKIs.

What is known and what is new?

- In FLAURA, osimertinib showed a positive benefit for the first-line strategy of patients with advanced *EGFR*-mutant NSCLC compared with first-generation EGFR-TKIs.
- In real-world settings, osimertinib also demonstrated longer PFS, OS, and a similar safety profile to comparator first-generation EGFR-TKIs when given as first-line strategy to Chinese NSCLC patients.

What is the implication, and what should change now?

- Osimertinib is safe and effective in real world populations. Studies with more patients are needed to confirm these results across diverse geographies and ethnicities.

Methods

Patients

The CAPTRA-Lung study (NCT03334864), collecting real-world data of patients with advanced or metastatic NSCLC, is a prospective, multicenter, observational study underway throughout China (23). As of October 31, 2022, the CAPTRA-Lung study encompassed the participation of 36 research centers and gathered data from 10,156 patients diagnosed with advanced or metastatic NSCLC. We conducted a retrospective cohort study using the data extracted from database of CAPTRA-Lung study. Patients were eligible for inclusion for our study according to the following standards: (I) with pathologically confirmed stage IIIc–IV NSCLC [according to the 8th tumor-node-metastasis (TNM) staging by the American Joint Committee on Cancer (AJCC)] in the CAPTRA-Lung database between January 1, 2010, and October 31, 2022; (II) having *EGFR* mutations and receiving either osimertinib or a first-generation EGFR-TKI as their first-line treatment; (III) with complete information regarding diagnosis, first-line treatment, and survival.

Patients were excluded from our study according to the following criteria: (I) with pathologically confirmed small cell lung cancer; (II) with TNM staging earlier than IIIc or receiving a first-generation EGFR-TKI for postoperative adjuvant therapy; (III) receiving a second-generation EGFR-TKI as their first-line treatment; (IV) with incomplete or unknown important clinical information. The observation period for all patients included in our study started from the initiation of EGFR-TKI treatment. Subsequently, all enrolled patients underwent regular follow-up assessments every three months until April 8, 2023, or death or loss to follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking Union Medical College Hospital on 24 December 2022 (Ethics Approval Number: I-22PJ1112) and the requirement for individual consent for this retrospective analysis was waived.

Data collection

Baseline information including gender, age, Eastern Cooperative Oncology Group (ECOG) performance status score, smoking history, family history of tumors, pathology, *EGFR* mutations, and central nervous system

(CNS) metastases was all collected from the CAPTRA-Lung database. A family history of tumor was defined as a self-reported history of cancer in first-degree or second-degree relatives. First-degree relatives included parents, siblings, or children, while second-degree relatives included nieces, nephews, aunts, uncles, or grandparents. In addition, data about the efficacy of EGFR-TKIs (treatment response, PFS, OS) and treatment-related adverse events (AEs) was also gathered.

Evaluation of efficacy and safety

The objective response rate (ORR) and disease control rate (DCR) were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) standard (24). PFS and OS were calculated from the initiation of EGFR-TKIs until tumor progression or death, respectively. The severity of AEs was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (25).

Statistical analysis

To adjust for differences in baseline characteristics between the osimertinib and reference groups, one-to-two propensity score matching (PSM) was performed using nearest neighbor matching (26). Variables that could influence the outcomes of treatment were used to generate a propensity score, including gender, age, ECOG, smoking history, pathology, EGFR mutations, and CNS metastases. Given that many studies have indicated a connection between a family history of malignancies and the prognosis of lung cancer patients, we also integrated "family history of tumor" into our propensity model (27-29). The standardized mean differences (SMD) before and after PSM were calculated to measure balance between groups. To minimize immortal time bias, only patients receiving osimertinib or first-generation EGFR-TKIs for the first time were included in this study and the observation period started from the initiation of EGFR-TKI treatment.

Statistical analysis was carried out with the software SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria). The χ^2 test or Fisher's exact test were used to compare categorical variables. Kaplan-Meier survival analysis was applied to evaluate mPFS and median overall survival (mOS), and the log-rank test was operated to determine the statistical difference. Cox regression models were carried out to evaluate the factors influencing survival. All statistical tests were 2-tailed and P<0.05 was considered as being statistically significant. Figures were generated using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) and R software (version 4.1.1, R Foundation for Statistical Computing).

Results

Baseline characteristics

From January 1, 2010 to October 31, 2022, 1,556 patients with *EGFR* mutant stage IIIc–IV NSCLC were included in the CAPTRA-Lung database, all of whom were Asian population. Among them, 202 patients received first-line osimertinib, and 1,354 patients received first-generation EGFR-TKIs (*Figure 1*). Before matching, baseline characteristics including gender, age, ECOG performance status, smoking history, family history of tumors, and pathology were similar between two groups (*Table 1*).

However, there was a significant difference in the distribution of *EGFR* mutation types between the osimertinib and comparator arms (P<0.001) as noted below. In the osimertinib group, 87 patients (43.1%) had exon 19 deletion, 80 patients (39.6%) had exon 21 L858R point mutation, 13 patients (6.4%) had uncommon mutations (any *EGFR* mutation other than common mutations), and data regarding specific *EGFR* mutation types were unknown for 22 patients (10.9%). In the comparator group, the distribution was 471 patients (34.8%), 474 patients (35.0%), 42 patients (3.1%), and 367 patients (27.1%) for exon 19 deletion, exon 21 L858R point mutation, uncommon mutations, and data unknown, respectively. Additionally, 31.7% of patients receiving first-line osimertinib exhibited CNS metastases at baseline, significantly higher than 21.1% in patients who received first-line first-generation EGFR-TKIs (P=0.001).

To adjust for imbalance in *EGFR* mutations and CNS metastases rates between the osimertinib and comparator groups, a 1:2 PSM was performed. After performing PSM, 202 patients in the osimertinib group and 404 patients in the comparator group were ultimately included in the matched cohorts (*Table 1*). Among 202 patients in the osimertinib group, 64 individuals (31.7%) presented with baseline CNS metastases, including 29 (14.4%) with stable CNS metastases, 9 (4.5%) with unstable symptomatic CNS metastases, and 26 (12.9%) with an undisclosed status. Among 404 patients in the first-generation EGFR-TKI group, 114 (28.2%) had baseline CNS metastases, including 80 (19.8%) with stable CNS metastases, 17 (4.2%) with

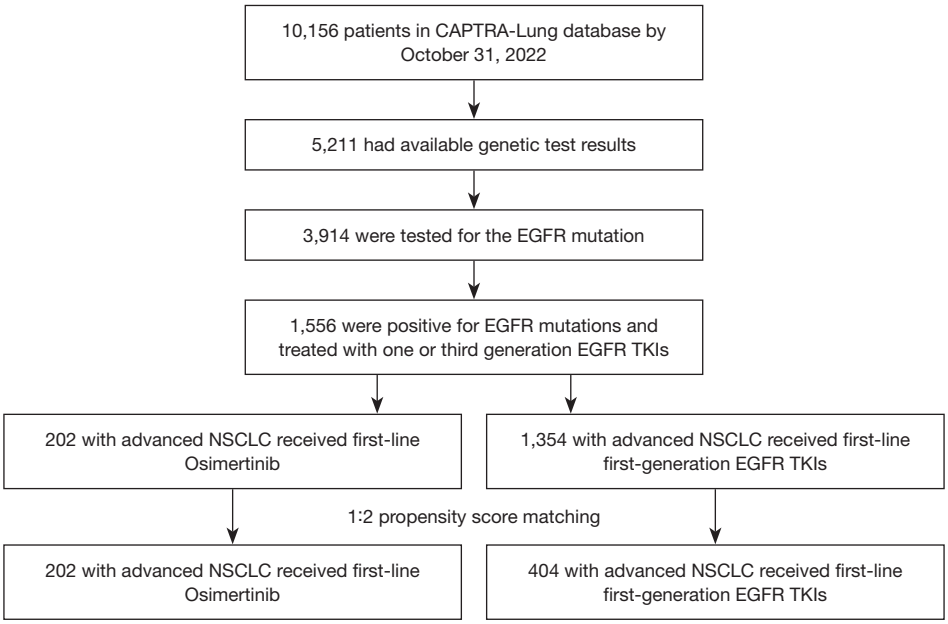

Figure 1 Flow diagram for details on the patient selection process. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

unstable symptomatic CNS metastases, and 17 (4.2%) with an unknown status. The distribution of 202 patients in the osimertinib group across the years 2010–2013, 2014–2018, and 2019–2022 was 0 (n=0), 10.0% (n=20), and 90.1% (n=182), respectively. In the first-generation EGFR-TKI group, the distribution of 404 patients was 7.7% (n=31), 69.6% (n=281), and 22.8% (n=92), respectively. Due to economic considerations, some patients with advanced NSCLC carrying EGFR mutations continued to receive first-generation EGFR-TKIs as their initial treatment after osimertinib was approved by the National Medical Products Administration (NMPA) for first-line treatment in 2019. SMD of all variables included in PSM reduced to less than 0.1, demonstrating a good balance between two groups.

Efficacy of osimertinib versus first-generation TKIs

At the cutoff date (April 8, 2023), the median follow-up period among patients in PSM cohort was 20.3 months in the osimertinib arm and 30.0 months in the comparator arm. In the matched cohort, the ORR was 63.4% in the osimertinib arm compared to 48.0% in the comparator arm (P<0.001). The DCR was 95.5% *vs.* 96.8% in two groups, respectively (P=0.443). None of the patients achieved a complete response in either arm.

Besides, the mPFS was 19.4 months [95% confidence interval (CI): 14.3–24.4] in the osimertinib group and 10.9 months (95% CI: 9.3–12.5) in the comparator group. The hazard ratio (HR) for progression was 0.47 (95% CI: 0.38–0.59), indicating a significantly reduction of risk for disease progression in the osimertinib group (P<0.001) (*Figure 2*). Furthermore, the osimertinib group exhibited mOS of 40.5 months (95% CI: 27.1–54.0), which was higher than that of 34.3 months (95% CI: 30.6–38.0) in the first-generation EGFR-TKI group (HR 0.76, 95% CI: 0.58–1.00; P=0.045) (*Figure 3*).

HRs for PFS and OS in subgroups

Subgroup analysis was performed to compare treatment outcomes between two groups among different *EGFR* mutations. Osimertinib was associated with significantly improved PFS compared with first-generation EGFR-TKIs for patients with either exon 19 deletions or exon 21 L858R substitutions (*Figure 4A*,*4B*). Furthermore, exon 19 deletions patients receiving osimertinib at first-line had PFS of 25.5 months (95% CI: 11.3–39.6), longer than 17.6 months (95% CI: 10.1–25.1) for patients with exon 21 L858R substitutions. The median OS for exon 19 deletions patients receiving osimertinib or first-generation EGFR-TKI at first-line was 44.5 months (95% CI: 32.0–57.0) *vs.* 36.7 (95% CI: 29.9–43.4), respectively (HR 0.85,

Table 1 Baseline characteristics of patients before and after PSM

Characteristics	Before PSM				After PSM			
	First-line osimertinib (n=202), n (%)	First-line first-generation EGFR-TKIs (n=1,354), n (%)	P value	SMD	First-line osimertinib (n=202), n (%)	First-line first-generation EGFR-TKIs (n=404), n (%)	P value	SMD
Gender			0.554	0.045			0.320	0.041
Male	76 (37.6)	539 (39.8)			76 (37.6)	169 (41.8)		
Female	126 (62.4)	815 (60.2)			126 (62.4)	235 (58.2)		
Age (years)			0.084	0.129			0.374	0.025
≤60	81 (40.1)	459 (33.9)			81 (40.1)	147 (36.4)		
>60	121 (59.9)	895 (66.1)			121 (59.9)	257 (63.6)		
ECOG performance status			0.813	0.018			0.084	0.097
0–1	173 (85.6)	1,151 (85.0)			173 (85.6)	365 (90.3)		
≥2	29 (14.4)	203 (15.0)			29 (14.4)	39 (9.7)		
Smoking history			0.326	0.075			0.305	0.011
No	151 (74.8)	967 (71.4)			151 (74.8)	286 (70.8)		
Yes	51 (25.2)	387 (28.6)			51 (25.2)	118 (29.2)		
Family history of tumor			0.579	0.043			0.397	0.008
No	178 (88.1)	1,174 (86.7)			178 (88.1)	365 (90.3)		
Yes	24 (11.9)	180 (13.3)			24 (11.9)	39 (9.7)		
Pathology			0.607	0.040			0.312	0.064
Adenocarcinoma	196 (97.0)	1,304 (96.3)			196 (97.0)	385 (95.3)		
Others[†]	6 (3.0)	50 (3.7)			6 (3.0)	19 (4.7)		
EGFR mutations			<0.001	0.440			0.188	0.025
Exon 19 deletion	87 (43.1)	471 (34.8)			87 (43.1)	143 (35.4)		
21L858R	80 (39.6)	474 (35.0)			80 (39.6)	180 (44.6)		
Uncommon mutations	13 (6.4)	42 (3.1)			13 (6.4)	21 (5.2)		
Detail unknown	22 (10.9)	367 (27.1)			22 (10.9)	60 (14.9)		
CNS metastases			0.001	0.241			0.377	0.005
No	138 (68.3)	1,068 (78.9)			138 (68.3)	290 (71.8)		
Yes	64 (31.7)	286 (21.1)			64 (31.7)	114 (28.2)		
Type of first-generation TKIs								
Gefitinib	N/A	638 (47.1)			N/A	171 (42.3)		
Icotinib	N/A	589 (43.5)			N/A	188 (46.5)		
Erlotinib	N/A	127 (9.4)			N/A	45 (11.1)		

[†], others include unclassified, squamous cell carcinoma and adenosquamous carcinoma. PSM, propensity score matching; SMD, standardized mean differences; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; CNS, central nervous system; TKI, tyrosine kinase inhibitor; N/A, not applicable.

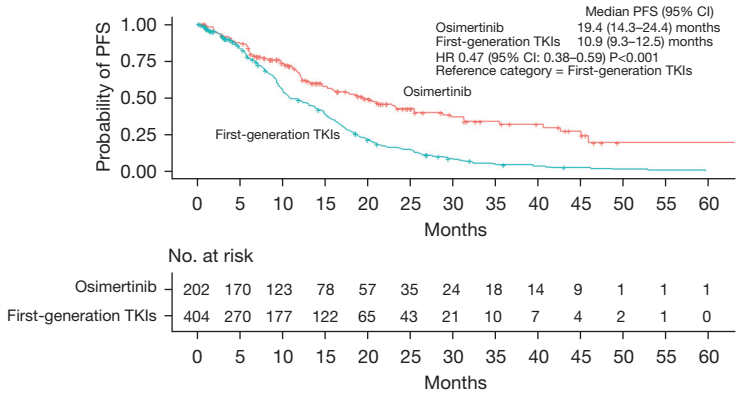

Figure 2 Progression-free survival curves for patients with advanced *EGFR*-mutant non-small cell lung cancer receiving first-line osimertinib or first-generation EGFR-TKIs. PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

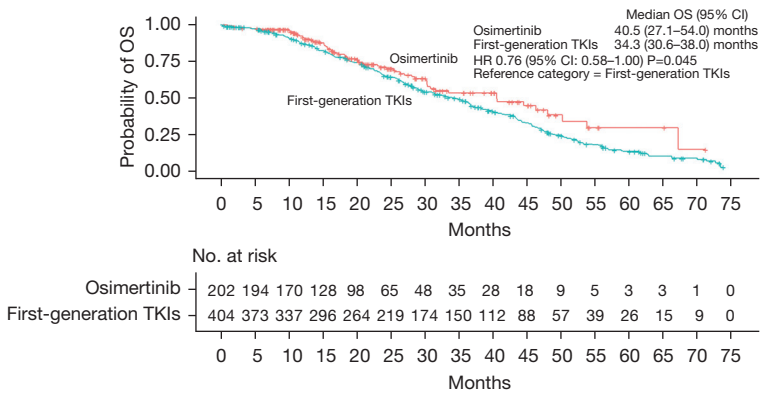

Figure 3 Overall survival curves for patients with advanced *EGFR*-mutant NSCLC receiving first-line osimertinib or first-generation EGFR-TKIs. OS, overall survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval.

95% CI: 0.54–1.35; P=0.497). Besides, the median OS for patients with exon 21 L858R substitutions in two groups was 33.5 months (95% CI: 22.4–44.6) *vs.* 33.4 (95% CI: 27.7–39.0), respectively (HR 0.75, 95% CI: 0.48–1.18; P=0.214) (*Figure 4C,4D*).

Additionally, we conducted subgroup analyses based on the presence or absence of baseline CNS metastases. Among patients without baseline CNS metastases, osimertinib was found to prolong PFS (18.5 *vs* 12.4 months; P<0.001) (Figure S1A). However, there were no significant differences in OS between the two groups (Figure S1B). Patients with baseline CNS metastases in the osimertinib group exhibited significantly longer PFS and OS compared to the comparator group, with mPFS being 21.0 *vs.* 8.7 months (P<0.001) and mOS being 40.5 *vs.* 25.8 months (P<0.001), respectively (Figure S1C,S1D).

We stratified patients based on the stability of their CNS metastasis status. Among patients with baseline stable CNS metastases, the osimertinib group showed significantly extended PFS compared to the comparator group, with median values of 25.5 months (95% CI: 3.1–47.9) *vs.* 8.4 months (95% CI: 6.3–10.5), respectively (HR 0.26, 95% CI: 0.13–0.53; P<0.001) (Figure S2A). OS was also significantly improved in the osimertinib group, with a median OS that was "not reached" *vs.* 25.8 months (95% CI: 22.3–29.3) in the comparator group (HR 0.03, 95% CI: 0–0.39; P<0.001) (Figure S2B). For patients with baseline unstable symptomatic CNS metastases, the median PFS ("not reached" *vs.* 14.1 months; P=0.190) and OS (33.5 *vs.* 23.4 months; P=0.320) were longer in the osimertinib group than that in the first-generation EGFR-TKI group, although without statistical significance (Figure S2C,S2D).

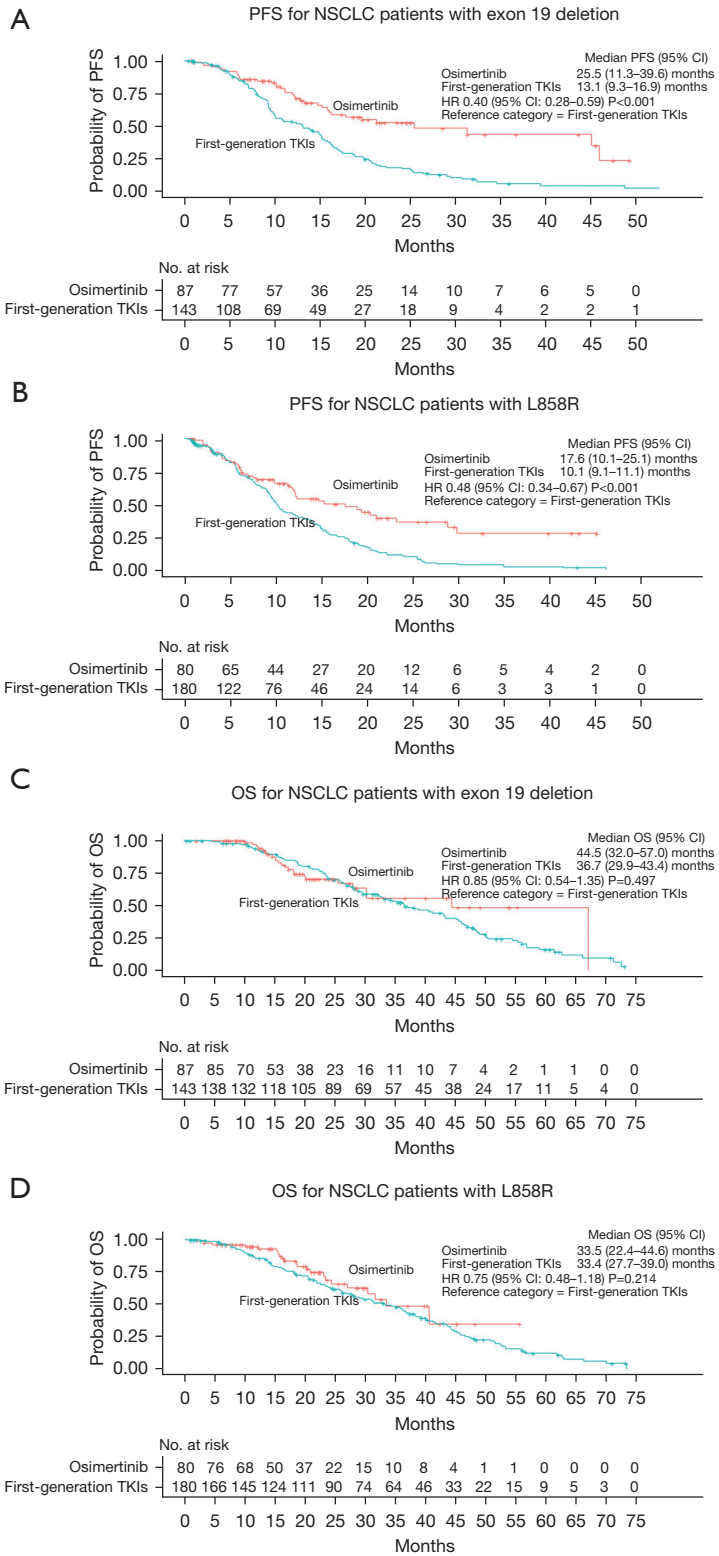

Figure 4 Progression-free survival curves for NSCLC patients with exon 19 deletion (A) and L858R substitution (B). Overall survival curves for NSCLC patients with exon 19 deletion (C) and L858R substitution (D). PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

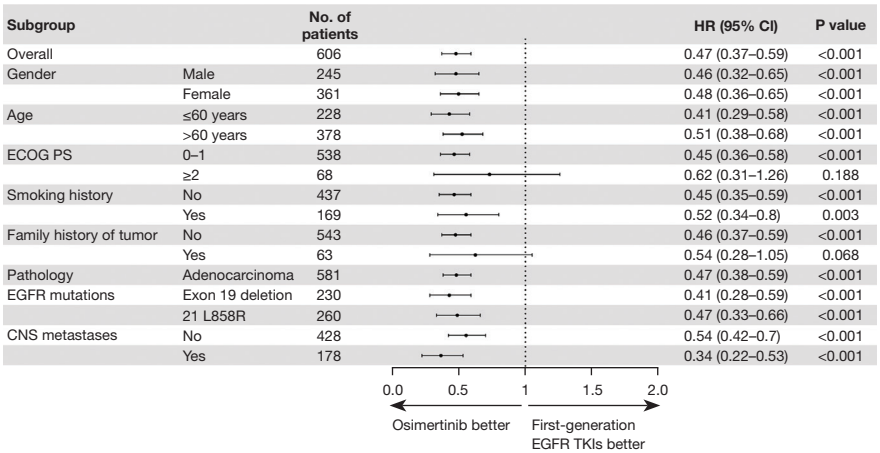

Figure 5 Forest plot for PFS. HR, hazard ratio; PFS, progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

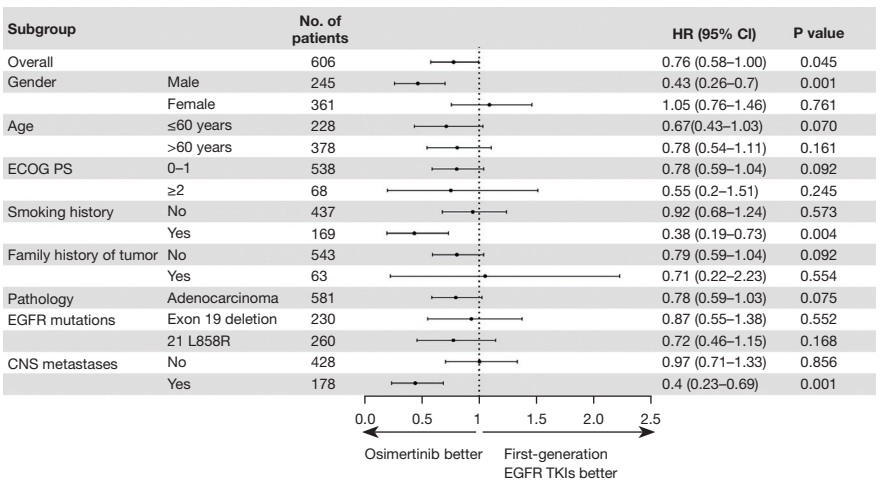

Figure 6 Forest plot for OS. HR, hazard ratio; OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

We further performed Cox regression analyses to confirm prognostic factors. Patients receiving osimertinib at first-line demonstrated a longer PFS than those receiving first-generation EGFR-TKIs, regardless of gender, age, ECOG, smoking history, family history of tumor, pathology, EGFR mutations, and CNS metastases (*Figure 5*). However, only patients who were male, or smokers, or with CNS metastases at baseline exhibited a significantly longer OS when receiving osimertinib at first-line (*Figure 6*). Besides, results in the subgroup with gefitinib, icotinib, and erlotinib were similar to those for the overall population (Figures S3,S4).

Safety of osimertinib versus first-generation TKIs

The treatment-emergent AEs for osimertinib and first-generation TKIs in matched cohort are summarized in *Table 2*. AEs of any grade were reported in 36 patients (17.8%) in the osimertinib arm and 64 patients (15.8%) in the comparator arm. Osimertinib resulted in 60 treatment-related adverse reactions, 96.7% of which were categorized as grade 1–2. While first-generation EGFR-TKIs led to 149 treatment-related adverse reactions, 88.6% of which were grade 1–2. Grade 3 AEs were observed in 2 patients (1.0%) and 17 patients (4.2%) in two groups, respectively. No grade 4 AEs and treatment-related deaths were reported

Table 2 Treatment-related adverse events of osimertinib and first-generation TKIs

Adverse event	Osimertinib (n=202), n (%)				First-generation TKIs (n=404), n (%)			
	Any grade	Grade 1	Grade 2	Grade 3	Any grade	Grade 1	Grade 2	Grade 3
Rash	25 (12.4)	22 (10.9)	3 (1.5)	0 (0.0)	116 (28.7)	89 (22.0)	25 (6.2)	2 (0.5)
Oral mucositis	6 (3.0)	5 (2.5)	1 (0.5)	0 (0.0)	3 (0.7)	2 (0.5)	1 (0.2)	0 (0.0)
AST/ALT elevation	4 (2.0)	2 (1.0)	0 (0.0)	2 (1.0)	55 (13.6)	29 (7.2)	18 (4.5)	8 (2.0)
Anorexia	3 (1.5)	3 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
Paronychia	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Hand-foot syndrome	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Diarrhea	12 (5.9)	10 (5.0)	2 (1.0)	0 (0.0)	48 (11.9)	37 (9.2)	6 (1.5)	5 (1.2)
Pruritus	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	6 (1.5)	6 (1.5)	0 (0.0)	0 (0.0)
Fatigue	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
QTc prolongation	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	7 (1.7)	4 (1.0)	2 (0.5)	1 (0.2)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.0)	7 (1.7)	1 (0.2)	0 (0.0)
Hyperbilirubinemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Albuminuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pulmonary interstitial fibrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Elevated creatinine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Low platelets	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)

TKI, tyrosine kinase inhibitor; AST/ALT, aspartate aminotransferase/alanine aminotransferase.

in both groups.

The most frequent AEs were rash (12.4%), diarrhea (5.9%), and oral mucositis (3%) in the osimertinib arm and rash (28.7%), elevation of aspartate aminotransferase/alanine aminotransferase (AST/ALT; 13.6%), and diarrhea (11.9%) in the comparator arm. Notably, only 1 patient in the comparator arm reported grade 3 pulmonary interstitial fibrosis.

Resistance pattern and follow-up treatment

Until the last follow-up (April 8, 2023), 98 patients (48.5%) in the osimertinib group and 38 patients (9.4%) in the first-generation EGFR-TKI group were still undergoing first-line treatment. Additionally, 22 (10.9%) and 57 patients (14.1%) were dead due to disease progression after first-line treatment within two groups, respectively, and these

patients did not have the chance to receive subsequent antineoplastic therapies (*Table 3*).

Among 82 patients (40.6%) who received second-line treatment in the osimertinib group, only 17 individuals underwent next-generation sequencing (NGS) genotyping. It is noteworthy that only 1 patient (5.9%) exhibited MET amplification and no patient harbored C797S mutation. Besides, BRAF V600E mutations were observed in 11.8% of the patients.

Information about second-line treatment strategies in the osimertinib group was accessible for 48 out of 82 patients (58.5%). Among 48 patients, 41 patients (85.4%) were administered chemotherapy, 18 patients (37.5%) underwent anti-angiogenic therapy, 11 patients (22.9%) received immunotherapy, 8 patients (16.7%) were prescribed alternative EGFR-TKIs apart from osimertinib, and 1 patient (2.1%) received mesenchymal-epithelial transition (MET) inhibitors. Remarkably, 10 patients (20.8%) continued osimertinib after progression. In these cases, osimertinib was administered in combination with chemotherapy for 6 patients, with anti-angiogenic therapy for 3 patients, and concurrently with both chemotherapy and anti-angiogenic therapy, as well as savolitinib, for one patient. Furthermore, during a median follow-up period of 20.3 months within the osimertinib group, 23 patients (11.4%) received third-line therapy, while 6 patients (3%) underwent fourth-line and subsequent treatments. The median number of lines of therapy was 1 (range, 1–5) (*Table 3*).

Within 309 patients (76.5%) who underwent second-line treatment in the first-generation EGFR-TKI group, 139 patients (45.0%) were tested positive for the T790M mutation via plasma or tissue-based NGS genotyping. All these individuals subsequently received second-line osimertinib therapy. In addition, 21 patients who were tested negative for the T790M mutation, along with 9 patients whose T790M status remained unknown, also underwent second-line osimertinib treatment. Besides, 118 patients (38.2%) received chemotherapy, 13 patients (4.2%) were administered anti-angiogenic therapy, 16 patients (5.2%) underwent immunotherapy, and 21 patients (6.8%) were treated with alternative EGFR-TKIs. Furthermore, during a median follow-up duration of 30.0 months in the comparator group, 147 patients (36.4%) underwent third-line therapy, and 82 patients (20.3%) received fourth-line and beyond treatments. The median number of therapy lines administered was 2 (range, 1–6).

Discussion

In this multicenter, real-world study in China, we observed that first-line osimertinib had better efficacy and similar safety profiles compared with first-generation EGFR-TKIs for *EGFR*-mutated stage IIIc–IV NSCLC patients, which was consistent with the findings of the FLAURA study. The mPFS was extended by 8.5 months in the osimertinib arm (19.4 months) compared to the comparator arm (10.9 months), with a 53% reduction of risk for disease progression. The Kaplan-Meier curves for PFS clearly showed a separation into two distinct groups at 5 months and remained separated throughout the follow-up period. Moreover, the mOS was 6.2 months longer in the osimertinib group (40.5 months) compared to the comparator group (34.3 months), with a 24% reduction of risk for death. The Kaplan-Meier curves for OS started very close together but diverged at around 20 months, and the gap between two groups increased with longer follow-up. Notably, the follow-up time in the osimertinib group was shorter than that in the first-generation EGFR-TKIs group, which might have an impact on the OS. Subgroup analysis indicated that the PFS advantage of osimertinib over first-generation EGFR-TKIs was consistent across all subgroups. However, only patients who were male, smokers, or had CNS metastases at baseline exhibited a significantly longer OS in the osimertinib group.

To date, numerous studies have affirmed the PFS advantages associated with first-line osimertinib in contrast to first-generation EGFR-TKIs. However, the question of whether first-line osimertinib confers an OS benefit has diverse findings across various investigations. In the FLAURA trial, first-line osimertinib significantly prolonged OS (38.8 *vs.* 31.8 months; P=0.046) (16). In the FLAURA China subgroup analysis, the osimertinib group exhibited a trend towards prolonged OS, although it did not reach statistical significance (33.1 *vs.* 25.7 months; P=0.442) (19). Conversely, in the Japanese subgroup, an opposite trend was observed, with the osimertinib group and the comparator group having OS of 39.9 months *vs.* "not reached" (P=0.215) (30). Furthermore, OS data from other studies exploring the efficacy of first-line osimertinib remained immature (17,31). To the best of our knowledge, our study stood as the first real-world research to support the significant OS extension achieved by osimertinib as observed in the FLAURA trial, further substantiating the superiority of first-line osimertinib over first-generation EGFR-TKIs.

Brain metastasis is a common complication of advanced

Table 3 Second-, third- and above-line of treatments between two groups

Treatment	First-line osimertinib (n=202), n (%)	First-line first generation EGFR-TKIs (n=404), n (%)
Still receiving first-line therapy	98 (48.5)	38 (9.4)
No subsequent anticancer therapy (dead)	22 (10.9)	57 (14.1)
Receiving second-line treatments	82 (40.6)	309 (76.5)
Detail unknown	34 (41.5)	0
Detail known	48 (58.5)	309 (100.0)
Chemotherapy	41 (85.4)	118 (38.2)
Immunotherapy	11 (22.9)	16 (5.2)
Anti-angiogenic therapy	18 (37.5)	13 (4.2)
Other first- or second-generation EGFR-TKIs	8 (16.7)	21 (6.8)
Osimertinib	10 (20.8)	162 (52.4)
MET inhibitors	1 (2.1)	0
Receiving third-line treatments	23 (11.4)	147 (36.4)
Chemotherapy	15 (65.2)	81 (59.1)
Immunotherapy	4 (17.4)	25 (18.2)
Anti-angiogenic therapy	10 (43.5)	33 (24.1)
Other first- or second-generation EGFR-TKIs	4 (17.4)	27 (19.7)
Osimertinib	4 (17.4)	35 (25.5)
MET inhibitors		1 (0.7)
Receiving forth and above-line treatments	6 (3.0)	82 (20.3)
Chemotherapy	4 (66.7)	58 (70.7)
Immunotherapy	1 (16.7)	21 (25.6)
Anti-angiogenic therapy	1 (16.7)	45 (54.9)
Other first- or second-generation EGFR-TKIs	1 (16.7)	28 (34.1)
Osimertinib	0	43 (52.4)

EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; MET, mesenchymal-epithelial transition.

NSCLC, which could influence treatment outcomes (32). Previous studies have demonstrated that osimertinib has better activity in the CNS than first- or second-generation EGFR-TKIs (33-36). Our study showed that osimertinib in the first-line treatment substantially improved PFS compared with standard EGFR-TKIs regardless of CNS metastases at baseline, consistent with results in the FLAURA study. Additionally, osimertinib also demonstrated a prolonged OS compared to first-generation EGFR-TKIs in patients with CNS metastasis, with a 60% reduction in the risk of death. These findings suggested that first-line osimertinib was particularly suitable for patients with brain metastases at baseline.

Approximately 90% of patients with *EGFR*-mutated NSCLC have either an exon 19 deletion or an exon 21 L858R substitution (3,37). Patients with exon 19 deletions have longer PFS compared to those with exon 21 L858R mutations after first-line EGFR-TKIs (38,39). In our study, patients with exon 19 deletions in the matched cohort accounting for 43.9% (230 out of 524) and exon 21 L858R substitutions accounting for 49.6% (260 out of 524) of the detected *EGFR* mutations. Besides, survival outcomes of patients with exon 19 deletion were better than those with exon 21 L858R substitutions, regardless of receiving

osimertinib or first-generation EGFR-TKIs.

Despite its remarkable efficacy, the development of resistance to osimertinib is unavoidable. Mechanisms of resistance can be categorized into two groups: on-target *EGFR*-dependent mechanisms, such as the C797S mutation, and off-target *EGFR*-independent mechanisms, including MET amplification and small cell transformation (40-43). Recently, potential treatments targeting specific acquired resistance, such as *EGFR* antibodies, MET inhibitors, and others have been explored (44-47). However, chemotherapy remains the standard therapy for patients who experience progression after first-line osimertinib. In this real-world study, only 20.7% (17 patients) underwent NGS genotyping after progression to first-line osimertinib. The prevalence of MET amplification or EGFR C797S was 5.9% and 0, respectively, lower than that in other researches (43). Most patients in the osimertinib group received chemotherapy as second-line treatment. Moreover, about 20% (10 patients) continued osimertinib after progression.

In *EGFR*-mutant advanced NSCLC patients, disease progression often occurs after a median of 10–14 months on first-generation EGFR-TKIs (5-9), with approximately half of these patients developing acquired resistance due to the T790M mutation (48,49). The AURA3 trial demonstrated that osimertinib significantly extended PFS of patients acquiring T790M mutation after first-line EGFR-TKIs compared with platinum-pemetrexed chemotherapy (50,51). In our study, among 404 patients in the first-generation EGFR-TKI arm, 309 experienced disease progression, and about half of them acquired the secondary EGFR T790M mutation and received second-line osimertinib.

However, it is essential to emphasize that within 404 patients initially treated with first-generation EGFR-TKIs, 57 patients (14.1%) encountered significant disease deterioration during first-line treatment, resulting in the loss of opportunities for subsequent-line therapies. Similarly, 30% of patients receiving first-line first-generation EGFR-TKIs in the FLAURA trial did not proceed to receive any subsequent therapy after first line of treatment. This underscores that the first-line treatment represented their sole therapeutic opportunity. Therefore, it's recommended to consider the utilization of osimertinib in the first-line setting (the best first).

Both osimertinib and first-generation EGFR-TKIs showed tolerable safety profiles in our study. Most AEs were mild, and there were no treatment-related deaths. Notably, no drug-associated pneumonitis was reported in the osimertinib group, though a real-world study from Japan reported a higher incidence of drug-associated pneumonitis (18% of patients with all grades and 4.6% with grade 3 or above) (52). It is important to consider that the occurrence of AEs in our study was lower than that in clinical trials, as AE reporting primarily relied on medical records from various medical centers due to the retrospective nature of this multicenter real-world study, which could potentially result in underreporting or underestimation of AEs. Additionally, patients experiencing severe AEs might seek medical attention at nearby hospitals and subsequently be lost to follow-up. These factors could contribute to a lower incidence of high-grade AEs and severe pneumonia in this study compared to previous researches. Although the occurrence of high-grade adverse reactions is notably low in this study, it remains crucial to maintain careful monitoring during the course of treatment.

There are several limitations in our study. Firstly, due to the real-world nature of the study, the follow-up duration in the osimertinib group was shorter than that of the first-generation EGFR-TKIs, as osimertinib was approved by the NMPA for first-line treatment later than first-generation EGFR-TKIs. This difference in follow-up duration might have influenced the OS outcomes. Secondly, our study did not include patients receiving second-generation EGFR-TKIs at first line due to the limited number of patients. Thirdly, we did not analyze the relationship between PDL1 expression levels and the efficacy of EGFR-TKIs because data on PDL1 expression in the CAPTRA-Lung database were severely lacking.

Conclusions

In the real-world setting, osimertinib demonstrated significantly longer PFS and OS and similar safety profile compared with first-generation EGFR-TKIs as a first-line treatment for patients with advanced *EGFR*-mutated NSCLC, indicating that osimertinib was an effective and well-tolerated treatment in real world populations. Studies with more patients are needed to confirm these results across diverse geographies and ethnicities.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-577/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-577/coif). A.R. received stock options by IQVIA Holdings Inc. H.H. has received consulting fees from Janssen and Astrazeneca and honoraria from Janssen, Astrazeneca, Neogenomics, and Foundation Medicine. The other authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking Union Medical College Hospital on 24 December 2022 (Ethics Approval Number: I-22PJ1112) and the requirement for individual consent for this retrospective analysis was waived.

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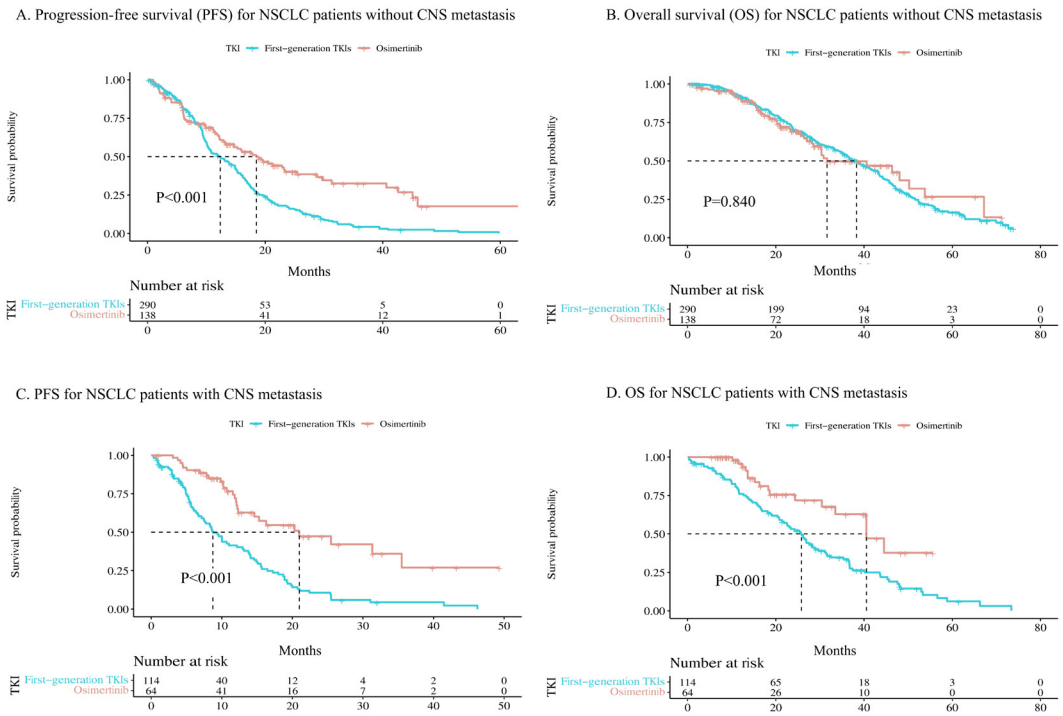

Figure S1 Progression-free survival curves (A,C) and overall survival curves (B,D) for NSCLC patients in subset stratified according to the absence or presence of baseline CNS metastases. PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

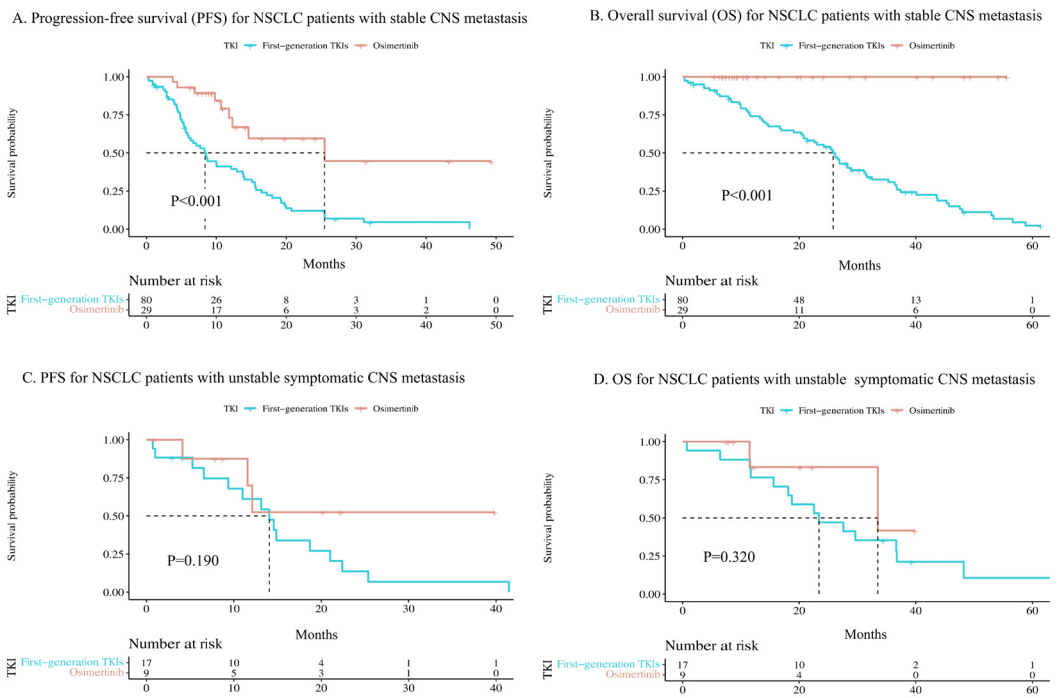

Figure S2 Progression-free survival curves (A,C) and overall survival curves (B,D) for NSCLC patients in subset stratified according to the status of baseline CNS metastases. PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

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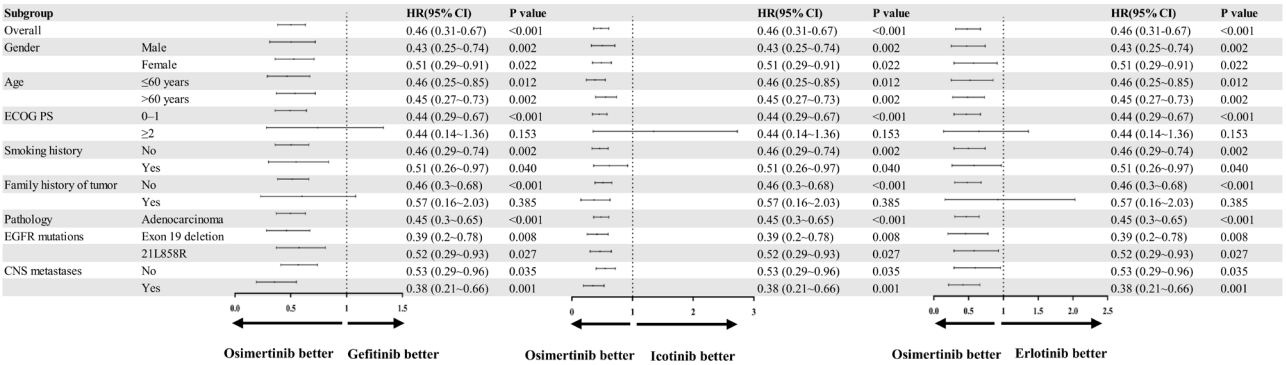

Figure S3 Forest plot for PFS of NSCLC patients in subset stratified according to the first-generation EGFR-TKI types. HR, hazard ratio; PFS, progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

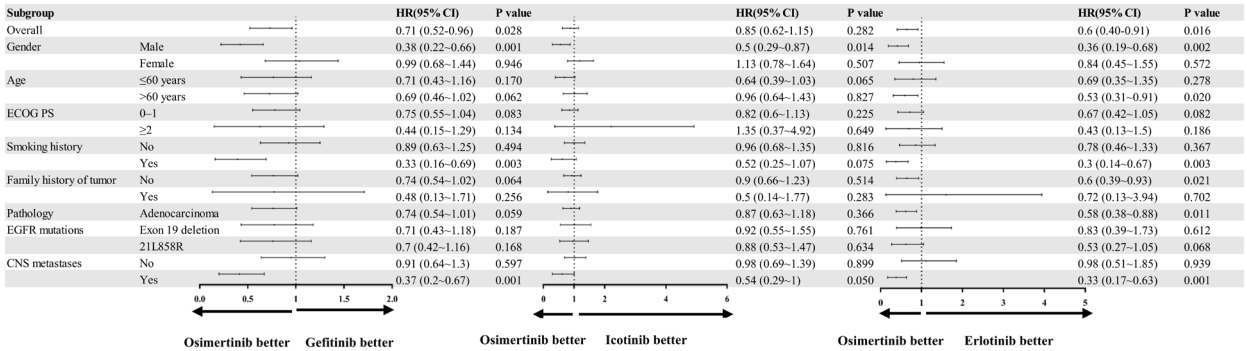

Figure S4 Forest plot for OS of NSCLC patients in subset stratified according to the first-generation EGFR-TKI types. HR, hazard ratio; OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitor.

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