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ORIGINAL ARTICLE

Efficacy and safety of first-line osimertinib in Chinese patients with *EGFR*-mutated advanced non-small cell lung cancer: a prospective, multicenter, non-interventional study (FLOURISH)

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ABSTRACT

Objective: Osimertinib has demonstrated superior efficacy as a first-line treatment for epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) in clinical trials. This study was aimed at providing real-world evidence of osimertinib treatment in Chinese populations.

Methods: This prospective, multicenter, non-interventional study was conducted from July 27, 2020, to April 27, 2022. Treatment-naïve adults (≥18 years of age) with locally advanced or metastatic *EGFR*-mutated NSCLC scheduled to receive first-line osimertinib were included. Of 507 patients screened, 481 were eligible in the full analysis set. The primary endpoint was time to treatment discontinuation (TTD). Secondary endpoints included real-world progression-free survival (rwPFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: Among 481 patients (median age 64.1 years; 62.2% women), the median follow-up was 31.3 months. The mTTD was 24.6 months (95% CI, 22.4–26.7), the median rwPFS was 19.4 months (95% CI, 16.2–20.4), and the mOS was 41.0 months [95% CI, 39.7 to not reached (NR)]. The mOS was 43.1 months (95% CI, 39.7 to NR) in FLAURA-eligible patients *vs.* 33.5 months (95% CI, 26.8 to NR) in FLAURA-ineligible patients. The mOS was 29.3 months (95% CI: 25.4 to NR) in patients with co-mutations *vs.* NR (95% CI: 32.9 to NR) in the cohort with *EGFR*-only mutations. Adverse events occurred in 71.7% of patients, and grade ≥3 events occurred in 11.4%. The safety profiles were similar between FLAURA-eligible and ineligible patients.

Conclusions: First-line osimertinib demonstrated robust effectiveness and manageable safety in real-world Chinese patients with *EGFR*-mutated advanced NSCLC, including those ineligible for clinical trials. Patients with co-mutations showed diminished clinical benefit, thus suggesting a potential need for intensified treatment strategies in this population.

KEYWORDS Osimertinib; epidermal growth factor receptor; non-small cell lung cancer; real-world; co-mutations

Introduction

Lung cancer is the leading cause of cancer-related mortality in China[1]. More than 50% of Asian patients with non-small cell lung cancer (NSCLC) exhibit epidermal growth factor receptor (*EGFR*) mutations[2,3]. Osimertinib, a third-generation *EGFR*-TKI, was approved as a first-line (1L) treatment for patients with *EGFR*m NSCLC, according to results from the FLAURA study. In that study, osimertinib, compared with erlotinib or gefitinib, significantly prolonged the median progression-free survival (PFS) [18.9 *vs*. 10.2 months; hazard ratio (HR), 0.46; 95% confidence interval (CI), 0.37–0.57; $P < 0.001$][4]. Similarly, in the FLAURA China study enrolling exclusively Chinese patients, osimertinib demonstrated a longer median PFS (mPFS) than first-generation *EGFR*-TKIs (17.8 *vs*. 9.8 months; HR, 0.56; 95% CI, 0.37–0.85)[5].

However, clinical trials differ from real-world practice because the latter often involves older patients or individuals with more comorbidities. For example, in a real-world study in the United States, 55% of patients were classified as FLAURA-ineligible and experienced shorter median osimertinib time to treatment discontinuation (TTD) than FLAURA-eligible populations (12.2 *vs*. 31.1 months)[6]. Therefore, prospective real-world studies with larger sample sizes are needed to validate the effectiveness and safety of osimertinib among Chinese patients with NSCLC with *EGFR* mutations in real-world settings.

In recent years, real-world studies have preliminarily confirmed the effectiveness and safety of osimertinib initiated in patients with *EGFR*m NSCLC[7-10]. Although existing real-world investigations have provided preliminary insights, several limitations remain. First, the predominance of retrospective study designs introduced inherent selection bias. Second, the limited sample sizes in the current published prospective real-world evidence have left unresolved questions, particularly regarding clinical efficacy in subgroups such as patients with *EGFR* co-mutations or those not meeting FLAURA criteria. These gaps further underscore the need for prospective, multicenter investigations.

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Materials and methods

Study design and patients

The FLOURISH study (NCT04391283) was a prospective, multicenter, non-interventional study conducted at 22 sites across China. All participating centers were tertiary care academic hospitals with expertise in thoracic oncology. Eligible patients were ≥18 years of age and had a histological or cytological diagnosis of locally advanced or metastatic NSCLC bearing *EGFR* mutations. Patients were treatment naïve and were scheduled to receive 1L osimertinib (80 mg once daily). Diagnosis and treatment decisions were made by clinical physicians according to treatment guidelines and clinical practice. Patients participating in other interventional clinical trials aimed at treating locally advanced or metastatic NSCLC and patients with concomitant conditions considered unsuitable for osimertinib by their physicians were excluded. The study protocol was approved by the institutional ethics committee at each participating center. All patients provided written informed consent to participate. Baseline data were obtained from hospital records and were therefore subject to potential missingness; missing data were not imputed, and cases with missing data were not excluded (trial registration No. NCT04391283).

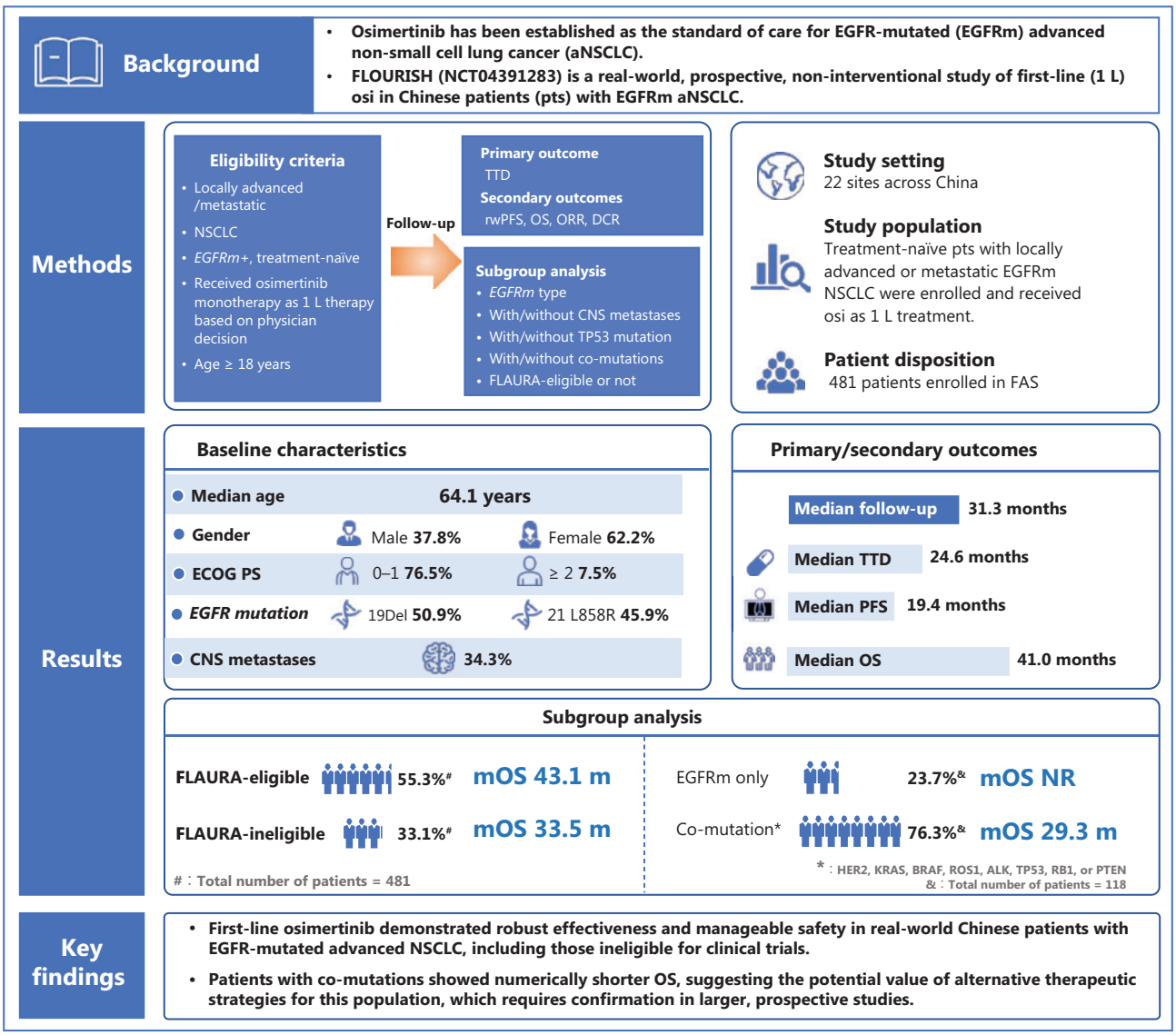
Endpoints

The primary endpoint was TTD, defined as the time from the first dose of osimertinib to the date of osimertinib discontinuation for any reason. Secondary endpoints included real-world progression-free survival (rwPFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. rwPFS was defined as the time from the first dose of osimertinib until disease progression recorded in the CRF or death, whichever occurred first. Disease progression was assessed by investigators according to real-world clinical practice, usually on the basis of the Response Evaluation Criteria In Solid Tumors (RECIST v1.1). OS was defined as the time from the first dose of osimertinib to death due to any cause. ORR was defined as the percentage of patients achieving a complete or partial response, as assessed by investigators and recorded in the CRF. DCR was defined as the percentage of patients with non-progression, as assessed by investigators and recorded in the CRF.

Tumor response was evaluated according to RECIST v1.1 criteria by the investigators. Safety and tolerability assessments included adverse events (AEs) graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, on the basis of clinical practice.

Next-generation sequencing

Tumor tissue samples were collected at baseline. Next-generation sequencing (NGS) was performed on FFPE tissue



Study flowchart The FLOURISH study (NCT04391283) was a prospective, multicenter, non-interventional study evaluating first-line osimertinib in 481 treatment-naïve Chinese patients with *EGFR*-mutated advanced NSCLC across 22 sites. First, the study background and rationale are presented, highlighting the limited real-world evidence of first-line osimertinib in Chinese populations. Subsequently, the study design, patient flow, endpoint definitions, and subgroup analysis framework are described, including analyses by *EGFR* mutation type, CNS metastasis status, FLAURA eligibility, and co-mutation status. Next, key efficacy outcomes are summarized for the FAS population. Consistent clinical benefit was also observed in FLAURA-ineligible patients, whereas patients bearing co-mutations exhibited diminished clinical benefit. Finally, the key findings and clinical implications are highlighted. CNS, central nervous system; DCR, disease control rate; *EGFR*, epidermal growth factor receptor; FAS, full analysis set; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; rwPFS, real-world progression-free survival; TTD, time to treatment discontinuation.

and plasma-derived cfDNA samples by using panels from Burning Rock Biotech (Guangzhou, China), the central laboratory in this study. Tissue samples were analyzed with the 518-gene OncoScreen™ Plus system at a sequencing depth of 1,000×. Variant detection and annotation were performed with specialized bioinformatics pipelines.

Statistical analysis

Because this study is descriptive in nature and involved no pre-planned hypotheses, no formal calculation of sample size was performed. A total of 500 patients were planned to be enrolled, on the basis of assumptions of an mTTD of 20.8 months and

a 95% CI for the median of approximately 18.6–23.3 months. Therefore, the target enrollment of approximately 500 patients was determined to ensure adequate representation of real-world clinical practice and sufficient precision for descriptive analyses of the primary endpoint.

Statistical analyses were performed in SAS version 9.4. Continuous variables are summarized as numbers of patients (*n*), mean, standard deviation (SD), median, quartiles (Q1, Q3), minimum, and maximum. Categorical variables are summarized as frequency counts and percentages. No imputation of missing data was performed, and all statistical analyses were conducted on non-missing data only. For ORR and DCR, the 95% CIs were calculated with the Clopper–Pearson exact method. For time-to-event endpoints (TTD, rwPFS, and OS), the Kaplan–Meier method was used to estimate the median, and corresponding 95% CIs were calculated with the Brookmeyer–Crowley method. To further explore osimertinib's efficacy in patients with NSCLC with various disease characteristics, we conducted subgroup analyses. TTD, rwPFS, and OS were analyzed according to *EGFR*m type (exon 21 L858R *vs*. exon 19 deletion) and central nervous system (CNS) metastasis (presence *vs*. absence).

In addition, patients were categorized into FLAURA-eligible and FLAURA-ineligible groups according to the critical inclusion/exclusion criteria from the FLAURA trial (**Table S3**). On the basis of baseline NGS results, subgroup analyses described outcomes in the *EGFR*-only mutation group and the *EGFR* co-mutation group (*EGFR* mutation combined with additional co-mutations in genes including *HER2*, *KRAS*, *BRAF*, *ROS1*, *ALK*, *TP53*, *RB1*, or *PTEN*). Patients were also categorized according to the presence or absence of *TP53* co-mutations. TTD, PFS, and OS were calculated for each subgroup. All subgroup analyses were descriptive and were not adjusted for multiplicity, and no formal hypothesis testing was performed for the subgroup analyses.

Results

From July 27, 2020, to April 27, 2022, a total of 507 patients were screened at 22 sites across China, among whom 481 eligible patients [denoted the full analysis set (FAS)] received at least 1 dose of osimertinib monotherapy as the 1L treatment. At the data cut-off (October 30, 2024), the median follow-up duration was 31.3 months (95% CI: 30.2–32.3).

Patients and treatment

The baseline characteristics of the FAS population are presented in **Table 1**. The median age was 64.1 years (range: 27.1–88.1). Overall, 62.2% of patients were women, and 76.5% had a performance status (PS) of 0–1. CNS metastases were present in 165 patients (34.3%). The most frequent *EGFR*-activating mutations were exon 19 deletions (50.9%) and exon 21 L858R mutations (45.9%). *De novo* T790M mutation was reported in 10 patients (2.1%).

Effectiveness evaluation

Overall effectiveness

At the data cut-off, 426 (88.6%) of 481 patients had tumor response evaluations. ORR and DCR were calculated for both the FAS and the evaluable population. The evaluable population analysis served as a sensitivity analysis to assess the robustness of response outcomes. For the FAS, the ORR was 56.3% (271/481; 95% CI: 51.8–60.8), and the DCR was 84.6% (407/481; 95% CI: 81.1–87.7). Among patients with available tumor response data (n = 426), the ORR was 63.6% (271/426; 95% CI: 58.8–68.2), and the DCR was 95.5% (407/426; 95% CI: 93.1–97.3) (**Table S4**). After a median follow-up of 31.3 months, 267 patients (55.5%) discontinued osimertinib therapy. The median TTD was 24.6 months (95% CI: 22.4–26.7) (**Figure 1**). Reasons for discontinuation included disease progression (33.3%), death (35.2%), AEs (7.9%), and other factors (23.6%) (**Table S2**). Progression events occurred in 274 patients (57.0%), and 169 patients (35.1%) died. The median rwPFS was 19.4 months (95% CI: 16.2–20.4), and the mOS was 41.0 months (95% CI: 39.7 to NR) (**Figure 1**).

Subgroup analysis of effectiveness

For the 245 patients (50.9%) with exon 19 deletion mutations, the median TTD, rwPFS, and OS were 28.6 months (95% CI: 25.2–32.7), 20.6 months (95% CI: 17.7–22.1), and 41.0 months (95% CI: 39.7 to NR), respectively (**Figures 2 and S1**). Among the 221 patients (45.9%) with exon 21 L858R mutations, the median TTD was 20.5 months (95% CI: 18.3–23.5), the median rwPFS was 15.4 months (95% CI: 13.2–19.5), and the mOS was 37.2 months (95% CI: 30.0 to NR) (**Figures 2 and S1**).

At baseline, CNS metastases were present in 165 patients (34.3%). For these patients, the median TTD was 22.2 months (95% CI: 19.6–25.7), the median rwPFS was 15.6 months (95% CI: 14.1–20.3), and the mOS was 40.1 months (95% CI: 39.7 to NR) (**Figures 2 and S1**). For the 207 patients (43.0%) without CNS metastases, the median TTD, rwPFS, and OS were 25.3 months (95% CI: 22.4–29.3), 19.7 months (95% CI: 15.7–21.4), and 41.0 months (95% CI: 36.8 to NR), respectively (**Figures 2 and S1**).

Additionally, patients in the FAS were categorized as FLAURA-eligible or FLAURA-ineligible according to the inclusion/exclusion criteria outlined in the FLAURA trial protocol[4] (**Table S3**). Of these, 159 patients (33.1%) were classified as FLAURA-ineligible (**Table S1**), and their median TTD, rwPFS, and OS were 21.4 months (95% CI: 17.7–26.8), 15.1 months (95% CI: 12.3–19.4), and 33.5 months (95% CI: 26.8 to NR), respectively (**Figures 2 and S1**). In the FLAURA-eligible group (n = 266, 55.3%), the median TTD, rwPFS, and OS were 25.6 months (95% CI: 23.3–28.8), 20.4 months (95%

Table 1 Demographics and disease characteristics of the FAS population at baseline

Characteristics	FAS (*n* = 481)
Age, years, median (range)	**64.1 (27.1, 88.1)**
Sex, *n* (%)	
Female	299 (62.2)
Male	182 (37.8)
Smoking status, *n* (%)	
Current	38 (7.9)
Never	328 (68.2)
Former	53 (11.0)
Unknown	62 (12.9)
ECOG PS, *n* (%)	
0–1	368 (76.5)
≥2	36 (7.5)
Unknown	77 (16.0)
Disease extent at trial entry, *n* (%)	
Locally advanced	31 (6.4)
Metastatic	450 (93.6)
Histologic type, *n* (%)	
Adenocarcinoma	462 (96.0)
Squamous cell carcinoma	7 (1.5)
Adenosquamous carcinoma	4 (0.8)
Others[a]	8 (1.7)
EGFR mutation type, *n* (%)	
Sensitive mutations[b]	
Exon 19 deletion	245 (50.9)
Exon 21 L858R	221 (45.9)
Uncommon mutations[c]	6 (1.2)
Unknown[d]	10 (2.1)
De novo T790M mutations[e]	10 (2.1)
CNS metastases, *n* (%)	165 (34.3)

[a]Others: 8 patients were diagnosed with NSCLC, but the specific histological subtypes were not obtained. [b]One patient had both the exon 19del and exon 21 L858R sensitive mutations simultaneously. [c]Uncommon mutations: 2 patients had T790M mutation, 3 patients had rare mutations (including 1 patient with G179S, E709K mutation, 1 patient with exon 21 L861Q mutation, and 1 patient with exon 18, exon 20 mutation), and 1 patient had a T790M mutation combined with a rare mutation (exon 21 L861Q mutation). [d]Unknown: *EGFR* mutation was confirmed, but the specific mutation site was undetermined. [e]*De novo* T790M mutations: 7 patients had *EGFR* sensitive mutations, and the other 3 patients did not. FAS, full analysis set; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; CNS, central nervous system; NSCLC, non-small cell lung cancer.

CI: 17.6–21.5), and 43.1 months (95% CI: 39.7 to NR), respectively (**Figures 2 and S1**). The ORR and DCR of each subgroup are shown in **Table S5**.

Effects of baseline co-mutations on osimertinib treatment efficacy

Baseline NGS data obtained from 118 patients revealed 2 distinct mutation profiles: 23.7% (28/118) patients had only *EGFR* mutations, whereas 76.3% (90/118) had additional gene co-mutations (in *HER2*, *KRAS*, *BRAF*, *ROS1*, *ALK*, *TP53*, *RB1*, or *PTEN*) (**Figure 3**). In these subgroups, the median TTD was 32.8 months (95% CI: 21.8 to NR) for patients with *EGFR* mutations alone and 24.6 months (95% CI: 20.2–26.6) for those with co-mutations (**Figure 2**). The median rwPFS was 20.8 months (95% CI: 7.4–25.1) in patients with only *EGFR* mutations, compared with 16.7 months (95% CI: 14.6–20.6) in those with co-mutations. Notably, the mOS was NR (95% CI: 32.9 to NR) in the *EGFR*-only group but was 29.3 months (95% CI: 25.4 to NR) in the co-mutation group (**Figures 2 and S1**).

Among the 80 (67.8%) patients bearing *TP53* co-mutations, the median TTD, rwPFS, and OS were 23.6 months (95% CI: 19.1–26.4) (**Figure 2**), 16.7 months (95% CI: 14.6–20.6), and 28.5 months (95% CI: 25.3 to NR), respectively (**Figure S1**). In contrast, for the 38 (32.2%) patients without *TP53* co-mutations, the median TTD, rwPFS, and OS were 32.8 months (95% CI: 24.0 to NR) (**Figure 2**), 20.8 months (95% CI: 9.6–23.7), and NR (95% CI: 32.9 to NR), respectively (**Figures 2 and S1**). The ORR and DCR of each subgroup are shown in **Table S5**.

Safety evaluation

In the FAS, 345 patients (71.7%) experienced at least 1 AE, and 252 (52.4%) experienced at least 1 treatment-related AE. Grade ≥3 AEs were reported in 55 patients (11.4%), and serious AEs occurred in 23 patients (4.8%). AEs leading to dose interruption were reported in 3 patients (0.6%), whereas AEs resulting in treatment discontinuation occurred in 22 patients (4.6%). Three patients (0.6%) experienced fatal AEs (**Table 2**). Among them, 2 fatal AEs (myocardial infarction, pneumonitis) were considered unrelated to the treatment by the investigators; however, the possibility that one fatal AE (myocardial infarction) was treatment related could not be excluded.

The safety profile of patients in the FLAURA-ineligible subgroup (*n* = 159) was comparable to that in the overall FAS

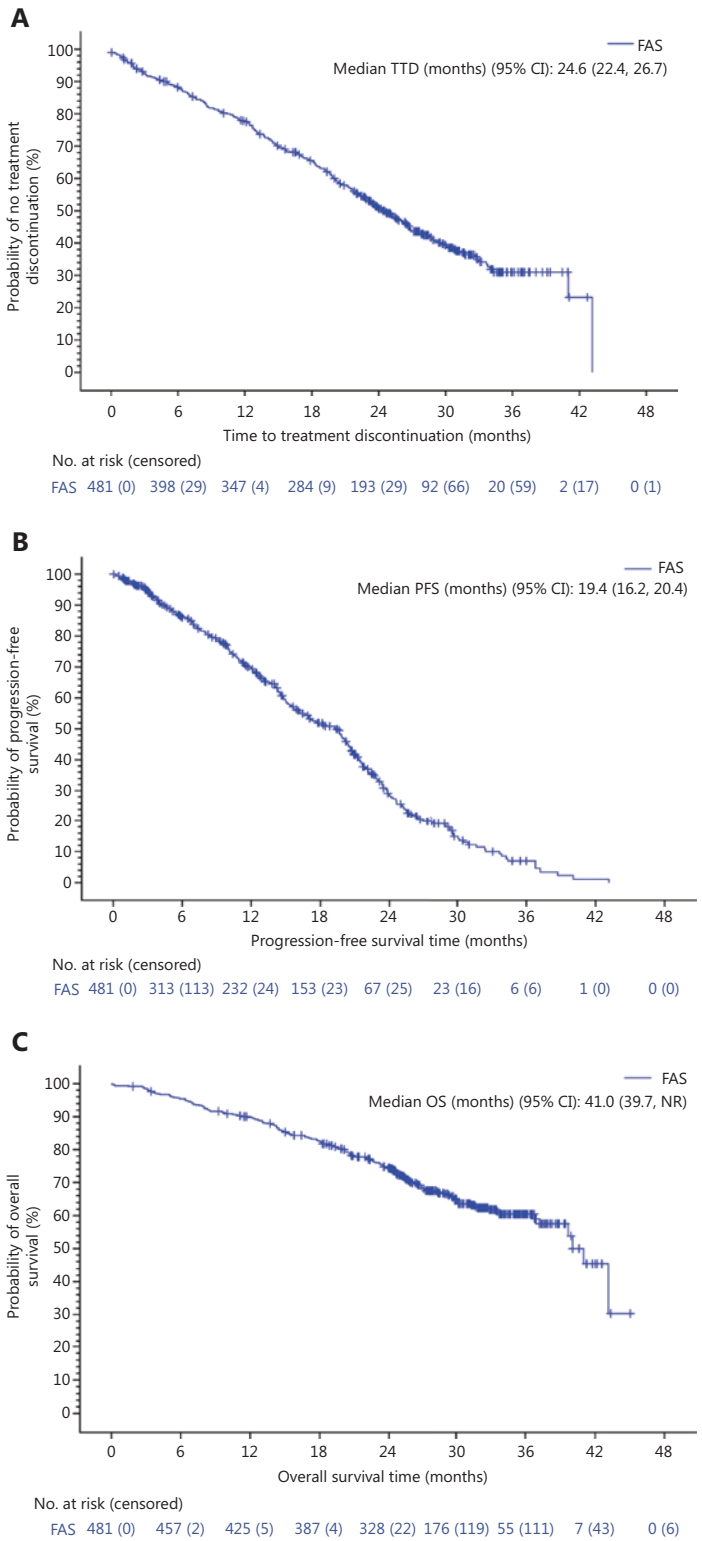


Figure 1 Kaplan–Meier estimates of TTD, PFS, and OS in the FAS population. (A) Median TTD. (B) Median rwPFS. (C) mOS. FAS, full analysis set; TTD, time to treatment discontinuation; rwPFS, real-world progression-free survival; OS, overall survival; CI, confidence interval.

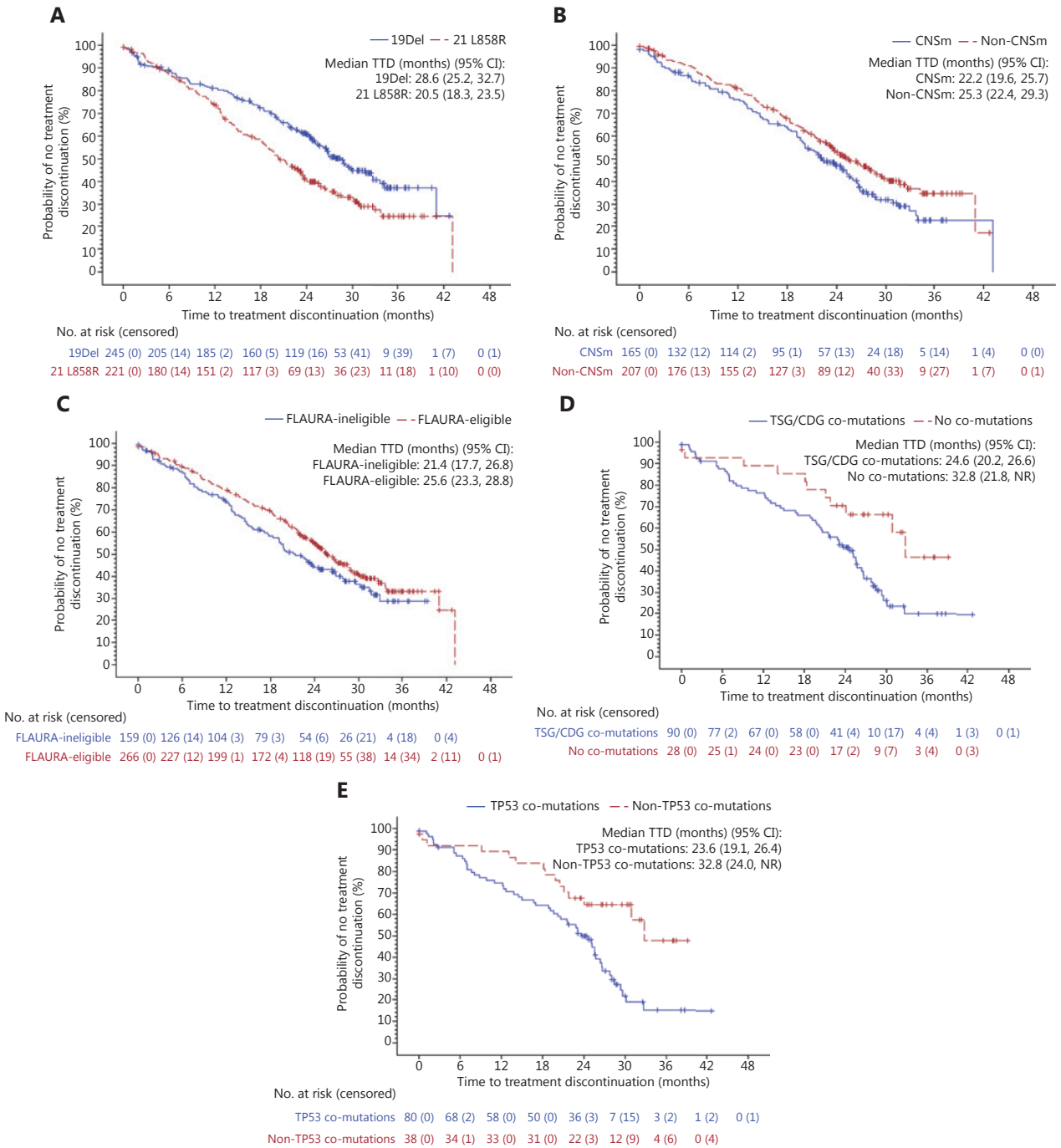


Figure 2 Kaplan–Meier estimates of TTD in patient subgroups. (A) Median TTD in the exon 19 deletion (blue curve) and exon 21 L858R mutation (red curve) subgroups. (B) Median TTD in the CNS metastasis (blue curve) and non-CNS metastasis (red curve) subgroups. (C) Median TTD in the FLAURA-ineligible (blue curve) and FLAURA-eligible (red curve) subgroups. (D) Median TTD in patients with co-mutations (blue curve) or without co-mutations (red curve). (E) Median TTD in patients with TP53 co-mutations (blue curve) or without TP53 co-mutations (red curve). TTD, time to treatment discontinuation; CNS, central nervous system; *EGFR*, epidermal growth factor receptor; CDG, cancer driver genes; TSG, tumor suppressor genes; CI, confidence interval.

population. In this subgroup, AEs occurred in 114 patients (71.7%), of whom 91 (57.2%) experienced treatment-related AEs. Grade ≥3 events occurred in 21 patients (13.2%), including 12 (7.5%) treatment-related cases. Among patients with PS ≥2 (n = 36), AEs were reported in 27 patients (75.0%), and grade ≥3 events were reported in 5 patients (13.9%).

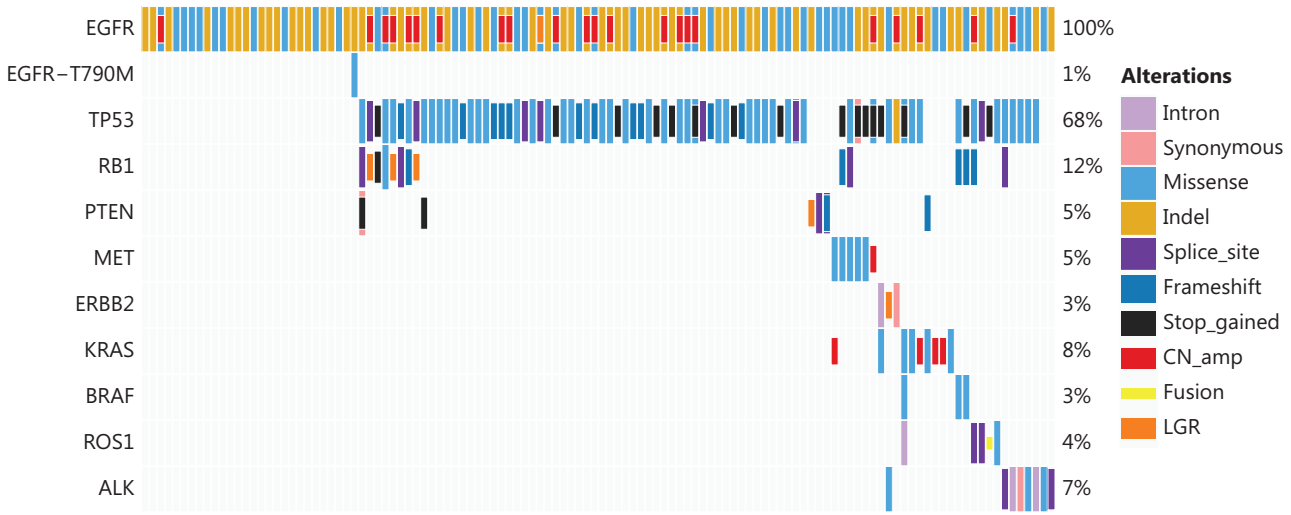


Figure 3 Distribution of gene aberrancies detected by baseline next-generation sequencing. Landscape of genetic alterations identified in 118 patients who underwent baseline NGS analysis. Each column represents an individual patient, and each row represents a specific gene. NGS, next-generation sequencing.

Table 2 Safety overview of patients in the FAS

	FAS (*n* = 481)	FLAURA ineligible (*n* = 159)
	Number of patients, *n* (%)	
Any grade AE*	345 (71.7)	114 (71.7)
Treatment related	252 (52.4)	91 (57.2)
Grade ≥3 AE*	55 (11.4)	21 (13.2)
Treatment related	30 (6.2)	12 (7.5)
Serious AE	23 (4.8)	9 (5.7)
Treatment related	2 (0.4)	1 (0.6)
AE leading to dose interruption	3 (0.6)	1 (0.6)
AE leading to treatment discontinuation	22 (4.6)	9 (5.7)
AE leading to death	3 (0.6)	0 (0)

*AE by maximum reported CTCAE grade. FAS, full analysis set; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Discussion

This study was the first large-scale, prospective, real-world investigation, to our knowledge, examining the outcomes of 1L osimertinib in Chinese patients with *EGFR*m NSCLC. Patients with poor PS, various comorbidities, and other exclusion criteria from the FLAURA trial were included, thereby confirming the effectiveness and safety of 1L osimertinib in a broader patient population. Furthermore, our findings suggested that patients with co-mutations might experience diminished clinical benefits from osimertinib monotherapy; therefore, intensified treatment strategies might be necessary in these patients.

Our real-world study indicated a median rwPFS of 19.4 months and an mOS of 41.0 months, values comparable to those in the FLAURA trial (mPFS 18.9 months, OS 38.6 months), despite our cohort's higher baseline CNS metastasis prevalence (34.3% *vs.* 20.8%) and higher ECOG ≥2 proportion (7.5% *vs.* 0%)[11]. These results aligned with those from previous real-world studies. For example, the prospective Reiwa study[9], in Japanese patients treated with 1L osimertinib, has reported an mPFS of 20 months and mOS of 41 months. Similarly, the retrospective CAPTRA-Lung study[12], in Chinese patients receiving 1L osimertinib, has reported an mPFS of 19.4 months and an mOS of 40.5 months. The prospective FLOWER study[13], evaluating osimertinib in Italy, has reported an mPFS of 18.9 months. In addition, our real-world study indicated an ORR of 56.3% (95% CI, 51.8–60.8) and a DCR of 84.6% (95% CI, 81.1–87.7) in the FAS. Notably, a substantial proportion of patients lacked tumor response evaluations, thus potentially influencing our estimates. To enhance interpretability, we also calculated ORR and DCR in the evaluable population. Our findings highlight the importance of systematically capturing tumor response assessments to minimize missingness in future real-world studies.

Exploratory subgroup analyses described variations across different patient groups. In our study, the median rwPFS was 19.7 months in patients without CNS metastases and 15.6 months in those with CNS metastases. Additionally, the median rwPFS was 20.6 months in patients bearing exon 19 deletion mutations and 15.4 months in those with exon 21

L858R mutations. These results were consistent with findings from the FLAURA study[4] and other real-world evidence[14]. Collectively, our findings reinforce osimertinib's position as a 1L therapy for *EGFR*m NSCLC.

Notably, inherent differences exist between patients in clinical trials *vs*. real-world practice. Therefore, our exploration of whether patients not meeting FLAURA criteria might still benefit from osimertinib was essential. In a study by Viray et al.[6], 55% of patients were classified as FLAURA-ineligible, and the mOS was 16.5 months in the FLAURA-ineligible group and NR in the FLAURA-eligible group. In our study, 55.3% (266/481) of patients were classified as FLAURA-eligible, whereas 33.1% (159/481) were classified as FLAURA-ineligible, predominantly because of comorbidities (71.7%) and ECOG ≥2 (22.6%). In the FLAURA-ineligible group, the median TTD, rwPFS, and OS were 21.4 months, 15.1 months, and 33.5 months, respectively. In the FLAURA-eligible group, these values were 25.6 months, 20.4 months, and 43.1 months, respectively. However, the mOS in our FLAURA-ineligible group was longer than that in the FLAURA-ineligible group reported by Viray et al.[6] This discrepancy might be due to differences in classification criteria between studies. The FLAURA-ineligible subgroup in the retrospective study by Viray et al.[6] had more severe clinical characteristics and did not include active infections as a criterion. Our study included more patients with active infections in the FLAURA-ineligible group, who might have met FLAURA criteria after antimicrobial treatment, thus potentially leading to improved outcomes. Nonetheless, our findings were consistent with those of Viray et al.[6] in indicating that patients classified as FLAURA-ineligible can still benefit from osimertinib, although the benefits are greater in FLAURA-eligible patients.

Although osimertinib has demonstrated superior efficacy, the considerable variation in the duration of responses among populations emphasized the need to identify subsets of patients with poorer outcomes who might benefit from more aggressive treatments. Previous studies on first-generation *EGFR*-TKIs have shown that concomitant gene mutations significantly compromise therapeutic efficacy in *EGFR*m NSCLC. The BENEFIT study[15] has demonstrated shorter PFS in patients bearing concurrent driver mutations (HR = 1.78) or tumor suppressor gene alterations (HR = 2.66) than in patients with *EGFR* mutations alone. Hu et al.[16] have also reported inferior outcomes in patients with *EGFR*m NSCLC with co-mutations in *PIK3CA*, *ALK*, *HER2*, *ROS1*, or *KRAS* (mPFS: 6.0 *vs*. 10.9 months; mOS: 17.6 *vs*. 21.0 months).

Although the predictive value of co-mutations has been well characterized for first-generation TKIs, the effects of co-mutation profiles on osimertinib efficacy remain inadequately defined. In a previous prospective study, patients with concurrent TP53 mutations or MET amplification experienced worse clinical outcomes than patients without these co-mutations when treated with 1L osimertinib in a real-world setting[17]. However, whether other co-mutations might affect osimertinib monotherapy outcomes has not been explored prospectively in real-world studies. To our knowledge, our study is the first prospective real-world analysis exploring the relationship between osimertinib efficacy and co-mutations involving other driver and tumor suppressor genes. Baseline NGS data from 118 patients revealed that 90 (76.3%) had additional gene co-mutations (in *HER2*, *KRAS*, *BRAF*, *ROS1*, *ALK*, *TP53*, *RB1*, or *PTEN*). Patients with these co-mutations had shorter median TTD and OS than patients with *EGFR* mutations alone (mTTD: 24.6 months *vs*. 32.8 months; mOS: 29.3 months *vs*. NR). Furthermore, *TP53* mutations, which are frequently observed in NSCLC, were detected in 80 (67.8%) of the patients who had baseline NGS data. Patients with *TP53* co-mutations had shorter median TTD and OS than those without *TP53* mutations. Collectively, our findings suggested that co-mutations might limit clinical benefit from osimertinib monotherapy.

The variability in treatment effectiveness among subgroups might arise from distinct molecular mechanisms across different co-mutation subtypes. Tumor suppressor genes such as *TP53*, *RB1*, and *PTEN* lose their normal function, thus resulting in inhibition of apoptosis and acceleration of cell cycle progression, and ultimately promoting tumor growth[18-20]. In contrast, driver gene co-mutations, such as *MET*/*HER2* amplifications and *KRAS*/*BRAF* mutations, enhance tumor invasiveness by activating alternative signaling pathways[21-24]. These findings underscore the importance of exploring alternative therapeutic strategies for patients bearing co-mutations.

Recent studies, including FLAURA-2[25] and MARIPOSA[26], have evaluated combination therapies for advanced *EGFR*m NSCLC. These studies have demonstrated that osimertinib combined with chemotherapy or lazertinib combined with amivantamab achieves superior outcomes to osimertinib monotherapy, regardless of patients' co-mutation status. Specifically, the FLAURA-2 study[25] analyzed baseline tissue samples from 141 patients, of whom 79 had *TP53* mutations. Patients with baseline *TP53* co-mutations who received osimertinib plus chemotherapy had longer mPFS than those receiving osimertinib alone (HR = 0.57). Similarly, in the MARIPOSA study[26], amivantamab combined with lazertinib, compared with osimertinib alone, significantly prolonged mPFS in patients with *TP53* co-mutations (18.2 *vs*. 12.9 months; HR = 0.65, P = 0.003). However, because of limited sample sizes, larger prospective studies remain necessary. To address this gap, the ongoing TOP study[27] is aimed at evaluating the efficacy and safety of osimertinib plus chemotherapy *vs*. osimertinib alone as a 1L treatment in patients with *EGFR*-sensitive NSCLC with concurrent *TP53* mutations. The results from the TOP study are highly anticipated. Our exploratory analysis highlighted a possible association between co-mutations and diminished osimertinib efficacy, thus underscoring the need for further evaluation through larger prospective trials.

Previous real-world studies have confirmed the safety profile of osimertinib. In the Reiwa study, the incidence of grade ≥3 AEs was 23.3%. In the FLOWER study[13], 87.3% of patients experienced AEs. Additionally, a real-world study by Kishikawa et al.[28] has reported an AE incidence of 89.3%, with grade ≥3 AEs occurring in 26.8% of patients. Our safety results aligned with these prior reports and identified no new safety signals. Additionally, previous studies did not specifically evaluate safety in FLAURA-ineligible populations. To our knowledge, our study is the first to demonstrate the safety and efficacy of osimertinib in this subgroup. Notably, patients with PS ≥2 exhibited an AE incidence comparable to that in the general population, thus supporting continued use of osimertinib in these patients in real-world clinical practice. The safety profile in the FLAURA-ineligible subgroup was similar to that observed in the FAS population, and no additional safety concerns were identified.

This study has several limitations. First, because of the study's real-world nature, data were primarily derived from medical records and investigator assessments, thus resulting in missing baseline characteristics for some patients. This aspect reflected routine clinical practice, in which comprehensive documentation was not always performed. The potential for selection bias from such missing data should be acknowledged. Second, in this observational study, subgroup analyses were descriptive, and were neither based on pre-specified statistical hypotheses nor adjusted for multiplicity. Furthermore, certain subgroups had relatively small sample sizes. Therefore, our results provide only preliminary signals and directions and should be interpreted with caution. Further validation is warranted.

In conclusion, osimertinib demonstrated robust efficacy and manageable safety profiles in treatment-naïve patients with *EGFR*m advanced NSCLC in real-world settings. Patients classified as FLAURA-ineligible also benefited clinically and exhibited tolerable safety profiles. Our exploratory analysis indicated inferior real-world clinical outcomes of 1L osimertinib in patients with *EGFRm* bearing driver and/or tumor suppressor genes co-mutations, thus suggesting a potential need for more aggressive treatment strategies for this population. However, further prospective studies are required to validate this finding.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Data availability statement

The data generated in this study are available on request from the corresponding author.

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