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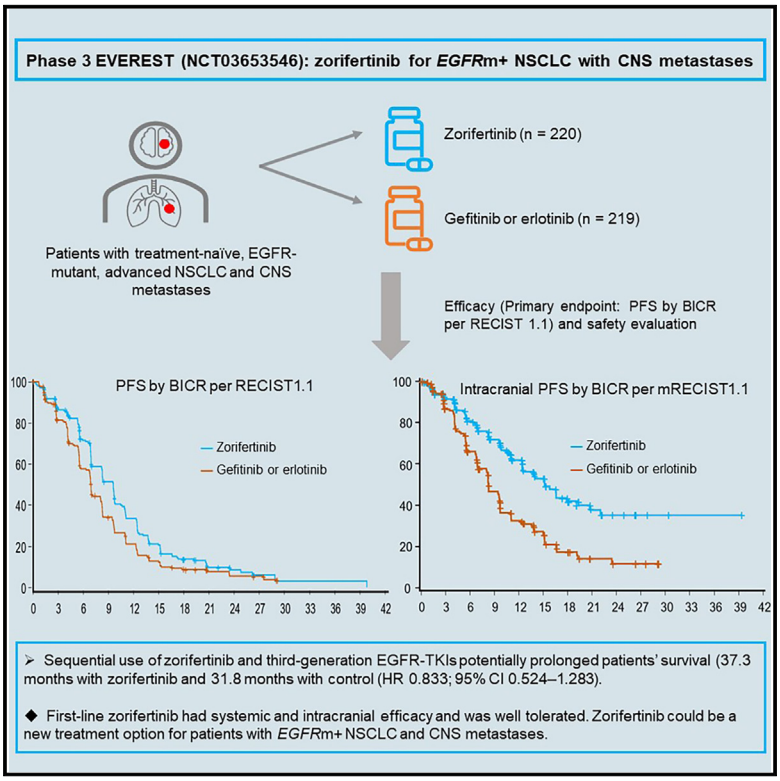
First-line zorifertinib for *EGFR*-mutant non-small cell lung cancer with central nervous system metastases: The phase 3 EVEREST trial

Graphical abstract



Highlights

- EVEREST was the first phase 3 RCT in patients with *EGFR*m+ NSCLC and CNS metastases
- Zorifertinib improved systemic and intracranial PFS versus first-generation EGFR-TKIs
- Zorifertinib followed by third-generation EGFR-TKIs potentially prolonged OS
- Zorifertinib could be a new treatment option for *EGFR*m+ NSCLC with CNS metastases

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In brief

Zhou et al. conducted the first phase 3 randomized controlled trial exclusively in patients with epidermal growth factor receptor gene-mutated non-small cell lung cancer and central nervous system metastases; the results suggest that zorifertinib is a promising new treatment option for this patient population.

Translation to Patients

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First-line zorifertinib for *EGFR*-mutant non-small cell lung cancer with central nervous system metastases: The phase 3 EVEREST trial

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CONTEXT AND SIGNIFICANCE Central nervous system (CNS) metastases are common and confer a poor prognosis in patients with epidermal growth factor receptor gene-mutated (*EGFR*m+) non-small cell lung cancer (NSCLC). There are currently no medications specifically for the treatment of brain metastases; a treatment that can target tumors both outside and inside of the CNS is needed. The EVEREST trial was the first randomized controlled trial exclusively in patients with advanced *EGFR*m+ NSCLC and CNS metastases. First-line zorifertinib significantly improved systemic and intracranial progression-free survival (PFS) versus first-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs). Sequential use of zorifertinib and third-generation EGFR-TKIs showed the potential to prolong patients' survival. The results favor zorifertinib as a novel, well-validated first-line option for patients with *EGFR*m+ NSCLC and CNS metastases.

SUMMARY

Background: Zorifertinib (AZD3759), an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) with high blood-brain barrier penetration capability, demonstrated promising intracranial and systemic antitumor activity in phase 1 and 2 studies in central nervous system (CNS)-metastatic patients.
Methods: In this phase 3 EVEREST trial (ClinicalTrials.gov: NCT03653546), patients with *EGFR*-sensitizing mutations, advanced treatment-naive non-small cell lung cancer (NSCLC), and non-irradiated symptomatic or asymptomatic CNS metastases were randomized (1:1) to zorifertinib or first-generation EGFR-TKI (gefitinib or erlotinib; control). The primary endpoint was blinded independent central review (BICR)-assessed progression-free survival (PFS) per RECIST1.1.
Findings: Overall, 439 patients were randomized (zorifertinib $n = 220$; control $n = 219$). Most patients had the *EGFR* L858R mutation (55%) or >3 CNS lesions (54%). Median PFS was significantly longer with zorifertinib

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versus control (9.6 versus 6.9 months; hazard ratio [HR], 0.719; 95% confidence interval [CI], 0.580–0.893; $p = 0.0024$). Zorifertinib significantly prolonged intracranial PFS versus control (BICR per modified RECIST1.1: HR, 0.467; 95% CI, 0.352–0.619; investigator per RANO-BM: HR, 0.627; 95% CI, 0.466–0.844). Overall survival (OS) was immature; the estimated median OS was 37.3 months with zorifertinib and 31.8 months with control (HR, 0.833; 95% CI, 0.524–1.283) in patients subsequently treated with third-generation EGFR-TKIs. Safety profiles were consistent with previously reported data for zorifertinib.

Conclusions: Zorifertinib significantly improved systemic and intracranial PFS versus first-generation EGFR-TKIs; adverse events were manageable. Sequential use of zorifertinib and third-generation EGFR-TKIs showed the potential to prolong patients' survival. The results favor zorifertinib as a novel, well-validated first-line option for CNS-metastatic patients with *EGFR*-mutant NSCLC.

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INTRODUCTION

Central nervous system (CNS) metastases are common and confer a poor prognosis in patients with epidermal growth factor receptor gene-mutated (*EGFR*m+) non-small cell lung cancer (NSCLC).[1] EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are the systemic therapy recommended by most treatment guidelines for patients with *EGFR*m+ NSCLC and CNS metastases, and some recommend third-generation EGFR-TKIs or icotinib as the preferred treatment.[2–6] However, evidence of current EGFR-TKIs in this patient population is mostly from subgroup analyses,[7–13] single-arm studies,[1,14,15] or retrospective analyses.[16] Phase 3 randomized controlled trials (RCTs) of head-to-head comparisons between EGFR-TKIs in patients with *EGFR*m+ NSCLC and CNS metastases are still lacking. In the phase 2 CTONG0803 study, erlotinib showed a median progression-free survival (PFS) of 15.2 months in eight patients with *EGFR*m+ NSCLC and asymptomatic brain metastases.[15] The phase 3 BRAIN study demonstrated superior intracranial PFS with icotinib compared to whole-brain radiotherapy (10.0 versus 4.8 months) in patients with *EGFR*m+ NSCLC and brain metastases that were naive to EGFR-TKIs or radiotherapy.[17] Evidence on the intracranial efficacy of third-generation EGFR-TKIs (e.g., osimertinib, lazertinib, aumolertinib, furmonertinib, and befotertinib) in patients with CNS metastases was all from subgroup analyses of phase 3 studies with small sample sizes, patients with mild intracranial disease, potentially unbalanced baselines between groups, and non-mandatory routine brain computed tomography (CT)/magnetic resonance imaging (MRI).[8–10,12,13] Other agents under investigation include the combination of chemotherapy and gefitinib/osimertinib.[18,19]

In addition, there appeared to be a lack of survival benefits with osimertinib versus first-generation EGFR-TKI in Asians and patients with the *EGFR* L858R mutation (hazard ratios [HRs] for both subgroups in FLAURA were 1.0).[20] Hence, osimertinib has been allowed for the treatment of lung adenocarcinoma with brain metastasis only in patients with exon 19 deletion (Exon 19Del) by Taiwan's National Health Insurance since April 2022.[21] The complex mechanisms of resistance to osimertinib and limited options of subsequent antitumor therapy have a negative impact on patients' survival. Novel treatment options for patients with *EGFR*m+ NSCLC and CNS metastases are needed.

Zorifertinib (AZD3759), unlike other EGFR-TKIs, is the first EGFR-TKI specifically designed and developed for patients with CNS metastases.[22,23] Zorifertinib is not a substrate of P-glycoprotein or breast cancer resistance protein and demonstrated complete blood-brain barrier penetration in patients (100%), which is much higher than that of other EGFR-TKIs (first- and second-generation EGFR-TKIs, 1.13%–3.3%; osimertinib, 2.5%–16%).[1,24] The phase 1 BLOOM study showed promising clinical antitumor activity of zorifertinib with confirmed overall and intracranial objective response rates (ORRs) of 67% and 87% at the 200 mg dose level, respectively, in patients with *EGFR*m+ NSCLC and CNS metastases.[1] The phase 2 CTONG1702 study reported an ORR of 80%, a median PFS of 15.8 months, and a median intracranial PFS of 18.5 months in patients with untreated *EGFR*m+ NSCLC and CNS metastases who received zorifertinib (200 mg). Upon progressive disease (PD), 59.0% patients developed an *EGFR* T790M mutation; the median OS was 33.7 months overall across 200 and 300 mg zorifertinib treatment and 34.1 months in patients subsequently treated with osimertinib.[25] The safety profile was manageable and comparable with those reported for currently approved EGFR-TKIs.[1,25]

The EVEREST trial (ClinicalTrials.gov: NCT03653546) was the first RCT conducted to compare the efficacy and safety of first-line zorifertinib versus first-generation EGFR-TKIs exclusively in patients with advanced *EGFR*m+ NSCLC and non-irradiated CNS metastases.

RESULTS

Patients and treatments

Between February 1, 2019, and January 12, 2021, of the 680 patients screened, 439 were randomized: 220 to the zorifertinib arm and 219 to the control arm (gefitinib $n = 211$ [96.3%], erlotinib $n = 8$ [3.7%]). One patient in the control arm did not take the medication (gefitinib) after randomization (Figure 1). At the data cutoff date (July 12, 2022), all 438 patients had discontinued the assigned treatment, with the main reason being PD (zorifertinib $n = 144$; control $n = 168$); other reasons included patient decision and adverse events (AEs), among others (Figure 1). The median duration of treatment exposure was 9.1 months (interquartile range [IQR], 4.3 to 14.3 months) for zorifertinib and 8.2 months (IQR, 4.6–12.5 months) for control.

Patient demographic and baseline characteristics were well balanced and comparable across the two arms (Table 1). In the total population, over half harbored the L858R mutation or had >3 intracranial lesions. A total of 36 patients with coexisting leptomeningeal metastases were enrolled ($n = 18$ in each arm), and all the leptomeningeal metastases were diagnosed with MRI.

Progression-free survival

By the data cutoff date, the median follow-up time was 20.4 months for both arms. 166 (75.5%) patients in the zorifertinib arm and 181 (82.6%) in the control arm had progressed or died. Median PFS assessed by blinded independent central review (BICR) per RECIST1.1 was significantly longer with zorifertinib than with control (Figure 2A) at 9.6 versus 6.9 months (HR, 0.719; 95% confidence interval [CI], 0.580–0.893; $p = 0.0024$). PFS favored zorifertinib across all analyzed subgroups (Figure 2B), including patients with >3 intracranial lesions (HR, 0.681; 95% CI, 0.511–0.909) or the L858R mutation (HR, 0.609; 95% CI, 0.453–0.818) (Figure 2B). Median PFS also favored zorifertinib in patients with CNS symptoms (neurological exam score >0; zorifertinib $n = 49$, control $n = 47$; 9.6 versus 6.9 months; HR, 0.697; 95% CI, 0.440–1.107).

PFS in the sensitivity analyses and that assessed by the investigator per RECIST1.1 or by BICR per mRECIST1.1 consistently showed a significant improvement with zorifertinib over control (Figures S1 and S2).

Intracranial PFS

Median intracranial PFS was significantly longer with zorifertinib versus control: 15.2 versus 8.3 months by BICR per mRECIST1.1

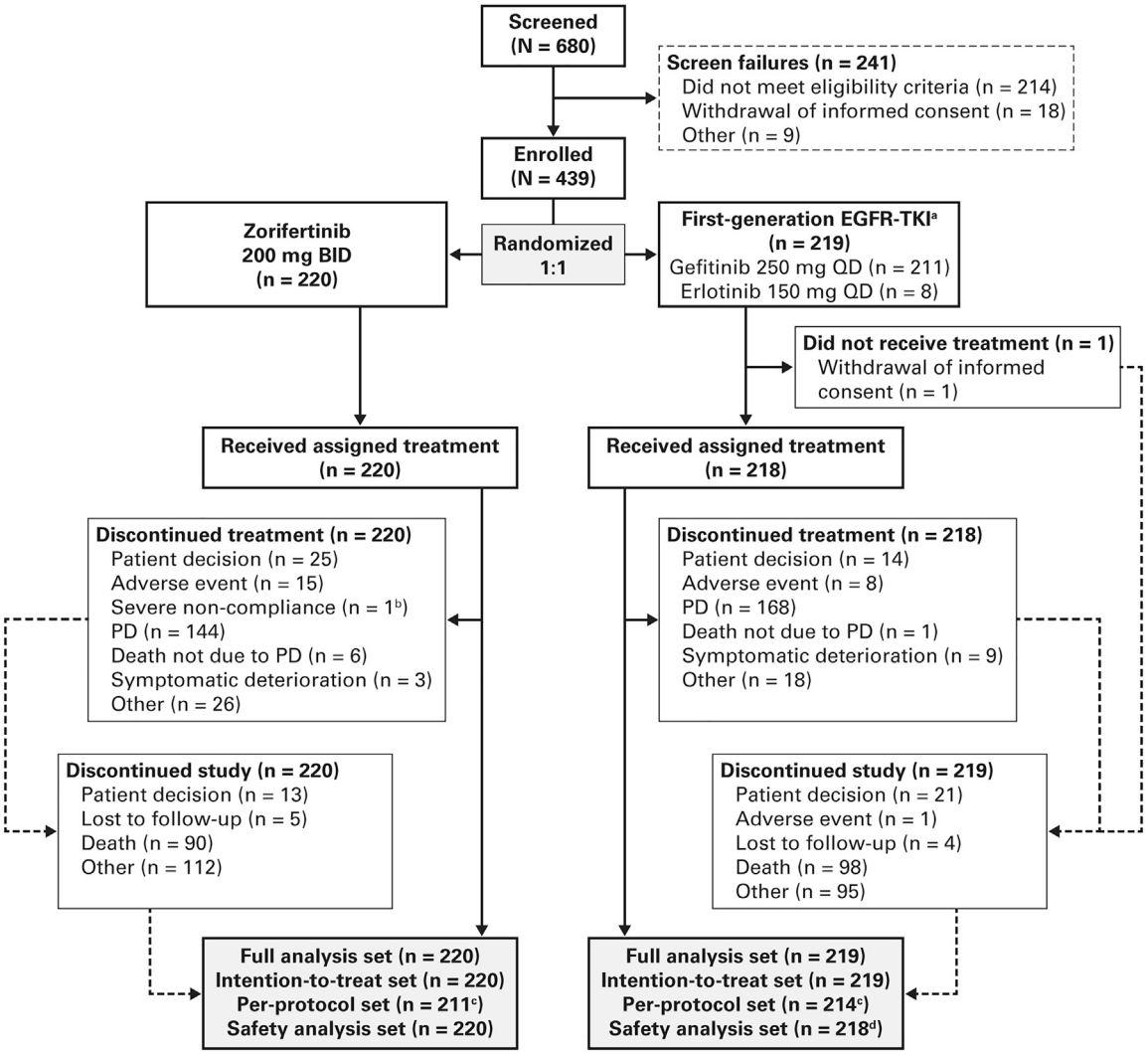

Figure 1. Trial profile

Of the 680 patients screened, 439 were randomized: 220 to the zorifertinib arm and 219 to the control arm. The main reason for screen failure (*n* = 241) was not meeting the eligibility criteria (*n* = 214). All 439 patients were included in the intention-to-treat population. BID, twice daily; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PD, disease progression.

[a]Patients from Mainland China and South Korea received gefitinib, whereas those from Taiwan China and Singapore received erlotinib.

[b]As judged by the investigator and/or sponsor.

[c]Fourteen patients in the intention-to-treat population were excluded from the per-protocol set: nine from the zorifertinib arm and five from the control arm.

[d]One patient who did not receive control treatment (gefitinib) after randomization was excluded from the safety analysis set.

and 17.9 versus 11.1 months by the investigator per RANO-BM (Figure 3). Median intracranial PFS assessed by BICR using mRECIST1.1 also favored zorifertinib for patients with leptomeningeal metastases (HR, 0.395; 95% CI, 0.136–1.141), the L858R mutation (HR, 0.327; 95% CI, 0.222–0.483), CNS symptoms (HR, 0.588; 95% CI, 0.314–1.100), or >3 intracranial lesions (HR, 0.454; 95% CI, 0.314–0.654).

Tumor response

Tumor response findings generally consistently favored zorifertinib regardless of the assessor (investigator/BICR) or the assessment criteria used (Table 2). The confirmed overall ORRs by investigator per RECIST1.1 (71.4% versus 64.8%), intracranial ORR by investigator per RANO-BM (75.6% versus 62.3%), and by BICR per RECIST1.1 (74.3% versus 62.8%) were all higher with zorifertinib than with control. The overall (by BICR per RECIST1.1: 8.2 versus 6.8 months) and intracranial (by investigator per RANO-BM: 13.8 versus 11.1 months) durations of response (DORs) were both longer with zorifertinib than with control.

Intracranial PD (BICR per RECIST1.1) developed in fewer patients receiving zorifertinib versus control (35.9% versus 61.2%). For patients receiving zorifertinib, most PD was due to extracranial progression (66.8%; Table S1). Mutations were tested in plasma circulating tumor DNA (ctDNA) for 24 patients

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Table 1. Baseline demographics and disease characteristics in the intention-to-treat population

	Zorifertinib (*n* = 220)	Control (*n* = 219)
Age (years), median (range)	58.0 (34.0–84.0)	59.0 (33.0–82.0)
Sex		
Male	80 (36.4)	78 (35.6)
Female	140 (63.6)	141 (64.4)
Smoking status		
Current/former	64 (29.1)	63 (28.8)
Never	156 (70.9)	156 (71.2)
ECOG PS		
0	49 (22.3)	50 (22.8)
1	171 (77.7)	169 (77.2)
Geographic location		
Mainland China	199 (90.5)	200 (91.3)
Taiwan China	7 (3.2)	8 (3.7)
South Korea	13 (5.9)	11 (5.0)
Singapore	1 (0.5)	0 (0)
Ethnicity		
Asian	220 (100)	219 (100)
Tumor histopathological classification		
Adenocarcinoma	218 (99.1)	209 (95.4)
Squamous cell carcinoma	1 (0.5)	1 (0.5)
Adenosquamous cell carcinoma	1 (0.5)	5 (2.3)
Others[a]	0 (0)	4 (1.8)
TNM stage (M)		
M1b	18 (8.2)	20 (9.1)
M1c	202 (91.8)	199 (90.9)
EGFR mutation status		
Exon 19Del	101 (45.9)	98 (44.7)
L858R	118 (53.6)	120 (54.8)
Co-mutations of Exon 19Del and L858R	1 (0.5)	1 (0.5)
Disease type[b]		
Without measurable lesions	1 (0.5)	2 (0.9)
Measurable IC lesion	144 (65.5)	137 (62.6)
Measurable EC lesion	210 (95.5)	207 (94.5)
Site of IC lesion (RECIST1.1)[b]		
No IC lesion	3 (1.4)	1 (0.5)
Brain and leptomeninges[c]	18 (8.2)	18 (8.2)
Brain only	199 (90.5)	200 (91.3)
No. of IC lesions[b]		
0	3 (1.4)	1 (0.5)
1	51 (23.2)	49 (22.4)
2–3	44 (20.0)	55 (25.1)
>3	122 (55.5)	114 (52.1)
Sum of the longest diameter of IC target lesions, mm (BICR mRECIST1.1)	25.8 (14.0–52.1)	23.8 (12.6–41.7)

Data are *n* (%) or median (IQR) unless stated otherwise. BICR, blinded independent central review; EC, extracranial; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IC, intracranial; IQR, interquartile range; (m)RECIST1.1, (modified) Response Evaluation Criteria in Solid Tumors v.1.1; NSCLC, non-small cell lung cancer.

[a]The histopathological classification for four patients was NSCLC (*n* = 2), adenocarcinoma or adenosquamous cell carcinoma (*n* = 1), and poorly differentiated cancer (NSCLC; *n* = 1).

[b]BICR assessed.

[c]Leptomeningeal metastases were diagnosed with MRI at baseline.

in the zorifertinib arm and 25 patients in the control arm upon disease progression, and 13 and 10 patients in the two arms were ctDNA positive, respectively. Among patients with positive ctDNA results, 61.5% (8/13) and 30% (3/10), respectively, had acquired the *EGFR* T790M mutation. For zorifertinib, *EGFR* T790M mutations occurred less commonly in patients who developed intracranial versus extracranial PD (Table S2).

Overall survival

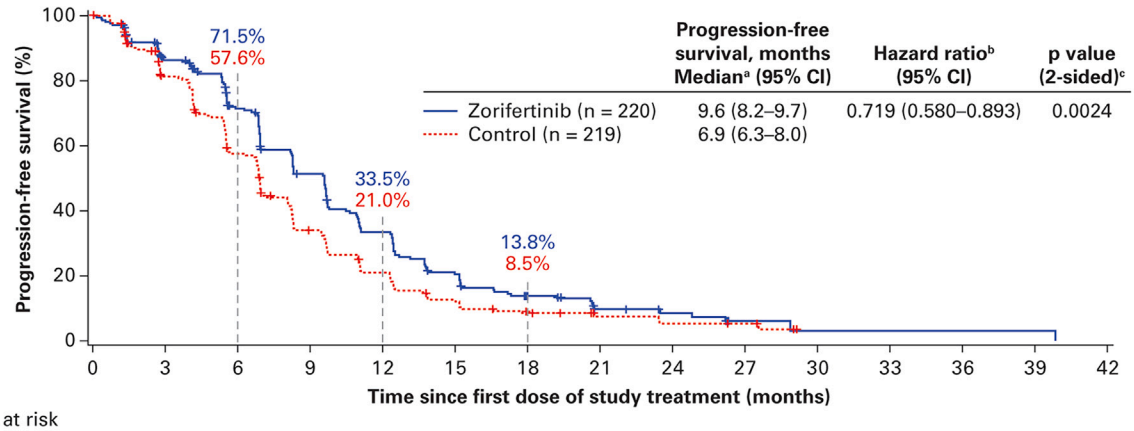
Subsequent antitumor therapies were received by 147 (66.8%) patients in the zorifertinib arm and 176 (80.4%) in the control arm. In addition, 10 (4.5%) patients in the zorifertinib arm (versus 0 in the control arm) continued with zorifertinib despite PD since investigators believed that they would derive clinical benefits from zorifertinib treatment, and therefore, they did not receive any new subsequent antitumor therapy. 109 (49.5%) patients in the zorifertinib arm and 118 (53.9%) in the control arm received marketed third-generation EGFR-TKI (osimertinib, aumolertinib, and furmonertinib) therapies. 30 (13.6%) patients in the zorifertinib arm and 38 (17.4%) in the control arm received subsequent intracranial radiotherapy.

By the data cutoff date, 90 (40.9%) patients in the zorifertinib arm and 98 (44.7%) in the control arm had died. OS data were not mature. The estimated median OS was 30.0 months in the zorifertinib arm and 28.4 months in the control arm (HR, 0.897; 95% CI, 0.671–1.198). The 3 year OS rates were 43.4% in the zorifertinib arm and 31.2% in the control arm. In patients who received subsequent marketed third-generation EGFR-TKI treatments, the estimated median OS was 37.3 months in the zorifertinib arm and 31.8 months in the control arm (HR, 0.833; 95% CI, 0.542–1.283), with 3 year OS rates of 51.7% versus 35.5%.

Safety

The rates of treatment-emergent AEs (TEAEs) were similar for the zorifertinib and control arms (98.2% versus 98.6%). The most common TEAEs with zorifertinib were increased aspartate aminotransferase (AST) (72.3% versus 57.8% with control), increased alanine aminotransferase (ALT) (68.2% versus 58.7%), diarrhea (64.5% versus 43.6%), and rash (55.9% versus 39.0%). The

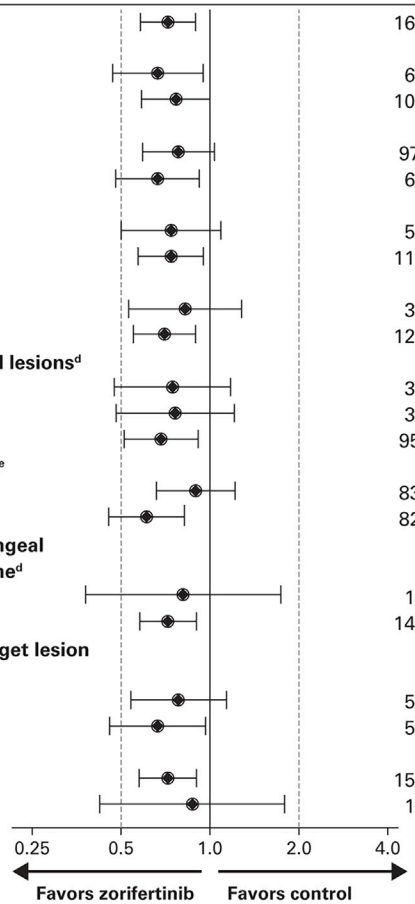
A



	Progression-free survival, months Median[a] (95% CI)	Hazard ratio[b] (95% CI)	p value (2-sided)[c]
Zorifertinib (n = 220)	9.6 (8.2–9.7)	0.719 (0.580–0.893)	0.0024
Control (n = 219)	6.9 (6.3–8.0)		

No. at risk (no. censored)															
Zorifertinib	220 (0)	169 (23)	130 (34)	90 (38)	57 (40)	34 (41)	20 (44)	10 (49)	7 (51)	2 (54)	1 (54)	1 (54)	1 (54)	1 (54)	0 (54)
Control	219 (0)	162 (18)	112 (21)	63 (25)	38 (26)	22 (27)	13 (29)	7 (34)	5 (34)	4 (35)	0 (38)	0 (38)	0 (38)	0 (38)	0 (38)

B



	Events/patients (n/N)		Median progression-free survival (months)[a]		
	Zorifertinib	Control	Zorifertinib	Control	HR (95% CI)[b]
All patients	166/220	181/219	9.6	6.9	0.719 (0.580–0.893)
Sex					
Male	64/80	63/78	8.3	6.8	0.665 (0.467–0.946)
Female	102/140	118/141	9.6	6.9	0.765 (0.586–0.998)
Age group, years					
<60	97/121	101/118	8.3	6.9	0.780 (0.590–1.033)
≥60	69/99	80/101	9.7	6.9	0.663 (0.478–0.919)
Smoking status					
Current/former	52/64	52/63	8.3	6.9	0.738 (0.500–1.087)
Never	114/156	129/159	9.6	6.9	0.736 (0.571–0.948)
ECOG PS					
0	39/49	41/50	8.3	8.1	0.822 (0.530–1.277)
1	127/171	140/169	9.6	6.9	0.700 (0.550–0.892)
Number of intracranial lesions[d]					
1	38/51	38/49	12.3	8.3	0.745 (0.473–1.175)
2–3	30/44	46/55	8.3	6.8	0.762 (0.480–1.209)
>3	95/122	97/114	8.3	6.8	0.681 (0.511–0.909)
***EGFR* mutation status[e]**					
Exon Del19	83/101	83/98	8.3	7.1	0.895 (0.659–1.215)
L858R	82/118	98/120	9.6	6.3	0.609 (0.453–0.818)
Coexistent leptomeningeal involvement at baseline[d]					
Yes	15/18	13/18	6.9	6.9	0.810 (0.379–1.733)
No	148/199	168/200	9.6	6.9	0.721 (0.577–0.900)
Size of intracranial target lesion at baseline[f]					
<Median (24.6 mm)	53/68	60/72	8.3	6.9	0.781 (0.538–1.136)
≥Median (24.6 mm)	56/76	57/65	7.0	6.8	0.665 (0.457–0.967)
Geographic location					
Mainland China	150/199	166/200	9.6	6.9	0.719 (0.576–0.898)
All others[g]	16/21	15/19	5.4	6.9	0.869 (0.423–1.786)

(legend on next page)

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rates of grade ≥3 TEAEs were 74.1% and 30.3%. The most common grade ≥3 TEAEs with zorifertinib were rash (13.6% versus 0.5% with control), dermatitis acneiform (13.6% versus 0.5%), diarrhea (13.2% versus 0.9%), hypokalemia (12.3% versus 1.8%), increased ALT (11.8% versus 11.5%), increased γ-glutamyltransferase (7.3% versus 2.3%), and increased AST (6.8% versus 7.8%). Treatment-related TEAEs of any grade (incidence ≥10%) and grade ≥3 (incidence ≥1%) assessed by the investigator are summarized in Table 3. Skin and subcutaneous tissue disorders and gastrointestinal events were the most common treatment-related TEAEs in the zorifertinib arm, and the most common events were diarrhea (63.6%), rash (55.9%), and dermatitis acneiform (33.6%). Any-grade treatment-related QT prolongation occurred in 26 (11.8%) patients in the zorifertinib arm and 23 (10.6%) in the control arm, while grade 3 events occurred in 8 (3.6%) patients and 3 (1.4%) patients, respectively; no grade 4–5 events occurred. No heart failure or cardiomyopathy occurred in either arm. Recovery rates for treatment-related TEAEs were high and similar between the two arms (any grade: 85.8% versus 84.9%; grade ≥3: 78.3% versus 78.6%). No confirmed interstitial lung disease was diagnosed in the zorifertinib arm (versus two patients in the control). The incidence of nervous system and psychiatric disorders (any grade) was similar between the two arms (24.5% versus 26.6% and 11.8% versus 11.0%, respectively); no new CNS-related safety signals arose.

The incidence of serious AEs (SAEs) was 29.5% with zorifertinib and 14.2% with control (Table S3). These were considered treatment related in 38 (17.3%) patients with zorifertinib and 9 (4.1%) with control. Treatment-related SAEs that occurred in ≥2% patients included increased AST (3.6% versus 2.8%), increased ALT (3.2% versus 2.8%), increased blood bilirubin (3.2% versus 0.5%), and diarrhea (2.3% versus 0%).

A total of 25 (5.7%) patients experienced TEAEs leading to death during the study and up to 28 days after their last dose of study drug treatment—14 (6.4%) in the zorifertinib arm and 11 (5.0%) in the control arm. For the 14 zorifertinib-treated patients, the investigator-assessed relationship of death to zorifertinib was unrelated in 13 (5.9%) patients, and the reasons for death were PD (*n* = 5, 2.3%), tumor and cachexia (*n* = 2, 0.9%), and sleeping pills, pneumonia, cerebral bleeding, depressed consciousness, pulmonary embolism, and aortic dissection (*n* = 1 each, 0.5%); one patient's death was of an unknown reason, and the relevance could not be determined because the patient died outside of hospital and no further details could be obtained. For the 11 deaths in the control arm, the investigator-assessed relationship of the deaths to control treatment was unrelated in all 11 patients, and the reasons for death were PD (*n* = 7, 3.2%) and pneumonia, respiratory failure, cerebral infarction, and suicide (*n* = 1 each, 0.5%).

Rates of TEAEs leading to dose modification (including dose reduction [50.0% versus 25.0%] and/or dose interruption [50.9% versus 18.8%], 72.7% versus 19.3%) were higher with zorifertinib than with control (Table S4). TEAEs leading to treatment discontinuation occurred in more patients with zorifertinib than with control (7.3% versus 3.7%), with each AE occurring in no more than two (i.e., <1%) patients (Table S5). Post hoc analyses showed that the efficacy with zorifertinib was not reduced in patients who underwent dose reduction (Table S6).

DISCUSSION

EVEREST is the first multi-national RCT designed specifically to address the unmet medical need for an up-front therapy for patients with *EGFR*m+ NSCLC and symptomatic or asymptomatic CNS metastases. It is also the first phase 3 trial with a head-to-head comparison of EGFR-TKIs in this patient population. The study met its primary endpoint—first-line zorifertinib significantly improved PFS compared with first-generation EGFR-TKIs in the study population. The benefit trends with zorifertinib were consistent across all subgroups and regardless of the assessor or assessment criteria. Good intracranial efficacy was also demonstrated, with significantly prolonged intracranial PFS and improved intracranial response with zorifertinib compared with first-generation EGFR-TKIs. In addition, the antitumor efficacy was consistent with those reported in BLOOM and CTONG1702.[1,25] These are important findings for a population of patients with a poor prognosis, poor quality of life, and currently no standard treatment.[26] In this study, third-generation EGFR-TKIs were not selected as the comparator because, at the time of study commencement, no third-generation EGFR-TKIs were approved as first-line options for the study patient population in China. Moreover, first-generation EGFR-TKIs remain the mainstay of recommended first-line treatment in many developing regions, including most Southeast Asian countries, due to cost and health insurance reimbursement considerations. Icotinib, a first-generation EGFR-TKI, is also the preferred therapy recommended in the ASCO-SNO-ASTRO guideline.[6]

Different from previous studies or subgroup analyses evaluating EGFR-TKIs in this setting, antitumor activity was more rigorously measured in this study. All CNS metastases in

Figure 2. Median PFS assessed by BICR per RECIST1.1 was significantly longer with zorifertinib than with control

Kaplan-Meier estimates of progression-free survival assessed by BICR using RECIST1.1 in the intention-to-treat population (A) and forest plot of subgroup analysis of progression-free survival (B). Tick marks in the Kaplan-Meier plot show censoring of the data at the last time the subject was known to be alive and progression free. BICR, blinded independent central review; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor. RECIST1.1, Response Evaluation Criteria in Solid Tumors v.1.1.

[a]Based on Kaplan-Meier analysis.

[b]Hazard ratios for all patients were based on a stratified Cox model, while those for subgroup analyses were based on an unstratified Cox model.

[c]Based on stratified log-rank test.

[d]Three patients in the zorifertinib arm and one patient in the control arm had no intracranial lesions assessed by BICR.

[e]One patient in each of the treatment arms harbored co-mutations of Exon 19Del and L858R; HR was not evaluable. For the patient in the zorifertinib arm, progression-free survival was 17.2 months; the patient in the control arm was censored, with a progression-free survival of 8.9 months to the date of censor.

[f]The longest diameter and category of intracranial target lesion.

[g]Zorifertinib: 13 patients from South Korea, 7 from Taiwan China, and 1 from Singapore; control: 11 patients from South Korea and 8 from Taiwan China.

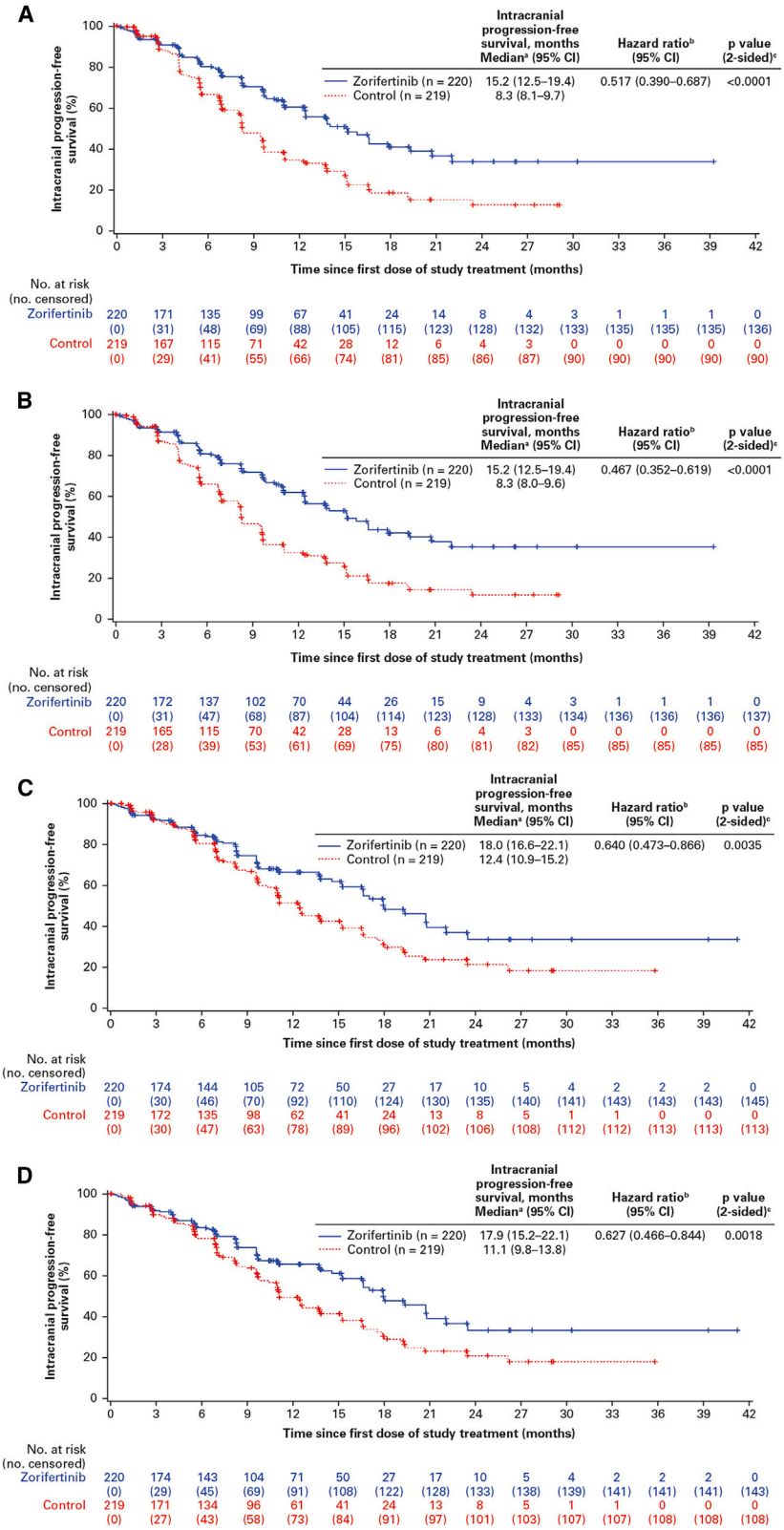

Figure 3. Median intracranial PFS was significantly longer with zorifertinib versus control

Kaplan-Meier estimates of intracranial progression-free survival assessed by BICR using (A) RECIST1.1 and (B) mRECIST1.1 and by the investigator per (C) RECIST1.1 and (D) RANO-BM (secondary endpoints). Tick marks in these plots show censoring of the data at the last time the subject was known to be alive and progression free. BICR, blinded independent central review; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; (m)RECIST1.1, (modified) Response Evaluation Criteria in Solid Tumors v.1.1; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases.

[a]Based on Kaplan-Meier analysis.

[b]Based on stratified Cox model.

[c]Based on stratified log-rank test.

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Table 2. Summary of overall and intracranial tumor responses in the intention-to-treat population

Location/assessor/assessment criteria	Zorifertinib	Control	HR or OR[a] (95% CI)	*p* value[b]
Overall tumor response by BICR per RECIST1.1	*n* = 220	*n* = 219	–	–
ORR,[c] %	68.6	58.4	1.553 (1.051–2.293)	0.0270
DCR, %	83.2	83.1	1.004 (0.609–1.654)	0.9878
BOR,[c] *n* (%)				
CR	1 (0.5)	0	–	–
PR	150 (68.2)	128 (58.4)	–	–
SD	32 (14.5)	54 (24.7)	–	–
PD	19 (8.6)	29 (13.2)	–	–
Not evaluable	18 (8.2)	8 (3.7)	–	–
DOR,[d] months				
Median (95% CI)	8.2 (6.9–8.3)	6.8 (5.6–7.0)	0.801 (0.613–1.047)	0.0997
TTR,[d] months				
Median (95% CI)	1.4 (1.4–1.4)	1.4 (1.4–1.4)	0.936 (0.732–1.196)	0.5670
Overall tumor response by Investigators per RECIST1.1	*n* = 220	*n* = 219	–	–
ORR,[c] %	71.4	64.8	1.349 (0.902–2.016)	0.1445
DCR, %	84.5	84.9	0.974 (0.580–1.636)	0.9213
BOR,[c] *n* (%)				
CR	0	0	–	–
PR	157 (71.4)	142 (64.8)	–	–
SD	29 (13.2)	44 (20.1)	–	–
PD	16 (7.3)	23 (10.5)	–	–
Not evaluable	18 (8.2)	10 (4.6)	–	–
DOR,[d] months				
Median (95% CI)	9.7 (8.5–12.4)	8.4 (7.6–9.7)	0.817 (0.628–1.062)	0.1276
TTR,[d] months				
Median (95% CI)	1.4 (1.4–1.4)	1.4 (1.4–1.4)	0.969 (0.766–1.225)	0.7731
Intracranial tumor response by BICR per RECIST1.1	*n* = 144	*n* = 137	–	–
Intracranial ORR,[c] %	74.3	62.8	1.710 (1.027–2.849)	0.0393
Intracranial DCR, %	84.0	81.8	1.152 (0.621–2.139)	0.6532
Intracranial BOR,[c] *n* (%)	–	–	–	–
CR	6 (4.2)	1 (0.7)	–	–
PR	101 (70.1)	85 (62.0)	–	–
SD	14 (9.7)	26 (19.0)	–	–
PD	9 (6.3)	14 (10.2)	–	–
Not evaluable	14 (9.7)	11 (8.0)	–	–
Intracranial DOR,[d] months	*n* = 107	*n* = 86	–	–
Median (95% CI)	12.4 (9.0–18.0)	7.0 (6.7–9.7)	0.547 (0.368–0.813)	0.0023
Intracranial TTR,[d] months	–	–	–	–
Median (95% CI)	1.4 (1.4–1.4)	1.4 (1.3–1.4)	0.761 (0.564–1.026)	0.0478
Intracranial tumor response by investigators per RANO-BM	*n* = 127[e]	*n* = 122[e]	–	–
Intracranial ORR,[c] %	75.6	62.3	1.904 (1.098–3.302)	0.0218
Intracranial DCR, %	85.8	82.0	1.313 (0.669–2.577)	0.4284
Intracranial BOR,[c] *n* (%)	–	–	–	–
CR	10 (7.9)	3 (2.5)	–	–
PR	86 (67.7)	73 (59.8)	–	–

(*Continued on next page*)

Table 2. *Continued*

Location/assessor/assessment criteria	Zorifertinib	Control	HR or OR[a] (95% CI)	*p* value[b]
SD	13 (10.2)	24 (19.7)	–	–
PD	8 (6.3)	12 (9.8)	–	–
Not evaluable	10 (7.9)	10 (8.2)	–	–
Intracranial DOR,[d] months	*n* = 96	*n* = 76	–	–
Median (95% CI)	13.8 (8.5–22.1)	11.1 (8.3–14.0)	0.789 (0.501–1.244)	0.3037
Intracranial TTR,[d] months	–	–	–	–
Median (95% CI)	1.4 (1.4–1.4)	1.4 (1.3–1.4)	0.821 (0.597–1.130)	0.1779

BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST1.1, Response Evaluation Criteria in Solid Tumors v.1.1; SD, stable disease; TTR, time to response.
[a]OR for ORR and DCR and HR for DOR and TTR. HR was based on the stratified Cox model.
[b]Based on the stratified log-rank test.
[c]Complete or partial response was confirmed by two consecutive assessments with ≥4 week intervals.
[d]Based on Kaplan-Meier analysis.
[e]Evaluable patients in the intention-to-treat population (only patients with intracranial target lesions).

EVEREST were MRI confirmed and followed up regularly. Target lesions were selected per the RECIST1.1 criteria. Comparatively, evidence of the CNS activities of third-generation EGFR-TKIs (e.g., osimertinib, lazertinib) was all derived from CNS subgroup analyses (sample sizes range from 86 to 128) that were based on retrospective review of available brain CT/MRI scans, which was not mandated for all patients, and this limited the accuracy of CNS PFS and CNS ORRs.[8,9,12,13] Per the FLAURA protocol, CNS lesions were assessed as non-target lesions in the primary analysis, which may impact an accurate assessment of PFS in CNS-metastatic patients.[27] For evaluation of CNS activity, intracranial efficacy of third-generation EGFR-TKIs was evaluated only per RECIST1.1 criteria, while besides RECIST1.1 criteria, RANO-BM criteria, which are based on imaging response, neurologic symptoms, and steroid use, were additionally used in EVEREST, and the results also supported the significant CNS activity of zorifertinib.

EVEREST was the first study well powered to analyze patients with previously non-irradiated CNS metastases. None of the enrolled patients had received prior intracranial radiotherapy. In the CNS subgroup of FLAURA, 24.2% patients had prior intracranial radiotherapy, and they showed numerically better CNS ORRs compared with those without this prior treatment.[12] The results of EVEREST demonstrated the efficacy of zorifertinib alone, excluding the impact of prior cranial radiotherapy.

The PFS and intracranial PFS of zorifertinib appeared to be shorter than those of third-generation EGFR-TKIs.[12,27] A plausible reason is that patients with more severe disease were enrolled in EVEREST. More patients had the L858R mutation or higher CNS burden (e.g., in the CNS subgroup for osimertinib in FLAURA, only 21 patients harbored L858R, 14 had >3 intracranial lesions, and 22 had measurable intracranial lesions; the corresponding data were 20, 4, and 18 patients, respectively, in the CNS subgroup of lazertinib in LASER301).[12,13] The PFS in patients harboring L858R or >3 intracranial lesions also supports the benefit of zorifertinib. Different from third-generation EGFR-TKIs,[27–29] the extent of PFS improvement in patients harboring L858R was similar to that for the overall population treated with zorifertinib. Patients with stable CNS symptoms were allowed in EVEREST, while the CNS subgroup analysis for almonertinib or furmonertinib only included patients without CNS symptoms.[8,9] The results of EVEREST support the benefit of zorifertinib in patients with diverse characteristics, including in those with L858R, higher CNS disease burden, or CNS symptoms.

There is limited available evidence from head-to-head phase 3 RCTs on the efficacy of first-line sequential treatment versus third-generation EGFR-TKIs. In the phase 2 APPLE trial, up-front treatment with osimertinib showed a clinically meaningful lower rate of brain progression, with no evidence of OS improvement versus the sequential treatment approach.[30] So far, no OS data of third-generation EGFR-TKIs as first-line monotherapy for patients with CNS metastases from prospective RCTs have been published. Of note, in the FLAURA China study, osimertinib did not appear to improve OS compared with gefitinib or erlotinib in patients with CNS metastases (HR, 0.95).[31] The median OS of osimertinib monotherapy in patients with brain metastases ranged from 19.6 to 28 months in retrospective studies.[32–36] In the EVEREST study, 62% of patients developed the *EGFR* T790M mutation on PD during first-line zorifertinib treatment, while 50% received subsequent third-generation EGFR-TKIs and achieved a median OS of 37.3 months; the data are consistent with the rate of *EGFR* T790M mutations (59%) and the OS results (median 34.1 months) in CTONG1702.[25] Based on the findings above, the sequential approach of zorifertinib and third-generation EGFR-TKIs could provide a novel sequential treatment option for patients with *EGFR*m+ NSCLC and CNS metastases.

The safety profile of zorifertinib was consistent with previous findings.[1,25] Gastrointestinal and skin toxicity were the most common treatment-related TEAEs in the zorifertinib arm. Grade ≥3 treatment-related TEAEs and serious TEAEs occurred more frequently with zorifertinib than with control, but all were common and expected, as they are effects of EGFR inhibitor class drugs and were manageable (most recovered) with dose modification and/or symptomatic therapies. The incidence of dose modification, which is one of the common clinical methods of safety management, was higher with zorifertinib than with

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Table 3. Treatment-related adverse events in the safety analysis set

	Zorifertinib (*n* = 220)					Control (*n* = 218)				
	Grade					Grade				
	1–2	3	4	5	All	1–2	3	4	5	All
Any	70 (31.8)	139 (63.2)	5 (2.3)	1 (0.5)	215 (97.7)	165 (75.7)	38 (17.4)	2 (0.9)	0 (0)	205 (94.0)
Increased aspartate aminotransferase	137 (62.3)	14 (6.4)	1 (0.5)	0 (0)	152 (69.1)	105 (48.2)	16 (7.3)	0 (0)	0 (0)	121 (55.5)
Increased alanine aminotransferase	121 (55.0)	23 (10.5)	1 (0.5)	0 (0)	145 (65.9)	100 (45.9)	22 (10.1)	1 (0.5)	0 (0)	123 (56.4)
Diarrhea	111 (50.5)	29 (13.2)	0 (0)	0 (0)	140 (63.6)	86 (39.4)	1 (0.5)	0 (0)	0 (0)	87 (39.9)
Rash	93 (42.3)	30 (13.6)	0 (0)	0 (0)	123 (55.9)	81 (37.2)	1 (0.5)	0 (0)	0 (0)	82 (37.6)
Decreased appetite	75 (34.1)	10 (4.5)	0 (0)	0 (0)	85 (38.6)	26 (11.9)	0 (0)	0 (0)	0 (0)	26 (11.9)
Increased blood bilirubin	76 (34.5)	4 (1.8)	0 (0)	0 (0)	80 (36.4)	36 (16.5)	1 (0.5)	0 (0)	0 (0)	37 (17.0)
Dermatitis acneiform	44 (20.0)	30 (13.6)	0 (0)	0 (0)	74 (33.6)	39 (17.9)	1 (0.5)	0 (0)	0 (0)	40 (18.3)
Paronychia	62 (28.2)	3 (1.4)	0 (0)	0 (0)	65 (29.5)	28 (12.8)	0 (0)	0 (0)	0 (0)	28 (12.8)
Proteinuria	56 (25.5)	0	0 (0)	0 (0)	56 (25.5)	19 (8.7)	0 (0)	0 (0)	0 (0)	19 (8.7)
Decreased weight	49 (22.3)	3 (1.4)	0 (0)	0 (0)	52 (23.6)	8 (3.7)	0 (0)	0 (0)	0 (0)	8 (3.7)
Alopecia	51 (23.2)	0	0 (0)	0 (0)	51 (23.2)	18 (8.3)	0 (0)	0 (0)	0 (0)	18 (8.3)
Stomatitis	39 (17.7)	9 (4.1)	0 (0)	0 (0)	48 (21.8)	11 (5.0)	0 (0)	0 (0)	0 (0)	11 (5.0)
Vomiting	40 (18.2)	4 (1.8)	0 (0)	0 (0)	44 (20.0)	13 (6.0)	0 (0)	0 (0)	0 (0)	13 (6.0)
Nausea	41 (18.6)	2 (0.9)	0 (0)	0 (0)	43 (19.5)	17 (7.8)	0 (0)	0 (0)	0 (0)	17 (7.8)
Increased γ-glutamyltransferase	28 (12.7)	12 (5.5)	2 (0.9)	0 (0)	42 (19.1)	22 (10.1)	5 (2.3)	0 (0)	0 (0)	27 (12.4)
Oral ulcer	39 (17.7)	1 (0.5)	0 (0)	0 (0)	40 (18.2)	18 (8.3)	0 (0)	0 (0)	0 (0)	18 (8.3)
Increased conjugated bilirubin	34 (15.5)	3 (1.4)	1 (0.5)	0 (0)	38 (17.3)	25 (11.5)	1 (0.5)	0 (0)	0 (0)	26 (11.9)
Increased blood alkaline phosphatase	27 (12.3)	9 (4.1)	0 (0)	0 (0)	36 (16.4)	15 (6.9)	0 (0)	0 (0)	0 (0)	15 (6.9)
Hypokalemia	16 (7.3)	13 (5.9)	1 (0.5)	0 (0)	30 (13.6)	7 (3.2)	0 (0)	0 (0)	0 (0)	7 (3.2)
Increased blood creatinine	26 (11.8)	1 (0.5)	0 (0)	0 (0)	27 (12.3)	9 (4.1)	0 (0)	0 (0)	0 (0)	9 (4.1)
Prolonged ECG QT	18 (8.2)	8 (3.6)	0 (0)	0 (0)	26 (11.8)	20 (9.2)	3 (1.4)	0 (0)	0 (0)	23 (10.6)
Anemia	22 (10.0)	3 (1.4)	0 (0)	0 (0)	25 (11.4)	14 (6.4)	2 (0.9)	0 (0)	0 (0)	16 (7.3)
Pruritus	24 (10.9)	0 (0)	0 (0)	0 (0)	24 (10.9)	32 (14.7)	0 (0)	0 (0)	0 (0)	32 (14.7)
Hypalbuminemia	23 (10.5)	0 (0)	0 (0)	0 (0)	23 (10.5)	8 (3.7)	0 (0)	0 (0)	0 (0)	8 (3.7)
Dry skin	20 (9.1)	1 (0.5)	0 (0)	0 (0)	21 (9.5)	23 (10.6)	0 (0)	0 (0)	0 (0)	23 (10.6)

Data are *n* (%). Treatment-related adverse events occurring in ≥10% of patients in either treatment arm for all grades or in ≥1% at grade ≥3 are shown. Patients with more than one event are counted only once in that category. ECG, electrocardiogram.

control, but AEs leading to treatment discontinuation were similar to other EGFR-TKIs (3.7%–18%).[27–29,37] Dose reduction did not affect the efficacy, and tolerability-guided dose modifications enabled patients to manage AEs, continue with zorifertinib treatment, and benefit from improved PFS, similar to the approach for dacomitinib. No CNS-related safety signals, interstitial lung disease, or definitive treatment-related fatal AEs occurred. We believe that the incidence of AEs will gradually decrease somewhat as physicians become more experienced in prescribing zorifertinib, as was observed in other marketed first-generation EGFR-TKIs.

The main strengths of this study are 4-fold: (1) EVEREST is the first RCT focusing on patients with *EGFR*m+ disease and non-irradiated symptomatic or asymptomatic CNS metastases, for whom there is currently no bespoke treatment; (2) patients enrolled were more clinically representative, being eligible regardless of the presence of CNS symptoms, and had a higher intracranial tumor burden and a higher proportion of patients with poor prognostic *EGFR* L858R; (3) brain MRI scans were mandatory, and all patients' CNS lesions were brain MRI confirmed at baseline and followed up regularly thereafter; and (4) besides RECIST1.1 criteria, RANO-BM was also used, which better validated the significant CNS activity of zorifertinib.

In conclusion, zorifertinib, a specifically designed EGFR-TKI for patients with *EGFR*m+ NSCLC and CNS metastases with complete CNS penetration and non-substrate of the blood-brain barrier efflux protein, can significantly prolong systemic and intracranial PFS compared with first-generation EGFR-TKIs as a first-line treatment in patients with advanced *EGFR*m+ NSCLC and non-irradiated CNS metastases. Particular benefit may be derived in patients with an *EGFR* L858R mutation, a higher intracranial tumor burden, or CNS symptoms. Patients may derive OS benefits with sequential use of zorifertinib and third-generation EGFR-TKIs. AEs were as expected and

manageable. This is the first RCT in patients with *EGFR*m+ NSCLC and non-irradiated CNS metastases, and the results suggest that zorifertinib is a promising new treatment option for this patient population.

Limitations of the study

There were several limitations. Firstly, the study was not double blinded, which may introduce bias to the investigator's assessment results; therefore, BICR assessments were adopted to minimize potential bias. Secondly, the third-generation EGFR-TKIs were not selected as the comparator, and this may limit its clinical applicability, as third-generation EGFR-TKIs are the preferred treatment recommended by most guidelines. Thirdly, the randomized stratification factors did not include *EGFR* mutation status (Exon 19Del versus L858R); however, the type of mutation was well balanced between the two arms and did not affect the validity of the study results. Finally, limited data were obtained regarding acquired resistance mechanisms, and further exploration is needed.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Yi-Long Wu (syylwu@live.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon request.
- This study did not generate any new codes.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Q.Z., M.-J.A., J. Wang, and Y.-L.W. conceived, designed, or planned the study. Q.Z., Y. Yu, L.X., M.-J.A., J. Wang, and Y.-L.W. analyzed the data and interpreted the results. All authors were involved in patient recruitment and data acquisition. Q.Z., Y. Yu, M.-J.A., J. Wang, and Y.-L.W. helped to interpret the results. Q.Z., Y. Yu, Y. Cheng, Z.W., M.-J.A., J. Wang, and Y.-L.W. drafted the manuscript. Z.W. was involved in statistical analysis and acted as project administrator. All authors had full access to the data reported in this article and vouch for the completeness and accuracy of the data and data analyses and adherence to the protocol. All authors revised and reviewed this work and approved the final version of the submitted manuscript for publication and take full responsibility of its content, including the accuracy of the data and the fidelity of the trial to the registered protocol and its statistical analysis. The corresponding authors had final responsibility for the decision to submit for publication.

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STAR★METHODS

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Human tumor tissues (for tumor *EGFR* mutations)	N/A	N/A
Human plasma (for ctDNA *EGFR* mutations)	N/A	N/A
Chemicals, peptides, and recombinant proteins		
Zorifertinib	Alpha Biopharma (Jiangsu) Co., Ltd	Zorifertinib (AZD3759)
Gefitinib	AstraZeneca	Gefitinib
Erlotinib	Roche	Erlotinib (Tarceva)
Critical commercial assays		
Detection of EGFR mutations in tumor/ctDNA.	MEDx TMC (http://www.MEDxTMC.cn)	QIASeq Comprehensive Cancer Panel (275) (NGS)
Deposited data		
Clinicaltrials.gov record	https://clinicaltrials.gov/study/NCT03653546	NCT03653546
Software and algorithms		
Statistical Analysis Software Version 9.4	SAS, Cary, NC, USA	N/A
Other		
CT	Sourced locally at study sites	N/A
MRI	Sourced locally at study sites	N/A

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design and participants

EVEREST was a phase 3, open-label RCT initiated at 58 sites across mainland China, South Korea, Taiwan, and Singapore (Table S7). Eligible patients were adults (aged ≥18 years) with histologically or cytologically confirmed advanced *EGFR*m+ (Exon 19Del and/or L858R) NSCLC and MRI-proven CNS metastases with stable CNS symptoms (without any systemic corticosteroid or anticonvulsant therapy for at least 2 weeks prior to study treatment) or without CNS symptoms, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients with coexisting leptomeningeal metastases were allowed (leptomeningeal metastases can be diagnosed with MRI or cerebrospinal fluid cytology). Patients with prior systemic treatment for advanced NSCLC and radiation therapy for CNS metastases were ineligible. Patients had to have at least one intracranial or extracranial (non-irradiated) target lesion. Exclusion criteria included *EGFR* T790M, or *KRAS* or *cMET* mutations, prior CNS injury with persistent neurological deficits that could confound neurological assessment, and inadequate organ function (Method S1).

Participant information on sex, age, and race was self-reported. Information on gender and socioeconomic status was not collected.

The ethics committee at each site approved the protocol (online only) and any amendments. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent to participate in the study.

METHOD DETAILS

Procedures

Patients were randomized 1:1 to receive zorifertinib (200 mg twice daily) or a first-generation EGFR-TKI (control arm: gefitinib [250 mg; mainland China and South Korea] or erlotinib [150 mg; Taiwan and Singapore] once daily) centrally via an interactive web-response system using a randomization scheme stratified by sex (male versus female), smoking status (never versus current/former), and ECOG PS (0 versus 1) (Figure S3). Study treatment continued until RECIST1.1-defined PD, unacceptable treatment-related toxicity, or other protocol-specified stopping criteria were met. Dose interruptions and dose reductions were allowed to manage grade ≥3 adverse events (AEs) or unacceptable treatment-related toxicity.

EGFR mutation (Exon 19Del and/or L858R) was detected by the regulatory authority-approved method using tumor tissue or plasma. Radiographic examination (CT/MRI), mini-mental state examination, EORTC QLQ-C30, and QLQ-BN20 were conducted

at baseline and every 6 weeks thereafter until documented objective PD. Neurological examinations per RANO criteria were performed at screening, on day 1 of the first cycle of treatment, and at the clinical visit for each subsequent treatment cycle until PD or death (not due to PD), or off study for any reason. Patients were followed for survival every 6 weeks after PD.

AEs were recorded from randomization to 28 days after study treatment discontinuation. TEAEs were defined as any AEs, regardless of relevance, that occurred from first dose to 28 days after the last dose. Treatment-related TEAEs were any AEs that were deemed by the investigator to be related to study treatments.

Outcomes

The primary endpoint was PFS assessed by blinded independent central review (BICR) per RECIST1.1. Secondary endpoints included PFS assessed by the investigator per RECIST1.1 and by BICR per modified RECIST1.1 (mRECIST1.1[1]), intracranial and extracranial PFS, overall/intracranial/extracranial ORR, disease control rate, duration of response (DOR), time to response assessed by the investigator and BICR per RECIST1.1, mRECIST1.1, or (for intracranial disease only) RANO-BM, and OS (definitions for endpoints are available in the protocol [online only]). Mechanisms of acquired resistance of first-line zorifertinib was an exploratory endpoint. AEs were graded for severity using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

QUANTIFICATION AND STATISTICAL ANALYSIS

Efficacy was analyzed in all randomized patients (intention-to-treat population, full analysis set; Method S2). Safety was analyzed in all patients who received at least one dose of study treatment (safety analysis set). The planned enrollment for this study was 432 patients (216 in each treatment arm), providing 80% power to detect (for the primary endpoint) a significant prolongation of PFS with zorifertinib over control, assuming a 10% annual dropout rate and a two-sided α of 0.05. Time-to-event parameters were evaluated using Kaplan–Meier methodology; comparisons between treatment arms used the stratified log rank test. The HR and corresponding 95% confidence intervals (CIs) between the two arms for the primary endpoint were calculated using a stratified Cox regression model. In the final primary analysis, superiority of zorifertinib over first-generation EGFR-TKIs required a log rank test two-sided p value of <0.05. Sensitivity analyses for primary endpoint were conducted in the per-protocol set and under the following alternative censoring conditions: the effect of new antitumor therapy, missing tumor assessment, and withdrawal from treatment. All statistical tests were two-sided with a type I error rate of 0.05.

All analyses were conducted using Statistical Analysis Software (Version 9.4).

ADDITIONAL RESOURCES

The protocol is provided in the supplemental information. The trial was registered on Clincaltrials.gov, NCT03653546: https://clinicaltrials.gov/study/NCT03653546.