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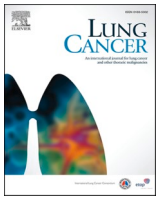

# Central nervous system efficacy of rezivertinib (BPI-7711) in advanced NSCLC patients with *EGFR* T790M mutation: A pooled analysis of two clinical studies

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ABSTRACT

*Background:* Rezivertinib (BPI-7711) is a novel third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) which revealed the systematic and central nervous system (CNS) antitumor activities for *EGFR* T790M-mutated advanced NSCLC in previous clinical studies and is further analyzed here.
*Methods:* Eligible patients from the previous phase I and phase IIb studies of rezivertinib were included for pooled analysis. Post-progressive patients who received a prescribed dosage (≥180 mg) of rezivertinib orally once daily were included in full analysis set (FAS), while those with stable, asymptomatic CNS lesions, including measurable and non-measurable ones at baseline were included in CNS full analysis set (cFAS). Patients with measurable CNS lesions were included in CNS evaluable for response set (cEFR). BICR-assessed CNS objective response rate (CNS-ORR), CNS disease control rate (CNS-DCR), CNS duration of response (CNS-DoR), CNS progression-free survival (CNS-PFS), and CNS depth of response (CNS-DepOR) were evaluated.
*Results:* 355 patients were included in FAS, among whom 150 and 45 patients were included in cFAS and cEFR. This pooled analysis showed the CNS-ORR was 32.0% (48/150; 95% CI: 24.6–40.1%) and the CNS-DCR was 42.0% (63/150; 95% CI: 34.0–50.3%) in cFAS, while that in cEFR were 68.9% (31/45; 95% CI: 53.4–81.8%) and 100% (45/45; 95% CI: 92.1–100.0%). In cEFR, the median CNS-DepOR and the mean of CNS-DepOR were -52.0% (range: -100.0 to 16.1%) and -46.8% (95% CI: –55.5 to -38.1%). In cFAS, the median CNS-DoR and CNS-PFS were 13.8 (95% CI: 9.6-not calculable [NC]) and 16.5 (95% CI: 13.7-NC) months.
*Conclusions:* Rezivertinib demonstrated encouraging clinical CNS efficacy among advanced NSCLC patients with *EGFR* T790M mutation and CNS metastases.

## 1. Introduction

Lung cancer is the second most diagnosed cancer and the leading cause of cancer death worldwide. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), including the first- or second-generation EGFR TKIs and the third-generation EGFR TKIs, had been recommended as the current standard treatment for non-small cell lung cancer (NSCLC) with *EGFR* mutation in the ASCO Living Guideline (Version 2022.2), the latest National Comprehensive Cancer Network (Version 1. 2023) and the Chinese guideline [1–3]. Publications revealed that most patients developed drug resistance after around one year of treatment with the first- or second-generation EGFR TKIs [4,5], while *EGFR* T790M mutation was reported to occur among over half of the patients with acquired drug resistance [6]. Since Osimertinib, the first world-widely available third-generation EGFR TKI was developed to overcome the secondary *EGFR* T790M mutation as a second or later-line treatment and further optimized the clinical efficacy as a first-line treatment, the situation shifted [7–26].

Brain metastases (BMs) imply a poor prognosis, especially among NSCLC patients with *EGFR*-sensitizing mutations who were reported with a high predilection of up to 50% for BMs. In past decades, stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) were used to treat patients with BMs palliatively, until the EGFR TKIs were available [27]. The central nervous system (CNS) efficacy of the first- or second-generation EGFR TKIs was improved when compared with conventional chemotherapy but still limited when compared with the third-generation EGFR TKIs osimertinib, aumolertinib, and furmonertinib with much more superior results from preclinical and clinical studies [27–33].

Rezivertinib (BPI-7711) is a novel third-generation EGFR TKI selective for *EGFR*-sensitizing and T790M mutations developed by Beta Pharma (Shanghai) Co., Ltd., Shanghai, the People's Republic of China. In preclinical studies, rezivertinib was observed to penetrate the blood–brain barrier of mice and rats, indicating the potential CNS

efficacy of rezivertinib in patients with CNS metastases. In the rezivertinib phase I dose-escalation and dose-expansion study enrolling patients with advanced NSCLC with *EGFR* T790M mutation, the rezivertinib as second- or later-line treatment was revealed with promising CNS efficacy [17]. Furthermore, the CNS efficacy for advanced NSCLC with *EGFR* T790M mutation was verified with the rezivertinib phase IIb study [18]. Here, we report the CNS efficacy of rezivertinib ≥180 mg orally once daily (180 mg was identified as the recommended phase 2 dose [RP2D]), for advanced NSCLC patients with *EGFR* T790M mutation and CNS metastases from a pooled analysis of phase I and phase IIb studies.

## 2. Materials and methods

### 2.1. Study design and patients

We combined individual data from two different single-arm, phase I and phase IIb studies to assess the CNS response of rezivertinib in advanced NSCLC patients with *EGFR* T790M mutation, who had progressed following prior treatment including first- or second-generation EGFR TKIs. The rezivertinib phase I dose-escalation and dose-expansion study was conducted across 20 hospitals in the People's Republic of China, while the rezivertinib phase IIb study was a single-arm, open-label study conducted across 50 hospitals in the People's Republic of China. The specific inclusion and exclusion criteria and procedures of these two studies were essentially analogous. Briefly, eligible patients were aged 18 years or above with a histologically or cytologically confirmed locally advanced or metastatic NSCLC with *EGFR*-sensitive mutations (including exon 19 deletion, L858R, G719X, L861Q, and S768I). All eligible patients were required to have radiologically confirmed disease progression after the latest first- or second-generation EGFR TKI treatment and centrally confirmed *EGFR* T790M mutation with either tumor tissue or plasma samples (the Cobas *EGFR* mutation test, Version 2, Roche Diagnostics, South Branchburg, NJ). CNS metastases patients with asymptomatic, stable brain metastases not requiring steroid therapy for at least 7 days before enrollment were eligible. Exclusion criteria included a history of interstitial lung disease, previous treatment with any third-generation EGFR TKI, major surgery within 28 days, or local radiotherapy within 7 days of starting rezivertinib treatment. More details of the methodology for each study are available in previous publications [17,18].

In the phase I study, eligible patients received rezivertinib orally once daily dosing from 30 to 300 mg, while all patients received 180 mg in the phase IIb study (one hour before or two hours after a meal) until disease progression, unacceptable toxicity, or withdrawal of consent. Dose interruption was implemented if a patient had a grade ≥3 treatment-related adverse event (TRAE) or intolerable toxicity caused by rezivertinib in the investigator's judgment. Treatment after systemic disease progression was permitted if clinical benefits could be obtained by the investigator's judgment.

Systemic tumor assessments, with computed tomography (CT) and magnetic resonance imaging (MRI) scans, were performed at baseline and every two treatment cycles (6 weeks) by blinded independent central review (BICR) and by investigators per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [34] in both studies, respectively. Meanwhile, intracranial tumor response was only evaluated by BICR according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) [35] alone with the same frequency. Additional CT or MRI scans could be performed on suspected lesions determined by investigators. Adverse events were monitored continuously according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 from the time when the informed consent was signed to 30 days after the last dose of rezivertinib. In the rezivertinib treatment period, physical examination results, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, and results of hematology, serum chemistry, urinalysis, 12-lead electrocardiogram, and echocardiography were documented and assessed at specified time points as per the protocols.

In the phase I study, circulating tumor DNA (ctDNA) was used as a biomarker to identify plasma *EGFR* mutation status at baseline and the end of 6 weeks with rezivertinib administration. *EGFR* mutations detection included exon 19 deletion, exon 20 insertion, L858R, S768I, G719X, L861Q, and T790M mutations.

### 2.2. Ethics

Both clinical studies were performed in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and the applicable regulatory requirements. Both protocols were approved by the institutional review board or independent ethics committee associated with each participating hospital. Written informed consent was obtained from each patient before enrollment in phase I and phase IIb studies of rezivertinib.

### 2.3. Endpoints and assessments

Endpoints evaluated in this pooled analysis were CNS objective response rate (CNS-ORR), CNS disease control rate (CNS-DCR), CNS duration of response (CNS-DoR), CNS progression-free survival (CNS-PFS), CNS depth of response (CNS-DepOR) by BICR according to RANO-BM. CNS-ORR was defined as the proportion of patients with a CNS best overall response (CNS-BOR) of complete response (CR) or partial response (PR); CNS-DCR was defined as the proportion of patients with a CNS-BOR of CR, PR, or stable disease (SD). CNS-DoR was defined as the time from the date of the first documented CNS response (CNS CR or PR) to the date of documented CNS disease progression or date of death, whichever occurred first. CNS-PFS was defined as the time lasting from the first dose date of rezivertinib to CNS progression or death, whichever occurred first. CNS-DepOR was defined as the best percentage change of CNS target lesions (TLs) from baseline.

Patients who received rezivertinib orally once daily at a dosage ≥180 mg from these two studies were included in the full analysis set (FAS), and those with measurable and non-measurable CNS lesions at baseline were defined as CNS full analysis set (cFAS). Patients with measurable CNS lesions at baseline were defined as CNS evaluable for response set (cEFR). For patients with only non-target lesions (NTLs), only CR of metastatic lesions could be reported as an objective response, while absolute change and percentage change from baseline in the sum of CNS TL size at each assessment were calculated and assessed as CR or PR for those with TLs. Given this, response in patients with only NTLs was classed as CR, Non-CR/Non-PD (NN), PD or not evaluable (NE); and response in patients with TLs was classed as CR, PR, SD, PD, or NE. All CNS responses required confirmation again at least 4 weeks later. The correlation between the plasma *EGFR* mutation status and the clinical CNS efficacy was analyzed among patients who were from the phase I study and included in cFAS. Treatment-emergent adverse events (TEAEs) were evaluated as per CTCAE version 4.03 by investigators. More details are available in previous publications [17,18]. A safety analysis was done among the FAS and cFAS populations.

### 2.4. Statistical analysis

In this pooled analysis, CNS-ORR and CNS-DCR were calculated based on the recorded BOR during the related studies, and the 95% confidence intervals (CIs) were calculated by the Clopper-Pearson method. The median CNS-DoR and CNS-PFS and related 95% CIs were calculated by the Kaplan-Meier method. In this post hoc analysis, the CNS-PFS by different *EGFR* mutation subtypes was analyzed using the same methods as mentioned previously, and $p$ values were calculated with the log-rank test. All statistical analyses were performed using

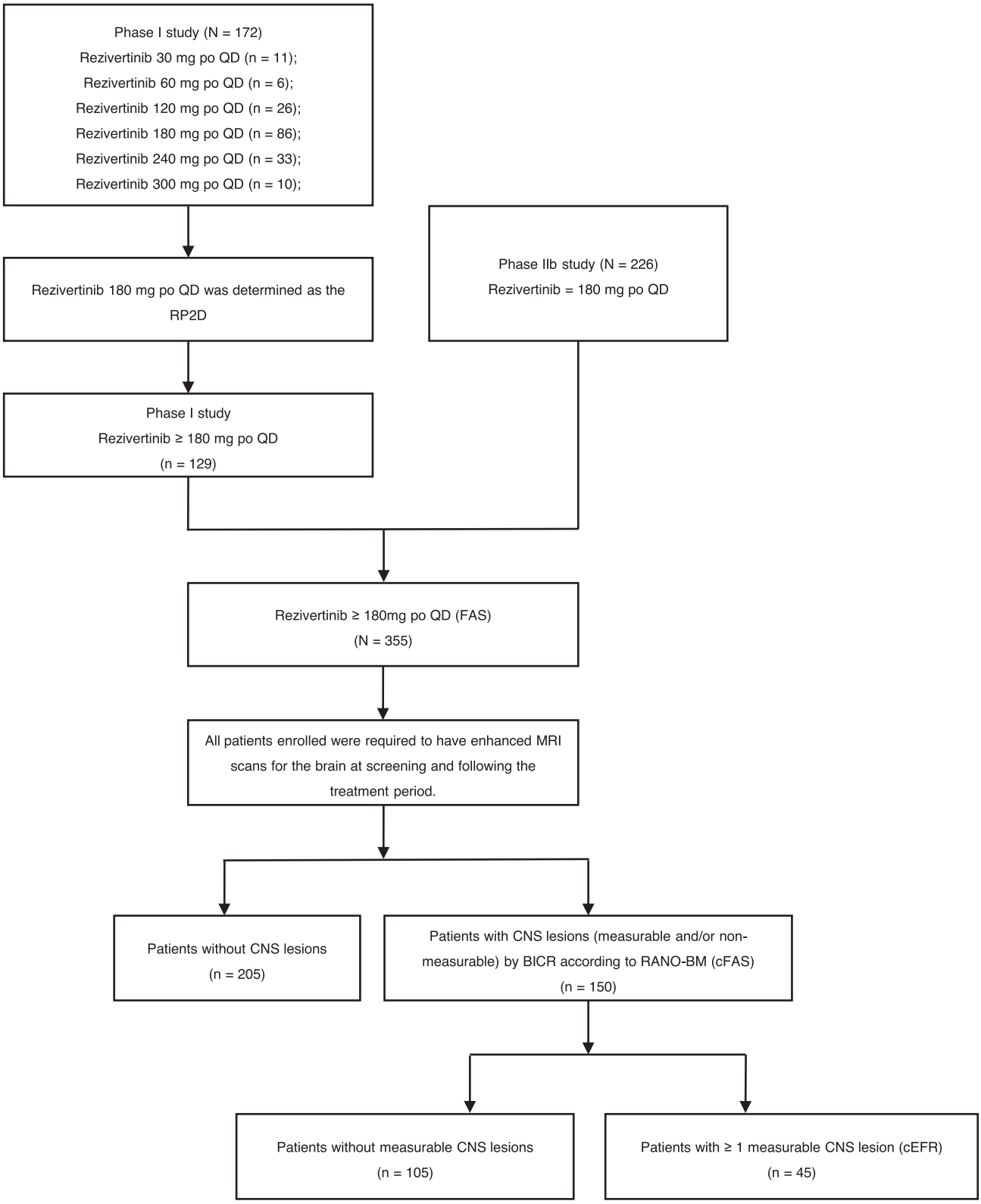


**Fig. 1.** Patient disposition. Abbreviation: FAS, full analysis set; MRI, Magnetic resonance imaging; CNS, central nervous system; BICR, blinded independent central review; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; cFAS, CNS full analysis set; cEFR, CNS evaluable for response set; po, *peros*; QD, *quaque die*; RP2D, recommended phase 2 dose.

**Table 1**
Baseline demographic and disease characteristics of patients in the FAS and cFAS.

| | FAS (n = 355) | cFAS (n = 150) |
|---|---|---|
| *Age, years* | | |
| Median | 59 (30–81) | 58 (30–81) |
| <65 | 255 (71.8) | 116 (77.3) |
| ≥65 | 100 (28.2) | 34 (22.7) |
| *Sex* | | |
| Female | 245 (69.0) | 103 (68.7) |
| Male | 110 (31.0) | 47 (31.3) |
| *ECOG PS* | | |
| 0 | 106 (29.9) | 45 (30.0) |
| 1 | 249 (70.1) | 105 (70.0) |
| *EGFR mutation subtype* | | |
| Exon 19 deletion | 224 (63.1) | 91 (60.7) |
| L858R mutation | 126 (35.5) | 56 (37.3) |
| Others[a] | 5 (1.4) | 3 (2.0) |
| *EGFR T790M positive sample type*[b] | | |
| Tissue | 180 (50.7) | 60 (40.0) |
| Plasma | 201 (56.6) | 103 (68.7) |
| CNS target lesion size, mm | NA | 20.8 (10.0–99.6) |
| CNS radiotherapy | NA | 26 (17.3) |

Note: Data are median (range) or n (%). [a] Others refer to patients who presented with neither *EGFR* Exon 19 deletion nor L858R mutations, among whom there were 3 patients with only *EGFR* T790M mutation; one with G719X, L861Q, and T790M mutations; one with G719X, S768I, and T790M mutations in FAS. Among these 5 patients, three were included in cFAS. [b] In FAS, 26 patients were confirmed *EGFR* T790M positive with both tissue and plasma at baseline (14 from phase I study and 12 from phase IIb study); in cFAS, 13 patients were confirmed *EGFR* T790M positive with both tissue and plasma at baseline (9 from phase I study and 4 from phase IIb study). Abbreviation: cFAS, CNS full analysis set; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; FAS, full analysis set; NA, not applicable; PS, performance status.

SAS® Version 9.3 or higher.

## 3. Results

### 3.1. Patients

From September 11, 2017, to August 23, 2019, of the phase I study, and from July 5, 2019, to January 22, 2020, of the phase IIb study, a total of 355 patients were included in the FAS in this pooled analysis; among them, 129 (36.3%) patients who received rezivertinib with a dose of ≥180 mg orally once daily were from the phase I study and 226 (63.7%) patients with a dose of 180 mg orally once daily were from the phase IIb study. 150 (42.3%) patients were included in the cFAS (phase I study, n = 59; phase IIb study, n = 91), and among them, 45 (30%) patients were included in the cEFR (phase I study, n = 16; phase IIb study, n = 29) (Fig. 1). The baseline demographic and disease characteristics in the cFAS were broadly similar with that of the FAS population (Table 1). The median size of the target CNS lesion was 20.8 (range: 10.0–99.6) mm. In FAS, 26 patients were confirmed *EGFR* T790M positive with both baseline tissue and plasma samples, 154 patients were confirmed with tissue *EGFR* T790M positive only, and 175 patients were confirmed with plasma *EGFR* T790M positive only; in cFAS, 13 patients were confirmed *EGFR* T790M positive with both baseline tissue and plasma samples, 47 patients were confirmed with tissue *EGFR* T790M positive only, and 90 patients were confirmed with plasma *EGFR* T790M positive only. Meanwhile, in cFAS, a total of 44 patients with tissue *EGFR* T790M positive provided plasma *EGFR* T790M mutation results at baseline. Totally 26 (17.3%) patients in cFAS had CNS radiotherapy before enrolment due to CNS metastases.

### 3.2. Efficacy

The data cutoff dates of phase I and phase IIb studies were December 23, 2021, and January 24, 2022, respectively. The median duration of rezivertinib exposure was 8.3 (range: 0.2–28.8) months in cFAS (Fig. 2A). 12.0% (18/150) patients achieved CNS-BOR of CR and 20.0% (30/150) patients with PR in the cFAS, while in cEFR, 2.2% (1/45) and 66.7% (30/45) patients achieved CNS-BOR of CR and PR, respectively. Overall, the CNS-ORR was 32.0% (48/150; 95% CI: 24.6–40.1%) and the CNS-DCR was 42.0% (63/150; 95% CI: 34.0–50.3%) in cFAS, while in cEFR, the CNS-ORR and CNS-DCR were 68.9% (31/45; 95% CI: 53.4–81.8%) and 100.0% (45/45; 95% CI: 92.1–100.0%), respectively (Table 2). For the cEFR population, the median CNS-DepOR was -52.0% (range: –100.0 to 16.1%) and the mean of CNS-DepOR was -46.8% (95% CI: –55.5 to 38.1%). Please refer to Fig. 2B-C for the BICR-assessed percentage change of tumor size from baseline in cEFR and Fig. 2D-E for the three-dimensional (3D) waterfall plots demonstrating the CNS-DepOR in cEFR.

At the data cutoff, 28.0% (42/150) patients had experienced CNS-PFS events. In cFAS, the median CNS-DoR was 13.8 (95% CI: 9.6- not calculable [NC]) months and the median CNS-PFS was 16.5 (95 %CI: 13.7-NC) months (Fig. 3A). In patients with *EGFR* exon 19 deletion mutation, the median CNS-PFS was 15.2 (95% CI: 12.4-NC) months while that in patients with *EGFR* L858R mutation was 16.6 (95% CI: 11.0-NC) months among the cFAS population ($p = 0.8105$; Fig. 3B). Among the 44 patients with positive tissue *EGFR* T790M provided plasma *EGFR* T790M mutation results at baseline, 31 were negative with plasma *EGFR* T790M mutation, and 13 were positive. The median CNS-PFS were significantly longer in baseline plasma *EGFR* T790M negative patients compared to baseline plasma *EGFR* T790M positive patients (NC [95% CI: 15.1-NC] months versus 8.2 [95% CI: 3.1-NC] months; $p = 0.0260$; Fig. 3C).

Among 17.3% (26/150) patients with prior brain radiotherapy history in cFAS, three with measurable CNS lesions achieved the CNS objective response (2 with PR and one with SD). The median CNS-PFS was NC (95% CI: 13.7-NC) months for 26 patients with prior brain radiotherapy and 15.1 (95% CI: 11.1-NC) months for 124 patients without prior brain radiotherapy (Table S1). Among those 45 patients in cEFR, 42 were without prior brain radiotherapy and the CNS-ORR and CNS-DCR were 69.1% (95% CI: 52.9–82.4%) and 100.0% (95% CI: 91.6–100.0%), respectively; 3 patients were with prior brain radiotherapy and the CNS-ORR and CNS-DCR was 66.7% (95% CI: 9.4–99.2%) and 100.0% (95% CI: 29.2–100.0%), respectively (Fig. S1).

In cFAS, 86.7% (130/150) patients received rezivertinib at the dosage of 180 mg orally once daily, and among them, 16 patients achieved the CNS-BOR of CR and 24 of PR. The CNS-ORR was 30.8% (95% CI: 23.0–39.5%) while the median CNS-PFS was 16.6 (95% CI: 13.7-NC) months. Among 11.3% (17/150) patients at the dosage of 240 mg orally once daily, 2 achieved the CNS-BOR of CR and 5 with PR. The CNS-ORR was 41.2% (95% CI: 18.4–67.1%) while the median CNS-PFS was 3.9 (95% CI: 5.6-NC) months. 2.0% (3/150) patients were at 300 mg orally once daily, and among them, one patient achieved the CNS-BOR of PR. The CNS-ORR was 33.3% (95% CI: 0.8–90.6%) while the median CNS-PFS was 15.1 (95% CI: NC-NC) months (Table S2).

For plasma *EGFR* mutations detection, no patient was detected with exon 20 insertion or G719X mutations at the end of 6 weeks. All 47 patients detected with *EGFR* T790M mutation at baseline turned undetected at the end of 6 weeks. The *EGFR* mutations detected at the end of 6 weeks included exon 19 deletion, L858R, L861Q, and S768I. Among 58 patients who received plasma *EGFR* mutations test at baseline, 51 patients were detected, and 7 patients were undetected with *EGFR* mutations. At the end of six weeks with rezivertinib administration, plasma *EGFR* mutations were detected for 19 patients and undetected

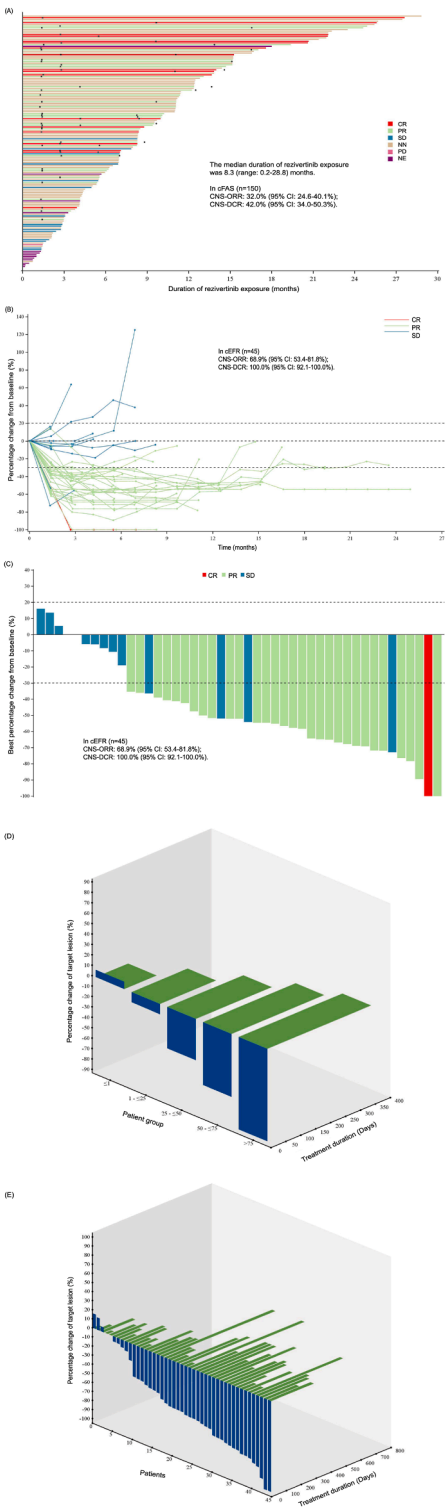


**Fig. 2.** (A) Swimmer plot for the duration of rezivertinib exposure in cFAS. Note: As per the protocol, after the patient's systematic disease progression, the patient may continue the rezivertinib treatment if investigator considered the patient would still benefit. In patients with a BICR-assessed confirmed CNS objective response, the time when the CNS objective response was first observed was indicated by an ×, and the time when the CNS objective response was terminated is indicated by a dot. (B) Spider plot for BICR-assessed percentage change of tumor size from baseline in cEFR. (C) Waterfall plot for BICR-assessed best percentage change of tumor size from baseline in cEFR. Note: The dashed line at 20% represents the boundary for the determination of PD, and the dashed line at −30% represents the boundary for the determination of PR. (D) Three-dimensional waterfall plot for BICR-assessed CNS-DepOR by patient quartile and rezivertinib treatment duration in cEFR; Note: The patient group of ≤1 represents those without shrinkage of the CNS target lesions. (E) Three-dimensional waterfall plot for BICR-assessed CNS-DepOR by individual patients and rezivertinib treatment duration in cEFR. Abbreviation: CNS, central nervous system; cFAS, CNS full analysis set; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NN, Non-CR/Non-PD; NE, not evaluable; CNS-ORR, CNS objective response rate; CNS-DCR, CNS disease control rate; BICR, blinded independent central review; CI, confidence interval; cEFR, CNS evaluable for response set; CNS-DepOR, CNS depth of response.

**Table 2**
BICR-assessed CNS response in cFAS and cEFR.

| | cFAS (n = 150) | cEFR (n = 45) |
|---|---|---|
| *CNS-BOR, n (%)* | | |
| CR | 18 (12.0) | 1 (2.2) |
| PR | 30 (20.0) | 30 (66.7) |
| SD | 15 (10.0) | 14 (31.1) |
| PD | 1 (0.7) | 0 (0.0) |
| NN | 73 (48.7) | 0 (0.0) |
| NE | 13 (8.7) | 0 (0.0) |
| CNS-ORR, n (%) | 48 (32.0) | 31 (68.9) |
| 95% CI | 24.6–40.1 | 53.4–81.8 |
| CNS-DCR, n (%) | 63 (42.0) | 45 (100.0) |
| 95% CI | 34.0–50.3 | 92.1–100.0 |

Note: Data are n (%). Abbreviation: BICR, blinded independent central review; CNS, central nervous system; cFAS, CNS full analysis set; cEFR, CNS evaluable for response set; CNS-BOR, CNS best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NN, Non-CR/Non-PD; NE, not evaluable; CNS-ORR, CNS objective response rate; CNS-DCR, CNS disease control rate; CI, confidence interval.

for 39 patients. The median CNS-PFS of patients undetected with plasma *EGFR* mutations at the end of six weeks was significantly longer than those detected with plasma *EGFR* mutations (15.1 [95% CI: 12.4-NC] months versus 12.5 [95% CI: 3.1-NC] months; $p = 0.0034$; Fig. S2 A). For 51 patients detected at baseline, plasma *EGFR* mutations were detected for 18 patients and undetected for 33 patients at the end of six weeks. The CNS-PFS of patients undetected with plasma *EGFR* mutations was significantly longer compared to patients detected with plasma *EGFR* mutations after six weeks' treatment (NC [95% CI: 13.9-NC] months versus 12.5 [95% CI: 3.1-NC] months; $p = 0.0012$; Fig. S2 B).

For patients who discontinued rezivertinib treatment in cFAS, among the 150 patients, 79 had received subsequent anti-cancer therapies, including 56 patients received targeted therapy, 29 patients experienced chemotherapy, 13 patients underwent radiotherapy, 8 patients had Chinese traditional medicine therapy, and 11 patients received other anti-cancer therapies. Within those who received targeted therapy, 42 patients took EGFR TKIs including the 1st-generation EGFR TKIs (icotinib, erlotinib, and gefitinib) and the 3rd-generation EGFR TKIs (osimertinib and aumolertinib).

### 3.3. Safety

In FAS, 98.3% (349/355) patients had at least one TEAE, among them 83.9% (298/355) had TRAEs. The safety profile in cFAS was consistent with that in the FAS population. In cFAS, 98.7% (148/150) patients had TEAEs and 85.3% (128/150) had TRAEs. 36.3% (129/355) patients in FAS and 37.3% (56/150) patients in cFAS experienced ≥grade 3 TEAEs, while 19.7% (70/355) and 16.0% (24/150) patients experienced ≥grade 3 TRAEs in FAS and cFAS, respectively. 3.1% (11/355) and 1.3% (2/150) patients experienced serious TRAEs in FAS and cFAS, respectively. 0.3% (1/355) and no patient died due to TRAEs in FAS and cFAS, respectively. Dose interruptions due to TRAEs happened in 10.7% (38/355) and 6.7% (10/150) patients in FAS and cFAS, respectively, while dose reductions due to TRAEs occurred in 4.8% (17/355) and 4.0% (6/150) patients in FAS and cFAS, respectively. 3.9% (14/355) and 4.0% (6/150) patients discontinued the study drug due to TRAEs in FAS and cFAS, respectively. The overall safety results were available in Table 3. The top three most common TRAEs were the same in FAS and cFAS, which were leukopenia, thrombocytopenia, and anemia (Table S3).

## 4. Discussion

In this pooled analysis of two single-arm clinical studies, rezivertinib showed promising clinical CNS efficacy in advanced NSCLC patients with *EGFR* T790M mutation. The favorable CNS-ORRs were 32.0% (95% CI: 24.6–40.1%) and 68.9% (95% CI: 53.4–81.8%) in cFAS and cEFR, respectively; while the CNS-DCRs were 42.0% (95% CI: 34.0–50.3%) and 100% (95% CI: 92.1–100.0%) in cFAS and cEFR, respectively. Meanwhile, rezivertinib was associated with an encouraging median CNS-DoR of 13.8 (95% CI: 9.6- NC) months and median CNS-PFS of 16.5 (13.7-NC) months in cFAS, and a favorable median CNS-DepOR of -52.0% (range: -100.0 to 16.1%) in cEFR. The safety profile was favorable. The efficacy and safety of rezivertinib in this pooled analysis were consistent with those of the two previous clinical studies [17,18].

In these two previous clinical studies, rezivertinib as a second- or later-line treatment was revealed with promising CNS efficacy for advanced NSCLC patients with *EGFR* T790M mutation. In the rezivertinib phase I dose-escalation and dose-expansion study (NCT03386955), among 172 patients, CNS metastases were found in 79 patients, and among whom 22 patients had at least one CNS target lesion at baseline. The BICR-evaluated intracranial ORR and DCR among these 22 patients with at least one CNS target lesion were 50.0% (95% CI: 28.2–71.8%) and 90.9% (95% CI: 70.8–98.9%), respectively. The median intracranial DoR and time to progression for these 22 patients were 11.2 (95% CI: 2.8–12.4) months and 13.9 (95% CI: 6.9-not reached [NR]) months, respectively [17]. In the phase IIb study (NCT03812809), among 226 patients, 91 patients had CNS metastases at baseline and 29 patients had ≥1 CNS target lesion. The CNS-ORR and CNS-DCR were 69.0% (95% CI: 49.2–84.7%) and 100% (95% CI: 88.1–100%), respectively. The median CNS-DoR and time to progression for these 29 patients were 15.2 (95% CI: 8.3-NC) and 16.5 (95% CI: 9.7-NC) months, respectively, while the median CNS-PFS was 16.6 (95% CI: 11.1-NC) months. The median OS for patients with brain metastases was 17.5 (95% CI: 12.9–20.2) months, while that in patients without brain metastases was NC (95% CI: 24.1-NC) months (Hazard ratio [HR]: 0.48; [95% CI: 0.33–0.69]; $p < 0.0001$) [18]. Furthermore, in the rezivertinib phase IIa study, the CNS efficacy as a first-line treatment among patients with locally advanced or metastatic/recurrent *EGFR* mutated NSCLC was also favorable. Among 27.9% (12/43) patients with CNS metastases at baseline, the CNS-ORR and CNS-DCR was 50.0% (95% CI: 21.1–78.9%) and 58.3% (95% CI: 27.7–84.8%), respectively; and the BICR-assessed median PFS was 15.2 (95% CI: 6.4-NC) months and 22.0 (95% CI: 13.8-NC) months, respectively ($p = 0.3991$), among patients with and without CNS metastases at baseline [19].

As reported, some third-generation EGFR TKIs showed superior systematic efficacy or prognosis for advanced NSCLC among patients with *EGFR* exon 19 deletion mutation than that with *EGFR* L858R mutation [9,12,13,15,16,36]. The subgroup efficacy of rezivertinib for different *EGFR* mutations was revealed without significant difference in the previous phase IIa and IIb studies [18,19]. In this pooled analysis, there were consistencies and encouraging findings in the CNS subgroup analysis for different *EGFR* mutations. The median CNS-PFS in patients with *EGFR* exon 19 deletion mutation was shorter but with no significant difference from that among patients with *EGFR* L858R mutation in cFAS (15.2 [95% CI: 12.4-NC] and 16.6 [95% CI: 11.0-NC] months; $p = 0.8105$). In the previous phase IIb study, the systematic efficacy, including ORR and PFS, showed more benefits for those with tissue *EGFR* T790M positive than that with plasma T790M positive [18]. In this pooled analysis, among the 44 patients with positive tissue *EGFR* T790M provided plasma *EGFR* T790M mutation results additionally, the median CNS-PFS was significantly longer in baseline plasma *EGFR* T790M negative patients compared to baseline plasma *EGFR* T790M positive patients (NC [95% CI: 15.1-NC] months versus 8.2 [95% CI: 3.1-NC] months; $p = 0.0260$).

In this pooled analysis, the CNS efficacy of patients according to their prior brain radiotherapy history was analyzed. In cFAS, the median CNS-PFS was NC (95% CI: 13.7-NC) months for 26 patients with prior brain radiotherapy and 15.1 (95% CI: 11.1-NC) months for 124 patients without prior brain radiotherapy (Table S1). The patients with prior brain radiotherapy history had longer CNS-PFS compared to patients

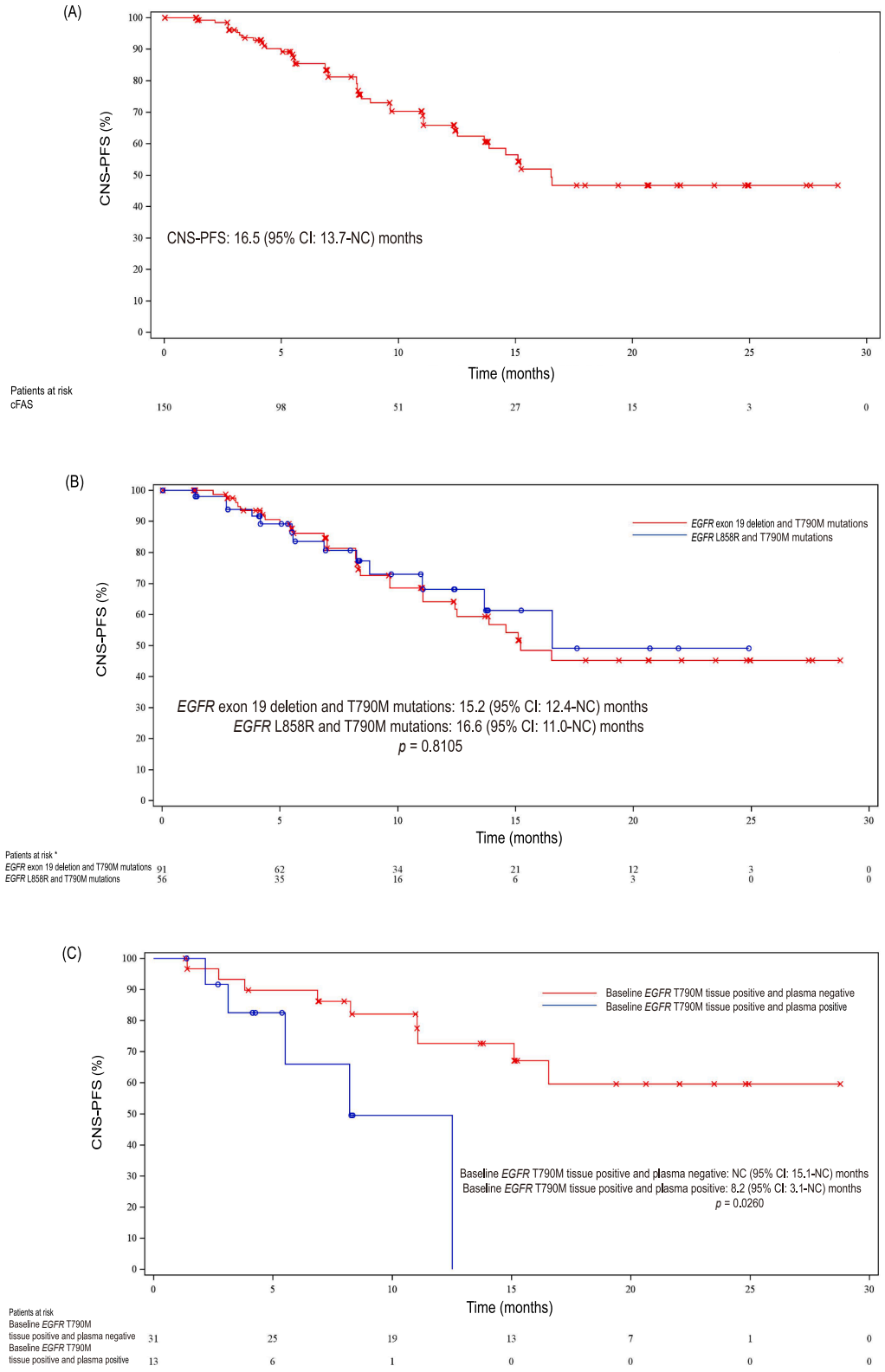


**Fig. 3.** (A) Kaplan-Meier curve of BICR-assessed CNS-PFS in cFAS. (B) BICR-assessed CNS-PFS Kaplan-Meier curves for patients with different *EGFR* mutations in cFAS. Note: * In cFAS, three patients presented with neither *EGFR* Exon 19 deletion nor L858R mutations at baseline. One patient was from the phase I study with only *EGFR* T790M mutation detected; two patients were from the phase IIb study, one with only *EGFR* T790M mutation detected and the other one with S768I, G719X, and *EGFR* T790M mutation detected. (C) BICR-assessed CNS-PFS for baseline tissue *EGFR* T790M positive patients with plasma *EGFR* T790M negative or positive. Abbreviation: BICR, blinded independent central review; CNS, central nervous system; CNS-PFS, CNS progression-free survival; cFAS, CNS full analysis set; *EGFR*: epidermal growth factor receptor; CI, confidence interval; NC, not calculable.

**Table 3**
Summary of AEs in FAS and cFAS.

| AEs | FAS (n = 355) | cFAS (n = 150) |
|---|---|---|
| TEAEs | 349 (98.3) | 148 (98.7) |
| Grade ≥3 TEAEs | 129 (36.3) | 56 (37.3) |
| TRAEs | 298 (83.9) | 128 (85.3) |
| Grade ≥3 TRAEs | 70 (19.7) | 24 (16.0) |
| Any SAEs | 73 (20.6) | 35 (23.3) |
| Treatment-related SAEs* | 11 (3.1) | 2 (1.3) |
| Death due to TEAEs | 14 (3.9) | 8 (5.3) |
| Death due to TRAEs | 1 (0.3) | 0 (0.0) |
| Dose interruption due to TEAEs | 50 (14.1) | 16 (10.7) |
| Dose reduction due to TEAEs | 19 (5.4) | 8 (5.3) |
| Discontinuation due to TEAEs | 19 (5.4) | 10 (6.7) |
| Dose interruption due to TRAEs | 38 (10.7) | 10 (6.7) |
| Dose reduction due to TRAEs | 17 (4.8) | 6 (4.0) |
| Discontinuation due to TRAEs | 14 (3.9) | 6 (4.0) |

Note: Data are n (%); AEs were evaluated per CTCAE version 4.03. * Assessed by investigators. Abbreviation: AEs, adverse events; FAS, full analysis set; cFAS, CNS full analysis set; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events; SAEs, serious adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

without prior brain radiotherapy history. Meanwhile, we calculated the CNS efficacy among patients at different rezivertinib dosage levels in cFAS. 86.7% (130/150) patients who received rezivertinib at the dosage of 180 mg orally once daily showed a CNS-ORR of 30.8% (95% CI: 23.0–39.5%) and the median CNS-PFS of 16.6 (95% CI: 13.7-NC) months; 11.3% (17/150) patients at the dosage of 240 mg orally once daily showed a CNS-ORR of 41.2% (95% CI: 18.4–67.1%) and the median CNS-PFS of 3.9 (95% CI: 5.6-NC) months; 2.0% (3/150) patients at 300 mg orally once daily showed a CNS-ORR of 33.3% (95% CI: 0.8–90.6%) and the median CNS-PFS of 15.1 (95% CI: NC-NC) months. These results revealed the dosage of 180 mg orally once daily to be optimal among patients with CNS metastases and further supported the determination with the dosage of 180 mg orally once daily as the RP2D for rezivertinib in the phase I study [17]. There might be a potential for better CNS efficacy with the dosage increased within a proper level. However, the link between the dosages and clinical CNS efficacy of rezivertinib was insufficient yet, and further investigations are wanted.

For plasma *EGFR* mutations detection, all 47 patients detected with plasma *EGFR* T790M mutation at baseline turned undetected at the end of 6 weeks, indicating the change of *EGFR* T790M mutation status wasn't a reliable predictor for CNS efficacy of rezivertinib. However, the patients undetected with plasma *EGFR* mutations at the end of 6 weeks were significantly associated with a longer median CNS-PFS, which revealed the correlation between the plasma *EGFR* mutations status and the CNS efficacy of advanced NSCLC treated with rezivertinib.

Nowadays, there are several third-generation EGFR TKIs available in China, including osimertinib, aumolertinib, and furmonertinib, and the superior CNS efficacies were revealed to be the important advantages over the first- and second-generation EGFR TKIs. For advanced NSCLC patients with *EGFR* T790M mutation, the third-generation EGFR TKIs displayed favorable CNS efficacy. In a pooled analysis of AURA extension and AURA2 studies, for 50 patients with ≥1 measurable CNS lesion, the CNS-ORR and CNS-DCR of osimertinib were 54% (95% CI: 39–68%) and 92% (95% CI: 81–98%), respectively [31]. In the FLAURA study, osimertinib as first-line treatment had reduced 52% of the risk of CNS progression or death compared with gefitinib or erlotinib (CNS-PFS: NR [95% CI: 16.5-NC] and 13.9 [95% CI: 8.3-NC] months, respectively; HR = 0.48 [95% CI: 0.26–0.86], $p = 0.014$) [29]. In the aumolertinib phase 2 APOLLO study, for 23 patients with assessable CNS metastases, the CNS-ORR and CNS-DCR were 60.9% (95% CI: 38.5–80.3%) and 91.3% (95% CI: 72.0–98.9%), respectively; and the CNS-PFS was 11.8 (95% CI: 5.5–15.3) months [12]. In the AENEAS study, aumolertinib had significantly prolonged CNS-PFS over gefitinib among *EGFR*-mutated patients with treatment-naïve NSCLC (CNS-PFS: 15.3 [95% CI: 10.8–20.8] and 8.2 [95% CI: 6.5–8.3] months respectively; HR = 0.38 [95% CI: 0.24–0.60], $p < 0.0001$) [32]. In the furmonertinib phase IIb study, among 29 patients with ≥1 measurable CNS lesions, the CNS-ORR and CNS-DCR were 66% (95% CI: 46.0–82.0%) and 100.0%, respectively; and the CNS-PFS was 11.6 (95% CI: 8.3–13.8) months [15]. In the FURLONG study, furmonertinib as first-line treatment for *EGFR*-mutated NSCLC presented superior efficacy over gefitinib in *EGFR*-mutated NSCLC patients with CNS metastases (CNS-PFS: 20.8 [95% CI: 15.2–25.3] and 9.8 [95% CI: 7.2–18.0] months, respectively; CNS-ORR: 91% [95% CI: 72–99%] and 65% [95% CI: 48–80%], respectively; the least-square mean of CNS-DepOR: 62% [95% CI: 51–72%] and 39% [95% CI: 30–47%], respectively) [33]. Compared with these third-generation EGFR TKIs, rezivertinib demonstrated a promising CNS efficacy in this pooled analysis study among advanced NSCLC patients with *EGFR* T790M mutation as second- or later-line treatment and the phase IIa study among patients with locally advanced or metastatic/recurrent *EGFR* mutated NSCLC as first-line treatment [19].

There were some advantages of this pooled analysis. This pooled analysis included quite a large number of advanced NSCLC patients with acquired *EGFR* T790M mutation and CNS metastases. All patients enrolled were required to have enhanced MRI scans for the brain at screening and the following rezivertinib treatment period, and the CNS efficacy was evaluated by BICR to reduce bias. However, there are also limitations. This pooled analysis was retrospectively and both previous clinical studies were single-arm non-comparative studies, conducted on Chinese patients only, thus, there might be potential bias when compared with other ethnic patients. Encouragingly, a randomized phase III study REZOR (NCT03866499) comparing rezivertinib with gefitinib in the first-line setting is undergoing.

## 5. Conclusions

In summary, in this pooled analysis, rezivertinib showed promising clinical CNS efficacy in advanced NSCLC patients with *EGFR* T790M mutation and CNS metastases. The CNS efficacy with favorable CNS-ORR, CNS-DepOR, CNS-DoR, CNS-PFS, and the safety profile was consistent with the previous publications. The CNS efficacy of rezivertinib would be further evaluated in future studies.

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## CRediT authorship contribution statement

**Yuankai Shi:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Tingting Wang:** Project administration, Resources, Software, Supervision, Writing - original draft, Writing - review & editing. **Anqi Zhou:** Software, Writing - original draft, Writing - review & editing. All authors: Resources; Writing - review & editing. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michael Greco, Tingting Wang, and Anqi Zhou are employees of Beta

Pharma, and all other authors declare no competing interests.

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## Appendix A. Supplementary data

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## References

[1] D.H. Owen, N. Singh, N. Ismaila, E. Blanchard, P. Celano, N. Florez, D. Jain, N. B. Leighl, H. Mamdani, G. Masters, P.R. Moffitt, J. Naidoo, T. Phillips, G.J. Riely, A. G. Robinson, E. Schenk, B.J. Schneider, L. Sequist, D.R. Spigel, I.A. Jaiyesimi, Therapy for stage IV non–small-cell lung cancer with driver alterations: ASCO living guideline, version 2022.2, JCO 41 (5) (2023) e10–e20.

[2] NCCN Clinical Practice Guidelines in Oncology: Non-small cell lung cancer. Version 1. 2023; https://www.nccn.org/guidelines.

[3] Chinese Association for Clinical Oncologists, Clinical practice guideline for stage IV primary lung cancer in China (2023 version) (in Chinese), Chin. J. Oncol. 45 (1) (2023) 1–30, https://doi.org/10.3760/cma.j.cn112152-20221009-00687.

[4] D.R. Camidge, W. Pao, L.V. Sequist, Acquired resistance to TKIs in solid tumours: learning from lung cancer, Nat. Rev. Clin. Oncol. 11 (8) (2014) 473–481, https://doi.org/10.1038/nrclinonc.2014.104.

[5] S.G. Wu, J.Y. Shih, Management of acquired resistance to EGFR TKI–targeted therapy in advanced non-small cell lung cancer, Mol. Cancer 17 (1) (2018) 38, https://doi.org/10.1186/s12943-018-0777-1.

[6] T. Nagano, M. Tachihara, Y. Nishimura, Mechanism of resistance to epidermal growth factor receptor-tyrosine kinase inhibitors and a potential treatment strategy, Cells 7 (11) (2018) 212, https://doi.org/10.3390/cells7110212.

[7] G. Goss, C.-M. Tsai, F.A. Shepherd, L. Bazhenova, J.S. Lee, G.-C. Chang, L. Crino, M. Satouchi, Q. Chu, T. Hida, J.-Y. Han, O. Juan, F. Dunphy, M. Nishio, J.-H. Kang, M. Majem, H. Mann, M. Cantarini, S. Ghiorghiu, T. Mitsudomi, Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study, Lancet Oncol. 17 (12) (2016) 1643–1652.

[8] T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F. A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, V.A. Papadimitrakopoulou, Osimertinib or platinum-pemetrexed in EGFR T790M–positive lung cancer, N. Engl. J. Med. 376 (7) (2017) 629–640.

[9] J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K. H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, S.S. Ramalingam, Osimertinib in untreated EGFR -mutated advanced non–small-cell lung cancer, N. Engl. J. Med. 378 (2) (2018) 113–125.

[10] S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K. H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, J.-C. Soria, Overall survival with osimertinib in untreated, EGFR -mutated advanced NSCLC, N. Engl. J. Med. 382 (1) (2020) 41–50.

[11] J.-H. Yang, D.R. Camidge, C.-T. Yang, J. Zhou, R. Guo, C.-H. Chiu, G.-C. Chang, H.-S. Shiah, Y. Chen, C.-C. Wang, D. Berz, W.-C. Su, N. Yang, Z. Wang, J. Fang, J. Chen, P. Nikolinakos, Y. Lu, H. Pan, A. Maniam, L. Bazhenova, K. Shirai, M. Jahanzeb, M. Willis, N. Masood, N. Chowhan, T.-C. Hsia, H. Jian, S. Lu, Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: A multicenter, open-label, phase 1 trial, J. Thorac. Oncol. 15 (12) (2020) 1907–1918.

[12] S. Lu, Q. Wang, G. Zhang, X. Dong, C.-T. Yang, Y. Song, G.-C. Chang, Y. Lu, H. Pan, C.-H. Chiu, Z. Wang, J. Feng, J. Zhou, X. Xu, R. Guo, J. Chen, H. Yang, Y. Chen, Z. Yu, H.-S. Shiah, C.-C. Wang, N. Yang, J. Fang, P. Wang, K. Wang, Y. Hu, J. He, Z. Wang, J. Shi, S. Chen, Q. Wu, C. Sun, C. Li, H. Wei, Y. Cheng, W.-C. Su, T.-C. Hsia, J. Cui, Y. Sun, S.-H. Ou, V.W. Zhu, J. Chih-Hsin Yang, Efficacy of aumolertinib (HS-10296) in patients with advanced EGFR T790M+ NSCLC: updated post-national medical products administration approval results from the APOLLO registrational trial, J. Thorac. Oncol. 17 (3) (2022) 411–422.

[13] S. Lu, X. Dong, H. Jian, J. Chen, G. Chen, Y. Sun, Y. Ji, Z. Wang, J. Shi, J. Lu, S. Chen, D. Lv, G. Zhang, C. Liu, J. Li, X. Yu, Z. Lin, Z. Yu, Z. Wang, J. Cui, X. Xu, J. Fang, J. Feng, Z. Xu, R. Ma, J. Hu, N. Yang, X. Zhou, X. Wu, C. Hu, Z. Zhang, Y. Lu, Y. Hu, L. Jiang, Q. Wang, R. Guo, J. Zhou, B. Li, C. Hu, W. Tong, H. Zhang, L. Ma, Y. Chen, Z. Jie, Y.u. Yao, L. Zhang, W. Jie, W. Li, J. Xiong, X. Ye, J. Duan, H. Yang, M. Sun, C. Sun, H. Wei, C. Li, S.M. Ali, V.A. Miller, Q. Wu, AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastaticnon-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations, J. Clin. Oncol. 40 (27) (2022) 3162–3171.

[14] Y. Shi, S. Zhang, X. Hu, J. Feng, Z. Ma, J. Zhou, N. Yang, L. Wu, W. Liao, D. Zhong, X. Han, Z. Wang, X. Zhang, S. Qin, K. Ying, J. Feng, J. Fang, L. Liu, Y. Jiang, Safety, clinical activity, and pharmacokinetics of alflutinib (AST2818) in patients with advanced NSCLC with EGFR T790M mutation, J. Thorac. Oncol. 15 (6) (2020) 1015–1026.

[15] Y. Shi, X. Hu, S. Zhang, D. Lv, L. Wu, Q. Yu, Y. Zhang, L.i. Liu, X. Wang, Y. Cheng, Z. Ma, H. Niu, D. Wang, J. Feng, C. Huang, C. Liu, H. Zhao, J. Li, X. Zhang, Y. Jiang, C. Gu, Efficacy, safety, and genetic analysis of furmonertinib (AST2818) in patients with EGFR T790M mutated non-small-cell lung cancer: a phase 2b, multicentre, single-arm, open-label study, Lancet Respir. Med. 9 (8) (2021) 829–839.

[16] Y. Shi, G. Chen, X. Wang, Y. Liu, L. Wu, Y. Hao, C. Liu, S. Zhu, X. Zhang, Y. Li, J. Liu, L. Cao, Y. Cheng, H. Zhao, S. Zhang, A. Zang, J. Cui, J. Feng, N. Yang, F. Liu, Y. Jiang, C. Gu, Furmonertinib (AST2818) versus gefitinib as first-line therapy for Chinese patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer (FURLONG): a multicentre, double-blind, randomised phase 3 study, Lancet Respir. Med. 10 (11) (2022) 1019–1028.

[17] Y. Shi, Y. Zhao, S. Yang, J. Zhou, L. Zhang, G. Chen, J. Fang, B.o. Zhu, X. Li, Y. Shu, J. Shi, R. Zheng, D. Wang, H. Yu, J. Huang, Z. Zhuang, G. Wu, L. Zhang, Z. Guo, M. Greco, X. Li, Y. Zhang, Safety, efficacy, and pharmacokinetics of rezivertinib (BPI-7711) in patients with advanced NSCLC with EGFR T790M mutation: A phase 1 dose-escalation and dose-expansion study, J. Thorac. Oncol. 17 (5) (2022) 708–717.

[18] Y. Shi, S. Wu, K. Wang, S. Cang, W. Yao, Y. Fan, L. Wu, M. Huang, X. Li, Y. Pan, Z. Yang, B. Zhu, G. Chen, J. Shi, M. Sun, J. Fang, L. Wang, Z. Chen, C. Liu, J. Li, J. Liu, S. Sun, Y. Zhao, Y. Guo, Z. Meng, Z. Liu, Z. Han, H. Lu, R. Ma, S. Hu, G. Zhao, Z. Liu, C. Xie, D. Zhong, H. Zhao, H. Yu, L. Zhang, M. Bi, S. Yi, S. Guo, T. Yi, W. Li, Y. Lin, Y. Shu, Z. Chen, Z. Guo, M. Greco, T. Wang, H. Shen, Efficacy and safety of rezivertinib (BPI-7711) in patients with locally advanced or metastatic/recurrent EGFR T790M-mutated NSCLC: A phase 2b study, J. Thorac. Oncol. 17 (11) (2022) 1306–1317.

[19] Y. Shi, J. Zhou, Y. Zhao, B. Zhu, L. Zhang, X. Li, J. Fang, J. Shi, Z. Zhuang, S. Yang, D. Wang, H. Yu, L. Zhang, R. Zheng, M. Greco, T. Wang, Results of the phase IIa study to evaluate the efficacy and safety of rezivertinib (BPI-7711) for the first-line treatment of locally advanced or metastatic/recurrent NSCLC patients with EGFR mutation from a phase I/IIa study, BMC Med. 21 (1) (2023), https://doi.org/10.1186/s12916-022-02692-8.

[20] Y. Shi, B. Li, L. Wu, Y. Pan, Z. Pan, Y. Liu, Y. Fan, Y. Ji, J. Fang, Q. Shi, J. Shi, H. Gao, Y. Hu, X. Wang, Z. He, R. Ma, Y. Zhang, D. Jiang, Y. Bai, Y.i. Zhang, L. Huang, T. Zhou, H. Liu, D. Wang, Q. Wen, G. Chen, A. Zang, X. Wang, X. Zhang, J. Hu, R. Yang, G. Zhang, K. Gu, L. Wang, Q. Wang, Z. Wei, Z. Li, H. Lu, H. Zhang, H. Chen, T. Song, Efficacy and safety of limertinib (ASK120067) in patients with locally advanced or metastatic EGFR Thr790Met-mutated NSCLC: a multicenter, single-arm, phase 2b study, J. Thorac. Oncol. 17 (10) (2022) 1205–1215.

[21] Jian H, Wang K, Cheng Y, Ding L, Wang Y, Shi Z, et al. Phase I Trial of a Third Generation EGFR Mutant-Selective Inhibitor (D-0316) in Patients with Advanced Non-Small Cell Lung Cancer. *Oncologist*. 2022;27(3):163-e213. doi:10.1093/oncolo/oyab007.

[22] S. Lu, Y. Zhang, G. Zhang, J. Zhou, S. Cang, Y. Cheng, G. Wu, P. Cao, D. Lv, H. Jian, C. Chen, X. Jin, P. Tian, K. Wang, G. Jiang, G. Chen, Q. Chen, H. Zhao, C. Ding, R. Guo, G. Sun, B. Wang, L. Jiang, Z. Liu, J. Fang, J. Yang, W. Zhuang, Y. Liu, J. Zhang, Y. Pan, J. Chen, Q. Yu, M. Zhao, J. Cui, D. Li, T. Yi, Z. Yu, Y. Yang, Y. Zhang, X. Zhi, Y. Huang, R. Wu, L. Chen, A. Zang, L. Cao, Q. Li, X. Li, Y. Song, D. Wang, S. Zhang, L. Ding, L. Zhang, X. Yuan, L. Yao, Z. Shen, Efficacy and safety of befotertinib (D-0316) in patients with EGFR T790M-mutated NSCLC that had progressed after prior EGFR tyrosine kinase inhibitor therapy: A phase 2, multicenter, single-arm, open-label study, *J. Thorac. Oncol.* 17 (10) (2022) 1192–1204.

[23] A. Xiong, S. Ren, H. Liu, L. Miao, L. Wang, J. Chen, W. Li, R. Li, X. Wang, Z. Lu, D. Wang, X. Wu, Z. Liu, L. Xing, Y. Mao, C. Liu, A. Zeng, H. Niu, Y. Du, Y. Sun, Y. Pan, Y. Hu, X. Zhang, X. Chen, Z. Ma, N. Li, J. Zhang, M. Zhao, X. Li, F. Ye, M. Li, G. Yu, X. Zhang, J. Min, D. Han, J. Li, C. Zhou, Efficacy and safety of SH-1028 in patients with EGFR T790M-positive NSCLC: A multicenter, single-arm, open-label, phase 2 trial, J. Thorac. Oncol. 17 (10) (2022) 1216–1226.

[24] L. Huang, S. Jiang, Y. Shi, Tyrosine kinase inhibitors for solid tumors in the past 20 years (2001–2020), J. Hematol. Oncol. 13 (1) (2020) 143, https://doi.org/10.1186/s13045-020-00977-0.

[25] Zhong Q, Tao Y, Chen H, Zhou Y, Huang L, Han X, et al. The changing landscape of anti-lung cancer drug clinical trials in mainland China from 2005 to 2020. *Lancet Reg Health West Pac*. 2021;11:100151.

[26] Y. Shi, Landscape of the clinical development of China innovative anti-lung cancer drugs, Cancer Pathogen. Ther. 1 (1) (2023) 67–75.

[27] J. Lee, M.J. Ahn, Brain metastases in patients with oncogenic-driven non-small cell lung cancer: Pros and cons for early radiotherapy, Cancer Treat. Rev. (2021) 100, https://doi.org/10.1016/J.CTRV.2021.102291.

[28] Ballard P, Yates JWT, Yang Z, Kim DW, Yang JCH, Cantarini M, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. *Clin Cancer Res*. 2016;22(20):5130–40. doi:10.1158/1078-0432.CCR-16-0399.

[29] T. Reungwetwattana, K. Nakagawa, B.C. Cho, M. Cobo, E.K. Cho, A. Bertolini, S. Bohnet, C. Zhou, K.H. Lee, N. Nogami, I. Okamoto, N. Leighl, R. Hodge, A. McKeown, A.P. Brown, Y. Rukazenkov, S.S. Ramalingam, J. Vansteenkiste, CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer, J. Clin. Oncol. 36 (33) (2018) 3290–3297.

[30] Y.-L. Wu, M.-J. Ahn, M.C. Garassino, J.-Y. Han, N. Katakami, H.R. Kim, R. Hodge, P. Kaur, A.P. Brown, D. Ghiorghiu, V.A. Papadimitrakopoulou, T.S.K. Mok, CNS efficacy of osimertinib in patients with T790M-positive advanced non–small-cell lung cancer: Data from a randomized Phase III trial (Aura3), J. Clin. Oncol. 36 (26) (2018) 2702–2709.

[31] G. Goss, C.-M. Tsai, F.A. Shepherd, M.-J. Ahn, L. Bazhenova, L. Crinò, F. de Marinis, E. Felip, A. Morabito, R. Hodge, M. Cantarini, M. Johnson, T. Mitsudomi, P.A. Jänne, J.-C.-H. Yang, CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials, Ann. Oncol. 29 (3) (2018) 687–693.

[32] S. Lu, X. Dong, H. Jian, J. Chen, G. Chen, Y. Sun, Y. Ji, Z. Wang, J. Shi, J. Lu, S. Chen, D. Lv, G. Zhang, C. Liu, J. Li, X. Yu, Z. Lin, Z. Yu, Z. Wang, J. Cui, X. Xu, J. Fang, J. Feng, Z. Xu, R. Ma, J. Hu, N. Yang, X. Zhou, X. Wu, C. Hu, Z. Zhang, Y. Lu, Y. Hu, L. Jiang, Q. Wang, R. Guo, J. Zhou, B. Li, C. Hu, W. Tong, H. Zhang, L. Ma, Y. Chen, Z. Jie, Y. Yao, L. Zhang, W. Jie, W. Li, J. Xiong, X. Ye, J. Duan, H. Yang, M. Sun, C. Sun, H. Wei, C. Li, S.M. Ali, V.A. Miller, Q. Wu, AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastaticnon–small-cell lung cancer with *EGFR* exon 19 deletion or L858R mutations, J. Clin. Oncol. 40 (27) (2022) 3162–3171.

[33] Y. Shi, G. Chen, X. Wang, Y. Liu, L. Wu, Y. Hao, C. Liu, S. Zhu, X. Zhang, Y. Li, J. Liu, L. Cao, Y. Cheng, H. Zhao, S. Zhang, A. Zang, J. Cui, J. Feng, N. Yang, F. Liu, Y. Jiang, C. Gu, Central nervous system efficacy of furmonertinib (AST2818) versus gefitinib as first-line treatment for EGFR-mutated NSCLC: results from the FURLONG study, J. Thorac. Oncol. 17 (11) (2022) 1297–1305.

[34] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2) (2009) 228–247.

[35] Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270–8. doi:10.1016/S1470-2045(15)70057-4.

[36] M.-J. Ahn, C.-M. Tsai, F.A. Shepherd, L. Bazhenova, L.V. Sequist, T. Hida, J.C. H. Yang, S.S. Ramalingam, T. Mitsudomi, P.A. Jänne, H. Mann, M. Cantarini, G. Goss, Osimertinib in patients with T790M mutation-positive, advanced non–small cell lung cancer: Long-term follow-up from a pooled analysis of 2 phase 2 studies, Cancer 125 (6) (2019) 892–901.