Rezivertinib versus gefitinib as first-line therapy for patients with *EGFR*-mutated locally advanced or metastatic non-small-cell lung cancer (REZOR): a multicentre, double-blind, randomised, phase 3 study

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Summary

Background This study aimed to compare the efficacy and safety of rezivertinib (BPI-7711) and gefitinib as first-line therapies in patients with *EGFR*-mutated locally advanced or metastatic non-small-cell lung cancer (NSCLC).

Methods This multicentre, double-blind, randomised, phase 3 study (REZOR) included eligible patients from 50 hospitals across China. Those who had been histologically or cytologically confirmed as having NSCLC with *EGFR* exon 19 deletion or exon 21 Leu858Arg mutation by central laboratory were randomly assigned (1:1) to receive once daily either rezivertinib 180 mg or gefitinib 250 mg, until unacceptable toxicity occurred, disease progression, or other treatment discontinuation criteria were met. Each cycle lasted for 21 days. The primary endpoint was progression-free survival evaluated by masked independent central review (MICR) in the intention-to-treat set. This trial is registered with ClinicalTrials.gov, NCT03866499 and follow-up is ongoing.

Findings Between July 15, 2019, and Feb 14, 2022, 695 patients were screened. Among them, 369 eligible patients were randomly assigned to receive either rezivertinib 180 mg/day plus placebo (n=184) or gefitinib 250 mg/day plus placebo (n=185) in a 1:1 ratio; all of eligible participants were included in the intention-to-treat set. Median MICR-assessed progression-free survival was 19·3 months (95% CI 13·8–22·1) in the rezivertinib group and 9·6 months (8·4–11·3) in the gefitinib group (hazard ratio [HR] 0·48, 95% CI 0·36–0·63; p<0·0001) and the prespecified subgroup efficacy analysis showed consistent results. Median duration of exposure was 16·0 months (95% CI 0·0–29·7) in the rezivertinib group and 11·0 months (0·0–28·9) in the gefitinib group. Grade 3 or higher treatment-emergent adverse events (82 [45%] of 184 in the rezivertinib group; 80 [43%] of 185 in the gefitinib group) and treatment-related adverse events (TRAEs; 43 [23%] of 184 in the rezivertinib group; 43 [23%] of 185 in the gefitinib group) were similar in both groups. One patient died from a TRAE in the rezivertinib group, due to pneumonia and interstitial lung disease.

Interpretation Our findings suggested that rezivertinib is a potential choice for patients with *EGFR*-mutated locally advanced or metastatic NSCLC as first-line therapy, owing to the superior overall efficacy and subgroup progression-free survival compared with gefitinib in targeted patients. No new safety signals were identified.

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Introduction

According to the 2022 global cancer statistics, lung cancer had the highest incidence and mortality (12% of total diagnosed cases and 19% of total cancer deaths worldwide, respectively, of 36 cancers in 185 countries). In 2022, adenocarcinoma was the most common subtype of lung cancer worldwide, and eastern Asia had the highest incidence of adenocarcinoma in both sexes.[1] Among patients with lung cancer, up to 80–85% had non-small-cell lung cancer (NSCLC), and more than 40% of patients with lung adenocarcinoma had epidermal growth factor receptor (*EGFR*) mutations in east Asia.[2–6] In 2022, the cancer statistics for China reflected consistency with the global and eastern Asia data, with 1 060 600 new cases and 733 300 deaths,[7] which indicates that enormous medical demands and high

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Research in context

Evidence before this study

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the standard of first-line therapy for *EGFR* mutated non-small-cell lung cancer (NSCLC). These included first-generation or second-generation EGFR TKIs and the third-generation EGFR TKIs including osimertinib, aumolertinib, furmonertinib, and befotertinib. We searched PubMed for related clinical studies limited to phase 3 trials, using the keywords "EGFR", "TKI", "NSCLC", and "first-line", published up to Aug 9, 2024, in English. The results revealed that third-generation EGFR TKIs showed superior efficacy compared with first-generation EGFR TKIs. Osimertinib was the first approved third-generation EGFR TKI that showed superior efficacy compared with gefitinib or erlotinib in the first-line setting. The other three third-generation EGFR TKIs available on mainland China have also showed clinical benefits over gefitinib (AENEAS, FURLONG, and the befotertinib phase 3 studies). The purpose of this study (REZOR) was to evaluate the efficacy and safety of rezivertinib among patients who are treatment-naive with *EGFR* mutated locally advanced or metastatic NSCLC.

Added value of this study

The REZOR study showed that rezivertinib could be a new option for patients with *EGFR*-mutated locally advanced or metastatic NSCLC and was superior to gefitinib in terms of progression-free survival as first-line treatment. The prespecified subgroup efficacy analysis showed consistent findings, and patient safety was manageable.

Implications of all the available evidence

Patients with *EGFR*-mutated locally advanced or metastatic NSCLC can achieve significant efficacy and safety benefits with rezivertinib compared with gefitinib as first-line therapy, regardless of the *EGFR* mutation type (*EGFR* exon 19 deletion or Leu858Arg mutation) or the presence of baseline CNS metastases. No new safety signals were identified. Our findings suggest that rezivertinib is a potential new treatment option for patients with NSCLC who are treatment-naive with an *EGFR* mutation.

safety requirements are still needed. Over the past 20 years, small-molecule tyrosine kinase inhibitors (TKIs) have changed the treatment modalities for advanced solid tumours.[8,9] For first-line therapy of NSCLC with EGFR exon 19 deletion or exon 21 Leu858Arg mutation, monotherapy of first-generation or second-generation EGFR TKIs such as gefitinib, erlotinib, icotinib, afatinib, and dacomitinib,[10–14] and the third-generation EGFR TKIs such as osimertinib, aumolertinib, furmonertinib, and befotertinib have been approved in China.[15–17] However, osimertinib is the only FDA-approved third-generation EGFR-TKI used as monotherapy and recommended by both American and European guidelines. Meanwhile, combination therapy has also been recommended in the latest National Comprehensive Cancer Network guidelines, such as osimertinib plus pemetrexed plus cisplatin or carboplatin, erlotinib plus ramucirumab or bevacizumab, and amivantamab plus lazertinib.[18] From the perspective of comprehensive patient benefits in clinical consideration, monotherapy might offer greater advantages over combination therapy, primarily owing to factors such as reduced side-effects, improved patient tolerability, lower costs, and clearer therapeutic outcomes. Clinical trials revealed that the monotherapy of third-generation EGFR TKIs can significantly improve clinical efficacy when compared with first-generation EGFR TKIs in first-line therapy.[19–25]

Rezivertinib (BPI-7711) is a novel, irreversible, third-generation EGFR TKI jointly developed by Beta Pharma (Shanghai), Shanghai, China, and Beta Pharma, Princeton, NJ, USA. Phase 1 and phase 2b studies had shown promising efficacy and a preferable safety profile for patients with NSCLC, with CNS metastasis and *EGFR* Thr790Met mutation after treatment with first-generation or second-generation EGFR TKIs.[26–28] Based on these results, rezivertinib was approved for the treatment of adult patients with locally advanced or metastatic NSCLC who had disease progression during or after previous treatment with EGFR TKIs and were confirmed to have positive *EGFR* Thr790Met mutation by the China National Medical Products Administration on May 15, 2024. The phase 2a study further showed promising efficacy and safety for the first-line treatment of patients with NSCLC with *EGFR* exon 19 deletion or exon 21 Leu858Arg mutation.[29] In this Article, we will elucidate and discuss the details of the REZOR study, in which rezivertinib versus gefitinib were used as first-line therapies for patients with *EGFR*-mutated locally advanced or metastatic NSCLC.

Methods

Study design and participants

This was a multicentre, randomised, phase 3 study, done across 50 hospitals in China. Eligible patients were at least 18 years old, with histologically or cytologically confirmed NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Patients without previous systemic therapy for locally advanced or metastatic NSCLC, and who were unsuitable for radical surgery or radiotherapy, were included. They needed to have at least one measurable lesion per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and central laboratory confirmation of one of the two common *EGFR* mutations (exon 19 deletion or Leu858Arg), excluding exon 20 insertions. *EGFR* mutation testing (Cobas EGFR Mutation Test, Version 2

of Roche Diagnostics, South Branchburg, NJ, USA) was done on tissue or plasma samples. Key exclusion criteria included previous systemic treatment for locally advanced or metastatic NSCLC, a positive primary Thr790Met mutation, or treatment within 14 days before the first dose with study drugs, strong CYP3A4 inhibitors or inducers, herbal anti-tumour medications, or labetalol. Cardiac exclusions included QTcF greater than 470 msec, substantial arrhythmias, or conduction abnormalities. A history of interstitial lung disease, radiation pneumonitis requiring steroids, active infections such as hepatitis B, hepatitis C, or HIV were also excluded, although well-controlled hepatitis B was considered. Patients with major surgery no more than 4 weeks or minor surgery no more than 2 weeks before the first dose of study drug were excluded as well.

The study was done in accordance with the Declaration of Helsinki, the International Council on Harmonisation Good Clinical Practice Guidelines, and the applicable regulatory requirements. The protocol was approved by the institutional review board or independent ethics committee in each participating hospital (appendix). An informed consent form was obtained from every patient before enrolment. This trial is registered with ClinicalTrials.gov, NCT03866499.

Randomisation and masking

Successfully screened patients were randomly assigned through the interactive web response system (IWRS, provided by Medidata, New York, NY, USA) on the basis of *EGFR* exon 19 deletion or Leu858Arg mutation status and the presence of brain metastases, in a 1:1 ratio to receive gefitinib tablets or rezivertinib capsules. Each patient was assigned a unique randomisation code via IWRS. Owing to the different appearances of rezivertinib and gefitinib, a double-dummy method was used to mask and code the study drug. This double-masked trial ensured that both patients and investigators were masked to treatment group assignments. A masking maintenance plan was implemented to maintain masking from randomisation, drug coding, and dosing to data monitoring, management, and statistical analysis, until the protocol's predefined unmasking conditions were met.

Procedures

Eligible patients were stratified by *EGFR* exon 19 deletion or Leu858Arg mutation and presence of brain metastases at baseline, then randomly assigned (1:1) to each treatment group with either oral rezivertinib 180 mg/day plus placebo, or oral gefitinib 250 mg/day plus placebo, until unacceptable toxicity occurred, disease progression, or other treatment discontinuation criteria were met. Each cycle lasted for 21 days. Treatment beyond progression was permitted if the investigators judged that clinical benefits could be obtained and the patient was willing. Eligible patients from the gefitinib group with investigator-confirmed disease progression with secondary Thr790Met mutation detected could enter the cross-over treatment phase, to receive open-label rezivertinib treatment until unacceptable toxicity occurred, re-evaluation showed disease progression, or other treatment discontinuation criteria were met.

Tumour assessments would be done with CT or magnetic resonance imaging scans every 6 weeks within the first 18 months after randomisation, then every 12 weeks until radiological disease progression, even if patients discontinued treatment before disease progression, unless patients withdrew consent or started new anti-tumour therapies. Survival status was followed up every 90 days (range 83–97) after 30 days post the last dose of study drug until death, or loss to follow-up. Physical examinations, haematology, blood biochemistry, urinalysis, 12-lead electrocardiogram, and ECOG performance status were done during screening, on the first day of cycle 1 and cycle 2, the fifteenth day of cycle 1, the first day of every other cycle starting from cycle 3, and at the end of treatment. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and Lung Cancer Questionnaire (QLQ-LC13) were used to assess patients' quality of life.

Safety was assessed by investigators from the time of signing the informed consent form until 30 days after the last dose of the study drug, regardless of whether it was related to the study drug.

Outcomes

The primary endpoint was progression-free survival evaluated by masked independent central review (MICR) per RECIST version 1.1,[30] which was defined as the time from randomisation to disease progression or death. The secondary endpoints included progression-free survival evaluated by the investigators, best overall response, objective response rate, disease control rate, duration of response, and time to response evaluated by both the MICR and investigators, overall survival, and quality of life by use of EORTC QLQ-C30 and QLQ-LC13. For patients in the gefitinib group who progressed and received cross-over treatment with rezivertinib, progression-free survival 2 (the time from randomisation to the second occurrence of disease progression or death from any cause after initiating cross-over treatment with rezivertinib, whichever occurred first), objective response rate 2, disease control rate 2, and duration of response 2 were evaluated by both MICR and the investigators, and quality of life was assessed by patients as well.

Best overall response was defined as the best response recorded during the study. Objective response rate was defined as the proportion of patients with complete response or partial response. Disease control rate was defined as the proportion of patients with complete response, partial response, or stable disease (lasting ≥39 days after the start of study treatment). Duration of response was defined as the time from achieving

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complete response or partial response to disease progression or death. Time to response was defined as the time from randomisation to the first occurrence of complete response or partial response. Overall survival was defined as the time from randomisation to death. The efficacy for patients with CNS metastases was measured by MICR according to the Response Assessment in Neuro-Oncology Brain Metastases.[31] For patients with baseline brain metastases assessed by the investigators, CNS objective response rate, CNS disease control rate, CNS duration of response, CNS time to progression, and CNS progression-free survival for brain metastases evaluated by MICR was done independently. CNS objective response rate was defined as the proportion of patients with brain metastases at baseline who achieved a complete response or partial response. CNS disease control rate was defined as the proportion of patients with brain metastases at baseline who achieved complete response, partial response, or stable disease. For patients reporting CNS response (complete response or partial response), CNS duration of response was defined as the time from the first CNS complete response or partial response to the first reported CNS disease progression or death due to any cause, whichever occurred first. CNS time to progression was defined as the time from randomisation to CNS disease progression, whereas CNS progression-free survival was defined as the time from randomisation to CNS disease progression or death. Meanwhile, the prespecified subgroup progression-free survival and hazard ratio (HR) for patients found to have *EGFR* mutations in tissue and plasma samples were evaluated as well. The clinically significant minimal change in patient quality of life was defined as an increase of at least 10 in the QLQ-C30 score and an increase of at least 5 in the QLQ-LC13 score compared with baseline. Safety was assessed by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

To establish the sample size, on the basis of historical data, the median progression-free survival of first-line treatment of patients with EGFR mutation-positive NSCLC was estimated to be around 15·0 months in the rezivertinib group and 10·5 months in the gefitinib group. Assuming a randomisation ratio of 1:1, considering a 10% dropout rate for progression-free survival, type I error α=0·05, 367 patients (approximately 275 events) were needed to achieve an 84% power to detect HR=0·7. A preplanned interim analysis was done when approximately 193 (70%) progression-free survival events evaluated by the MICR had been collected. The corresponding two-sided α value was 0·0148 on the basis of the Lan–DeMets approximation to the O'Brien–Fleming boundary. On Mar 24, 2023, 189 (69%) MICR-assessed progression-free survival events were collected and the corresponding two-sided α value was 0·0136. On Jun 16, 2023, the independent data monitoring committee established that the primary endpoint (progression-free survival evaluated by MICR) had met the presupposed α level. All data reported here were based on the updated analysis (data cutoff date Nov 30, 2023). This updated analysis was descriptive in nature and not subject to multiplicity control. Two-sided p values are shown.

Statistical analysis in this study was done in the intention-to-treat set and safety set. The intention-to-treat set involved all randomly assigned patients. The efficacy analysis was based on the intention-to-treat set. Patients who have received at least one non-zero dose of the study drugs would be included in the safety set. Safety analysis was based on the safety according to the actual treatment group. Summary of time-to-event variables would be based on the Kaplan–Meier method. The primary efficacy analysis for progression-free survival was based on the stratified log-rank test with stratification factors used for randomisation (baseline exon 19 deletion versus Leu858Arg mutation and presence of brain metastases). The HR and its corresponding 95% CI were calculated on the basis of the stratified Cox proportional hazards model. For the primary efficacy endpoint, additional subgroup analysis included age (<65 years, ≥65 years), sex (male, female), baseline ECOG performance status score (0, 1), and type of *EGFR* testing sample (tissue, plasma). Subgroup analysis focused on HR. For each subgroup, the HR (rezivertinib compared with gefitinib) and corresponding 95% CIs were estimated by use of a stratified Cox proportional hazards model.

The clinically significant minimal change in patient quality of life was done for the intention-to-treat set and cross-over rezivertinib treatment group. Statistical analyses were done with SAS version 9.4.

Role of the funding source

The funder of the study had a role in data collection, data analysis, data interpretation, and writing of the report.

Results

From July 15, 2019, to Feb 14, 2022, 695 patients were screened across 50 hospitals in China. Among them, 369 eligible patients were randomly assigned to receive either rezivertinib 180 mg/day plus placebo (n=184) or gefitinib 250 mg/day plus placebo (n=185) in a 1:1 ratio and all participants were included in the intention-to-treat set. Patient baseline characteristics are shown in table 1. At the data cutoff date on Nov 30, 2023, 53 (29%) patients in the rezivertinib group and 22 (12%) patients in the gefitinib group remained on the main study treatment, while ten (5%) patients from the gefitinib group were still on cross-over treatment (figure 1).

The study met its primary endpoint of MICR-assessed progression-free survival according to RECIST version 1.1.[30]

The median follow-up duration was 24·9 months (95% CI 24·4–25·8) for the rezivertinib group and 24·4 months (95% CI 23·1–25·1) for the gefitinib group. 94 MICR-assessed progression-free survival events occurred in the rezivertinib group and 127 in the gefitinib group. The MICR-assessed median progression-free survival was 19·3 months (95% CI 13·8–22·1) months in the rezivertinib group and 9·6 months (8·4–11·3) in the gefitinib group (HR 0·48, 95% CI 0·36–0·63; p<0·0001; figure 2). No patient had a critical protocol violation which had a substantial effect on the primary endpoint.

A consistent efficacy for MICR-assessed progression-free survival was observed across prespecified subgroups (appendix pp 1–2). For patients with *EGFR* exon 19 deletion, 43 MICR-assessed events occurred in the rezivertinib group and 65 MICR-assessed events occurred in the gefitinib group (appendix p 1), whereas the MICR-assessed median progression-free survival was 22·1 months (95% CI 13·8–not calculated [NC]) and 9·7 months (8·4–13·8; HR 0·38; 95% CI 0·26–0·57; p<0·0001; appendix p 2). For those with a Leu858Arg mutation, 51 and 62 BICR-assessed events occurred (appendix p 1), and the MICR-assessed median progression-free survival was 13·9 months (95% CI 9·7–17·9) and 9·6 months (6·9–12·4); (HR 0·59; 0·40–0·85; p=0·0053; appendix p 2). For patients without CNS metastases at baseline, 53 MICR-assessed events occurred in the rezivertinib group and 79 in the gefitinib group (appendix p 1), and the MICR-assessed median progression-free survival was 22·0 months (95% CI 13·8–25·2) and 9·6 months (7·0–12·4; HR 0·46; 0·32–0·65; p<0·0001; appendix p 2). For those with CNS metastases at baseline, 41 MICR-assessed events occurred in the rezivertinib group and 48 in the gefitinib group (appendix p 1), and the MICR-assessed median progression-free survival was 16·0 months (95% CI 12·5–22·2) and 9·7 months (8·5–13·8; HR 0·52; 0·34–0·80; p=0·003; appendix p 2). Among 130 (71%) patients with *EGFR* mutations detected with tissue samples in the rezivertinib group, 64 (49%) MICR-assessed events occurred. Among 140 (76%) patients with *EGFR* mutations detected with tissue samples in the gefitinib group, 96 (69%) MICR-assessed events occurred (appendix p 1), and the MICR-assessed median progression-free survival was 20·7 months (95% CI 13·9–24·9) in the rezivertinib group and 9·7 months (8·3–12·4) in the gefitinib group (HR 0·47; 0·34–0·66; p<0·0001; appendix p 2). Among 76 (41%) patients with *EGFR* mutations detected with plasma samples in the rezivertinib group, 38 (50%) MICR-assessed events occurred. Among 62 (34%) patients with *EGFR* mutations detected with plasma samples in the gefitinib group, 43 (69%) MICR-assessed events occurred (appendix p 1), and the MICR-assessed median progression-free survival was 16·0 months (95% CI 9·7–24·9) and 9·6 months (6·9-11·0; HR 0·48; 0·30-0·75; p=0·0014; appendix p 2).

	Rezivertinib (n=184)	Gefitinib (n=185)
Age, years		
Median (IQR)	61 (53–68)	62 (54–68)
<50	26 (14%)	22 (12%)
50–64	87 (47%)	82 (44%)
≥65	71 (39%)	81 (44%)
Sex		
Male	72 (39%)	80 (43%)
Female	112 (61%)	105 (57%)
Race		
Asian	184 (100%)	185 (100%)
ECOG performance status		
0	41 (22%)	32 (17%)
1	143 (78%)	153 (83%)
Histology type		
Adenocarcinoma not otherwise specified	179 (97%)	177 (96%)
Acinar adenocarcinoma	2 (1%)	2 (1%)
Solid adenocarcinoma	1 (1%)	1 (1%)
Invasive mucinous adenocarcinoma	1 (1%)	4 (2%)
Minimally invasive adenocarcinoma	1 (1%)	0
Adenosquamous carcinoma	0	1 (1%)
EGFR-sensitive mutation type		
Exon 19 deletion	93 (51%)	97 (52%)
Leu858Arg	91 (50%)	88 (48%)
CNS metastases		
Yes	75 (41%)	72 (39%)
No	109 (59%)	113 (61%)
Disease status		
Locally advanced	1 (1%)	1 (1%)
Metastatic	183 (99%)	184 (99%)
Metastatic site		
Lung	183 (99%)	183 (99%)
Lymph node	146 (79%)	144 (78%)
Bone	108 (59%)	105 (57%)
Brain	75 (41%)	72 (39%)
Pleural effusion	74 (40%)	72 (39%)
Pleura	61 (33%)	54 (29%)
Liver	29 (16%)	35 (19%)
Adrenal gland	23 (13%)	24 (13%)
Mediastinum	1 (1%)	6 (3%)
Retroperitoneum	0	4 (2%)
Others	23 (13%)	37 (20%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *EGFR*=epidermal growth factor receptor.

Table 1: **Baseline characteristics of patients in the intention-to-treat set**

120 investigator-assessed progression-free survival events occurred in the rezivertinib group and 151 in the gefitinib group. The investigator-assessed median progression-free survival was 16·6 months (95% CI 13·6–19·3) in the rezivertinib group and 10·5 months (8·4–12·4) in the gefitinib group (HR 0·56; 95% CI 0·44–0·72; p<0·0001; appendix p 3), showing

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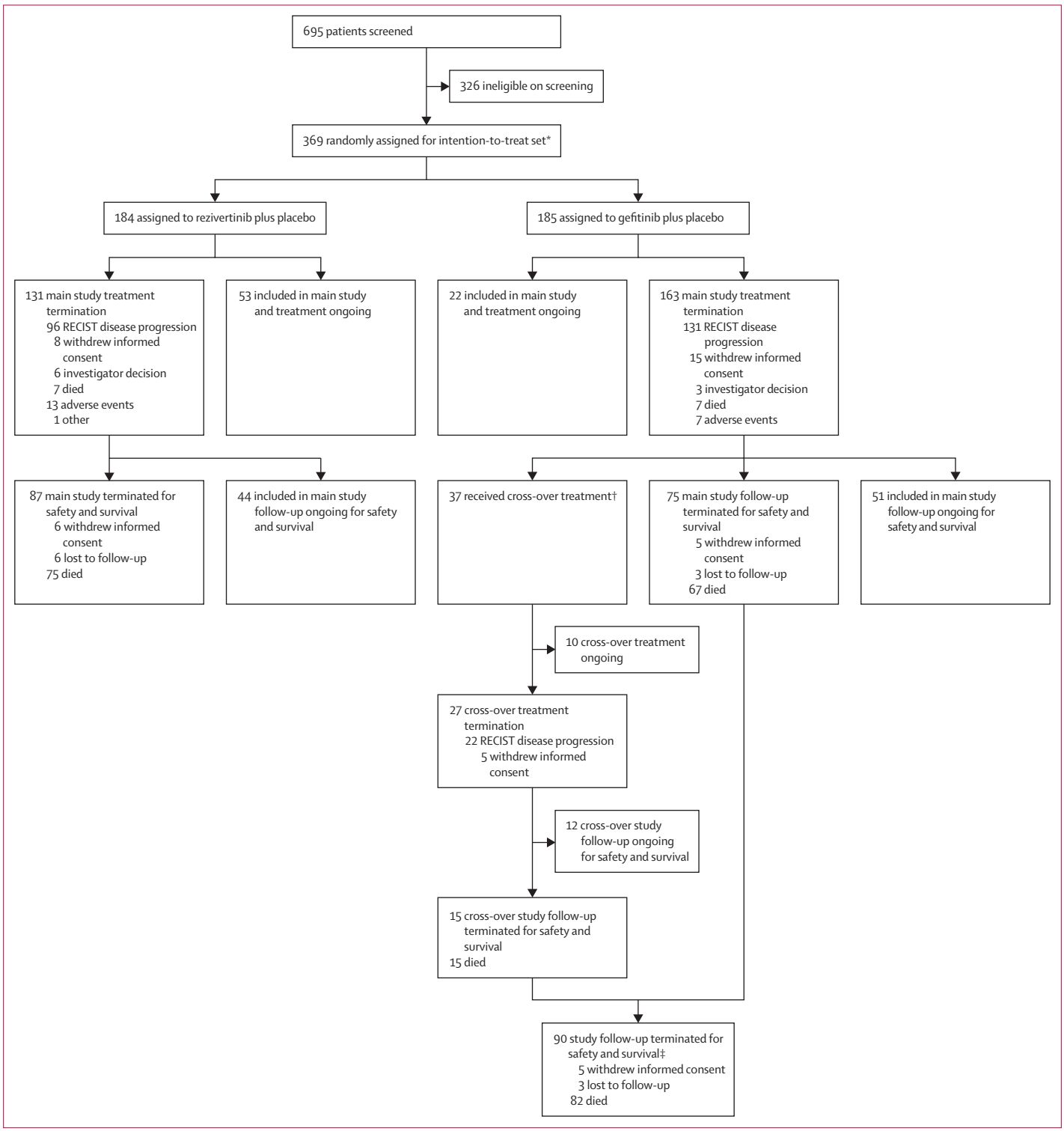

Figure 1: **Trial profile**

*The intention-to-treat set included all randomly assigned patients, and the safety set included all patients who received at least one dose of study treatment. In this study, all randomly assigned patients received at least one dose of study treatment, so the patients in the intention-to-treat set and safety set were the same. †In the gefitinib group, 131 patients discontinued treatment owing to radiological disease progression according to RECIST version 1.1 assessed by MICR from the main study treatment period. Among them, 95 patients participated in the cross-over group screening, of whom 37 patients entered the cross-over treatment group. ‡At the data cutoff date, 90 patients in total had met the criteria of study follow-up terminated for safety and survival in the gefitinib group, including 75 patients who discontinued the main study treatment and did not enter rezivertinib cross-over treatment then met the criteria of study follow-up terminated for safety and survival and 15 patients who discontinued cross-over treatment then met the criteria of study follow-up terminated for safety and survival. MICR=masked independent central review. RECIST=Response Evaluation Criteria in Solid Tumours.

consistency with the MICR-assessed progression-free survival for the intention-to-treat set. The results of other secondary endpoints including MICR-assessed objective response rate, disease control rate, time to response, and duration of response are shown in the appendix (p 7). The details for post-trial treatment of patients for whom the study was terminated due to death are given in the appendix (p 9). Overall survival remained immature with 157 (43%) of 369 patient deaths, among whom 75 (41%) were from the rezivertinib group and 82 (44%) were from the gefitinib group (HR 0·85; 0·62–1·16; p=0·29; figure 3). The final overall survival analysis will be done when approximately 221 overall survival events have occurred and the results will be reported in future publications. The intention-to-treat set tumour shrinkage is shown in the appendix (p 4). For 75 (41%) patients with CNS metastases at baseline in the rezivertinib group and 72 (39%) patients in the gefitinib group, the CNS progression-free survival was 22·5 months (95% CI 16·6–NC) and 15·2 months (11·0–NC), respectively (HR 0·61; 0·36–1·05; p=0·074). 95 (51%) of 185 patients in the gefitinib group received *EGFR* Thr790Met detection after disease progression, and 37 (39%) of 95 patients with secondary *EGFR* Thr790Met mutation entered the cross-over rezivertinib treatment phase, 19 events occurred in 37 patients and the MICR-assessed median progression-free survival 2 was 19·8 months (95% CI 16·9–23·6; appendix pp 5–6). The MICR-assessed objective response and duration of response 2 for cross-over rezivertinib treatment are shown in the appendix (p 11). The descriptive summaries of EORTC QLQ-C30 and EORTC QLQ-LC13 were done for the intention-to-treat set and cross-over rezivertinib treatment phase (appendix pp 12–15). The advantage of improvements of patients' health-related quality of life, role functioning, emotional functioning, cognitive functioning, social functioning, and symptoms such as fatigue, constipation, and diarrhoea are presented for the rezivertinib group versus the gefitinib group.

All 369 patients who were randomly assigned and received treatment were included in the safety set (table 2). The median duration of exposure was 16·0 months (range 0·0–29·7) for the rezivertinib group and 11·0 months (range 0·0–28·9) for the gefitinib group. Treatment-emergent adverse events (TEAEs) were reported in 182 (99%) patients in the rezivertinib group and 181 (98%) patients in the gefitinib group. The five most common treatment-related adverse events (TRAEs) were decreased white blood cell (WBC) count (40%), decreased platelets (33%), increased alanine aminotransferase (ALT; 28%), anaemia (26%), increased aspartate aminotransferase (AST; 26%), and decreased absolute neutrophil count (ANC; 26%) in the rezivertinib group, while those in the gefitinib group were increased ALT (38%), increased AST (36%), diarrhoea (27%),

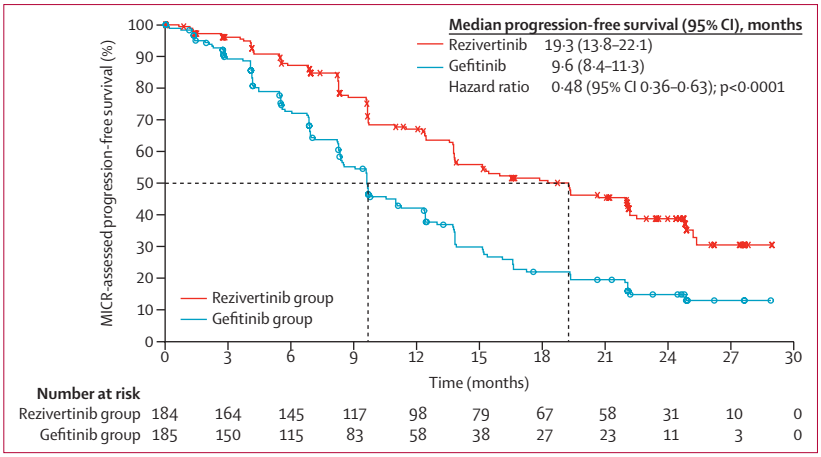

Figure 2: **Kaplan–Meier curves of MICR-assessed progression-free survival in the intention-to-treat set**
MICR=masked independent central review.

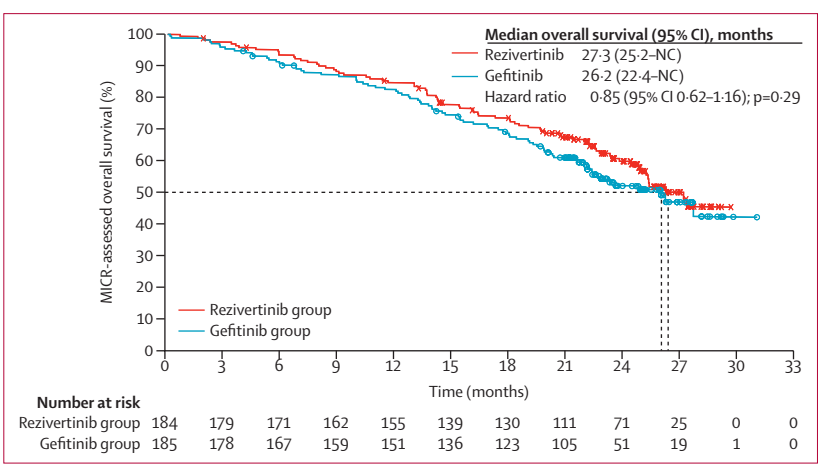

Figure 3: **Kaplan–Meier curves of overall survival in the intention-to-treat set**
Overall survival was still immature by the data cutoff date. NC=not calculated

rash (26%), and increased blood bilirubin (18%). Grade 3 or higher TEAEs (45% in the rezivertinib group; 43% in the gefitinib group) and TRAEs (23% in the rezivertinib group; 23% in the gefitinib group) were similar in both groups, and the number of patients who had TEAEs (28% in the rezivertinib group; 26% in the gefitinib group) and TRAEs (20% in the rezivertinib group; 22% in the gefitinib group) leading to dose adjustment was similar as well. One patient died from a TRAE in the rezivertinib group, due to pneumonia and interstitial lung disease. Patients had less serious TRAEs in the rezivertinib group (n=13, 7%) compared with the gefitinib group (n=21, 11%). The three most common TRAEs were absolute neutrophil count decreased (3%), white blood cell count decreased (2%) and platelets decreased (2%) for dose interruption of rezivertinib, whereas ALT increased (2%), AST increased (2%), GGT increased (1%), nausea (1%), mouth ulceration (1%), vomiting (1%), and alkaline phosphatase increased (1%) in the gefitinib group. For dose reductions, the top three common TRAEs were

	Rezivertinib (n=184)		Gefitinib (n=185)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
TEAE	182 (99%)	82 (45%)	181 (98%)	80 (43%)
Leading to death	9 (5%)	..	7 (4%)	..
Leading to treatment termination	14 (8%)	..	7 (4%)	..
Leading to dose adjustment	51 (28%)	..	49 (26%)	..
Leading to dose interruption	38 (21%)	..	27 (15%)	..
Leading to dose reduction	29 (16%)	..	30 (16%)	..
TRAE	176 (96%)	43 (23%)	168 (91%)	43 (23%)
Leading to death	1 (1%)	..	0	..
Leading to treatment termination	9 (5%)	..	7 (4%)	..
Leading to dose adjustment	36 (20%)	..	41 (22%)	..
Leading to dose interruption	19 (10%)	..	17 (9%)	..
Leading to dose reduction	29 (16%)	..	30 (16%)	..
Serious TEAE	45 (24%)	..	54 (29%)	..
Serious TRAE	13 (7%)	..	21 (11%)	..
Serious TEAE leading to discontinuation of study drug	9 (5%)	..	3 (2%)	..

(Table 2 continues on next page)

absolute neutrophil count decreased (3%), platelets decreased (2%), white blood cell count decreased (2%), ALT increased (2%) and eruption (2%) in the rezivertinib group, whereas they were ALT increased (6%), AST increased (4%) and hepatic function abnormal (2%) in the gefitinib group.

A summary of adverse events for the rezivertinib crossover treatment is shown in the appendix (p 16).

Discussion

The REZOR study met its primary endpoint, with an estimated prolongation of MICR-assessed median progression-free survival of 9·7 months (HR 0·48). showing similar prolongation of median progression-free survival and HR over gefitinib–erlotinib– icotinib among all China NMPA approved third-generation EGFR TKIs (the FLAURA study with prolonged median progression-free survival of 8·7 months [osimertinib 18·9 months *vs* gefitinib–erlotinib 10·2 months; HR 0·46, 0·37–0·57; p<0·001];[19,20,32] the AENEAS study of 9·4 months [almonertinib 19·3 months versus gefitinib 9·9 months; HR=0·46, 95% CI 0·36–0·60; p<0·0001];[21] the FURLONG study of 9·7 months [furmonertinib 20·8 months *vs* gefitinib 11·1 months; HR 0·44, 0·34–0·58; p<0·0001][22] and befotertinib first-line phase 3 study of 8·3 months [befotertinib 22·1 months versus icotinib 13·8 months; HR 0·49, 0·36–0·68; p<0·0001].[25] Apart from being ethnically homogeneous (all patients were Asian), the REZOR study included a higher proportion of patients with poor prognosis compared with other similar studies. Specifically, the study included a lower proportion of patients with *EGFR* exon 19 deletion and a higher proportion of patients with baseline CNS metastases. Despite this, rezivertinib showed similar efficacy, doubling the progression-free survival period compared with gefitinib and showing consistent efficacy across prespecified subgroups defined by stratification factors, including *EGFR* mutation types and the presence or absence of baseline CNS metastases. The subgroup results suggested that a better overall efficacy might be expected if the enrolled patient population were more aligned with those in other third-generation EGFR TKI studies, such as the proportion of EGFR 19del, L858R, and CNS at baseline, sampling types.

The *EGFR* exon 19 deletion is associated with longer median progression-free survival compared with the *EGFR* Leu858Arg mutation.[33] However, the percentage of patients enrolled with *EGFR* exon 19 deletion in the REZOR study was numerically the lowest among similar studies (REZOR study [*EGFR* exon 19 deletion 51% *vs* Leu858Arg mutation 52% in the rezivertinib group]; FLAURA study [63% *vs* 37% in the osimertinib group]; AENEAS study [65% *vs* 35% in the almonertinib group]; FURLONG study [51% *vs* 49% in the furmonertinib group]; befotertinib phase 3 study [64% *vs* 36% in the befotertinib group]).[19,21–25] The estimated prolongation of progression-free survival in the REZOR study was 12·4 months for patients with *EGFR* exon 19 deletion and was advantageous (HR [0·38]) when compared with other third-generation EGFR TKIs, and data for patients with Leu858Arg mutation was 4·3 months longer with an HR of 0·59 (findings for these subgroups in the FLAURA study were a median progression-free survival of 10·4 months [HR 0·46; p<0·001] for patients with *EGFR* exon 19 deletion and of 4·9 months [HR 0·51; p<0·001] for patients with *EGFR* Leu858Arg mutation];[19] in the the AENEAS study were 8·5 months [HR 0·39; p<0·0001] for *EGFR* exon 19 deletion and 5·1 months [HR 0·51; p=0·0102] for *EGFR* Leu858Arg mutation];[21] and in the FURLONG study HRs of 0·35 for *EGFR* exon 19 deletion and 0·54 for *EGFR* Leu858Arg mutation were noted;[22] compared with the icotinib group; and in the befotertinib study were an HR of 0·42 for *EGFR* exon 19 deletion and no significantly prolonged progression-free survival for Leu858Arg mutation).[25] Therefore, although the rezivertinib subgroup efficacy for different *EGFR* mutations was more advantageous in terms of reduction of risk over other third-generation EGFR TKIs, a better overall efficacy might be expected if the proportion of patients enrolled with *EGFR* exon 19 deletion had been higher in the REZOR study.

Previous studies revealed that patients with CNS metastasis had contributed to a worse prognosis.[19,20] In the subgroup analysis of those with CNS metastasis, a consistently prolonged progression-free survival and lower risk for progression or death for treatment with rezivertinib was shown when compared with all other third-generation EGFR TKIs (REZOR study [rezivertinib 16·0 months *vs* gefitinib 9·7 months; HR 0·52; p=0·003]; the FLAURA study [osimertinib 15·2 months versus

gefitinib–erlotinib 9·6 months; HR 0·47; p<0·0001]; the AENEAS study [almonertinib 15·3 months *vs* gefitinib 8·2 months; HR 0·38; p<0·0001]; the FURLONG study [furmonertinib 18·0 months *vs* gefitinib 12·4 months; HR 0·50; p=0·0028]; and the befotertinib phase 3 study [befotertinib 19·4 months *vs* icotinib 13·7 months; HR 0·48; p=0·0086]).[19–22,25,32] Compared with other similar studies, the REZOR study had the highest proportion of patients enrolled with baseline CNS metastasis; however, the CNS efficacy of rezivertinib was still similar to other third-generation EGFR TKIs, and a better overall efficacy might be expected if a lower proportion of patients with baseline CNS metastasis had been enrolled (the REZOR study [rezivertinib 41% *vs* gefitinib 39%]; the FLAURA study [osimertinib 19% *vs* gefitinib–erlotinib 23%]; the FURLONG study [furmonertinib 35% *vs* gefitinib 32%]; the AENEAS study [almonertinib 26% *vs* gefitinib 27%]; and the befotertinib phase 3 study [befotertinib 26% *vs* icotinib 25%]).[19–22,25,32]

In the REZOR study, the consistent clinical benefits for patients shown to have *EGFR* mutations via tissue or plasma samples at screening also provide a valuable treatment option for patients with unavailable tissue samples. In real-world clinical practice, not all patients undergo tissue *EGFR* mutation testing. When tissue samples are unavailable, patients might opt for plasma testing instead. Therefore, we enrolled patients with tissue samples unavailable in the REZOR study. For patients shown to have *EGFR* mutations via tissue sampling, the MICR-assessed median progression-free survival was longer than in those shown to have *EGFR* mutations via plasma sampling, which was consistent with previous studies of rezivertinib.[26,27,29] Among third-generation EGFR TKIs, plasma *EGFR* mutation detection was not done in the first-line treatment studies, except for the REZOR and the AENEAS studies. In the AENEAS study,[21] among 280 patients detected via a tissue sample, 176 progression-fre survival events occurred with an HR of 0·44 (0·32–0·60) in the aumolertinib group versus the gefitinib group, and among 149 patients detected with a plasma sample, 87 events occurred with an HR of 0·53 (0·34–0·82) in the aumolertinib group versus the gefitinib group. The results from the REZOR and AENEAS studies indicated that the efficacy for patients with *EGFR* mutations detected by plasma samples was worse than that for patients with mutations detected by tissue samples at screening, and this could further reduce the overall efficacy. In other words, a better overall efficacy of rezivertinib might be expected if patients without *EGFR* mutations detected by plasma samples were enrolled.

In the FLAURA study, osimertinib reduced the risk of CNS progression or death over gefitinib–erlotinib (HR 0·48; 0·26–0·86; p=0·014)[34] In the AENEAS study, almonertinib achieved significantly longer median CNS-progression-free survival in those with CNS metastases at baseline over gefitinib (29·0 *vs* 8·3 months; HR 0·323; 0·18–0·58; p<0·0001).[35] In the FURLONG study, furmonertinib significantly prolonged the median CNS-progression-free survival versus gefitinib (20·8 *vs* 9·8 months; HR 0·40; 0·23–0·71; p=0·0011).[23] The median investigator-assessed intracranial progression-free survival was not estimable (95% CI 9·7–not estimable) in the befotertinib group versus 15·2 months (10·4–22·1; HR 0·69 [0·36–1·33]; p=0·26) in the icotinib group.[25] The therapeutic effects of rezivertinib in patients with CNS metastases can be attributed to its optimised drug properties, achieved through structural innovation by introducing an *N*,*N*-dimethyl-substituted oxyethylamine side chain, which balanced lipophilicity

	Rezivertinib (n=184)		Gefitinib (n=185)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
(Continued from previous page)				
TEAE (incidence ≥10%)				
White blood cell count decreased	75 (41%)	6 (3%)	17 (9%)	2 (1%)
Anaemia	66 (36%)	2 (1%)	40 (22%)	2 (1%)
Platelets decreased	65 (35%)	5 (3%)	12 (6%)	1 (1%)
ALT increased	55 (30%)	4 (2%)	73 (39%)	15 (8%)
Decreased appetite	55 (30%)	4 (2%)	41 (22%)	1 (1%)
AST increased	51 (28%)	3 (2%)	68 (37%)	12 (6%)
Diarrhoea	49 (27%)	2 (1%)	68 (37%)	0
Absolute neutrophil count decreased	48 (26%)	10 (5%)	22 (12%)	4 (2%)
Cough	45 (24%)	0	43 (23%)	0
Lymphocyte count decreased	39 (21%)	10 (5%)	16 (9%)	3 (2%)
Vomiting	36 (20%)	1 (1%)	37 (20·0)	1 (1%)
Constipation	36 (20%)	0	36 (19%)	0
Weight decreased	36 (20%)	0	26 (14%)	0
Urinary tract infection	30 (16%)	1 (1%)	29 (16%)	1 (1%)
Back pain	29 (16%)	1 (1%)	28 (15%)	0
Hypoalbuminaemia	29 (16%)	0	28 (15%)	0
Pain in extremity	29 (16%)	0	16 (9%)	0
Hypertriglyceridaemia	26 (14%)	1 (1%)	25 (14%)	2 (1%)
Drug eruption	25 (14%)	4 (2%)	28 (15%)	1 (1%)
COVID-19	25 (14%)	2 (1%)	12 (6%)	1 (1%)
Nausea	24 (13%)	2 (1%)	26 (14%)	1 (1%)
Alopecia	23 (13%)	0	26 (14%)	0
Hyperuricaemia	22 (12%)	0	21 (11%)	1 (1%)
Arthralgia	22 (12%)	0	19 (10%)	0
Hypokalaemia	21 (11%)	2 (1%)	30 (16%)	3 (2%)
Rash	21 (11%)	1 (1%)	51 (28%)	1 (1%)
Hyponatraemia	20 (11%)	5 (3%)	12 (6%)	2 (1%)
Alkaline phosphatase increased	20 (11%)	1 (1%)	28 (15%)	6 (3%)
Dyspnoea	18 (10%)	2 (1%)	22 (12%)	1 (1%)
GGT increased	12 (7%)	0	23 (12%)	1 (1%)
Blood bilirubin increased	5 (3%)	0	36 (19%)	0

Data are n (%). Note: Safety was established by investigator as per Common Terminology Criteria for Adverse Events version 4.03. TEAE=treatment-emergent adverse event. TRAE=treatment-related adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyltransferase.

Table 2: **Summary of adverse events in the safety set**

and hydrophilicity. Therefore, the molecule is not effluxed by P-glycoprotein or breast cancer resistance protein, showing good blood–brain barrier penetration. The adequate efficacy in patients with CNS metastases among all clinical trials of rezivertinib was consistent.[26–29]

The safety profile of rezivertinib was manageable without new safety signals. The safety findings in the REZOR study revealed that the EGFR TKI-related adverse events such as dermatological or gastrointestinal toxicities were less commonly reported in the rezivertinib group, and the main adverse events were haematological and hepatological toxicities, which was consistent with previous results.[26,27,29] Both the haematological and hepatological adverse events of rezivertinib were clinically well-manageable. The frequency of grade 3 and higher haematological TEAEs with rezivertinib decreased (ANC decreased by 5%; white blood cell count decreased by 3%; lymphocyte decreased by 5%; platelets decreased by 3%, and anaemia by 1%) among 184 patients, whereas compared with osimertinib among 71 Chinese patients in the FLAURA study (ANC decreased by 6%; white blood cell count decreased by 4%; lymphocyte decreased by 4%; platelets decreased by 3%).[32,36] Meanwhile, among 184 patients in the rezivertinib group, no patient had serious haematological TEAEs or TEAEs leading to death. Patients who had dose adjustment were rare (the three most common TRAEs for dose interruption were ANC decreased by 3%, WBC decreased by 2%, and platelets decreased by 2%; the top three TRAEs for dose reductions, ANC decreased 3%, platelets decreased by 2%, white blood cell count decreased by 2%) and one (1%) patient in the rezivertinib group had their treatment terminated owing to anaemia. For the hepatological adverse events, no patient had TEAEs leading to treatment termination or death. Patients who had dose adjustment (ALT increased 2%; AST increased 1%) with rezivertinib were rare. The frequency of grade 3 or higher hepatological TEAEs and serious TRAEs (≥ grade 3 hepatological TEAEs, ALT increased by 2%; AST increased by 2%; serious TRAEs: ALT increased by 1%; AST increased by 1%) of rezivertinib was generally lower than osimertinib among Chinese patients in the FLAURA study (ALT increased by 1%; AST increased by 4%; serious TRAEs, ALT increased by 1%; AST increased by 1%).[32,36]

In the GPS study (NCT05219162), 86 patients with *EGFR*-mutated locally advanced or metastatic NSCLC who did not respond to post-osimertinib first-line treatment were prospectively enrolled. The genomic profiles of paired tissues and plasma samples at progression were analysed by use of next generation sequencing. At progression, *EGFR* Cys797Ser mutation (tissue 4%; plasma 5%), other non-sensitive *EGFR* mutation (tissue 15%; plasma 17%), *EGFR* amplification (tissue 30%; plasma 11%), mesenchymal-epithelial transition factor (*MET*) amplification (tissue 28%; plasma 8%), other amplifications (tissue 16%; plasma 7%), cell cycle gene alterations (tissue 26%; plasma 5%), fusion (tissue 12%; plasma 14%), and other mutations (tissue 21%; plasma 12%) were detected. Two patients (2%) had histological transformation.[37] However, the REZOR study did not investigate resistance mechanisms; studies of the resistance mechanisms are warranted.

There are strengths to this study. Firstly, this study was rigorously designed with prespecified subgroups showing consistent efficacy; although the enrolment proportion of patients with *EGFR* exon 19 deletion was low, the results met the primary endpoint; patients with either positive tissue or plasma tests were accepted, and the results showed the potential clinical efficacy for patients who had a positive plasma sample, which could be of benefit for real-world clinical practice, where not all patients undergo tissue *EGFR* mutation testing. When tissue samples are unavailable, patients might opt for plasma testing instead. In this study, the use of rezivertinib showed potential efficacy. So, if the patient was not able to get the tissue sample, they could still get a option for treatment if the plasma samples was qualified; owing to the innovated optimal properties, the efficacy for patients with CNS metastasis was further consistently verified; secondly, rezivertinib showed superior safety potential compared with osimertinib for the same ethnic population.

There are also limitations to this study. Firstly, all patients were enrolled from China; therefore applicability to the global population might be limited. Secondly, the first-generation EGFR TKI gefitinib was chosen as the comparator since osimertinib was only approved by China NMPA for the indication of first-line treatment for EGFR-sensitising mutation-positive locally advanced or metastatic NSCLC on Sept 3, 2019, after the initiation of this rezivertinib, phase 3 trial. Thirdly, the overall survival data are immature, so the long-term benefits of rezivertinib are still being followed up. Lastly, the first-line treatment resistance mechanisms of rezivertinib require further exploration. Further studies, including those on adjuvant and neoadjuvant therapies, are in the planning.

In conclusion, this study met its primary endpoint: rezivertinib (BPI-7711) showed superior overall and subgroup progression-free survival efficacy and a manageable safety profile for treatment of patients with locally advanced or metastatic NSCLC with *EGFR* mutations in the first-line setting, when compared with gefitinib.

Contributors

YS was the leading principal investigator and designed the trial with the sponsor. YS and TW were responsible for administrative support. All authors contributed to patient recruitment and data acquisition, and accessed and verified the data. YS, TW, and AZ were involved in data analysis and data interpretation and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.
All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
DZ and JP are employees of Beta Pharma (Princeton, NJ, USA). HS, FG, TW, and AZ are employees of Beta Pharma (Shanghai, China). All other authors declare no competing interests.

Data sharing
The data and materials that support the findings of this study are available from the corresponding author on reasonable request.

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