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Zorifertinib for EGFR-mutant Non-small Cell Lung Cancer after Leptomeningeal Metastasis on Double-Dose Third-generation EGFR-TKI: A Case Report and Literature Review

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Abstract: *Background*: Leptomeningeal metastasis (LM) after third-generation EGFR-TKIs resistance carries a dismal prognosis. Limited blood–brain-barrier penetration rather than secondary EGFR mutations is the dominant resistance mechanism. We report a case managed with CNS-penetrant EGFR inhibition of zorifertinib. *Method*: A 53-year-old, never-smoking woman with EGFR L858R-mutant stage IVb non-small-cell lung cancer (NSCLC) developed LM after progression on osimertinib 160 mg and firmonertinib 160 mg. Salvage therapy with zorifertinib (200 mg BID) plus firmonertinib (80 mg qd) was initiated. *Results*: Within 14 days, the coma resolved. Karnofsky Performance Status improved from 20 to 70. Serial imaging at 3 and 5 months revealed stable disease with shrinkage according to RECIST 1.1. Only grade 1–2 diarrhea, rash, and transaminitis occurred and resolved with symptomatic care. *Conclusion:* The combination of zorifertinib plus firmonertinib provides durable intracranial control and rapid neurological recovery after third-generation EGFR-TKI failure. Prospective validation is warranted.

Keywords: Zorifertinib; Third-generation EGFR-TKI resistance; Leptomeningeal metastasis

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1. Introduction

Lung cancer persists as the most lethal malignancy globally, with non-small-cell lung cancer (NSCLC) constituting 80-85% of cases [1]. Epidermal growth factor receptor (EGFR) mutations are predominantly found in East Asian, female, non-smoking individuals with lung adenocarcinoma. Among the various EGFR mutations, the exon 19 deletion (19 del) and the exon 21 Leu858Arg (L858R) mutation are the two most common subtypes, together representing 85–90% of all EGFR mutations [2,3]. EGFR-mutant NSCLC patients are more likely to develop central

nervous system (CNS) metastases, especially leptomeningeal metastasis (LM), compared to those with wild-type EGFR. The incidence rate of LM is as high as 9.4% with the median overall survival being less than 1 year [4].

Despite the efficacy of osimertinib, a third-generation EGFR-tyrosine kinase inhibitor (TKI), CNS metastases, particularly LM, remain a major challenge [5,6]. While dose escalation to 160 mg osimertinib has shown investigator-assessed LM objective response rates of 41 % and median LM-progression-free survival (PFS) of 8.6 months in the BLOOM study, durable control is still limited [7], which is mainly due to the limited penetration of most TKIs across the blood–brain barrier (BBB) [8], and EGFR sensitive mutations are still the main type (69.2%) in the CSF of patients who experience CNS progression after treatment with third-generation EGFR TKIs [9]. Osimertinib is a substrate of ABCB1 (P-glycoprotein, P-gp) and ABCG2 (breast cancer resistance protein, BCRP), which can actively pump osimertinib out of the BBB [10]. Osimertinib 160 mg daily just achieves a CSF penetration rate of 16%, and this is still insufficient compared to the in vitro EGFR L858R IC_{90}, resulting in limitation of its sustained inhibition for leptomeningeal lesions [5]. Though firmonertinib may have greater penetration of BBB compared to osimertinib or aumolertinib [11,12] the PFS and intracranial-PFS of firmonertinib 160mg in patients with LM after resistance to third-generation EGFR-TKIs were only 4.3–5.5months [9,12]. Whether the CSF concentration of firmonertinib is sufficient to fully address the issue of inadequate drug concentration still requires more data to support [13].

Zorifertinib was specifically engineered to overcome the BBB limitations of existing EGFR inhibitors [14]. In contrast to osimertinib and other TKIs that are substrates for P-gp/ABCB1 and BCRP/ABCG2 efflux transporters, zorifertinib is not recognised by either pump, resulting in a CSF-to-unbound plasma concentration ratio (UPR) reaching 1.11 (around 100 % BBB penetration), significantly exceeding the 2.5–16% observed for osimertinib. While firmonertinib demonstrated high brain penetration in mice, with a CSF-to-UPR of 3.31, which is also higher than osimertinib [14–17]. In phase III EVEREST trial, zorifertinib significantly extended intracranial-PFS (15.2 vs. 8.3 months, HR = 0.467, $p < 0.001$), demonstrating excellent intracranial disease control, and intracranial PFS also favored zorifertinib for patients with LM (HR, 0.395) [18]. The intracranial and extracranial response duration in a patient even lasted over 7 years [19].

In the treatment dilemma of LM after resistance to third-generation TKIs, the combination of firmonertinib and zorifertinib shows a synergistic mechanism. Firmonertinib mainly acts to maintain systemic EGFR inhibition. It can irreversibly bind to EGFR, effectively blocking the EGFR signaling pathway and inhibiting tumor cell growth in the body, especially in extracranial lesions [20]. On the other hand, zorifertinib focuses on compensating for insufficient intracranial exposure. This results in a synergistic effect of the two drugs in treating LM after resistance to third-generation TKIs.

This case reported a patient with EGFR-mutant (L858R) NSCLC who developed LM after progressing on osimertinib 160 mg, and we aimed to explore the efficacy and safety of subsequent salvage therapy with zorifertinib in combination with firmonertinib. This study has obtained informed consent from the patient.

2. Case presentation

2.1. Patient and baseline characteristics

A 53-year-old Chinese female non-smoker with well-controlled hypertension was diagnosed with invasive adenocarcinoma (T2bN2M1c, stage IVb) in July 8, 2022. Contrast-enhanced chest Computed Tomography (CT) revealed a 43 × 41 × 35 mm mass in the apical-posterior segment of the left upper lobe, accompanied by multiple

bilateral pulmonary nodules, and enlarged mediastinal and left hilar lymph nodes. Brain Magnetic Resonance Imaging (MRI) confirmed brain metastases. Genetic testing identified an EGFR exon 21 L858R mutation.

2.2. Therapeutic course

2.2.1. First-line therapy (July 19, 2022 – April 12, 2023)

On July 19, 2022, the patient initiated oral osimertinib 80 mg once daily. From July 21 to October 2022, bevacizumab was added to the regimen. She completed radiotherapy for brain metastases at a dose of 50 Gy in 10 fractions from August 28 to September 2, 2022. Re-evaluation in August 2022 showed a partial response (PR) in both intracranial and pulmonary lesions, with further tumor shrinkage observed in October 2022.

2.2.2. Intracranial progression and dose adjustment (April 13, 2023 – December 2024)

A cranial enhanced MRI on April 12, 2023, showed enlarged and newly emerged brain metastases. The dose of osimertinib was increased to 160 mg once daily starting from April 13, 2023. Follow-up in October 2023 revealed stable disease (SD) in both extracranial and intracranial disease. In August 2024, she experienced epileptic seizures, which were controlled with regular anti-epileptic treatment.

2.2.3. Confirmation of LM (December 2024)

In December 2024, the patient developed severe headache, vomiting, blurred vision and delirium. Cranial MRI indicated new LM, with positive cerebrospinal fluid (CSF) cytology and significantly elevated intracranial pressure. CSF genetic testing on January 13, 2025, still detected the EGFR exon 21 L858R mutation.

2.2.4. Salvage therapy and regimen adjustment (December 2024 – January 2025)

On December 24, 2024, she started oral firmonertinib 160 mg once daily. However, her symptoms did not improve and she developed stupor on January 9, 2025, and received dehydration and intracranial pressure-lowering therapy. She underwent 3 sessions of intrathecal pemetrexed injection on January 10, January 17, and February 7, however, she was still in a coma.

2.2.5. Combination therapy of zorifertinib and firmonertinib (from January 22, 2025)

The treatment regimen was adjusted to zorifertinib 200 mg twice daily combined with firmonertinib 80 mg once daily on January 22, 2025.

2.3. Efficacy assessments

After 7 days of combination therapy of zorifertinib and firmonertinib, her coma started to improve, and she fully recovered from the coma on February 4, 2025. Her headache and vomiting significantly improved, and her vision recovered. The performance status improved significantly, with the KPS increasing from 20 to 70 at 8 weeks. Imaging assessments showed that there were two target lesions before combination therapy: one intracranial target lesion with of 60 mm and one extracranial target lesion in left pulmonary with a maximal diameter of 27 mm. Re-evaluations around May and July, 2025 showed SD with shrinkage according to RECIST 1.1 criteria. The intracranial and extracranial target lesions decreased to 53.72 mm and 23.69 mm, respectively, on 1 July 2025 (**Figure 1**). As of the cut-off date of July 31, 2025, the PFS and intracranial-PFS were both more than 6 months, and the patient continues the combination therapy with sustained disease control and manageable AEs.

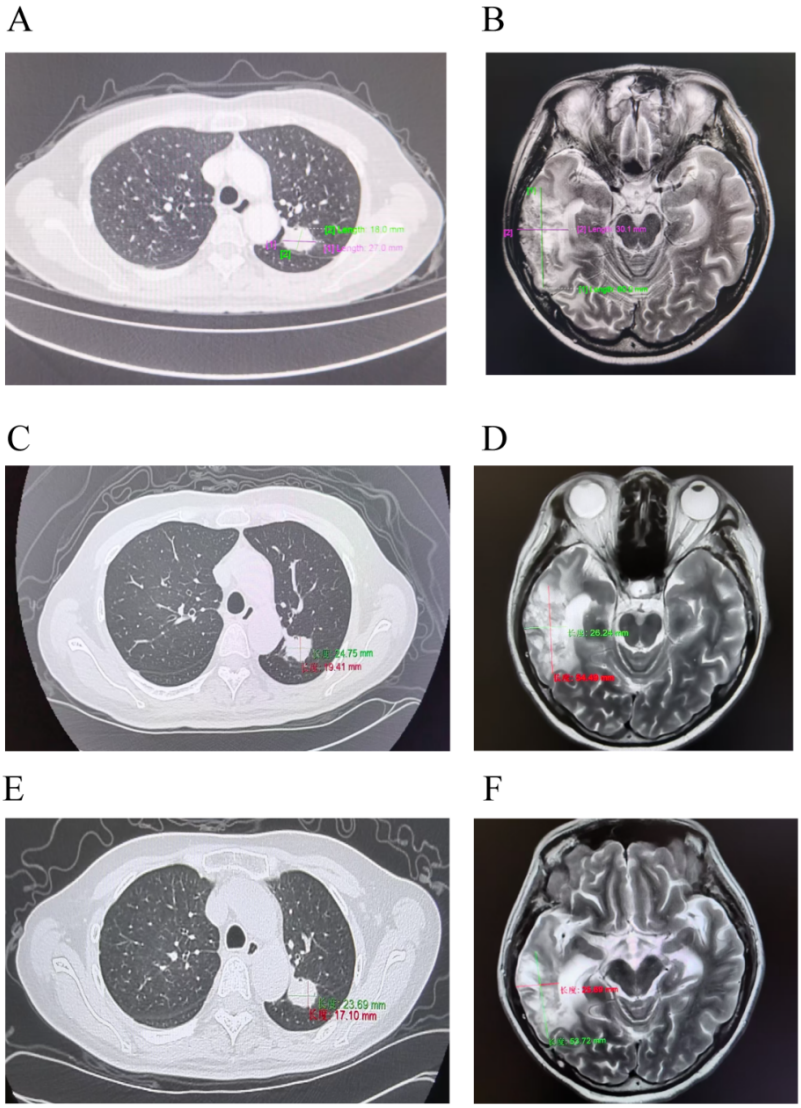

Figure 1. Follow-up imaging of lung and brain lesions in EGFR-mutant NSCLC treated with zorifertinib + firmonertinib combination therapy. (A) Chest CT before combination therapy. (B) Brain MRI before combination therapy. (C) Chest CT on 30 April 2025, stable pulmonary lesions at 3-month follow-up. (D) Brain MRI on 29 April 2025, residual leptomeningeal enhancement at 3-month follow-up. (E) Chest CT on 30 June 2025, continued stable disease at 5-month follow-up. (F) Brain MRI on 1 July 2025, further reduction of sulcal enhancement at 5-month follow-up. CT: Computed Tomography; LM: leptomeningeal metastasis; MRI: Magnetic Resonance Imaging.

2.4. Safety

During the combination therapy, grade 1 diarrhea, grade 2 Aspartate Aminotransferase (AST) elevation, and grade 2 scattered rash on the limbs and trunk occurred. All adverse events (AEs) improved with symptomatic treatment, and no grade ≥ 3 toxicities were observed.

3. Discussion

In this case, a female patient with EGFR L858R-mutant stage IVb NSCLC developed LM after disease progression on osimertinib (160 mg). Following the failure of salvage therapy with firmonertinib 160 mg monotherapy and intrathecal chemotherapy, she was switched to combination therapy with zorifertinib (200 mg BID) and firmonertinib (80 mg QD). Within 14 days, the patient's neurological symptoms improved, with the KPS increasing from 20 to 70 at 8 weeks. And per RECIST 1.1 criteria, the best overall response was SD with shrinkage; the therapeutic effect was sustained at 6 months, with no grade ≥ 3 AEs. The result indicates that the combination of zorifertinib and firmonertinib achieved durable control of LM after osimertinib resistance.

After progression on third-generation EGFR-TKIs, LM in EGFR-mutant NSCLC is driven by two converging factors. First, limited BBB penetration keeps intracranial drug concentrations below the therapeutic threshold. CSF-UPR reflects the distribution of the drug in the CSF, which is crucial for managing LM. The CSF-UPR of osimertinib is about 2.5%, 16%, 22% and 31.7% [7,21,22]. Both the parent drug and its metabolites efficiently enter the CSF, which may be the basis for its CNS efficacy advantage. This higher brain penetration could contribute to its potential for treating CNS-related conditions, such as LM. Second, molecular profiling of cerebrospinal fluid reveals that the original EGFR-activating mutation (L858R or Ex19del) persists in 70%-80% cases, while classic resistance mutations such as C797S or MET amplification are less [23,24].

The treatment of LM in NSCLC patients after third-generation EGFR-TKIs failure remains largely palliative. Intrathecal chemotherapy (ITC) is the historical standard for treating LM. According to the results of multiple studies, the objective response rates (ORR) of systemic therapy and intrathecal chemotherapy is 53%-76%, but the median overall survival (mOS) is 8-12 months [25,26]. These data indicate that while ITC provides high CSF clearance and symptomatic benefit, its LM-specific ORR remains modest, underscoring a need for more effective CNS-penetrant strategies.

Dose-escalated third-generation EGFR-TKIs monotherapy or combination therapy is another choice. A prospective real-world study enrolled 48 EGFR-mutant NSCLC patients with LM, including 35 who had received prior third-generation EGFR-TKIs. All patients were treated with high-dose firmonertinib (240 mg QD) either as monotherapy or in combination regimens. The results demonstrated that the mOS in the overall cohort is 8.43 months, and it is 7.07 months in the prior third-generation EGFR-TKIs exposure subgroup [27]. Another retrospective analysis of 105 Chinese EGFRm+ NSCLC patients with cytologically confirmed LM demonstrated that OS of high-dose third-generation EGFR-TKIs (osimertinib 160 mg, fumeitinib 160 mg, aumolertinib 165 mg) was 10.0 months in the third-generation EGFR-TKIs resistance group; combination with chemotherapy, anti-angiogenic therapy, or WBRT failed to prolong OS (12.3 vs 13.4 months) [28].

Zorifertinib was specifically engineered to overcome the two major limitations of existing EGFR-TKIs in CNS disease: sub-therapeutic intracranial exposure and efflux-mediated clearance. Pre-clinical pharmacokinetic studies demonstrate that zorifertinib is not a substrate for P-gp or BCRP, thereby eliminating active efflux at the BBB [18]. Consequently, its CSF-UPC ratio is 1.11, corresponding to 100 % BBB penetration, which is substantially higher than the 2.5–31.7% reported for osimertinib [14]. This superior CNS exposure underpins the significantly prolonged intracranial antitumor activity of zorifertinib. In the treatment of EGFR mutation-positive ($EGFRm^+$) NSCLC with CNS metastases. The Phase I BLOOM study demonstrated an overall ORR of 67% for zorifertinib, with an intracranial ORR as high as 87% [16].

The Phase II CTONG1702 study further confirmed this advantage. In untreated $EGFRm^+$ NSCLC patients with CNS metastases, zorifertinib showed an overall ORR of 80%, a mPFS of 15.8 months, and a median

intracranial PFS of 18.5 months [29]. The EVEREST study is the first large-scale, global, registrational, prospective clinical trial focused on the treatment of brain metastases in lung cancer, achieving significant clinical findings. The EVEREST trial compared first-line zorifertinib with first-generation EGFR-TKIs in patients with advanced EGFRm$^+$ NSCLC with CNS metastases. Patients enrolled were more clinically representative, being eligible regardless of the presence of CNS symptoms, and had a higher intracranial tumor burden and a higher proportion of patients with poor prognostic EGFR L858R in this study. The results showed that the zorifertinib group had particularly notable advantages in controlling intracranial lesions: investigator-assessed intracranial PFS (17.9 months vs 11.1 months), and intracranial ORR were all significantly better in the zorifertinib group. These benefits were consistent across subgroups, including those with the L858R mutation, LM and high intracranial tumor burden. The mOS was 37.3 months in patients who received subsequent third-generation EGFR-TKI treatments. This study confirms that zorifertinib is a superior first-line treatment option for patients with CNS metastases, significantly improving intracranial lesion control [18].

The mechanism of combination treatment with firmonertinib and zorifertinib for EGFR-mutant non-small cell lung cancer (NSCLC) with leptomeningeal metastasis (LM) can be summarized as "synergistic extracranial-intracranial dual-pathway": Firmonertinib (80 mg) maintains extracranial EGFR inhibition, providing sustained control of extracranial lesions. Zorifertinib (200 mg BID) directly compensates for insufficient intracranial drug exposure, continuously blocking EGFR signaling and overcoming resistance caused by the BBB.

In this case report, a 53-year-old female patient with EGFR L858R-mutant NSCLC progressed to LM after developing resistance to osimertinib. CSF testing still detected the L858R mutation, consistent with the characteristic feature of EGFR mutation-driven LM, also suggesting that the inadequate drug concentration, rather than the occurrence of a secondary mutation. After switching to the combination of firmonertinib 80 mg and zorifertinib 200 mg BID, the patient's condition showed notable improvement: the coma resolved rapidly, and the KPS improved from 20 to 70. Although a partial response (PR) was not achieved, tumor regression within SD criteria suggests biological activity of the combination treatment, the CNS symptoms significantly improved, and the patient's quality of life (QoL) showed significant improvement. In summary, the combination regimen, through the synergistic approach of "low systemic toxicity + high intracranial exposure," continuously suppresses EGFR-driven progression, providing a new therapeutic paradigm for LM after resistance to third-generation TKIs. In this case, the AEs were mild to moderate (grade 1–2), including diarrhea, rash, and elevated AST. These AEs were alleviated with symptomatic treatment, and no grade ≥ 3 toxicities were observed. Overall, the treatment demonstrated good tolerability, making it suitable for long-term maintenance therapy.

This report is confined to a single patient, and the observed efficacy and safety profile require confirmation in larger, prospective cohorts. Furthermore, serial cerebrospinal fluid (CSF) cytological analysis was not conducted to monitor malignant cell clearance, and RANO-LM-based response assessment for LM was unavailable, potentially underestimating CNS-specific treatment effects. Future work should prospectively validate the zorifertinib–firmonertinib combination in larger LM cohorts while simultaneously integrating serial CSF pharmacokinetics and genomic profiling to establish a precision-based, penetration-driven treatment paradigm.

4. Conclusion

The regimen of zorifertinib plus firmonertinib theoretically sustains systemic EGFR inhibition and overcomes the BBB. This case provides proof-of-concept that such a penetration-driven strategy can achieve durable CNS

control and rapid symptom relief after third-generation EGFR-TKIs resistance. Multicenter, prospective trials are warranted to confirm efficacy, safety, and optimal dosing for EGFR-mutant NSCLC patients with LM.

Disclosure statement

The authors declare no conflict of interest.

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