

Combined Zorifertinib and Almonertinib in EGFR-Mutant NSCLC with Leptomeningeal Metastasis: A Two-Case Report with Serial Plasma and Cerebrospinal Fluid Drug Concentration Monitoring

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Abstract: *Background:* Leptomeningeal metastasis (LM) is a devastating complication of EGFR-mutant non-small cell lung cancer (NSCLC) with a dismal prognosis. Optimal CNS-penetrating EGFR-tyrosine kinase inhibitors (TKIs) and combination strategies remain poorly defined, and real-time pharmacokinetic data in LM patients are scarce. *Case presentation:* We report two female patients (Z005, aged 50, EGFR exon 19 deletion; Z006, aged 62, EGFR L858R/T790M) with LM who received combination therapy with zorifertinib and almonertinib. Serial paired plasma and cerebrospinal fluid (CSF) samples were collected via the Ommaya reservoir for targeted drug concentration measurements, alongside longitudinal RANO-LM assessments. Patient Z005 demonstrated a dramatic response, with neurological score improving from 3 to 0 and MRI showing marked improvement within two months. Patient Z006 received the combination regimen for five months, after which her cerebrospinal fluid cytology turned negative and neurological symptoms resolved completely, suggesting effective disease control. Both patients tolerated the combination therapy with manageable adverse events, and at the time of last follow-up, both remained clinically stable with no evidence of disease progression. *Results:* CSF total concentrations of almonertinib ranged from 0.770 to 14.9 nmol/L. zorifertinib achieved substantially higher CSF penetration, with CSF total concentrations of 20.9–27.2 nmol/L and K_{puu}, CSF values of 0.81–0.94, consistent with near-complete blood-brain barrier penetration. *Conclusion:* This report provides the detailed pharmacokinetic characterization of combined zorifertinib and almonertinib in LM patients using Ommaya reservoir-based CSF sampling. Two similar clinical outcomes suggest that combination regimens may produce favorable therapeutic effects in patients with LM, and also reflect the potential clinical value of therapeutic drug monitoring (TDM).

Keywords: Leptomeningeal metastasis; Non-small cell lung cancer; EGFR-TKI; Zorifertinib; Almonertinib; Cerebrospinal fluid; Therapeutic drug monitoring

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1. Introduction

Leptomeningeal metastasis (LM) is a fatal complication of advanced non-small cell lung cancer (NSCLC), characterized by dissemination of cancer cells to the leptomeninges, subarachnoid space, and cerebrospinal fluid (CSF). The reported incidence of LM in NSCLC ranges from 3% to 5% overall, increasing substantially to approximately 9% in patients harboring epidermal growth factor receptor (EGFR) mutations ^[1,2]. Historically, the prognosis for patients with LM has been extremely poor, with untreated individuals facing a median survival of only weeks to a few months ^[1,3]. Despite the advent of EGFR-tyrosine kinase inhibitors (TKIs), LM remains exceedingly difficult to treat, largely due to the blood-brain barrier (BBB) and blood-CSF barrier (BCSFB), which restrict drug penetration into the central nervous system (CNS) ^[4,5]. The primary obstacle is inadequate drug crossing of the BBB, resulting in subtherapeutic concentrations in brain parenchyma and CSF ^[5]. First- and second-generation EGFR-TKIs exhibit limited CSF penetration rates of only 1.13%–3.3% ^[1]. Osimertinib, a third-generation TKI, has demonstrated superior BBB penetration and higher CSF drug concentrations relative to its predecessors ^[6]. Nevertheless, CNS progression remains a major challenge even with osimertinib, and optimal CNS-penetrating strategies continue to be defined.

Zorifertinib is a third-generation EGFR-TKI specifically designed as a non-BBB-efflux-protein substrate, enabling near-complete (approximately 100%) BBB penetration. Preclinical data have demonstrated that zorifertinib achieves CSF and brain tissue concentrations comparable to those in plasma, with unbound brain-to-unbound blood ratios (K_{puu}) of approximately 1 ^[7]. The phase III EVEREST trial showed that first-line zorifertinib significantly prolonged intracranial progression-free survival (iPFS) in EGFR-mutant NSCLC patients with CNS metastases compared with first-generation EGFR-TKIs (15.2 vs. 8.3 months; HR = 0.467) ^[8]. Almonertinib (aumolertinib), another third-generation EGFR-TKI, has also shown promising activity against CNS metastases, with subgroup analyses from the AENEAS study demonstrating a 62% reduction in the risk of brain metastasis progression (HR = 0.38) ^[9].

Herein, we report two cases of EGFR-mutant NSCLC with LM who had experienced disease progression on prior single-agent almonertinib therapy following surgical resection and subsequent leptomeningeal relapse. Both patients then received combination therapy with zorifertinib and almonertinib, with longitudinal pharmacokinetic monitoring via Ommaya reservoir ^[10]. These cases illustrate the feasibility of real-time therapeutic drug monitoring (TDM) in LM and provide critical insights into CNS drug penetration dynamics.

2. Case presentation

2.1. Case 1: Patient Z005

A 50-year-old female was diagnosed with lung adenocarcinoma (EGFR exon 19 deletion) in July 2020. She underwent left upper lobe resection but subsequently developed brain and LM, diagnosed in March

2024. Prior treatment included almonertinib 165 mg daily, on which she experienced progressive LM. In November 2025, her condition deteriorated rapidly: neurological score was 3, contrast-enhanced MRI showed progression with new leptomeningeal enhancement (**Figure 1A-1C**), and CSF cytology was positive. Extracranial disease remained stable. An air-liquid interface (ALI) culture assay demonstrated that zorifertinib monotherapy achieved a tumor cell inhibition rate of 14.3%, while the combination of almonertinib and zorifertinib yielded a substantially higher inhibition rate of 67.62%, supporting the synergistic potential of the dual-TKI regimen.

Combination therapy with zorifertinib 200 mg twice daily and almonertinib 165 mg daily was initiated on December 14, 2025. Remarkably, by Jun 24, 2026, her neurological score had improved from 3 to 0 (complete resolution of neurological deficits), MRI demonstrated marked improvement with reduced LM (**Figure 1D-1F**), though CSF remained cytologically positive. This was documented as the best overall response. Extracranial disease remained stable throughout this period. Serial paired plasma and CSF samples were collected via Ommaya reservoir for pharmacokinetic analysis. Adverse events included grade 2 skin rash, grade 2 paronychia, and urinary incontinence (CTCAE v5.0). At the time of last follow-up (6 months after combination therapy initiation), the patient remained clinically stable with ongoing extra-cranial stability.

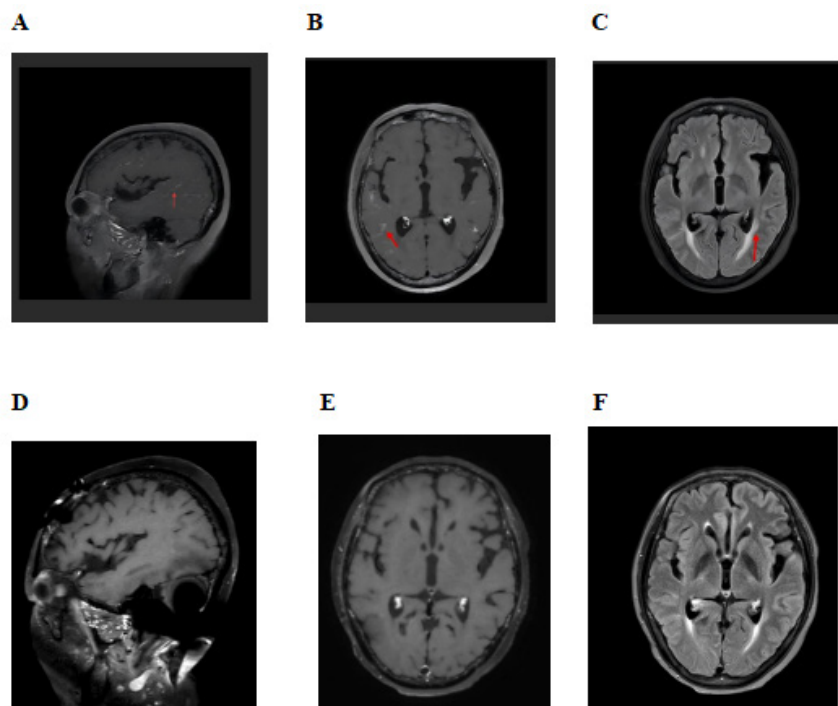


Figure 1. Serial fluid-attenuated inversion recovery (FLAIR) MRI of patient Z005 before and after combination therapy with zorifertinib and almonertinib.(A, B, C) FLAIR images prior to combination therapy initiation.(D, E, F) FLAIR images at the best response after treatment.

2.2. Case 2: Patient Z006

A 62-year-old female was diagnosed with lung adenocarcinoma (EGFR L858R and T790M) in May 2022. LM was diagnosed in September 2025. Prior treatment with almonertinib 165 mg daily was administered,

during which she experienced progressive LM. Extracranial disease remained stable. Combination therapy with zorifertinib 200 mg twice daily and almonertinib 110 mg daily was initiated on January 24, 2026. Five months after adding zorifertinib to her treatment regimen, follow-up evaluation conducted on July 9, 2026 yielded negative cerebrospinal fluid cytology results, with a RANO-LM neurological score of 2 and stable neurological symptoms (**Figure 2**). Adverse events included bone marrow suppression (grade 1 leukopenia, grade 2 hemoglobin reduction), grade 1 skin rash, and grade 2 anorexia (CTCAE v5.0). At the time of last follow-up (5 months after combination therapy initiation), the patient continued on treatment with ongoing neurological monitoring and stable extracranial disease.

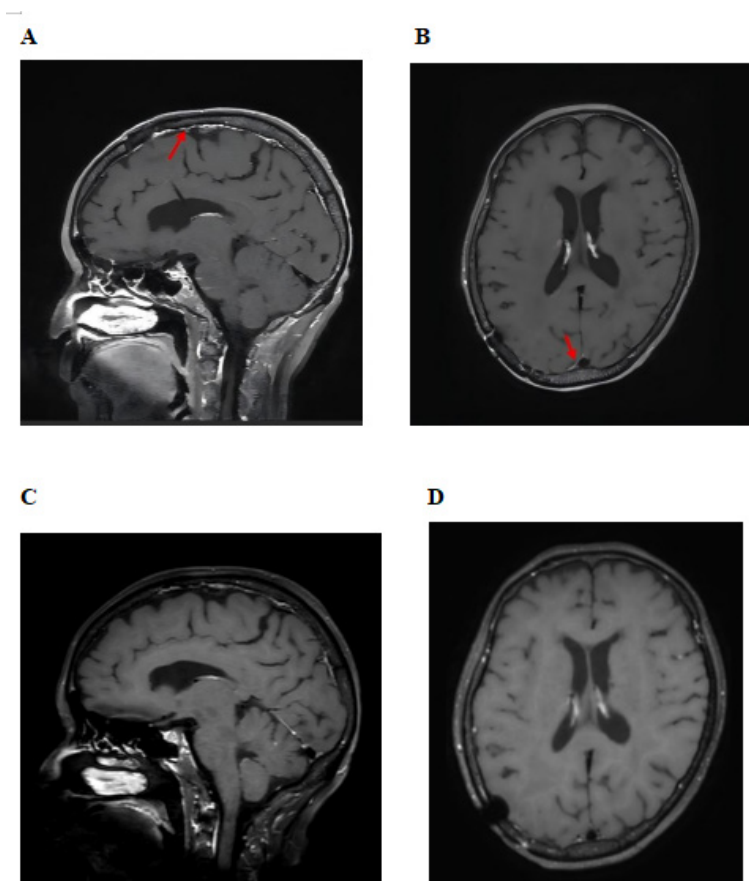


Figure 2. Serial fluid-attenuated inversion recovery (FLAIR) MRI of patient Z006 before and after combination therapy with zorifertinib and almonertinib.(A, B) FLAIR images prior to combination therapy initiation.(C, D) FLAIR images at the best response after treatment.

3. Results

The demographic and clinical characteristics of the two patients are summarized in **Table 1**. The longitudinal clinical course, treatment regimens, and paired pharmacokinetic data at each sampling time point are presented in **Table 2**. Key pharmacokinetic parameters derived from the paired plasma and CSF samples, including unbound fractions (F_u) and CSF-to-plasma concentration ratios, are summarized in **Table 3**. In both patients, zorifertinib achieved CSF total concentrations of 20.9–27.2 nmol/L, with CSF-to-plasma

total ratios of approximately 5.2%–5.3% (**Table 2** and **Table 3**). When calculated as K_pu, CSF (CSF total/plasma unbound)—a pharmacologically more relevant metric accounting for plasma protein binding—zorifertinib achieved values of 0.81–0.94. These values, approaching unity, are consistent with near-complete equilibration between the plasma and CSF compartments. The F_u of zorifertinib was 6.44% in Z005 and 5.63% in Z006. Almonertinib, despite its high plasma protein binding, achieved CSF total concentrations of 2.72–14.9 nmol/L, with CSF-to-plasma total ratios ranging from 0.37% to 0.48% across the evaluated time points (**Table 2** and **Table 3**). Notably, when comparing CSF total concentration to plasma unbound concentration, the ratios were 2.14 for Z005 and 4.91 for Z006, substantially exceeding unity. These elevated ratios likely reflect disruption of the blood-cerebrospinal fluid barrier in the setting of leptomeningeal metastasis, which increases CSF protein content and facilitates passive diffusion of protein-bound drug into the CSF compartment. The F_u of almonertinib was 0.18% in Z005 and 0.10% in Z006.

The Clinical Outcomes: Z005 achieved a remarkable response after initiation of combination therapy. Her neurological score improved from 3 to 0 within one month, and MRI demonstrated marked improvement with reduced leptomeningeal metastases (**Figure 1D-1F**). Although CSF cytology remained positive at the time of best response, this clinical and radiographic improvement was documented as a partial response per RANO-LM criteria. Extracranial disease remained stable throughout the observation period. The patient remained clinically stable at 6 months of follow-up. Z006 received combination therapy with zorifertinib after disease progression occurred under single-agent aumolertinib. Five months later, her neurological function improved significantly, cerebrospinal fluid cytology turned negative, and her overall disease stayed stable (**Figure 2C-2D**).

Table 1. Patient demographics and clinical characteristics.

Characteristic	Z005	Z006
Age (years)	50	62
Gender	Female	Female
NSCLC diagnosis date	2020-07-29	2022-05-16
EGFR mutation	Exon 19 deletion	L858R + T790M
LM diagnosis date	2024-03-14	2025-09-30
Prior EGFR-TKI	Almonertinib 165 mg	Almonertinib 165 mg
Combined therapy initiation (Zorifertinib + Almonertinib)	2025-12-14	2026-01-24
Best overall response (RANO-LM)	Neurological score 3→0	Neurological score 3→2
Extracranial response	Stable	Stable
Follow-up duration	6 months	5 months

Table 2. Serial pharmacokinetic and clinical data.

Patient	Time	Sample	Regimen	Almonertinib (nmol/L)	Zorifertinib (nmol/L)	Clinical Status
Z005	2025-12-01	Z005C0BP (total)	Almonertinib 165 mg qd	692	–	Neuro score 3
		Z005C0BP (unbound)		0.955	–	
		Z005C0CS		14.9	–	
	2026-01-13*	Z005C1BP (total)	Almonertinib 165 mg qd + Zorifertinib 200mg bid	727	522	Neuro score 0
		Z005C1BP (unbound)		1.27	33.6	

Patient	Time	Sample	Regimen	Almonertinib (nmol/L)	Zorifertinib (nmol/L)	Clinical Status
Z006	2026-07-09	Z005C1CS		2.72	27.2	
						Neuro score 0
	2025-12-29	Z006C0BP (total)	Almonertinib 110mg qd	369	—	Neuro score 3
		Z006C0BP (unbound)		0.521	—	
		Z006C0CS		1.48	—	
	2026-01-22	Z006C1BP (total)	Almonertinib 165mg qd	342	—	Neuro score 2
		Z006C1BP (unbound)		0.411	—	
		Z006C1CS		0.770	—	
	2026-02-11*	Z006C2BP (total)	Almonertinib 110 mg qd + Zorifertinib 200mg bid	687	396	Neuro score 2
		Z006C2BP (unbound)		0.670	22.3	
		Z006C2CS		3.29	20.9	
	2026-07-09					Neuro score 2

*Z005 combination therapy with zorifertinib was initiated on December 14, 2026. The C1 time point reflects post-combination pharmacokinetic data. Z006 combination therapy with zorifertinib was initiated on January 24, 2026. The C2 time point reflects post-combination pharmacokinetic data.

Table 3. Pharmacokinetic parameters.

Parameter	Z005 (Almonertinib)	Z005 (Zorifertinib)	Z006 (Almonertinib)	Z006 (Zorifertinib)
Plasma total (nmol/L)	727	522	687	396
Plasma unbound (nmol/L)	1.27	33.6	0.670	22.3
CSF total (nmol/L)	2.72	27.2	3.29	20.9
Fu (%)	0.282	7.73	0.139	7.95

Calculation	$Fu (\%) = 100 \times PAR_{pbs} / PAR_{plasma}$
	$\% Recovery = 100 \times (100 \times PAR_{plasma} + 100 \times PAR_{pbs}) / 100 \times PAR_{c0}$
	$\% Bound = 100 - Fu (\%)$
	PAR _{plasma} represents the concentration value on the plasma side after incubation
	PAR _{pbs} represents the concentration value on the PBS side after incubation
	PAR _{c0} represents the concentration value of the initial sample before incubation

4. Discussion

The combination of zorifertinib and almonertinib represents a rationally designed strategy to maximize CNS drug exposure through complementary mechanisms: zorifertinib provides near-complete BBB penetration, ensuring reliable CNS delivery, while almonertinib contributes potent third-generation EGFR-TKI activity with moderate CNS penetration, potentially offering additive or synergistic efficacy against leptomeningeal tumor cells. However, pharmacokinetic data on this combination specifically in patients with LM are lacking. This two-case report provides the first pharmacokinetic characterization of combined zorifertinib and almonertinib therapy in LM patients using Ommaya reservoir-based CSF sampling^[12].

The elevated CSF-to-plasma unbound concentration ratios for almonertinib (2.14-4.91) exceeded the typical 0.8-1.2 range. This likely reflects blood-CSF barrier disruption and impaired active drug transport. Under normal physiological conditions, CSF drug concentrations do not substantially exceed their peripheral counterparts. However, given the low free fraction of almonertinib, the proportion of unbound drug within

the CSF remains to be clarified in further investigations. Zorifertinib maintained CSF-to-plasma unbound ratios of 0.81–0.94, consistent with its unique property of near-complete BBB penetration. This property, attributed to its F_u of 5.63% and 6.44% and non-substrate status for P-gp and BCRP efflux transporters, ensures consistent CNS drug exposure regardless of barrier integrity^[7]. In the responding patient (Z006), adequate zorifertinib exposure was associated with progressive reduction and eventual normalization of CSF malignant cell counts, supporting the correlation between therapeutic drug levels and cytological response.

All CSF samples were obtained via Ommaya reservoir, which enabled reliable, repeated ventricular CSF sampling with minimal procedural variability^[10]. Importantly, consistent concordance was observed between MRI results, cerebrospinal fluid cytology and neurological manifestations in both patients, demonstrating that multimodal assessment combining neurological examination, CSF testing and imaging enables more refined clinical management of patients with leptomeningeal metastasis^[11]. Both patients maintained stable intracranial and extracranial lesions, which indicates that the efficacy of combination therapy exhibits central nervous system-specific characteristics and is associated with multiple factors including drug penetration, intrinsic tumor biology, and resistance mechanisms. Resistance alterations such as MET amplification and C797 mutations frequently emerge in patients with leptomeningeal metastasis who progress on EGFR-TKIs, which can be further validated via cerebrospinal fluid-based genetic sequencing in future studies.

Several limitations warrant acknowledgment: the absence of precise drug administration-to-sampling time intervals, small sample size ($n=2$), lack of P-gp/BCRP expression data, and short follow-up (5–6 months). The CSF total concentration was used as a surrogate for unbound CSF concentration, assuming negligible CSF protein binding—a reasonable approximation requiring future verification.

5. Conclusion

In this two-case report, zorifertinib achieved stable and nearly complete penetration into cerebrospinal fluid (CSF), achieving roughly consistent drug concentrations intracranially and extracranially. The consistent concordance between MRI scans, CSF examinations, neurological evaluations, and ex vivo ALI culture assays indicates that this dual-TKI combination regimen can produce durable intracranial disease control. Multimodal monitoring based on Ommaya reservoirs helps accurately evaluate intracranial lesions and track treatment response, further validating the important clinical value of therapeutic drug monitoring for patients with leptomeningeal metastasis.

Disclosure statement

The authors declare no conflict of interest.

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