



Furmonertinib Combined with Intraventricular Chemotherapy in Third-Generation EGFR-TKI Resistant Leptomeningeal Metastases

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INTRODUCTION

- Leptomeningeal metastasis (LM) that emerges after resistance to third-generation EGFR TKIs is inevitable¹, characterized by extremely poor survival and the absence of standardized effective therapies in real-world practice².
- This study evaluated the efficacy and safety of high-dose furmonertinib plus intraventricular pemetrexed for LM, alongside CSF-derived ctDNA profiling to monitor tumor dynamics and predict outcomes.

METHODS

- This single-arm, prospective study was conducted at the Affiliated Brain Hospital of Nanjing Medical University between January 2024 and March 2025 (NCT06339242).
- Eligible patients were 18-75 years of age with histologically confirmed EGFR-mutant NSCLC and had developed LM following progression on a third-generation EGFR TKI. Key exclusion criteria included inadequate organ function, active CNS infection, or contraindications to Ommaya reservoir placement. All patients received oral furmonertinib at a dose of 160mg once daily combined with intraventricular chemotherapy delivered via an implanted Ommaya reservoir.
- The primary endpoints were intracranial progression-free survival (iPFS) and intracranial objective response rate (iORR). Secondary endpoints included overall survival (OS), intracranial disease control rate (iDCR), and safety.

REFERENCES & ACKNOWLEDGEMENTS

References

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- All authors declare no conflict of interest.

RESULTS

Table 1. Baseline characteristics

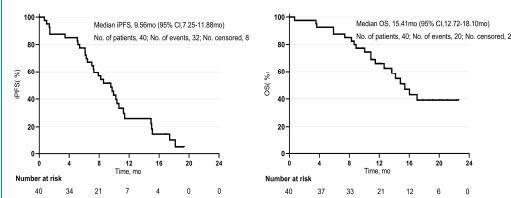
Characteristics	No. of patients(%)
Gender	Male 16(40.0) Female 24(60.0)
Age (years)	Median (range) 57(41-73)
Histological type	Adenocarcinoma 40(100)
ECOG PS at diagnosis of LM	2 11(27.5) 3 29(72.5)
Smoking status	Current/former smoker 4(10.0) Nonsmoker 36(90.0)
EGFR gene mutation	EGFR L858R 25(62.5) EGFR 19del 12(30.0) Compound EGFR mutations* 3(7.5)
Other sites of metastasis	Brain 23(57.5) Bone 18(45.0) Liver 1(2.5) Adrenal 2(5.0) Pleural 6(15.0) Peritoneal 2(5.0)
Furmonertinib treatment line	≤3 22(55.0) >3 18(45.0)
Prior WBRT	Yes 4(10.0) No 36(90.0)
Prior immunotherapy	Yes 7(17.5) No 33(82.5)
Prior systemic chemotherapy	Yes 27(67.5) No 13(32.5)
Prior three-generation EGFR TKI therapy	Furmonertinib 7(17.5) Osimertinib 13(32.5) Almonertinib 10(25.0) Furmonertinib+Osimertinib 2(5.0) Furmonertinib+Almonertinib 4(10.0) Osimertinib+Almonertinib 4(10.0)
Pemetrexed cumulative dose for IVC	≥200mg 23(57.5) <200mg 17(42.5)

Compound EGFR mutations*: EGFR L858R+EGFR R776H / EGFR 19del+EGFR L718V / EGFR L858R+EGFR A298V

Efficacy

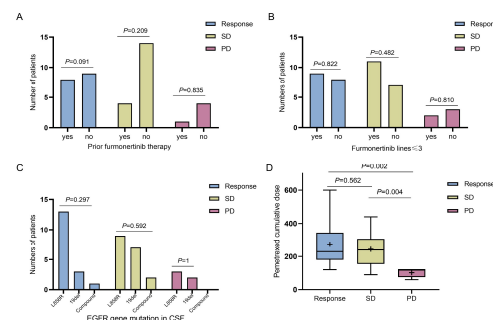
- The median iPFS was 9.56 months (95% CI, 7.25-11.88) and median OS was 15.41 months (95% CI, 12.72-18.10). The iORR was 42.5% and the iDCR was 87.5%.

Figure1. Kaplan-Meier curves of iPFS and OS



- Patients who achieved an objective response or stable disease received significantly higher cumulative doses of intraventricular pemetrexed than those with progressive disease. No other baseline or treatment factors were statistically significantly associated with response.

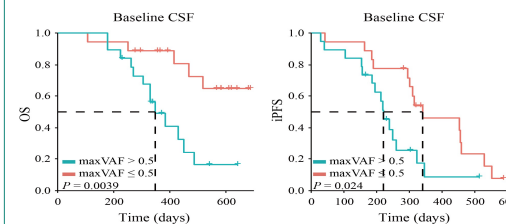
Figure2. Subgroup analyses of clinical efficacy



ctDNA Analysis

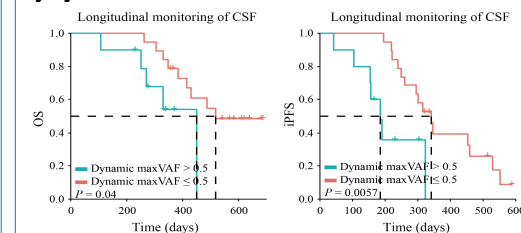
- Patients with a baseline CSF maxVAF >0.5 (n=15) had significantly shorter iPFS (6.2 vs. 12.1 months; HR = 2.48, 95% CI, 1.18-5.23; P = 0.024) and OS (10.5 vs. 19.8 months; HR = 3.12, 95% CI, 1.32-7.35; P = 0.0039) compared with those whose maxVAF was ≤0.5 (n=22).

Figure3. Kaplan-Meier curves of OS and iPFS stratified by baseline CSF maxVAF



- For each patient, we calculated the mean value of CSF maxVAF across post-baseline time points, defined as the "dynamic mean maxVAF."
- Patients with a mean maxVAF >0.5 (n=11) experienced significantly inferior iPFS (median, 5.8 vs. 13.3 months; HR = 3.05, 95% CI, 1.34-6.94; P = 0.0057) and OS (median, 9.1 vs. 20.4 months; HR = 2.61, 95% CI, 1.01-6.74; P = 0.04) compared with those whose mean maxVAF was ≤0.5 (n=18).

Figure4. Kaplan-Meier curves of OS and iPFS stratified by dynamic mean maxVAF



Safety

- The most common TRAEs were hematologic, followed by gastrointestinal toxicities.
- Non-hematologic events such as fatigue, rash, and diarrhea were also frequently reported.
- Grade 3-4 TRAEs occurred in 12 patients (30.0%). No treatment-related deaths were observed.

Table2. Treatment-related adverse events

TRAEs	All Grade n(%)	Grade 1-2 n(%)	Grade 3-4 n(%)
Myelosuppression	15(37.5)	9(22.5)	6(15.0)
Nausea	9(22.5)	8(20.0)	1(2.5)
Vomiting	8(20.0)	7(17.5)	1(2.5)
Fatigue	8(20.0)	8(20.0)	0
Rash	7(17.5)	7(17.5)	0
Diarrhea	6(15.0)	5(12.5)	1(2.5)
Hepatic Impairment	5(12.5)	3(7.5)	2(5.0)
Paronychia	3(7.5)	3(7.5)	0
Chemical Meningitis	1(2.5)	0	1(2.5)
Epilepsy	1(2.5)	0	1(2.5)
CNS Infection	1(2.5)	0	1(2.5)
Acid Reflux	1(2.5)	1(2.5)	0
Elevated Creatinine	1(2.5)	1(2.5)	0

CONCLUSIONS

- The combination of high-dose furmonertinib and intraventricular pemetrexed demonstrates promising efficacy and a manageable safety profile as a salvage regimen for patients with EGFR-mutant NSCLC and LM after failure of third-generation EGFR TKIs.
- CSF ctDNA analysis serves as a highly sensitive tool for disease monitoring and prognosis. These findings support further evaluation in larger, prospective studies.