Efficacy and Safety of High Dose Furmonertinib in Patients with *EGFR*-mutated Non-small Cell Lung Cancer and Leptomeningeal Metastases Site-specific Progressed on Osimertinib

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Background

- Leptomeningeal metastasis (LM) occurs in approximately 3%-4% of patients with advanced non–small-cell lung cancer (NSCLC). The incidence of LM rises to approximately 9% in epidermal growth factor receptor (*EGFR*)-mutated NSCLC[1].
- We observed that LM could occur in patients resistant to *EGFR*-TKIs, especially resistant to osimertinib, while these patients lacked of efficient therapy.
- Furmonertinib 160mg has been demonstrated encouraging efficacy in patients with *EGFR*-mutated advanced NSCLC and central nervous system (CNS) metastases[2-4].
- Here we reported the efficacy of high dose furmonertinib in patients with *EGFR*-mutated NSCLC and leptomeningeal metastases (LMs) mostly site-specific progressed on osimertinib.

Methods

- This retrospective single-arm study analysed the efficacy and safety of high dose furmonertinib in patients with *EGFR*-mutated NSCLC and LMs mostly site-specific progressed on osimertinib at Beijing Tiantan Hospital, Capital Medical University between Jun 2021 and Aug 2023.
- All patients received furmonertinib 160mg or 240mg orally once daily until disease progression or intolerable toxicity. All patients had received ≥1 intrathecal injection.
- All patients had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- The clinical efficacy for this analysis included LM response assessment according to RANO-LM (including assessments of neurological examination, presence or absence of CSF circulating tumor cells, and neuraxis imaging)[5], CNS PFS, PFS and OS according to RECIST v1.1.
- Additional efficacy evaluations included the changes of CSF cytology/protein/CEA level, neurological examination, and ECOG PS score from baseline.

Results

Patients

- From Jun 2021 to Aug 2023, a total of 23 patients received furmonertinib 160mg or 240mg orally once daily, defined as full analysis set (FAS), 19 patients completed ≥2 CSF cytology assessments, defined as evaluable for response set (EFR).
- The baseline characteristics (Table 1) included, the median age was 63 years (range: 41-78), female 69.6%, ECOG PS≥2 65.2%, 82.6% patients received prior osimertinib treatment , 95.7% patients were adenocarcinoma, 95.7% patients received furmonertinib 160mg.

Table 1. Baseline characteristics of patients

Characteristics Data were n (%) or median (range)		FAS n=23
Age	Median	63 (41-78)
Sex	Female Male	16 (69.6) 7 (30.4)
Smoking history	Yes No	4 (17.4) 19 (82.6)
ECOG PS	0 1 2 3	0 (0) 8 (34.8) 6 (26.1) 9 (39.1)
EGFR status in CSF prior to furmonertinib	Ex19del L858R T790M C797S *EGFR* uncommon mutations Unknown	4 (17.4) 11 (47.8) 2 (8.7) 1 (4.3) 7 (30.4) 4 (17.4)
Previous lines of systemic therapy	1 2-3 > 3 Unknown	4 (17.4) 10 (43.5) 7 (30.4) 2 (8.7)
Prior osimertinib treatment	Yes No	19 (82.6) 4 (17.4)
Dose of furmonertinib	160mg 240mg	22 (95.7) 1 (4.3)

Efficacy

LM Response

- At data cut-off, median follow-up was 286 days, 10 (43.5%) of 23 patients had progressed or died.
- In EFR (n=19), 6 (31.6%) patients were achieved response, CSF tumor cells clearance rate was 31.6%,13 (68.4%) patients kept stable diseases, and no patient was defined as disease progression according to RANO-LM.

PFS and OS

- The median PFS was 10.8 months, and the median CNS PFS was not reached (Figure 1), the median OS was not reached (Figure 2).

Figure 1. Kaplan-Meier curve of PFS and CNS PFS in the FAS assessed by investigator

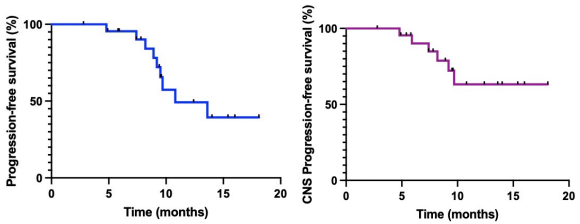
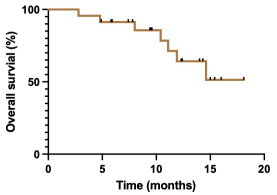


Figure 2. Kaplan-Meier curve of OS in the FAS assessed by investigator



CSF Cytology, Protein, and CEA level

- The CSF tumors cells decreased from baseline was observed in 14 (73.7%) of 19 patients.
- The CSF protein content decreased from baseline was observed in 17 (85.0%) of 20 patients.
- The CSF CEA level decreased from baseline was observed in 15 (88.2%) of 17 patients.

Neurological Examination

- Neurologic function was improved in 18 (90.0%) of 20 patients with an abnormal neurologic assessment at baseline.

ECOG PS

- ECOG PS score was decreased in 9 (39.1%) of 23 patients. Among 8 patients with ECOG PS 1, the score of 2 (25%) patients decreased to 0. Among 15 patients with ECOG PS 2-3, the score of 7 (46.7%) patients decreased to 1.

Safety

- 18 of 23 (78%) patients experienced treatment related adverse events (TRAEs) of any grade. The most common TRAEs were diarrhoea (5/23, 22%) and elevated aspartate aminotransferase/alanine aminotransferase(5/23, 22%). No grade ≥3 TRAE was observed.
- Dose reductions were reported in 2 (8.7%) patients, not caused by TRAEs. There was no incidence of dose interruption, treatment discontinuation or deaths due to TRAEs (Table 2).

Table 2. Overview of TRAEs

Adverse Event	n (%)
TRAE	18 (78)
Grade ≥3 TRAE	0 (0)
Dose interruption	0 (0)
Dose reduction	2 (8.7)
Discontinuation	0 (0)

Conclusions

- High dose furmonertinib showed encouraging efficacy in patients with EGFR-mutated advanced NSCLC and LMs site-specific progressed on osimertinib. Patients were well tolerated and the AEs were consistent with previous studies.

References

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