Furmonertinib Plus Icotinib for First-Line Treatment of EGFR-mutated Non-Small Cell Lung Cancer

Hualin Chen*, Muwen Lin, Junhong Jiang, Meilian Liu, Shujun Li, Zhennan Lai, Yiping Luo, Haiyin Ye, Huoguang Chen, Zhixiong Yang

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Background

- Furmonertinib (AST2818) is a highly brain-penetrant, pan epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with activity against EGFR classical, T790M resistance and Ex20ins mutations[1].
- In the phase III FURLONG study (NCT03787992), the progression-free survival (PFS) was significantly longer with furmonertinib compared with that of gefitinib (20.8 vs 11.1 months, hazard ratio [HR] 0.44 [95%CI 0.34-0.58], p<0.0001) in EGFR mutation-positive non-small-cell lung cancer (NSCLC)[2].
- In the phase IIb study (NCT03452592), acquired EGFR C797X mutation was the most common EGFR-dependent resistance mechanism to furmonertinib treatment[3].
- Icotinib is a first-generation EGFR TKI widely used in China and may overcome the resistance of furmonertinib due to EGFR C797S mutation.
- Evidence suggested that dual (first-generation plus third–generation) EGFR inhibition may delay emergence of acquired resistance, including T790M and C797S[4].
- Furmonertinib plus icotinib may delay emergence of acquired resistance to furmonertinib in first-line setting.

Methods

- This is an ongoing single-arm, open-label, phase II study conducted at the Affiliated Hospital of Guangdong Medical University in mainland China.
- Key inclusion criteria were age ≥18 years, histologically or cytologically confirmed locally advanced or metastatic NSCLC, EGFR Ex19del or L858R or Ex20ins mutation positive, with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients with asymptomatic, stable CNS metastases not requiring steroids for at least four weeks before the first dose of furmonertinib were allowed to be included.
- Eligible patients received furmonertinib (80mg p.o, qd) and icotinib (125mg p.o, tid) until disease progression or intolerable toxicity.
- The primary endpoint was progression free survival (PFS) assessed by investigator. Secondary endpoints included, objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results

Patients

- A total of 40 patients were planned to be enrolled in this study. As of Nov 30 2022, 18 patients were enrolled and received study treatment.
- Baseline characteristics of the enrolled patients are presented in Table 1.
- The baseline characteristics included median age 61.5-years (range: 43-82 years), female 55.6%, ECOG PS 0/1/2 0%/88.9%/11.1%, Ex19Del/L858R/Ex20ins 55.6%/38.9%/5.6%, CNS metastases 83.3%.

Table 1. Baseline characteristics of patients

Characteristics Data were n (%) or median (range)		n=18
Age	Median	61.5 (43-82)
Sex	Female Male	10 (55.6) 8 (44.4)
Smoking history	Yes No	5 (27.8) 13 (72.2)
ECOG PS	0 1 2	0 (0) 16 (88.9) 2 (11.1)
EGFR mutation	Ex19Del L858R Ex20ins	10 (55.6) 7 (38.9) 1（5.6）
CNS metastases*	Yes No	15 (83.3) 3 (16.7)
Disease stage	III IV	1 (5.6) 17 (94.4)

*CNS metastases were identified from baseline data for the CNS lesion site and medical history, including previous surgery and radiotherapy for CNS lesions, all of which were reported by investigators.

Efficacy

- At the data cutoff (DCO, Nov 30 2022), median follow-up was 230 days and the median PFS was not yet reached.
- With a high proportion of CNS metastases patients (15/18, 83.3%), the confirmed ORR assessed by investigator based on RECIST 1.1 was 88.9% (16 PR), DCR was 100% (16 PR, 2 SD) (Table 2).
- In 15 patients with CNS metastases, the ORR was 86.7%, and the DCR was 100% (Table 3).
- Tumor shrinkage was observed in all patients, with a median best percent change of -34.3% (range: -76.1, -27.1) (Figure 1).

Safety

- 18 of 18 (100%) patients experienced treatment emergent adverse event (TEAE) of any grade, irrespective of attribution (Table 4).
- TEAEs (≥20%) included diarrhea (5, 27.8%), elevated aspartate aminotransferase (5, 27.8%), elevated alanine aminotransferase (4, 22.2%), and rash (4, 22.2%).
- One patient experienced a grade 3 diarrhea resulting in treatment interruption for seven days, after which administration of 80 mg was resumed.
- No other grade ≥3 TEAE was observed.
- There was no incidence of dose reduction or treatment discontinuation due to TEAEs.

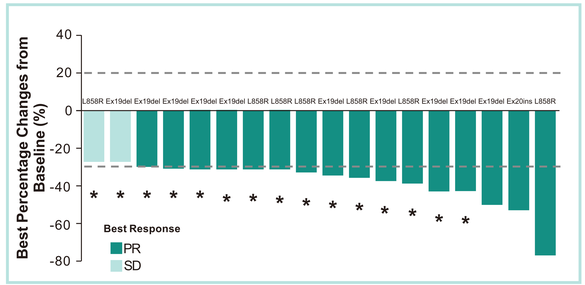
Table 2. Tumor response assessed by investigator

Response, n (%)	n=18
Complete response (CR)	0 (0)
Partial response (PR)	16 (88.9)
Stable disease (SD)	2 (11.1)
Disease progression (PD)	0 (0)
Confirmed objective response (ORR)	16 (88.9)
Disease control (DCR)	18 (100)

Table 3. Tumor response in patients with CNS metastases assessed by investigator

Response, n (%)	n=15
ORR	13(86.7)
DCR	15(100)

Figure 1. Waterfall plot for best percentage change in target lesion size (investigator assessment)



*CNS metastases were identified from baseline data for the CNS lesion site and medical history, including previous surgery and radiotherapy for CNS lesions, all of which were reported by investigators.

Table 4. Overview of TEAEs

Adverse Event	n (%)
TEAE	18 (100)
Grade ≥3 TEAE	1 (5.6)
SAE	0 (0)
Dose interruption	1 (5.6)
Dose reduction	0 (0)
Discontinuation	0 (0)
TEAE (≥20%)	**n (%)**
Diarrhea	5 (27.8)
Elevated aspartate aminotransferase	5 (27.8)
Elevated alanine aminotransferase	4 (22.2)
Rash	4 (22.2)

Conclusions

- In EGFR-mutated NSCLC patients with a high proportion of CNS metastases, furmonertinib plus icotinib as first-line treatment showed encouraging anti-tumor activity.
- This combination therapy was well tolerated in EGFR-mutated NSCLC. The observed adverse events were consistent with previous report.
- This study is ongoing and more results will be evaluated in the future, which may help elucidate a role of dual EGFR TKI therapy in first-line setting.

References

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Affiliated Hospital of Guangdong Medical University, Zhanjiang/CN

*Corresponding to: Hualin Chen, MD. E-mail: warren2008@163.com