Preclinical and Preliminary Clinical Investigations of Furmonertinib in NSCLC with EGFR exon 20 insertions (20ins)

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Abstract 1325

BACKGROUND

- Currently neither chemotherapy nor any of the approved epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have satisfactory efficacy in EGFR 20ins NSCLC.[1,2]
- Activity of furmonertinib, a novel 3rd generation EGFR TKI, against EGFR 20ins and tolerability were assessed in preclinical models and a phase Ib proof of concept study.

METHODS

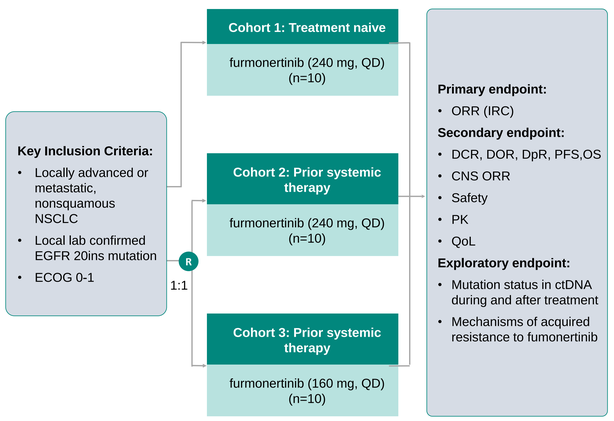
Preclinical Study:

- The preclinical activity of furmonertinib were evaluated in in vitro and in vivo.
- in vitro activity was assessed in A431-EGFR WT and Ba/F3-EGFR 20ins cell lines。
  in vivo activity was assessed in subcutaneous LU0387 lung cancer patient-derived xenograft (PDX) model harboring EGFR 20ins (p.N771_H773dup).

Clinical Study:

- Study type: Phase Ib clinical trial (FAVOUR , NCT04858958)
- Participants: 30 patients with advanced NSCLC with EGFR 20ins were planned to be enrolled.
- Treatment cohorts: Cohort 1(10 patients): treatment-naïve, furmonertinib 240mg qd; cohort 2 and 3: previously treated, 240mg qd and 160mg qd, respectively (Figure 1).
- Here, we present data of Cohort 1.

Figure 1: FAVOUR 1 Study Design



RESULTS

Preclinical Investigation

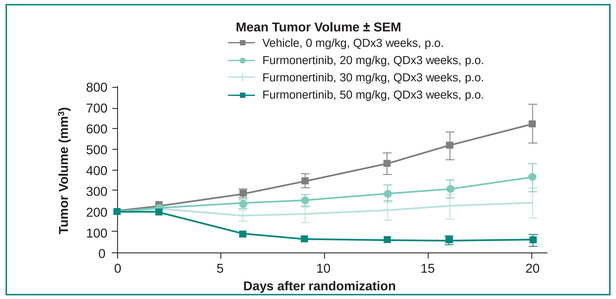
- Furmonertinib effectively inhibited growth of Ba/F3 cells expressing EGFR 20ins with mean half inhibitory concentration (IC50) of 11~20 nM (Table 1).

Table 1: *In Vitro* Cell Activity: IC50 in Cellular Assay

Cellular assay	IC50 (nM)
A431-EGFR WT	109.9
Ba/F3-EGFR 20ins p.S768_D770dup	11
Ba/F3-EGFR 20ins p.A767_V769dup	14
Ba/F3-EGFR 20ins p.N771_H773dup	20

- At 50 mg/kg, furmonertinib as a single agent showed good efficacy and was tolerated in patient derived xenograft models harboring EGFR 20ins.
- A tumor growth inhibition of 132.85% was observed which was statistically significant in comparison to vehicle control group (*P*<0.001) (Figure 2).

Figure 2: *In Vivo* Efficacy: Tumor Growth Curves



Clinical Investigation

Patients

- Ten EGFR 20ins advanced NSCLC patients were enrolled in cohort 1 from Nov 30th 2020 to Mar 3rd 2021.
- Furmonertinib was administered at 240mg qd.
- Demographics and baseline characteristics information are given in Table 2.

Table 2: Patient Demographics and Baseline Characteristics

Characteristic	N=10
Median age, years (range)	68 (47–69)
Male / Female	3 (30.0%) / 7 (70.0%)
Smoker / Non-smoker	0 / 10 (100.0%)
ECOG 0/1	3 (30.0%) / 7 (70.0%)
Disease stage IVA/IVB	7 (70.0%) / 3 (30.0%)
History of brain metastases	1 (10.0%)

Effectiveness

- At data cut-off date (4 June 2021), confirmed objective response rate (ORR) by independent review committee (IRC) (primary endpoint) was 60.0% and by investigator assessment was 70.0% (Table 3).
- The best response was partial response (PR) in 6 patients and stable disease (SD) in 4 patients according to IRC assessment. (Table 3).

Table 3: Tumor Response

	N=10	
	IRC	Investigator
Best response, n (%)		
CR	0	0
PR	6 (60.0)	7 (70.0)
SD	4 (40.0)	3 (30.0)
PD	0	0
ORR, % (95% CI)	60.0 (26.2, 87.8)	70.0 (34.8, 93.3)
DCR, % (95% CI)	100.0 (69.2, 100.0)	100 (69.2, 100.0)

Notes:
ORR: The percentage of subjects with the best response of CR or PR in the post-treatment tumor radiological evaluation will be statistically described.
DCR: The percentage of subjects with response (PR+CR) and SD (duration of SD needs to be ≥ 6 weeks) will be calculated using the same method described for ORR.

- All patients showed tumor shrinkage in target lesions with a median best percent change of – 51.8% (range – 58.2%, -24.7%) (Figure 3).
- Median duration of exposure was 4.1 months (range 2.7, 5.6) and all the patients remained on treatment (Figure 4).

Figure 3: Waterfall Plot for Best Percentage Change in Target Lesion Size (IRC assessment)

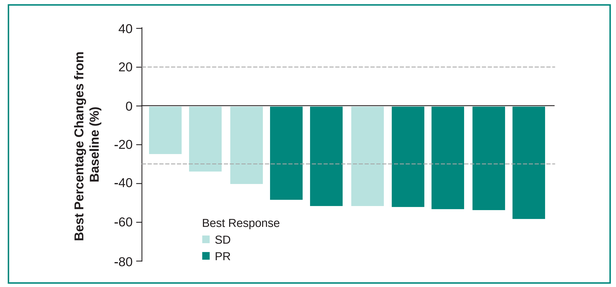
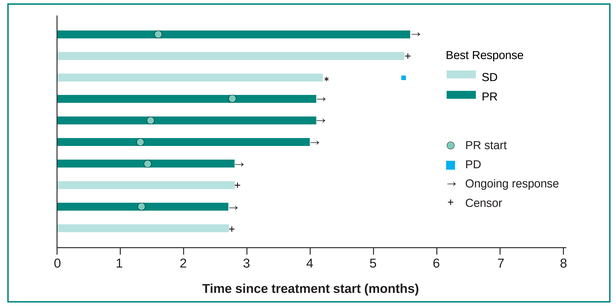


Figure 4: Swimlane Plot for Duration of Treatment Exposure and Best Response (IRC assessment)



Notes: length of each bar represent the duration from first dose to last dose recorded in EDC by DCO.
* The gap is due to the dose record for the last visit was submitted on 7th Jun after the DCO.

Safety

- 9 of 10 (90%) patients experienced treatment emergent adverse event (TEAE) of any grade, irrespective of attribution (Table 4); AEs were manageable and reversible.
- One patient experienced a serious adverse event (SAE) due to diarrhea resulting in dose interruption. Duration of dose interruption was 6 days, and administration with 240mg was resumed afterwards.
- No grade ≥3 TEAE was observed.
- There were no incidence of dose reduction or treatment discontinuation due to AEs.

Table 4: Safety Profile

Adverse Event	n (%)
TEAE	9 (90.0)
Treatment-related AE, TRAE	8 (80.0)
Grade ≥3 TEAE	0
SAE	1 (10.0)
Dose interruption	1 (10.0)
Dose reduction	0
Dose discontinuation	0
TEAE (≥20% of Patients)	
Diarrhea	4 (40.0)
Paronychia	3 (30.0)
Skin fissures	3 (30.0)
Rash	3 (30.0)
Mouth ulceration	3 (30.0)
Stomatitis	2 (20.0)
Anorexia	2 (20.0)
Upper respiratory tract infection	2 (20.0)
Creatinine renal clearance decreased	2 (20.0)
Pain in extremity	2 (20.0)
Blood creatine phosphokinase increased	2 (20.0)
Electrocardiogram QT prolonged	2 (20.0)
Bradycardia	2 (20.0)
Face oedema	2 (20.0)

CONCLUSION

- The preclinical data and preliminary results of the phase Ib study reveals that furmonertinib has encouraging antitumor activity in treatment-naïve NSCLC patients with EGFR Exon 20 insertion mutations and is well tolerated.
- Further exploration of Cohorts 2 and 3 is ongoing.

DISCLOSURES
Qing Li, Fei Liu and Chen Shen are employees of Shanghai Allist Pharmaceuticals Co., Ltd.
All other authors declare no competing interests.

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