

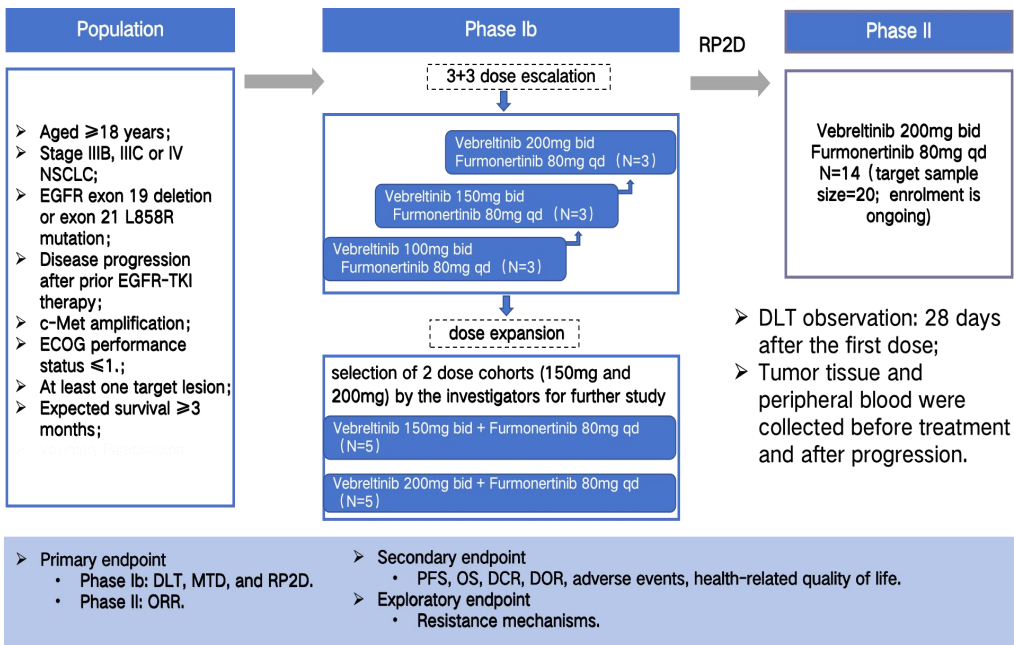
Background

- MET amplification commonly mediates resistance to EGFR TKIs in non-small-cell lung cancer (NSCLC) patients with EGFR-mutation. Several clinical trials showed that the combination of MET inhibition with EGFR-TKI was a promising therapeutic strategy to overcome the MET amplification-mediated resistance.
- Vebreltinib is a potent and selective MET inhibitor with preclinical activity.
- This phase Ib/II study investigated the safety and efficacy of Vebreltinib plus Furmonertinib in patients with EGFR-mutated, MET-amplification NSCLC who experienced disease progression after EGFR-TKI treatment.

Methods

- Patients in the phase Ib cohort received Vebreltinib capsules at 100 mg, 150 mg, or 200 mg twice daily, combined with furmonertinib 80 mg once daily. Participants in the phase II cohort were treated at the recommended phase II dose (RP2D). The primary endpoints of this phase I study were assessment of doselimiting toxicities (DLTs), determination of the maximum tolerated dose (MTD), and identification of RP2D. For the phase II study, the primary endpoint was the overall response rate (ORR) evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Detailed findings are illustrated in Figure 1.

Figure 1: Study design



Result

- Nine patients were enrolled in the dose-escalation phase of the phase Ib study, with 3 patients treated at each of the 3 dose levels (100 mg, 150 mg, and 200 mg twice daily). The 150 mg and 200 mg twice daily dose levels were selected for dose expansion, with 5 patients enrolled in each expansion cohort.
- No DLTs were observed in either the dose-escalation or dose-expansion phase.
- Following comprehensive integrated evaluation of efficacy and safety data, the RP2D was established as vebretinib 200 mg twice daily in combination with firmonertinib 80 mg once daily. Enrollment in the phase II study is currently ongoing.

Table 1: Patient characteristics

Baseline Characteristics		Total (N=33)
Age, Median (Range)	Years	62(37–84)
Gender, N(%)	Male	10(30.3)
	Female	23(69.7)
Smoking history, N(%)	Yes	7(21.2)
	No	26(78.8)
Brain Metastases, N(%)	Yes	11(33.3)
	No	22(66.7)
Pathology, N(%)	Adenocacinoma	33(100.0)
EGFR mutation, N(%)	21L858R	19(57.6)
	19del	14(42.4)
MET amplification by NGS, N(%)	Not tested	2(6.1)
	Tested	31(93.9)
	GCN<2.3	1(3.0)
	2.3≤GCN<5	12(36.4)
	GCN≥5	18(54.5)
MET amplification by FISH, N(%)	Not tested	28(84.8)
	Tested	5(15.2)
	Positive	5(15.2)
	Negative	0
	Prior treatment before enrolment, N(%)	EGFR-TKI
	Cytotoxic chemotherapy	11(33.3)
	Bevacizumab or anlotinib	7(21.2)
	ICIs	1(3.0)

EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; FISH, fluorescence insitu hybridization; GCN, gene copy number; TKI, tyrosine kinase inhibitor; ICIs, Immune checkpoint inhibitors.

Acknowledgement

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Disclosure

All authors have declared no conflicts of interest.

Figure 2. Antitumor activity, ORR, PFS outcomes

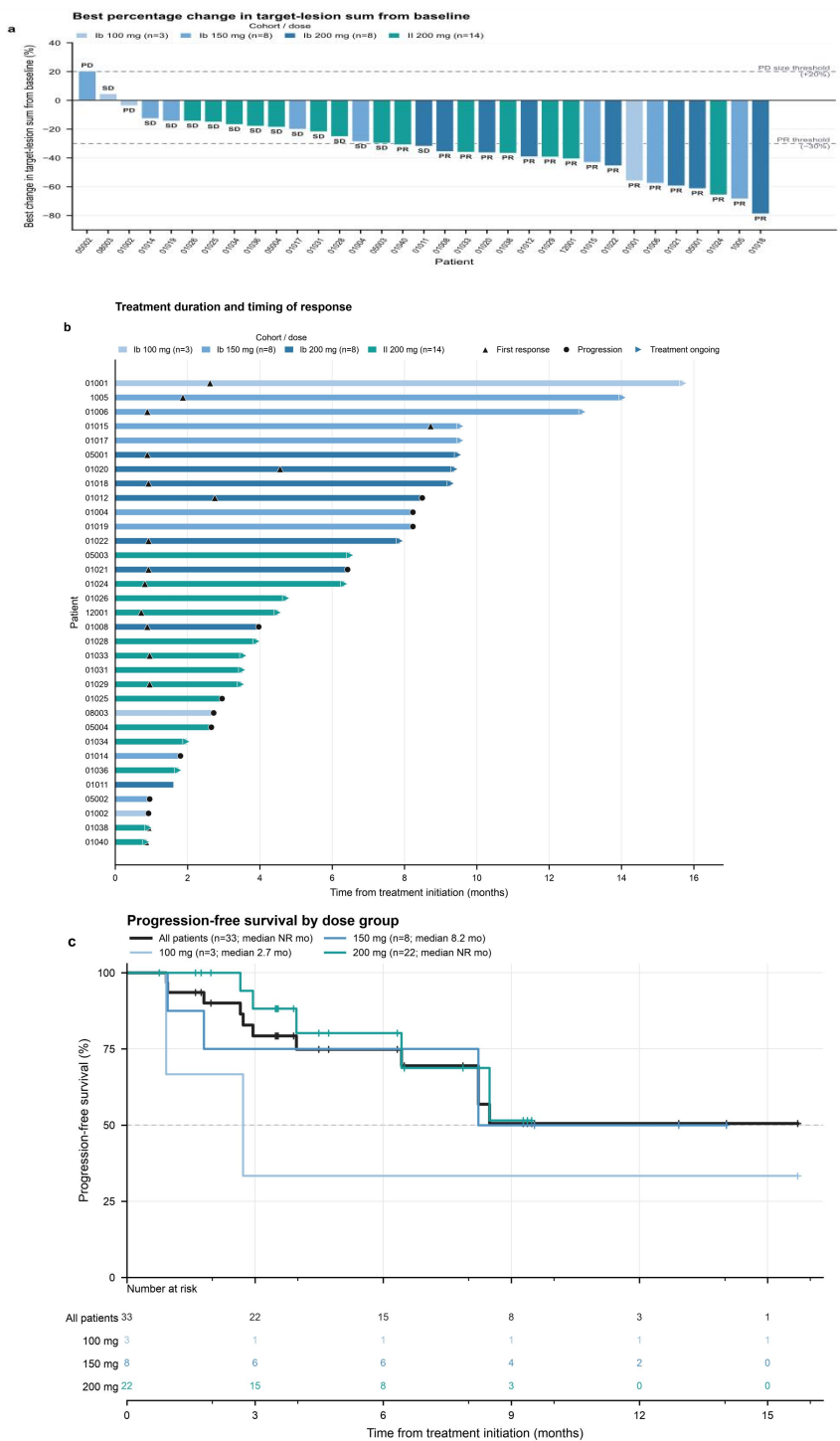


Table 2: Efficacy of each dose level

Efficacy	Vebreltinib 100mg bid + Furmonertinib 80mg qd (Phase Ib) N=3	Vebreltinib 150mg bid + Furmonertinib 80mg qd (Phase Ib) N=8	Vebreltinib 200mg bid + Furmonertinib 80mg qd (Phase Ib) N=8	RP2D total (Vebreltinib 200mg bid + Furmonertinib 80mg qd) (Phase Ib + II) N=22	All dose level total N=33
Best overall response, N(%)					
CR	0	0	0	0	0
PR	1(33.3)	3(37.5)	7(87.5)	13(59.1)	17(51.5)
SD	1(33.3)	4(50.0)	1(12.5)	9(40.9)	14(42.4)
PD	1(33.3)	1(12.5)	0	0	2(6.1)
ORR, N(%)	1(33.3)	3(37.5)	7(87.5)	13(59.1)	17(51.5)
DCR, N(%)	2(66.7)	7(87.5)	8(100.0)	22(100.0)	31(93.9)
Median PFS, months	2.7	8.2	not reached	not reached	not reached

Table 3: Safety summary

AE, N(%)	All grades, N(%)	Grades ≥3, N(%)
TEAE	30(90.9)	8(24.2)
TRAЕ	30(90.9)	1(3.0)
SAE	5(15.2)	5(15.2)
Treatment-related SAE	0	0
TEAE leading to death	1(3.0)	1(3.0)
TRAЕ leading to death	0	0
TRAЕ occurring in ≥15% of patients		
Edema peripheral	23(69.7)	0
White blood cell decreased	9(27.3)	0
Anemia	8(24.2)	0
Hyperbilirubinemia	7(21.2)	0
Hypoalbuminemia	7(21.2)	0
Fatigue	6(18.2)	0
Rash	6(18.2)	0

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; SAE, serious adverse event.

Conclusions

- This study demonstrates that the combination of vebreltinib and firmonertinib represents a promising therapeutic strategy for patients with EGFR-mutant, c-Met-amplified NSCLC who have progressed after EGFR-TKI failure. The safety profile of this combination regimen was acceptable and manageable.