EMB-01, an EGFR-cMET bispecific Antibody, in advanced/metastatic solid tumors Phase I results

Poster No. 22P

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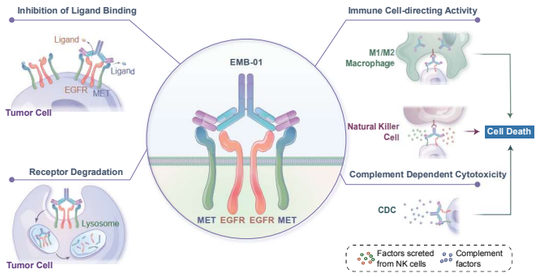
Introduction

- Tyrosine kinase inhibitors (TKIs) confer clinical benefit on EGFR mutant non-small cell lung cancer (NSCLC), but patients eventually develop progressive disease, and acquired resistance is observed[1].
- The mechanisms of acquired resistance include a variety of mutations of the EGFR and cross talk with the adjacent cMET receptors that allow the tumor to partially compensate the EGFR activity.
- EMB-01, a novel bispecific antibody targeting both EGFR and cMET with fully human framework sequences and a wild-type human IgG1 Fc, demonstrates potential antitumor activity through multiple mechanisms including inhibition of ligand binding, receptor co-degradation, immune cell-directing activity, and complement dependent cytotoxicity[2] (Figure 1).
- Here we report Phase I results on the safety, pharmacokinetics (PK) and preliminary efficacy from the ongoing multicenter, first-in-human (FIH), Phase I/II trial of EMB-01 (NCT03797391).

Figure 1 EMB-01 Mode of Action



Methods

Study Population

- Patients aged ≥ 18 years with measurable disease according to Response Criteria in Solid Tumors (RECIST) v1.1.
- For phase I, unselected (i.e. EGFR mutations or other gene aberrations unknown or unconfirmed) advanced/metastatic solid tumors including NSCLC refractory to standard therapy or no standard therapy is available or accessible, Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
- For phase II, advanced/metastatic NSCLC with EGFR and/or cMET aberrations confirmed and progressed on standard treatment or are intolerant to standard treatment, ECOG ≤2 (Data not presented in this poster).

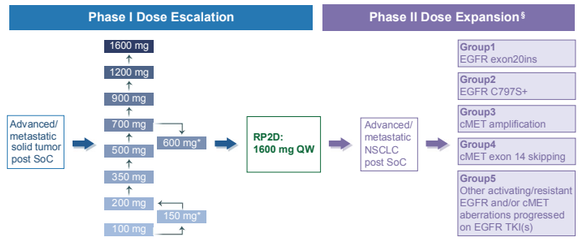
Study Design

- This FIH, open-label, multicenter, Phase I/II study is being conducted in US and China (Figure 2).
- Phase I follows the standard '3+3' design. Dose-limiting toxicities (DLTs) are evaluated during the first cycle (28 days).
- EMB-01 is administered intravenously (iv) once weekly (QW), with 28 days in each cycle.
- The primary objectives of Phase I (dose escalation) are to evaluate the safety and determine maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of EMB-01; the primary objectives of Phase II (dose expansion) are to evaluate preliminary antitumor activities and to further evaluate the safety of EMB-01 in advanced/metastatic NSCLC at RP2D.

Study Assessments

- Tumor assessments are performed at baseline and every 2 cycles for the first 12 cycles, then every 3 cycles thereafter, and assessed according to RECIST v1.1.
- Adverse Events (AEs) are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- Intensive PK samples and multiple anti-drug antibody (ADA) samples are collected for PK and immunogenicity analyses.

Figure 2 Study design



PR2D=Recommended Phase 2 Dose; SoC=Standard of Care; TKI=Tyrosine kinase inhibitor. QW=Once Weekly. EMB-01 is given intravenously once weekly. *Intermediate dose levels. §Ongoing, data not presented.

Results

Results were from Phase I only.

Patients

- As of 20 August 2021, 60 patients (48 NSCLC, 12 other solid tumors) had received at least one dose of EMB-01 in 10 dose levels (Figure 2).
- Patient demographics and disease characteristics were summarized in Table 1.
- 5 (8.3%) patients still remained on treatment, 55 (91.7%) had discontinued from study treatment due to the following: progressive disease 28 (46.7%), withdrawal by participant 12 (20.0%), AE 10 (16.7%), or investigator's discretion 5 (8.3%). For patients who discontinued due to AE, only three of them were due to treatment-related AEs.
- In patients with NSCLC, the median duration of exposure was 7.79 (ranges 1 to 73) weeks.

Table 1 Patient Demographics and Baseline Characteristics

Demographics	Total (N=60), n (%)
Age, years, median (range)	61 (34-73)
Sex, n (%)	
Male	31 (51.7)
Female	29 (48.3)
Race, n (%)	
Asian	36 (60.0)
White	22 (36.7)
Black or African American	2 (3.3)
Baseline ECOG, n (%)	
0	6 (10.0)
1	54 (90.0)
Indication, n (%)	
NSCLC	48 (80.0)
Other	12 (20.0)
Median prior lines of therapy	
All indications	3 (0-11)
NSCLC only	3 (1-11)
Tumor subtype (NSCLC only)	
Adenocarcinoma	47 (97.9)
Squamous cell carcinoma	1 (2.1)
Smoking history (NSCLC only)	
Yes	17 (35.4)
No	31 (64.6)
CNS metastasis (NSCLC only)	
Yes	17 (35.4)
No	31 (64.6)

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; CNS=Central Nervous System

Safety

- 1 DLT (Grade 3 dermatitis acneiform) occurred at 700 mg QW. MTD was not reached.
- 59 (98.3%) experienced at least one AE, irrespective of grade or attribution, including 23 (38.3%) patients with Grade ≥ 3 events.
- 55 (91.7%) patients experienced treatment-related AEs (TRAEs) irrespective of grade. Most common TRAEs were rash, myalgia, nausea, paronychia, alanine aminotransferase (ALT) increased and blood creatine phosphokinase (CK)MB increased (Table 2).
- No infusion related reaction (IRR) event was reported; 1 patient (in 350 mg QW) experienced Grade 2 chill during the first dose, however, the full dose was administered after a short period of dose suspension.
- 10 (16.7%) patients experienced Grade≥3 TRAEs, most common were rash (8.3%), others including vomiting, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, diarrhea, malaise, anaemia, hepatic function abnormal, hypoatraemia (1 patient each).
- Serious AEs (SAE) were reported in 25 (41.7%) patients. Treatment-related SAEs were reported in 6 (10%) patients, including hepatic function abnormal, muscular weakness, decreased appetite, diarrhea, malaise, vomiting (1 patient each).
- TRAE leading to dose interruption/reduction and discontinuation occurred in 15 (25.0%) and 4 (6.7%) patients, respectively. Among patients with dose interruption/reduction, only 4 (6.7%) patients had dose reduction.
- AE leading to death occurred in 9 (15.0%) patients, none of them were considered treatment related.

Table 2 Most Common Treatment-Related Adverse Event of any Grade (≥20% in All Patients)

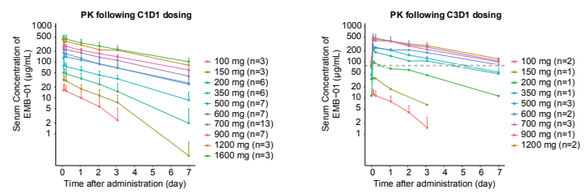
Preferred Term n (%)	100 mg QW	150 mg QW	200 mg QW	350 mg QW	500 mg QW	600 mg QW	700 mg QW	900 mg QW	1200 mg QW	1600 mg QW	Total
	N = 3	N = 3	N = 6	N = 6	N = 7	N=7	N = 13	N=7	N=5	N=3	N = 60
Any TRAE for all Grade	3 (100.0)	2 (66.7)	5 (83.3)	5 (83.3)	7 (100.0)	6 (85.7)	12 (92.3)	7 (100.0)	5 (100.0)	3 (100.0)	55 (91.7)
Any TRAE for Grade ≥3	0	0	1 (16.7)	1 (16.7)	1 (14.3)	0	5 (38.5)	2 (28.6)	0	0	10 (16.7)
Rash*	0	0	2 (33.3)	4 (66.7)	6 (85.7)	5 (71.4)	10 (76.9)	6 (85.7)	4 (80.0)	3 (100)	40 (66.7)
Myalgia	3 (100)	2 (66.7)	4 (66.7)	4 (66.7)	6 (85.7)	2 (28.6)	9 (69.2)	4 (57.1)	1 (20.0)	3 (100)	38 (63.3)
Nausea	1 (33.3)	0	1 (16.7)	1 (16.7)	1 (14.3)	3 (42.9)	5 (38.5)	3 (42.9)	0	2 (66.7)	17 (28.3)
Paronychia	0	0	0	1 (16.7)	3 (42.9)	2 (28.6)	4 (30.8)	2 (28.6)	1 (20.0)	2 (66.7)	15 (25.0)
ALT increased	0	0	0	0	2 (28.6)	2 (28.6)	3 (23.1)	2 (28.6)	2 (40.0)	1 (33.3)	12 (20.0)
CKMB increased	0	0	1 (16.7)	1 (16.7)	2 (28.6)	0	6 (46.2)	1 (14.3)	1 (20.0)	0	12 (20.0)

TRAE=Treatment-related Adverse Event; ALT=Alaine aminotransferase; CKMB=Creatine phosphokinase MB
*Rash includes dermatitis acneiform, rash, rash maculo-papuler, acne, skin exfoliation, rash generalised.

Pharmacokinetics and Immunogenicity

- The systemic exposure of EMB-01 (AUC) following C1D1 increased in a greater than dose proportional manner at <500 mg QW, and displayed approximately linear PK at ≥ 500 mg QW (Figure 3).
- The accumulation ratio derived from PK exposure metrics following C3D1 dosing compared with those following C1D1 dosing ranged from 1.3 to 2.3 for AUC, and 1.5 to 2.1 for C_{max} at ≥ 350 mg QW; average elimination $t_{1/2}$ is ~ 3 days at dose levels ≥ 500 mg QW.
- For immunogenicity, among 53 patients with both pre- and post-treatment ADA evaluation, 4 (7.5%) were positive for antibodies to EMB-01 with negative ADA at baseline. No correlation between dose and ADA incidence/titer is identified.

Figure 3 Pharmacokinetic profiles of EMB-01 following C1D1 and C3D1 dosing

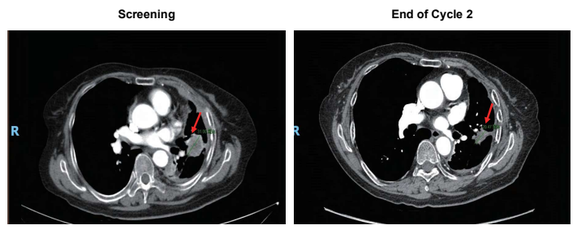


C1D1=Cycle 1 Day 1; C3D1=Cycle 3 Day 1; PK=Pharmacokinetics; Dashed line represents efficacious concentration established from the xenograft mouse model.

Preliminary Efficacy

- Among total 48 NSCLC with unconfirmed/unknown status of EGFR and/or cMET aberrations patients, 38 were response-evaluable with at least one post-treatment tumor assessment.
  - 2 partial response (PR) were observed per RECIST v1.1, including 1 confirmed PR. 2 PR patients included 1 with primary EGFR exon20ins disease based on local historical molecular data, and 1 disease progressed after a third-generation EGFR TKI (Figure 4).
  - 14 stable disease (SD) as the best response.
  - Disease control rate (DCR) was 42.1% among 38 response-evaluable patients.
- The longest duration of treatment was 73 weeks.

Figure 4 Preliminary Antitumor Activity in a 69-year old Asian Female whose disease progressed on 3rd generation EGFR TKI



Conclusions

- EMB-01 demonstrated a manageable safety profile consistent with EGFR and cMET inhibition.
- EMB-01 displayed linear PK at doses ≥500 mg QW, and the immunogenicity incidence and magnitude of EMB-01 seems low.
- Preliminary antitumor evidence suggests EMB-01 can have activity in EGFR driven NSCLC, including patients with acquired EGFR TKI resistance and EGFR Exon20ins mutations.
- 1600 mg QW was determined as the RP2D.
- The expansion phase (Phase II) is currently enrolling biomarker selected NSCLC patients with EGFR and/or cMET aberrations as identified by next-generation sequencing in circulating tumor DNA (ctDNA) and/or tumor tissue.

References

1. Lindeman NI et al. ***Arch Pathol Lab Med.*** 2013;8(7):823-859.
2. Fang R et al. ***American Association for Cancer Research 2020***; Abstract #4004.

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Conflicts of Interest

The study is funded by Shanghai EpimAb Biotherapeutics Co., Ltd. The first author declares honoraria from AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, and Sanofi, outside the submitted work.

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