First-In-Human Phase I Study of Givastomig, A Novel Claudin 18.2/4-1BB Bispecific Antibody in Advanced Solid Tumors

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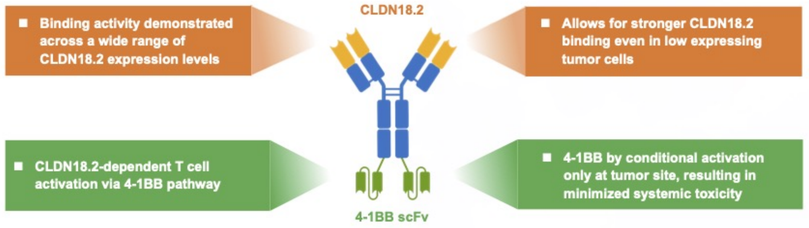
ESMO 2023
Poster #1039P

BACKGROUND

- Givastomig (TJ-CD4B/ABL111) is a first-in-class bispecific antibody targeting Claudin 18.2 (CLDN18.2) and 4-1BB with two key differentiations:
  - Binding to tumors with a wide range of CLDN18.2 expression levels, including lower expression which makes givastomig unique among the CLDN18.2-targeted agents whose anti-tumor activity is limited by higher CLDN18.2 expression in tumor.
  - Stimulating 4-1BB pathway upon local tumor engagement as a mechanism of conditional activation which makes givastomig a unique T cell activator only localized at the tumor site without systemic toxicities.

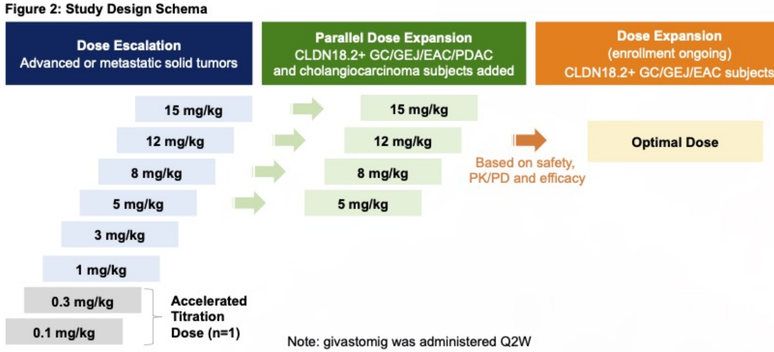
Figure 1: Molecular Design and Key Features of Givastomig



METHODS

- NCT04900818 is an open label, first-in-human, phase 1 study in patients with advanced solid tumors utilizing the Bayesian Optimal Interval (BOIN) design to evaluate the safety, tolerability, maximal tolerable dose (MTD), or maximum administered dose (MAD), pharmacokinetics (PK), pharmacodynamics (PD), recommended phase 2 dose (RP2D), and preliminary efficacy of givastomig as monotherapy.
- Dose escalation started at 0.1 mg/kg administered intravenously every 2 weeks (Q2W) and escalated up to 15 mg/kg over 8 different dose levels regardless of CLDN18.2 preselection. Dose levels 5, 8, 12, and 15 mg/kg were expanded to include an additional 6 patients per cohort with CLDN18.2-positive (CLDN18.2+) tumors, defined as membrane intensity score of ≥ 1+ on ≥1% of tumor cells, including relapsed, refractory gastric/gastro-esophageal junction adenocarcinoma (GC/GEJ), esophageal adenocarcinoma (EAC), pancreatic ductal adenocarcinoma (PDAC), or cholangiocarcinoma.
- An expansion cohort will enroll up to 30 patients with CLDN18.2 positive GC/GEJ/EAC.
- At designated time points, givastomig concentrations were measured by a validated ELISA method and soluble 4-1BB (s4-1BB) in serum was measured using an electrochemiluminescence immunoassay.
- Anti-tumor activity was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and iRECIST.
- Clinical data as of 01-AUG-2023 for patients enrolled to the dose escalation and parallel dose expansion are reported.

Figure 2: Study Design Schema



Note: givastomig was administered Q2W

RESULTS

Patient Demographics

- 55 patients with advanced relapsed/refractory solid tumors have been enrolled (32 in dose escalation and 23 in parallel dose expansion). CLDN18.2 expression were evaluable in 87.3% of patients and 65.5% of all enrolled patients were CLDN18.2 positive.
- Subjects enrolled had a median age of 66 years old, ECOG 0/1 (30.9%/69.1%), and 3 median prior lines of systemic therapy (range 1 -10).

Table 1: Baseline Characteristics

Variables	Statistics	0.1 mg/Kg (N=1) n (%)	0.3 mg/Kg (N=1) n (%)	1 mg/Kg (N=4) n (%)	3 mg/Kg (N=4) n (%)	5 mg/kg (N=12) n (%)	8 mg/kg (N=10) n (%)	12 mg/kg (N=12) n (%)	15 mg/kg (N=11) n (%)	Total (N=55) n (%)
Age	Median	68.0	66.0	44.0	63.5	67.5	61.5	68.0	67.0	66.0
	Min, Max	68, 68	66, 66	27, 70	43, 70	38, 82	36, 76	43, 76	43, 75	27, 82
Sex	Male	1 (100.0)	0	3 (75.0)	1 (25.0)	8 (66.7)	4 (40.0)	7 (58.3)	8 (72.7)	32 (58.2)
Race	Asian	0	0	1 (25.0)	0	3 (25.0)	5 (50.0)	2 (16.7)	4 (36.4)	15 (27.3)
	White	1 (100.0)	1 (100.0)	2 (50.0)	4 (100.0)	8 (66.7)	5 (50.0)	7 (58.3)	6 (54.5)	34 (61.8)
ECOG	1	1 (100.0)	1 (100.0)	2 (50.0)	3 (75.0)	7 (58.3)	6 (60.0)	10 (83.3)	8 (72.7)	38 (69.1)
CLDN18.2 expression	Positive	1 (100.0)	0	2 (50.0)	2 (50.0)	10 (83.3)	9 (90.0)	7 (58.3)	5 (45.5)	36 (65.5)
	Not Available	0	0	0	1 (25.0)	2 (16.7)	0	3 (25.0)	1 (9.1)	7 (12.7)
Prior lines of systemic therapy	Median	2.0	9.0	3.5	4.0	3.0	3.0	3.0	3.0	3.0
	Min, Max	2, 2	9, 9	2, 6	1, 7	1, 6	1, 8	2, 6	2, 10	1, 10
Prior PD-L1/PD-1	Yes	0	0	3 (75.0)	1 (25.0)	6 (50.0)	6 (60.0)	6 (50.0)	6 (54.5)	28 (50.9)

Safety

- No DLT was reported up to 15mg/kg, and MTD was not reached.
- The most commonly reported TRAEs (reported from >10% of subjects) were Grade 1 or 2 nausea (23.6%), vomiting (16.4%), fatigue (14.5%), and anemia (10.9%).
- 10 subjects (18.2%) experienced at least one Grade 3 TRAE. No Grade 3 TRAEs occurred in more than 1 subject.
- Event onset of gastrointestinal TRAEs were generally after 14 days of treatment and recovered within 1 week; none led to drug withdrawal.

Table 2: Treatment-related Adverse Events (TRAEs) Occurred in ≥5% (N=55)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Nausea	10 (18.2)	3 (5.5)	0	0	0	13 (23.6)
Vomiting	7 (12.7)	2 (3.6)	0	0	0	9 (16.4)
Fatigue	7 (12.7)	1 (1.8)	0	0	0	8 (14.5)
Anemia	1 (1.8)	4 (7.3)	1 (1.8)	0	0	6 (10.9)
Abdominal pain	2 (3.6)	1 (1.8)	0	0	0	3 (5.5)
Alanine aminotransferase increased	2 (3.6)	0	1 (1.8)	0	0	3 (5.5)
Diarrhea	3 (5.5)	0	0	0	0	3 (5.5)
Headache	1 (1.8)	2 (3.6)	0	0	0	3 (5.5)
Lymphocyte count decreased	1 (1.8)	1 (1.8)	1 (1.8)	0	0	3 (5.5)
Pruritus	2 (3.6)	0	1 (1.8)	0	0	3 (5.5)
Pyrexia	3 (5.5)	0	0	0	0	3 (5.5)
White blood cell count decreased	0	2 (3.6)	1 (1.8)	0	0	3 (5.5)

Pharmacokinetics and Pharmacodynamics

- Linear PK of givastomig were observed in all subjects with an apparent effective half-life of 5.5-6.7 days at ≥ 5 mg/kg Q2W.
- At ≥ 8 mg/kg Q2W, all individual C_{trough} after one cycle reached the target concentration (12 μg/mL), derived from non-clinical ex vivo co-culture and in vivo PK/PD study data.
- Sustained and dose-dependent increase in soluble 4-1BB is observed with the highest induction of biomarker in the peripheral blood seen at 8 mg/kg and 12 mg/kg.

Figure 3A: Mean Serum Concentration of Givastomig

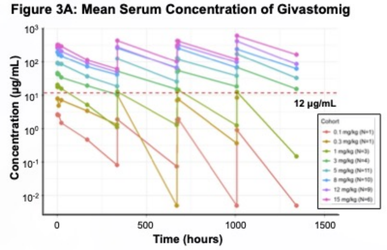
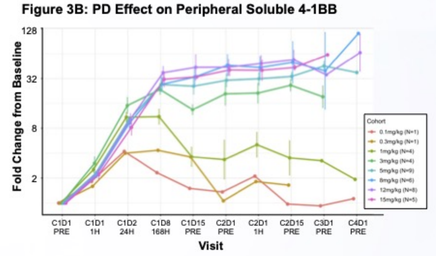


Figure 3B: PD Effect on Peripheral Soluble 4-1BB



Efficacy

- Total of 55 subjects enrolled: 21 GC (20 CLDN18.2+), 2 GEJ (2 CLDN18.2+), 5 EAC (4 CLDN18.2+), 14 PDAC (8 CLDN18.2+), and 13 other various types of cancers (2 CLDN18.2+).
- Of the 26 patients with GC/GEJ/EAC whose tumors were CLDN18.2+, 20 patients were efficacy evaluable and dosed at 5, 8, 12, and 15mg/kg. Partial response (PR) was observed in 3 out of 20 subjects that included 1 at 5mg/kg (CLDN18.2 IHC 1+, 10%; 2+, 1%), 1 at 8mg/kg (CLDN18.2 IHC 1+, 20%; 2+, 30%), and 1 at 12mg/kg (CLDN18.2 IHC 2+, 10%; 3+, 90%). All three PR occurred at the time of first tumor assessment (8 weeks). Two responding patients had received prior anti-PD-(L)1 therapy, both concluding approximately 4 months before starting givastomig (Figure 4A and 4B).
- Stable disease (SD) was also observed in 4 out of the 20 efficacy evaluable patients. One patient had a PR on the first scan and subsequently withdrew from the study, meeting criteria for SD.
- An additional PR was observed in one patient with head and neck squamous cell carcinoma receiving 12mg/kg, who remains on study at 280 days.

Figure 4A: Best Percentage Change in Target Lesions

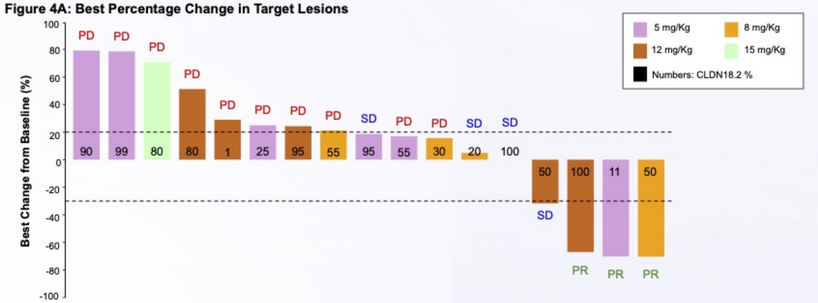


Figure 4B: Duration of Treatment

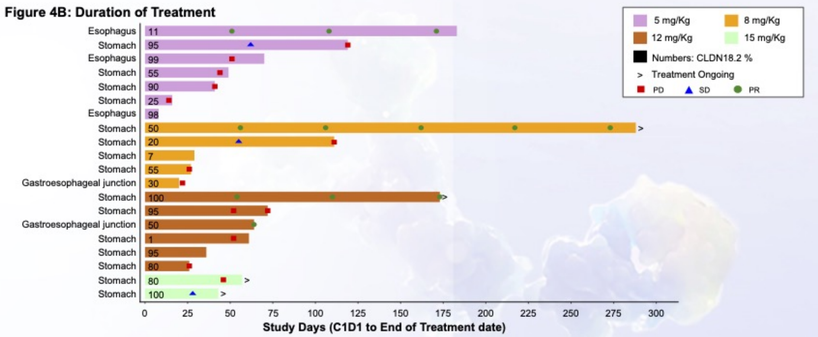
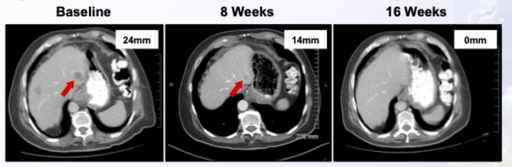


Figure 5: Partial Response in Patient with Metastatic Esophageal Adenocarcinoma



- **Treatment history:** 1L: FOLFOX + nivolumab; 2L: FOLFIRI + nivolumab; 3L: Paclitaxel + ramucirumab; *(last nivolumab dose administered 4 months prior to the study)*
- **Biomarker: Claudin18.2 expression:** 11%, (IHC 1+ 10%, IHC 2+ 1%); **PD-L1 CPS:** 5, HER2 IHC 0
- **Study treatment:** Givastomig 5 mg/kg Q2W
- **Duration of treatment:** 169 days

CONCLUSIONS

- **Givastomig monotherapy is safe and well tolerated up to 15 mg/kg Q2W in patients with advanced solid tumors. No DLT was observed and MTD was not reached.**
- **Encouraging monotherapy activity was observed in heavily pre-treated GC, GEJ, and EAC patients with a wide range of CLDN18.2 expression, including low CLND18.2 tumors.**
- **Linear PK profile and dose dependent s4-1BB induction without systemic changes in peripheral T cell activation or circulating cytokines, and objective responses were observed with givastomig at 5-12 mg/kg administered every 2 weeks, including those who failed prior PD-(L)1 therapy.**
- **Enrollment is ongoing in 15 mg/kg CLDN18.2-positive parallel dose expansion and 12 mg/kg dose expansion cohorts.**
- **Future development of givastomig in the treatment of third- and first-line GC, GEJ, and EAC patients is planned.**

Lead author disclosures: advisory/consulting from I-Mab Biopharma, Astellas, Carsgen, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Jazz, Merck, Oncolys, Pieris, Trimuvira, Zymeworks; ESMO travel, accommodations, and expenses from I-Mab.
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Study sponsored by: I-Mab Biopharma and ABL Bio
ClinialTrial.gov Identifier: NCT04900818
Acknowledgements:
I-Mab would like to thank all the patients, their families, and clinical sites for participating in this study.

Reference:
Gao J, et al. *Journal for ImmunoTherapy of Cancer* 2023;11:e006704.