1017P Updated Safety and Efficacy from the Phase I Study of Givastomig, a Novel Claudin 18.2/4-1BB Bispecific Antibody, in Claudin 18.2 Positive Advanced Gastroesophageal Carcinoma (GEC)

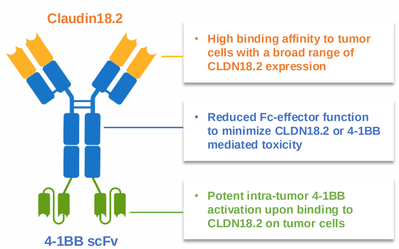
S. Klempner[1], L. Shen[2], D. Liu[2], F. Dayyani[3], J. Kratz[4], H. Pan[5], X. Liang[6], Z. Wang[7], S. Kim[8], Y. Deng[9], T. Deng[10], T. Liu[11], E. Girda[12], C. Xu[13], M. Nguyen[13], J. Xia[14], X. Wang[14], S. Lee[15], J. Jeon[15], G. Ku[16]

[1]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA, [2]GI Oncology Department, Peking University Cancer Hospital and Institute, Beijing, China, [3]Medicine Department, UCI - University Of California Irvine - Health Manchester Pavilion, Orange, CA, USA, [4]Department of Medicine, University of Wisconsin School of Medicine and Public Health Medical Physics, Madison, WI, USA, [5]Medical Oncology Department, Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, Hangzhou, China, [6]Medicine Department, HuBei Cancer Hospital, Wuhan, China, [7]Medical Oncology, The First Affiliated Hospital of China Medical University, Shenyang, China, [8]Department of Medicine, UCHealth Cancer Care - Anschutz Medical Campus - University of Colorado Cancer Center, Aurora, CO, USA, [9]Medical Oncology Department, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, [10]Medical Oncology Department, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China, [11]Oncology Dept., Zhongshan Hospital Affiliated to Fudan University, Shanghai, China, [12]Gynecologic Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, USA, [13]Research and Development Department, I-Mab Biopharma, Rockville, MD, USA, [14]Research and Development, TJBio, Shanghai, China, [15]Clinical Development, ABL Bio, Inc., Seongnam, Korea, Republic of, [16]Gastrointestinal Oncology Service, Department of Medicine, MSKCC - Memorial Sloan Kettering Cancer Center, New York, USA

BACKGROUND

- Claudin 18.2 (CLDN18.2) is a validated cancer target across several tumor types, but the optimal CLDN18.2 targeting strategy is not known and novel approaches are needed.
- Givastomig/ABL503 is a first-in-class, bispecific antibody targeting CLDN18.2 and engaging 4-1BB through a unique conditional activation mechanism in tumor sites. Givastomig induces T-cell activation only in the presence of CLDN18.2-expressing cell engagement to avoid systemic immune toxicity and liver toxicity.
- Givastomig binding activity is observed across various levels of CLDN18.2 expression in pre-clinical models and allows for stronger CLDN18.2 binding, even in low-expressing tumor cells.
- The current study (NCT04900818) is an open label, first-in-human, phase 1 study in patients with advanced solid tumors and was designed to evaluate safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of givastomig.
- Data on all subjects who enrolled in escalation and parallel expansion were reported previously at ESMO 2023.

Figure 1: Givastomig Molecular Design

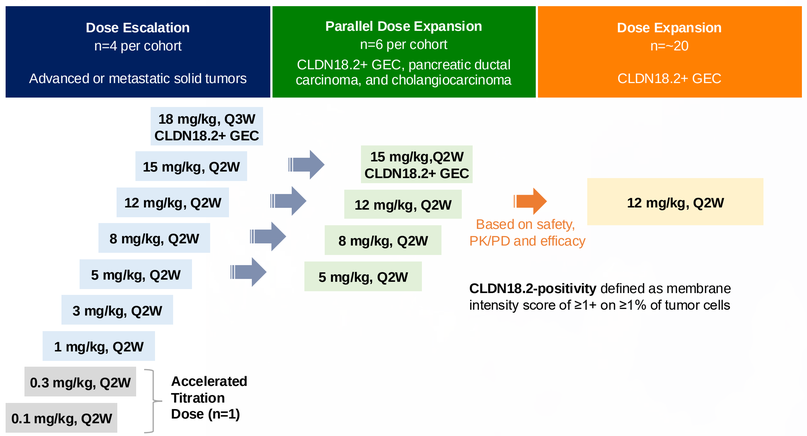


- High binding affinity to tumor cells with a broad range of CLDN18.2 expression
- Reduced Fc-effector function to minimize CLDN18.2 or 4-1BB mediated toxicity
- Potent intra-tumor 4-1BB activation upon binding to CLDN18.2 on tumor cells

METHODS

- The study consists of a dose escalation phase using the Bayesian Optimal Interval design (BOIN), followed by dose expansion.
- During dose escalation, patients with solid tumors, irrespective of CLDN18.2 expression were enrolled and administered givastomig intravenously (IV) every 2 weeks (Q2W) across eight dose levels (0.1, 0.3, 1, 3, 5, 8, 12, 15 mg/kg). After the 15 mg/kg cohort was demonstrated as safe, an 18 mg/kg Q3W cohort was added to explore additional schedule. The 12 mg/kg dose was selected for initial dose expansion (n=15).
- For the 12 mg/kg and 15 mg/kg parallel dose expansion cohorts, and the 18 mg/kg Q3W cohort, participants were required to have GEC tumors that are centrally confirmed CLDN18.2 positive (CLDN18.2+), defined as ≥1% of tumor cells with ≥1+ intensity by immunohistochemistry (IHC) using the CLDN18.2 (SP455) IHC assay.
- At designated time points, patients' serum samples were collected and measured for givastomig with a validated ELISA method along with measurements of soluble 4-1BB (s4-1BB), serum cytokines, and immunophenotypes in peripheral blood mononuclear cells.
- Anti-tumor activity was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and iRECIST.
- The clinical data from patients with CLDN18.2+ GEC at doses ≥5 mg/kg as of June 1, 2024, are reported here.

Figure 2: Phase 1 Study Design



RESULTS

Demographics

- 43 patients with CLDN18.2+ GEC were enrolled in expansion and received givastomig at 5 mg/kg (n=7), 8 mg/kg (n=5), 12 mg/kg (n=21), and 15 mg/kg (n=6) Q2W, and 18 mg/kg (n=4) Q3W.
- Patients had a median age of 59 years old, ECOG 0/1 (27.9%/72.1%), and a median of 3 prior lines of systemic therapy (range 1-6).

Table 1: Baseline Characteristics

Demographics		5 mg/kg (N=7) n (%)	8 mg/kg (N=5) n (%)	12 mg/kg (N=21) n (%)	15 mg/kg (N=6) n (%)	18 mg/kg (N=4) n (%)	Total (N=43) n (%)
Age, years	Median	67.0	59.0	57.0	64.5	56.0	59.0
	Min, Max	38, 82	36, 75	32, 76	55, 70	42, 77	32, 82
Gender, n (%)	Female	2 (28.6%)	3 (60.0%)	10 (47.6%)	1 (16.7%)	1 (25.0%)	17 (39.5%)
	Male	5 (71.4%)	2 (40.0%)	11 (52.4%)	5 (83.3%)	3 (75.0%)	26 (60.5%)
Race, n (%)	Asian	3 (42.9%)	4 (80.0%)	13 (61.9%)	3 (50.0%)	0	23 (53.5%)
	White	4 (57.1%)	1 (20.0%)	6 (28.6%)	2 (33.3%)	4 (100.0%)	17 (39.5%)
ECOG, n (%)	0	3 (42.9%)	2 (40.0%)	4 (19.0%)	1 (16.7%)	2 (50.0%)	12 (27.9%)
	1	4 (57.1%)	3 (60.0%)	17 (81.0%)	5 (83.3%)	2 (50.0%)	31 (72.1%)
Prior lines of systemic therapy	Median	3.0	2.0	3.0	2.5	2.0	3.0
	Min, Max	2, 5	1, 3	1, 6	2, 3	1, 3	1, 6
Prior PD-1/PD-L1, n (%)	Yes	4 (57.1%)	2 (40.0%)	16 (76.2%)	4 (66.7%)	4 (100.0%)	30 (69.8%)
Tumor type	EAC	3 (42.9%)	0	2 (9.5%)	1 (16.7%)	1 (25.0%)	7 (16.3%)
	GC	4 (57.1%)	4 (80.0%)	18 (85.7%)	5 (83.3%)	3 (75.0%)	34 (79.1%)
	GEJ	0	1 (20.0%)	1 (4.8%)	0	0	2 (4.7%)

Safety

- No dose-limiting-toxicity was reported up to 15 mg/kg Q2W and 18 mg/kg Q3W. Maximum-tolerated-dose was not reached.
- The most commonly reported treatment-related adverse events (TRAEs; >20%) were nausea (25.6%), anemia (23.3%), and white blood cell count decreased (23.3%). Grade ≥ 3 TRAE were reported in 15 patients (34.9%) [and/which] included one Grade 4 event of platelet count decreased and no Grade 5 TRAE.
- Most gastrointestinal TRAEs were Grade 1 or 2 and do not appear to be dose-related.

Table 2: Treatment Related Adverse Events Occurring in ≥5% of Subjects (N=43)

Adverse Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Nausea	6 (14.0%)	4 (9.3%)	1 (2.3%)	0	0	11 (25.6%)
Anemia	2 (4.7%)	5 (11.6%)	3 (7.0%)	0	0	10 (23.3%)
White blood cell count decreased	4 (9.3%)	3 (7.0%)	3 (7.0%)	0	0	10 (23.3%)
Vomiting	4 (9.3%)	2 (4.7%)	1 (2.3%)	0	0	7 (16.3%)
Decreased appetite	3 (7.0%)	2 (4.7%)	1 (2.3%)	0	0	6 (14.0%)
Alanine aminotransferase increased	2 (4.7%)	2 (4.7%)	1 (2.3%)	0	0	5 (11.6%)
Aspartate aminotransferase increased	3 (7.0%)	0	2 (4.7%)	0	0	5 (11.6%)
Gamma-glutamyltransferase increased	1 (2.3%)	3 (7.0%)	1 (2.3%)	0	0	5 (11.6%)
Neutrophil count decreased	1 (2.3%)	3 (7.0%)	1 (2.3%)	0	0	5 (11.6%)
Infusion related reaction	1 (2.3%)	2 (4.7%)	1 (2.3%)	0	0	4 (9.3%)
Lymphocyte count decreased	0	0	4 (9.3%)	0	0	4 (9.3%)
Fatigue	2 (4.7%)	1 (2.3%)	0	0	0	3 (7.0%)
Headache	2 (4.7%)	1 (2.3%)	0	0	0	3 (7.0%)
Hypoalbuminemia	2 (4.7%)	1 (2.3%)	0	0	0	3 (7.0%)
Lipase increased	1 (2.3%)	1 (2.3%)	1 (2.3%)	0	0	3 (7.0%)
Platelet count decreased	1 (2.3%)	1 (2.3%)	0	1 (2.3%)	0	3 (7.0%)
Weight decreased	2 (4.7%)	1 (2.3%)	0	0	0	3 (7.0%)

Pharmacokinetics and Pharmacodynamics

- At doses ≥5 mg/kg Q2W, a linear PK was observed and the average C_{trough} reached the target threshold (12 µg/mL).
- At doses ≥8 mg/kg Q2W, all patients would be predicted to achieve the target givastomig concentration threshold.
- Dose-dependent induction in soluble 4-1BB reached a plateau for givastomig at 8 mg/kg to 18 mg/kg.

Figure 3A: Mean Serum Concentration of Givastomig

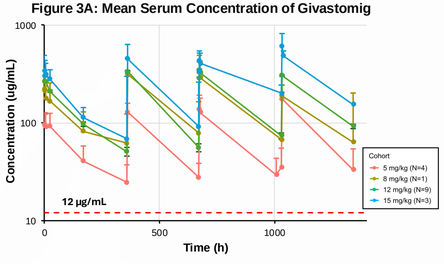
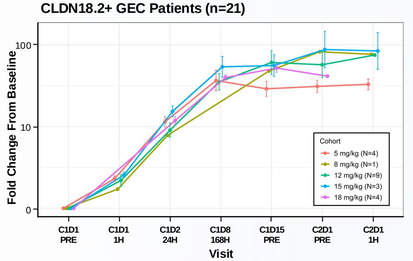


Figure 3B: PD Effect on Peripheral Soluble 4-1BB in CLDN18.2+ GEC Patients (n=21)



Clinical Activity

- Of the 43 patients with CLDN18.2+ GEC who received givastomig monotherapy at doses ranging from 5 to 18 mg/kg, a partial response (PR) was observed in seven patients (one at 5 mg/kg, one at 8 mg/kg, four at 12 mg/kg, and one at 18 mg/kg) with an objective response rate (ORR) of 16.3% for single agent givastomig.
- Stable disease (SD) was reported in 14 patients (disease control rate = 48.8%).
- CLDN18.2 expression in responders ranged from 11% to 100%. Additionally, five responders had received prior treatment with programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors.
- Response to therapy was generally observed at the first scan with a median time to response of 1.7 months. Median duration of response was 9.4 months and median progression-free survival was 3.0 months.
- As of the cutoff date, four PR patients remain on the study.

Figure 4A: Best Percentage Change in Target Lesions

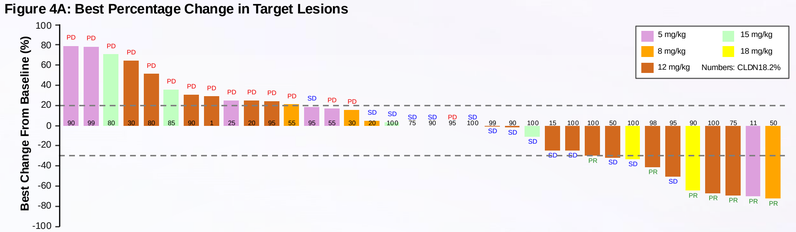


Figure 4B: Duration of Treatment

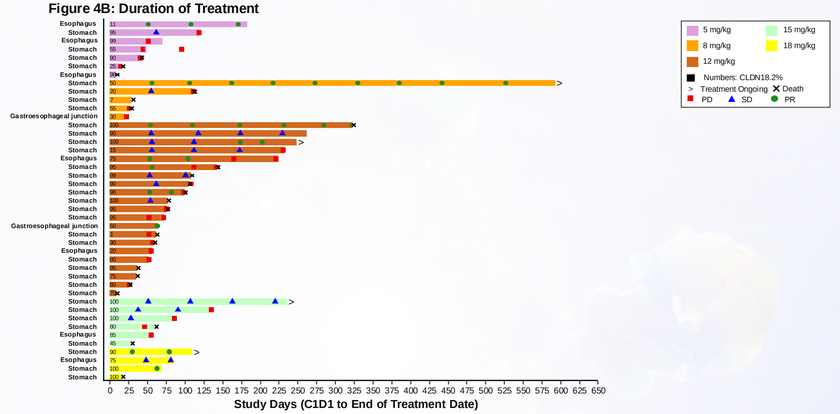
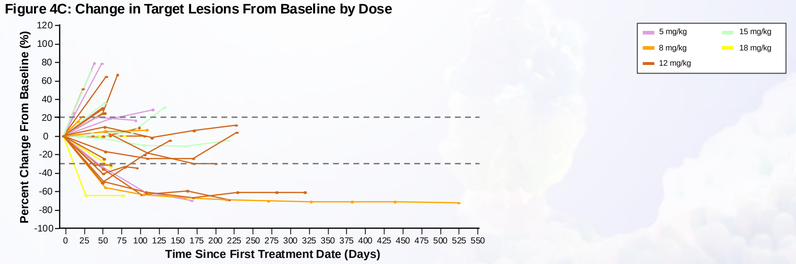


Figure 4C: Change in Target Lesions From Baseline by Dose



CONCLUSIONS

- **Givastomig was well tolerated up to 15 mg/kg Q2W and 18 mg/kg Q3W and has shown single agent activity in heavily pre-treated GEC patients with a wide range of CLDN18.2 expression.**
- **The optimal dose range was determined to be 8-12 mg/kg Q2W based on the totality of safety, PK/PD and efficacy.**
- **A study of givastomig in combination with standard of care treatment (chemotherapy + nivolumab) in the first line treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative, CLDN18.2+ metastatic GEC is ongoing (NCT04900818).**

ESMO 2024, Poster #1017P

Lead author disclosures: advisory/consulting from I-Mab Biopharma, Astellas, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Merck, Mersana, Natera, Novartis, Sanofi-Aventis, Taiho Oncology, Mbrace Therapeutics, Turning Point Therapeutics.

Email: sklempner@mgb.org

Study sponsored by: I-Mab Biopharma and ABL Bio, **ClinicalTriaLgov Identifier:** NCT04900818

Acknowledgements: I-Mab would like to thank all the patients, their families, and participating clinical sites.

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