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

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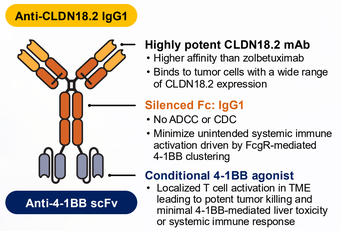
BACKGROUND

- Givastomig, a CLDN18.2 x 4-1BB bispecific antibody, exerts anti-tumor activity through CLDN18.2-based, tumor-directed T-cell activation.[1]
- NCT04900818 is an open label, first-in-human, phase 1 study of givastomig in patients with advanced solid tumors that was designed to evaluate safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of givastomig.
- Initial data presented from this study showed that givastomig was well tolerated, had activity in heavily pretreated CLDN18.2-positive gastric cancer patients, and exhibited dose-dependent pharmacokinetics and induction of soluble 4-1BB.[2]
- Here we report updated safety, efficacy and biomarker data with over 1 year of additional follow up from patients with CLDN18.2-positive GEC treated with monotherapy givastomig at doses ≥5 mg/kg.

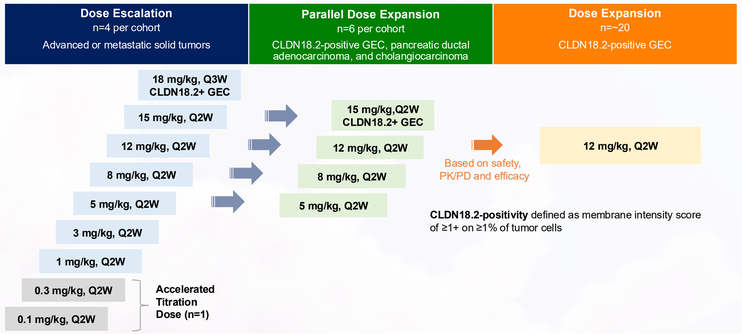
Figure 1: Givastomig Molecular Design



METHODS

- This phase 1 study comprised a dose escalation phase using the Bayesian Optimal Interval design, followed by a dose expansion phase.
- During dose escalation, patients with solid tumors, irrespective of CLDN18.2 expression were enrolled and administered givastomig across 9 dose levels (0.1, 0.3, 1, 3, 5, 8, 12, 15 and 18 mg/kg). There were no dose-limiting toxicities.
- Patient preselection for the parallel dose expansion cohort of 15 mg/kg Q2W, dose escalation cohort of 18 mg/kg Q3W, and dose expansion cohort of 12 mg/kg Q2W required that participants have GEC tumors that are CLDN18.2 positive (≥1% of tumor cells with ≥1+ intensity by immunohistochemistry) prior to starting treatment with givastomig monotherapy.
- Anti-tumor activity was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and iRECIST.
- Differences in objective response rate (ORR) and disease control rate (DCR) between CLDN18.2-high patients and CLDN18.2-low patients were evaluated by Chi-square test. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier method and Cox proportional hazards.
- The clinical data from patients with CLDN18.2-positive GEC at doses ≥5 mg/kg as of 27-Aug-2025 are reported here.
- The median duration of follow up was 7.1 months, with a range of 0.2 to 35 months.

Figure 2: Phase 1 Study Design



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References:
1. Shen JITC 2024
2. Ku ESMO 2024
3. Ku, G. et al. Clinical Cancer Research 2025

RESULTS

Baseline Characteristics

- 45 patients with CLDN18.2-positive GEC were enrolled into cohorts of escalating doses of givastomig 5-15 mg/kg Q2W, and 18 mg/kg Q3W.
- Patients had received a median of 3 prior therapies, including 74% with prior therapy with a programmed death-(ligand) 1 inhibitor.
- Tumor CPS ranged from 0 to 85; CLDN18.2 expression ranged from 1% to 100% of tumor cells with a membrane intensity score of ≥1+.

Safety

- No dose-limiting toxicities were observed up to 15 mg/kg Q2W and 18 mg/kg Q3W. Maximum-tolerated-dose was not reached.
- Common treatment-related adverse events (TRAEs) (≥10%) included anemia (27%), white blood cell count decreased (22%), nausea (20%), ALT increased (16%), AST increased (16%), decreased appetite (16%), neutropenia (16%), GGT increased (11%), and vomiting (11%).
- Grade ≥3 TRAE occurred in 33% of patients. One patient experienced a Grade 4 platelet count decreased. Grade 3 TRAE occurring in more than one patient were anemia (9%), lymphocyte count decreased (9%), WBC decreased (7%), AST increased (4%), neutropenia (4%), and upper GI hemorrhage (4%).
- TRAE leading to permanent withdrawal of givastomig occurred in 9% of patients. These events were Grade 3 ALT increased (n=1, 5 mg/kg) Grade 3 infusion related reaction (n=1, 5 mg/kg), Grade 2 pulmonary embolism (n=1, 12 mg/kg) and Grade 3 nausea (n=1, 18 mg/kg).
- There were no Grade 5 treatment-related adverse events.

Efficacy

- Partial responses (PR) were observed in 8 patients (1 PR each at 5 and 8 mg/kg, 4 PRs at 12 mg/kg, and 2 PRs at 18 mg/kg) with an ORR of 18%. DCR was 49%.
- The median time to response was 1.8 months, with a range of 1.0 to 5.7 months.
- The median duration of response was 5.6 months; the longest duration of response was 26.3 months with 35 months of follow up in a patient treated with 8 mg/kg Q2W.
- Median progression free survival (PFS) was 2.96 months, and median overall survival (OS) was 7.49 months.
- The median duration of givastomig treatment was 2.3 months, with a range of 0.3 to 28.8 months.
- 3 of 6 responders with available PD-L1 data were CPS <5 (Figure 4).
- There were no statistically significant differences in efficacy outcomes (ORR, DCR, PFS, OS) by CLDN18.2 expression (Table 2).

Table 1: Efficacy Summary Table

	5 mg/kg (n=7)	8 mg/kg (n=5)	12 mg/kg (n=21)	15 mg/kg (n=6)	18 mg/kg Q3W (n=6)	All (n=45)
Confirmed ORR						
n (%)	1 (14%)	1 (20%)	4 (19%)	0	2 (33%)	8 (18%)
95% CI	(0.2, 33.9)	(0.3, 44.5)	(2.7, 22.6)	(0.0, 45.9)	(2.1, 48.4)	(3.9, 16.8)
DCR (PR + SD)						
n (%)	2 (29%)	2 (40%)	11 (52%)	3 (50%)	4 (67%)	22 (49%)
95% CI	(1.8, 42.8)	(2.5, 55.6)	(13.9, 42.0)	(5.5, 57.2)	(9.9, 65.1)	(16.0, 34.6)
PFS (mo.)						
Median (95% CI)	1.45 (0.46, 3.91)	3.19 (0.72, NA)	3.22 (1.81, 7.03)	2.32 (1.22, NA)	6.24 (0.53, NA)	2.96 (1.71, 3.91)
6 mo. (%) (95% CI)	NA	20.0 (0.84, 58.19)	33.3 (14.88, 53.07)	16.7 (0.77, 51.68)	66.7 (19.46, 90.44)	30.0 (17.36, 43.79)
OS (mo.)						
Median (95% CI)	11.93 (0.46, NA)	8.97 (3.19, NA)	7.03 (4.21, 13.01)	10.25 (1.22, NA)	7.49 (0.53, NA)	7.49 (4.96, 12.49)

Figure 3: Treatment Duration

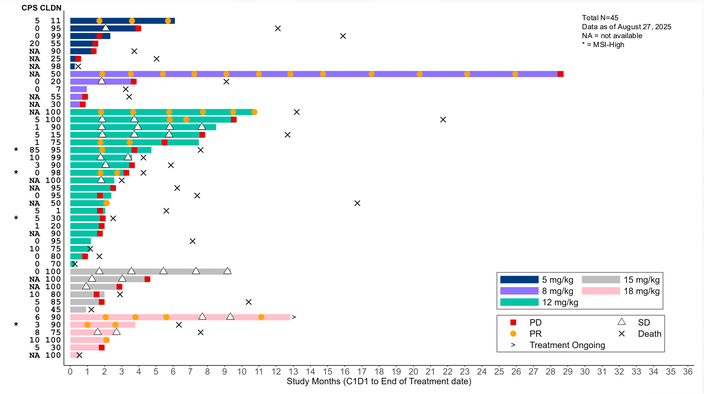

Figure 4: Best Percentage Change from Baseline in Target Lesions

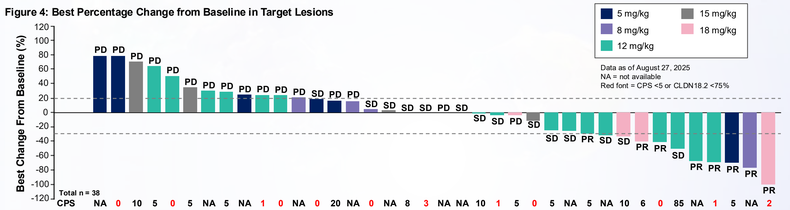

Table 2. Clinical Efficacy Stratified by CLDN18.2 Expression

CLDN18.2 Expression Cutoff	CLDN18.2-Low (< Cutoff)					CLDN18.2-High (≥ Cutoff)					PFS Hazard Ratio (High vs. Low)	OS Hazard Ratio (High vs. Low)
	n	ORR	DCR	mPFS (months)	mOS (months)	n	ORR	DCR	mPFS (months)	mOS (months)		
2+/3+, 10%	4	25%	50%	5.39 (1.71, NA)	9.0 (3.19, NA)	41	17%	49%	2.83 (1.71-3.91)	7.49 (4.96-11.9)	1.47 (0.43-4.63)	0.88 (0.26-2.91)
2+/3+, 40%	15	20%	40%	1.87 (0.85-5.42)	8.97 (3.19-16.5)	30	17%	53%	2.96 (1.71-4.21)	7.49 (4.21-11.9)	1.13 (0.56-2.24)	1.20 (0.55-2.64)
2+/3+, 75%	24	17%	42%	1.84 (1.22-3.65)	7.49 (3.19-16.5)	21	19%	57%	3.68 (1.71-6.24)	7.49 (4.21-13.0)	0.87 (0.46-1.65)	0.88 (0.43-1.82)

ORR = Overall Response Rate; DCR = Disease Control Rate; mPFS = median Progression-Free Survival; mOS = median Overall Survival; numbers in parenthesis for mPFS, mOS, and Hazard Ratio are corresponding 95% confidence intervals.

CONCLUSION

- **With over a year of additional follow up, givastomig continues to be well tolerated up to 15 mg/kg Q2W and 18 mg/kg Q3W and continues to show encouraging monotherapy activity in heavily pre-treated GEC patients with a wide range of CLDN18.2 expression (confirmed ORR 18%).**
- **There was no statistically significant difference in ORR, DCR, PFS, or OS between CLDN18.2-high and CLDN18.2-low groups, using a variety of cutoffs.**
- **Givastomig may have utility in patients with lower CLDN18.2 expression compared with other CLDN18.2 agents.**
- **The sustained tolerability and efficacy support the development of givastomig in combination with nivolumab and mFOLFOX6 in CLDN18.2-positive advanced or metastatic gastric, gastroesophageal and esophageal adenocarcinomas (NCT04900818), as well as other CLDN18.2-positive GI malignancies.**