2025 ESMO GASTROINTESTINAL CANCERS
Annual Congress

A Phase Ib dose escalation study of givastomig, a CLDN18.2 x 4-1BB bispecific antibody, in combination with immunochemotherapy in HER2-negative, CLDN18.2-positive gastric, esophageal or gastro-esophageal junction adenocarcinoma

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EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

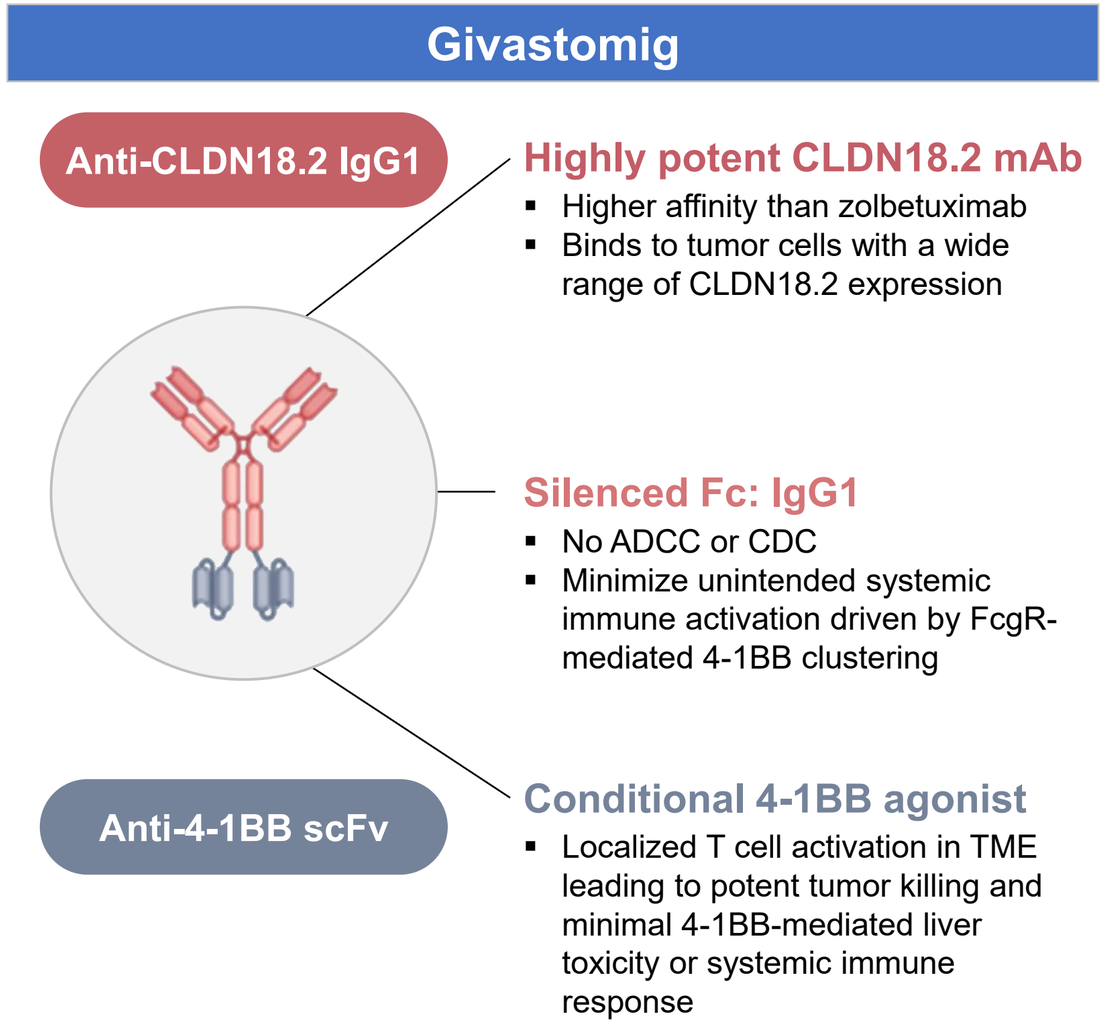
DECLARATION OF INTERESTS

SJK has served as a consultant and/or in an advisory role for Bristol-Myers Squibb, Merck, Astellas, Daiichi-Sankyo, Natera, Novartis, AstraZeneca, Mersana, Sanofi-Aventis, Amgen, Boehringer-Ingelheim, Taiho Oncology, Eisai, BeiGene, Elevation Oncology, EsoBiotec, and Gilead. SJK reports prior stock/equity in Turning Point Therapeutics and Nuvalent.

SJK is currently participating as an investigator on the study being presented.

Background

- Givastomig, a CLDN18.2 x 4-1BB bispecific antibody, was well tolerated as monotherapy and showed activity in heavily pretreated CLDN18.2-positive gastric cancer patients.[1]
- Givastomig exerts anti-tumor activity through CLDN18.2-based, tumor-directed T-cell activation.[2]
- Dose-dependent pharmacokinetics and induction of soluble 4-1BB were observed.
- Here we present the preliminary data from the dose escalation of givastomig combined with nivolumab and FOLFOX.



1. Ku ESMO 2024
2. Shen JITC 2024

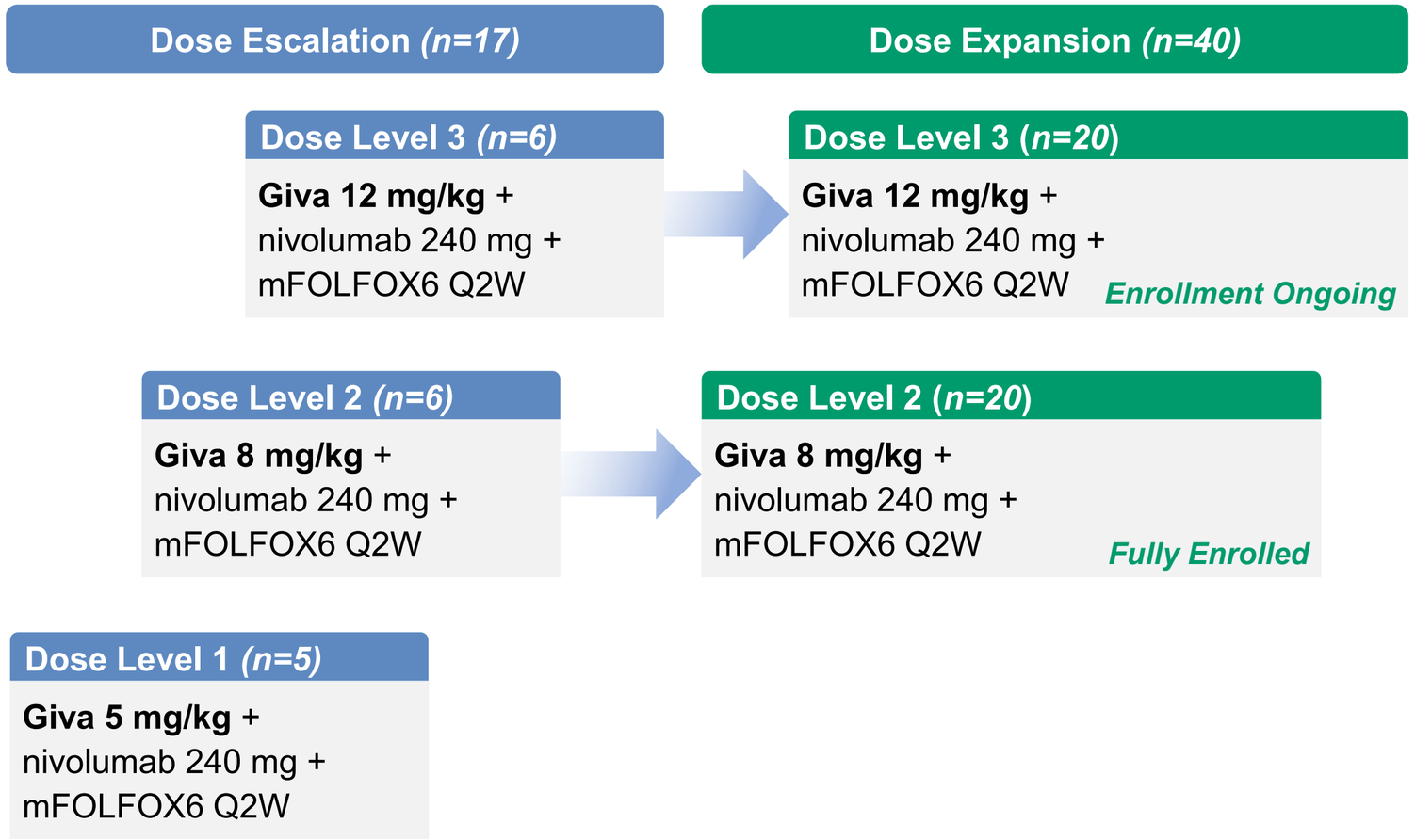
Phase Ib Study Design of Givastomig Combined with Immunochemotherapy

Study Design:

- Multi-center, dose-escalation and expansion phase Ib study
- Enrolled only US patients
- Bayesian optimal interval design with at least four subjects per dose

Eligibility:

- 1L unresectable or metastatic GC/GEJ/EAC (GEA)
- HER2-negative
- **CLDN18.2 ≥1+ on ≥1% of tumor cells**
- **All comers PD-L1**



Endpoints:

Primary: Safety

Secondary:

Response rate: ORR, BoR, DoR

Survival: PFS, OS

PK/PD

Notes: GC = gastric cancer; GEJ = gastroesophageal junction; EAC = esophageal adenocarcinoma; mFOLFOX6 = standard of care chemotherapy regimen; Q2W = every two weeks; giva = givastomig; ORR = objective response rate; PK = pharmacokinetic; PD = pharmacodynamic; BoR = best overall response; DoR = duration of response; PFS = progression free survival; OS = overall survival; 1L = first line

Baseline Patient Characteristics

Feature(s)		5 mg/kg *(n=5)*	8 mg/kg *(n=6)*	12 mg/kg *(n=6)*	Total *(n=17)*
Age	Median	45	54	57	56
	(range)	(41, 65)	(35, 69)	(43, 79)	(35, 79)
Gender	Female	3 (60%)	4 (67%)	5 (83%)	12 (71%)
	Male	2 (40%)	2 (33%)	1 (17%)	5 (29%)
Race	White	5 (100%)	3 (50%)	3 (50%)	11 (65%)
	Asian	0	2 (33%)	2 (33%)	4 (23%)
	Black	0	1 (17%)	0	1 (6%)
	NR	0	0	1 (17%)	1 (6%)
ECOG PS	0	4 (80%)	4 (67%)	1 (17%)	9 (53%)
	1	1 (20%)	2 (33%)	5 (83%)	8 (47%)
Tumor Location	Gastric	3 (60%)	5 (83%)	6 (100%)	14 (82%)
	GEJ	1 (20%)	1 (17%)	0	2 (12%)
	Esophageal	1 (20%)	0	0	1 (6%)
CLDN18.2	≥ 75%	3 (60%)	5 (83%)	4 (67%)	12 (71%)
	< 75%	2 (40%)	1 (17%)	2 (33%)	5 (29%)
	≥ 40%	4 (80%)	5 (83%)	5 (83%)	14 (82%)
	< 40%	1 (20%)	1 (17%)	1 (17%)	3 (18%)
PD-L1 CPS	≥ 1	4 (80%)	5 (83%)	6 (100%)	15 (88%)
	< 1	1 (20%)	1 (17%)	0	2 (12%)
MSI	MSI-H	0	0	0	0
	MSS	5 (100%)	6 (100%)	6 (100%)	17 (100%)

Notes: DCO May 15, 2025

ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastroesophageal junction; CPS = combined positive score; MSI = microsatellite instability; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NR = not reported

Givastomig Was Well Tolerated in Combination with Immunochemotherapy

No Dose Limiting Toxicity was observed

	5 mg/kg *(n=5)* (%)	8 mg/kg *(n=6)* (%)	12 mg/kg *(n=6)* (%)	Total *(n=17)* (%)
TEAE	100%	100%	100%	100%
TRAE giva	80%	83%	100%	88%
TRAE any drug	100%	100%	100%	100%
SAE	60%	67%	17%	47%
Related SAE giva	20%	0	17%	12%
Related SAE any drug	40%	17%	17%	24%
Grade ≥3 TEAE	80%	67%	50%	65%
Grade ≥3 TRAE giva	20%	17%	33%	24%
Grade ≥3 TRAE any drug	60%	67%	33%	53%
TRAE → interruption	0	50%	17%	24%
TRAE → treatment DC	20%	0	17%	12%
Disease progression	0	33%	0	12%
TRAE any drug → death	0	0	0	0

Key Adverse Events Related to Any Drug in ≥ 10%

Adverse Event *(n=17)*	Grades ≤ 2	Grade 3	Grade 4	All Grades
Neutropenia	6 (35%)	4 (24%)	2 (12%)	12 (71%)
Peripheral neuropathy	10 (59%)	0	0	10 (59%)
Nausea	9 (53%)	0	0	9 (53%)
Vomiting	6 (35%)	0	0	6 (35%)
Infusion related reaction	6 (35%)	1 (6%)	0	7 (41%)
Diarrhea	5 (29%)	0	0	5 (29%)
Abdominal pain	2 (12%)	1 (6%)	0	3 (18%)
Gastritis	1 (6%)	1 (6%)	0	2 (12%)
ALT increased	1 (6%)	1 (6%)	0	2 (12%)
AST increased	1 (6%)	1 (6%)	0	2 (12%)

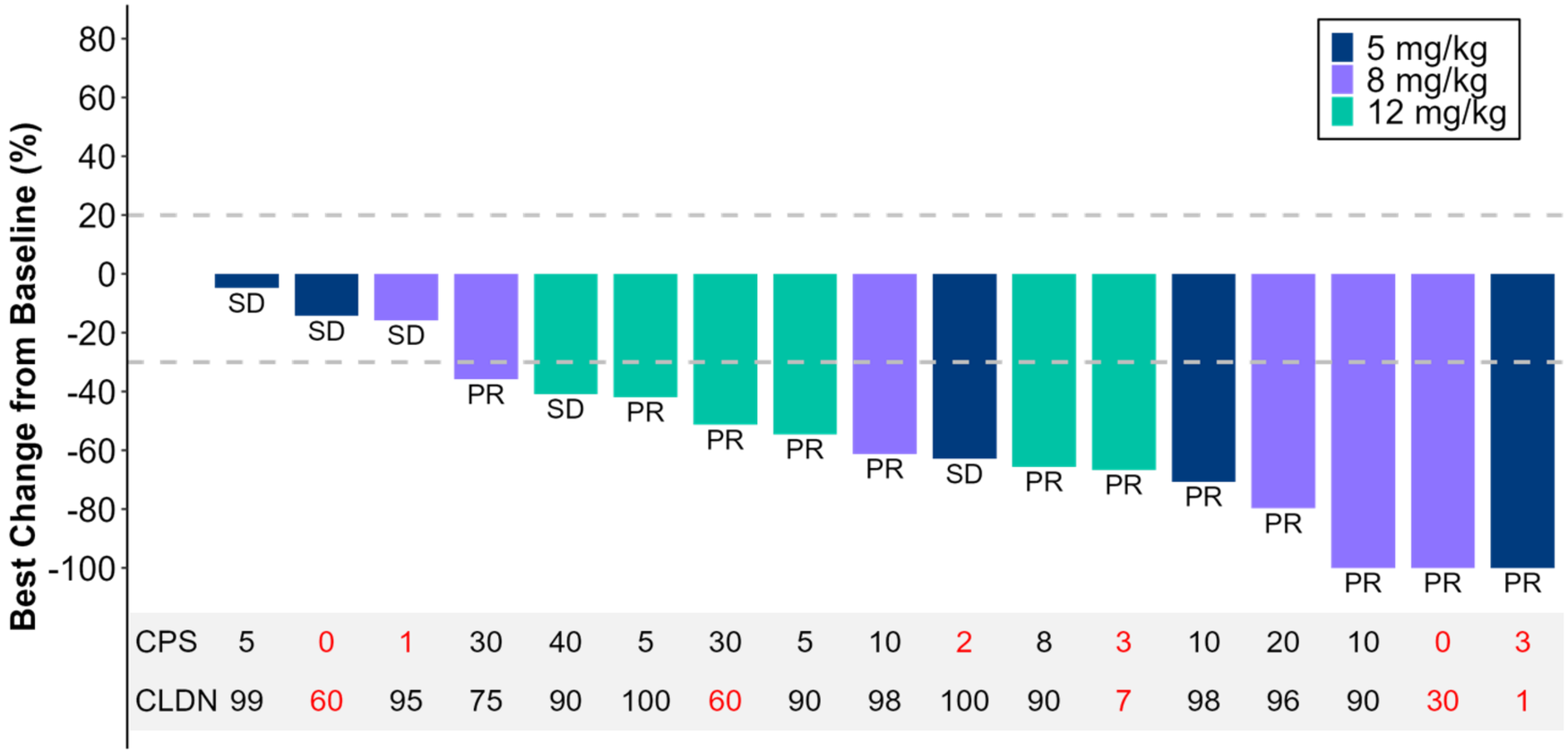
Immune Related Adverse Events

Adverse Event *(n=17)*	Grades ≤ 2	Grade 3	Grade 4	All Grades
Pneumonitis	1 (6%)	0	0	1 (6%)
Immune nephritis	0	1 (6%)	0	1 (6%)
Rash maculo-popular	2 (12%)	0	0	2 (12%)

Notes: DCO May 15, 2025

TEAE = treatment emergent adverse event; TRAE = treatment related adverse event; SAE = serious adverse event; DC = discontinuation; giva = givastomig

Objective Response Rate of 71% Across Range of PD-L1 & CLDN18.2 Expression



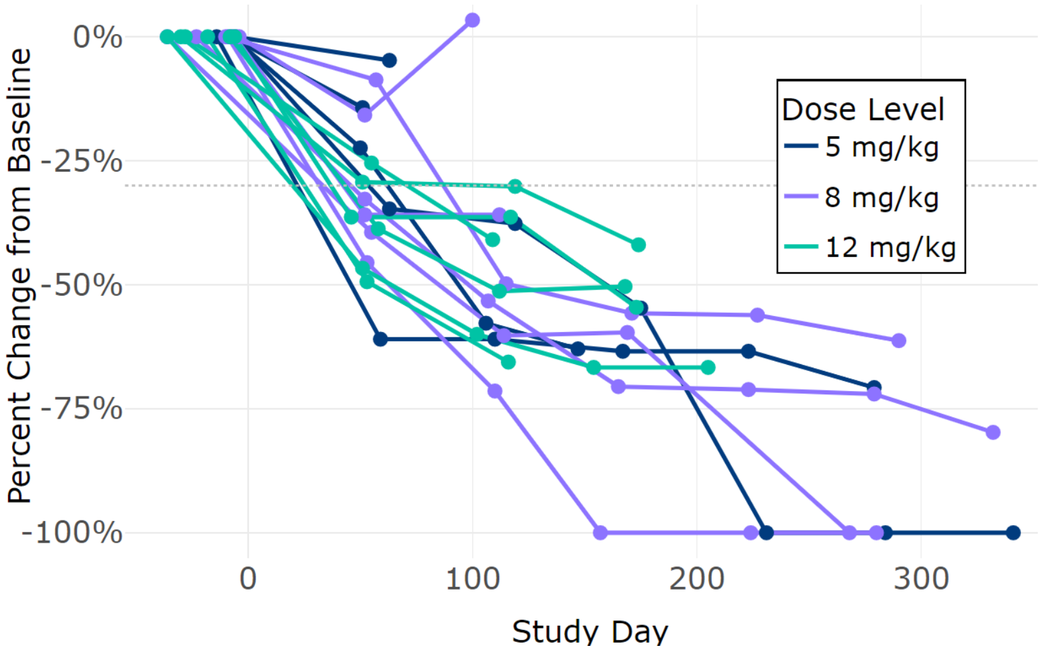
Biomarker	Confirmed ORR: % (n)	
	All Escalation (*n=17*)	Cohorts Chosen for Expansion (8 & 12 mg/kg) (*n=12*)
Total	**71 (12/17)**	**83 (10/12)**
PD-L1		
≥ 5	**82 (9/11)**	**89 (8/9)**
< 5	**50 (3/6)**	**67 (2/3)**
≥ 1	**73 (11/15)**	**82 (9/11)**
< 1	**50 (1/2)**	**100 (1/1)**
CLDN18.2		
≥ 75	**67 (8/12)**	**78 (7/9)**
< 75	**80 (4/5)**	**100 (3/3)**

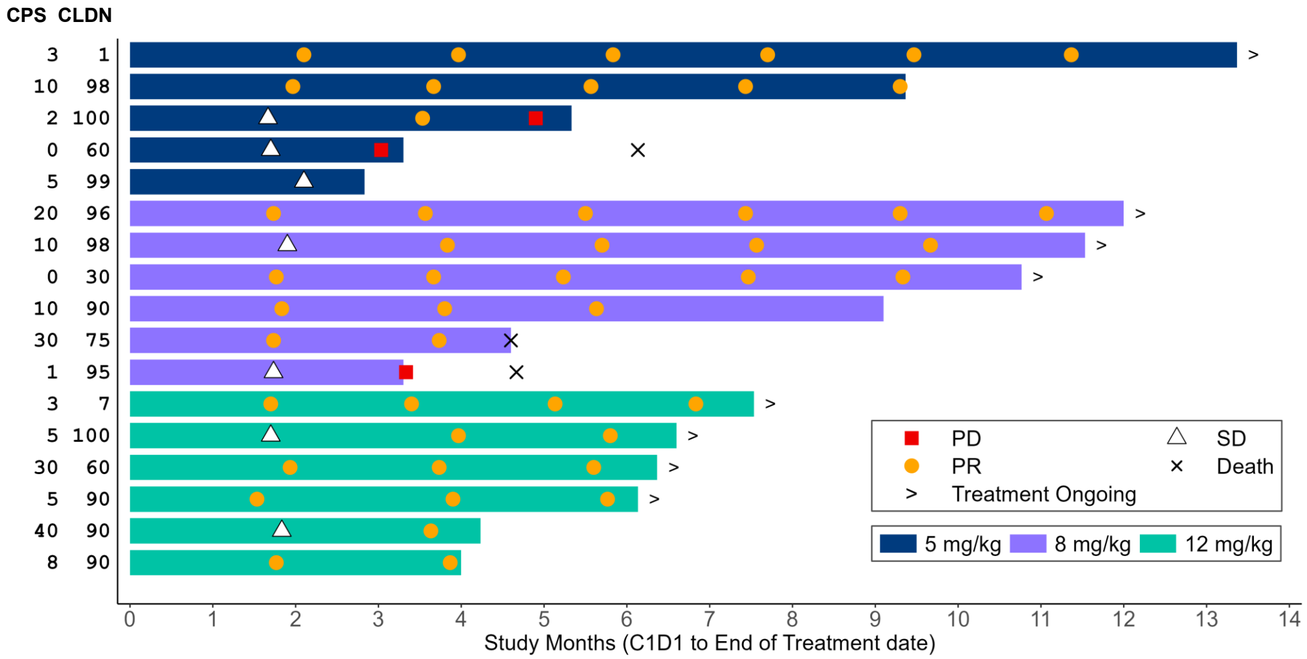
Confirmed ORR: % (n)	PD-L1 ≥ 5	PD-L1 < 5
CLDN18.2 ≥ 75	**80 (8/10)**	**0 (0/2)**
CLDN18.2 < 75	**100 (1/1)**	**75 (3/4)**

Notes: DCO May 15, 2025; PD-L1 assays:22C3 pharmDX, or local test; CLDN: Ventana SP455 or 43-14A

SD = stable disease; PR = confirmed partial response; ORR = objective response rate; CPS = combined positive score; CLDN = Claudin 18.2

Responses are Rapid, Deep, and Sustained





	8 and 12 mg/kg (*n=12*)	All (*n=17*)
Median follow up (months) (95% CI)	7.8 (5.7, 10.2)	9.0 (6.1, 11.5)
Median duration of response (months) (95% CI)	NE (4.5, NE)	NE (4.8, NE)
PFS median (months) (95% CI)	NE (4.5, NE)	NE (4.8, NE)
PFS 6 months (%) (95% CI)	81.5 (43.5, 95.1)	72.9 (42.6, 89.0)

Notes: DCO May 15, 2025

PFS = progression free survival; CI = confidence interval; PD = progressive disease; PR = partial response; SD = stable disease; NE = not evaluable

Conclusions

- Givastomig appears to be well tolerated at 5 mg/kg, 8 mg/kg, and 12 mg/kg in combination with nivolumab and FOLFOX, without significant GI, hepatic, or immune-related toxicities.
- Dose-dependent pharmacokinetics and induction of soluble 4-1BB were observed with the combination, similar to monotherapy (data not shown).
- Promising preliminary efficacy of the combination with overall ORR of 71% and 83% at doses being explored in expansion (8 mg/kg and 12 mg/kg).
- Anti-tumor activity was observed in patients with a wide range of CLDN18.2 expression (e.g. 3/3 PRs < 40%) as well as low PD-L1 expression (CPS < 5%).
- Enrollment of dose expansion cohort at 8 mg/kg is completed and ongoing at 12 mg/kg (NCT04900818).

Notes: DCO May 15, 2025

GI = gastrointestinal; ORR = objective response rate; PR = confirmed partial response; CPS = combined positive score

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