Abstract 709

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Phase 1/2 study of spevatamig (PT886) in combination with gemcitabine plus nab-paclitaxel (GnP) in frontline (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC); TWINPEAK Study

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Background

Spevatamig (PT886) is an IgG1-based bispecific antibody targeting claudin 18.2 (CLDN18.2) and CD47 with an optimized anti-CD47 arm that has higher binding to CD47 on cancer cells than on human red blood cells (RBCs). Spevatamig is expected to mediate enhanced killing of CLDN18.2-expressing cancer cells by innate immune cells and potentially by T cells. In addition, the binding of CD47 on cancer cells by spevatamig potentially enables anti-tumor activity against low CLDN18.2-expressing cancer cells. In combination with chemotherapy which induces "eat me" signals, the immune-activation and cancer killing activities of spevatamig are expected to be further stimulated.

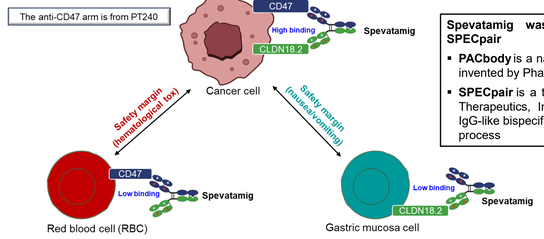
Design of spevatamig with a two-step approach: 1. Optimize anti-CD47 mAb; 2. Construct a native IgG1-like bsAb

Table 1: Mapping the CD47 biology using three distinct molecules to de-risk clinical development

	PT248 (similar to magrolimab)	PT240	PT246 (similar to lemzoparlimab)
Cancer cell binding	High	High	Low
Red blood cell (RBC) binding	High	Low	Low
In vivo efficacy	Complete tumor regression	Complete tumor regression	Nearly complete tumor regression
Hematological tox in monkeys	Severe	Borderline severe	Moderate

- Three distinct anti-CD47 mAbs were used to build empirical correlation between efficacy and risk of hematological toxicity
- PT240 was selected as the **optimized anti-CD47 mAb**
- Spevatamig was constructed using one anti-CD47 arm from PT240 and one anti-CLDN18.2 arm

Figure 1: Spevatamig's optimized design mitigates hematological toxicity and improves tolerability



Spevatamig was constructed with PACbody and SPECpair

- **PACbody** is a native IgG-like bispecific antibody platform invented by Phanes Therapeutics, Inc.
- **SPECpair** is a technology platform invented by Phanes Therapeutics, Inc.; it enables manufacturing of native IgG-like bispecific antibodies with the mAb manufacturing process

✓ Hematological toxicity is resolved

- Spevatamig monotherapy: No Grade ≥3 anemia/thrombocytopenia and no neutropenia
- Combo (spevatamig 2 mg/kg QW + GnP) in 1L PDAC: Cytopenias comparable to GnP alone

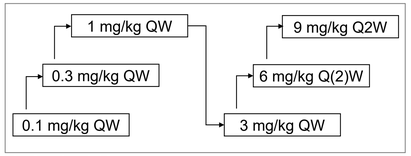
✓ Nausea and vomiting are reduced

- Combo (spevatamig 2 mg/kg QW + GnP) in 1L PDAC: No nausea/vomiting-related dose reductions or discontinuations; no Grade ≥3 events
- Vomiting rates (all grades) comparable to pivotal GnP studies

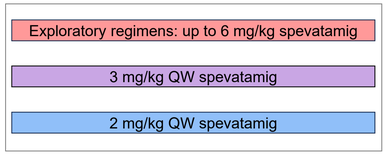
GnP = gemcitabine + *nab*-paclitaxel

Methods

Previously treated a/m GC/GEJC, PDAC and BTC



Treatment naïve for metastatic PDAC (mPDAC)



a/m: advanced or metastatic

The trial is being conducted at 11 clinical sites in the US. As of December 8, 2025, more than 100 patients have been treated with spevatamig collectively in monotherapy and combination therapy studies.

Monotherapy

- No CRS; no DLT observed; MTD not reached.
- No Grade ≥ 3 treatment-emergent neutropenia or thrombocytopenia. One patient experienced Grade 3 anemia following termination of the study, deemed not related to spevatamig, and recovered (**Table 2**), validating the designed safety features of spevatamig.
- Nausea and vomiting were observed. Starting from 3 mg/kg QW, an optimized premedication regimen and infusion time adjustment improved patient symptoms.

Table 2: Treatment-emergent cytopenia in monotherapy dose escalation

	0.1 mg/kg QW	0.3 mg/kg QW	1 mg/kg QW	3 mg/kg QW	6 mg/kg Q2W	6 mg/kg QW	9 mg/kg Q2W	Total	Total Grade ≥ 3
# of patients treated	2	1	1	10	7	6	4	**31**	**31**
Anemia	0 (0%)	1 (100%)	0 (0%)	3 (30%)	3 (43%)	3 (50%)	0 (0%)	**10 (32%)**	**1 (3%)**
Neutropenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**
Platelet count decreased	0 (0%)	0 (0%)	1 (100%)	3 (30%)	1 (14%)	0 (0%)	1 (25%)	**6 (19%)**	**0 (0%)**

Combination therapy: 2 mg/kg QW spevatamig + GnP in 1L mPDAC

- No CRS. The rates of anemia, neutropenia and thrombocytopenia were comparable to those observed in the GnP treatment arms from pivotal trials (NAPOLI-3[1]), see **Table 3**.
- No Grade ≥ 3 treatment-emergent nausea or vomiting event was reported, and no dose reduction or treatment discontinuation due to nausea or vomiting occurred.

Table 3: TEAEs associated with CD47 and CLDN18.2 class-effects

	2 mg/kg QW spevatamig + GnP (n=16)		GnP (historical data from NAPOLI-3[1])	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Anemia	6 (38%)	2 (12%)	153 (40.4%)	66 (17%)
Neutropenia	11 (69%)	5 (31%)	192 (51%)	144 (38%)
Platelet count decreased	5 (31%)	1 (6%)	154 (41%)	23 (6%)
Nausea	12 (75%)	0 (0%)	162 (42.7%)	10 (3%)
Vomiting	5 (31%)	0 (0%)	100 (26.4)	8 (2%)

Table 4: Patient baseline characteristics (n=15)

Median Age	65
ECOG PS	
0	53%
1	47%
Primary tumor location	
Head	47%
Other	53%
Patients with metastatic disease	100%
Liver metastases	80%
Peritoneal metastases	33%
Patients with recurrent disease	6.6%

Table 5: Efficacy metrics in efficacy analysis patient population (n=15)

DCR (CR/PR/SD), n (%)	14 (93%)
ORR, n (%)	6 (40%)
Complete Response (CR)	0 (0%)
Partial Response (PR); 5 confirmed, 1 pending confirmation	6 (40%)
Stable Disease (SD)	8 (53%)
Progressive Disease (PD)	1 (7%)
mPFS (months)	7.3
6-month PFS rate (%)	59%
6-month OS rate (%)	93%
Patients receiving subsequent anti-cancer therapy (%)	91%

Note: In comparison, the efficacy endpoints in the GnP arm in MPACT[2] are: ORR, 23%; mPFS, 5.5 months; 6-month PFS rate, 44%; 6-month OS rate, 67%; patients receiving subsequent anti-cancer therapy, 38%.

Figure 2: Waterfall plot

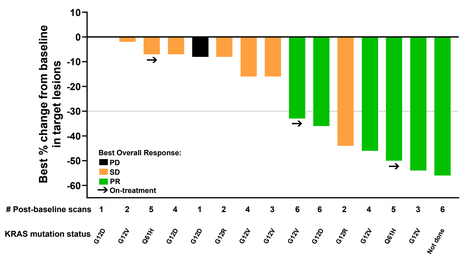


Figure 3: Spider plot

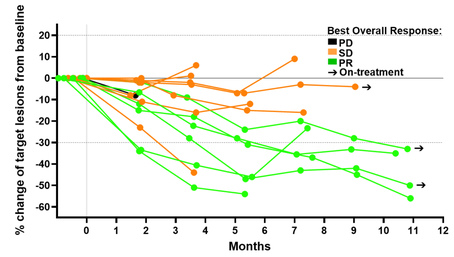


Figure 4: PDAC biomarker CA19-9

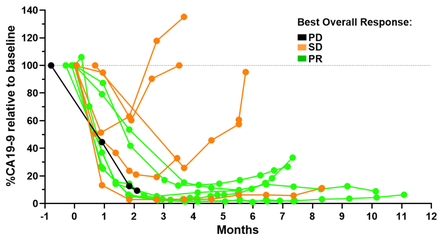


Figure 5. Responses across CLDN18.2 scores

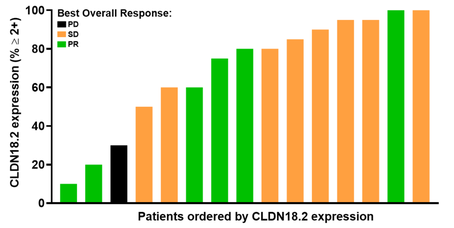


Figure 6: Progression free survival (PFS)

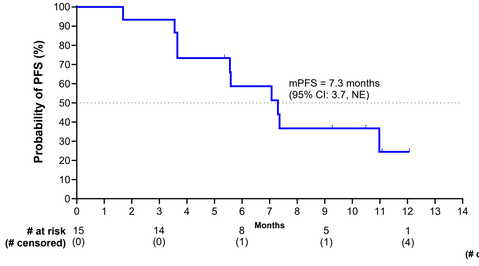
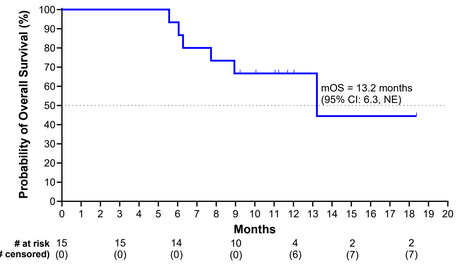


Figure 7: Overall survival



Conclusions

- The design of spevatamig mitigates hematological toxicity and improves GI tolerability, as evidenced by the clinical data from the spevatamig monotherapy and combination therapy with GnP cohorts (collectively more than 100 patients in the US).
- Overall, spevatamig + GnP combination is well tolerated in 1L patients with mPDAC, with no significant additive toxicity to GnP.
- 2 mg/kg QW spevatamig + GnP showed promising efficacy when compared with published studies of GnP in 1L mPDAC.
- The data for an additional dose level, 3 mg/kg spevatamig + GnP is still maturing.
- Overall, the data supports further development of the combination therapy in a randomized phase 3 trial.

References

1. Wainberg et al., Lancet 2023; 402:1272-1281.
2. Von Hoff et al., NEJM 2013; 369: 1691-1703.