Abstract: 4192
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Spevatamig (PT886), a claudin 18.2 (CLDN18.2)/CD47 bispecific antibody, in combination with gemcitabine plus nab-paclitaxel (GnP) in frontline (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)

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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, a design aimed to resolve hematological toxicity associated with CD47-targeting agents. Spevatamig is an **innate immunity enhancer (I_2E)**, a new class of immune checkpoint inhibitors (ICIs) that activate the innate immune cells by blocking the "don't eat me" signal on 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. **As of May 14, 2026, 193 patients globally have been dosed with spevatamig collectively in monotherapy and combination therapy settings**.

Design of spevatamig with a two-step approach[1]

Step 1: Optimize anti-CD47 mAb

Table 1: Mapping the CD47 biology using three distinct mAbs to optimize CD47 targeting

	PT248 (magrolimab-like)	PT240	PT246 (lemzoparlimab-like)
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 toxicity 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

Step 2: Construct a native IgG1-like bsAb using the anti-CD47 arm from PT240 and one anti-CLDN18.2 arm

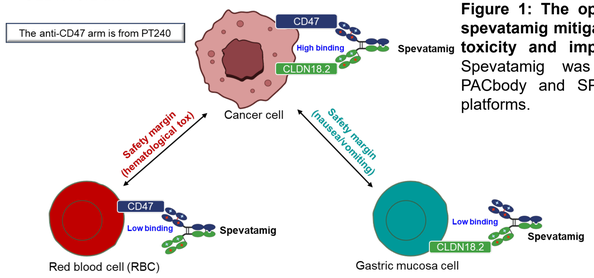
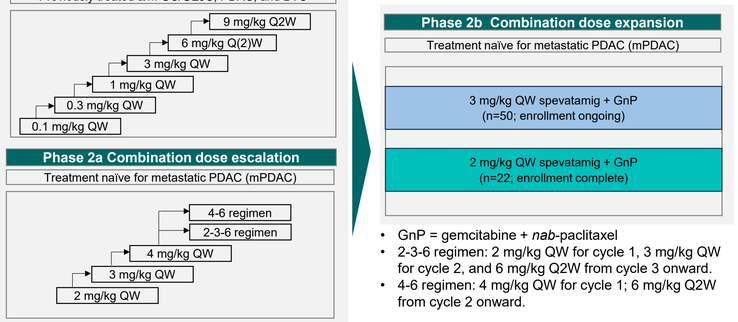


Figure 1: The optimized design of spevatamig mitigates hematological toxicity and improves tolerability. Spevatamig was constructed with PACbody and SPECpair technology platforms.

✓ Hematological toxicity is resolved

✓ Nausea and vomiting are reduced

Methods



- GnP = gemcitabine + *nab*-paclitaxel
- 2-3-6 regimen: 2 mg/kg QW for cycle 1, 3 mg/kg QW for cycle 2, and 6 mg/kg Q2W from cycle 3 onward.
- 4-6 regimen: 4 mg/kg QW for cycle 1; 6 mg/kg Q2W from cycle 2 onward.

Safety: spevatamig monotherapy at 3 mg/kg QW and 6 mg/kg Q(2)W

- In spevatamig monotherapy, rates of Grade ≥ 3 anemia, neutropenia or thrombocytopenia were comparable in patients from the US and China. No dose response was observed in these AEs.

Table 2: Grade ≥ 3 TEAEs associated with CD47 class-effects in spevatamig monotherapy

	US study			China study		
	3 mg/kg QW (n=10)	6 mg/kg Q2W (n=7)	6 mg/kg QW (n=16)	3 mg/kg QW (n=6)	6 mg/kg Q2W (n=3)	6 mg/kg QW (n=4)
	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Anemia	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neutropenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Safety: 2 vs. 3 mg/kg QW spevatamig + GnP in 1L mPDAC

- Rates of Grade ≥ 3 TEAEs of class-effects were comparable at the two dose levels chosen for expansion (2 mg/kg QW and 3 mg/kg QW spevatamig) in patients in the same region.
- No CRS was observed at either dose level.

Table 3: Grade ≥ 3 TEAEs associated with CD47 and CLDN18.2 class-effects in spevatamig + GnP combination therapy

	The NAPOLI-3 study[2]	Spevatamig US study		Spevatamig China study	
	GnP arm (n=379)	2 mg/kg QW + GnP (n=16)	3 mg/kg QW + GnP (n=24)	2 mg/kg QW + GnP (n=6)	3 mg/kg QW + GnP (n=20)
	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Anemia	66 (17%)	2 (12.5%)	3 (12.5%)	2 (33.3%)	3 (15.0%)
Neutropenia	144 (38%)	5 (31.3%)	10 (41.7%)	4 (66.7%)	14 (70.0%)
Thrombocytopenia	23 (6%)	1 (6.3%)	1 (4.2%)	0 (0.0%)	3 (15.0%)
Nausea	10 (3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	8 (2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)

Note: Neutropenia rates were higher in patients in China, consistent with literature reports that chemotherapies tend to cause more cytopenia in Asian populations[3, 4]. Enrollment is ongoing in the 3 mg/kg QW cohort.

Key patient baseline characteristics

Table 4: Key patient baseline characteristic metrics in the 2 mg/kg QW spevatamig + GnP efficacy analysis set (n=21) are comparable to those in pivotal trials

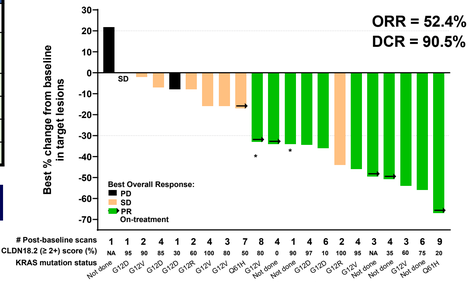
	2 mg/kg QW spevatamig + GnP (n=21)	MPACT[5] (GnP arm) (N= 431)	NAPOLI-3[2] (GnP arm) (N= 387)
Age (median, years)	62	62	65
ECOG (% ≥ 1)	61.9%	42%	57%
% with de novo metastatic disease	90.5%	93%*	93%*
% with recurrent disease	9.5%	7%	7%
% with liver metastases	85.7%	85%	80%
% with peritoneal metastases	28.6%	4%	Not reported

* Calculated based on the assumption that all patients in the study were with metastatic disease at enrollment.

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

- The median follow-up of the 2 mg/kg QW cohort was 8.9 months for the 21 patients in US and China, and 14.5 months for the 15 patients in the US. Data cutoff date is May 14, 2026.

Figure 2: Waterfall plot; US and China



Note: 9 responses have been confirmed. *2 responses remain to be confirmed with subsequent scans.

Figure 3: Spider plot; US and China

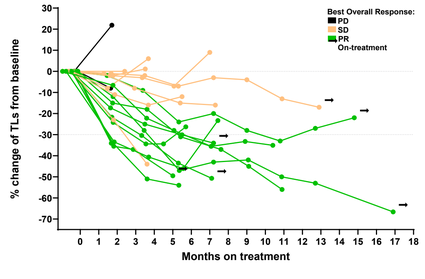


Figure 4: Responses across CLDN18.2 scores; US and China

Note: PR, partial response in a patient whose CLDN18.2 score is zero.

Figure 5: Progression free survival (PFS); US only

Figure 6: Overall survival (OS); US only

Note: Only 1 patient received a RAS inhibitor in 2L treatment.

Phase 3 study design

Note: The study design will be adjusted based on the emerging data from the phase 2 dose expansion study.

Conclusions

- The design of spevatamig with an optimized anti-CD47 arm mitigates hematological toxicity and improves GI tolerability, as evidenced by the results from the spevatamig monotherapy and combination therapy studies (collectively 133 patients in the US)[1].
- Overall, the 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 the GnP arm in pivotal trials in 1L mPDAC; importantly, more than 90% patients at this dose level had de novo metastatic disease, consistent with the baseline characteristics of the patient populations in pivotal phase 3 trials.
- The efficacy data for 3 mg/kg spevatamig + GnP is still maturing. 3 mg/kg has the potential to be the dose level for a phase 3 registrational study.
- Overall, the data support further development of spevatamig + GnP in a randomized phase 3 trial in patients with 1L mPDAC.

References

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