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Resolved hematological toxicities associated with anti-CD47 agents using a bispecific design involving an optimized anti-CD47 arm: A clinical proof of concept (POC) study

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Background

Introduction

Anti-CD47 agents, including anti-CD47 antibodies and signal regulatory protein alpha (SIRPα)/Fc fusion proteins, have been associated with hematological toxicities in multiple clinical trials. These adverse events (AEs) are believed to be driven by the expression of CD47 on red blood cells (RBCs), platelets and neutrophils, which are rapidly cleared by monocytes/macrophages activated by the CD47-targeting agent.

Spevatamig 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. **As of March 2026, more than 160 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 molecules to de-risk clinical development

	PT248	PT240	PT246
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

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

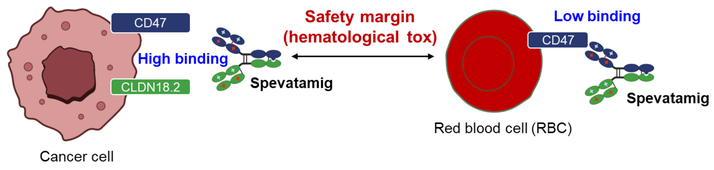

Figure 1: Spevatamig’s optimized, bispecific design mitigates hematological toxicity.

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

Results

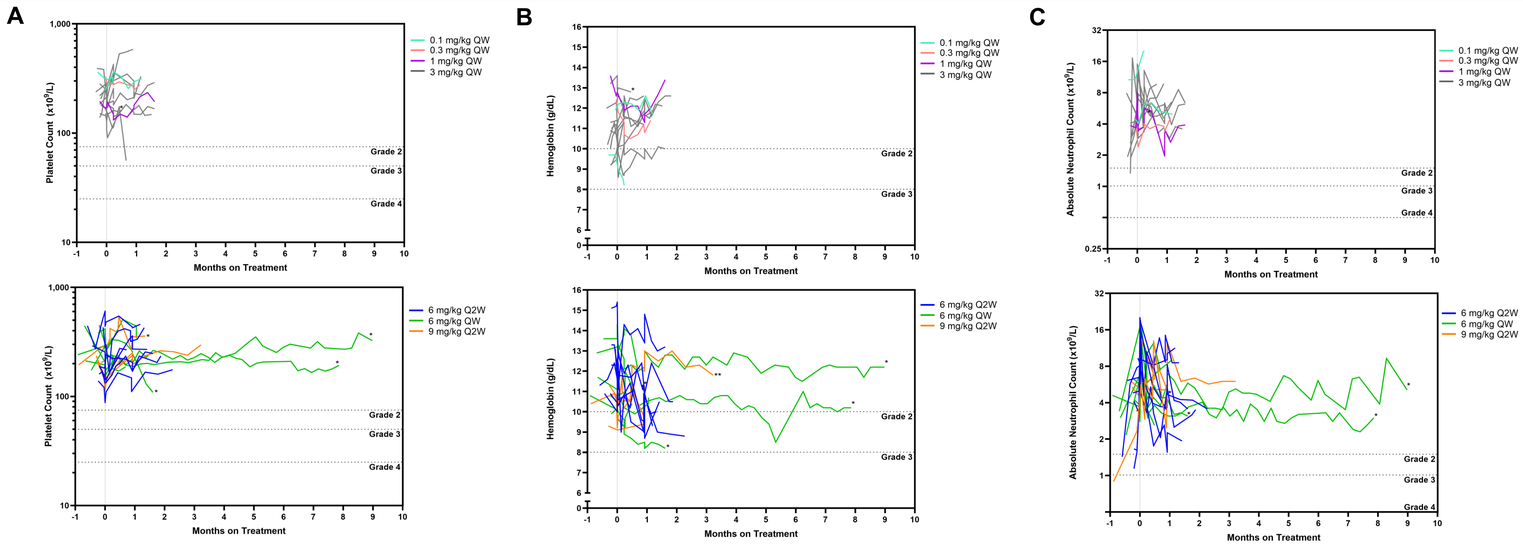

Figure 2: Levels of (A) platelet count, (B) hemoglobin, and (C) neutrophil count, during spevatamig treatment in the monotherapy study. The data for each patient was plotted separately. *Patients had reduced doses either post the first dose or at the first dose. **One patient at 9 mg/kg Q2W who had RBC transfusions during the screening phase prior to dosing is denoted in panel B.

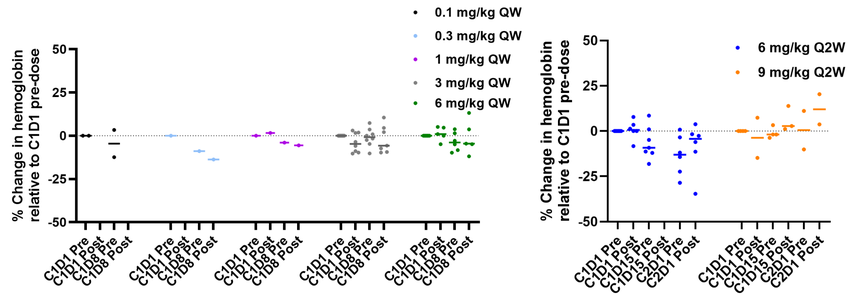

Figure 3: Relative changes in hemoglobin level post dose as shown in the spevatamig monotherapy study. All available data are presented.

Table 2: Treatment-related select cytopenias in 2 mg/kg QW spevatamig + pembrolizumab combination study

	2 mg/kg QW spevatamig + pembrolizumab (n=14)	
	All grades	Grade ≥ 3
Anemia	2 (14%)	0 (0%)
Neutropenia	0 (0%)	0 (0%)
Platelet count decreased	0 (0%)	0 (0%)

Conclusions

- Hematological toxicity associated with anti-CD47 binding has been mitigated with spevatamig’s optimized design.
- There is no observed dose-dependent change in cytopenias with increasing spevatamig monotherapy doses.
- Observed hematological AEs suggest spevatamig is well tolerated, despite dosing occurring in the context of underlying disease and known AEs of chemotherapy, allowing spevatamig to be safely combined with standard of care therapies.
- Combination of 2 mg/kg QW spevatamig with pembrolizumab was well tolerated, with hematological AEs comparable to those in spevatamig monotherapy.

References

1. Saeed et al., J Clin Oncol 2026;44(709).
2. Wainberg et al., Lancet 2023; 402:1272-1281.
3. Wilke et al., Lancet 2014;15(11): 1224-1235.