Nonclinical Safety Evaluation of MTA-Cooperative PRMT5 Inhibitors: Implications for Therapeutic Selectivity and Tolerability

Alice Tsai, Charles B Davis, Kenjie Amemiya, Ewa Budzynski, Stephene Ford, Kim J Briggs, Kevin M Cottrell, John P Maxwell, Adam S Crystal, and Jannik N Andersen
Tango Therapeutics, Boston, MA USA

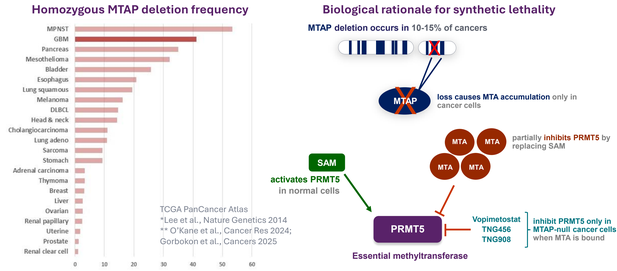
Poster# P437

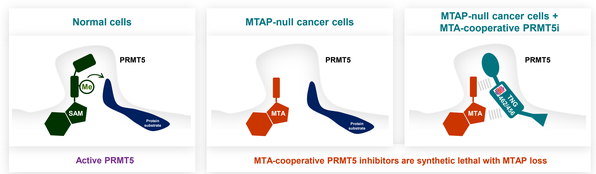
Abstract

Loss of MTAP, which is observed in 10-15% of all human cancers, creates a synthetic lethal dependency on PRMT5 and multiple, small-molecule inhibitors of PRMT5 are currently in clinical development for tumors with MTAP loss. While first-generation PRMT5 inhibitors showed some clinical activity, their development was hindered by limited tolerability—most notably toxicities in the bone marrow and gastrointestinal tract. These early agents lacked selectivity, showing comparable potency in both MTAP wild-type and MTAP-null cells, thereby failing to exploit the synthetic lethal vulnerability conferred by tumor-specific loss of MTAP.

In contrast, MTA-cooperative PRMT5 inhibitors— exemplified by TNG908, vopimetostat (TNG462), and TNG456—selectively inhibit PRMT5 in the MTAP-null cancer cells while sparing wildtype normal cells providing a larger therapeutic index. Here, we present nonclinical safety data from rodent and nonrodent models demonstrating that toxicity correlates with PRMT5 inhibition potency in MTAP wild-type human cell lines and with free drug exposure levels. Observed target organ toxicities—including bone marrow and GI tract effects—align with those seen in clinical studies of non-selective PRMT5 inhibitors. Off-mechanism toxicities have been minimized through improved in vitro MTAP selectivity. Emerging clinical data suggest that observed intolerances are consistent with on-target, off-mechanism pharmacology, and can be predicted based on exposure levels characterized in preclinical toxicology studies. Concordance between clinical pathology and histopathological findings in affected target organs support the translatability of these nonclinical observations.

MTA-cooperative PRMT5 inhibitors are synthetic lethal with MTAP deletion





Comparative safety profile of first generation PRMT5 inhibitors (Phase I Oncology Studies)

Drug (Sponsor)	Most Common TRAEs (All Grades)	Frequent TRAEs (Grade ≥3)	Notable Safety Observations
GSK3326595 (GSK)	• Fatigue • Nausea • Anemia • Alopecia • Dysgeusia	• Anemia • Thrombocytopenia • Neutropenia • Fatigue	Hematologic AEs were dose-limiting; infections occurred secondary to cytopenias; most events manageable with dose interruptions.
JNJ-64619178 (Janssen)	• Thrombocytopenia • Neutropenia • Anemia • Dysgeusia	• Thrombocytopenia • Neutropenia • Anemia	Hematologic AEs were dose-dependent and reversible; few non-hematologic severe AEs; isolated cardiac events rare.
PF-06939999 (Pfizer)	• Anemia • Thrombocytopenia • Neutropenia • Fatigue • Nausea • Dysgeusia	• Anemia • Thrombocytopenia • Neutropenia	Cytopenias were the main toxicity; mostly reversible and manageable with dose modification; no treatment-related deaths reported.
PRT543 (Prelude)	• Fatigue • Nausea • Thrombocytopenia • Anemia	• Thrombocytopenia • Anemia	Cytopenias reversible with dose holds/reductions; treatment discontinuations infrequent; maintained tolerability across cycles.

MTA-Cooperative (Tumor-Targeting) vs other PRMT5 Inhibitor

Novel	Potency (GI_{50})	WT Potency (GI_{50})	MTAP Selectivity
TNG456	20 nM	1,100 nM (1.1 µM)	55×
Vopimetostat (TNG462)	4 nM	180 nM	45×
TNG908	110 nM	1,650 nM (1.65 µM)	15×
First Gen	**Potency (GI_{50})**	**WT Potency (GI_{50})**	**MTAP Selectivity**
GSK3326595	80 nM	130 nM	1.6×
JNJ-64619178	0.88 nM	1.4 nM	1.6×

MTA-cooperative PRMT5 inhibitors exploit the buildup of MTA in MTAP-deleted tumors to selectively inhibit PRMT5, while leaving MTAP-wildtype and normal cells largely unaffected. This mechanism confers a broader therapeutic window and greater tumor selectivity.

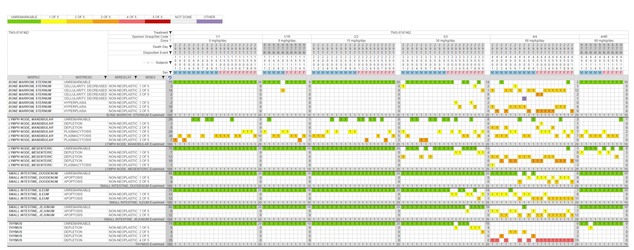
Toxicology dose strategy: top dose above WT benchmark

28-Day GLP Toxicology Study in Sprague-Dawley Rats

Exposure Target	TNG908		Vopimetostat		TNG456	
	Dose (mg/kg/day)	Exposure Multiples over WT	Dose (mg/kg/day)	Exposure Multiples over WT	Dose (mg/kg/day)	Exposure Multiples over WT
High Dose (> WT)	**100**	**1.7×**	**60**	**1.8×**	**75 (M) / 50 (F)**	**1.1×**
Mid Dose (~0.8× of WT)	50	1.1×	30	0.8×	30	0.6×
Low Dose (> MTAP- GI_{50})	25	0.3×	15	0.3×	15	0.3×

Dose levels for the 28-day GLP rat study were selected to span exposures from above the MTAP-deleted tumor GI_{50} up to and exceeding WT benchmark exposure levels.

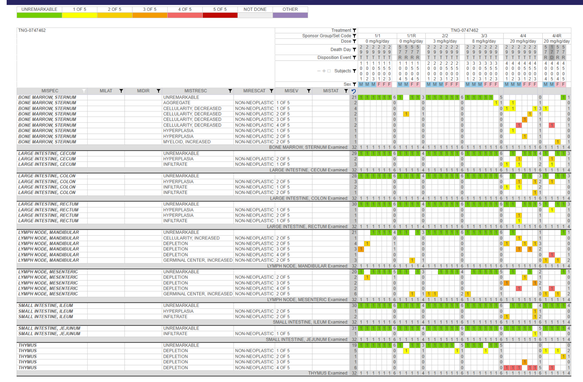
Key histopathology findings for vopimetostat: gastrointestinal and hematologic effects



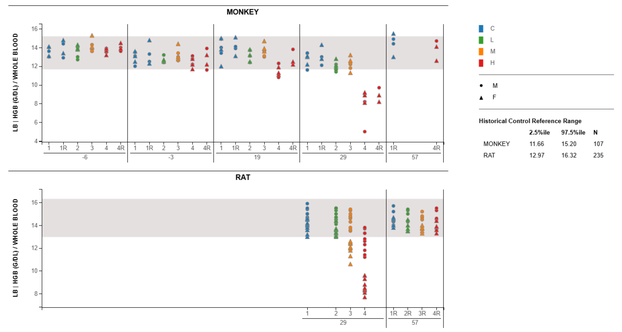
Set code: 1: vehicle control; 1R: vehicle control recovery; 2: low dose; 3: medium dose; 4: high dose; 4R: high dose recovery

Vopimetostat-related gastrointestinal, hematologic, and lymphoid histopathological findings in the rats were dose-dependent, with pronounced effects observed mostly at the highest dose, where exposures exceeded the wild-type benchmark. These findings showed evidence of reversibility by the end of the recovery period (monkey data in next graph).

Key histopathology findings for vopimetostat: gastrointestinal and hematologic effects



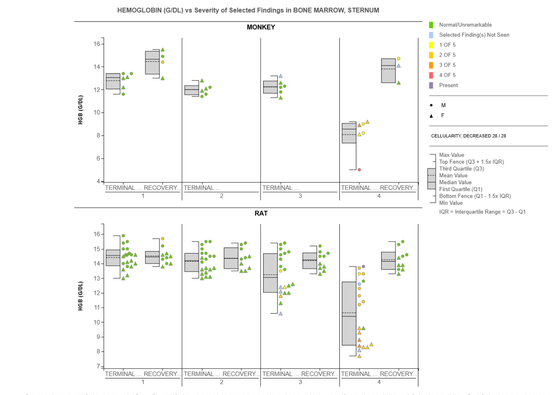
Vopimetostat caused dose-dependent hemoglobin reductions, most significant at the highest dose above WT benchmark



Set code: 1: vehicle control (C); 1R: vehicle control recovery; 2: low dose (L); 3: medium dose (M); 4: high dose (H); 4R: high dose recovery.
M: males; F: females

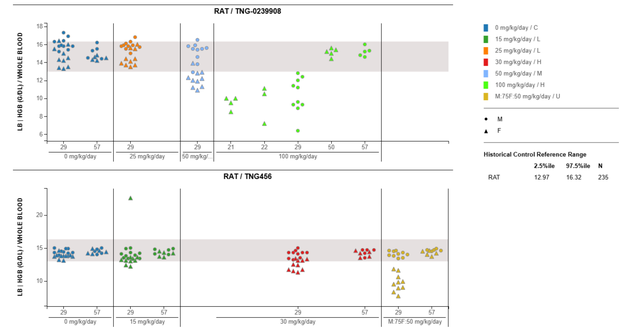
Hemoglobin reduction was greater in females, consistent with their higher Vopimetostat exposures, and fully recovered by the end of the 28-day recovery period.

Concordance between vopimetostat hematologic changes and bone marrow histopathology



Set code: 1: vehicle control (C); 1R: vehicle control recovery; 2: low dose (L); 3: medium dose (M); 4: high dose (H); 4R: high dose recovery.
M: males; F: females

TNG908 and TNG456 dose-dependent hemoglobin reductions are also most significant at the highest dose above WT benchmark



C: vehicle control ; L: low dose; M: medium dose; H: high dose; U: unspecified due to sex-specific doses in the TNG456 high dose group.
M: males; F: females

Conclusions and summary

- First-generation PRMT5 inhibitors show on-target adverse effects primarily in GI and hematology.
- Newer MTA-cooperative PRMT5 inhibitors exploit MTA buildup in MTAP-deleted tumors, providing cancer selectivity and sparing normal tissues like bone marrow.
- IND-enabling GLP toxicology studies doses were selected to span above MTAP-deleted tumor GI_{50} and exceed wild-type benchmark exposures, where on-mechanism, off-tumor toxicities are expected.
- Key histopathology findings for vopimetostat are GI and hematology effects, which are dose-dependent and most pronounced above wild-type benchmark exposures.
- Hematological changes mainly involve red blood cell mass reduction, which is dose-dependent and reversible by the end of the recovery period in rodent and nonrodent 28 day GLP toxicology studies.
- Strong concordance observed between bone marrow histopathology and clinical hematology endpoints was observed.
- Vopimetostat is generally well tolerated at 250 mg QD, the go-forward dose with a potentially best-in-class safety profile.
- A pivotal study of vopimetostat in second line (2L) pancreatic cancer is planned to initiate in 2026, with the potential to be first-to-market in 2L MTAP-del pancreatic cancer

Acknowledgements

We gratefully acknowledge our colleagues in Toxicology at WuXi and Labcorp for their invaluable support in conducting the GLP toxicology studies.

We sincerely thank the patients and their caregivers who participated in the TNG462-C101, TNG456-C101 and TNG908-C101 clinical trials, as well as the investigators and clinical sites that supported them, for their vital contributions to the safety data analysis.

References

1. Bewersdorf JP, Mi X, Lu B, Kuykendall A, Sallman D, Patel M, et al. Phase Ib study of PRT543, an oral protein arginine methyltransferase 5 (PRMT5) inhibitor, in patients with advanced splicing factor-mutant myeloid malignancies. Leukemia. 2025;39:765–9.

2. Vieito M, Moreno V, Spreafico A, Brana I, Wang JS, Preis M, et al. Phase 1 Study of JNJ-64619178, a Protein Arginine Methyltransferase 5 Inhibitor, in Advanced Solid Tumors. Clin Cancer Res. 2023;29:3592–602.

3. Rodon J, Rodriguez E, Maitland ML, Tsai FY-C, Socinski MA, Berlin JD, et al. A phase I study to evaluate the safety, pharmacokinetics, and pharmacodynamics of PF-06939999 (PRMT5 inhibitor) in patients with selected advanced or metastatic tumors with high incidence of splicing factor gene mutations ☆. ESMO Open. 2024;9:102961.

4. Postel-Vinay S, Italiano A, Romano PM, Cassier PA, Siu LL, Lossos IS, et al. 456MO METEOR-1: A phase I study of the safety and efficacy of the protein arginine methyltransferase 5 (PRMT5) inhibitor GSK3326595 in advanced solid tumors. Ann Oncol. 2022;33:S746–7.