Evaluation of the impact of homozygous MTAP truncations on the clinical activity of MTA-cooperative PRMT5 inhibitors

Poster #4608

Kimberly J. Briggs[1], Andre Mignault[1], Jordi Rodon[2], Victor Moreno[3], David Spigel[4], Phillippe Cassier[5], Capucine Baldini[6], Candace Haddox[7], Angela Hirbe[8], Ignacio Garrido-Laguna[9], Ibiayi Dagogo-Jack[10], Emiliano Calvo[11], Alexander Spira[12], Matthew R. Tonini[1], Douglas A. Whittington[1], Steven A. Lombardo[1], Binzhang Shen[1], Hannah Stowe[1], Shangtao Liu[1], Hongxiang Zhang[1], Satoshi Yoda[1], Minjie Zhang[1], Kevin M. Cottrell[1], Samuel Meier[1], Yi Yu[1], Teng Teng[1], Heidi Rego[1], Jennifer Morawiak[1], Heather DiBenedetto[1], Ellen Hooper[1], and Adam S. Crystal[1]

[1]Tango Therapeutics, Boston, MA, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain, [4]Sarah Cannon Research Institute, Nashville, TN, [5]Centre Léon Bérard, Lyon, France, [6]Gustave Roussy, Paris, France, [7]Dana Farber Cancer Institute, Boston, MA, [8]Washington University School of Medicine in St. Louis, St. Louis, MO, [9]Huntsman Cancer Institute - University of Utah Health, Salt Lake City, UT, [10]Massachusetts General Hospital, Boston, MA, [11]START Madrid-CIOCC, Madrid, Spain, [12]Next Oncology, Fairfax, VA

Abstract

Homozygous deletion of the MTAP gene occurs in 10-15% of all human cancers. To benefit this large patient population, MTA-cooperative PRMT5 inhibitors, including TNG908, TNG462, and TNG456 were developed to leverage the synthetic lethal relationship between MTAP deletion and PRMT5 inhibition. Clinical trial eligibility for most MTA-cooperative PRMT5 inhibitors is restricted to patients with tumors with confirmed MTAP loss either detected by next-generation sequencing or immunohistochemistry. MTAP loss most commonly occurs as a co-deletion event with the proximal CDKN2A gene and the chromosomal 9p breakpoints are not uniform. Previously, we reported that homozygous loss of only the terminal exon (exon 8), an event reported to occur in only 0.5% of MTAP-deleted tumors, is insufficient for complete loss of MTAP activity in preclinical assays. Here, we report initial evidence for the clinical impact of MTAP truncations, as opposed to complete deletion, on the activity of MTA-cooperative PRMT5 inhibitors.

MTA-cooperative PRMT5 inhibitors are synthetic lethal with MTAP deletion

Homozygous MTAP deletion frequency

Biological rationale for synthetic lethality

TNG462 first-in-human clinical trial includes retrospective MTAP molecular profiling

93% concordance between retrospective MTAP IHC and NGS

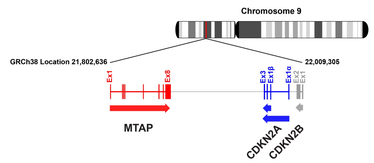
Retrospective MTAP IHC and NGS analysis		Overall percentage
MTAP IHC and NGS are concordant	MTAP-intact	7%
	MTAP-loss	86%
MTAP IHC and NGS are discordant		7%

*Retrospective TNG908-C101 and TNG462-C101 data cutoff 5 March 2025

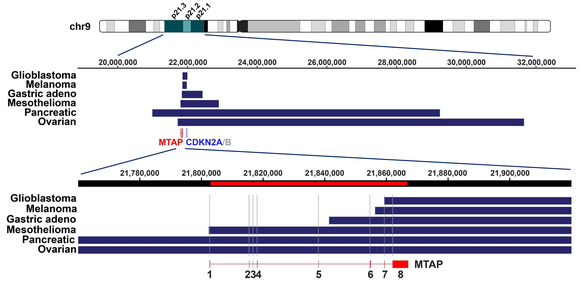
Tumor biology and assay methodology may cause discordances

Discordance type	Tumor diagnosis	MTAP screening method	Retrospective MTAP IHC (H-score)		Retrospective FoundationONE MTAP status
			Pre-Tx	C2D1	
MTAP IHC-pos and NGS MTAP-loss	Glioblastoma	FMI	165	N/A	Exon8-only deletion
	Melanoma	FMI	300	300	Exon8-only deletion
	Osteosarcoma	FMI	180	5	Exon8-only deletion
Evidence of tumor heterogeneity	Spindle cell sarcoma	Tempus	135	4	Intact (PreTx biopsy) Full deletion (C2D1 biopsy)
NGS assay discrepancy	Soft tissue sarcoma	BostonGene	20	0	Intact
	Gastrointestinal stromal tumor (GIST)	Tempus	0	0	Intact

Exon 8-only deletions possible due to tail-to-tail orientation with CDKN2A

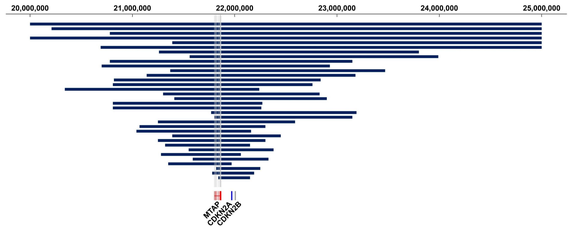


Chr9p breakpoints are variable in tumors representing multiple histologies

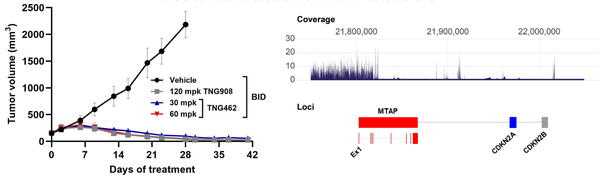


PDX model with partial MTAP loss responds to MTA-cooperative PRMT5 inhibitors

Chr9p deletions are variable in PDX models representing multiple histologies



MTA-cooperative PRMT5 inhibitors drive near complete response in PDX model with deletion of MTAP exons 5-8



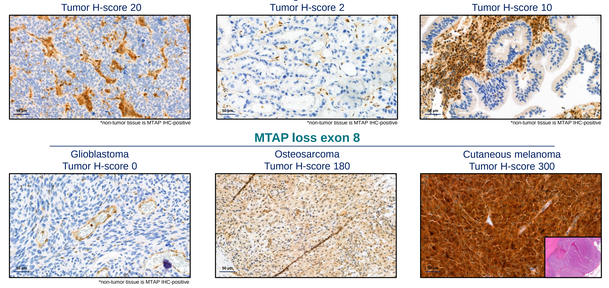
MTAP exon 8-only deletions are not common

MTAP deletion type from retrospective NGS analysis	Observed in TNG908-C101 and TNG462-C101	Reported by FMI (>540,000 clinical samples)*
Exon 8-only deletion	3%	0.48%
Partial deletion with loss of > exon 8	11%	35.24%
Full deletion (exons 1-8)	77%	63.73%
No observed deletion	9%	N/A

*Necchi et al., ASCO 2024

Loss of exon 8 may not be sufficient for loss of MTAP protein

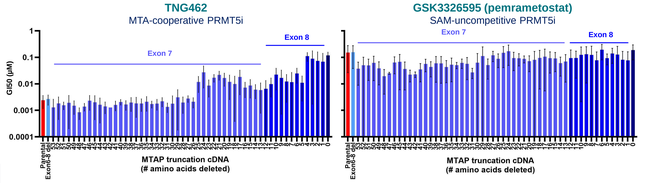
MTAP immunohistochemistry of tumors



Loss of exon 8 is insufficient to ablate MTAP activity in preclinical studies

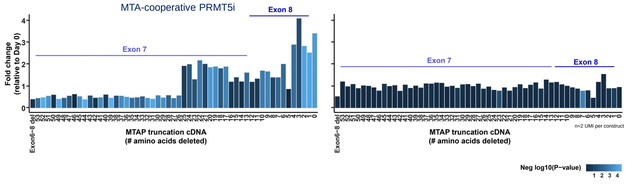
7-day viability assay (CellTiter-Glo)

LN18 cell lines

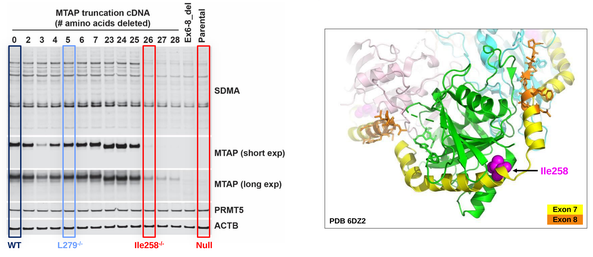


14-day enrichment assay (UMI barcodes)

LN18 cell lines

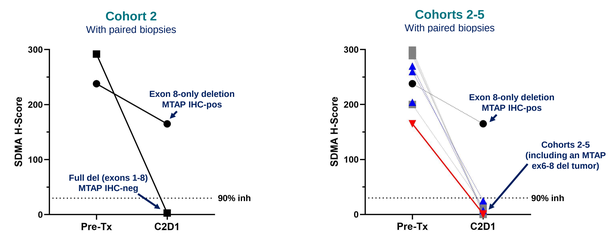


Ile258 likely contributes to protein stability and activity



TNG462 has limited pharmacodynamic activity in an MTAP exon 8-only deleted tumor

SDMA immunohistochemistry of tumors

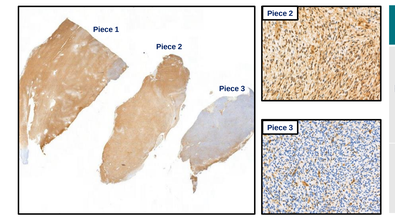


*Retrospective TNG908-C101 and TNG462-C101 data cutoff 5 March 2025

Tumor genetic heterogeneity in sarcoma biopsy

MTAP immunohistochemistry of Pre-Tx sample

Spindle cell sarcoma



	Biopsy collection	MTAP status
Retrospective NGS	Pre-Tx	MTAP-intact
	C2D1	MTAP full deletion (exons 1-8)
MTAP IHC H-score	Pre-Tx	135
	C2D1	4

Summary

- Excellent concordance between MTAP IHC and NGS
- Discordances between MTAP IHC and NGS can be caused by technical issues, partial deletions, and tumor heterogeneity
- Homozygous loss of exon 8 occurs rarely, but is insufficient for sensitivity to MTA-cooperative PRMT5 inhibitors
- Preliminary clinical data suggest that partial loss of MTAP, when deletions are larger than exon 8, is sufficient for sensitivity to MTA-cooperative PRMT5 inhibitors
- Data suggest that clinical NGS providers should report exon-level detail when calling homozygous MTAP deletions to improve patient outcomes on MTA-cooperative PRMT5 inhibitor clinical trials
- TNG456 monotherapy is currently enrolling in a Phase 1/2 clinical trial (NCT06810544)
- TNG462 alone or in combination with pembrolizumab is currently enrolling in the Phase 1/2 clinical trial (NCT05732831)

Acknowledgements

The authors gratefully acknowledge the generous contributions from their colleagues at Tango Therapeutics and from the scientific teams at BostonGene, CellCarta, FMI, Biortus, ChemPartner, Champions Oncology, Crown Biosciences, Enamine, Pharmaron, WuXi AppTec, and XenoSTART, as well as all of the participating TNG908-C101 and TNG462-C101 clinical sites and investigators.

We extend our deepest gratitude to the TNG908-C101 and TNG462-C101 patients, families, and caregivers.

References

Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-4.
Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013;6(269):pl1.
Lee W, Teckie S, Wiesner T, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Genet. 2014; 46(11):1227-32
Necchi A, Cigliola A, Tateo V, et al. Genomic classification of clinically advanced solid tumors based on methylthioadenosine phosphorylase (MTAP) genomic loss. ASCO 2024.