The MTA-cooperative PRMT5 Inhibitor MRTX1719 Demonstrates Increased Anti-Tumor Activity in Combination with *KRAS* Pathway or Immune Checkpoint Inhibitors in *MTAP* del Cancers

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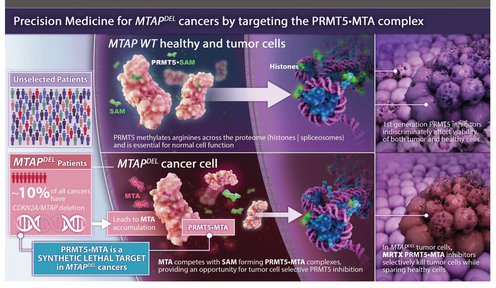
BACKGROUND

- MRTX1719 is an MTA-cooperative PRMT5 inhibitor with demonstrated clinical proof of concept for treating cancer patients harboring homozygous deletion of the *MTAP* gene (*MTAP* del). The Phase 1/2 clinical trial (NCT05245500) is on-going and actively recruiting patients with *MTAP* del cancers.
- *MTAP* del is found in ~10% of all cancers and patients exhibit remarkably poor survival vs. *MTAP* wildtype (*MTAP* WT) cancers. First-generation inhibitors of Protein Arginine Methyltransferase 5 (PRMT5) have demonstrated on-target dose-limiting hematological toxicities in clinical trials.
- MRTX1719 was designed to preferentially bind to the PRMT5•MTA complex, leveraging the increased concentration of the MTAP substrate, methylthioadenosine (MTA), that accumulates in *MTAP* del cancer cells and selectively inhibits PRMT5 activity in *MTAP* del cancer cells while sparing PRMT5 activity in normal *MTAP* WT cells.
- With a growing number of cancer types that include immunotherapy as standard of care in 1st or later lines of therapy, MRTX1719 treatment in combination with checkpoint inhibitors in *MTAP* del cancers provides an important opportunity for these patients. Here we present MRTX1719 in combination with αCTLA-4 and αPD-1 in a syngeneic *MTAP* del model.
- A diverse set of cancer types harbor *MTAP* del. This results in a diverse array of co-alterations that may act as predictive secondary biomarkers of response, contribute to mechanisms of resistance and/or enable combination treatment opportunities in sub-populations of *MTAP* del that, if implemented, could lead to improved clinical outcomes.
- MRTX1719 combinations with variant selective KRAS inhibitors in *MTAP* del / *KRAS* mutant co-altered CDX models of PDAC and NSCLC resulted in increased anti-tumor activity compared to either single agent alone.
- Malignant peripheral nerve sheath tumors (MPNST) have a high prevalence of both *MTAP* del and LOF *NF1* mutations that activate the RAS/MAPK pathway. Combination treatment of MRTX1719 and the SOS1 inhibitor MRTX0902 improved efficacy in an *MTAP* del PDX model of MPNST.

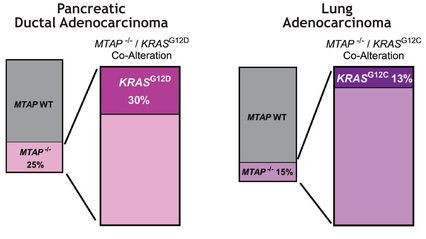
MRTX1719 preferentially binds to the PRMT5•MTA complex, selectively targeting *MTAP* del tumor cells over normal cells



Homozygous deletion of *MTAP* occurs at a significant frequency in many cancer types, creating a diverse array of co-alterations creating several actionable strategies with potential combination benefit

Cancer Type	MPNST^	Mesothelioma	PDAC	Lung Squamous	Lung Adeno	Bladder	HNSCC *	Esophageal	DLBCL	Stomach	Melanoma
MTAP del (%)‡	25	41	25	23	15	30	20	15	15	11	25
SOC includes Immunotherapy	–	✓	–	✓	✓	✓	✓	✓	–	✓	✓

‡TCGA PanCancer Atlas - 3/1/2021 *Lip & Oral Cavity
^Cortes-Ciriano et al. Cancer Discov. 2023.



MRTX1719 demonstrates greatest *MTAP* del selectivity and maintains significant potency in the HCT116 isogenic pair

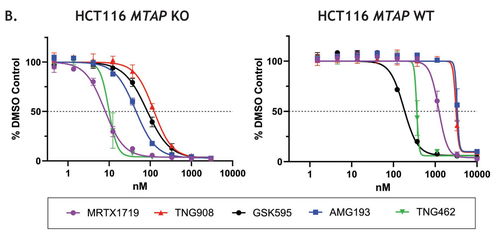
A.

	HCT116 Viability Day 10 IC_{50} (nM)		Fold Change
	MTAP KO	MTAP WT	
MRTX1719	11.3	1600	142
AMG193	61.2	3657	60
TNG462	12.5	460	37
TNG908	195	3335	17
GSK595	158	252	1.6

Average of three separate experiments

Head-to-head in vitro comparison of MRTX1719 selectivity when compared to other MTA-cooperative PRMT5 inhibitors in active clinical development with publicly disclosed structures[3-5], and GSK-3326595, a first generation PRMT5 inhibitor.

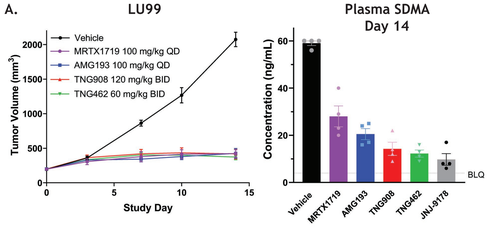
B.



Representative 10-day CTG viability assay dose response curves in HCT116 isogenic cell line models.

At doses resulting in equivalent in vivo efficacy, MRTX1719 demonstrates a favorable selectivity profile and results in reduced inhibition of plasma SDMA when compared to other MTA-cooperative PRMT5 inhibitors

A.



MRTX1719 and indicated MTA-cooperative PRMT5 inhibitors were administered via oral gavage at the indicated doses and schedules to mice bearing established LU99 cell line-derived tumor xenografts. Average tumor volumes +/- SEM were plotted over time.

Plasma samples collected from on study mice following 14 days of treatment were analyzed via mass spectrometry for symmetric dimethylarginine (SDMA). JNJ-64619178 was dosed at 10 mg/kg QD as a positive control.

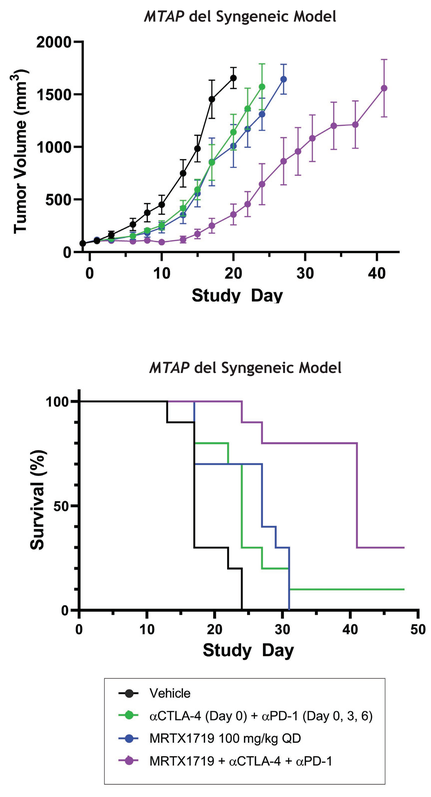
B.

Treatment (mg/kg)			Efficacy (100 - %TGI)	Plasma SDMA ng/mL	Plasma SDMA % Inhibition
MRTX1719	100	QD	12	28	53%
AMG193	100	QD	12	21	64%
TNG908	120	BID	12	14	76%
TNG462	60	BID	9	12	80%
JNJ646	10	QD	NA	10	83%

Summary of anti-tumor efficacy and plasma SDMA from LU99 in vivo study in A.

Combination treatment with MRTX1719 and dual immunotherapy checkpoint inhibitors against PD-1 and CTLA-4 enhances in vivo efficacy compared to single agent treatments in an *MTAP* del syngeneic in vivo model

A.



B.

Treatment	Median Survival (Days)	Hazard Ratio Estimate	Hazard Ratio 95% CI	Complete Response
Vehicle	17	1	NA	0
αCTLA-4 + αPD-1	24	0.18	0.06 - 0.49	1
MRTX1719	27	0.22	0.08 - 0.58	0
Combination	41	0.05	0.02 - 0.15	2

MRTX1719 and αCTLA-4 + αPD-1 were administered either alone or in combination at the indicated doses to mice bearing established mouse CDX tumors.

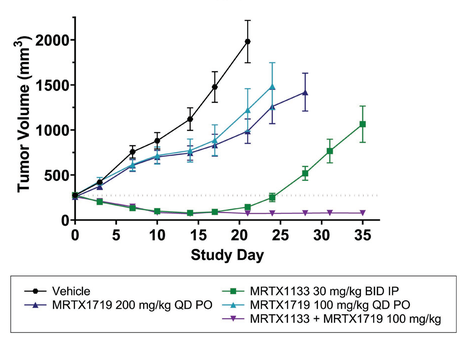
MRTX1719 was dosed daily via oral gavage while the dual checkpoint inhibitors were dosed via intraperitoneal injection, αCTLA-4 dosed day 0 and αPD-1 dosed days 0, 3, and 6.

A. Average tumor volumes +/- SEM and percent survival were plotted over time. The combination treatment group was statistically significant from all other treatments on Day 20 using a One-Way ANOVA with Dunnett's multiple comparisons test ($p<0.05$).

B. Summary of median survival analysis for syngeneic in vivo study in A.

Combination treatment with MRTX1719 and the KRAS G12D inhibitor MRTX1133 enhances in vivo efficacy in *MTAP* del / *KRAS* G12D mutant CDX models and prevents adaptive resistance observed following MRTX1133 single agent treatment

A.



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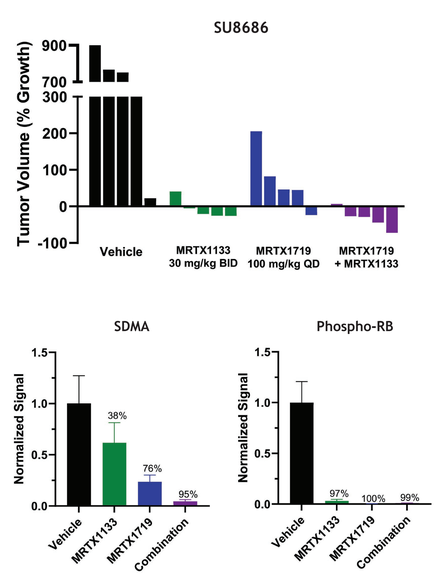
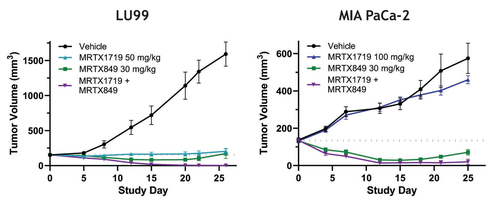


MRTX1719 and MRTX1133 were administered alone or in combination at the indicated doses to mice bearing established *KRAS* G12D xenograft models. MRTX1719 was dosed once daily via oral gavage while MRTX1133 was dosed twice per day via intraperitoneal injection.

A. Average tumor volumes +/- SEM of each treatment group for the KP4 pancreatic human xenograft model were plotted over time. The combination treatment group was statistically significant from all other treatments using a One-Way ANOVA with Dunnett's multiple comparisons test ($p<0.05$)

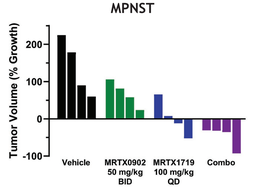
B. Percent growth was calculated from fold change in volume of each SU8686 tumor at the end of study compared to study day 0. Tumors were collected 4 hours post last dose and protein lysates were analyzed by western blot and quantified by densitometry for SDMA and phospho-RB signal.

Combination with MRTX1719 and KRAS G12C inhibitor MRTX849 enhances in vivo efficacy in *MTAP* del / *KRAS* G12C CDX models



MRTX1719 and MRTX849 were administered once daily via oral gavage either alone or in combination at the indicated doses to mice bearing established *KRAS* G12C CDX models. Average tumor volumes +/- SEM were plotted over time. Data sourced from previous disclosure[2]

Combination of MRTX1719 and SOS1 inhibitor MRTX0902 enhances in vivo efficacy compared to single agent treatments in an *MTAP* del / *NF1* mutant MPNST PDX model



MRTX1719 and MRTX0902 were administered alone or in combination at the indicated doses and schedules via oral gavage to mice bearing established patient-derived tumor xenographs, n=4 per group.

Percent growth of individual tumor volumes were calculated from fold change in volume at end of study day 35 compared to the start of dosing on study day 0.

CONCLUSIONS

- MRTX1719 demonstrates enhanced in vitro selectivity against *MTAP* knockout versus *MTAP* wildtype HCT116 cells compared to other MTA-cooperative PRMT5 inhibitors with disclosed structures.
- At doses that result in equivalent in vivo efficacy, MRTX1719 demonstrates a reduced effect on plasma SDMA compared to other competitor MTA-cooperative PRMT5 inhibitors with disclosed structures.
- Combination with dual checkpoint inhibitors targeting PD-1 and CTLA-4 produces enhanced TGI activity and survival in vivo compared to either treatment alone.
- Combined inhibition of the PRMT5•MTA complex with MRTX1719 and the RAS/MAPK pathway using KRAS mutant selective or SOS1 inhibitors leads to enhanced in vivo TGI activity compared to either single agent alone.

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ACKNOWLEDGMENTS

- Charles River Laboratories for in vivo MPNST PDX study.
- This study was sponsored by Mirati Therapeutics, a Bristol Myers Squibb company.

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Presented at the American Association for Cancer Research (AACR) Annual Meeting; April 5-10, 2024; San Diego, CA

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