Identification of Mechanism-based Combination Targets Effective with the MTA-cooperative PRMT5 Inhibitor MRTX1719 for the Treatment of *MTAP* Deleted Cancers

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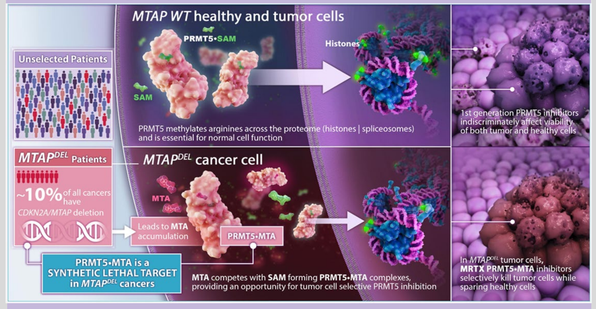
Abstract # 2779

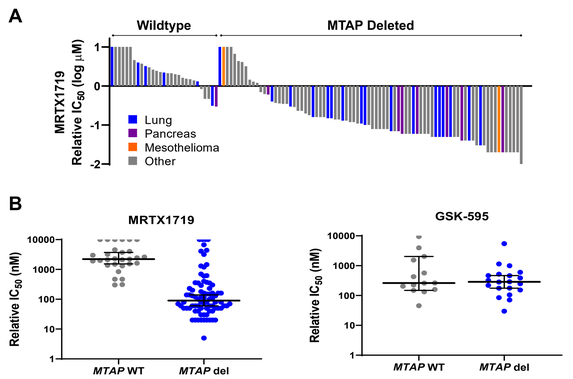
BACKGROUND

- MRTX1719 is an MTA cooperative PRMT5 inhibitor that preferentially binds to the PRMT5•MTA complex, leveraging the increased MTA concentration associated with *MTAP* deletion to selectively target *MTAP* del cancer cells.
- *MTAP* is adjacent to and co-deleted with the most commonly deleted tumor suppressor gene, *CDKN2A*, with significant prevalence in several indications of high unmet medical need including mesothelioma, cholangiocarcinoma, pancreatic, lung adeno/squamous, gastric, and esophageal cancer.
- MRTX1719 inhibited the growth of *MTAP* del CDX and PDX tumor models across various indications.
- An MRTX1719-anchored CRISPR screen identified several clinically feasible combination hypotheses.
- Prioritized strategies were tested *in vivo* where MRTX1719, in combination with agents inhibiting complementary mechanisms of action, demonstrated enhanced tumor growth inhibition compared to either agent alone, including MRTX849 (KRAS G12C), Palbociclib (CDK4/6), Olaparib (PARP), and Bcl-xL inhibitors.
- These data suggest MRTX1719, an MTA cooperative PRMT5 inhibitor currently in a Phase I clinical trial (NCT05245500), has the potential to be a synthetically lethal precision medicine for multiple indications harboring *MTAP* del with high unmet medical need, either as a single agent or in combination with clinically feasible rational combination partners.

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



MRTX1719 selectively inhibits *in vitro* growth across a broad panel of *MTAP* del cell lines

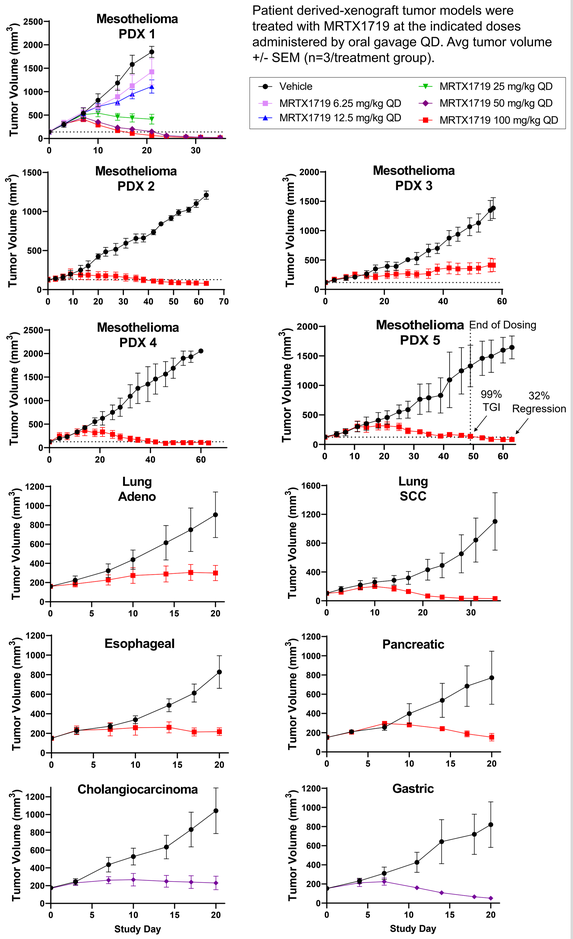


A. and **B.** MRTX1719 and GSK3326595 (B) in vitro activity across a panel of *MTAP* WT and *MTAP* del cell line models (5-day viability assay, Crown Biosciences) along with table listing median IC_{50}s and *MTAP* WT over *MTAP* del fold selectivity (B)

	Median IC_{50} (nM)	
	MRTX1719	GSK595
***MTAP* WT**	2200	286
***MTAP* del**	90	262
Fold Selectivity	24	1

RESULTS

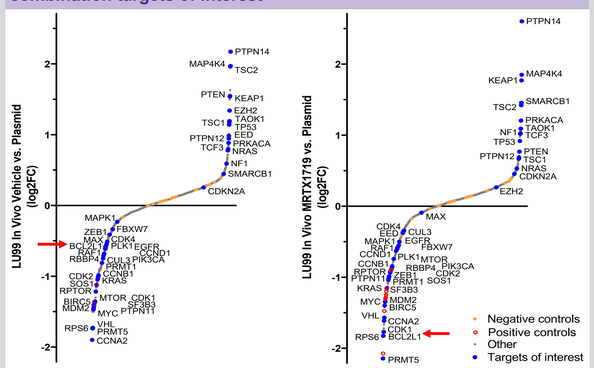
MRTX1719 exhibits tumor growth inhibition and regression in *MTAP* del mesothelioma, pancreatic, lung, gastric, esophageal, and cholangiocarcinoma PDX models



Patient derived-xenograft tumor models were treated with MRTX1719 at the indicated doses administered by oral gavage QD. Avg tumor volume +/- SEM (n=3/treatment group).

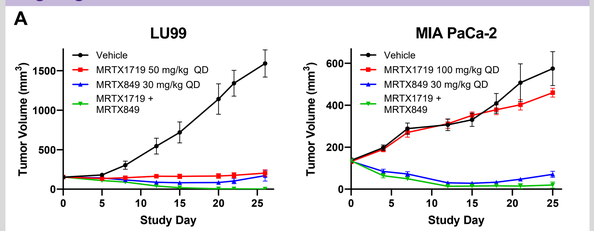
- Vehicle
- MRTX1719 6.25 mg/kg QD
- MRTX1719 12.5 mg/kg QD
- MRTX1719 25 mg/kg QD
- MRTX1719 50 mg/kg QD
- MRTX1719 100 mg/kg QD

MRTX1719-anchored CRISPR/Cas9 screens point to potential combination targets of interest

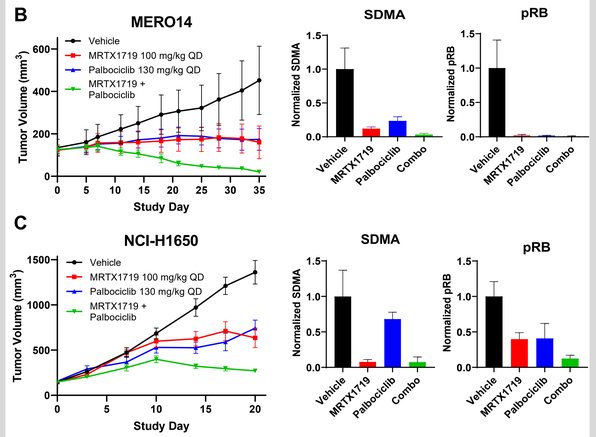


Log2 fold-change CRISPR/Cas9 screens in the LU99 model vehicle-treated tumors (left) and tumors treated with 100mg/kg MRTX1719 (right) for two weeks normalized to sgRNA plasmid library sequencing reads. Red arrow points to *BCL2L1* (Bcl-x), which stands out as a notable target with further depletion in MRTX1719 treated samples compared to vehicle.

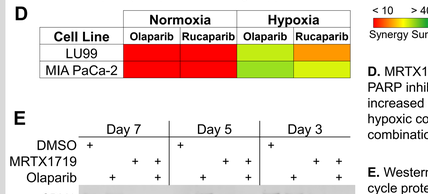
MRTX1719 in combination with KRAS G12C, CDK4/6, or PARP1 inhibitors demonstrates increased anti-tumor activity relative to single agent treatment



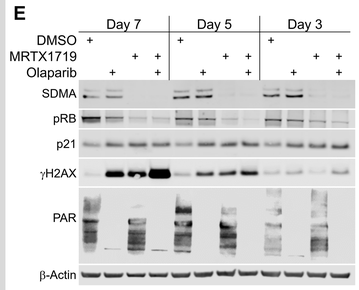
MRTX1719 and MRTX849 at the indicated doses were administered alone or in combination QD via daily oral gavage to mice bearing established cell line-derived tumor xenografts. Average tumor volumes +/- SEM were plotted over time



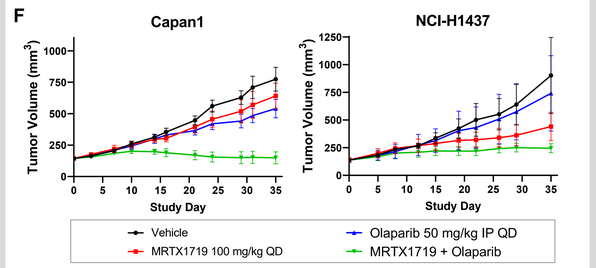
B. and C. MRTX1719 and Palbociclib at the indicated doses were administered alone or in combination QD via daily oral gavage to mice bearing established CDX MERO14 (B) and NCI-H1650 (C) tumors. Average tumor volumes +/- SEM were plotted over time. Protein lysates collected 4 hours post last dose were analyzed by western blot and quantified by densitometry for SDMA and pRb (n=3 per treatment group)



D. MRTX1719 in combination with PARP inhibitors demonstrate increased activity *in vitro* under hypoxic conditions in a 7-day viability combination screen.

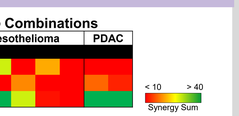


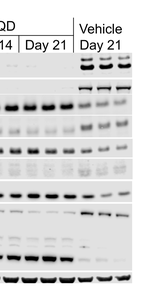
E. Western blots of selected cell cycle proteins or pharmacodynamic targets of PRMT5 or PARP from LU99 cells treated with DMSO, MRTX1719 at 250nM, Olaparib at 1000nM, or in combination; PAR = poly ADP ribose.

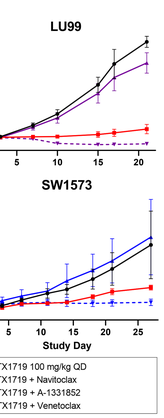


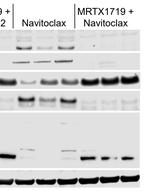
F. MRTX1719 and olaparib were administered alone or in combination to mice bearing established CDX tumors, as indicated. Average tumor volume +/- SEM were plotted over time.

MRTX1719 in combination with Bcl-xL inhibitors demonstrates synergistic activity *in vitro* and *in vivo*









A. *In vitro* MRTX1719 combination viability screen testing a panel of Bcl-2 family inhibitors across a panel of *MTAP* del cancer cell lines. Synergy scores were determined using Synergy Finder **B.** Western blot analysis of SDMA along with proliferation and apoptosis biomarkers in LU99 CDX tumors from 3 mice treated with vehicle or MRTX1719 over a time course. **C.** MRTX1719 dosed as a single agent or in combination with venetoclax, navitoclax, or A-1331852 at the doses indicated and average tumor volume ± SEM were plotted over time. **D**. Western blot of NCI-H1650 tumor lysates collected at the end of treatment from C.

CONCLUSIONS

- MRTX1719 demonstrates activity against *MTAP* deleted CDX and PDX models both in single agent and combination treatments with select targeted therapies that may be translatable to the clinic
- Increased single agent anti-tumor activity is observed following extended *in vivo* dosing of MRTX1719
- Combinations with inhibitors targeting CRISPR screen hits, including KRAS G12C, CDK4/6, PARP, and Bcl-xL, demonstrate *in vitro* synergy and/or increased tumor growth inhibition and increased effects on pathway biomarkers

ACKNOWLEDGEMENTS

- Crown Biosciences for *in vitro* breadth of efficacy assays, *in vivo* PDX and select *in vivo* CDX studies
- Charles River Laboratories for *in vivo* PDX studies
- Monoceros Biosystems for bioinformatic analysis