TNG462 is a potential best-in-class MTA-cooperative PRMT5 inhibitor for the treatment of peripheral MTAP-deleted solid tumors

Abstract # 234

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ABSTRACT

MTAP deletions occur in 10-15% of all human cancers, providing one of the largest precision oncology patient populations. MTA-cooperative PRMT5 inhibitors leverage the well-characterized synthetic lethal relationship between PRMT5 inhibition and *MTAP* deletion. TNG908, AMG 193, and MRTX1719 are all clinical stage MTA-cooperative PRMT5 inhibitors for the treatment of *MTAP*-deleted solid tumors. TNG462 is an investigational stage MTA-cooperative PRMT5 inhibitor with significantly enhanced potency, selectivity and extended target coverage designed to be a best-in-class treatment for patients with peripheral *MTAP*-deleted cancer. *In vitro*, TNG462 is 45X selective for *MTAP*-deleted cancer cell lines over isogenic MTAP WT cell lines and has marked selectivity for *MTAP*-deleted cancer cell lines independent of lineage in a large, diverse cell line panel. TNG462 demonstrates durable PD modulation *in vitro* and *in vivo* consistent with high affinity binding to PRMT5. Oral administration of TNG462 drives dose-dependent antitumor activity including durable tumor regressions and complete responses in multiple cell line- and patient-derived xenograft models. With enhanced potency and selectivity for *MTAP*-deleted cancer cells, and improved pharmacokinetic properties to extend target coverage, TNG462 has the potential for broader and deeper clinical activity in peripheral *MTAP*-deleted solid tumors.

MTA-cooperative PRMT5 inhibitors are synthetic lethal with *MTAP* deletion

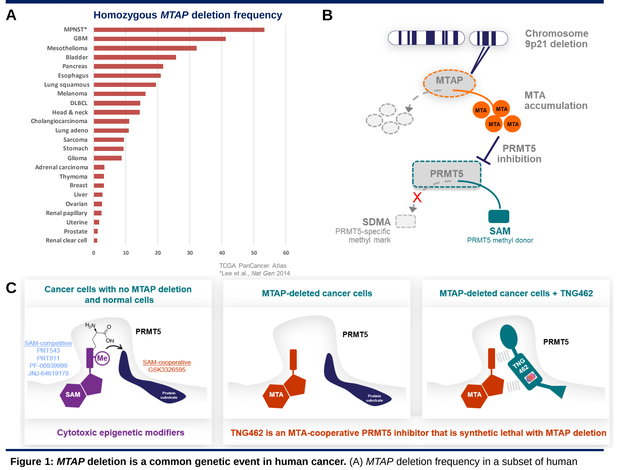


Figure 1: *MTAP* deletion is a common genetic event in human cancer. (A) *MTAP* deletion frequency in a subset of human cancers (Cerami et al 2012; Gao et al 2013; Lee et al 2014). (B) Biological rationale for sensitivity of *MTAP*-deleted cells to PRMT5 perturbation. (C) Differentiating strategy between non-MTA-cooperative PRMT5 inhibitors and TNG462.

PD modulation is on-target and selective for *MTAP*-deleted cells

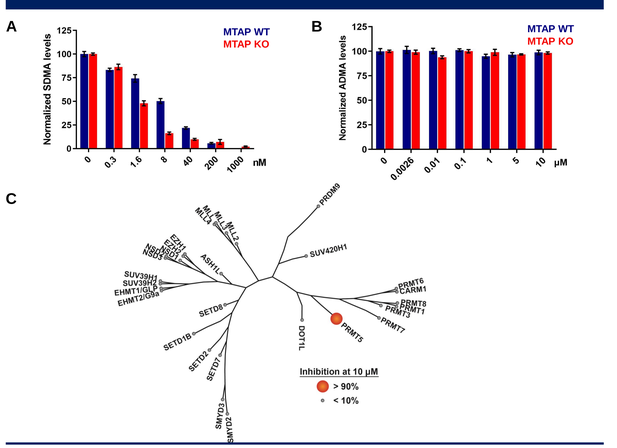


Figure 2: TNG462 PD modulation is on-target and is selective for *MTAP*-deleted cells *in vitro*. (A) TNG462 pharmacodynamic activity to inhibit PRMT5 in the HAP1 MTAP-isogenic cell line pair. The data are normalized to a DMSO control for each cell line and presented as mean ± SD. (B) Pharmacodynamic activity of TNG462 to inhibit Type I PRMTs in the HAP1 MTAP-isogenic cell line pair. The data are normalized to a DMSO control for each cell line and presented as mean ± SD. (C) Dendrogram demonstrating biochemical selectivity of TNG462 for PRMT5 in a histone methyltransferase panel.

TNG462 antiproliferative activity is potent and 45X selective for *MTAP*-deleted cancer cells

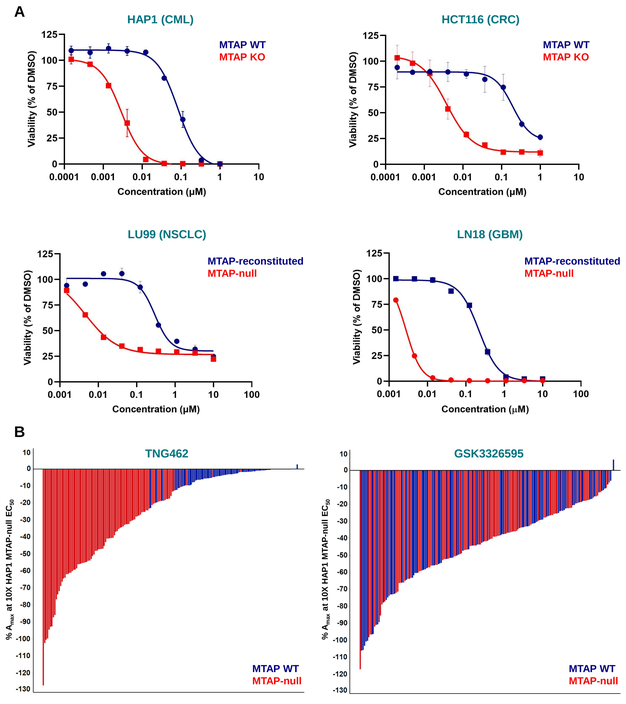


Figure 3: TNG462 antiproliferative activity is selective for *MTAP*-deleted cells *in vitro*. (A) Antiproliferative activity of TNG462 in MTAP-isogenic cell lines engineered by either CRISPR-mediated MTAP gene knockout (HAP1 and HCT116) or by reconstituting exogenous MTAP in an endogenous *MTAP*-deleted cell line (LU99 and LN18). Data are presented as mean ± SD. (B) 180 cancer cell lines representing multiple cancer lineages including NSCLC, PDAC, bladder, CNS, and heme malignancies were profiled with either TNG462 or GSK3326595, a non-MTA-cooperative PRMT5 inhibitor, in a 7-day CellTiter-Glo assay. For each cell line, the maximum effect at a concentration equal to 10X the HAP1 MTAP-null GI_{50} is reported for each compound, and the cell lines are colored by MTAP status. TNG462 is >20x more potent than GSK3326595 in MTAP-null cell lines *in vitro*.

TNG462 binds PRMT5 with high affinity in *MTAP*-deleted cells

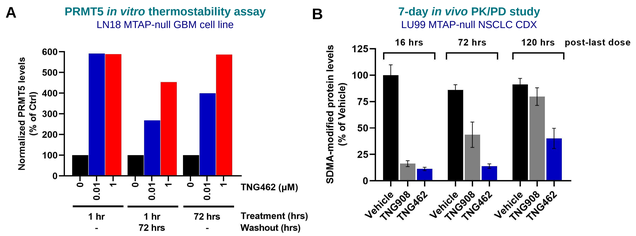
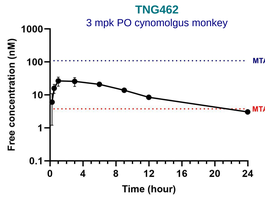


Figure 4: TNG462 binds PRMT5 with high affinity in *MTAP*-deleted cancer cells *in vitro* and *in vivo*. (A) Cellular thermostability assay where the LN18 *MTAP*-deleted cancer cell line was treated with TNG462 at the indicated concentrations. Cells were either treated for 1 hr and assayed immediately (1 hr treatment, no washout), treated for 1 hr and assayed after 72 hrs incubation in compound-free media (1 hr treatment, 72 hrs washout), or following 72 hrs compound treatment without washout. (B) An SDMA-modified substrate was quantified by immunoblot and normalized to a loading control from tumors treated for 7 days with either TNG462 (30 mpk BID in 5% DMA/20% Captisol) or TNG908 (120 mpk BID in 5% DMA/20% Captisol). The free exposures for the molecules were matched to ensure similar coverage of the *in vitro* PD IC_{50}. n=4 tumors per group. Data are presented as mean ± SEM.

Superior TNG462 PK properties predict QD clinical dosing



	Predicted human properties
DDI risk	Low risk of CYP or transporter-mediated DDI
$T_{1/2}$	Long T1/2 across preclinical species predicts daily clinical dosing regimen
Peak-to-trough ratio	≤ 2X $C_{max}/C_{24\ hrs}$ at steady-state

Figure 5: TNG462 demonstrates superior PK properties to extend target coverage. Free plasma exposures following 3 mg/kg oral gavage of TNG462 in cynomolgus monkeys. Table content summarizes human PK predictions based on preclinical *in vitro* and *in vivo* studies. The HAP1 MTAP-null and MTAP WT GI_{50}s from a 7-day viability assay are indicated for TNG462. n=3 per group. Data are presented as mean ± SD.

TNG462 efficacy *in vivo* is on-target

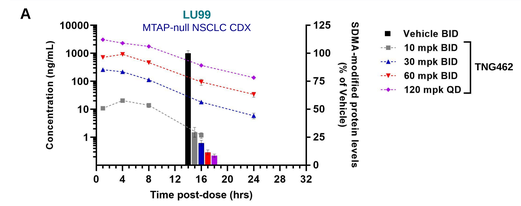


Figure 6: TNG462 antitumor activity is on-target in cell line-derived xenograft models. (A) Antitumor activity in LN18 MTAP-null CDX model with TNG462 dosed as indicated. n=8 mice per group. Data are presented as mean ± SEM. (B) 7-day PK/PD study using the LU99 *MTAP*-deleted xenograft model. TNG462 was dosed as indicated, and PK and tumor samples were harvested at the indicated timepoints. n=4 tumors per group, and data are presented as mean ± SEM. (C) Antitumor activity in the LU99 MTAP-null CDX model with TNG462 or TNG908 dosed as indicated. n=8 mice per group. Data are presented as mean ± SEM. Regression is defined as final mean tumor volume < 30% initial mean tumor volume. (D) Terminal pharmacodynamic analysis of tumors from (C). An SDMA-modified substrate was quantified by immunoblot and normalized to a loading control from tumors processed at the indicated timepoints. n=4 tumors per group. Data are presented as mean ± SEM.

TNG462 drives dose-dependent antitumor activity and deep regressions in *MTAP*-deleted xenograft models

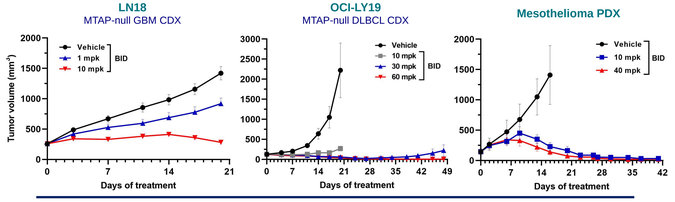


Figure 7: TNG462 antitumor activity is dose-dependent in xenograft models. Antitumor activity in the LN18 MTAP-null CDX model (A), the OCI-LY19 MTAP-null DLBCL CDX model (B) or a MTAP-null mesothelioma PDX model with TNG462 dosed as indicated. n=6-8 mice per group. Data are presented as mean ± SEM. TNG462 was dosed in acidified ddH20 for LN18 and the mesothelioma PDX model, and in 5% DMA/20% Captisol for OCI-LY19.

TNG462 antitumor activity is histology-agnostic in *MTAP*-deleted PDX models

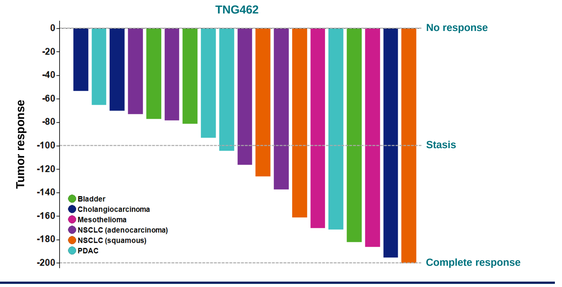


Figure 8: TNG462 antitumor activity is histology-agnostic in *MTAP*-deleted patient-derived xenograft models. (A) Waterfall plot demonstrating activity of TNG462 in PDX models representing the indicated tumor histologies. TNG462 was dosed as either one of two formulations: 40 mpk BID in acidified water or 60 mpk BID in 5% DMA/20% Captisol. Each formulation gave equivalent TNG462 exposure. n=3 mice per group for all of the PDX models, except one bladder and one cholangiocarcinoma model which had n=6 mice per group. -%TGI is reported for tumors with Tumor $Volume_{final} \geq$ Tumor $Volume_{initial}$ (values -100 to 0). %Tumor $Volume_{initial}$ -100 is reported for models with Tumor $Volume_{final} <$ Tumor $Volume_{initial}$ (values -200 to -100). "Stasis" is defined as 100% TGI and "Complete response" is defined as %Tumor $Volume_{initial}$ equal to -100%.

TNG462 re-sensitizes tumors with incomplete response to an MTA-cooperative PRMT5 inhibitor

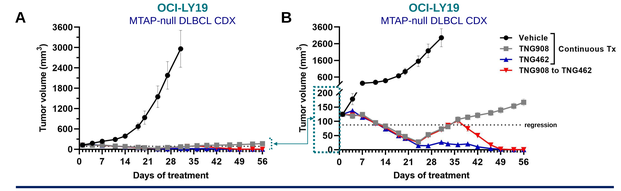


Figure 9: TNG462 overcomes incomplete response to an MTA-cooperative PRMT5 inhibitor in a DLBCL CDX model. (A) The MTAP-null OCI-LY19 DLBCL model was either dosed continuously with 120 mpk BID TNG908 or 40 mpk BID TNG462, or switched from 120 mpk BID TNG908 to 40 mpk BID TNG462 when mean tumor volume recovered to approximate mean starting tumor volume. (B) Same data as (A) with broken y-axis to highlight region of interest. n=8 mice Vehicle group, n=10 mice for continuous TNG462 treatment group, n=12 mice for continuous TNG908 treatment group and "TNG908 to TNG462" group. Data are presented as mean ± SEM. Regression is defined as final mean tumor volume < 30% initial mean tumor volume.

SUMMARY

- **TNG462 is a potent and selective molecule that inhibits PRMT5 selectively in *MTAP*-deleted cancer cells**
- **TNG462 is 45X selective for MTAP-null cells in MTAP-isogenic cell lines representing different cancer lineages, and is selective for *MTAP-deleted* cells in a large cancer cell line panel**
- **Efficacy *in vivo* in MTAP-null cell-line derived xenograft models is consistent with TNG462 on-target and dose-dependent PRMT5 inhibition**
- **TNG462 efficacy in patient-derived xenograft models is lineage-agnostic**
- **Durable PD modulation *in vitro* and *in vivo* is consistent with high affinity binding of TNG462 to PRMT5 in *MTAP*-deleted cancer models**
- **TNG462 drives a complete response in an MTAP-null CDX model pre-treated with an MTA-cooperative PRMT5 inhibitor**
- **Superior PK properties of TNG462 supports predicted QD clinical dosing with minimal peak-to-trough ratio and low risk of DDI**
- **Preclinical data package suggests TNG462 has the potential for broader and deeper clinical activity in peripheral *MTAP*-deleted solid tumors relative to other MTA-cooperative PRMT5 inhibitors**

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the generous contributions from the scientific teams at ChemPartner, Champions Oncology, Crown Biosciences, Enamine, Pharmaron, WuXi AppTec, and XenoSTART

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