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

Abstract #4970

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INTRODUCTION

MTAP deletions occur in 10-15% of all human cancers, which provides 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 is a clinical stage MTA-cooperative PRMT5 inhibitor 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 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. Oral administration of TNG462 drives dose-dependent antitumor activity including durable tumor regressions and complete responses in cell line- and patient-derived xenograft models representative of clinically relevant histologies. Preclinical data suggest a low risk for drug-drug interactions, supporting clinical combination strategies. 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 MTAP-deleted solid tumors than other MTA-cooperative PRMT5 currently being evaluated in clinical trials.

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

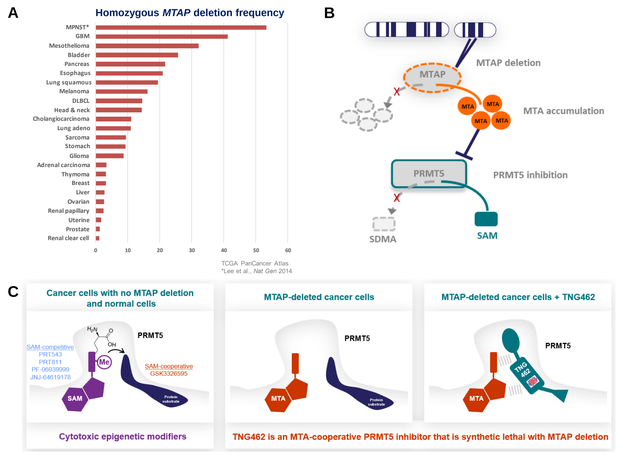


Figure 1: *MTAP* deletion is a common genetic event in human cancer. (A) *MTAP* deletion frequency in a subset of human cancers (Cerami et al 2012; Gao et al 2013; Lee et al 2014). (B) Biological rationale for sensitivity of *MTAP*-deleted cells to PRMT5 perturbation. (C) Differentiating strategy between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

TNG462 is on-target and selective for *MTAP*-deleted cells

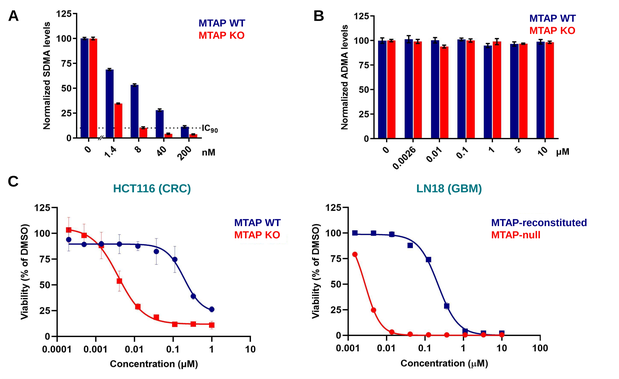


Figure 2: TNG462 PD modulation is on-target and is selective for *MTAP*-deleted cells *in vitro*. (A) TNG462 pharmacodynamic activity to inhibit PRMT5 in the HAP1 MTAP-isogenic cell line pair. The data are normalized to a DMSO control for each cell line and presented as mean ± SD. (B) Pharmacodynamic 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) Antiproliferative activity of TNG462 in MTAP-isogenic cell lines engineered by either CRISPR-mediated MTAP gene knockout (HCT116) or by reconstituting exogenous MTAP in an endogenous *MTAP*-deleted cell line (LN18). Data are presented as mean ± SD.

TNG462 antiproliferative activity is selective for MTAP-null models across histologies

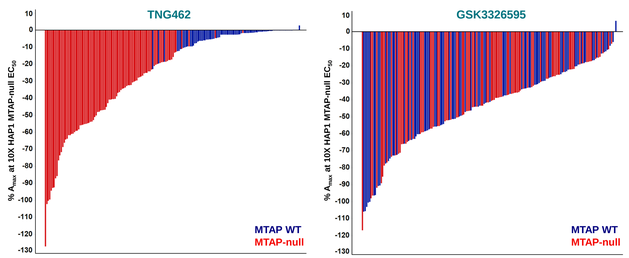


Figure 3: TNG462 antiproliferative activity is selective for *MTAP*-deleted cells *in vitro*. 180 cancer cell lines representing multiple cancer lineages including NSCLC, PDAC, bladder, CNS, and heme malignancies were profiled with either TNG462 or GSK3326595, a non-MTA-cooperative PRMT5 inhibitor, in 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 efficacy *in vivo* is on-target

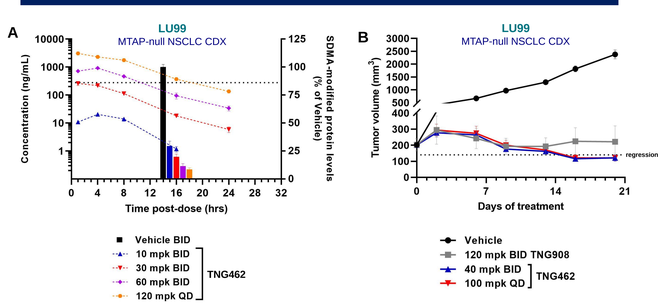


Figure 4: TNG462 antitumor activity is on-target in an MTAP-null cell line-derived xenograft model. (A) 7-day PK/PD study using the LU99 *MTAP*-deleted xenograft model. TNG462 was dosed as indicated, and PK and tumor samples were harvested at the indicated timepoints. n=4 tumors per group, and data are presented as mean ± SEM. (B) Antitumor activity in the LU99 MTAP-null CDX model with TNG462 or TNG908 dosed as indicated. In the efficacy study, 40 mpk BID and 100 mpk QD TNG462 were dosed in an acidified water formulation that provided similar exposure 60 mpk BID or 120 mpk QD dosed in 5% DMA/20% Captisol, which was used in the PK/PD. n=8 mice per group. Data are presented as mean ± SEM. Regression is defined as final mean tumor volume < 30% initial mean tumor volume.

TNG462 drives strong responses across histologies in *MTAP*-deleted PDX models

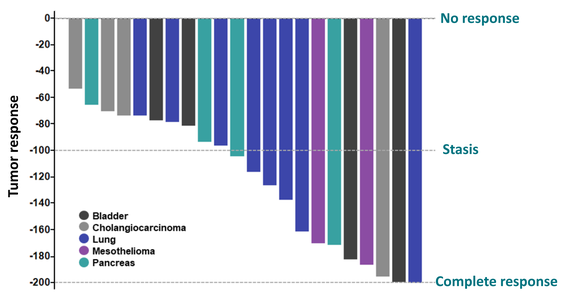


Figure 5: TNG462 antitumor activity is histology-agnostic in *MTAP*-deleted patient-derived xenograft models. (A) Waterfall plot demonstrating activity of TNG462 in PDX models representing the indicated tumor histologies. TNG462 was dosed as either one of two formulations: 40 mpk BID in acidified water 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 drives dose-dependent antitumor activity and deep regressions in *MTAP*-deleted xenograft models

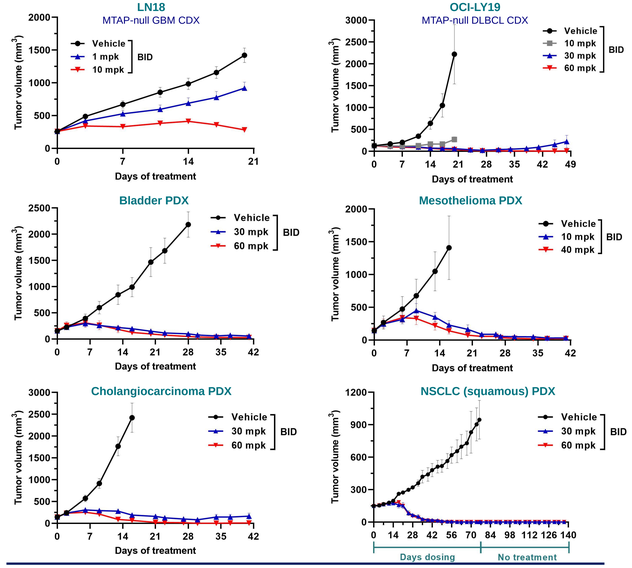


Figure 6: TNG462 antitumor activity is dose-dependent in xenograft models. Antitumor activity in the LN18 MTAP-null CDX model, the OCI-LY19 MTAP-null DLBCL CDX model, or MTAP-null PDX models representing the indicated histologies. TNG462 dosed as indicated. n=3-8 mice per group. Data are presented as mean ± SEM. TNG462 was dosed in acidified ddH20 for LN18 and the mesothelioma PDX model, and in 5% DMA/20% Captisol for the remaining models. For the NSCLC (squamous) PDX model, the mice were either dosed, or monitored after discontinuation of dosing, for the indicated time periods.

TNG462 re-sensitizes tumors with incomplete response to 1st generation MTA-cooperative PRMT5 inhibitor

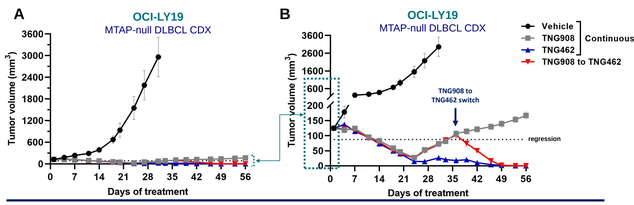
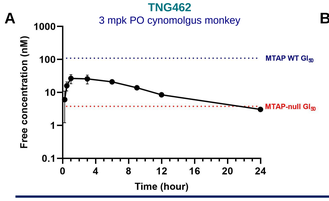


Figure 7: TNG462 overcomes incomplete response to an MTA-cooperative PRMT5 inhibitor in a DLBCL CDX model. (A) The MTAP-null OCI-LY19 DLBCL model was either dosed continuously with 120 mpk BID TNG908 or 40 mpk BID TNG462, or switched from 120 mpk BID TNG908 to 40 mpk BID TNG462 when mean tumor volume recovered to an approximate mean starting tumor volume (Day 36). (B) Same data as (A) with broken *y*-axis to highlight region of interest. Arrow denotes time of compound switch. 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.

Superior TNG462 PK properties support QD clinical dosing



B

	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 8: 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. (B) Key TNG462 characteristics.

PRMT5 inhibitors synergize with targeted therapeutics *in vivo*

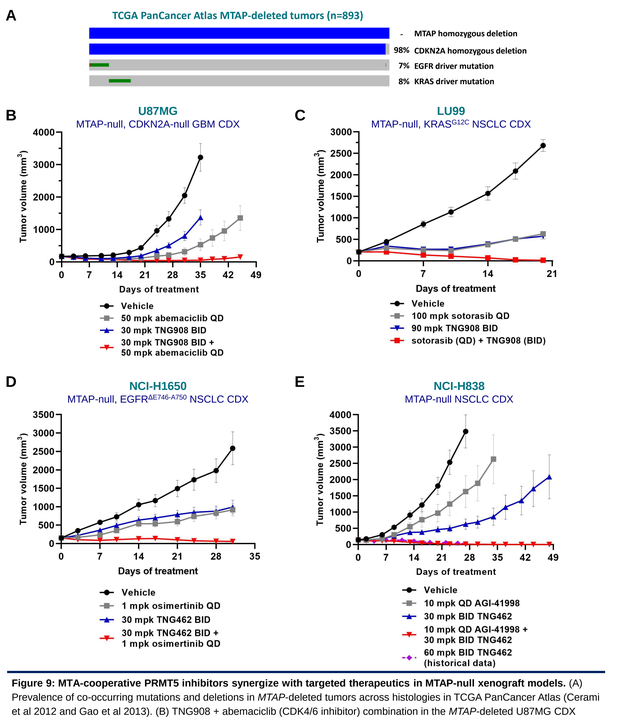


Figure 9: MTA-cooperative PRMT5 inhibitors synergize with targeted therapeutics in MTAP-null xenograft models. (A) Prevalence of co-occurring mutations and deletions in *MTAP*-deleted tumors across histologies in TCGA PanCancer Atlas (Cerami et al 2012 and Gao et al 2013). (B) TNG908 + abemaciclib (CDK4/6 inhibitor) combination in the *MTAP*-deleted U87MG CDX model. (C) TNG908 + sotorasib (KRAS G12C inhibitor) combination in the *MTAP*-deleted, $KRAS^{mut}$ LU99 CDX model. The sotorasib dose was adjusted in combination to provide an equivalent exposure to single agent. (D) TNG462 + osimertinib (EGFR inhibitor) in the *MTAP*-deleted, $EGFR^{mut}$ NCI-H1650 CDX model. This study was on-going at the time of poster preparation. (E) TNG462 + AGI-41998 (MAT2A inhibitor) in the *MTAP*-deleted NCI-H838 CDX model. TNG908 and TNG462 were both dosed sub-therapeutically in these studies.

SUMMARY

- **TNG462 is a potent and selective molecule that inhibits PRMT5 selectively in *MTAP*-deleted cancer cells and spares PRMT5 in MTAP WT cells**
- **TNG462 is 45X selective for MTAP-null cells in isogenic cell lines from different cancer lineages and maintains selectivity 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 histology-agnostic**
- **TNG462 drives a complete response in an MTAP-null CDX model pre-treated with a 1st generation MTA-cooperative PRMT5 inhibitor**
- **Superior PK properties of TNG462 support QD clinical dosing with minimal peak-to-trough ratio and low risk of DDI**
- **TNG462 synergizes with targeted therapeutics in MTAP-deleted xenograft models**
- **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**

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