TNG908 is an MTAPnull-selective PRMT5 inhibitor that drives tumor regressions in MTAP-deleted xenograft models across multiple histologies

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ABSTRACT

TNG908 is an investigational PRMT5 inhibitor with a novel MTAP-selective binding mode designed to leverage the synthetic lethal interaction (MTAP−/−/PRMT5−/−) and a novel strategy to target human cancers with a common MTAP deletion. TNG908 displays robust antitumor activity against MTAP−/−/PRMT5−/− cells and shows negligible activity in MTAP−/−/PRMT5+ cells, a hallmark of synthetic lethality. TNG908 selectively kills MTAP−/−/PRMT5−/− cells in heterologous cell populations and with minimal MTA accumulation for efficacy and selectivity in preclinical tumor models across many histologies. In a nonclinical xenograft model, TNG908 inhibited tumor growth and induced regression of MTAP−/−/PRMT5−/− xenografts independent of MTAP−/−/PRMT5−/− deletion and KRAS mutation status. TNG908 selectively kills MTAP−/−/PRMT5−/− cells in multiple xenograft models, including skin (head and neck squamous), lung (adenocarcinoma and squamous), and pancreatic adenocarcinoma xenograft models. Preclinical studies demonstrate that TNG908 is efficacious in MTAP−/−/PRMT5−/− xenograft models across multiple histologies, including lung (adenocarcinoma and squamous), pancreatic adenocarcinoma, and head and neck squamous xenografts. The authors gratefully acknowledge the generous contributions from: AppTec, EMD Serono, Enanta, Genentech, Labcorp, Pharmaron, Takeda, and Verastem.

KEYWORDS

MTAP deficiency, PRMT5, synthetic lethality, xenograft models, head and neck squamous, lung adenocarcinoma, pancreatic adenocarcinoma, KRAS inhibition

TNG908 is an MTAPnull-selective PRMT5 inhibitor

TNG908 is effective in MTAPnull xenograft models across histologies

MAT2A and PRMT5 inhibition are synergistic

SUMMARY

- MTAP-selective PRMT5 inhibitors are efficacious in an admixture of MTAP−/− and MTAP+ tumors, and require minimal MTA accumulation for efficacy and selectivity.
- TNG908 demonstrates IC50 selectivity for MTAP-null cells in MTAP-negative cell lines representing different cancer lineages, and is MTAP-selective in a large cancer cell line panel.
- TNG908 is MTAP-selective in vivo, and shows tumor regressions as a single agent in MTAP null xenograft models representing multiple tumor histologies.
- TNG908 is brain-penetrant and effective in MTAP-null GBM xenograft models.
- Treatment of KRASG12Cmutant lung adenocarcinomas with TNG908 and a KRASG12C mutant inhibitor may be of clinical benefit in lung cancers with concurrent MTAP deletion and KRASG12C mutation.
- MAT2A and PRMT5 inhibition are synergistic, and may provide a beneficial therapeutic strategy.

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