TNG908, a brain-penetrant MTA-cooperative PRMT5 inhibitor, is efficacious in preclinical MTAP-deleted models, including glioblastoma

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Abstract #DDR3-33

ABSTRACT

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The median overall survival of GBM patients is 11 months with standard of care therapies, demonstrating the significant need for the development of more effective novel therapies. TNG908 is a clinical-stage MTA-cooperative PRMT5i that is selectively active in MTA-cooperative PRMT5i tumors in vivo through OXPHOS inhibition. Amino acid biosynthesis/mRNA translation are among the most significantly depleted with TNG908 treatment. (B) Proteomic analysis in GBM patient samples showed co-expressed genes between TNG908 and PRMT5i treatment. (C) Protein expression is not significantly altered in TNG908 treated GBM tumors, which is consistent with TNG908 being a systemic anti-angiogenic strategy. (D) Differentiating strategy between non-MTA-deleted GBM and MTA-deleted GBM are inferences as follows: TNG908 driven near tumor stasis and increased median survival by 34 weeks.

RESULTS

TNG908 is selective and efficacious in MTAP-null GBM cell lines regardless of MGMT status. (A) TNG908 shows high selectivity compared to MTA-null cancer cell lines across multiple cell lines, including non-GBM tumors. TNG908 is 15X selective for MTAP deletion null cells. (B) TNG908 dose-dependent efficacy across GBM subcutaneous xenograft models. TNG908 drives strong, histology-agnostic antitumor responses. (C) TNG908 drives durable tumor regressions in MTAP-null patient-derived xenograft models. TNG908 drives strong antitumor responses in GBM subcutaneous and orthotopic models. (D) TNG908 drives antitumor responses in MTA-deleted glioblastoma xenograft models. The survival curves for TNG908 treated mice are significantly longer than for either MTAP deletion or untreated control mice. (E) TNG908 demonstrates histology-agnostic antitumor activity in GBM xenograft models. TNG908 shows strong preclinical efficacy across histologies, including non-GBM tumors. TNG908 has high permeability and is not a substrate for the breast cancer resistance protein (BCRP) efflux transporters. Consistent with these favorable attributes, TNG908 demonstrated in vivo brain penetration in multiple preclinical models, including non-GBM tumors. Consistent with these favorable attributes, TNG908 demonstrated in vivo brain penetration in multiple preclinical models, including non-GBM tumors. TNG908 oncoselectivity is not brain penetrant in organoids and xenograft models. TNG908 oncoselectivity and CDK4/6 inhibition synergize preclinically in MTAP-deleted GBM cell lines.

TNG908 and CDK4/6 inhibition synergize preclinically in MTAP-null, CDKN2A-null xenograft models

SUMMARY

• MTAP deletion occurs in 10-30% solid tumors and ~40% GBM
• TNG908 is an MTA-cooperative PRMT5 inhibitor with 10X selectivity for MTAP-deleted cells
• TNG908 shows strong preclinical efficacy across histologies
• TNG908 is brain-penetrant and efficacious in subcutaneous and orthotopic MTAP-null GBM models
• Rational and data-supported combination strategies with CDK4/6 inhibitors
• PTEN loss is a potential sensitizing genetic context for PRMT5 inhibitors in TNG908
• TNG908 is a clinical-stage, potent, brain-penetrant MTA-cooperative PRMT5i in vivo.

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REFERENCES