TNG462, an MTA-cooperative PRMT5 inhibitor, demonstrates strong efficacy in combination with clinically relevant targeted therapies in MTAP-null preclinical models

Abstract #2996

Minjie Zhang, Alice Tsai, Kevin M. Cottrell, Brian Haines, Yi Yu, Alan Huang, Jannik N. Andersen, Adam S. Crystal and Kimberly J. Briggs

Tango Therapeutics, Boston, MA, USA

Abstract

TNG462 is a clinical-stage, MTA-cooperative PRMT5 inhibitor currently being evaluated in an ongoing phase I/II clinical trial for solid tumors with MTAP loss. Approximately 10-15% of all human cancers exhibit MTAP deletions, including 10-15% of lung cancer and more than 20% of pancreatic adenocarcinomas.

MTAP deletion frequently co-occurs with other genetic alterations: ~20-30% of MTAP-deleted lung adenocarcinomas and ~90% of MTAP-deleted pancreatic ductal adenocarcinomas (PDAC) also harbor KRAS mutations, while ~25% of MTAP-deleted lung adenocarcinomas are also EGFR mutant. Although TNG462 monotherapy drives deep and durable tumor regressions in MTAP-null preclinical models, we investigated its potential in combination with therapies targeting actionable genetic alterations. In relevant preclinical models, the combination of TNG462 with either KRAS or EGFR inhibitors led to significant tumor regressions, surpassing the effects of either agent alone. This supports our clinical development plans for TNG462, which include targeted combinations with two RAS(ON) inhibitors, daraxonrasib (RMC-6236) and zoldonrasib (RMC-9805) from Revolution Medicines, as well as the EGFR inhibitor osimertinib from AstraZeneca.

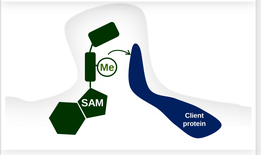
Additionally, nearly all MTAP-deleted cancers are also CDKN2A-deleted due to the proximity of the two genes on chromosome 9p, resulting in de-repression of the cyclin D-dependent CDK4/6 complexes, which creates a susceptibility to CDK4/6 inhibition. Significant efficacy was observed in preclinical models with the combination of TNG462 and CDK4/6 inhibitors, supporting a potential development path in GBM for our next generation CNS penetrant PRMT5 inhibitor, TNG456, with abemaciclib.

Lastly, MTAP loss also sensitizes cells to MAT2A inhibition, providing strong rationale for combining PRMT5 inhibitors with MAT2A inhibitors. Preclinical data demonstrated significant efficacy when subtherapeutic doses of both agents are combined. However, TNG462 monotherapy at a clinically relevant dose achieved comparable benefits to the combination.

Collectively, these findings strongly support evaluating TNG462 in combination with other targeted therapies in clinical trials for patients with cancers that exhibit MTAP loss.

TNG462 is an MTA-cooperative PRMT5 inhibitor

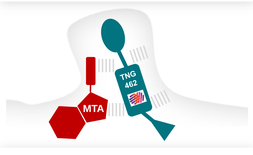
Normal cells



Active PRMT5

- Active SAM-PRMT5 complexes are predominant in normal cells
- Non-MTA cooperative PRMT5 inhibitors are equally cytotoxic in normal and MTAP-null cells

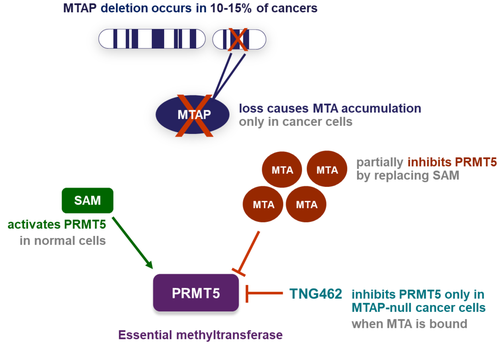
MTAP-null cancer cells



Inactive PRMT5

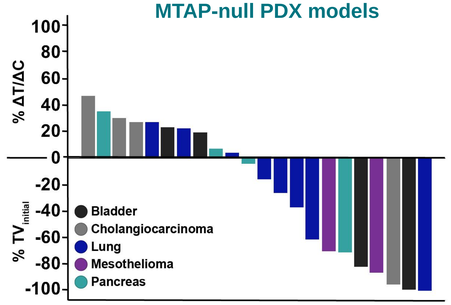
- Inactive MTA-PRMT5 complexes predominate in MTAP-null cancer cells
- MTA-cooperative PRMT5 inhibitors preferentially kill cells with MTAP-loss

MTA-cooperative PRMT5 inhibitors are synthetic lethal with MTAP loss



TNG462 is efficacious across histologies

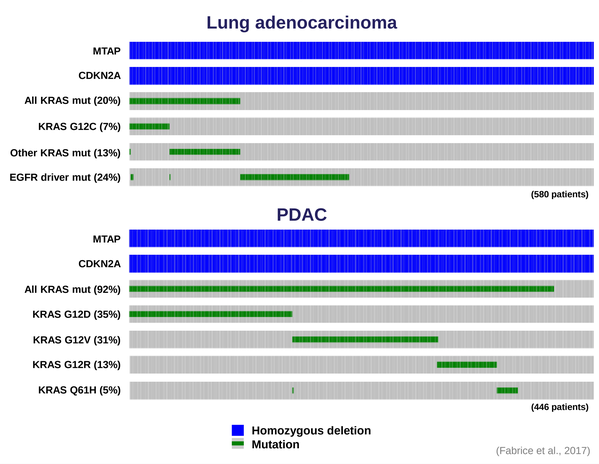
MTAP-null PDX models



TNG462 was dosed orally at 60 mg/kg BID. N = 3-5 mice/group/model. Lung PDX models represent either squamous or adenocarcinoma subtypes.

MTAP deletions commonly co-occur with KRAS and EGFR mutations

AACR Project GENIE

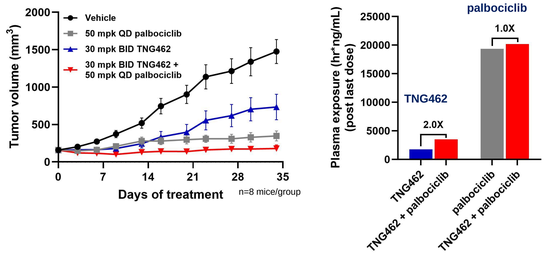


(Fabrice et al., 2017)

TNG462 + CDK4/6i drives a combination benefit in vivo

MIA PaCa-2

MTAP-null PDAC CDX

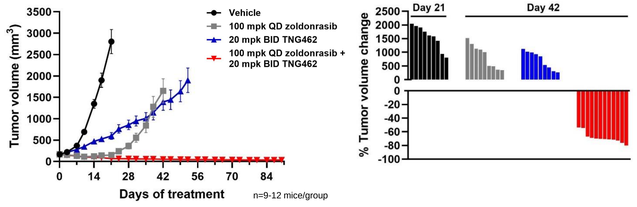


TNG462 + RAS(ON) inhibitor combination drives durable regressions in MTAP-null, KRAS-mut tumors

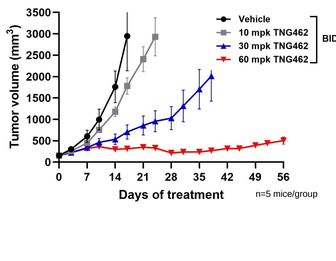
KP4

MTAP-null, KRAS^{G12D} PDAC CDX

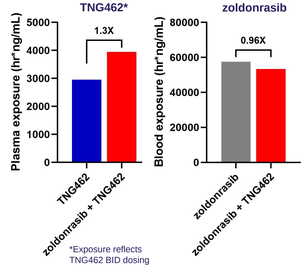
TNG462 + zoldonrasib (RMC-9805)



TNG462 monotherapy



Terminal exposures from combination

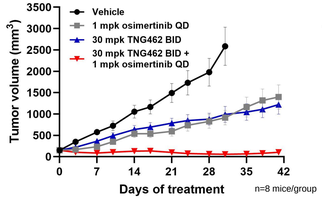


TNG462 + EGFRi (osimertinib) drives regressions in MTAP-null, EGFR-mut tumors

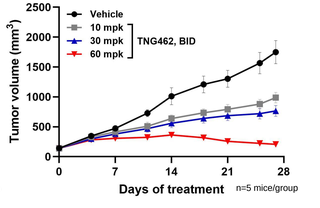
NCI-H1650

MTAP-null, EGFR^{mut} NSCLC CDX

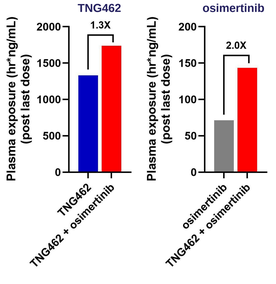
TNG462 + osimertinib



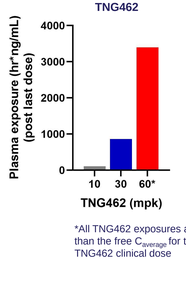
TNG462 monotherapy



Terminal exposures from combination



Terminal monotherapy exposures

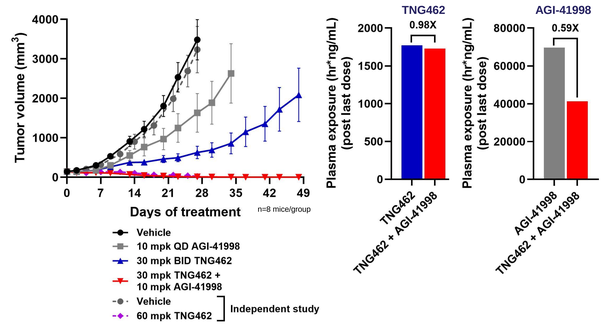


*All TNG462 exposures are lower than the free $C_{average}$ for the 160 mg TNG462 clinical dose

Single agent TNG462 is as efficacious as combination with MAT2Ai

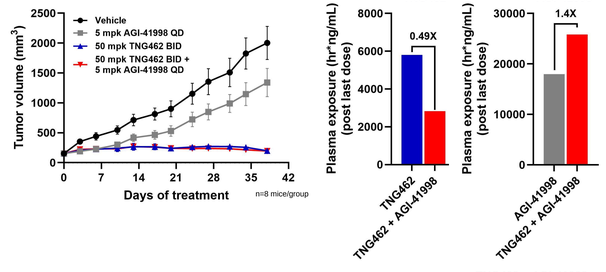
NCI-H838

MTAP-null NSCLC CDX

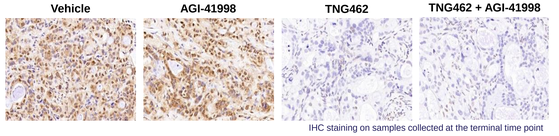


CAPAN-1

MTAP-null PDAC CDX



SDMA IHC



IHC staining on samples collected at the terminal time point

Summary

- MTAP loss frequently co-occurs with genetic alterations served by targeted therapies
- Preclinical TNG462 combination studies demonstrate combination benefit including durable tumor regressions. All treatments for all the studies were generally tolerated with an average body weight loss of < 5%
- Preclinical tumor response to combination of a sub-therapeutic TNG462 dose with the RAS(ON) G12D-selective inhibitor zoldonrasib supports clinical collaboration with Revolution Medicines for TNG462 + zoldonrasib and TNG462 + RAS(ON) multi-selective inhibitor daraxonrasib
- TNG462 combined with the EGFR inhibitor osimertinib (AstraZeneca) showed superior efficacy compared to monotherapy
- TNG462 demonstrated strong efficacy in combination with CDK4/6 inhibitor palbociclib
- TNG462 at an efficacious dose demonstrates robust efficacy, matching its combination with the MAT2A inhibitor AGI-41998
- These preclinical findings provide strong support for evaluating TNG462 in combination with other targeted therapies in clinical trials for patients with cancers featuring MTAP loss
- TNG462 alone or in combination with pembrolizumab is currently enrolling in the Phase 1/2 clinical trial (NCT05732831)

Acknowledgements

The authors gratefully acknowledge the generous contributions from the scientific teams at Pharmaron and WuXi AppTec. Combination of TNG462 with zoldonrasib in KP4 tumors was performed by Revolution Medicines under MTA.

References

The Cancer Genome Atlas Pan-Cancer analysis project. Cancer Genome Atlas Research Network; Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K, Shmulevich I, Sander C, Stuart JM. Nat Genet. 2013

AACR Project GENIE: Powering Precision Medicine through an International Consortium. AACR Project GENIE Consortium. Cancer Discov. 2017