TNG908, a Brain-Penetrant MTA-Cooperative PRMT5 Inhibitor, is Efficacious in Preclinical Glioblastoma Models

Minjie Zhang*, Alice Tsai*, Kevin M Cottrell, Brian B Haines, Erik Wilker, Heather DiBenedetto, Ron Weitzman, Alan Huang, Charles B Davis, John P Maxwell and Kimberly J Briggs

*These authors contributed equally

Tango Therapeutics, Boston, MA

TANGO therapeutics

Disclosure Information

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Kimberly J Briggs

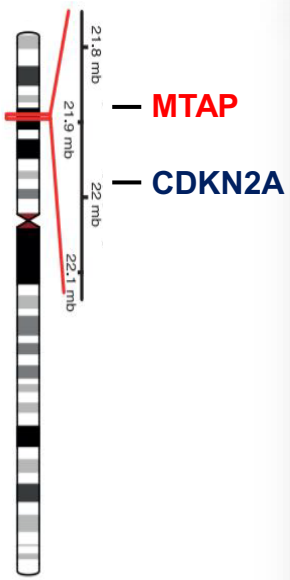
I have the following relevant financial relationships to disclose:

Employee of Tango Therapeutics

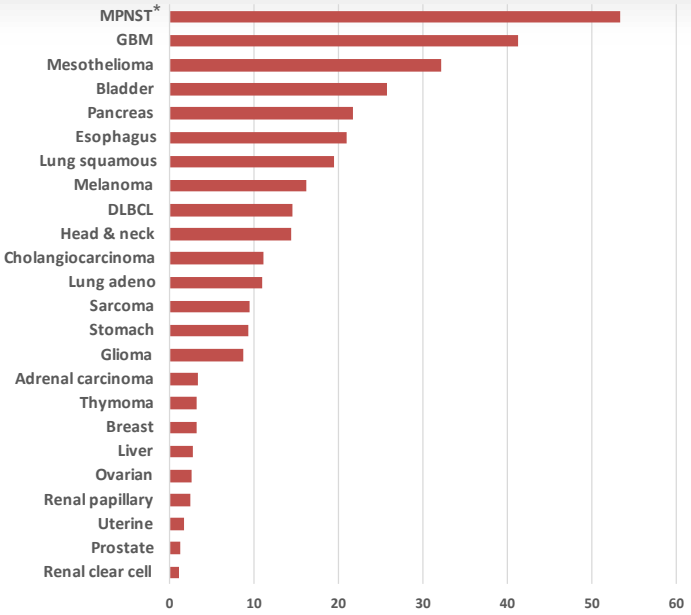
Stockholder in Tango Therapeutics

MTAP deletion occurs in 10-15% of all human cancers

Chromosome 9



MTAP homozygous deletion frequency



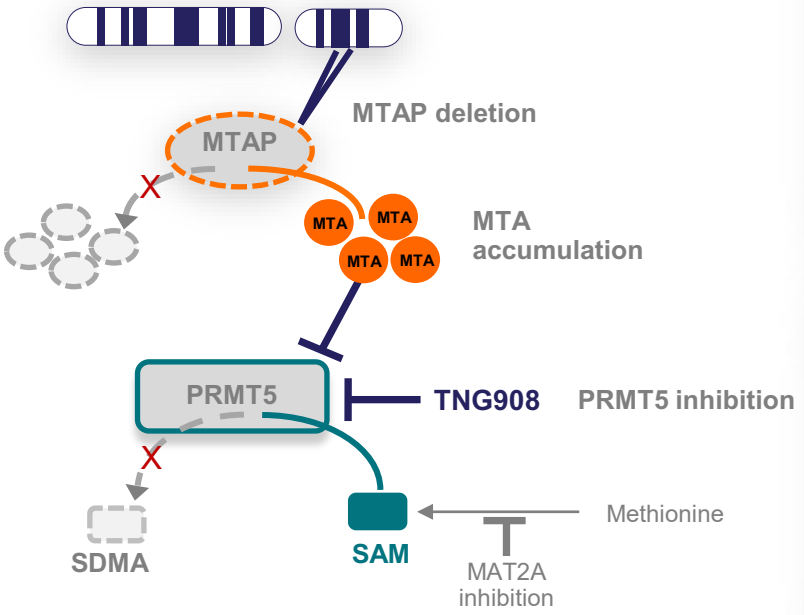
TCGA PanCancer Atlas
*Lee et al, Nature Genetics 2014

- MTAP is co-deleted with CDKN2A
- >40% of glioblastoma is MTAP-deleted
- A synthetic lethality approach to target MTAP loss may fulfill a significant unmet clinical need

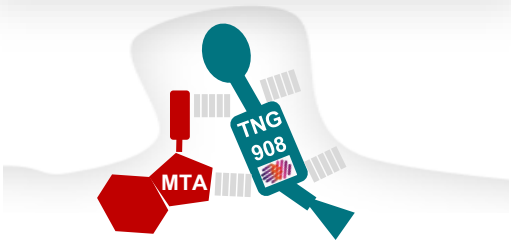
TNG908 is a synthetic lethal MTA-cooperative PRMT5 inhibitor

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Cancers with MTAP deletion are more vulnerable to PRMT5 inhibition than normal cells

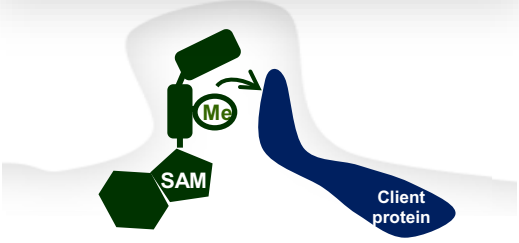


MTAP-deleted cancer cells



Inactive PRMT5

Normal cells



Active PRMT5

TNG908 mechanism of action

- MTAP deletion leads to MTA accumulation
- MTA binds to and inhibits PRMT5
- TNG908 selectively binds to the PRMT5-MTA complex
- PRMT5 can be fully inhibited by TNG908 in MTAP-deleted cancer cells while sparing normal cells

TANGO therapeutics

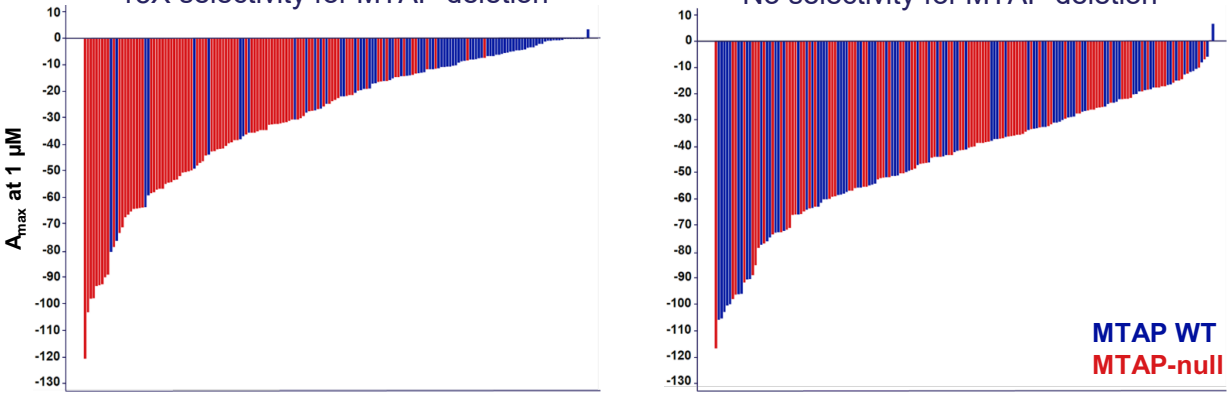
TNG908 is 15X selective for MTAP-null cancer cells

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

200 cancer cell lines from multiple lineages

TNG908
IC_{50} = 110 nM
15X selectivity for MTAP deletion

GSK3326595
IC_{50} = 120 nM
No selectivity for MTAP deletion



7-day viability assay
Same cell lines represented in all panels

TNG908 selectivity is differentiated from early PRMT5 inhibitors

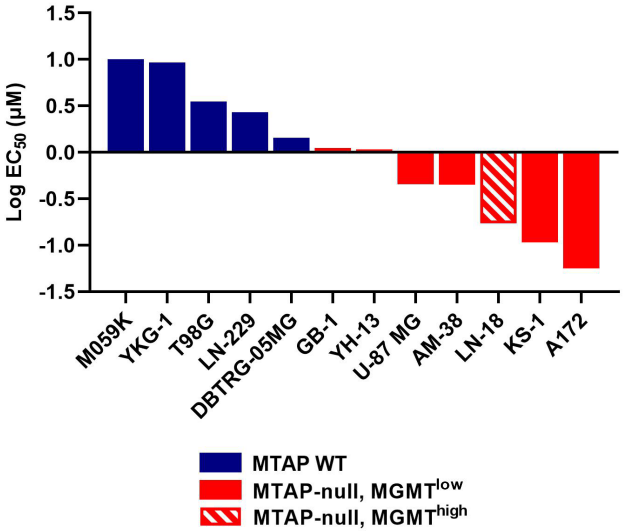
- TNG908 is highly selective for MTAP-null cancer cells
- Potential for broad clinical activity with a large therapeutic index

TNG908 is selective and efficacious in MTAP-null GBM cell lines regardless of MGMT status

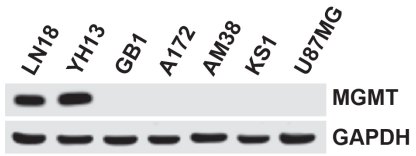
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

TNG908 is selective for MTAP-null GBM cell lines

7-day viability assay



MGMT immunoblot



MGMT status and TNG908 sensitivity are independent

- MGMT status is associated with higher chemotherapy response rates and longer OS
- MTAP-deletion and MGMT methylation are independent events
- Both MGMT high and low-expressing tumors may be responsive

TANGO therapeutics

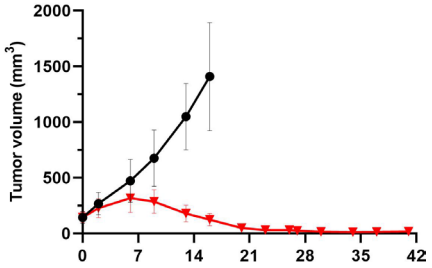
TNG908 drives deep tumor regressions in MTAP-null xenograft models

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

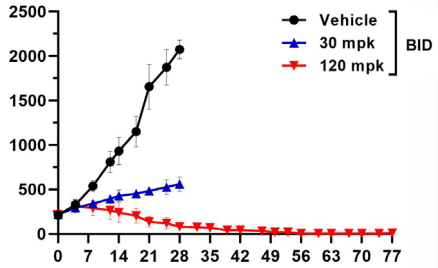
Continuous TNG908 treatment

MTAP-null PDX models

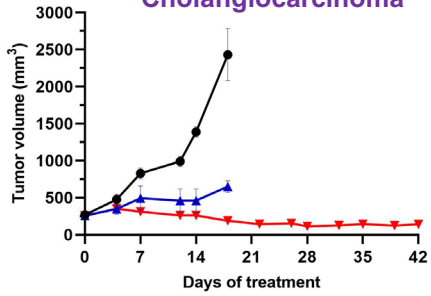
Mesothelioma



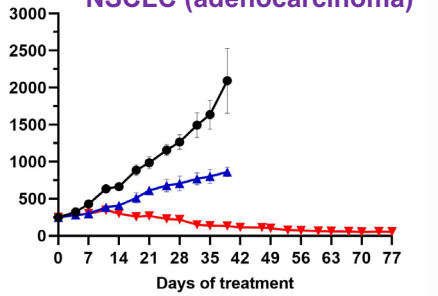
Bladder



Cholangiocarcinoma



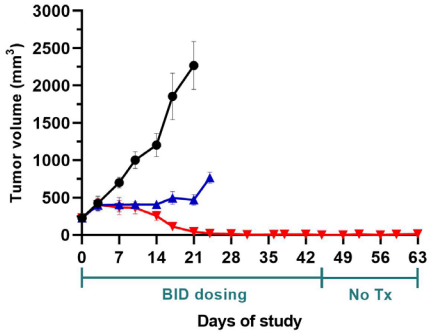
NSCLC (adenocarcinoma)



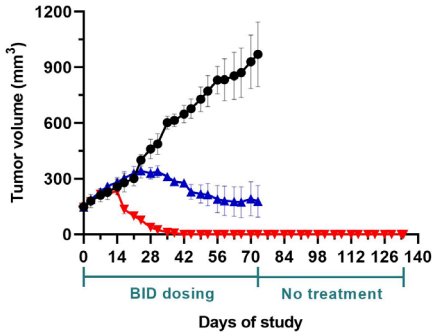
Sustained response after completion of dosing

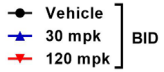
MTAP-null PDX models

Glioblastoma



NSCLC (squamous)

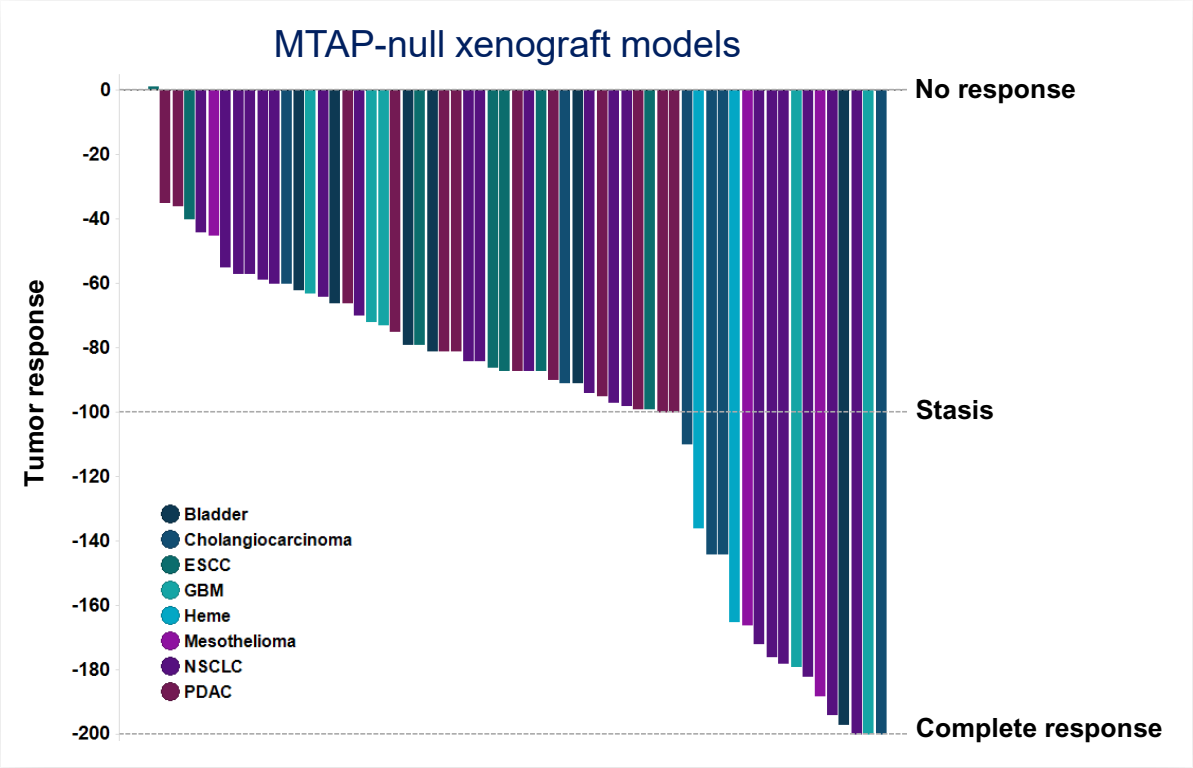




TANGO therapeutics

TNG908 drives strong, histology-agnostic antitumor responses

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



TNG908 antitumor activity is histology-agnostic

- Strong antitumor activity and tumor regressions including complete responses with no histology bias
- Data support histology-agnostic clinical development

Preclinical data predict TNG908 is brain penetrant in humans

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

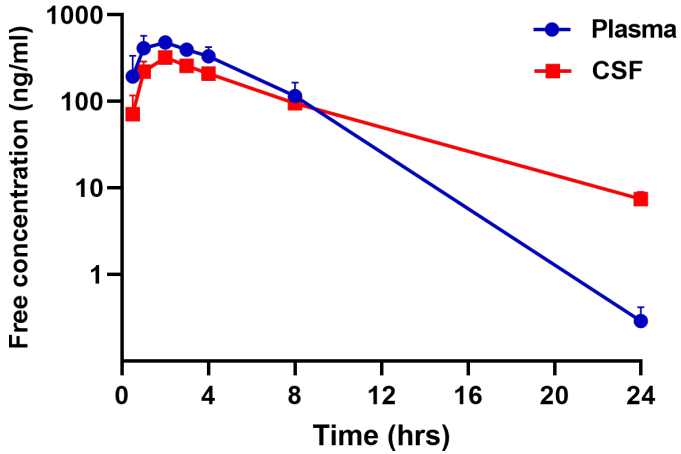
PK properties of TNG908 are consistent with brain penetrance

In vitro assays	TNG908
MDCKII A to B (cm/s)	19.7 x 10^{-6}
P-gp efflux ratio	2
BCRP efflux ratio	< 2

Highly permeable

Not a sensitive substrate of major efflux transporters at blood-brain barrier

TNG908 is brain penetrant in non-human primates

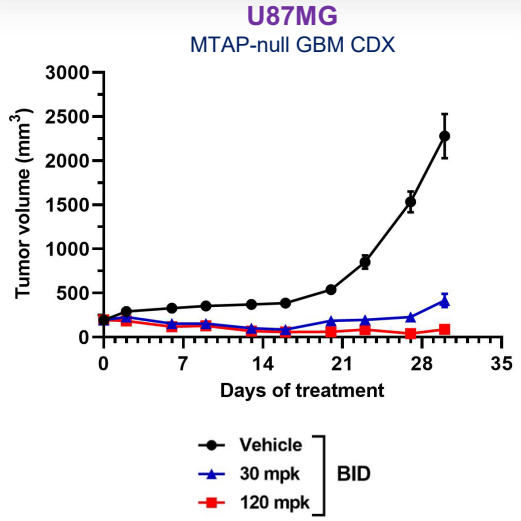


$Kpuu_{brain}$ = 0.9

TNG908 drives strong antitumor responses in GBM model independent of tumor microenvironment

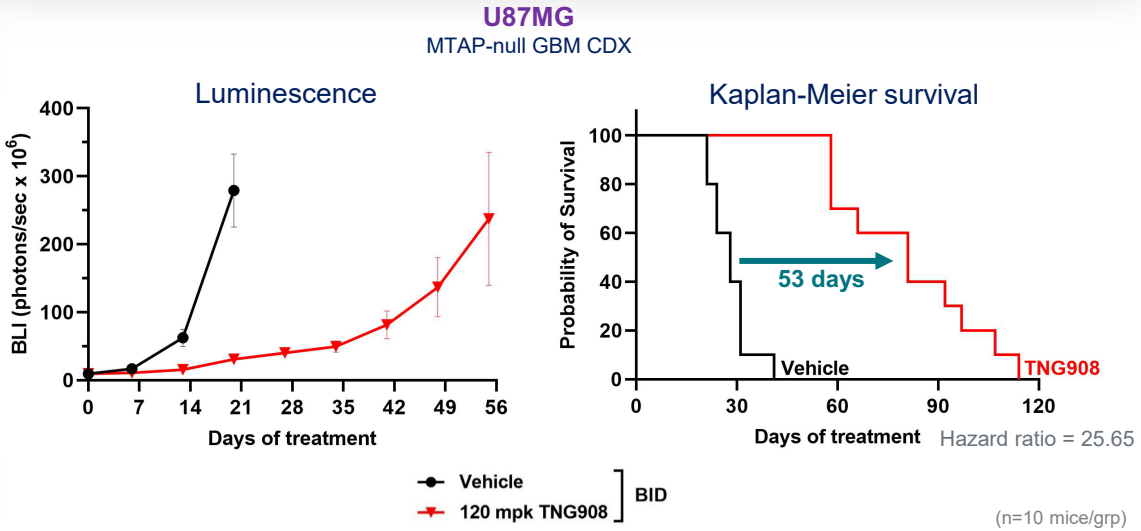
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

TNG908 drives tumor regression in a subcutaneous GBM model



Dose-dependent antitumor activity in heterotopic model

TNG908 extends survival in an orthotopic GBM model

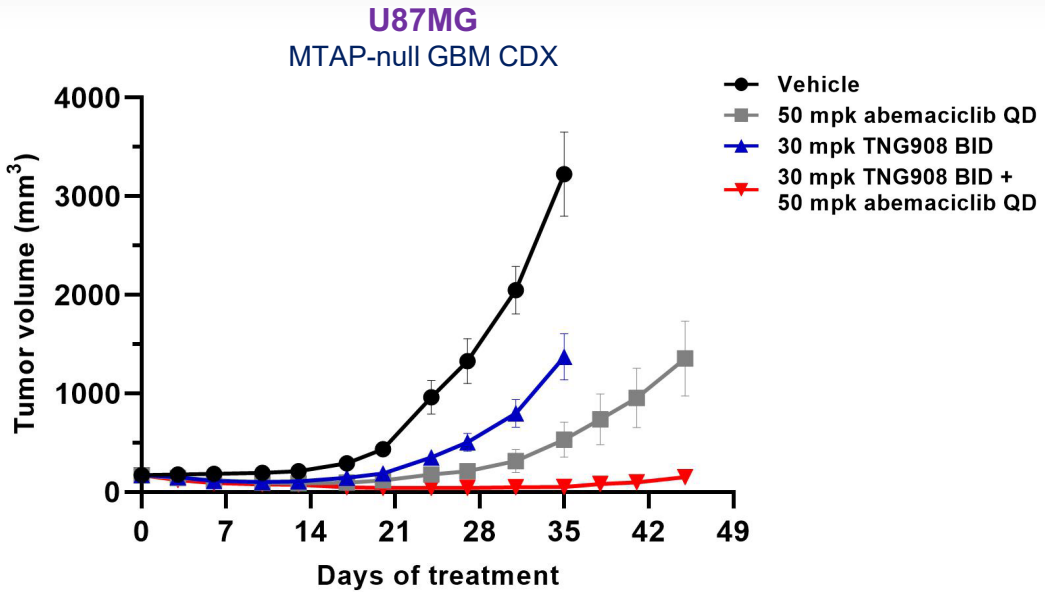


- TNG908 mouse brain exposure is ~15% of plasma
- TNG908 has longer survival benefit than Avastin (37 days) or temozolomide (23 days) reported in the same model

TNG908 and CDK4/6 inhibitor synergize preclinically in GBM model

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

CDK4/6 inhibitor combination



Rationale

- MTAP is co-deleted with CDKN2A
- 60% of CDKN2A-del GBM are also MTAP-del
- CDKN2A deletion may sensitize tumors to CDK4/6 inhibitors
- Combination benefit demonstrated using clinically relevant doses
- Abemaciclib is clinically brain penetrant

Efficient trial design to evaluate efficacy in multiple indications including GBM

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

DOSE ESCALATION

Solid tumors with MTAP deletion

DOSE EXPANSION

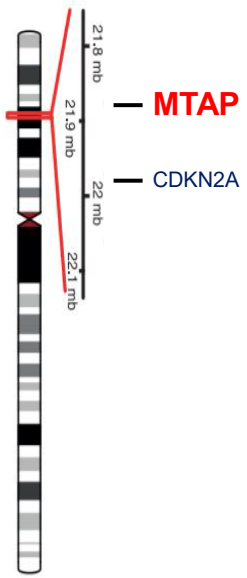
- Malignant peripheral nerve sheath tumors (MPNST)
- Non-small cell lung
- Mesothelioma
- Cholangiocarcinoma
- Glioblastoma
- Histology-agnostic cohort

PHASE 1/2 STUDY

- ~10-15% of all human cancers are MTAP-del
- Safety, PK/PD and efficacy as primary endpoints
- Expansion cohorts provide optionality for multiple registration strategies
- FDA Fast Track Designation
- FDA Orphan Drug Designation for MPNST and malignant glioma

Conclusions

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



TNG908:

- 10-15% solid tumors and ~40% GBM
- MTA-cooperative PRMT5 inhibitor with 15X selectivity for MTAP-deleted cells
- Strong preclinical efficacy across histologies
- Brain-penetrant and efficacious in subcutaneous and orthotopic MTAP-null GBM xenograft models
- Rational and data-supported combination strategy with CDK4/6 inhibitors
- Strong rationale for histology-agnostic clinical development in MTAP-deleted solid tumors including GBM

Tango at AACR

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

TNG260: A novel, orally active, CoREST-selective deacetylase inhibitor for the treatment of STK11-mutant cancers
Session: New Drugs on the Horizon
Presenter: Leanne Ahronian, Ph.D., Senior Scientist, Tango Therapeutics
Session date and time: April 17, 2023, 10:15-11:45 a.m. ET

TNG462 is a potential best-in-class MTA-cooperative PRMT5 inhibitor for the treatment of MTAP-deleted solid tumors
Abstract #: 4970
Poster session date and time: April 18, 2023, 1:30-5:00 p.m. ET

Characterization of the clinical development candidate TNG348 as a potent and selective inhibitor of USP1 for the treatment of BRCA1/2mut cancers
Abstract #: 4968
Poster session date and time: April 18, 2023, 1:30-5:00 p.m. ET

TANGO therapeutics

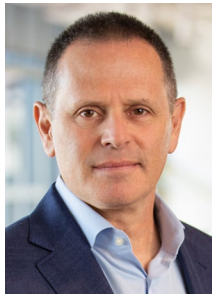
Acknowledgements

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23










We gratefully acknowledge the contributions from former and current TNG908 team members as well as the scientific teams at ChemPartner, Champions Oncology, Crown Biosciences, Enamine, Pharmaron, WuXi AppTec, and XenoSTART

For information on the TNG908 clinical trial:

For additional questions:

info@tangotx.com

TANGO therapeutics