Targeting tumor suppressor loss

to unmask vulnerabilities in cancer
for the next generation of precision medicines

Corporate Overview

November 2023

Disclaimer and Safe Harbor Statement

Certain statements in this presentation may be considered forward-looking statements. Forward-looking statements generally relate to future events, Tango's future financial and operating performance, goals, expectations, beliefs, development plans, as well as development and clinical trial objectives for Tango's product pipeline (as individual therapies and combination therapies with other party's drugs). In some cases, you can identify forward-looking statements by terminology such as "may", "should", "expect", "intend", "will", "path", "achievable", "milestones", "goal", "forecast", "estimate", "potential", "anticipate", "believe", "predict", or "continue", or the negatives of these terms or variations of them or similar terminology. For example, express or implied statements concerning the following include or constitute forward-looking statements: Company has a cash runway into 2026 (including POC readouts for all four clinical programs); dose escalation is on-going in the TNG462 clinical trial and the TNG260 trial which is being evaluated in combination with pembrolizumab; the Company expects to provide additional TNG908 clinical trial data in 2024; MAT2A inhibitors are indirect PRMT5 inhibitors and may add benefit in MTAP-del cancers in combination with TNG908 and TNG462; the dosing in the TNG908 clinical trial is not yet within the predicted efficacious range; Company has a state-of-the-art discovery platform supporting a sustainable pipeline of novel targets; the anticipated milestones for the Company's drug programs, including the timing for first patient dosed and dose escalation data and clinical updates, timing of initial and interim (and final) safety and efficacy or clinical activity data and results from clinical trial(s), the timing of first-in-human clinical trials, the timing of IND-enabling studies, the timing of IND filings, the timing of clinical trial initiation; the potential for a large patient population to be treated with Tango's PRMT5 inhibitors; Tango has a sustainable pipeline of novel precision oncology targets; the Company's lead program is a potentially first-in-class PRMT5 inhibitor that is synthetic lethal with MTAP deletion; TNG462 PK profile optimized for maximal target coverage; predictions regarding bone marrow suppression with use of PRMT5 inhibitors; there is a clear path to clinical POC for PRMT5 inhibitor in MTAP-null solid tumors with potential for histology-agnostic registration; potential combination strategies for PRMT5i; potential for histology-agnostic registration for PRMT5 inhibitor with broad based activity across tumor types; the Company will be pursuing novel combination therapies with inhibitors that have a complementary mechanism of action; the Company is actively enrolling patients in the TNG908 clinical trial; TNG908 expansion cohorts provide optionality for multiple registration strategies; TNG908 expected to be brain penetrant in clinical study; TNG462 is potential best-in-class PRMT5 inhibitor (and has potential for broader and deeper clinical activity and is expected to have an increased therapeutic index and efficacy and extended target coverage); the development plans for the PRMT5 franchise (including future clinical trials); future clinical trial designs (including for TNG348); TNG260 and TNG348 future clinical trials implementation; the significant patient opportunities for the Company's pipeline therapies; the strong anti-tumor activity in HRD+ xenograft broadens the addressable patient population for TNG348; Tango has sufficient cash balance to fund operations into 2026 (and is sufficient to achieve multiple projected key milestones); the Company's key milestones for 2023; the anticipated benefits of synthetic lethal drugs; planned expansion cohort of the TNG908 phase 1/2 clinical trial for glioblastomas; and the anticipated benefits of future product candidates including those identified in the future through the Tango discovery platform. Such forward-looking statements are subject to risks, uncertainties, and other factors which could cause actual results to differ materially from those expressed or implied by such forward looking statements. These forward-looking statements are based upon estimates and assumptions that, while considered reasonable by Tango and its management, are inherently uncertain. Drug development, clinical trials and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Factors that may cause actual results to differ materially from current expectations include, but are not limited to: Tango has a limited operating history and has not generated any revenue to date from drug sales, and may never become profitable (and may utilize cash resources more quickly than anticipated and may exhaust cash resources prior to 2026); Tango has limited experience with conducting clinical trials (and will rely on a third party to operate its clinical trials) and may not be able to commence any clinical trial, enroll and dose patients when expected and may not generate results in the anticipated timeframe (or at all); IND filings may not be made in the time expected or the FDA (or similar regulatory agencies) may not accept such IND applications (or may require that significant changes be made to the IND application that could significantly delay or prevent the commencement of clinical trials); the benefits of Tango pipeline products (stand-alone and as potential combination therapies) that are seen in pre-clinical experiments may not be present in clinical trials or in use commercially or may not be safe and/or effective in humans (and Tango or a third-party may not be able to obtain approval or commercial sales of any stand-alone or combination therapies); Tango has incurred significant operating losses and anticipates continued losses for the foreseeable future; Tango will need to raise capital in the future and if it is unable to raise capital when needed or on attractive terms, the Company would be forced to delay, scale back or discontinue some development programs or future commercialization efforts; Tango may be unable to advance the preclinical development programs into and through the clinic for safety or efficacy reasons or experience significant delays in doing so as a result of factors beyond Tango's control; Tango's approach to the discovery and development of product candidates is novel and unproven, which makes it difficult to predict the time, cost of development, and likelihood of successfully developing any products; Tango may not identify or discover development candidates (including next generation products) or may expend a portion of its limited resources to pursue a particular product candidate or indications and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success; delays or difficulties in the initiation, enrollment or dosing of patients in clinical trials could delay or prevent receipt of regulatory approvals or reporting trial results; our products candidates may cause adverse or other undesirable side effects that could, among other things, delay or prevent regulatory approval; our dependence on third parties for conducting clinical trials and producing drug product; our ability to obtain and maintain patent and other intellectual property protection for our technology and product candidates or the scope of intellectual property protection obtained is not sufficiently broad; and delays and other impacts on product development and clinical trials from the COVID-19 pandemic. Additional information concerning risks, uncertainties and assumptions can be found in Tango's filings with the SEC, including the risk factors referenced in Tango's Annual Report on Form 10-K for the year ended December 31, 2022, as may be supplemented and/or modified by its most recent Quarterly Report on Form 10-Q. You should not place undue reliance on forward-looking statements in this presentation, which speak only as of the date they are made and are qualified in their entirety by reference to the cautionary statements herein. Tango specifically disclaims any duty to update these forward-looking statements.'

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COMPANY OVERVIEW

Tango summary

Clinical-stage precision oncology company leveraging synthetic lethality

State-of-the-art discovery platform supporting a sustainable pipeline of novel targets

Three Phase 1/2 clinical trials ongoing and one clinical trial initiation planned for 1H 2024

- TNG908 in dose escalation, proof-of-mechanism demonstrated with marked differential PRMT5 inhibition in MTAP-deleted cancers vs. normal tissue
- TNG462, a next-generation MTA-cooperative PRMT5 inhibitor, in dose escalation
- TNG260, a CoREST inhibitor targeting immune evasion caused by STK11 mutations, being evaluated in combination with pembrolizumab in dose escalation
- TNG348, a USP1 inhibitor for BRCA1/2 mutant and other HRD+ cancers, trial initiation planned 1H 2024

Cash runway into 2026

A sustainable pipeline of novel precision oncology targets

PROGRAM	PATIENT SELECTION	DISCOVERY	IND-ENABLING	CLINICAL TRIALS		STATUS
				Phase 1/2	Phase 3	
PRMT5 TNG908	MTAP-del cancers					Additional clinical data 2024
PRMT5 TNG462						Dose escalation ongoing
CoREST TNG260	STK11-mut cancers					Dose escalation ongoing
USP1 TNG348	BRCA1/2-mut and other HRD+ cancers					Trial initiation 1H 2024
Multiple synthetic lethal targets	Tumor suppressor gene loss					

Gilead optioned and licensed targets not listed

A strong strategic partnership with Gilead

SCOPE	• 15 validated immune evasion targets • Three targets licensed, two optioned to date
RESEARCH AND DEVLOPMENT	• Target discovery and validation at Tango with option to extend to clinical POC • Gilead to lead post-POC development and commercialization
RIGHTS	• Full rights to TNG260 and all cell autonomous targets not associated with immune evasion retained by Tango
SHARED ECONOMICS	• Option to co-develop/co-promote up to five programs • 50/50 US profit/loss sharing on co-developed programs • Low double-digit royalties on all other programs
TERMS	• $175 million upfront • $20 million equity • Up to $110M to clinical POC, $410M per program and up to $6 billion in milestones

TANGO therapeutics

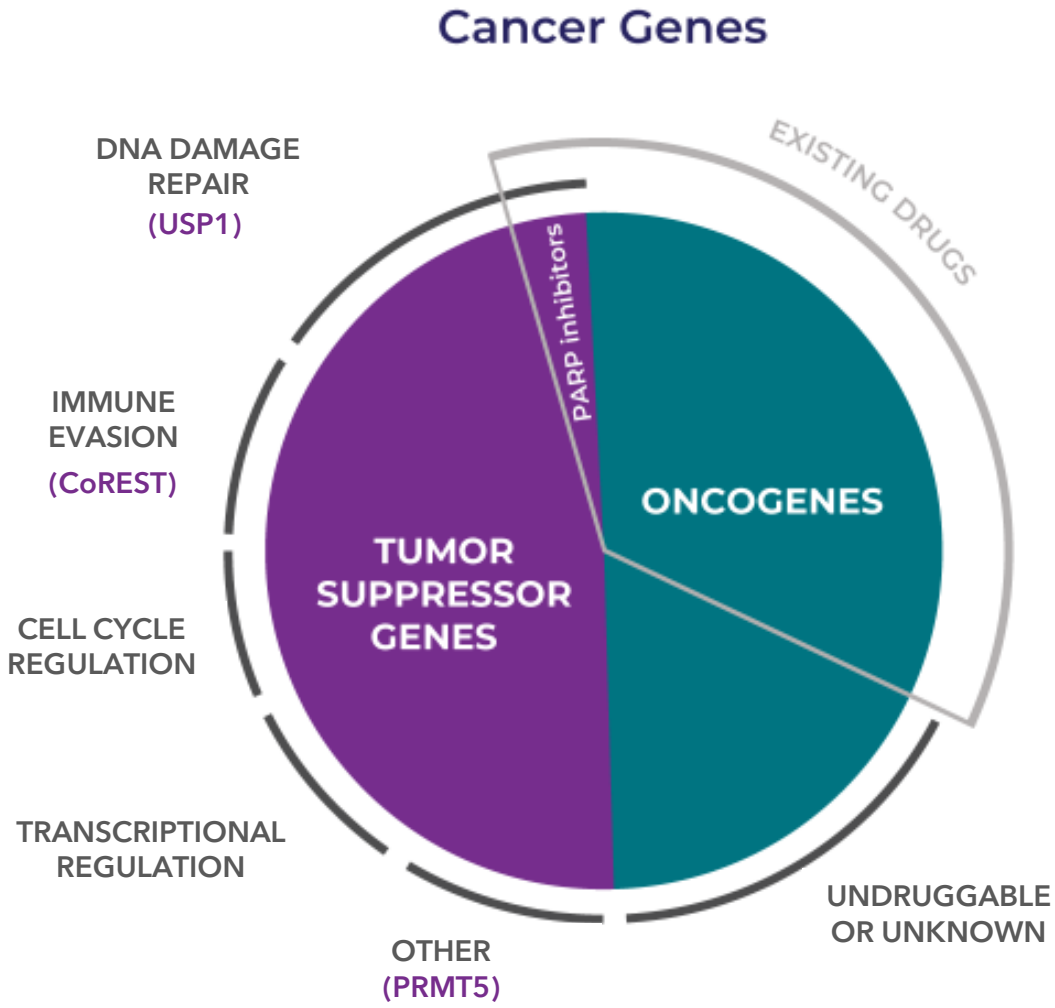
GILEAD

SYNTHETIC LETHALITY FOR CANCER THERAPEUTICS

Most cancer targets are not drugged yet

TUMOR SUPPRESSOR GENES

- Important drivers of cancer inactivated or deleted in almost all human cancers
- Not directly druggable



SYNTHETIC LETHALITY

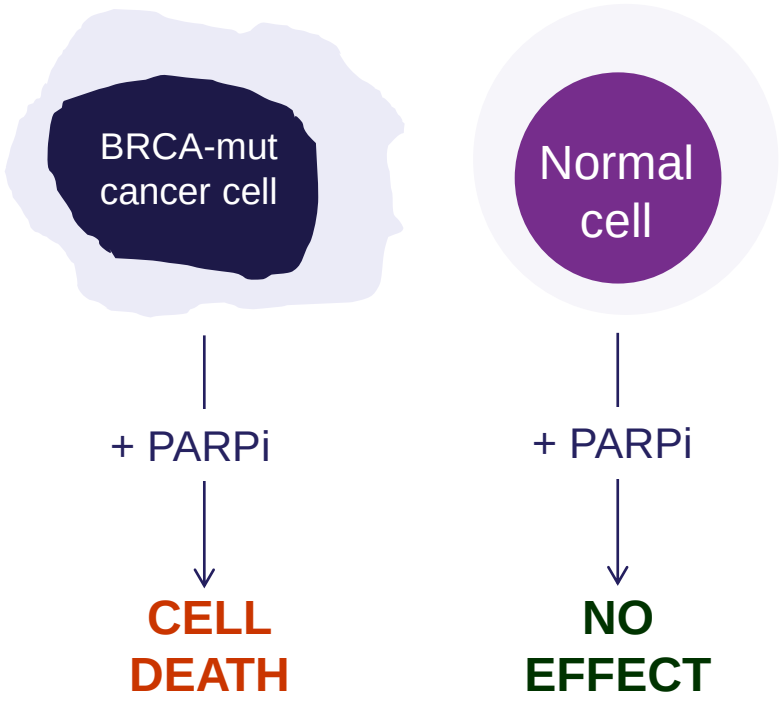
Primary approach to targeting tumor suppressor gene loss

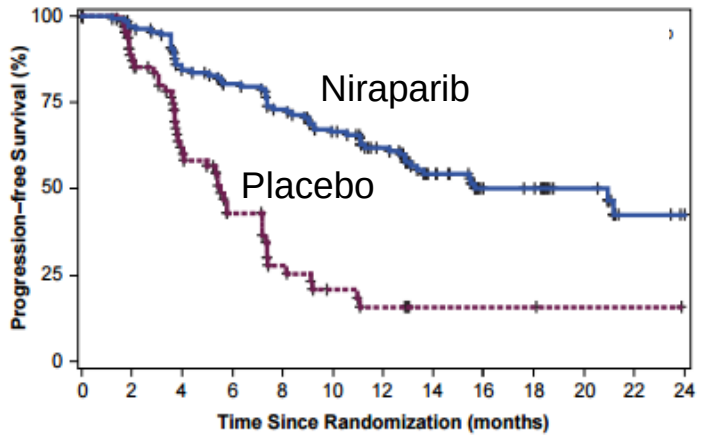
CRISPR TECHNOLOGY

Essential for large scale synthetic lethal discovery efforts

PARP is the first clinically validated synthetic lethal drug target

BRCA1/2 mutation and PARP inhibition are a synthetic lethal pair





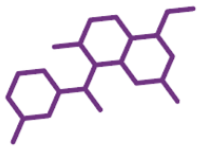
- PARP inhibitors are approved in BRCA-mutant breast, ovarian, pancreatic and prostate cancer
- Synthetic lethal drugs inherently have a wide therapeutic index
- Multiple analyses suggest hundreds of synthetic lethal pairs exist in human cancer

A unique approach to target discovery and clinical development in the same genetic context

DEVELOP
drugs in same genetic context used for target discovery

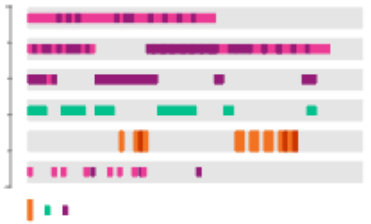
SELECT
cancer subtypes with high unmet need

DISCOVERY AND DEVELOPMENT IN THE SAME GENETIC CONTEXT



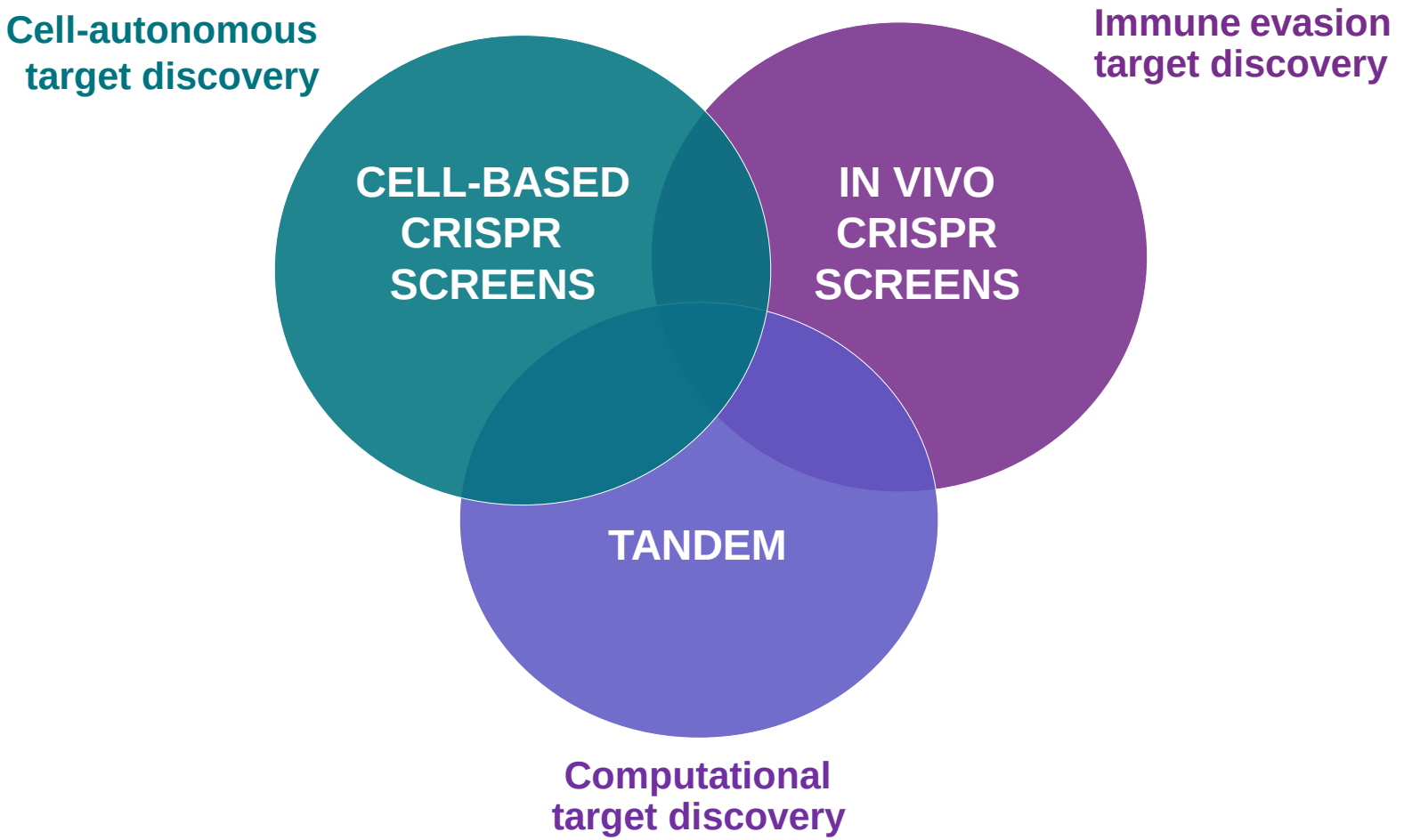
DISCOVER
drugs against context-specific target

DEFINE
genetic alterations in cancer subtype "genetic context"



IDENTIFY
drug targets dependent on genetic context for activity "context-specific"

A robust synthetic lethal target discovery platform drives our precision medicine approach

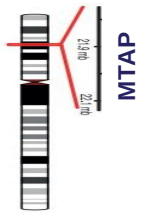


- Powerful CRISPR vector systems yield precision oncology targets with inherent patient selection strategies
- Custom libraries drive efficient discovery of novel targets
- TANDEM integrates large internal genetic perturbation data sets with massive public data sets

TNG908 and TNG462

PRMT5 inhibition in MTAP-deleted cancers

Leveraging synthetic lethality to develop PRMT5 inhibitors for a large patient population



TNG908

MTA-cooperative, brain penetrant PRMT5 inhibitor that is synthetic lethal with MTAP deletion

TNG462

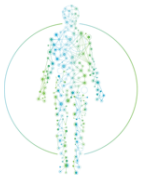
Next-generation MTA-cooperative PRMT5 inhibitor with enhanced potency and MTAP-selectivity

DIFFERENTIATED MECHANISM

Novel MTA-cooperative mechanism highly selective for cancer cells with MTAP deletion with a large therapeutic index

LARGE OPPORTUNITY FOR PATIENTS

10-15% of all human cancers have MTAP deletion - one of the largest precision oncology patient populations



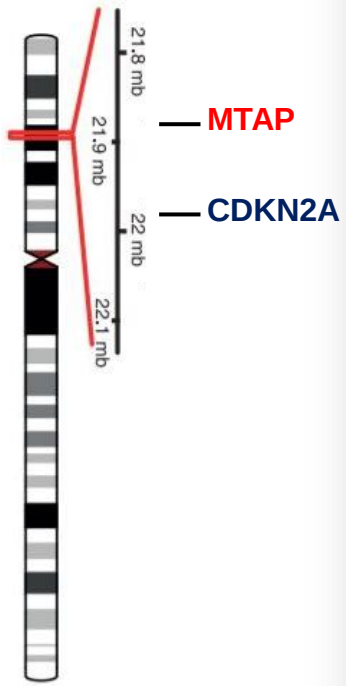
STATUS

TNG908 proof-of-mechanism demonstrated in phase 1 update, additional clinical data in 2024

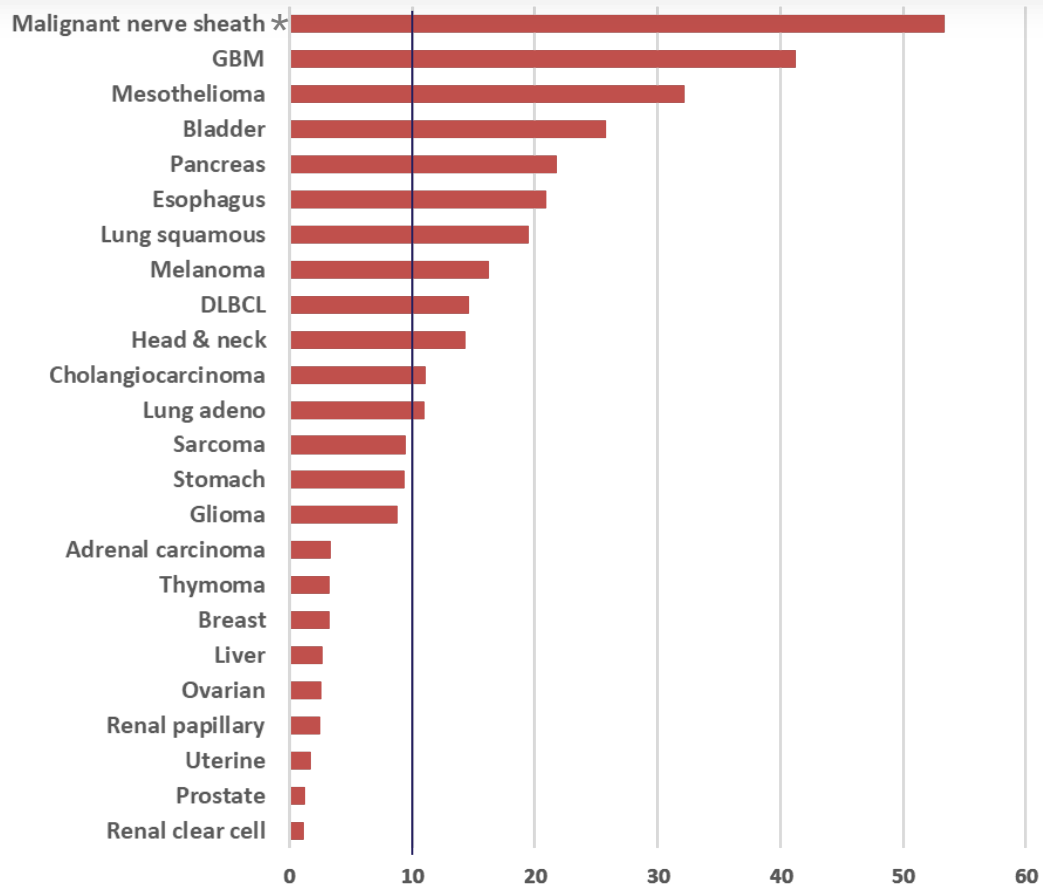
TNG462 dose escalation ongoing

Investing in our PRMT5 franchise with TNG908 and TNG462

Chromosome 9



MTAP homozygous deletion frequency



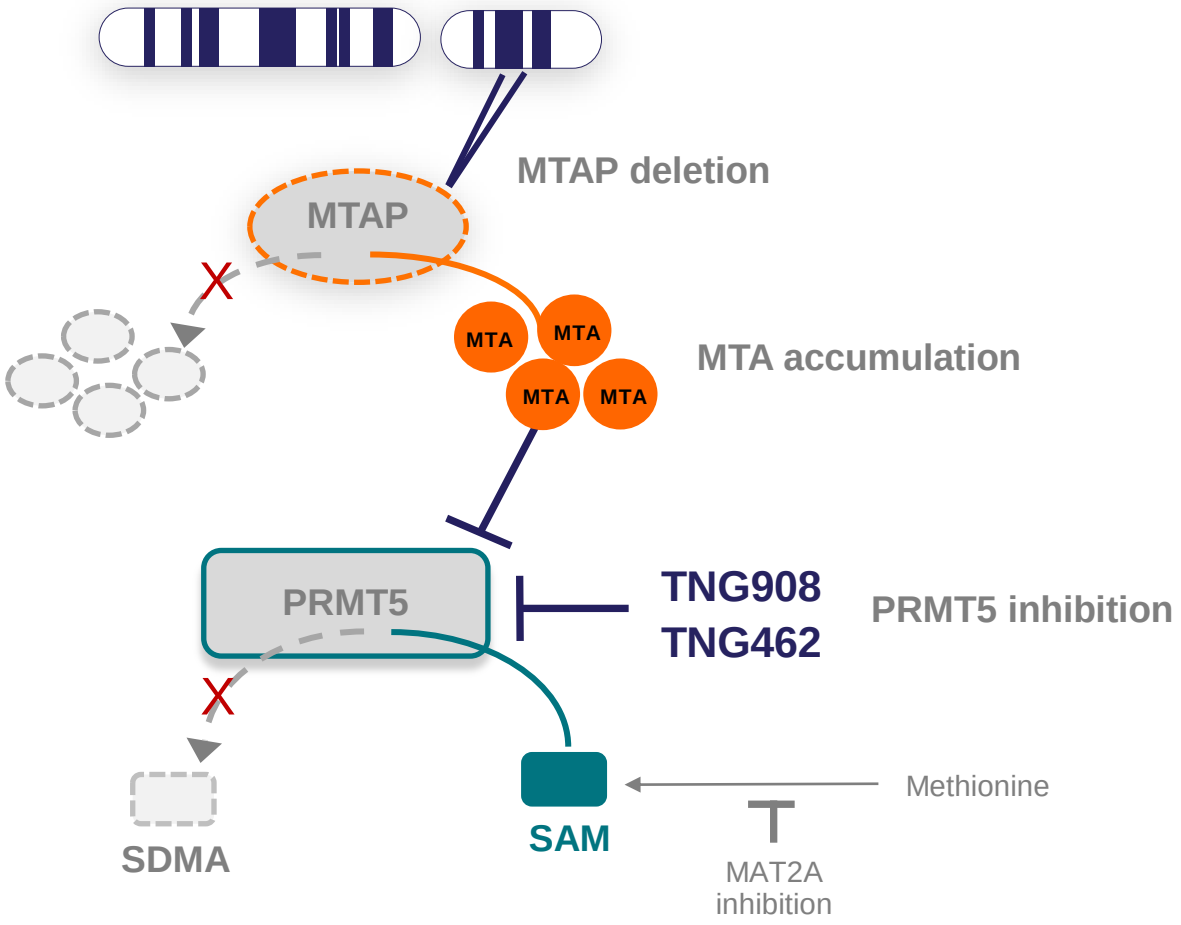
10-15% of all human cancers are MTAP-deleted

- MTAP is co-deleted with CDKN2A
- Clear path to clinical POC in MTAP-null solid tumors with potential for histology-agnostic registration
- TNG908 is brain penetrant thus potentially active in GBM patients
- TNG462 is ~30X more potent than TNG908 and 45X selective for MTAP deletion but not brain penetrant

TCGA PanCancer Atlas
*Lee et al, Nature Genetics 2014

PRMT5 and MTAP are a synthetic lethal pair

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

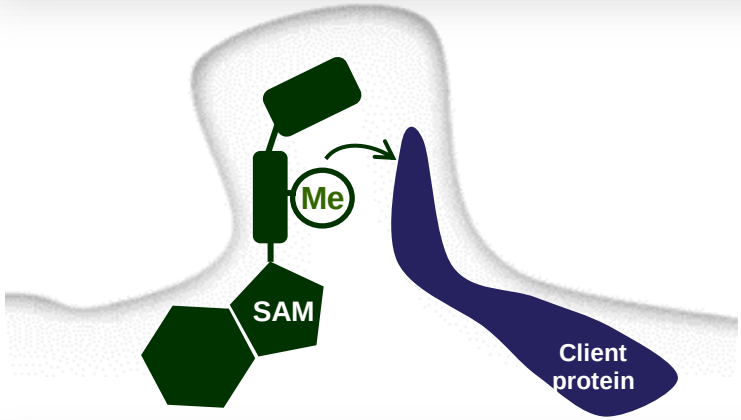


Mechanism of action

- MTAP deletion causes MTA to accumulate
- MTA binds to and inhibits PRMT5
- MTA-cooperative PRMT5 inhibitors selectively bind to the PRMT5-MTA complex
- TNG908 and TNG462 can fully inhibit PRMT5 activity in MTAP-deleted cancer cells while sparing normal cells
- TNG908 MTA-cooperative proof-of-mechanism demonstrated in phase 1 update

TNG908 and TNG462 are synthetic lethal MTA-cooperative PRMT5 inhibitors

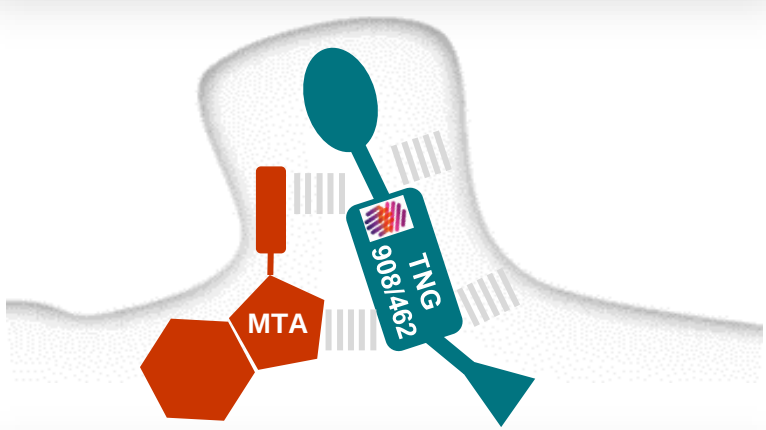
Normal cells



Active PRMT5

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

MTAP-deleted cancer cells



Inactive PRMT5

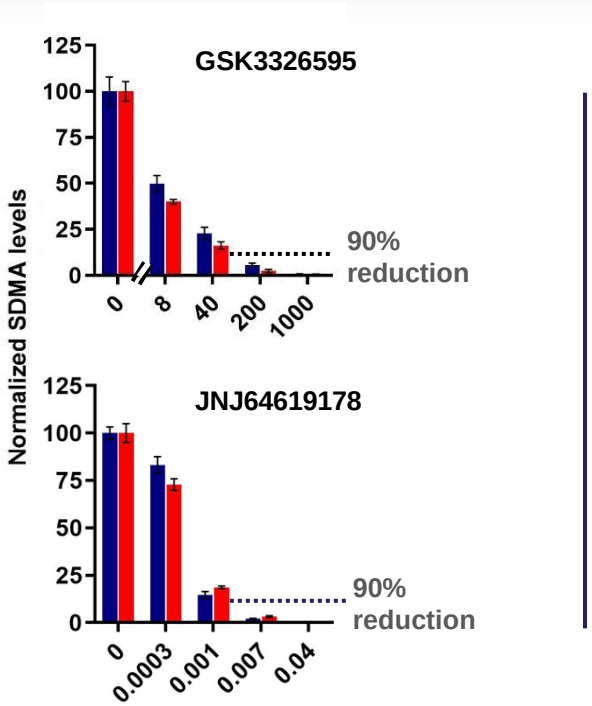
- Inactive MTA-PRMT5 complexes accumulate in MTAP-deleted cancer cells
- MTA-cooperative PRMT5 inhibitors preferentially kill MTAP-deleted cells

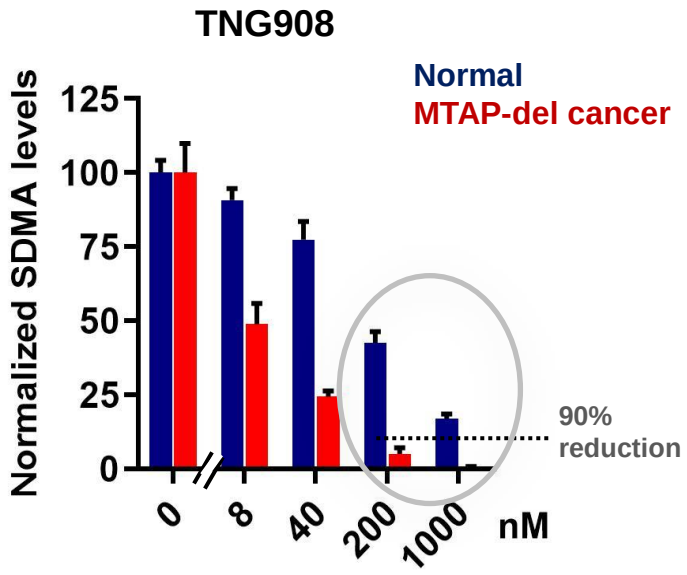
Key points

- TNG908 and TNG462 are designed to kill MTAP-deleted cancer cells while sparing normal cells
- TNG908 and TNG462 selectively bind to PRMT5-MTA complexes and lock them into an inactive state

Differential PRMT5 inhibition in normal and MTAP-del cancer cells is essential for efficacy

HAP1 MTAP isogenic cell lines

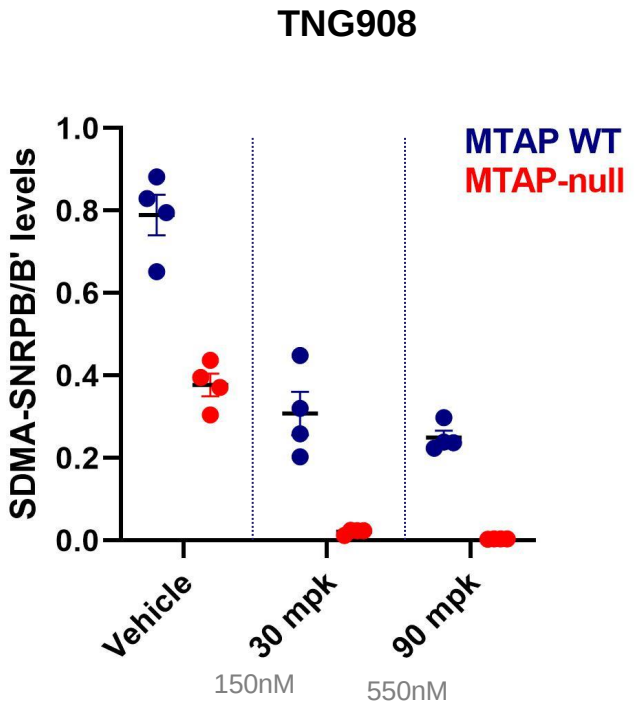




- SDMA suppression is equivalent in normal and MTAP-del cells
- Bone marrow suppression predicted to occur with > 90% SDMA reduction

TNG908 therapeutic index driven by 15X selectivity for PRMT5 inhibition in MTAP-del cells

HCT116 colon cancer xenografts

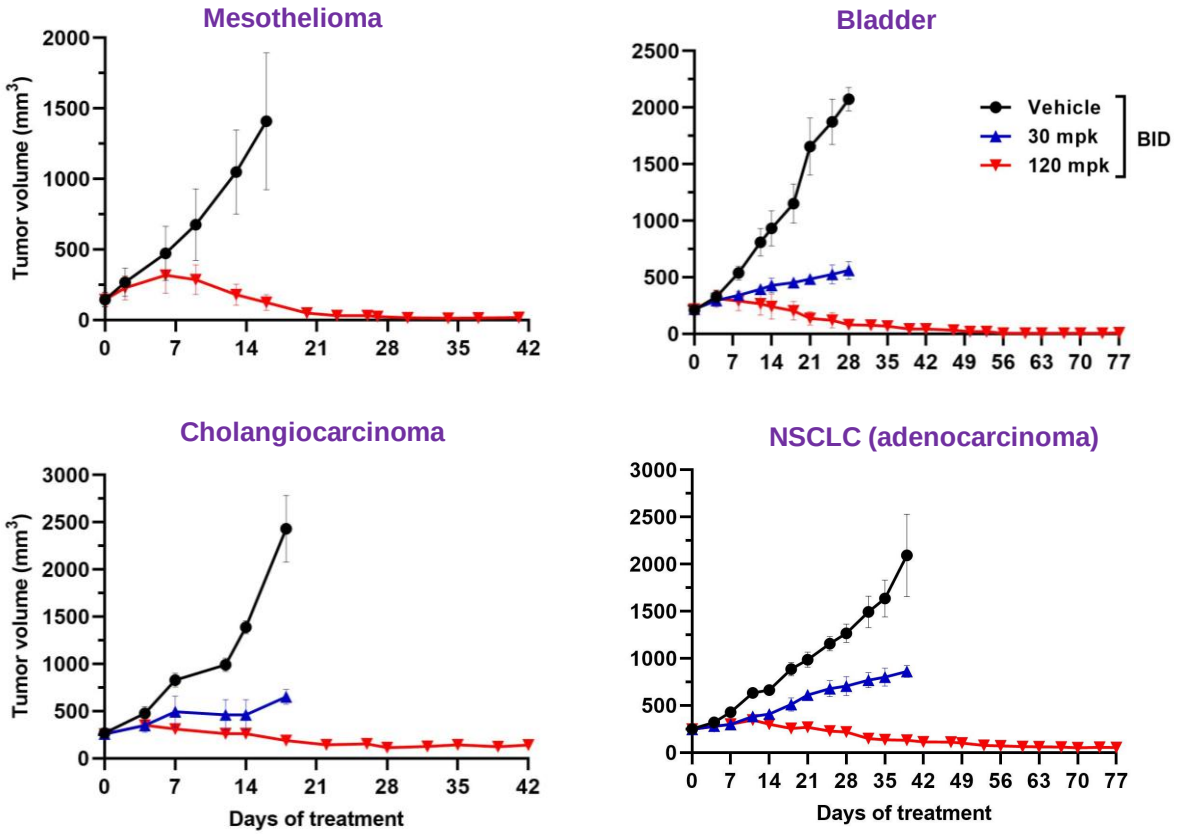


TNG908 drives regressions in MTAP-null xenografts across lineages

TNG908 IC50 110 nM, 15X selectivity for MTAP deletion

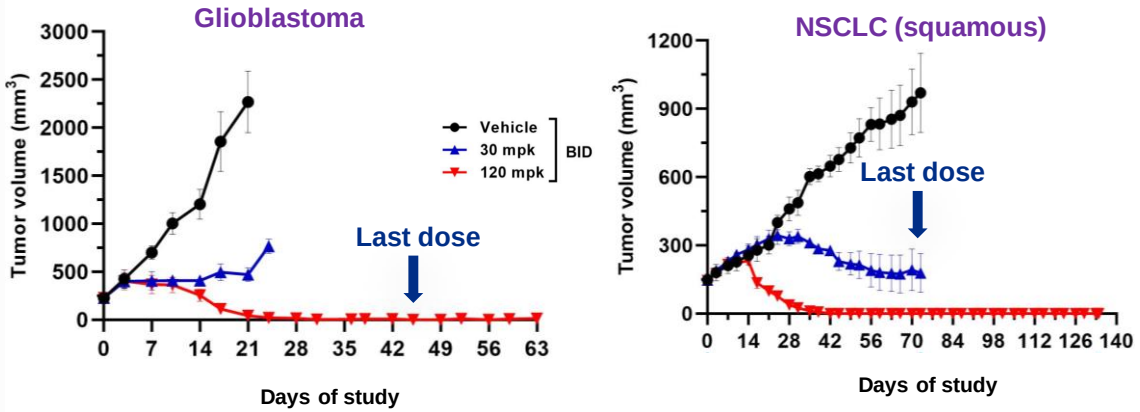
Continuous TNG908 treatment

MTAP-null PDX models



Sustained response after completion of dosing

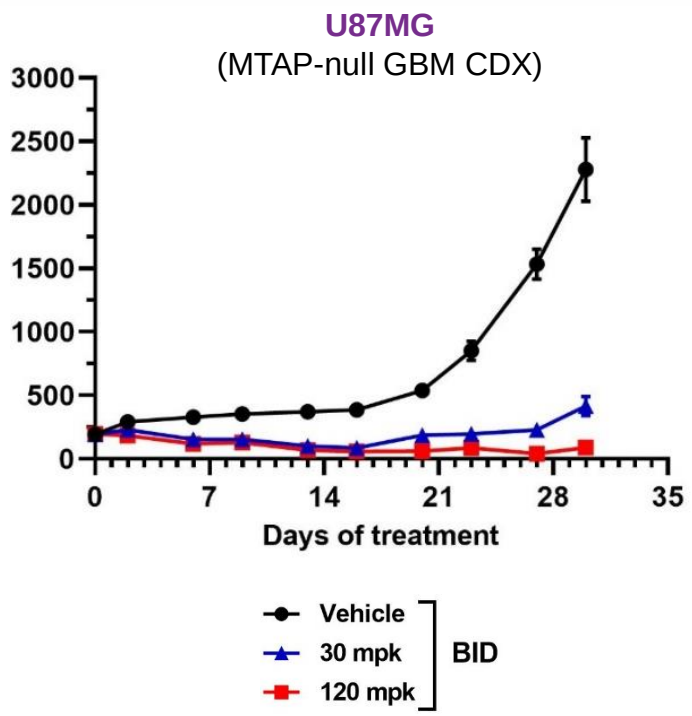
MTAP-null PDX models



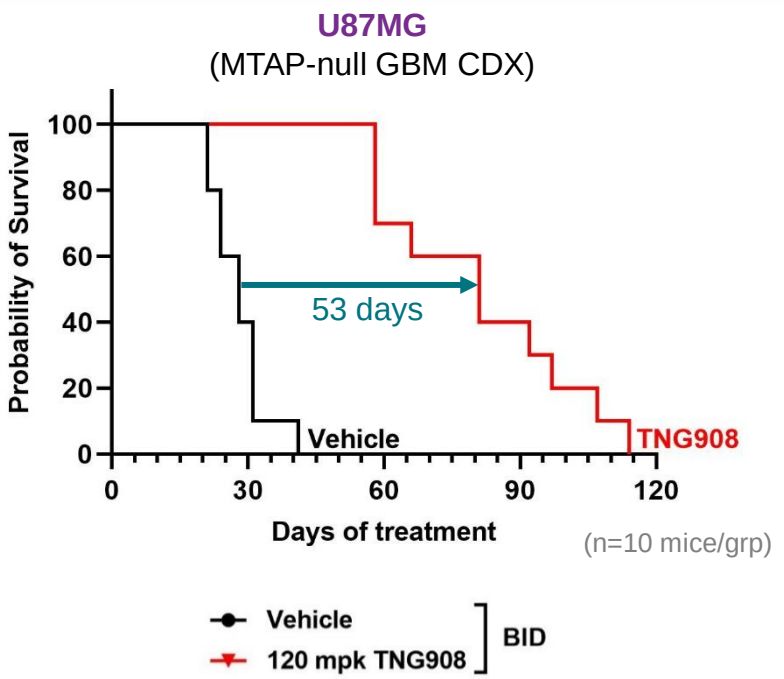
61/62 xenografts are sensitive to TNG908 with regression in 30%, no histology bias

TNG908 is more effective than standard of care in an orthotopic glioblastoma model

TNG908 drives deep regression in a subcutaneous glioblastoma model



TNG908 drives survival benefit in an orthotopic glioblastoma model



Reported survival benefit

- Avastin 37 days
- temozolomide 23 days

Summary

- TNG908 free exposure is equivalent in non-human primate brain (CSF) and plasma
- TNG908 exposure in rodent brain is ~15% of plasma

TNG908: Efficient trial design to evaluate efficacy in multiple indications

DOSE ESCALATION

- Solid tumors with MTAP deletion

DOSE EXPANSION

- Glioblastoma
- Non-small cell lung
- Pancreatic
- Sarcoma
- Mesothelioma
- Histology-agnostic cohort

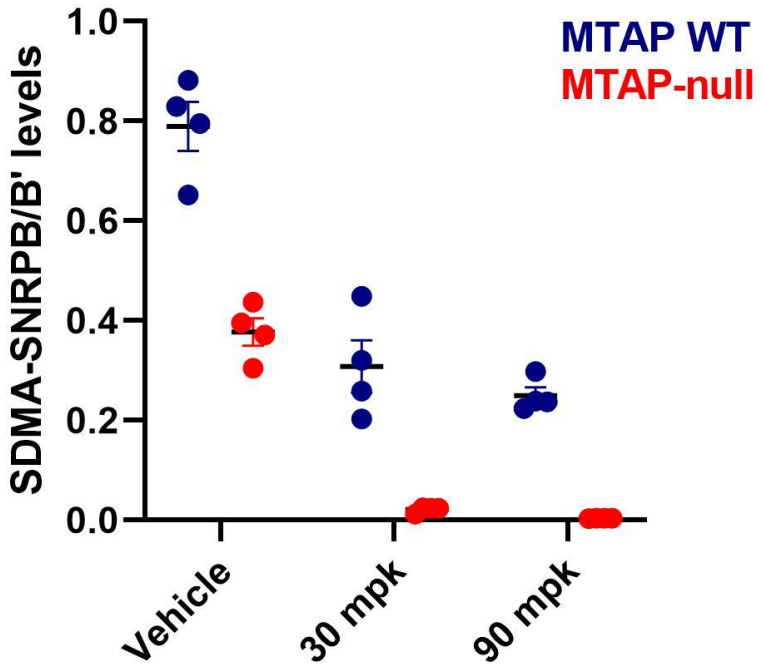
PHASE 1/2 STUDY

- ~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 malignant glioma, including glioblastoma

Complete SDMA IHC ablation is insufficient to drive efficacy

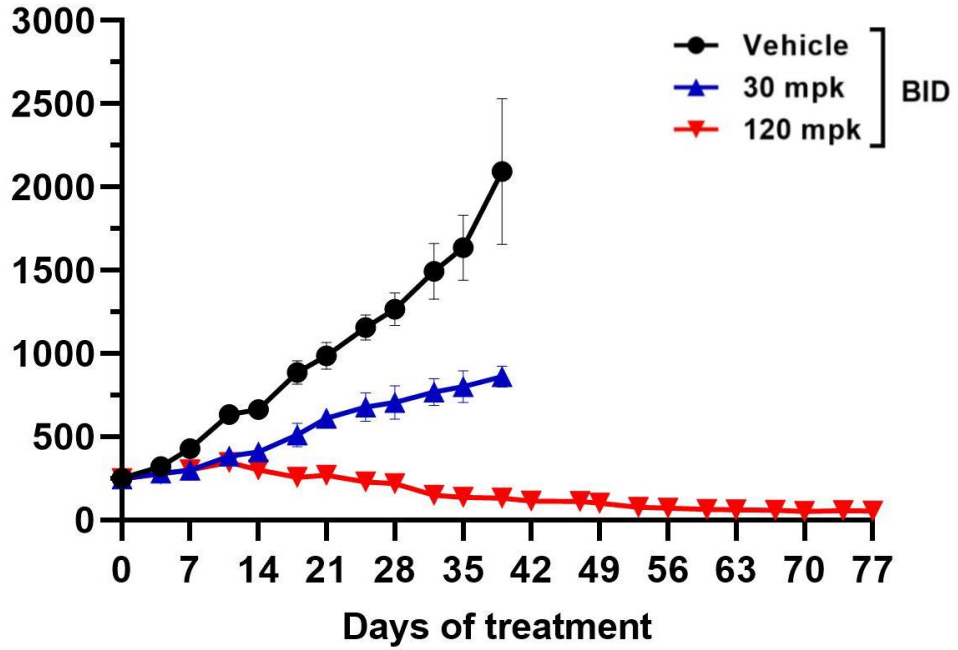
SDMA signal ablation in xenograft

HCT116



Dose dependent efficacy of TNG908 after SDMA IHC signal ablation

NSCLC (adenocarcinoma)



TNG908 in phase 1 dose escalation

First proof-of-mechanism for MTA-cooperative PRMT5 inhibition

- Dose-dependent decreases in tumor SDMA with minimal or no decrease in normal tissue
- Favorable pharmacokinetics with dose-proportional increases in exposure across cohorts
- Exposure in cohorts 1 and 2 not yet within the efficacious range predicted by preclinical modeling
- No evidence of bone marrow suppression as determined by peripheral blood counts or other safety signal (May 2023)

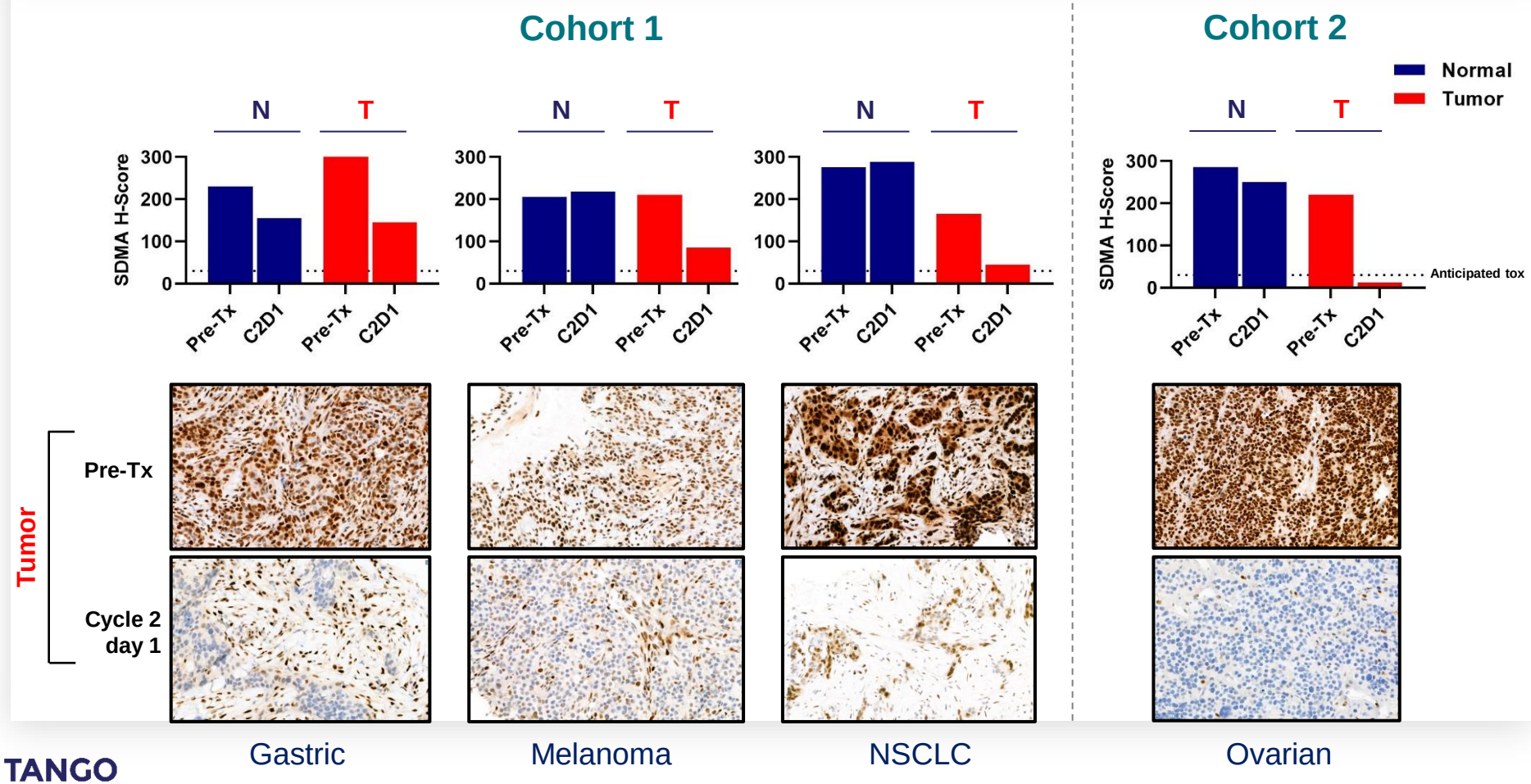
May 2023 update

- 16 patients, 12 different histologies
- PK/PD on cohorts 1 and 2
- Safety on cohorts 1-4
- Ongoing brisk enrollment
- Additional data expected in 2024

Differential PRMT5 inhibition, as shown by selective SDMA reduction in MTAP-del cancer vs. normal tissue, is essential to enable the therapeutic index needed for efficacy

TNG908 clinical proof-of-mechanism

SDMA IHC



May 2023 update

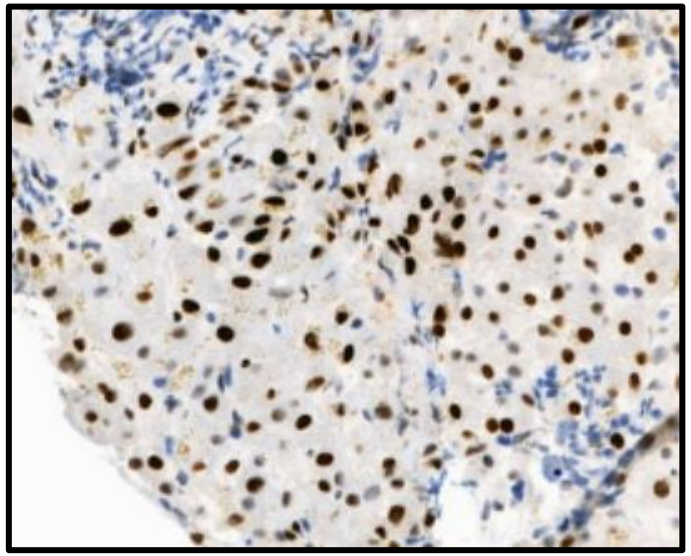
- Dose dependent PRMT5 inhibition in tumor in cohorts 1 and 2
- Minimal PRMT5 inhibition in normal tissue
- TNG908 exposure in these cohorts not yet within the efficacious range

All available paired biopsies presented

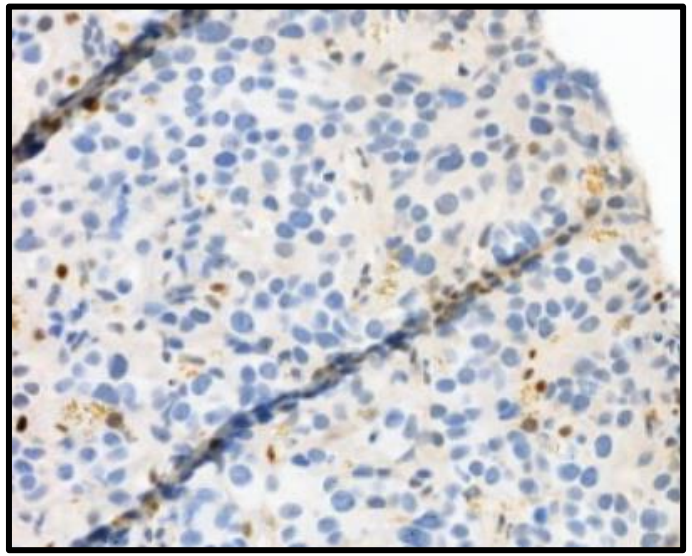
MTA-cooperative PRMT5 inhibition: proof-of-mechanism in the cohort 2 ovarian cancer patient

Cohort 2 (cycle 2/day 1) core biopsy

MTAP-WT
normal adjacent liver



MTAP-del
ovarian metastasis



Differential PRMT5 inhibition in normal and MTAP-deleted cancer cells is essential for therapeutic index and efficacy

Proof-of-mechanism

In one core biopsy:

- Minimal/no SDMA staining in MTAP-deleted tumor tissue
- Strong SDMA staining in adjacent normal liver cells

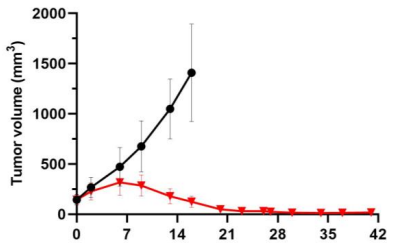
TNG908 is comparable or superior to MRTX1719 in multiple MTAP-null patient-derived xenografts

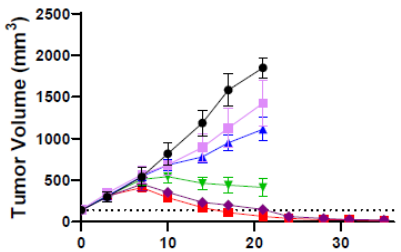
Mesothelioma and cholangiocarcinoma

TNG908

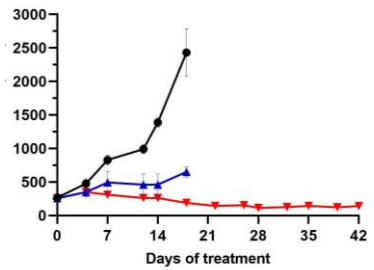
MRTX1719

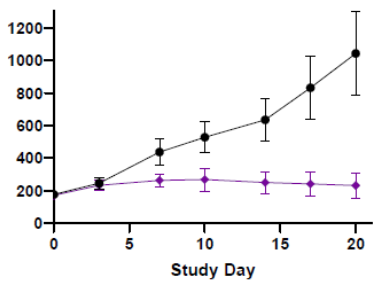
Mesothelioma





Cholangiocarcinoma



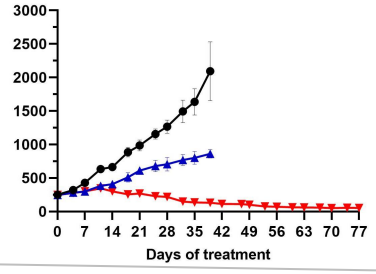


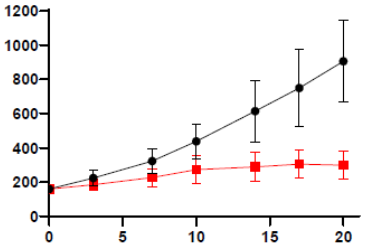
Non-small cell lung cancer

TNG908

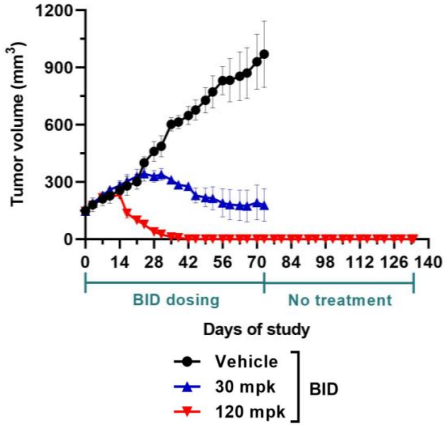
MRTX1719

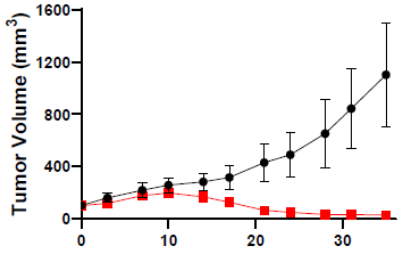
Adenocarcinoma





Squamous cell carcinoma





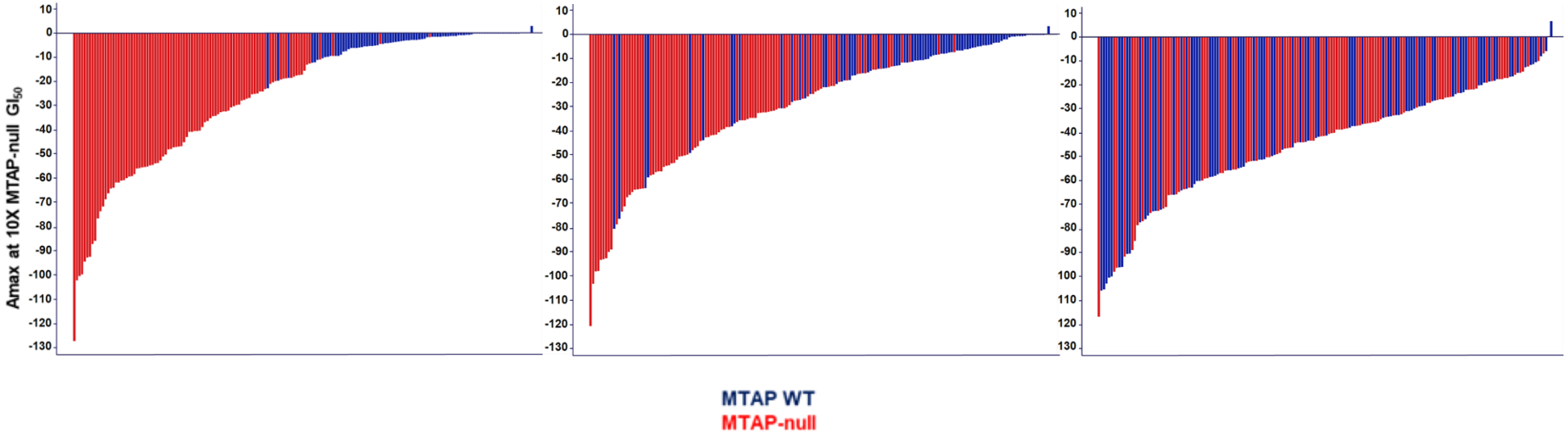
TNG462 is highly potent and selective for MTAP deletion

180 cancer cell lines from multiple lineages

TNG462
IC_{50} = 4 nM
45X selectivity for MTAP deletion

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

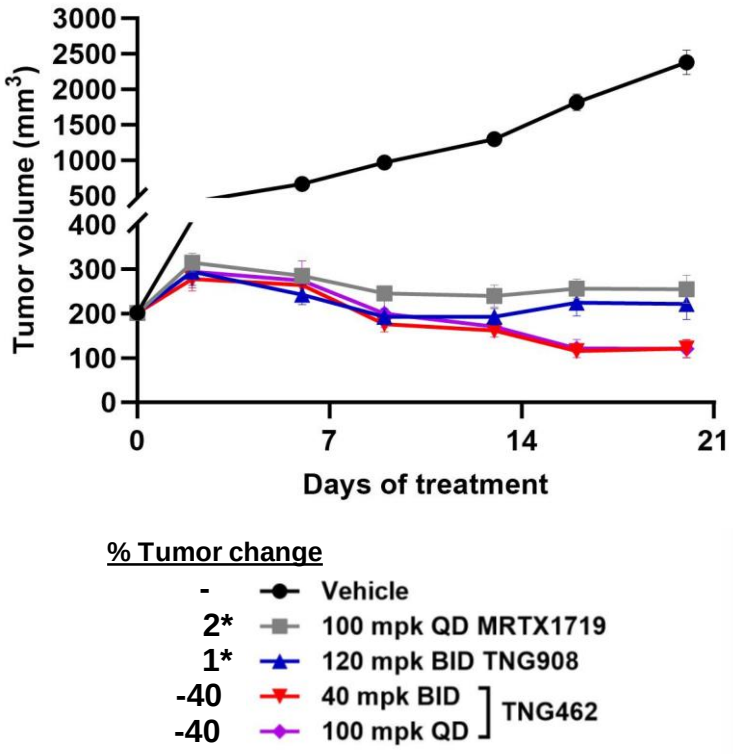
TNG462

- TNG462 PK profile optimized for maximal target coverage
- Enhanced potency and MTAP selectivity provides potential for broader and deeper clinical activity
- Only TNG908 is brain penetrant in non-human primates

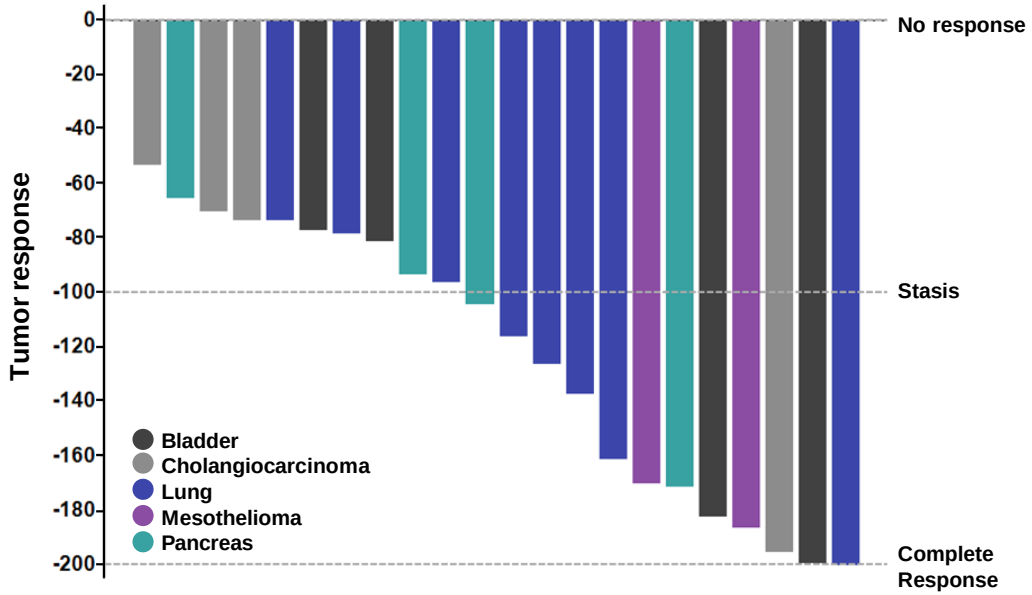
TNG462 is a potentially best-in-class PRMT5 inhibitor

TNG462 increases depth and durability of response in xenograft models

LU99
MTAP-null NSCLC CDX



Multiple histologies
MTAP-null PDX



Strong efficacy across histologies

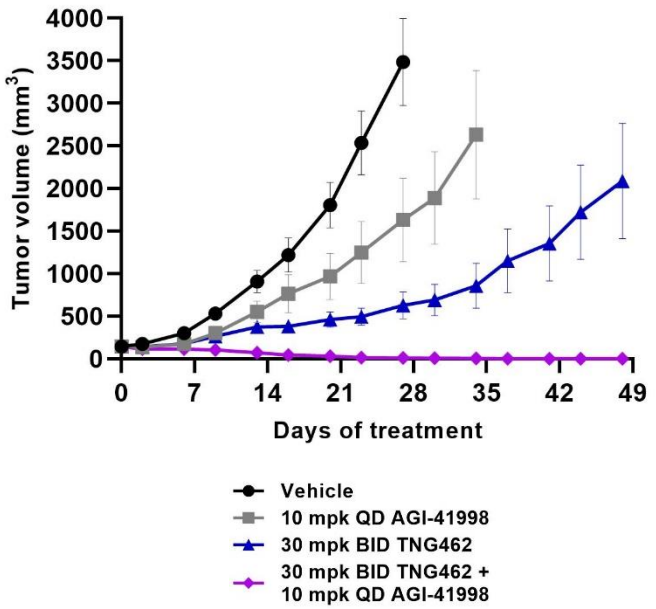
- Tumor growth inhibition, stasis or regression in all models (n=22) with no bias for specific histologies
- Regression achieved in ~55% of models (vs 30% with TNG908)

*data presented as % ΔT/ΔC

Combination with MAT2A inhibitor may be beneficial in MTAP-del tumors

TNG462 + MAT2Ai combination efficacy

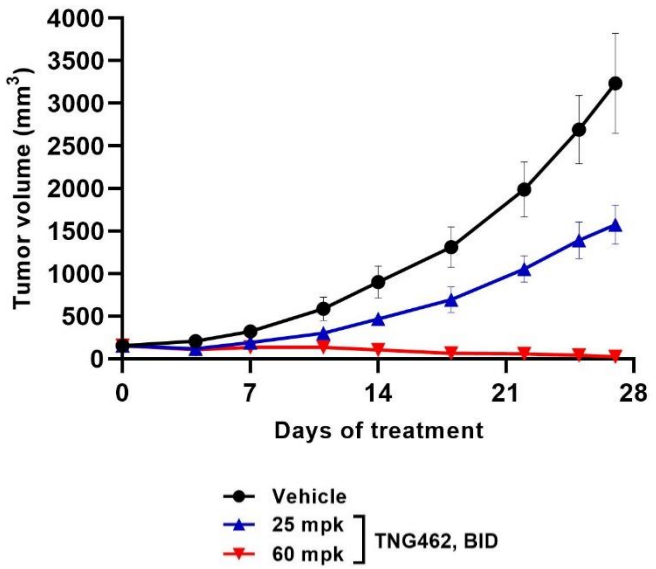
NCI-H838
(MTAP-del NSCLC)



Synergy demonstrated with well-tolerated combination of sub-therapeutic doses

TNG462 single agent efficacy

NCI-H838
(MTAP-del NSCLC)



Tumor regression achievable with single agent activity

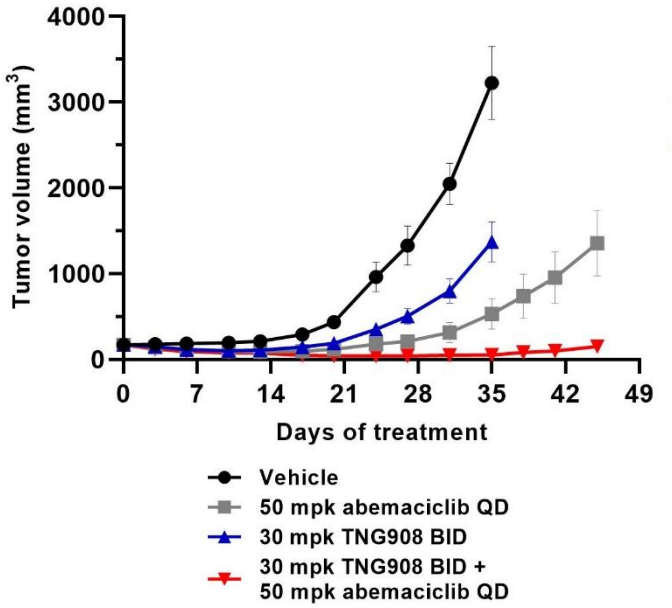
Rationale

- MAT2A inhibitors are indirect PRMT5 inhibitors and may add benefit in MTAP-del cancers in combination with TNG908 and TNG462
- TNG462 single agent activity at therapeutic dose can drive equivalent response to MAT2A combination in the same xenograft model

Combination strategies driven by co-occurring genetic alterations

TNG908 + CDK4/6i

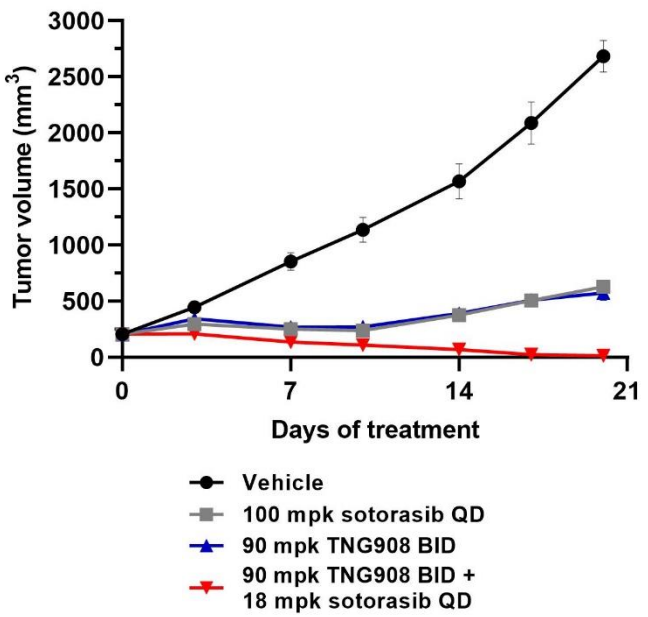
U87MG
(MTAP-del/CDKN2A-del GBM)



MTAP-del cancers are also CDKN2A-del

TNG908 + KRAS^{G12C}

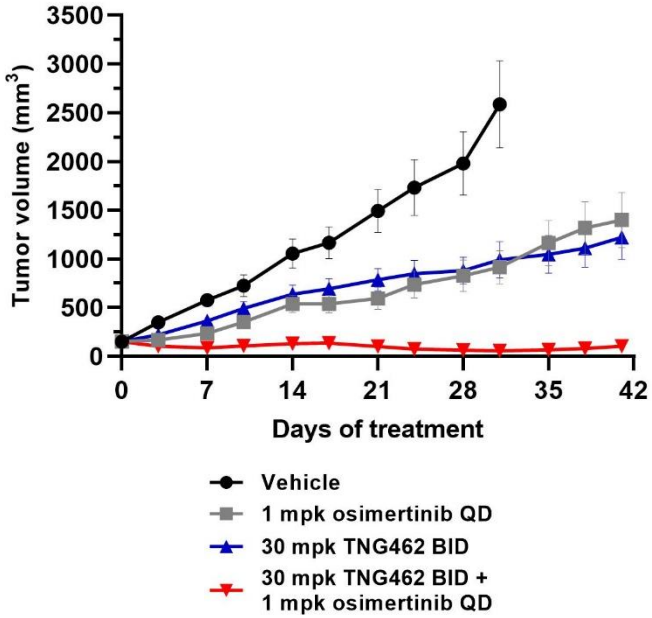
LU99
(MTAP-del/KRAS^{G12C}/CDKN2A-del NSCLC)



10-15% of MTAP-del lung (adeno) cancers also are KRAS G12C-mut

TNG462 + EGFRi

NCI-H1650
(MTAP-del/EGFR$^{\Delta E746\text{-}A750}$ NSCLC)



20% of MTAP-del lung (adeno) cancers also are EGFR-mut

TNG908 and TNG462 summary

PROGRAM	PATIENT SELECTION	DISCOVERY	IND-ENABLING	CLINICAL TRIALS		STATUS
				Phase 1/2	Phase 3	
PRMT5 TNG908	MTAP-deleted cancers					Additional clinical data in 2024
PRMT5 TNG462						Dose escalation ongoing

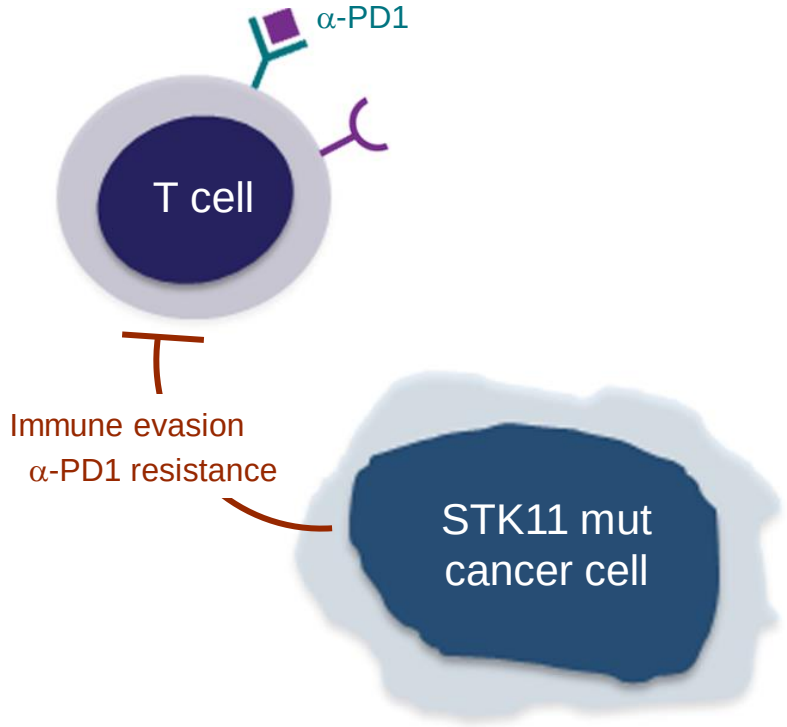
- TNG908 and TNG462 induce deep regressions and some cures in multiple xenografts with no bias for specific histologies, predicating strong single agent activity
- TNG462 has more potency, greater MTAP selectivity and has a longer half life than TNG908
- TNG908, but not TNG462, is brain-penetrant in non-human primates

TNG260

CoREST inhibition in STK11-mutant cancers

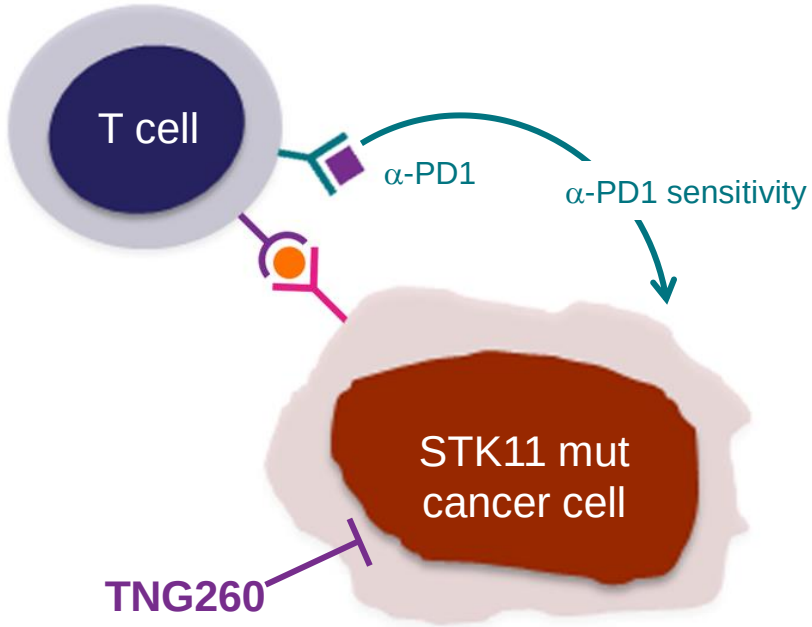
TNG260 reverses immune evasion caused by STK11 mutations

Immune evasion driven by tumor suppressor gene loss



STK11 re-activation is not feasible

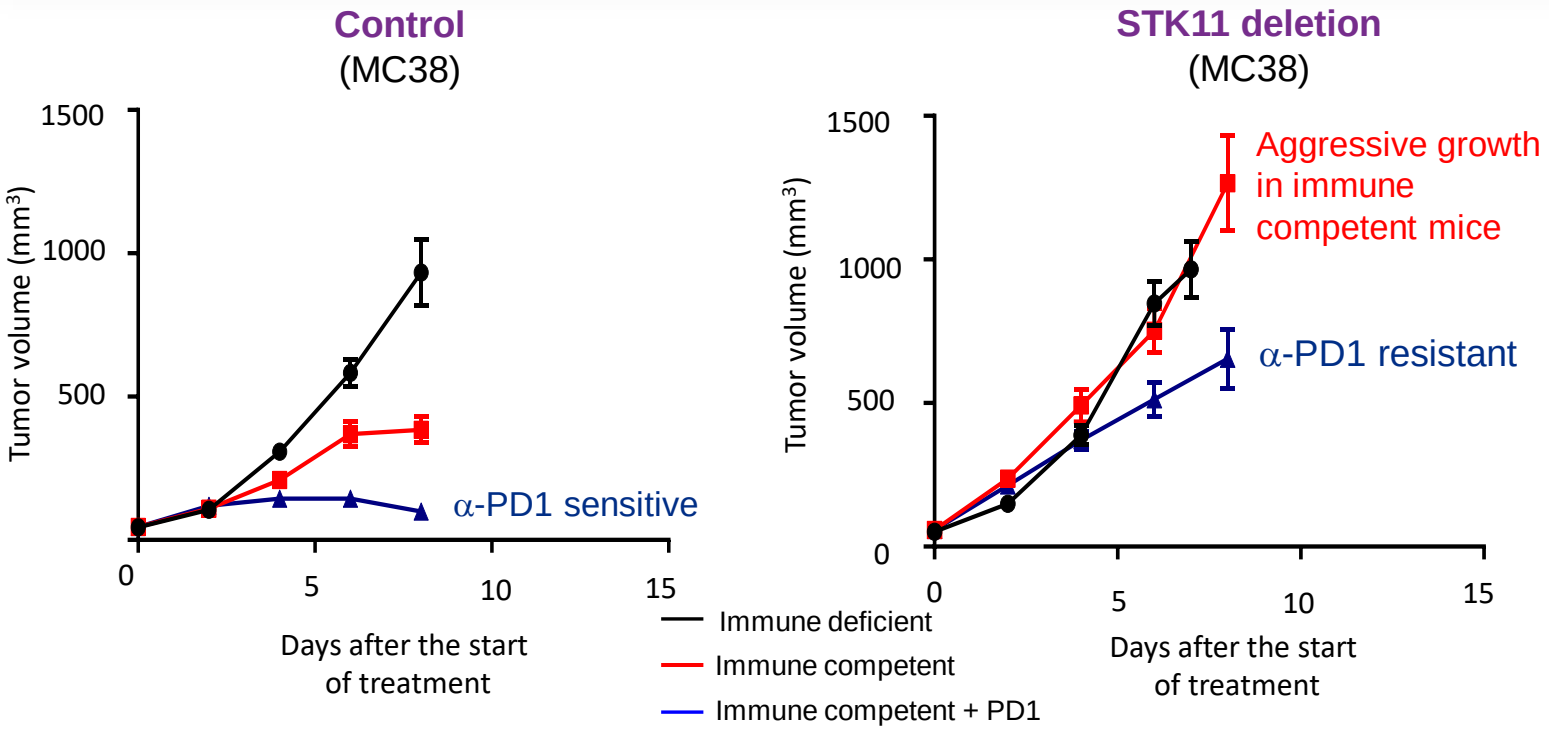
TNG260 reverses tumor-intrinsic immune evasion



Selective CoREST inhibition in cancer cells enables immune-mediated cytotoxicity

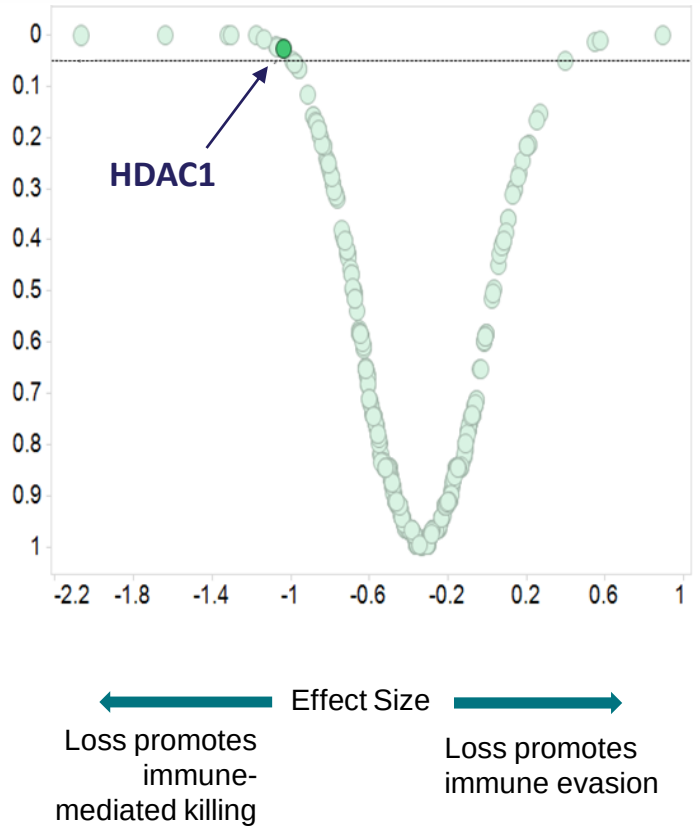
STK11 loss-of-function mutations drive immune evasion

STK11 deletion causes α-PD1 resistance

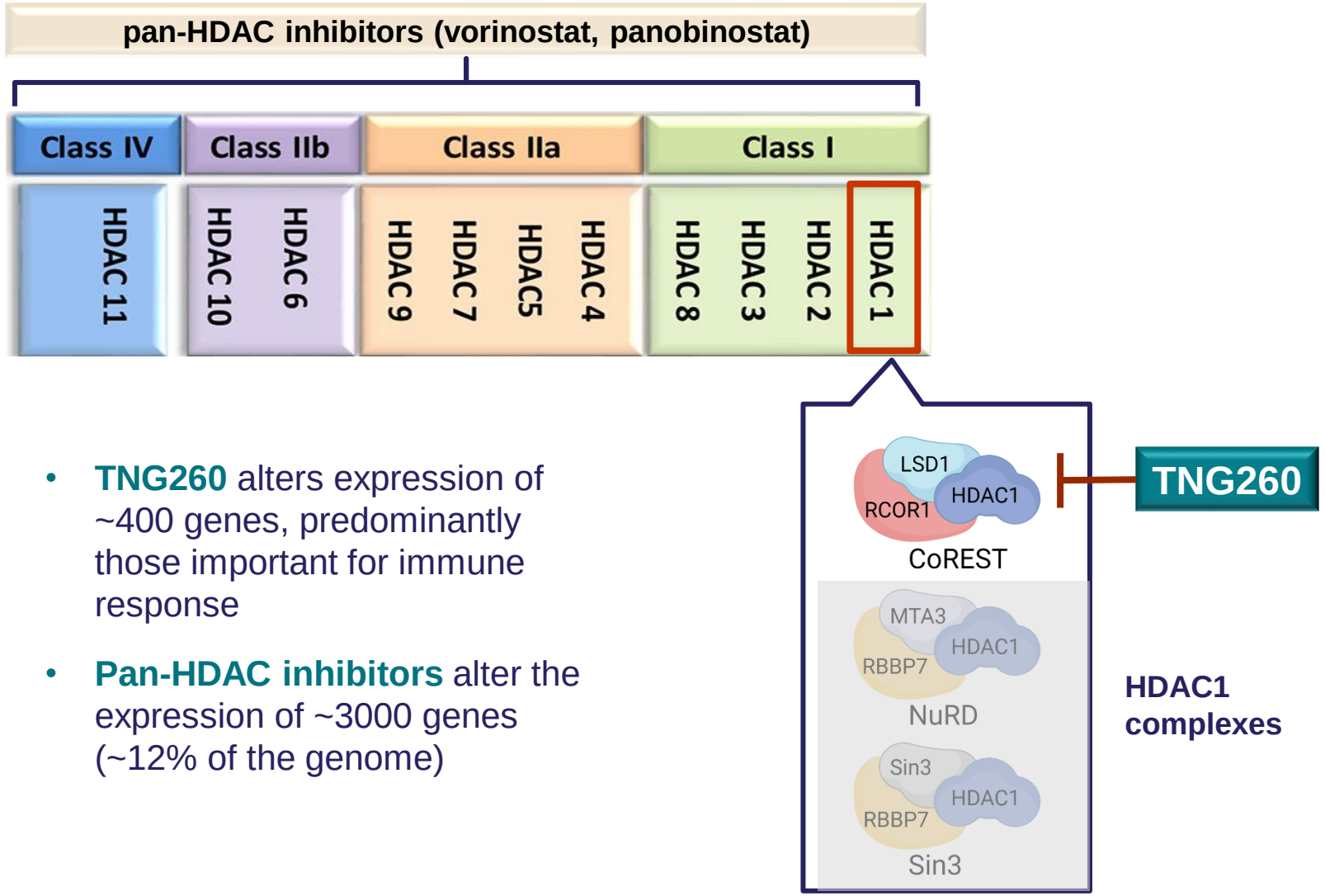


STK11 loss-of-function mutations are associated with clinical immune checkpoint inhibitor resistance

In vivo CRISPR screening identifies mediators of immune evasion reversion



TNG260 is a highly selective CoREST complex inhibitor



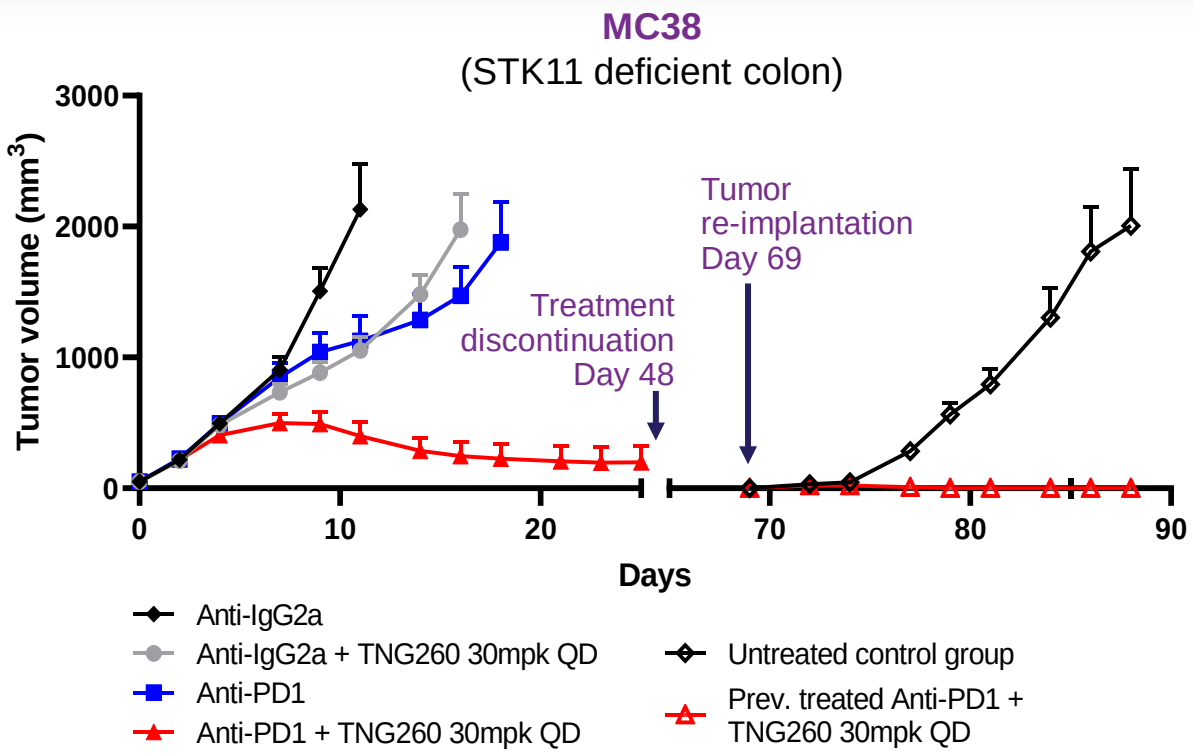
- **TNG260** alters expression of ~400 genes, predominantly those important for immune response
- **Pan-HDAC inhibitors** alter the expression of ~3000 genes (~12% of the genome)

Key points

- CoREST-mediated deacetylation regulates transcription of a specific set of immune response genes
- Sin3 is the predominant HDAC1 complexes involved in hematopoiesis
- Pan-HDAC inhibitors target all 11 HDAC isoforms
- HDAC3 is an essential gene and likely a primary contributor to pan-HDACi toxicity

TNG260 + α-PD1 induces complete regression and prevents re-implantation in STK11-mutant xenografts

TNG260 IC50 5nM, 10X CoREST complex selectivity



- 5/8 mice had complete tumor regression at day 34, treatment discontinued at day 48
- All mice with complete regression remained tumor free off treatment for 21 days
- 5/5 mice with complete regression rejected tumor reimplantation

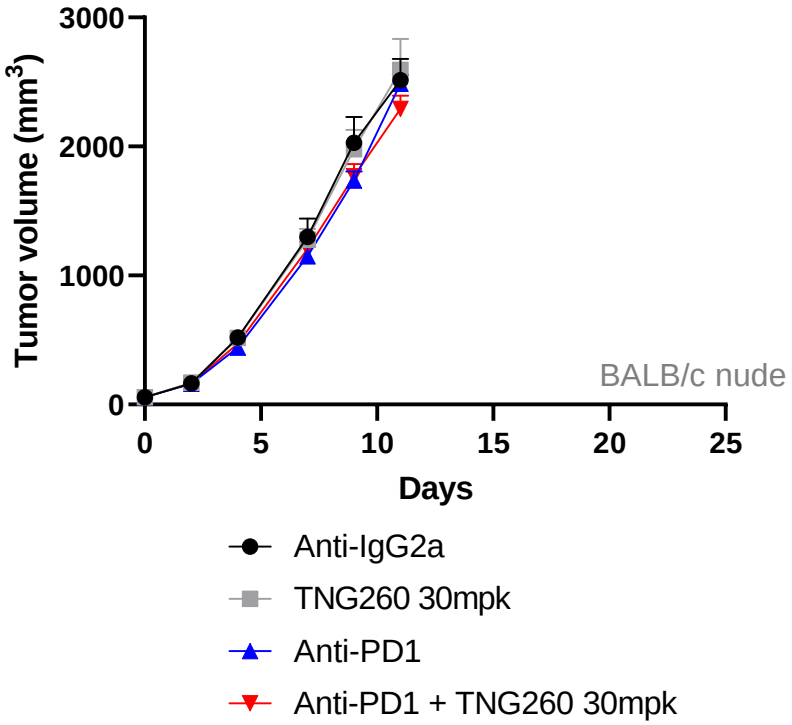
TNG260

- Potent, highly selective molecule with good pharmacologic properties
- Marked *in vivo* efficacy in combination with anti-PD1 antibody
- Induces immune memory and renders treated mice resistant to tumor re-implantation

Anti-tumor efficacy of TNG260 requires an intact immune system

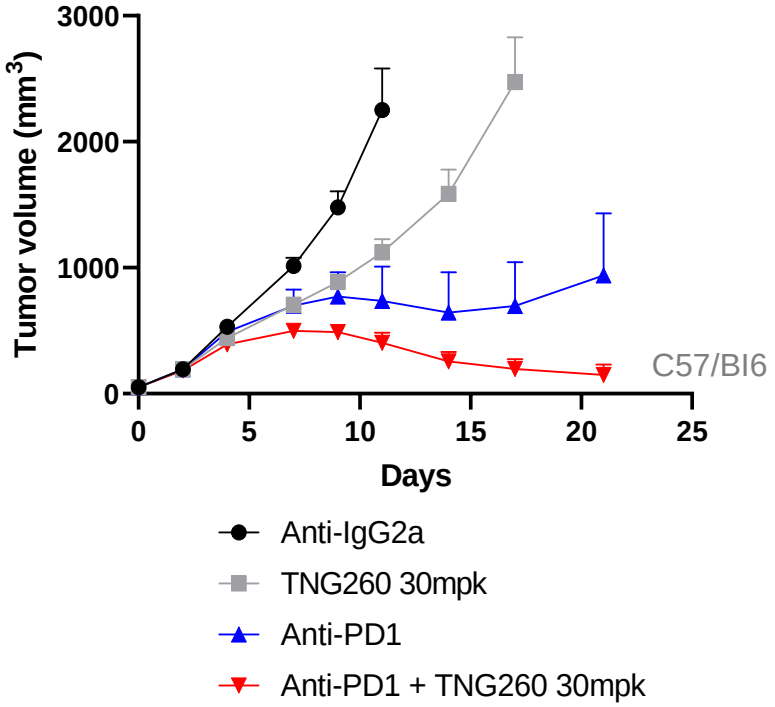
Immunocompromised mice

MC38
(STK11 deficient colon)



Immunocompetent mice

MC38
(STK11 deficient colon)



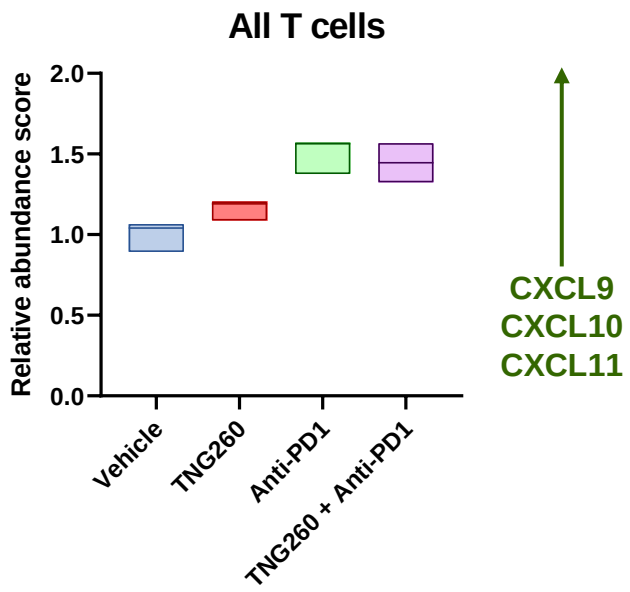
TNG260

- TNG260 anti-tumor effect not observed in mice without T cells

TNG260 eliminates Treg infiltration caused by α-PD1 without reducing cytotoxic T cell recruitment

α-PD1 induces tumor cell cytokine secretion that recruits T cells

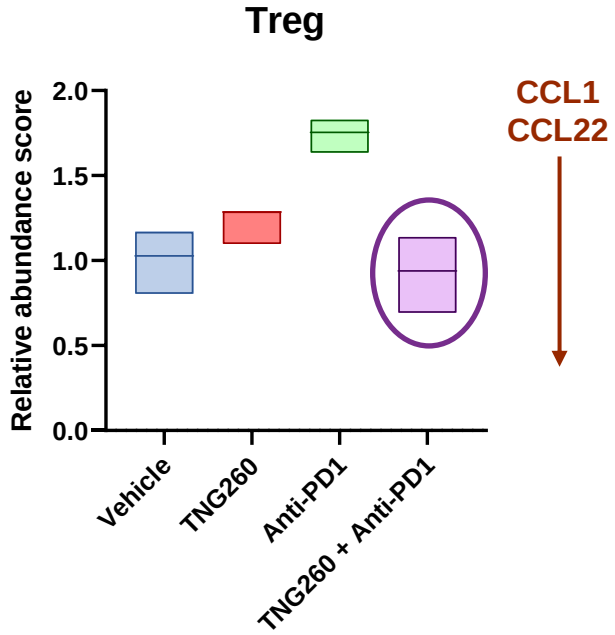
MC38
(STK11 deficient colon)



- CXCL9, CXCL10 and CXCL11 attract cytotoxic T cells
- α-PD1 recruits both cytotoxic T cells and suppressive Tregs

TNG260 eliminates immune suppressive Treg infiltration caused by α-PD1

MC38
(STK11 deficient colon)



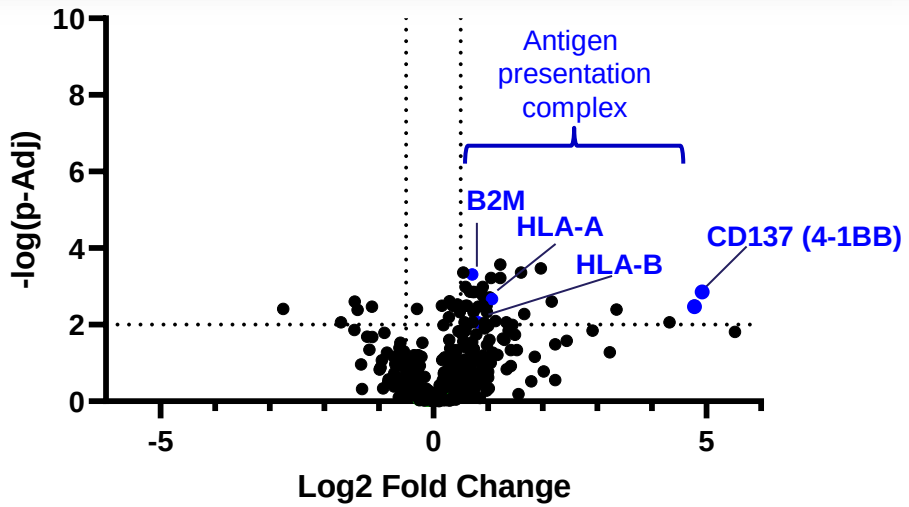
- CLL1 and CCL22 attract suppressive Treg cells
- TNG260 prevents α-PD1-driven Treg recruitment

Mechanism of action

- TNG260 causes transcriptional reprogramming in STK11-mut cells
- TNG260-mediated transcriptional changes alter tumor secretion of specific cytokines
- Changes in cytokine secretion caused by TNG260 + α-PD1 change the tumor T cell ratio to strongly favor immune-mediated tumor cell killing

TNG260 selectively regulates immune function

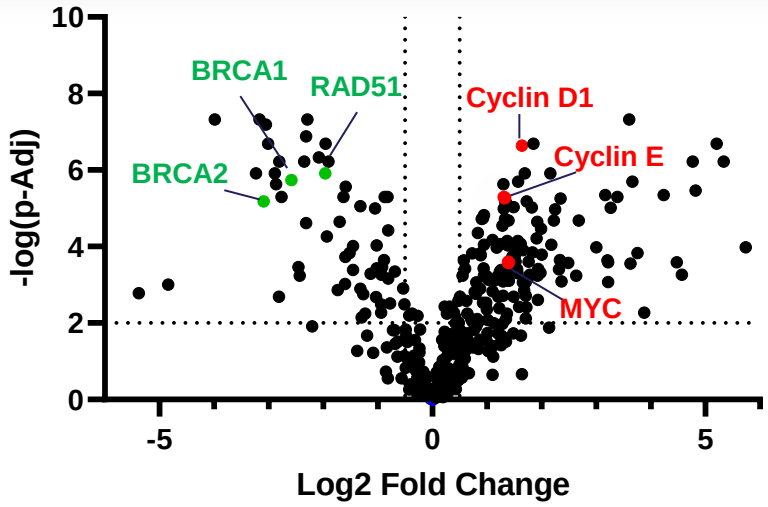
TNG260 (CoREST)
Cell line (STK11 mutant)



	Rank
Immune Cell Adhesion and Migration	1
Matrix Remodeling and Metastasis	2
Antigen Presentation	3

Top scoring genes activated by CoREST inhibition are immunomodulatory

Vorinostat (pan-HDAC)
Cell line (STK11 mutant)

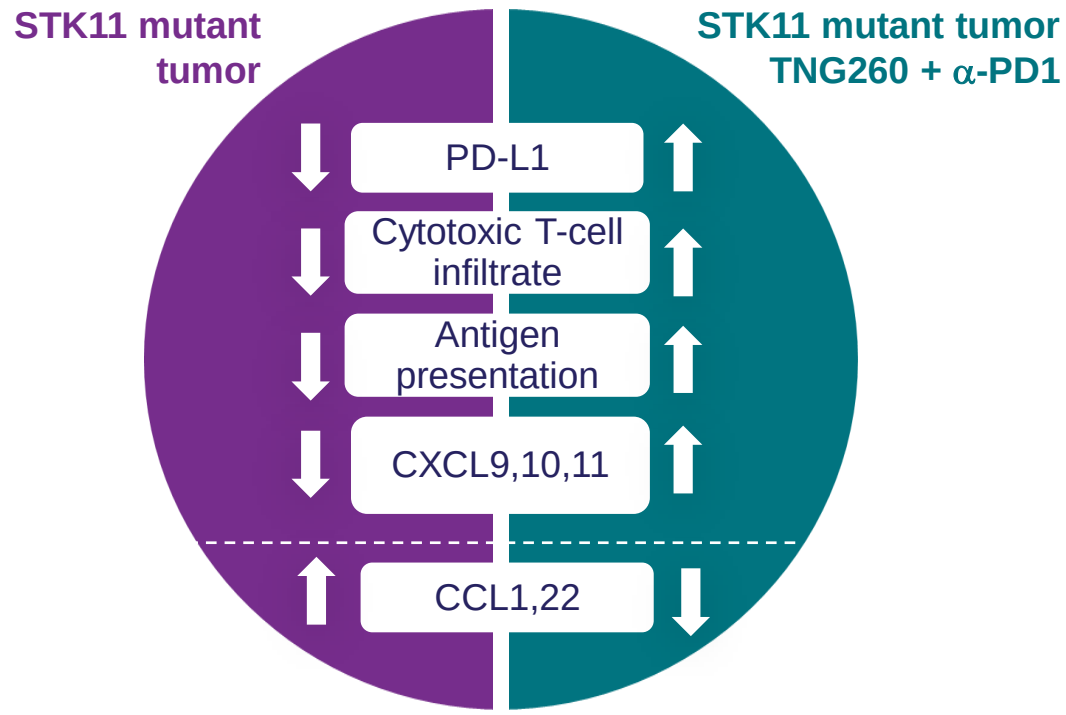


	Rank
Cell Proliferation	1
DNA Damage Repair	2
Wnt Signaling	3

Top scoring genes activated by pan-HDAC inhibition regulate cell cycling and DNA damage repair

TNG260 reverses key immune evasion mechanisms of STK11-mutant tumors

TNG260 reverses immune evasion in STK11-mutant xenografts



Summary

- STK11 loss of function creates a tumor micro-environment that prevents immune-meditated tumor cell killing
- Transcriptional reprogramming by TNG260:
  - Increases PDL-1 expression
  - Increases antigen presentation
  - Increases tumor secretion of cytotoxic T-cells attractant cytokines
  - Decreases tumor secretion of suppressive T-regulatory cell attractant cytokines

TNG260 first-in-human trial design

DOSE ESCALATION

- Any solid tumor with STK11 mutation

DOSE EXPANSION

STK11 mut lung cancer

STK11 mut histology-agnostic cohort

(enriched for cervical, unknown primary, pancreatic, breast)

PHASE 1/2 STUDY

- STK11 mutations occur in ~15% NSCLC, 15% cervical, 10% carcinoma of unknown primary, 5% breast and 3% pancreatic cancers
- Combination with pembrolizumab to assess safety, PK/PD and efficacy as primary endpoints
- FDA Fast Track designation

TNG260 summary

PROGRAM	PATIENT SELECTION	DISCOVERY	IND-ENABLING	CLINICAL TRIALS		STATUS
				Phase 1/2	Phase 3	
CoREST TNG260	STK11-mut cancers					Dose escalation ongoing

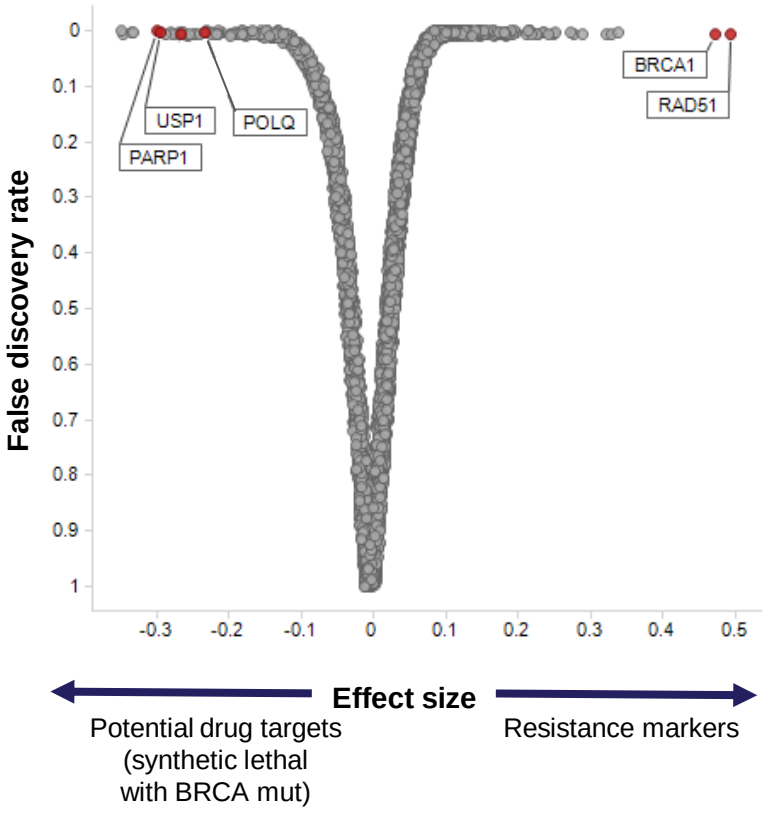
- STK11 mutations are associated with checkpoint inhibitor resistance in lung cancer patients
- TNG260 is a novel, highly selective CoREST complex inhibitor
- TNG260 reverses checkpoint inhibitor resistance in preclinical STK11-mut models and induces immune memory that prevents tumor regrowth in responders
- Phase 1/2 clinical study ongoing evaluating efficacy in combination with pembrolizumab in STK11-mutant cancers

TNG348

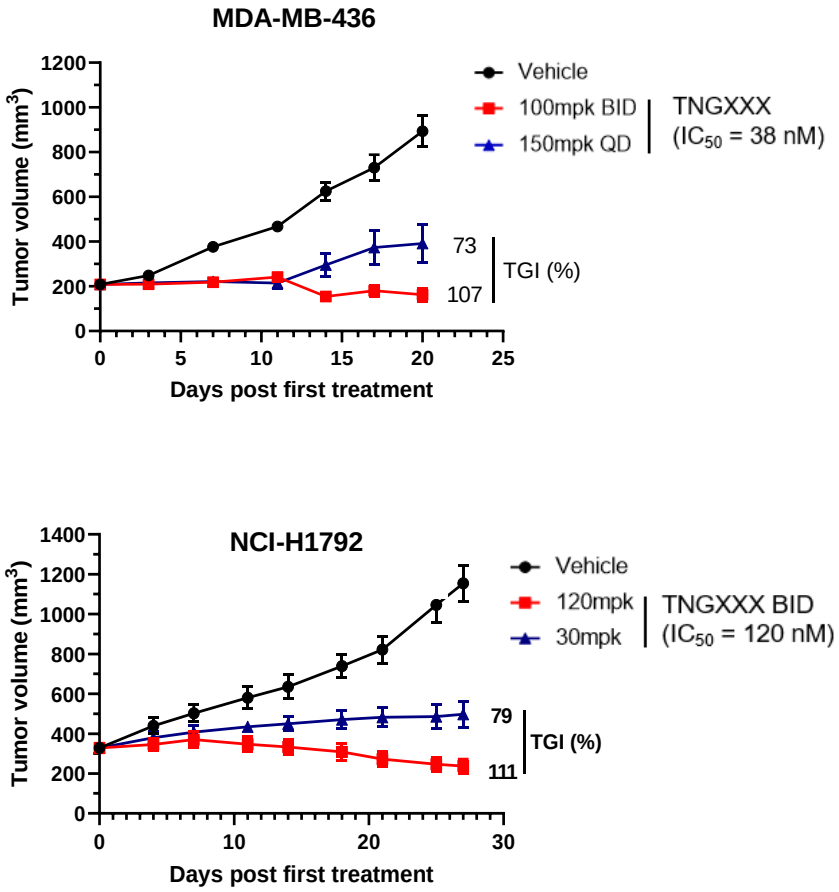
USP1 inhibition in HRD+ cancers

USP1 inhibition is synthetic lethal with BRCA1/2 mutations

USP1 is a strong hit in a druggable genome CRISPR screen



USP1i is effective in BRCA1/2 mutant xenografts



USP1

- USP1 is a de-ubiquitinating enzyme (DUB)
- Loss of USP1 results in impaired DNA replication in BRCA1/2 mutant cells
- USP1 inhibition selectively kills BRCA1/2-mut breast and ovarian xenografts

USP1 and BRCA1/2 are a synthetic lethal pair

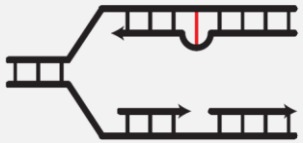
Multiple mechanisms exist to repair damaged DNA

BRCA1/2 mutations (HRD+)

Prevent repair of double strand breaks (homologous and non-homologous end-joining)

USP1 inhibitors

Prevent efficient repair of single strand breaks (translesion synthesis)



PARP inhibitors

Prevent efficient repair of single strand breaks (base excision repair)

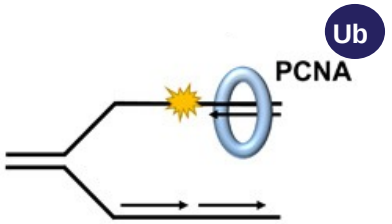
Blocking DNA damage repair causes cell death

- Normal cells have multiple mechanisms to repair damaged DNA and prevent cell death (or cancer)
- BRCA1/2 mutant cells rely on translesion synthesis and base excision repair
- Both USP1 and PARP inhibition severely impair DNA damage repair in BRCA1/2 mutant cells
- Combining USP1 and PARP inhibition largely eliminates DNA damage repair in BRCA1/2 mutant cells

TNG348 blocks an important DNA damage repair pathway

USP1 inhibition blocks translesion synthesis

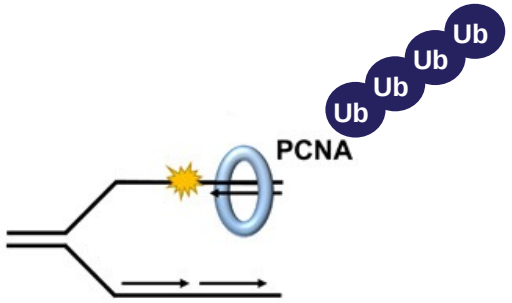
USP1 removes ubiquitin from PCNA to complete the repair



Mono-ubiquitinated PCNA encircles damaged DNA

TNG348

TNG348 blocks ubiquitin removal from PCNA



Poly-ubiquitinated PCNA accumulates, is degraded and translesion synthesis repair blocked

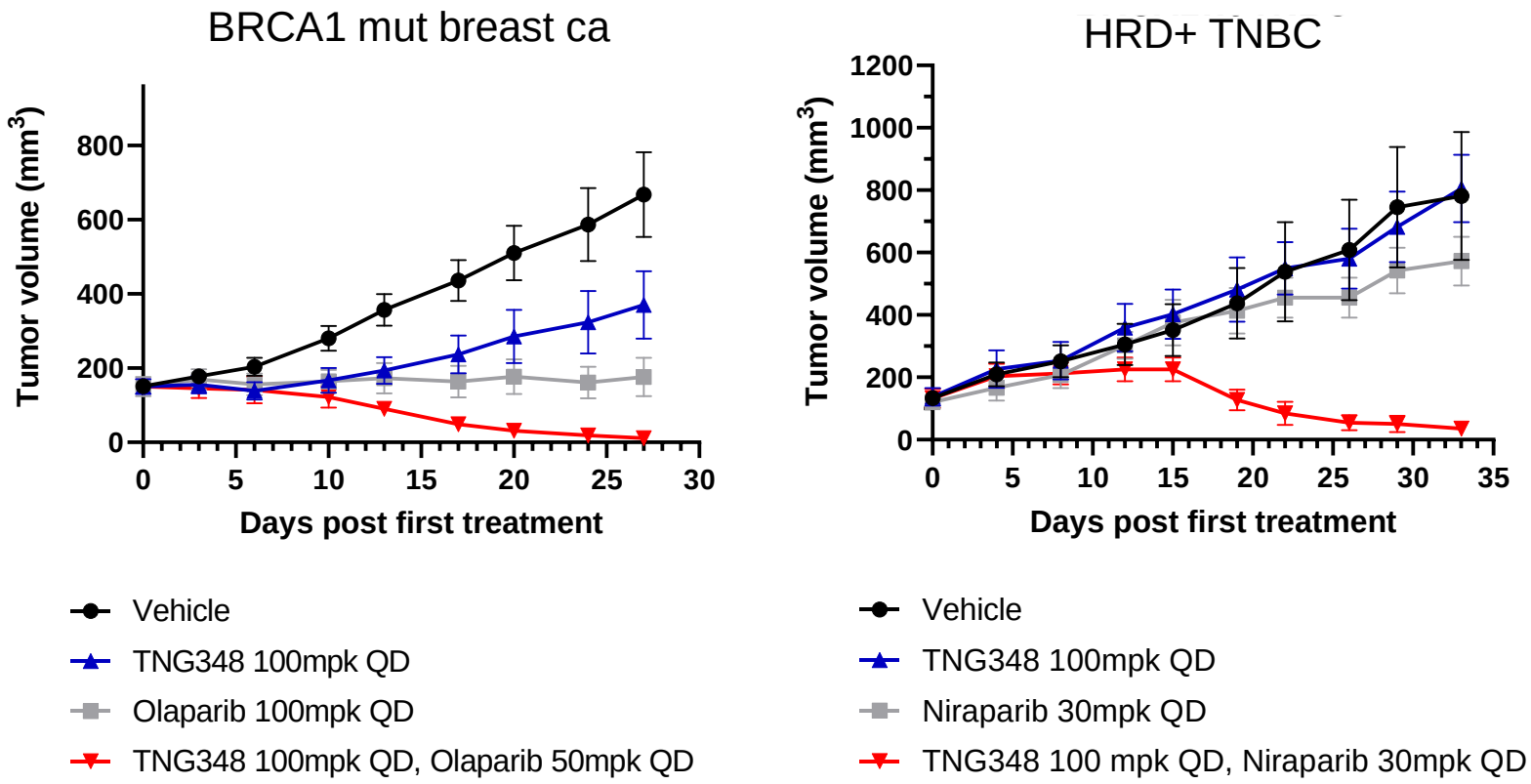
BRCA1/2 mutant cells rely on translesion synthesis because they lack efficient double-strand break repair

Summary

- DNA damage blocks DNA replication
- Mono-ubiquitinated PCNA is required for translesion synthesis to read through damaged DNA
- USP1 inhibition causes accumulation of poly-Ub PCNA blocking translesion synthesis repair

TNG348 is active alone and in combination with PARP inhibitors

In vivo efficacy in PDX models

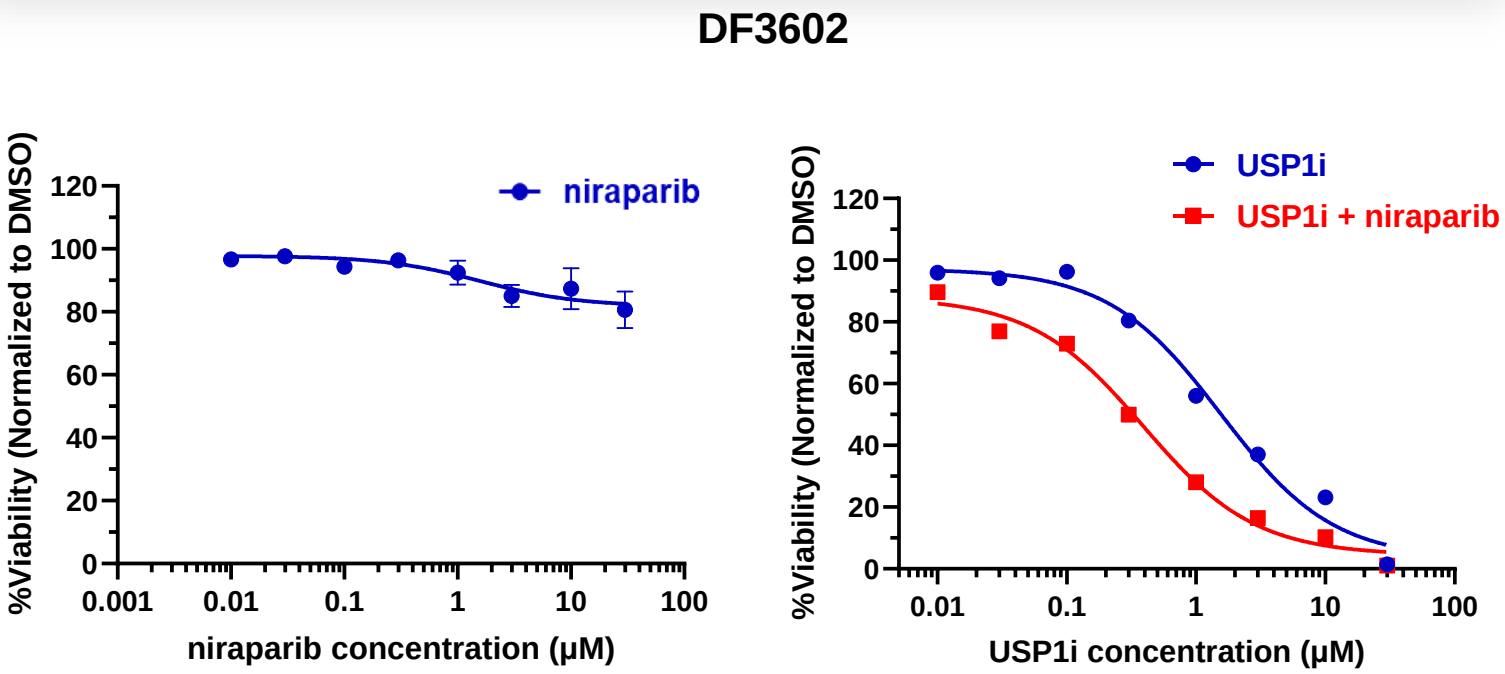


TNG348

- Single-agent activity equivalent to or better than olaparib in multiple models
- Synergy with PARP inhibition in both PARPi sensitive and resistant models
- Strong anti-tumor activity in HRD+ BRCA wt xenograft models broadens the addressable patient population beyond BRCA mutations

PARP inhibitor resistant patient-derived organoids are sensitive to USP1 inhibition

Ex vivo efficacy in a PARP resistant patient-derived organoid



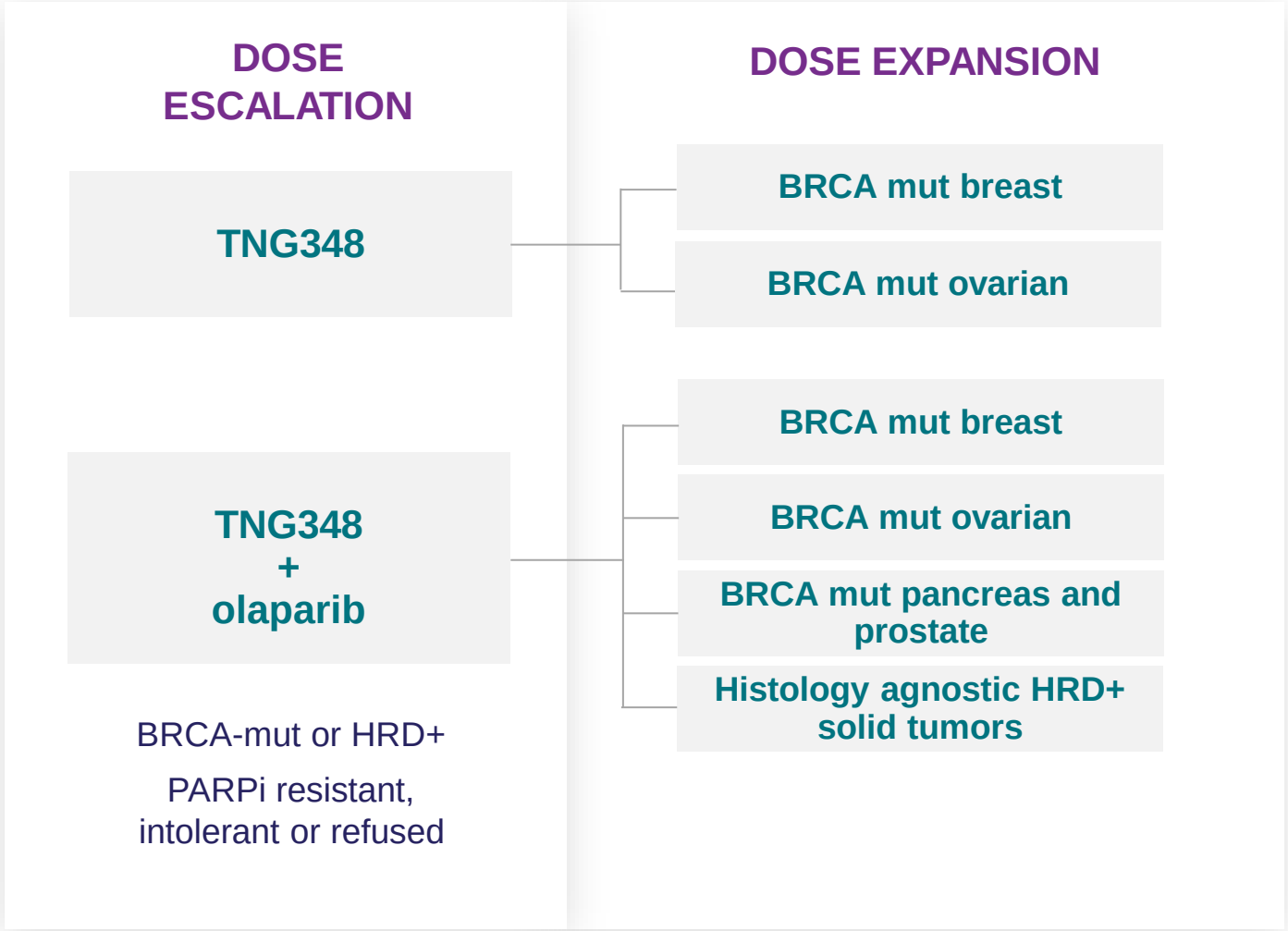
DF3602 was derived from a tumor exposed to more than 10 prior lines of therapy

Unpublished data, Dr Alan D'Andrea, Dana-Farber Cancer Institute

PARP resistance

- Multiple PARP-resistant patient-derived organoid models are sensitive to USP1 inhibition
- USP1i overcomes known PARP resistance mechanisms including TP53BP1 deletion
- PARPi + USP1i are synergistic in PARP-resistant organoids and in patient and cell line-derived xenografts

TNG348 first-in-human trial design



PHASE 1/2 STUDY

- HRD+ as defined by RAD51 or PALB2 mutation or FDA-approved panel (Myriad, Foundation Medicine)
- BRCA reversion mutations excluded
- PARPi combination to start at lowest pharmacologically active TNG348 dose + 300 mg BID olaparib
- IND cleared Aug 2023

TNG348 summary

PROGRAM	PATIENT SELECTION	DISCOVERY	IND-ENABLING	CLINICAL TRIALS		STATUS
				Phase 1/2	Phase 3	
USP1 TNG348	BRCA1/2-mut, other HRD+ cancers					Trial initiation 1H 2024

- HRD+ cancers, including BRCA1/2 mutations, represent up to 50% of ovarian, 25% of breast, 10% of prostate and 5% of pancreatic cancers
- USP1 inhibition is synthetic lethal with BRCA1/2 mutations and is synergistic with PARP inhibitors
- Distinct mechanism of action from PARP inhibitors
- Well tolerated at high exposures in preclinical safety studies
- Single agent activity and strong PARPi synergy in xenografts with BRCA1/2-mutations and other HRD defects
- Synergy in both PARPi sensitive and resistance models

FINANCIAL HIGHLIGHTS AND MILESTONES

Sufficient cash to achieve multiple projected key milestones

Milestones

- ✓ TNG462 (next-gen PRMT5) IND cleared 1H
- ✓ TNG260 (CoREST) IND cleared 1H
- ✓ TNG908 (PRMT5) clinical proof-of-mechanism 1H
- ✓ TNG462 first patient dosed 3Q
- ✓ TNG260 first patient dosed 3Q
- ✓ TNG348 (USP1) IND cleared August 2023
- ☐ TNG348 trial initiation 1H 2024
- ☐ TNG908 clinical efficacy data 2024

Cash balance

- $360M cash, cash equivalents and marketable securities (9/30)
- Cash runway into 2026 including POC readouts for all four clinical programs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