Targeting tumor suppressor loss

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

Corporate Overview

December 2024

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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: the Company's expected cash runway into the third quarter of 2026**;** the Company's planned and ongoing clinical trials, including the anticipated timing for enrollment and the timing to report results and updates of such trials;**;** the Company's belief that TNG462 has the potential to be a best-in-class molecule for multiple MTAP-deleted solid tumors; the Company's belief that TNG456 has the potential to be a best-in-class brain-penetrant PRMT5 inhibitor; the anticipated milestones for the Company's drug programs, including the timing for patient dosing 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 clinical trial initiation; the timing of dose escalation and dose expansion (including for combination studies); the timing of disclosure for initial, interim, additional and final clinical trial results; and the expected benefits of the Company's development candidates and other product candidates (including for combination studies the potential for a large patient population to be treated with Tango's PRMT5 inhibitors**;** the expected benefits of the Company's development candidates and other product candidates (including for combination studies; potential combination strategies for PRMT5 inhibitors, including TNG462 and TNG456**;** the development plans for the PRMT5 franchise (including future clinical trials); future clinical trial designs TNG260 future clinical trials strategy and implementation; the significant patient opportunities for the Company's pipeline therapies; the Company's key future milestones; the anticipated benefits of synthetic lethal drugs; expectations regarding the benefits and success of collaborations and combination clinical trials; and the anticipated benefits of its current and future product candidates including those identified in the future through the Tango discovery platform; the potential of TNG462 to have broader and deeper clinical activity in MTAP-deleted solid tumors; the potential of TNG456 to treat glioblastoma and central nervous system metastases; the development and regulatory pathway for TNG462 or TNG456. 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 at the time of this presentation, 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; future clinical trial data releases may differ materially from initial or interim data from our current and future clinical trials; Tango has limited experience with conducting clinical trials (and will rely on a third parties 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); dosing (including dose expansion) in clinical trials may need be delayed or may be stopped for various reasons, including due to any potential issues at the site, safety issues or supply disruptions; any significant changes required to be made to an applicable IND application or protocol could significantly delay on-going clinical trials); the benefits of Tango pipeline products (stand-alone and as potential combination therapies) that are seen in preclinical 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, reduce, or eliminate 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; future clinical trial data releases may differ materially from initial or interim data from our current and future clinical trials; the expected benefits of our product candidates in patients as single agents and/or in combination may not be realized; the Company may experience delays or difficulties in the initiation, enrollment, or dosing of patients in clinical trials or the announcement of clinical trial results; 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 product 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 (including the potential impact of the BIOSECURE Act on our supplier of drug substance); 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 public health events. 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, 2023, 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 Therapeutics

State-of-the-art target discovery platform and a pipeline of novel precision oncology targets

Gilead partnership to discover and develop up to 15 targeted immune evasion targets

- PRMT5 inhibitor franchise addressing large patient populations in multiple MTAP-deleted tumor types
  - TNG462 is a potential best-in-class molecule for multiple MTAP-deleted solid tumors
  - TNG462 is moving rapidly into full development, including in combination trials with multiple targeted and standard of care combinations to support registration in NSCLC and pancreatic cancer
  - TNG456 is highly potent, 55X selective for MTAP deletion and CNS penetrant, with the potential to treat glioblastoma and brain metastases
- TNG260 (CoRESTi) in phase 1/2 study in STK11-mut NSCLC and other cancers

Cash runway into Q3 2026

A sustainable pipeline of novel precision oncology targets

PROGRAM	PATIENT SELECTION	DISCOVERY	IND-ENABLING	CLINICAL TRIALS		STATUS
				Phase 1/2	Phase 3	
TNG462 (PRMT5)	MTAP-del non-CNS cancers					Dose expansion ongoing, clinical data update 2025
TNG456 (PRMT5)	MTAP-del GBM, NSCLC and other cancers					Enrollment to begin 1H 2025
TNG462 (PRMT5)	Multiple combinations					Enrollment to begin 1H 2025
TNG260 (CoREST)	STK11-mut cancers					Dose expansion ongoing, clinical data 2025
Novel target	Novel					

Gilead optioned and licensed targets not listed

TANGO therapeutics

A strong strategic partnership with Gilead

SCOPE	• 15 validated immune evasion targets • Four targets licensed, one 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

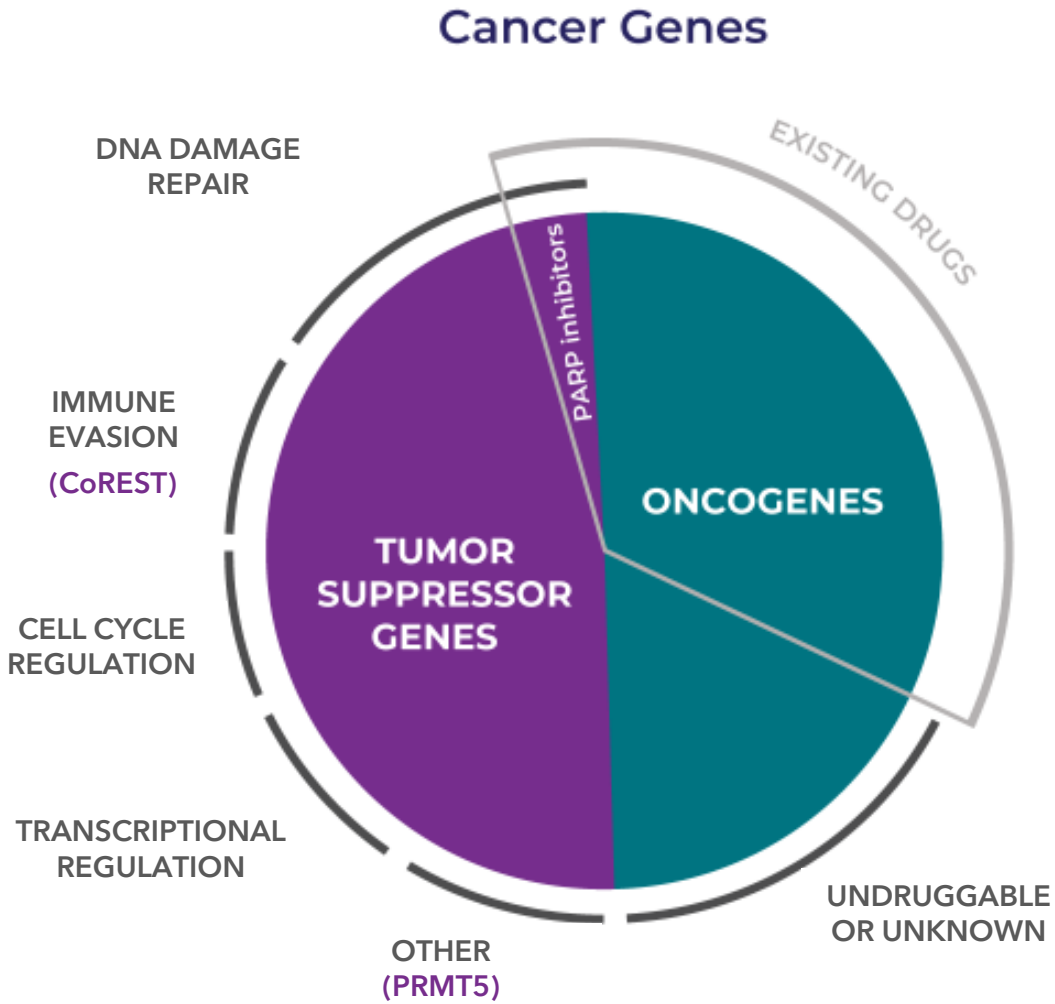
GILEAD

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

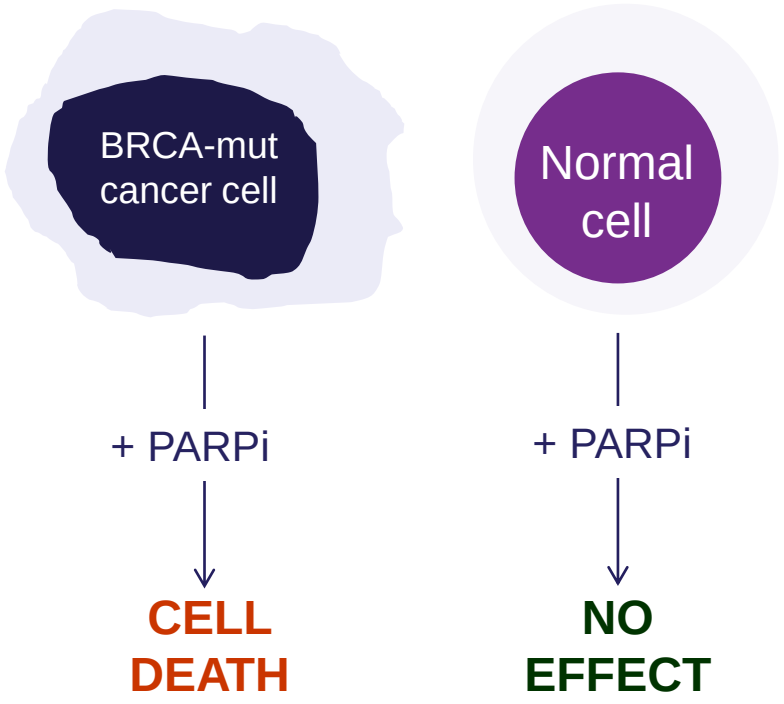
Primary approach to targeting tumor suppressor gene loss

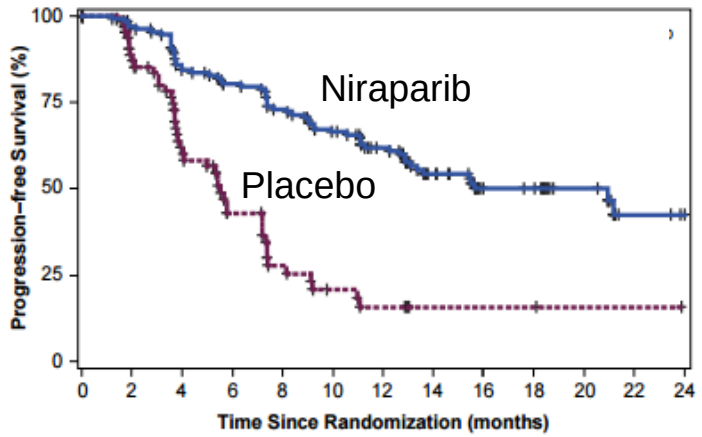
CRISPR TECHNOLOGY

Essential for large scale synthetic lethal discovery efforts

PARP is the first clinically validated synthetic lethal drug target

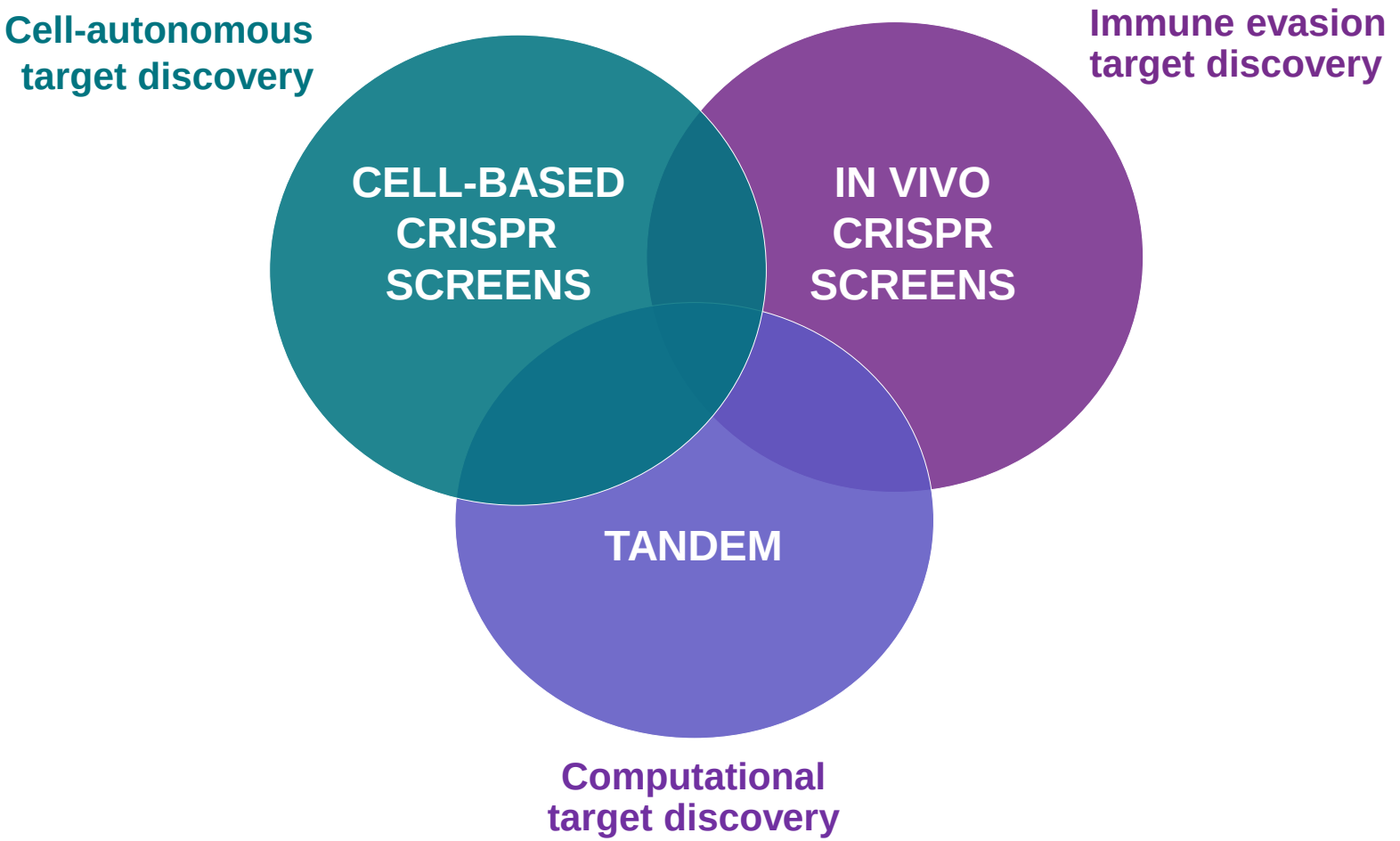
BRCA1/2 mutation and PARP inhibition are a synthetic lethal pair





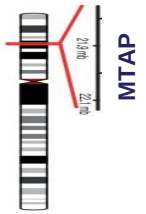
- PARP inhibitors are approved in BRCA-mutant breast, ovarian, pancreatic and prostate cancer
- Synthetic lethal drugs inherently have a wide therapeutic index
- Multiple analyses suggest hundreds of synthetic lethal pairs exist in human cancer

A 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

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

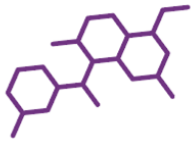


TNG462

Potent, 45X MTAP-selective, MTA-cooperative PRMT5 inhibitor active in multiple solid tumors

TNG456

Potent, 55X MTAP-selective and brain penetrant MTA-cooperative PRMT5 inhibitor



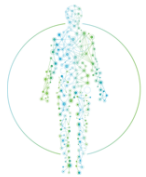
DIFFERENTIATED MECHANISM

MTA-cooperative mechanism highly selective for cancer cells with MTAP deletion

LARGE OPPORTUNITY FOR PATIENTS

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

Opportunity for combinations driven by co-occurring genetic alterations

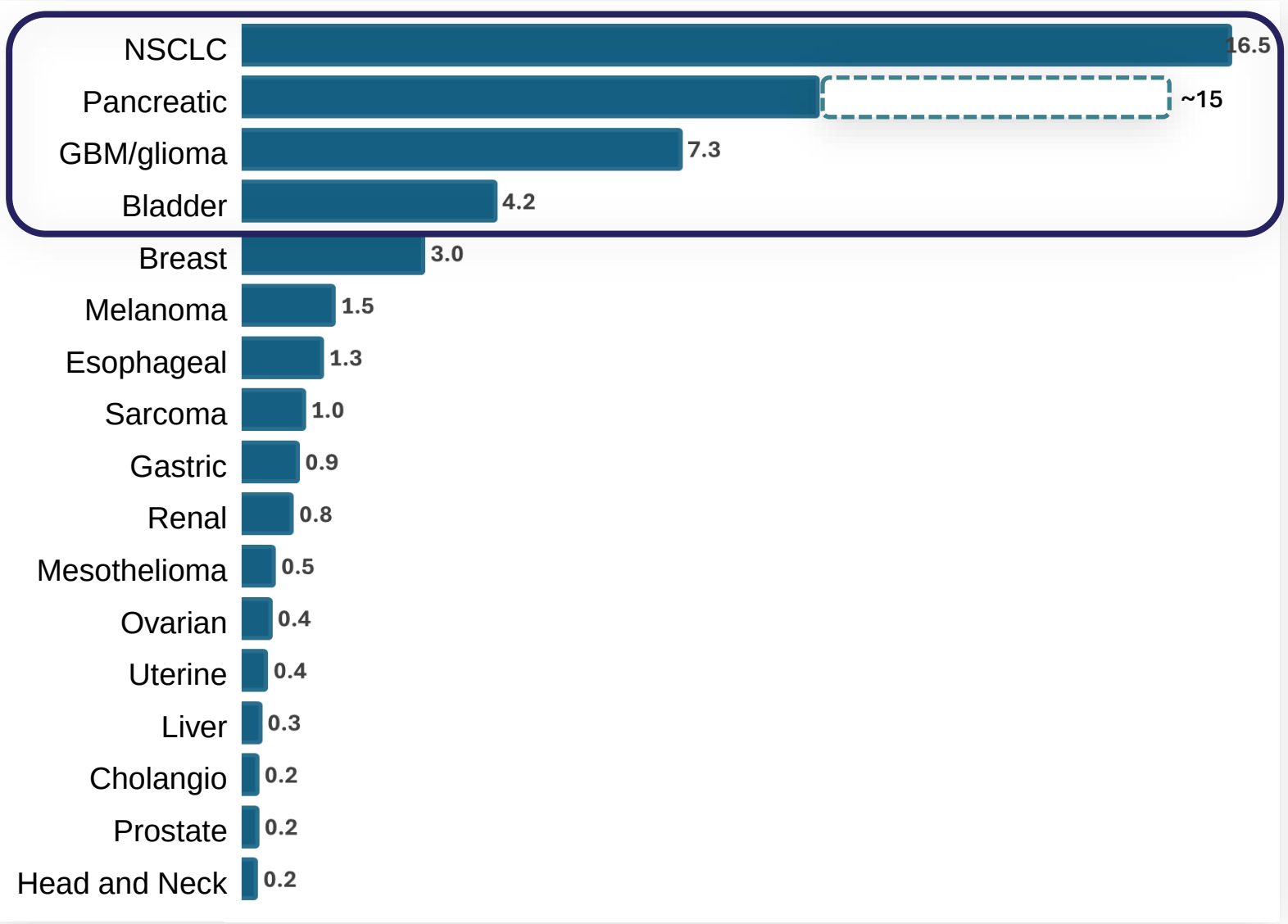


STATUS

TNG462 dose expansion ongoing, additional clinical data 2025

TNG456 phase 1/2 study enrollment expected 1H 2025

~50K metastatic disease patients annually in US

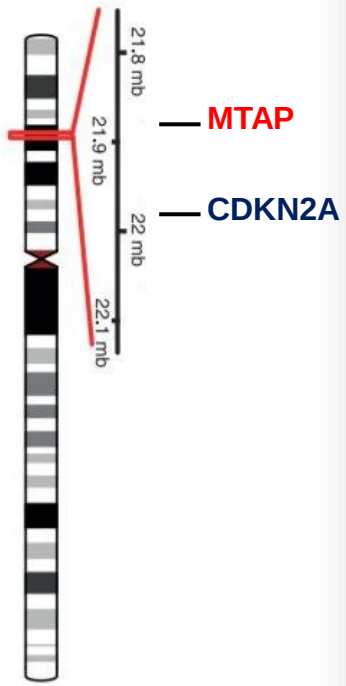


Large unmet need

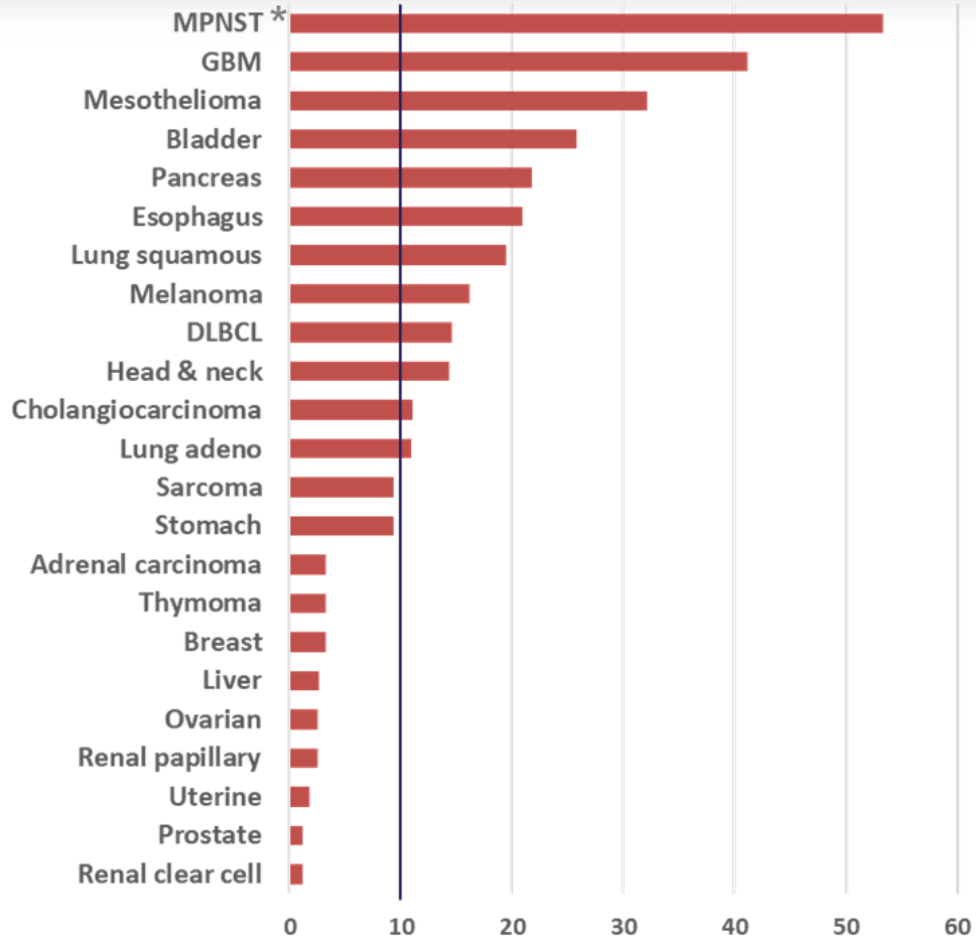
- No approved therapies for MTAP-deleted cancers
- Four common cancers account for ~80% of the value of a PRMT5 inhibitor (~40K patients)
- Incidence of MTAP deletion in pancreatic cancer could be 35-40% rather than 22% as estimated by TCGA

Investing in our PRMT5 franchise with TNG462 and TNG456

Chromosome 9



MTAP homozygous deletion frequency



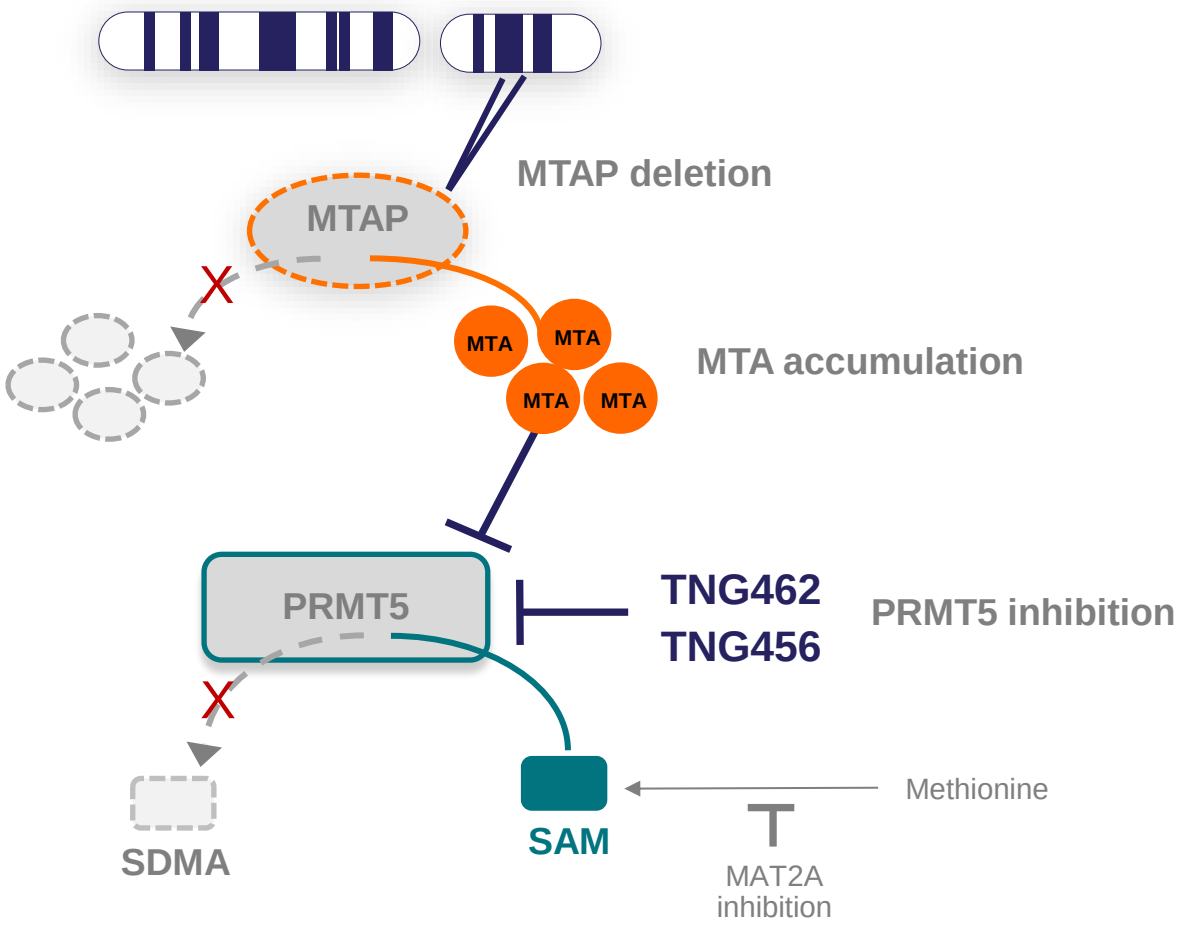
10-15% of all human cancers are MTAP-deleted

- MTAP is co-deleted with CDKN2A
- TNG462 with clear path to registration in MTAP-deleted NSCLC and pancreatic cancer
- Initiating TNG462 combinations driven by co-occurring genetic alterations including KRAS and EGFR
- TNG456 has potential to treat glioblastoma and CNS metastases – phase 1/2 study enrollment to begin 1H 2025

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

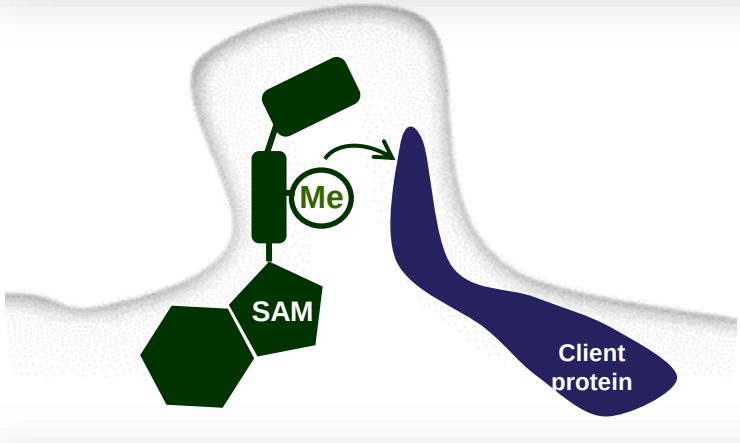


Mechanism of action

- MTAP deletion causes MTA to accumulate
- MTA binds to and inhibits PRMT5
- MTA-cooperative PRMT5 inhibitors selectively bind to the PRMT5-MTA complex
- TNG462 and TNG456 fully inhibit PRMT5 activity in MTAP-deleted cancer cells while sparing normal cells

TNG462 and TNG456 are synthetic lethal MTA-cooperative PRMT5 inhibitors

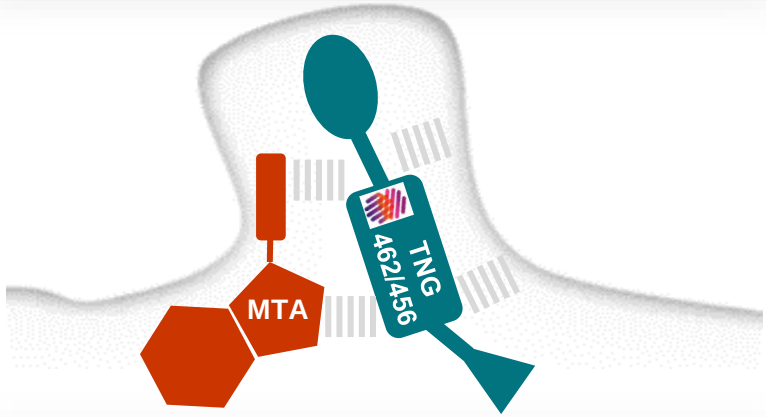
Normal cells



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

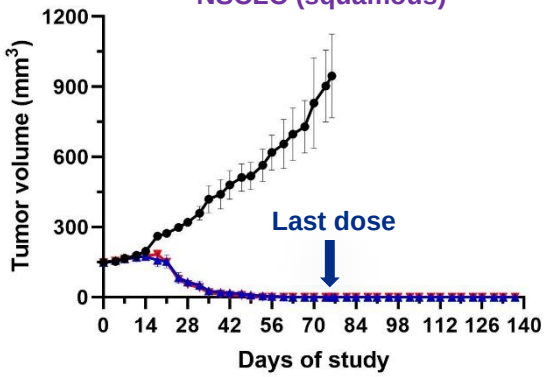
- TNG462 and TNG456 are designed to kill MTAP-deleted cancer cells while sparing normal cells
- TNG462 and TNG456 selectively bind to PRMT5-MTA complexes and lock them into an inactive state

TNG462 and TNG456 drive regressions in MTAP-null xenografts across lineages

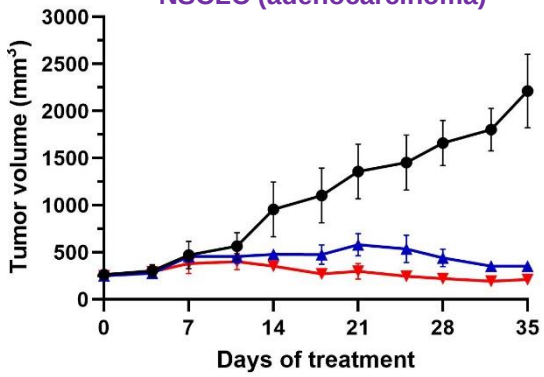
TNG462 IC50 4 nM, 45X selectivity for MTAP deletion

TNG462
MTAP-null PDX models

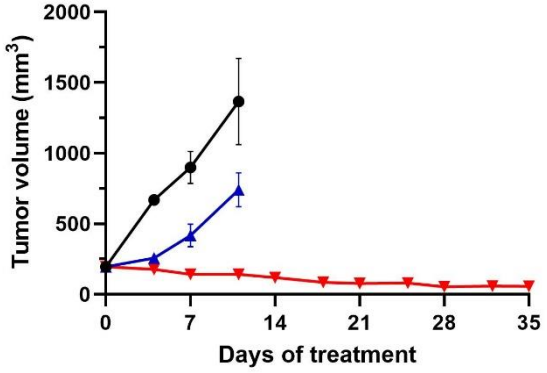
NSCLC (squamous)



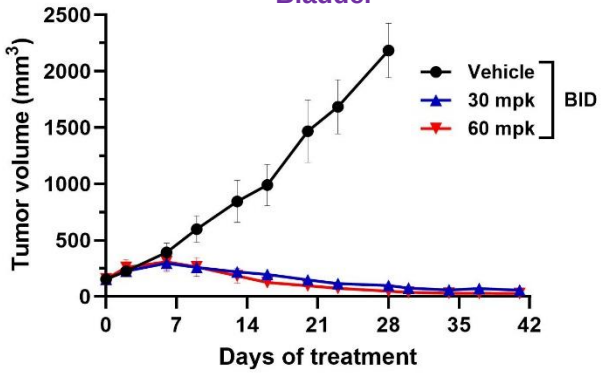
NSCLC (adenocarcinoma)



Pancreatic



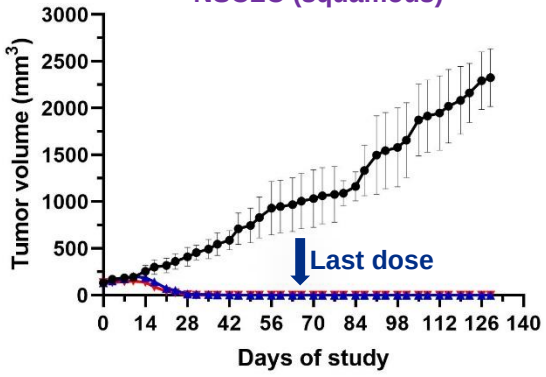
Bladder



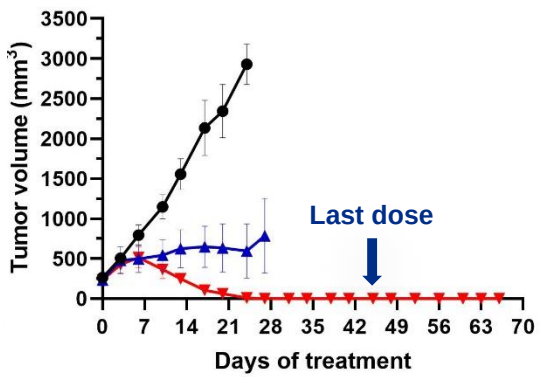
TNG456 IC50 20 nM, 55X selectivity for MTAP deletion

TNG456
MTAP-null PDX models

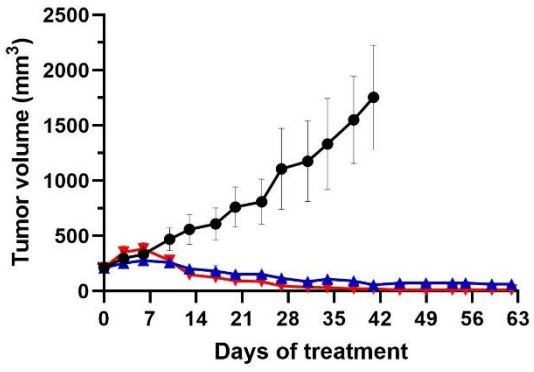
NSCLC (squamous)



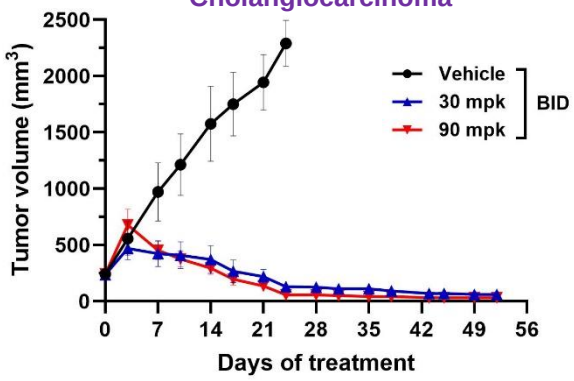
Glioblastoma



Pancreatic

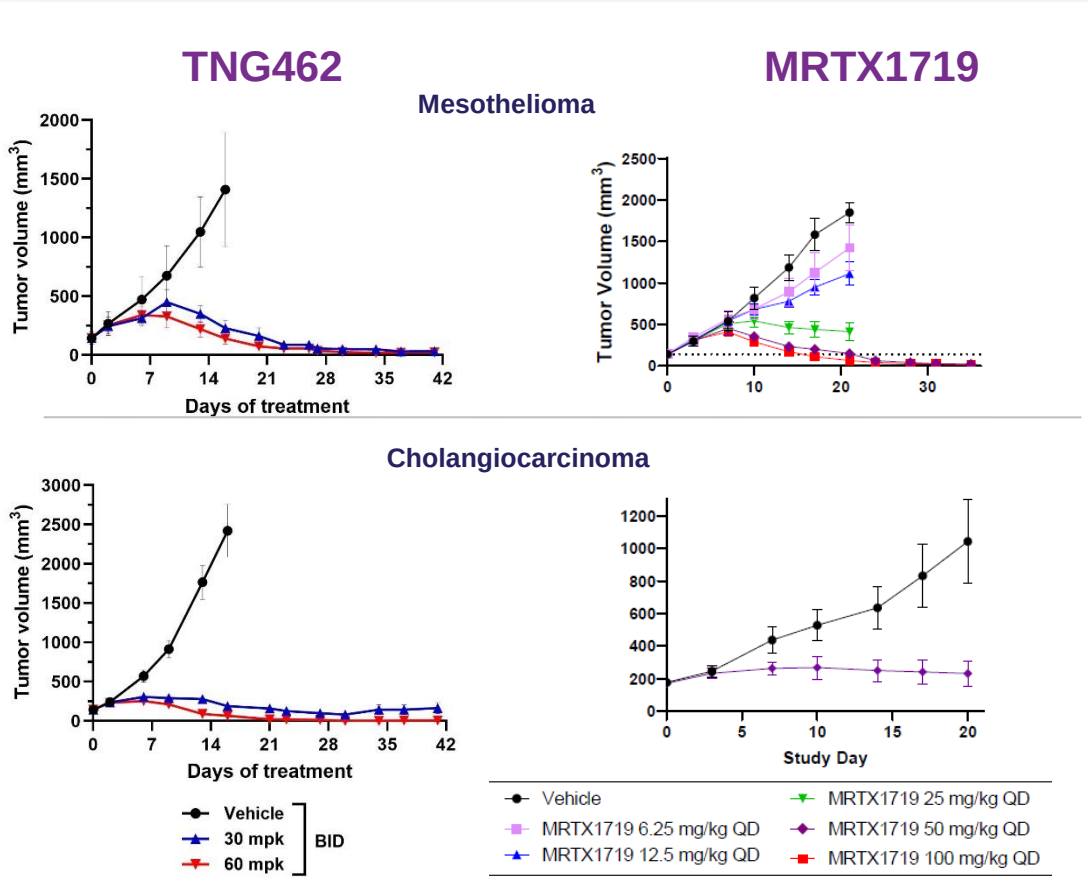


Cholangiocarcinoma

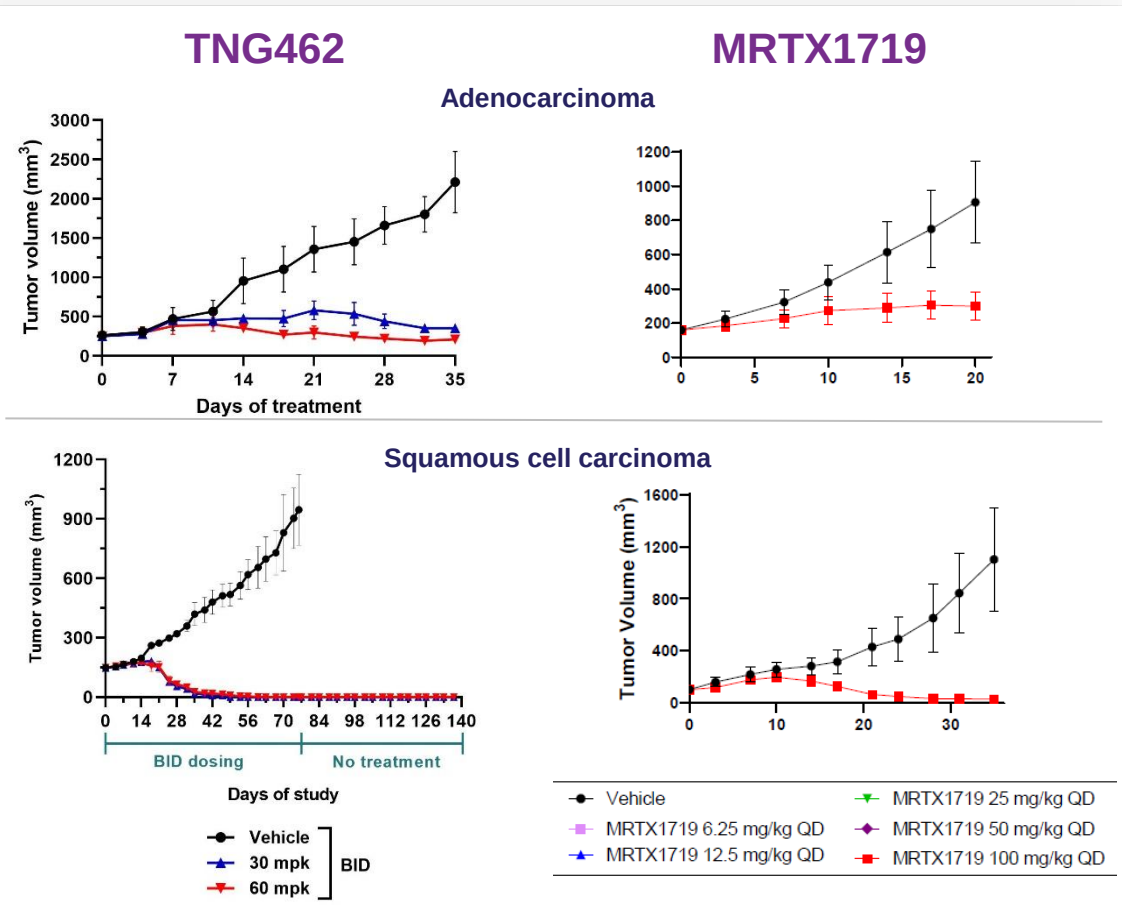


TNG462 is comparable or superior to MRTX1719 in multiple MTAP-null patient-derived xenografts

Mesothelioma and cholangiocarcinoma



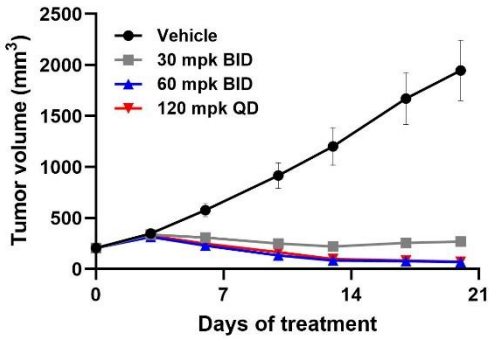
Non-small cell lung cancer



Tango PRMT5 inhibitors have superior preclinical efficacy

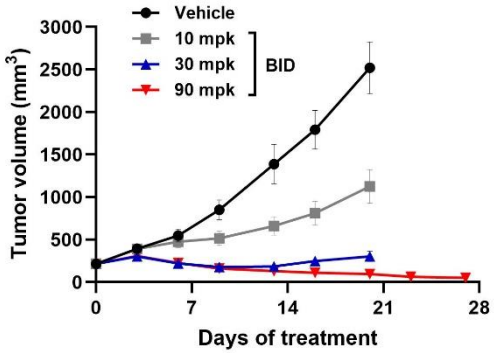
LU99 non-small cell lung cancer
MTAP del, KRAS mut

TNG462
45X
MTAP del selectivity



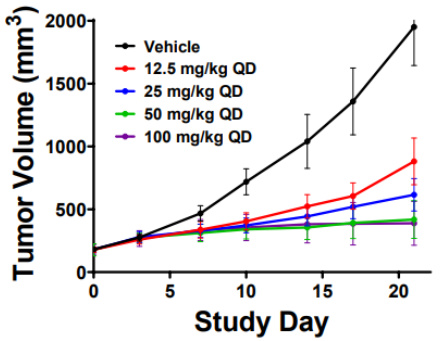
Deep regression

TNG456
55X
MTAP del selectivity



Deep regression

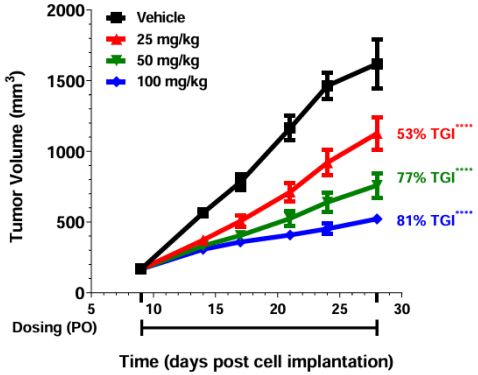
MRTX1719
74X
MTAP del selectivity



Engstrom et al., 2023

Tumor stasis

AMG 193
40X
MTAP del selectivity



Belmontes et al., 2024

Tumor growth inhibition

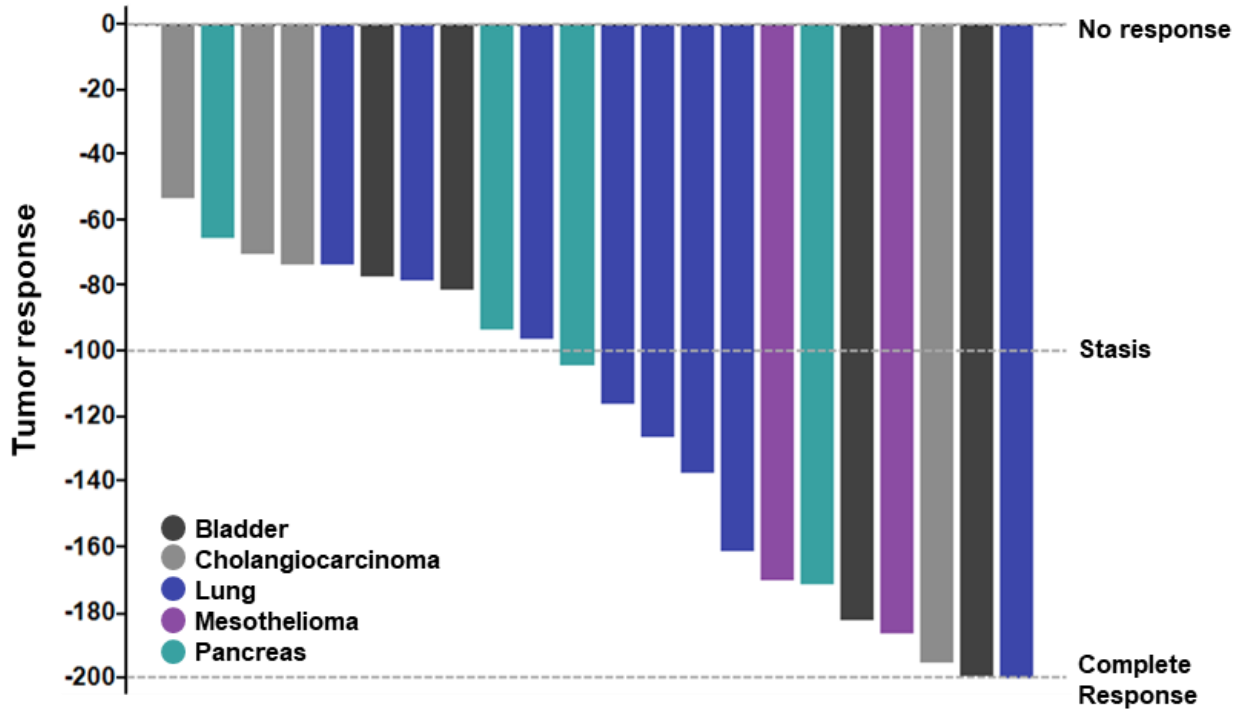
TNG462

PRMT5 inhibition in MTAP-deleted cancers

TNG462 is a potentially best-in-class PRMT5 inhibitor

TNG462 increases depth and durability of response in xenograft models

Multiple histologies
MTAP-null PDX



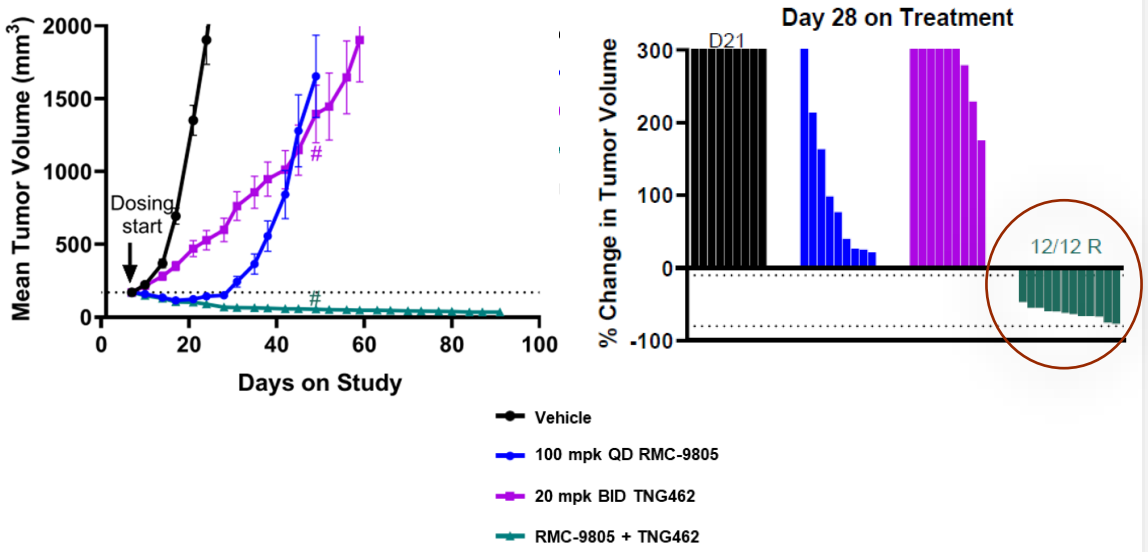
Strong efficacy across histologies

- 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)
- TNG456 induced regressions in 70% of a subset of these models (n=10)

TNG462+RMC-9805 (G12D) has strong preclinical combination benefit

TNG462 + RMC-9805

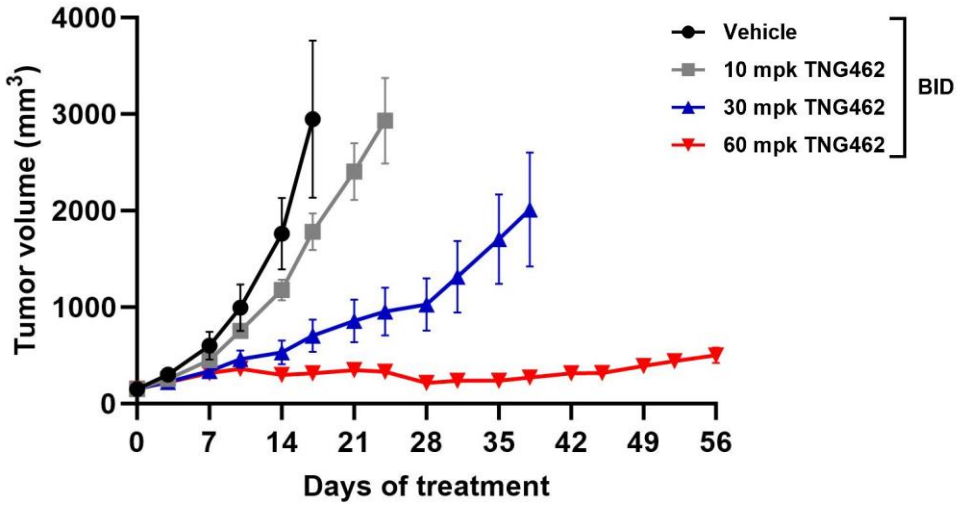
KP4
MTAP-null, KRAS$^{G12D/WT}$ PDAC CDX



*TNG462 exposure in combination formulation predicted equivalent to 30 mpk monotherapy

TNG462 monotherapy

KP4
MTAP-null, KRAS$^{G12D/WT}$ PDAC CDX

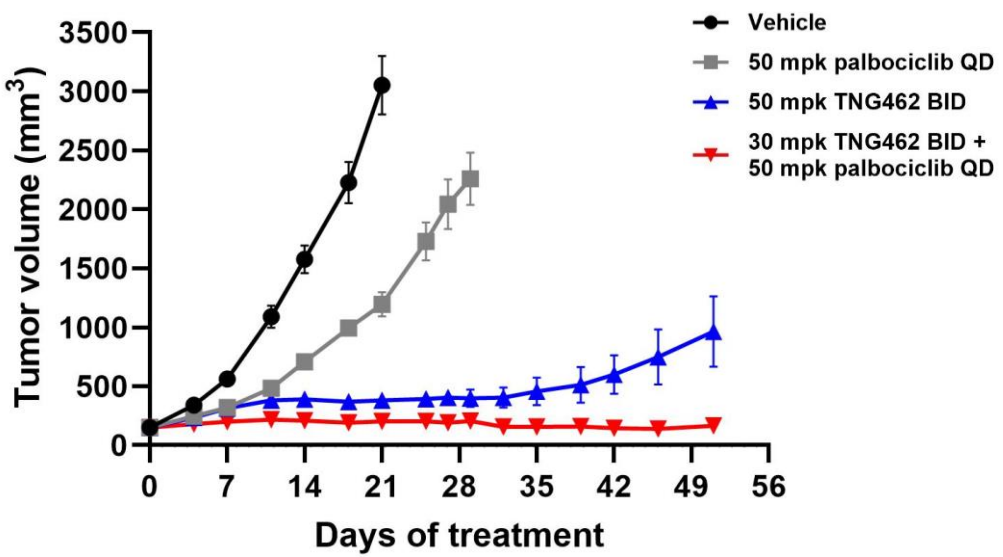


- 40% of pancreatic cancers have a KRAS G12D driver mutation
- Clinical collaboration with Revolution Medicines supports evaluation of TNG462 + RMC-9805 (RAS(ON) G12D-selective) and TNG462 + RMC-6236 (RAS(ON) multi-selective)

Combination strategies driven by co-occurring genetic alterations

TNG462 + CDK4/6i

KP4
(MTAP-del,CDKN2A-del pancreatic ca)

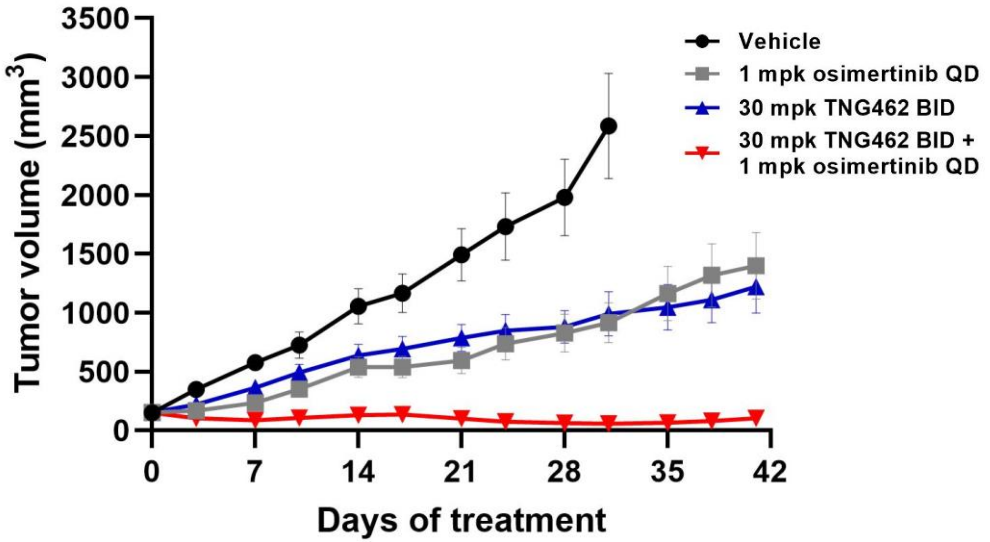


All MTAP-del cancers
have co-occurring CDKN2A deletions

*TNG462 combination dose reduced to match 50 mpk BID monotherapy exposure

TNG462 + EGFRi

NCI-H1650
(MTAP-del, EGFR mut NSCLC)

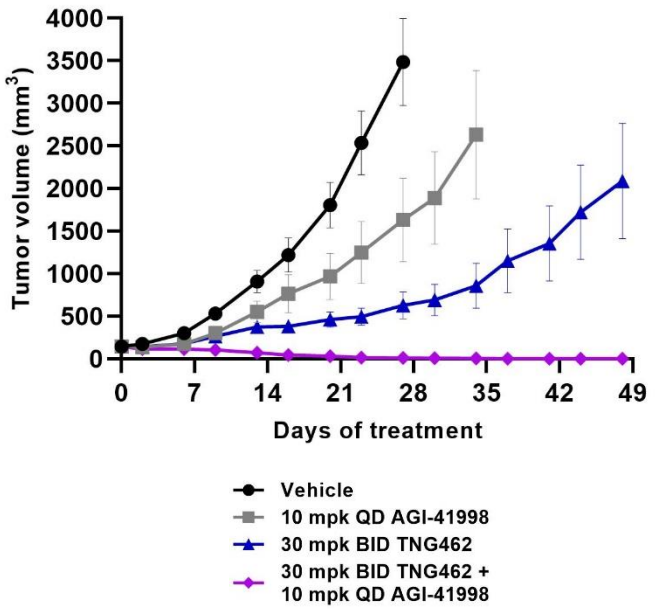


20% of MTAP-del lung cancers
have co-occurring EGFR mutations

Single agent TNG462 is as efficacious as combination with MAT2Ai

TNG462 + MAT2Ai combination efficacy

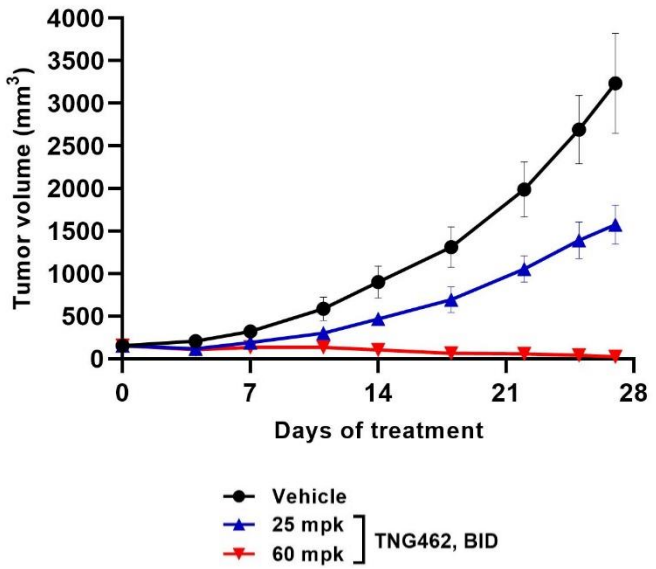
NCI-H838
(MTAP-del NSCLC)



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 that could add benefit in combination with TNG462 or TNG456
- TNG462 single agent activity is equivalent to MAT2A combination in the same xenograft model

TNG462 first-in-human trial

DOSE ESCALATION

- Solid tumors with MTAP deletion

DOSE EXPANSION (ongoing)

Non-small cell lung

Pancreatic

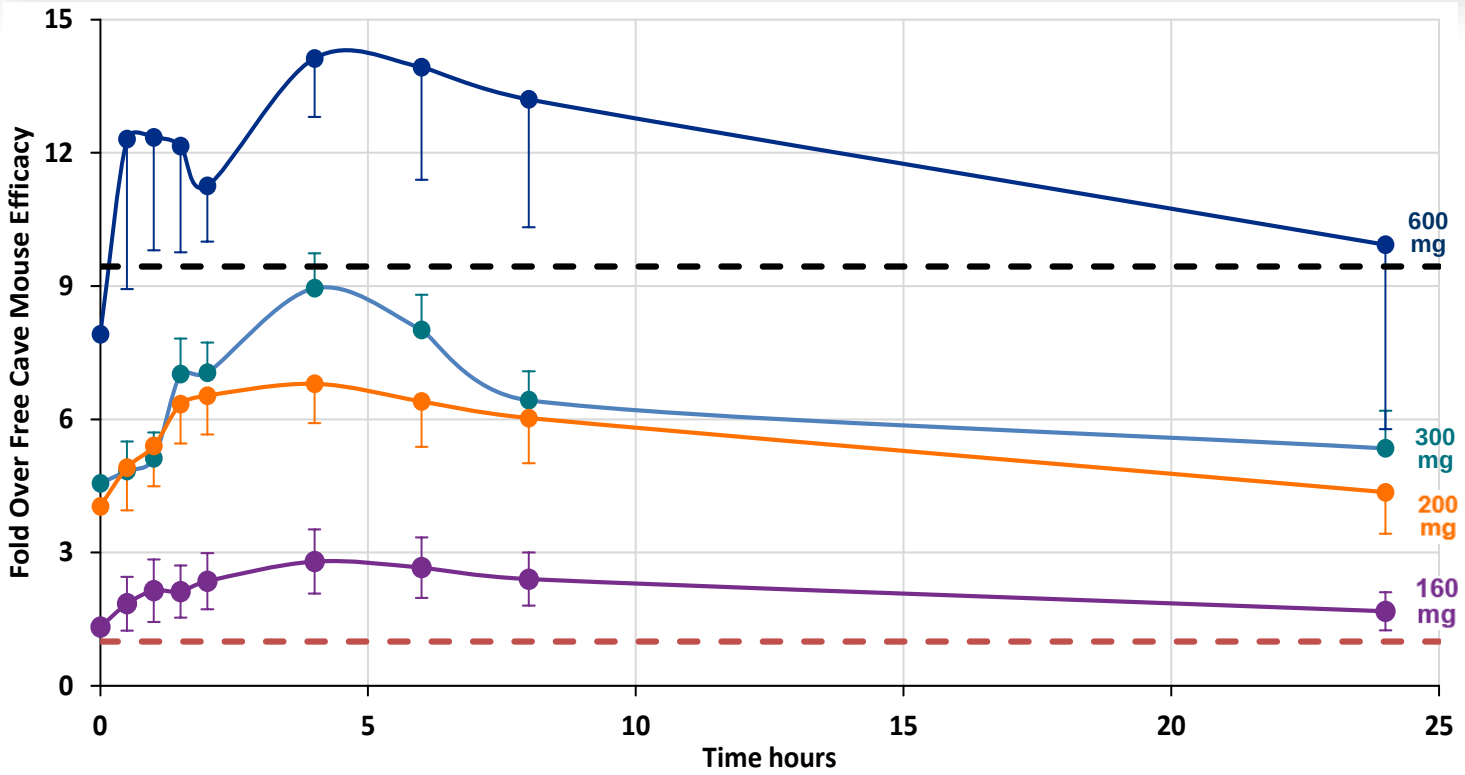
Histology-agnostic solid tumors
Enriched for cholangiocarcinoma, mesothelioma, and bladder cancers

PHASE 1/2 STUDY

- Enrollment in dose escalation began July 2023 and dose expansion began June 2024
- Dose expansion ongoing at 200 mg, 250 mg and 300 mg QD
- Safety, PK/PD and efficacy as primary endpoints
- FDA Fast Track designation
- Additional data updates in 2025
- First registration trials planned as monotherapy in 2L pancreatic and lung cancer

TNG462 exposure at expansion doses 2-8X over maximally effective preclinical exposure

Mean steady-state concentration-time profiles



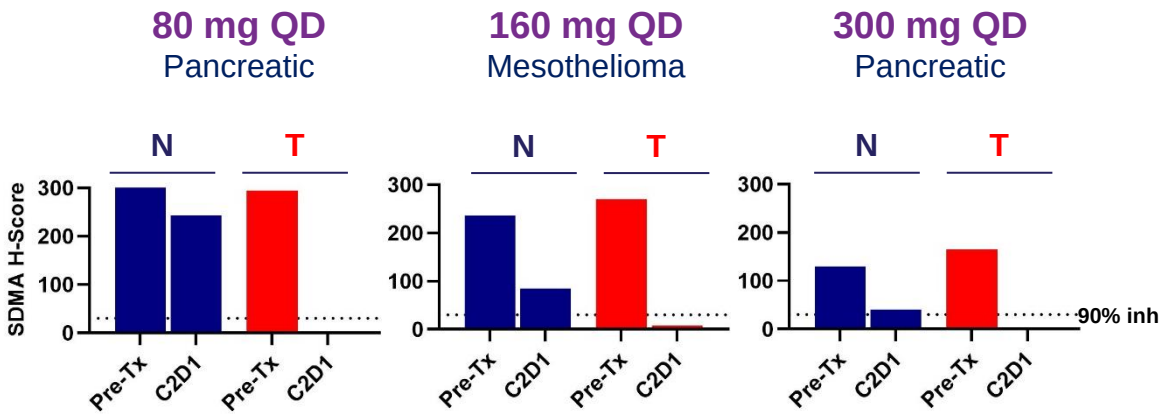
Error bars represent SEM

TNG462

- 200 mg, 250 mg and 300 mg QD being evaluated in expansion
- Clinical exposure over maximally efficacious mouse exposure
  - TNG462 200 mg 4-7X
  - TNG462 300 mg 5-9X
  - TNG462 600 mg 8-14X
  - AMG 193 1200 mg 1-2X
  - BMS-504 (MRTX1719) data not available
- 600 mg QD exceeds predicted hematologic toxicity threshold

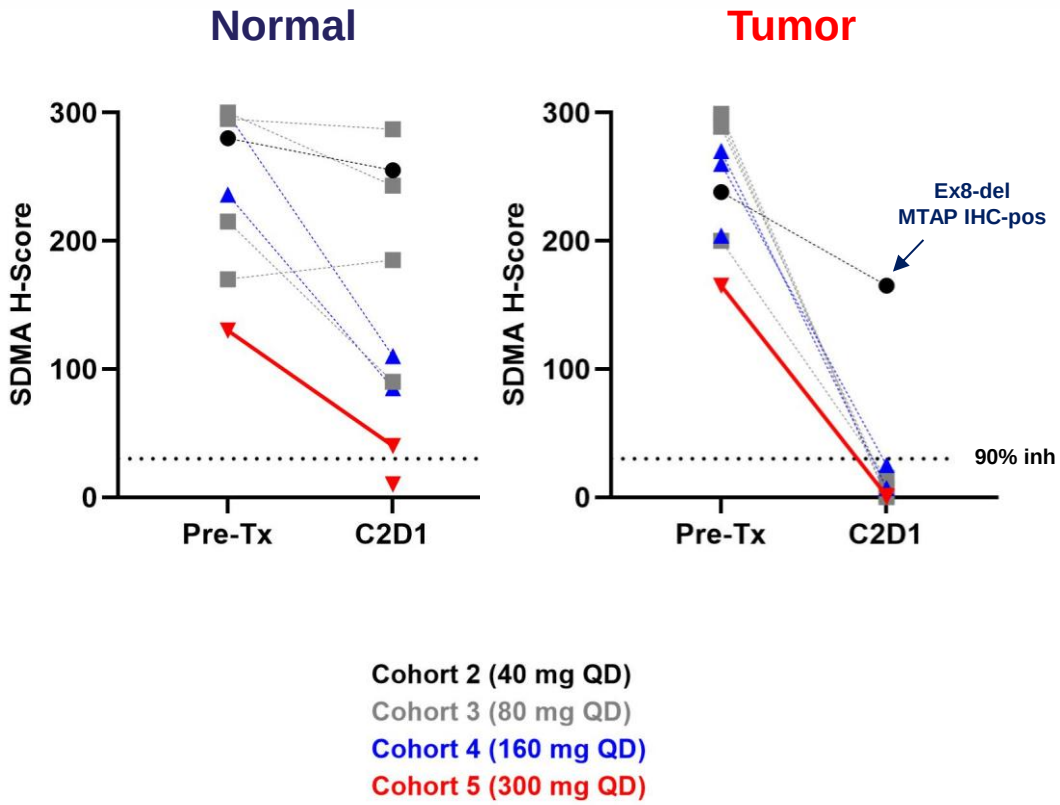
TNG462 selectively inhibits PRMT5 in tumor cells

Selected SDMA IHC cohorts 3-5



Dose dependent tumor-specific SDMA suppression

SDMA IHC cohorts 1-5



TNG462 is clinically active in multiple solid tumors

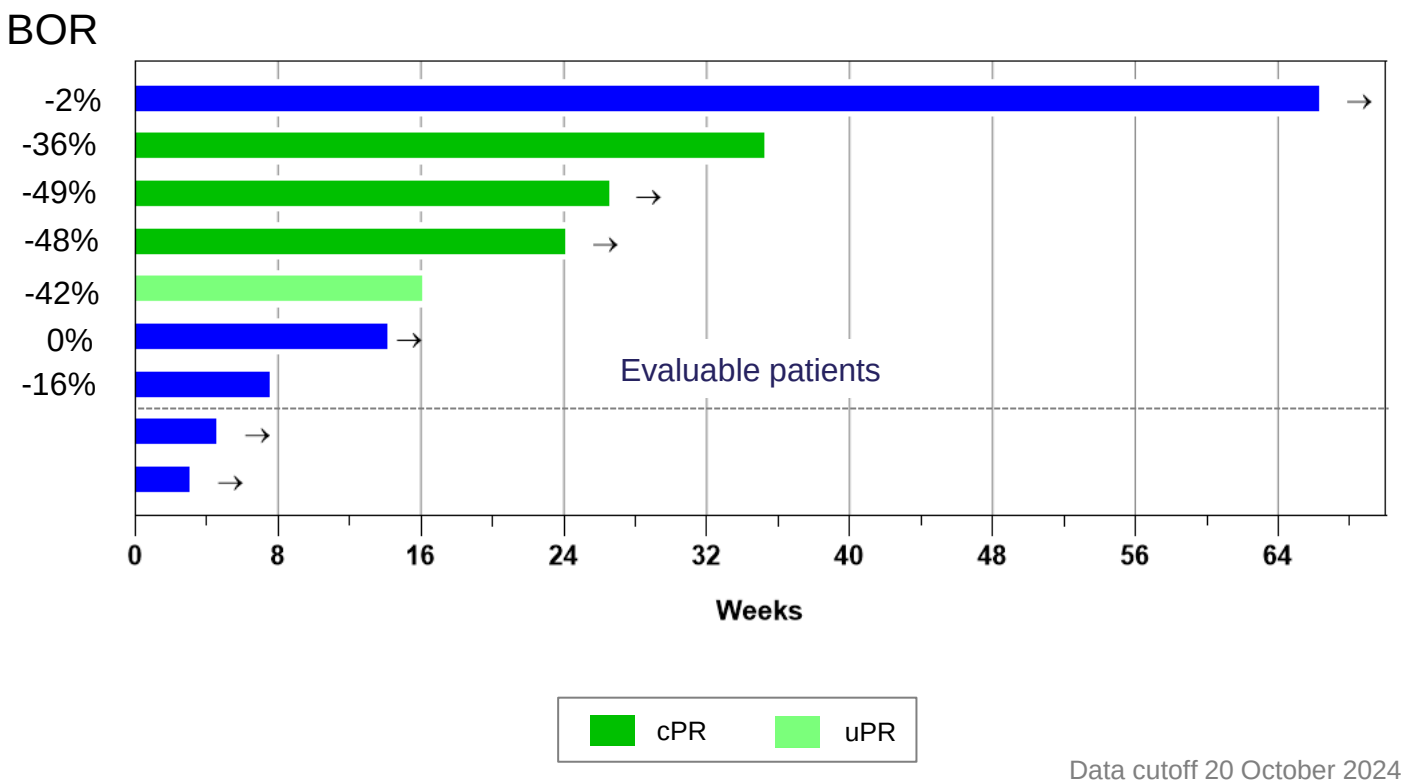
Demonstrated best-in-class potential

- Dose escalation began July 2023 and enrollment in dose expansion cohorts began in June 2024, 59 total patients were enrolled
- 39 evaluable patients across 13 histologies at active doses (160-300 mg QD)
- Active across multiple tumor types in the trial, including NSCLC and pancreatic cancer
- Median time on treatment currently 24 weeks (still increasing, updated 4 Nov)
- Median time to response 16 weeks
- Confirmed RECIST partial responses in 3/7 evaluable cholangiocarcinoma patients (ORR 43%)
    - 4/7 patients ongoing with median time on study 24 weeks (still increasing, updated 4 Nov)
- Safe and well-tolerated at active doses with limited GI toxicity and fatigue

Data cutoff 20 October 2024

TNG462 is active at 160mg – 300mg QD in cholangiocarcinoma

TNG462 ORR 43%



Data cutoff 20 October 2024

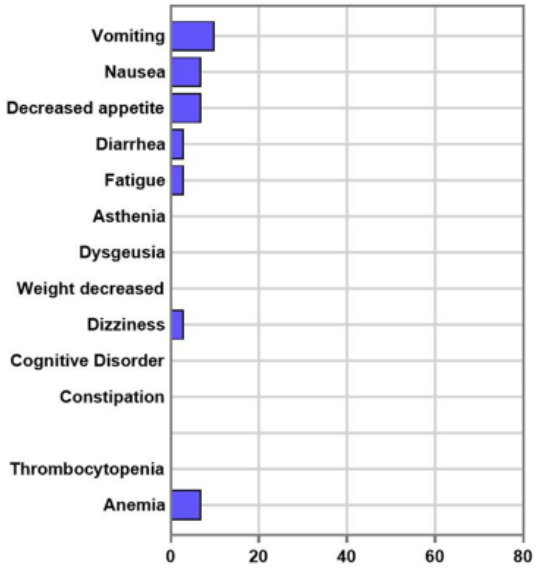
Key points

- 3/7 (ORR 43%) evaluable patients treated at active doses with cPRs
  - BMS-504: 18% (2/11)
  - AMG 193: 15% (2/13)
- 4/7 evaluable patients ongoing with median time on study 24 weeks and still increasing
- Compares favorably to previously treated biliary tract cancer patients receiving chemotherapy*
  - ORR ~7% (standard of care)
  - PFS 14 weeks

*Amonkar et al, Future Oncology, 2024

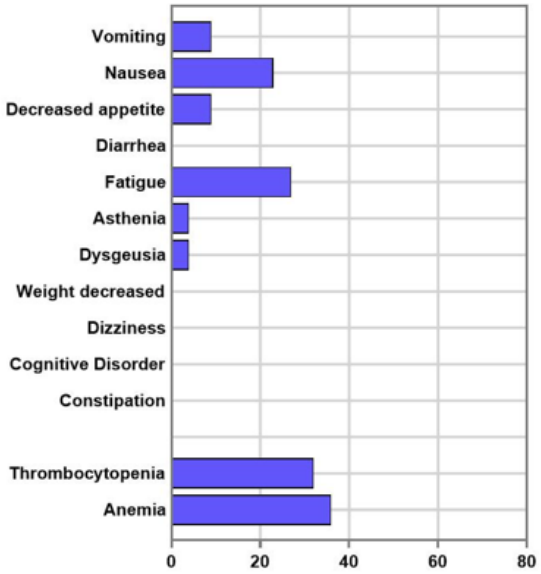
TNG462 is well-tolerated at expansion doses

TNG462 160/200 mg



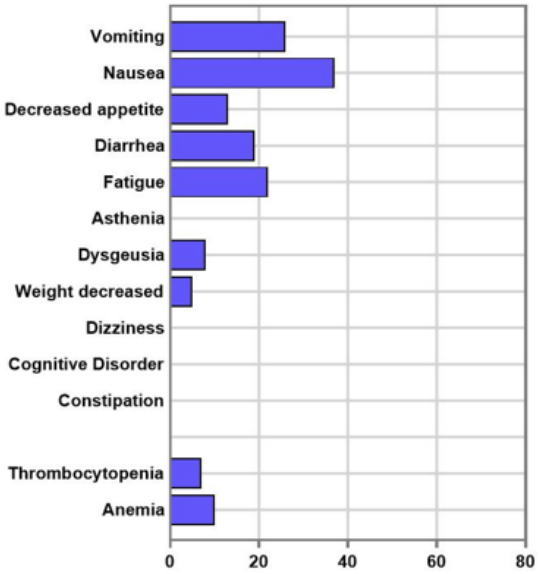
0/30 dose reductions (0%)
No thrombocytopenia
Minimal nausea and fatigue
No dysgeusia

TNG462 300 mg



10/22 dose reductions (45%)
Increased anemia and thrombocytopenia
4% dysgeusia

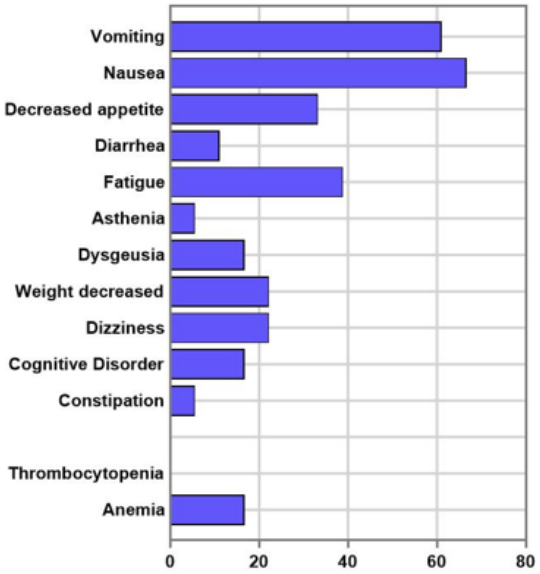
BMS-504 200-600 mg



Dose reductions unknown
Frequent GI side effects
10% dysgeusia

ENA 2024

AMG 193 1200 mg



6/18 dose reductions (33%)
Significant nausea, vomiting, decreased appetite, fatigue, dysgeusia and CNS effects

ESMO 2024

As of 20 October 2024

Development plans enable large opportunity for patients

Multiple TNG462 combinations to start enrolling 1H 2025

Targeted combinations driven by strong preclinical data

- RMC-6236 - RAS(ON) multi-selective inhibitor in NSCLC and pancreatic cancer (Revolution Medicines)
- RMC-9805 - RAS(ON) G12D-selective inhibitor in NSCLC and pancreatic cancer (Revolution Medicines)
- Osimertinib - EGFR mutant inhibitor in NSCLC

Standard of care combinations support path to approval in first line settings

- Pembrolizumab in NSCLC and other solid tumors
- Carboplatin/pemetrexed in NSCLC
- Carboplatin/paclitaxel in NSCLC
- FOLFIRINOX in pancreatic cancer
- Gemcitabine/abraxane in pancreatic cancer

Initiating conversations with FDA in preparation for multiple registration studies

TNG908

PRMT5 inhibition in MTAP-deleted cancers

TNG908 is active and well-tolerated in non-CNS solid tumors

All patients

- TNG908 dose escalation began August 2022 and enrollment in dose expansion cohorts began in April 2024
- Data cutoff of 20 October 2024, 103 total patients enrolled
- Safe and well-tolerated, nausea and fatigue reported in ~40% patients at active doses (400-600 mg BID)

All non-CNS solid tumors

- 70 patients enrolled, 31 evaluable at active doses across 24 histologies
- Four partial responses observed - pancreatic cancer (2/9), NSCLC (1/4) and urothelial cancer (1/1)
- Median time on study at active doses 16 weeks

Pancreatic cancer

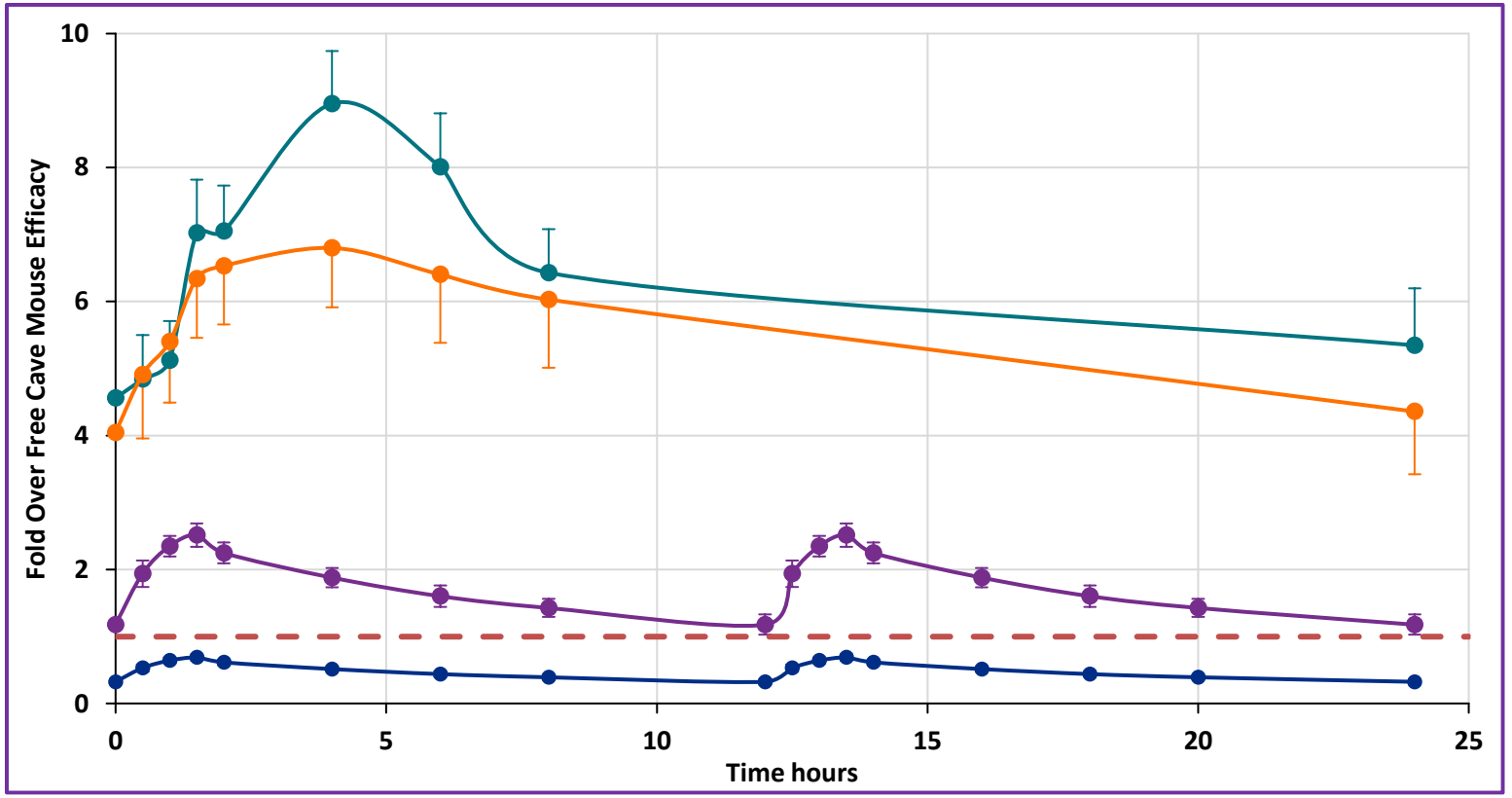
- 2/9 patients with partial responses (ORR 22%), 5/9 patients with stable disease
- Five pancreatic cancer patients ongoing for an average of 24 weeks, the longest for 72 weeks

Glioblastoma

- 33 patients enrolled, 23 evaluable glioblastoma patients at active doses, no partial responses by RANO criteria
- Median time on study less than 8 weeks
- CSF exposure ~30% of plasma exposure in three patient samples and below the threshold required for efficacy

TNG908 target coverage lower than TNG462 and not sufficient for CNS activity

Steady-state exposure as fold over mouse efficacy



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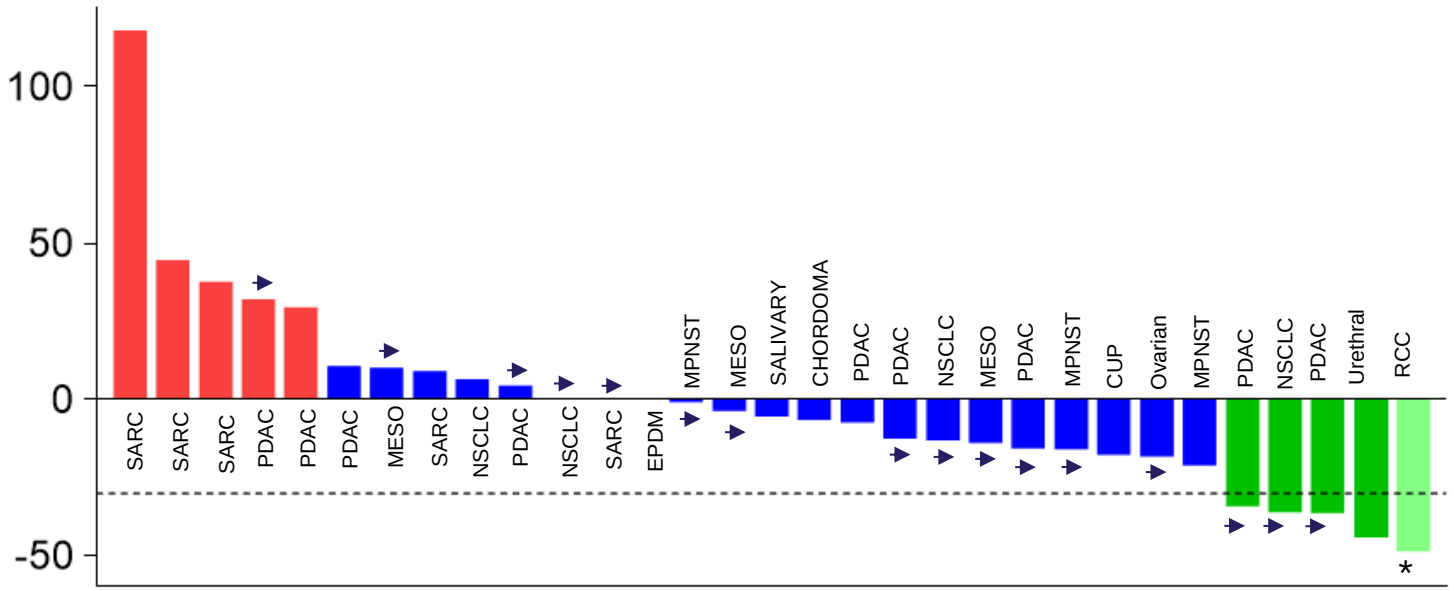
TNG908 is active in multiple cancer types

TNG908 400-600 mg QD
(n=31)



*Did not confirm

Data cutoff 20 October 2024

Histology-specific activity

Pancreatic cancer

- 9 evaluable, n=11
- 2 cPRs
- 5 SD (3 ongoing)

Non-small cell lung cancer

- 4 evaluable, n=12
- 1 PR (yet to confirm)
- 3 SD (2 ongoing)

TNG908 is clinically active, TNG462 has the potential to be best-in-class

TNG462

- TNG462 target coverage is 2-4X better than TNG908
- TNG462 median time on treatment of 24 weeks (still increasing) is notably longer than TNG908 (16 weeks)
- TNG462 tolerability profile is superior to TNG908 with less nausea, vomiting and fatigue
- Clinical activity of TNG908 in NSCLC and pancreatic cancer highlights the potential for TNG462 to be best-in-class

TNG462 has the potential to for broader and deeper clinical activity in MTAP-deleted solid tumors

TNG456

PRMT5 inhibition in MTAP-deleted cancers

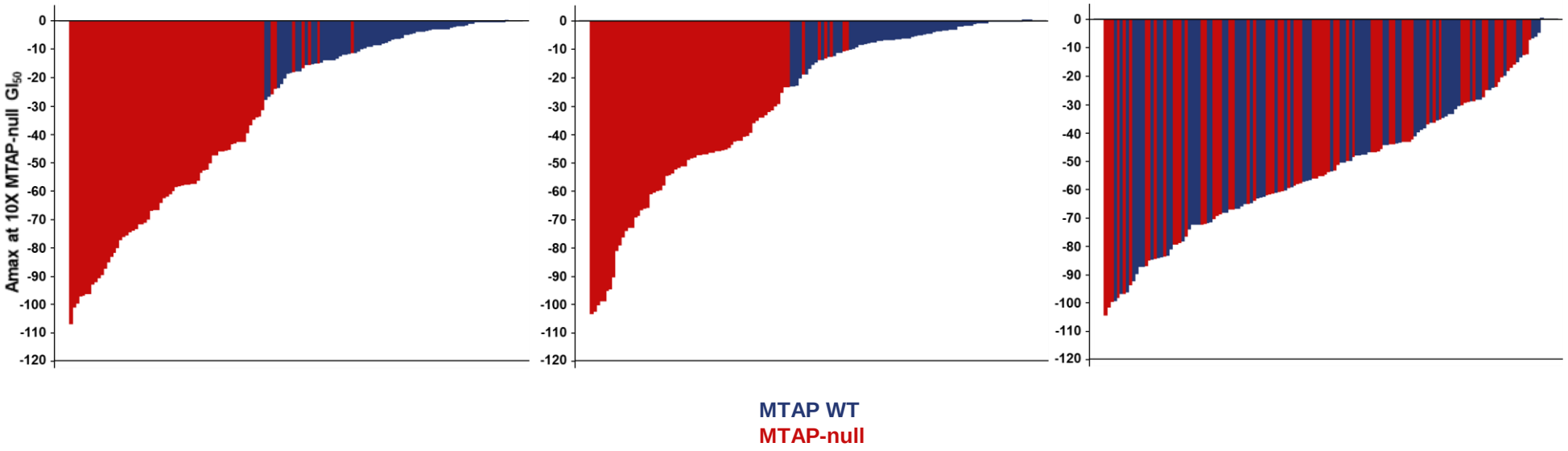
TNG456 is highly potent and selective for MTAP deletion with brain penetrance

143 cancer cell lines from multiple lineages

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

TNG456
IC_{50} 20 nM
55X selective for MTAP deletion

GSK595
IC_{50} 120 nM
Not selective for MTAP deletion



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

TNG456

- TNG456 is highly potent and selective for MTAP-null cells
- TNG456 is brain-penetrant in pre-clinical species with Kpuu 0.5-1.1

TNG456 is a potentially best-in-class brain penetrant PRMT5 inhibitor

TNG456

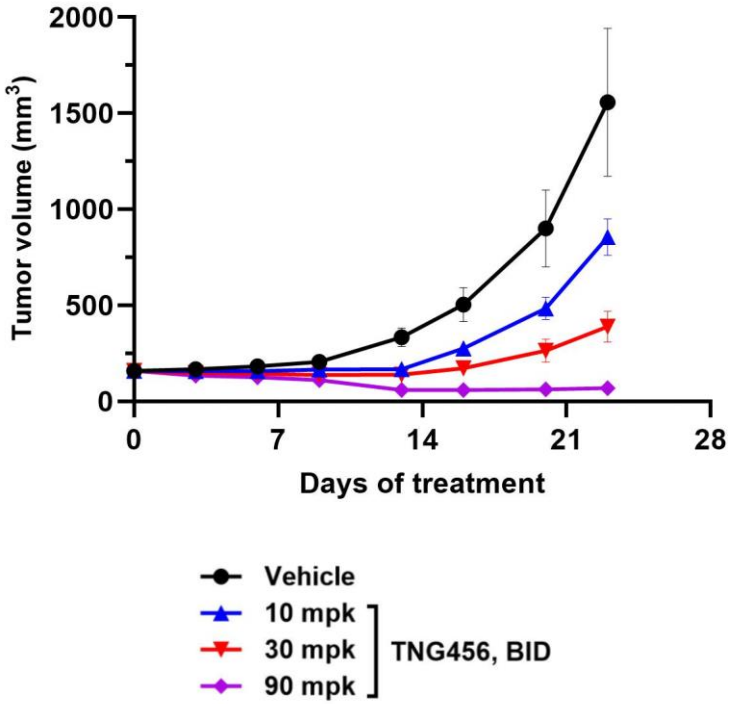
- Phase 1/2 clinical trial enrollment planned for 1H 2025 in GBM, NSCLC and selected other cancers
- Potential for activity in glioblastoma and cancers with high risk of brain metastasis

		TNG908	TNG462	TNG456
		Discontinued	Phase1/2	IND-enabling
Cellular activity (nM)	PD IC_{50}	9	1	2
	GI_{50}	110	4	20
MTAP-deleted selectivity		15X	45X	55X
Preclinical Kpuu		0.5 - 0.65 (cyno CSF)	< 0.1 (cyno CSF)	0.5 - 1.1 (cyno CSF, dog brain)

TNG456 is active as monotherapy and in combination with CDK4/6i in a glioblastoma xenograft

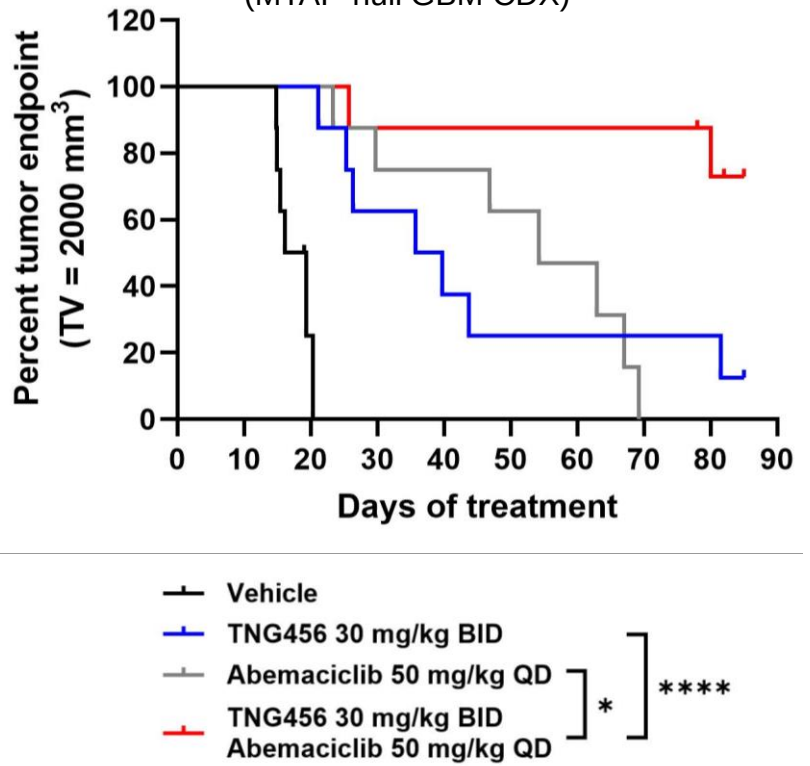
TNG456 monotherapy

U87MG
(MTAP-null GBM CDX)



TNG456 + abemaciclib drives additional survival benefit

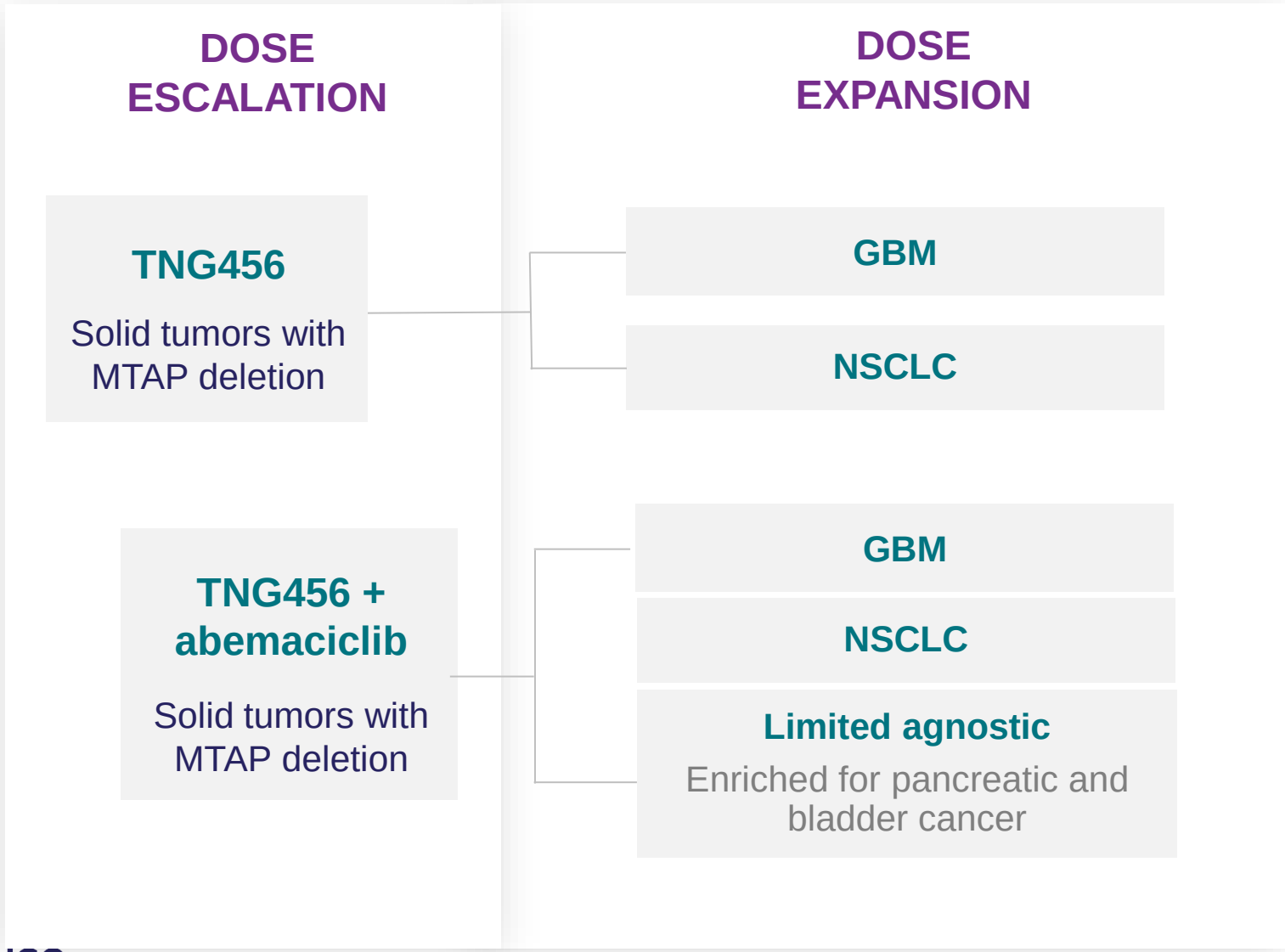
U87MG
(MTAP-null GBM CDX)



Summary

- TNG456 preclinical Kpuu 0.5-1.1 in NHP CSF and dog brain
- TNG456 + abemaciclib median survival greater than 67 days
- Reported survival benefit of current standard of care treatments in orthotopic models
  - Avastin 37 days
  - Temozolomide 23 days

TNG456 phase 1/2 clinical study



SUMMARY

- Safety, PK/PD and efficacy as primary endpoints
- Combination with abemaciclib to start at pharmacologically active TNG456 dose
- Enrollment planned 1H 2025

Differentiated molecules with significant strategic optionality

TNG462

Best-in-class potential with favorable durability, efficacy and safety

- Activity in multiple tumor types, including NSCLC and pancreatic cancer
- 43% ORR in cholangiocarcinoma (n=7)
- Median time on treatment 24 weeks (still increasing)
- Low rates of nausea, vomiting, fatigue and no dysgeusia
- Initiating multiple targeted and standard of care combinations as part of rapid registration strategy

TNG456

Potent, MTAP-del selective brain-penetrant molecule

- Increased potency, selectivity and brain penetrance
- Phase 1/2 trial enrollment expected 1H 2025
- Combination with abemaciclib planned in phase 1/2 study based on strong preclinical data
- Potential to succeed in GBM with increased CNS exposure, potency, MTAP-deleted selectivity

Large patient population

~50,000 patients in US annually

MTAP is frequently deleted in four common cancers

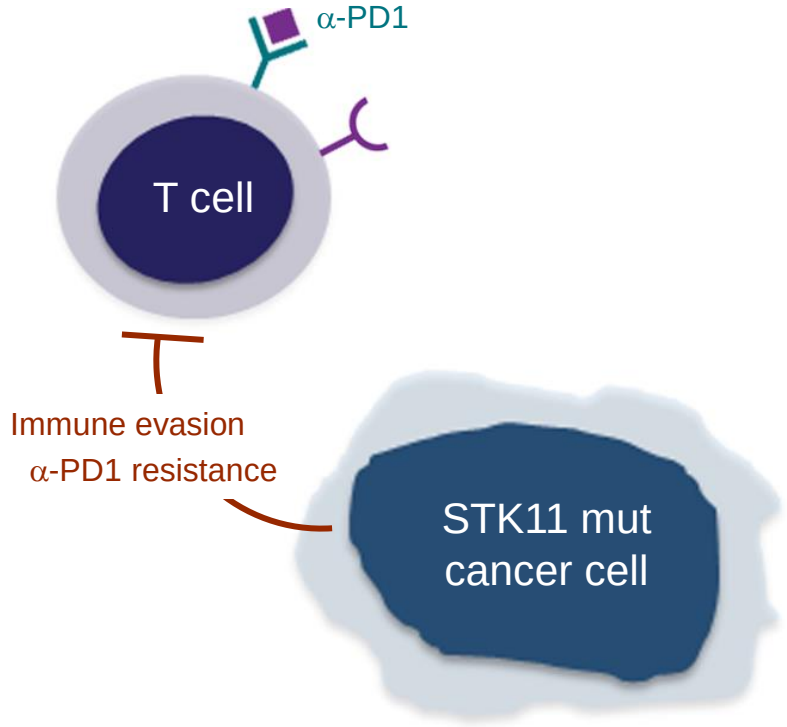
- Pancreatic cancer 25-40%
- Non-small cell lung cancer
  - Squamous ~20%
  - Non-squamous ~10%
- Glioblastoma ~40%
- Bladder cancer ~25%

TNG260

CoREST inhibition in STK11-mutant cancers

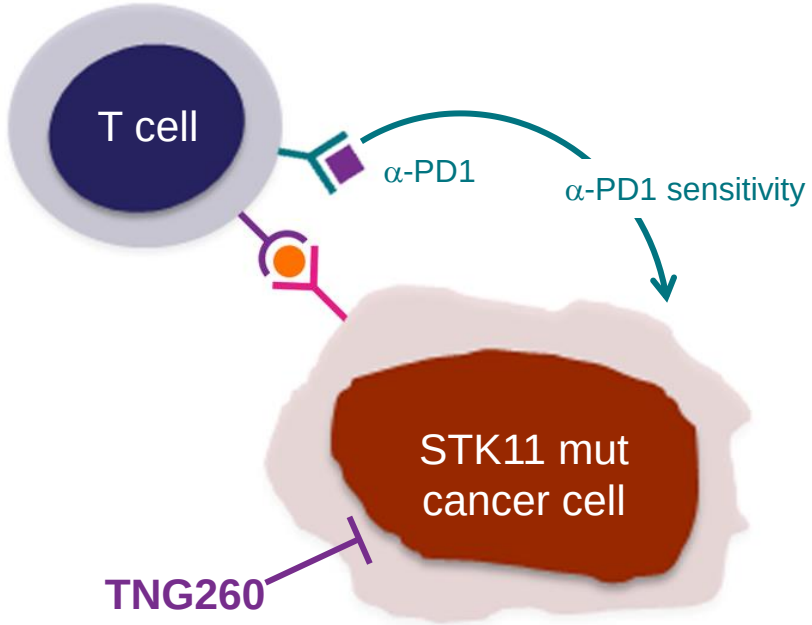
TNG260 reverses immune evasion caused by STK11 mutations

Immune evasion driven by tumor suppressor gene loss



STK11 re-activation is not feasible

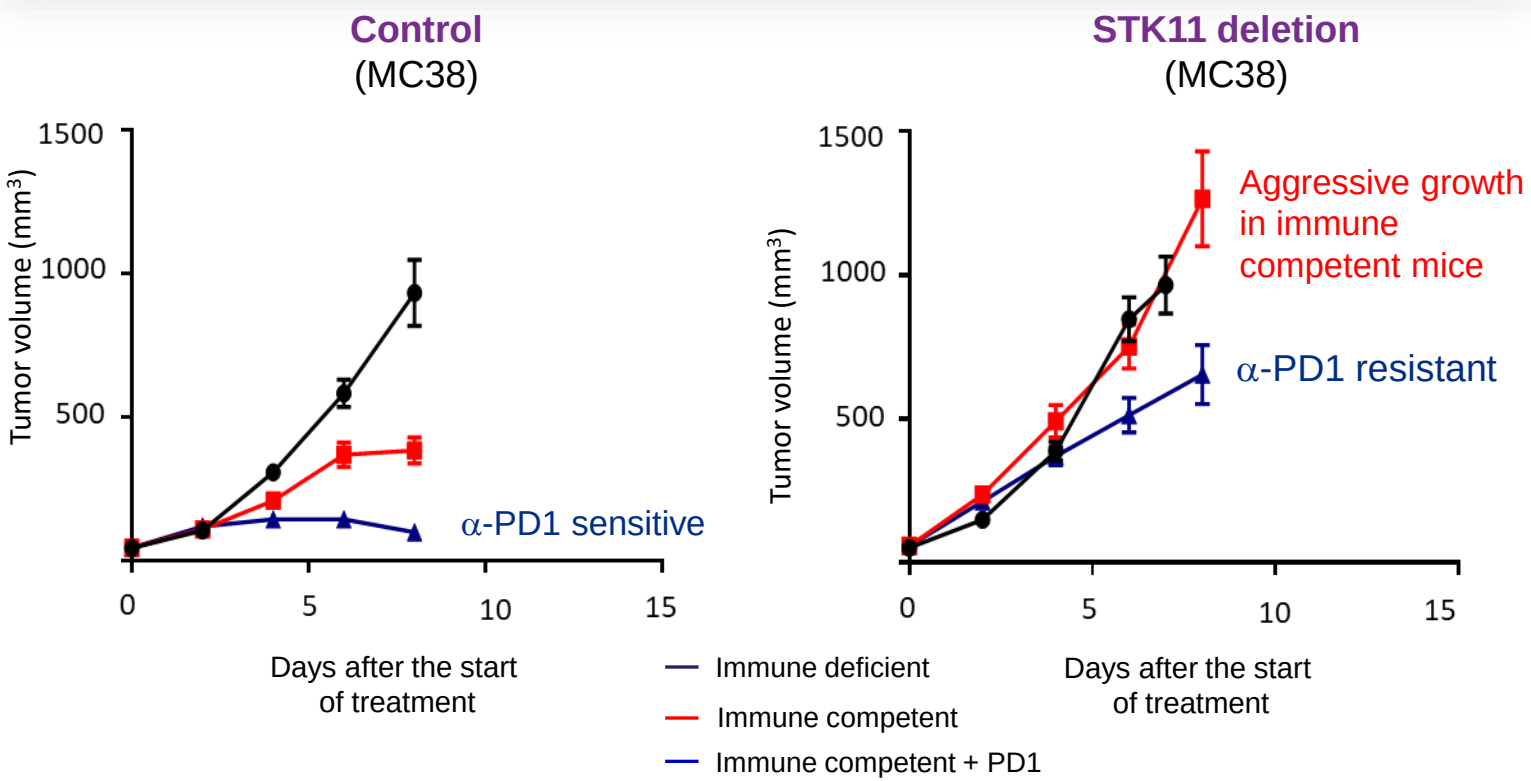
TNG260 reverses tumor-intrinsic immune evasion



Selective CoREST inhibition in cancer cells enables immune-mediated cytotoxicity

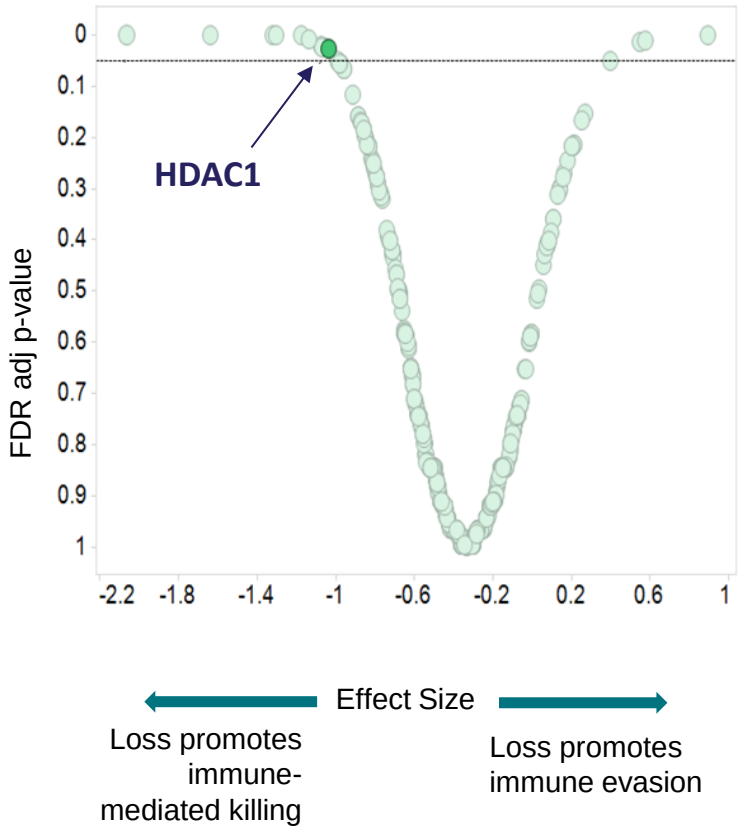
STK11 loss-of-function mutations drive immune evasion

STK11 deletion causes α-PD1 resistance

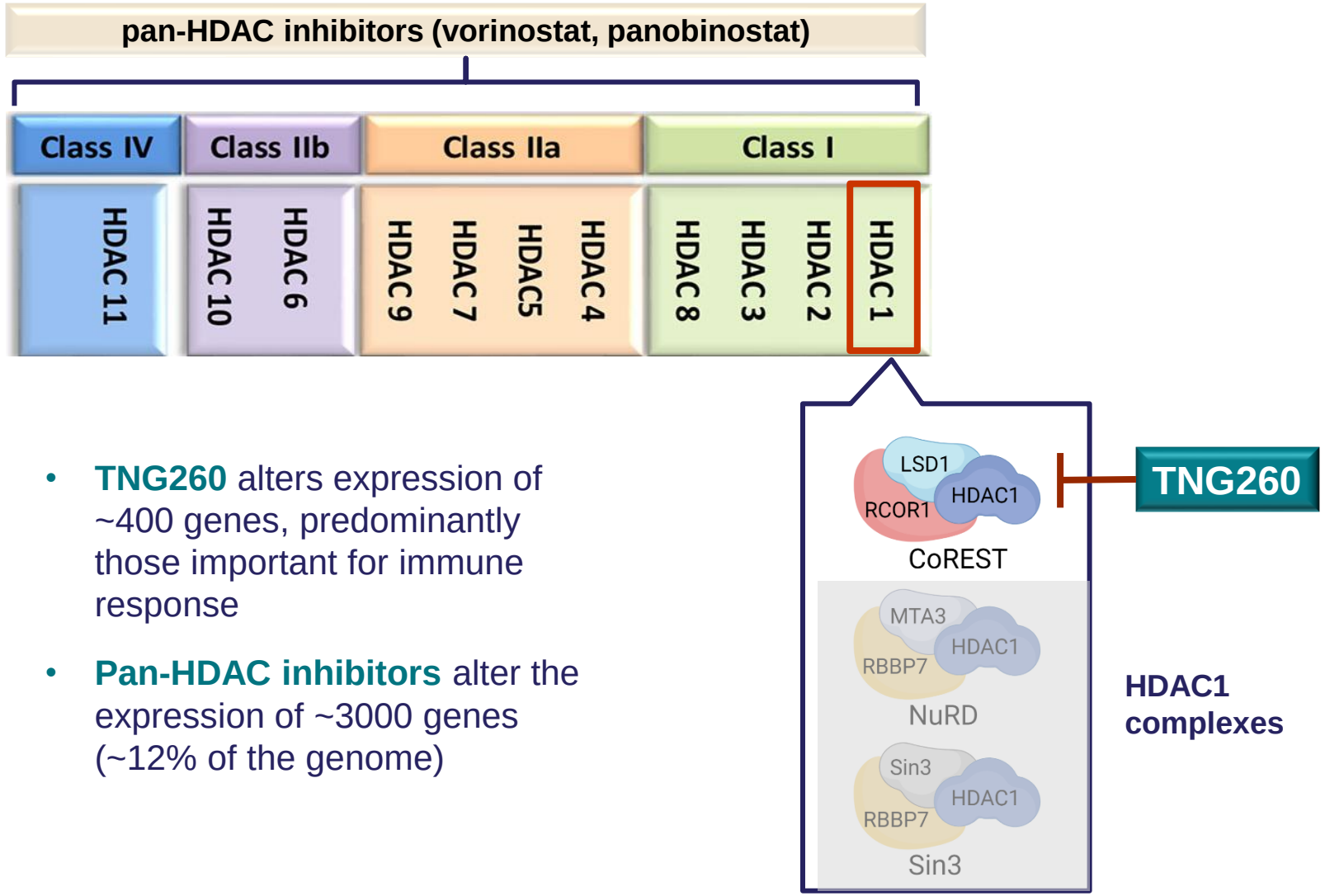


STK11 loss-of-function mutations are associated with clinical immune checkpoint inhibitor resistance

In vivo CRISPR screening identifies mediators of immune evasion reversion



TNG260 is a highly selective CoREST complex inhibitor



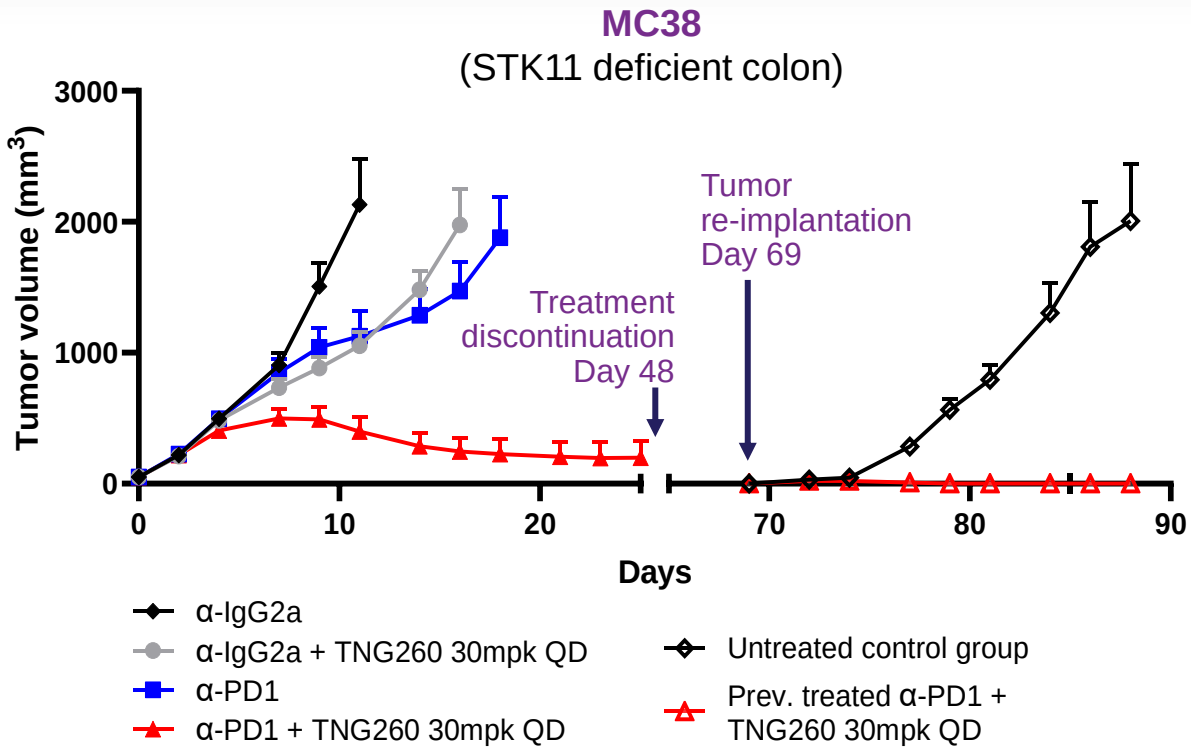
- **TNG260** alters expression of ~400 genes, predominantly those important for immune response
- **Pan-HDAC inhibitors** alter the expression of ~3000 genes (~12% of the genome)

Key points

- CoREST-mediated deacetylation regulates transcription of a specific set of immune response genes
- Sin3 is the predominant HDAC1 complex 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 100nM, 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

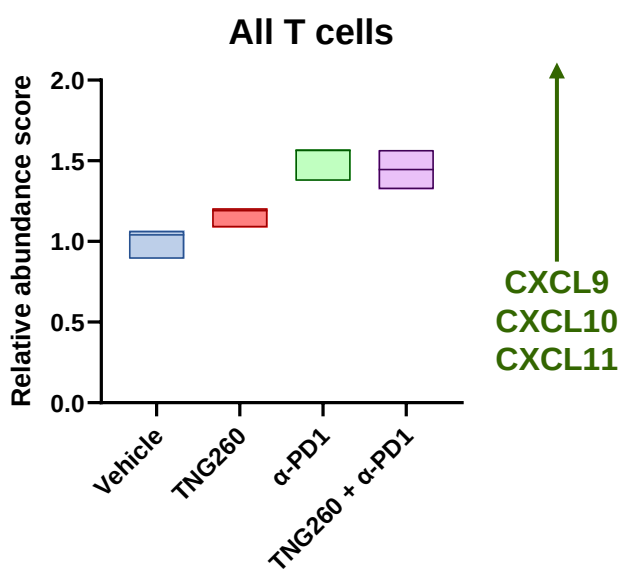
TNG260

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

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

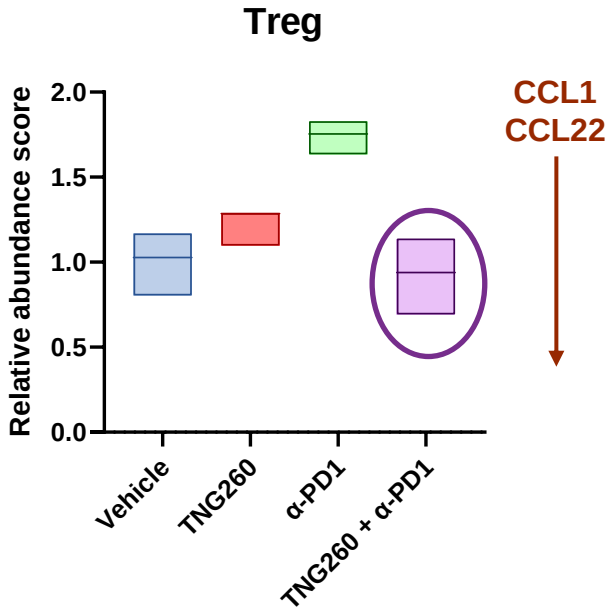
MC38
(STK11 deficient colon)



- 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)



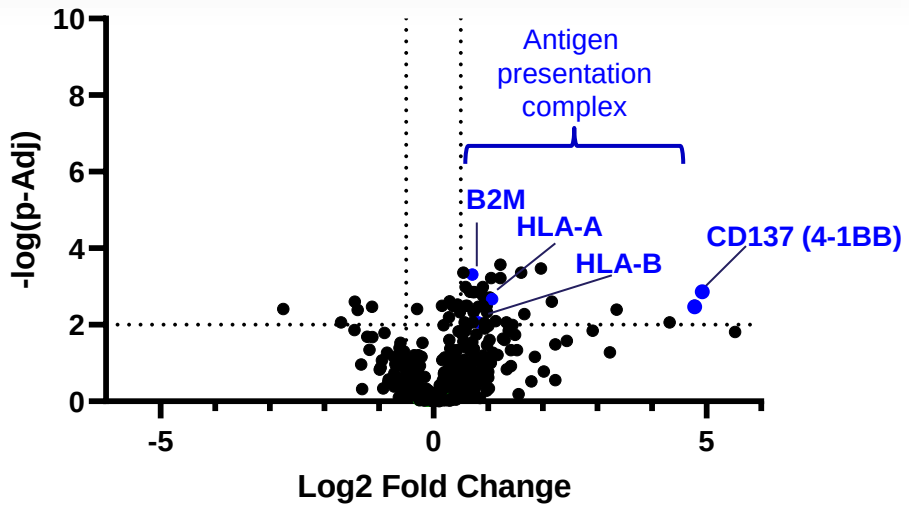
- CLL1 and CCL22 attract suppressive Treg cells
- TNG260 prevents α-PD1-driven Treg recruitment

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

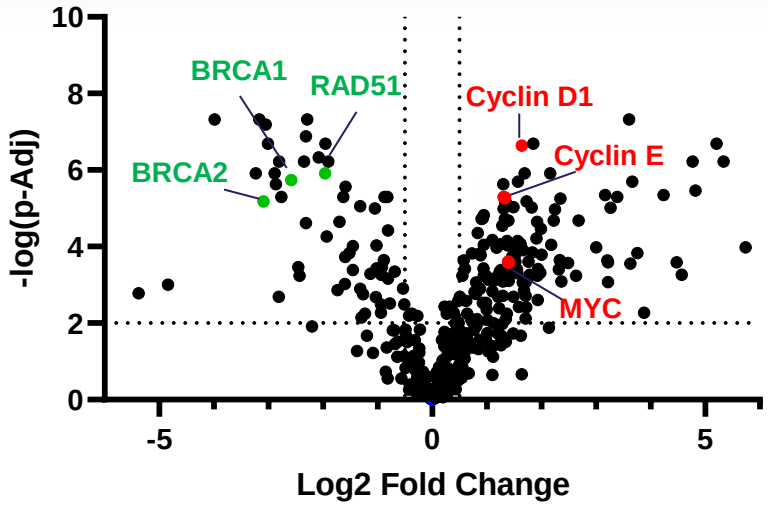
TNG260 (CoREST)
A549 (STK11-mutant NSCLC)



	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)
A549 (STK11-mutant NSCLC)



	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 + pembrolizumab first-in-human trial

DOSE ESCALATION

- Any solid tumor with STK11 mutation

DOSE EXPANSION (ongoing)

STK11 mut NSCLC cancer

STK11 mut histology-agnostic cohort

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 expansion ongoing, clinical data 2025

- 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

FINANCIAL HIGHLIGHTS AND MILESTONES

Multiple projected key milestones and strong balance sheet

Clinical milestones

- ☐ TNG462 clinical data update 2025
- ☐ TNG462 combination trials enrollment begin 1H 2025
- ☐ TNG456 phase 1/2 trial enrollment begin 1H 2025
- ☐ TNG260 clinical data 2025

Cash balance

- $294M cash, cash equivalents and marketable securities as of September 2024
- Cash runway into Q3 2026, including additional TNG462 and TNG456 clinical trials


TANGO
therapeutics™