VI Curso
Medicina de precisión en cáncer de pulmón
19 de mayo de 2026 Formato virtual

MTAP

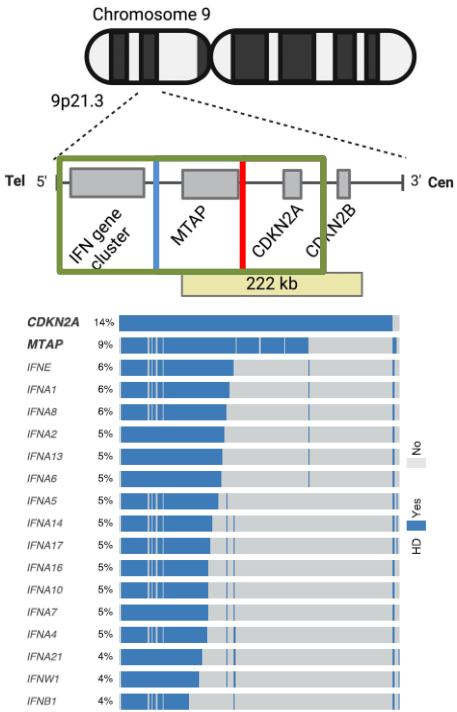
Clinical evidence and treatment strategies in thoracic malignancies

Mihaela Aldea

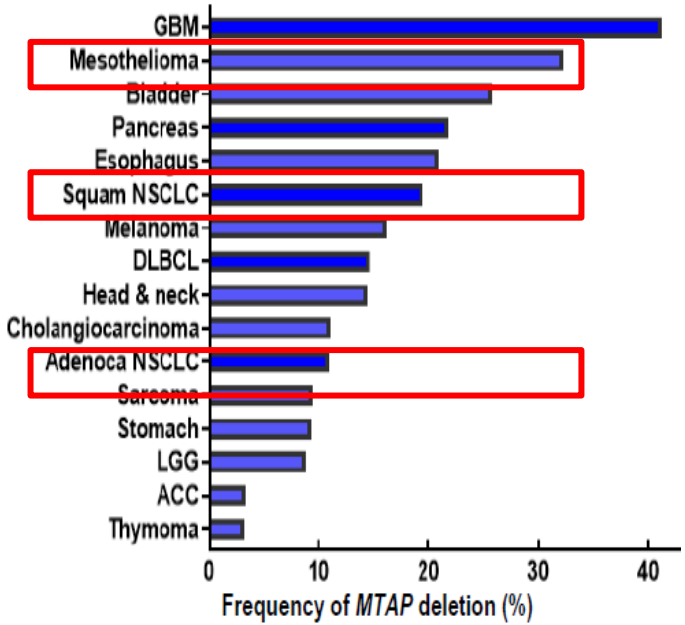
Thoracic Cancer Unit, Department of Cancer Medicine, Gustave Roussy

MTAP Loss is a frequent event of poor prognosis

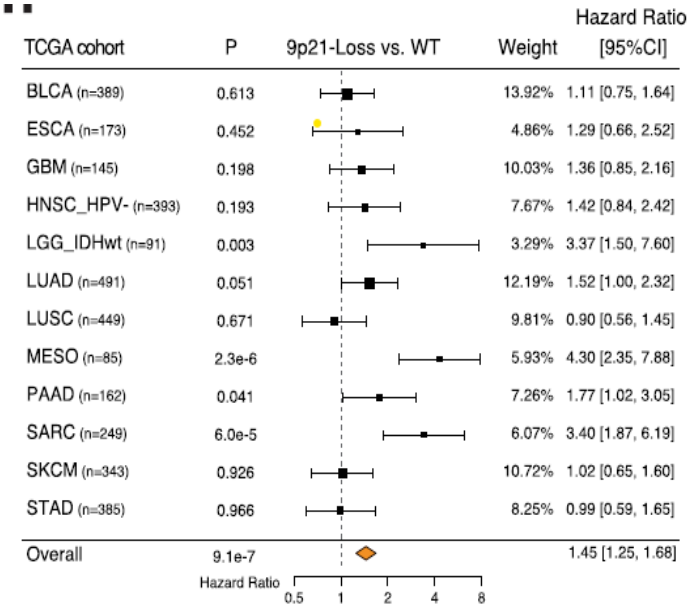
9p21 deletion: CDKN2A +/- MTAP +/- IFN gene loss



MTAP loss in 15% of cancers



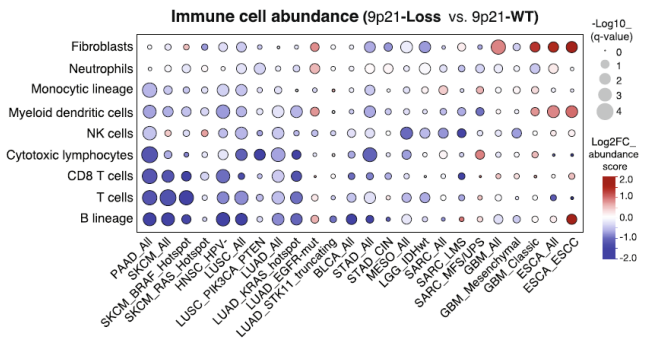
9p21 and MTAP loss are associated with worse overall survival across tumors

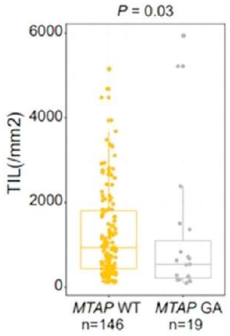


Febres Aldana, Modern Pathology 2024; Brune et al, Lung Cancer 2024; Han G, Nat Comm 2021

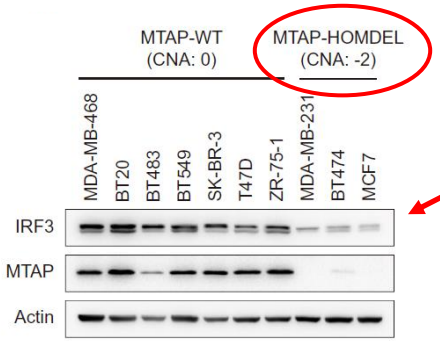
MTAP Loss induces immunosuppression

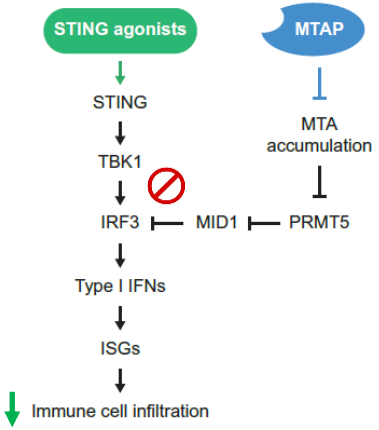
Downregulation of immune cell abundace across tumors with MTAP loss

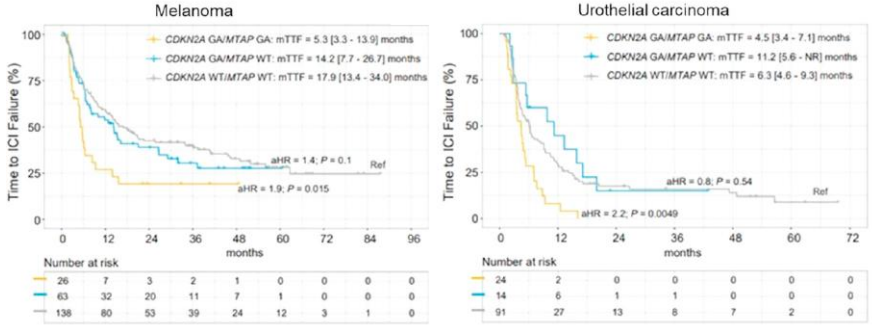




MTA accumulation in MTAP del cells inhibits IRF3





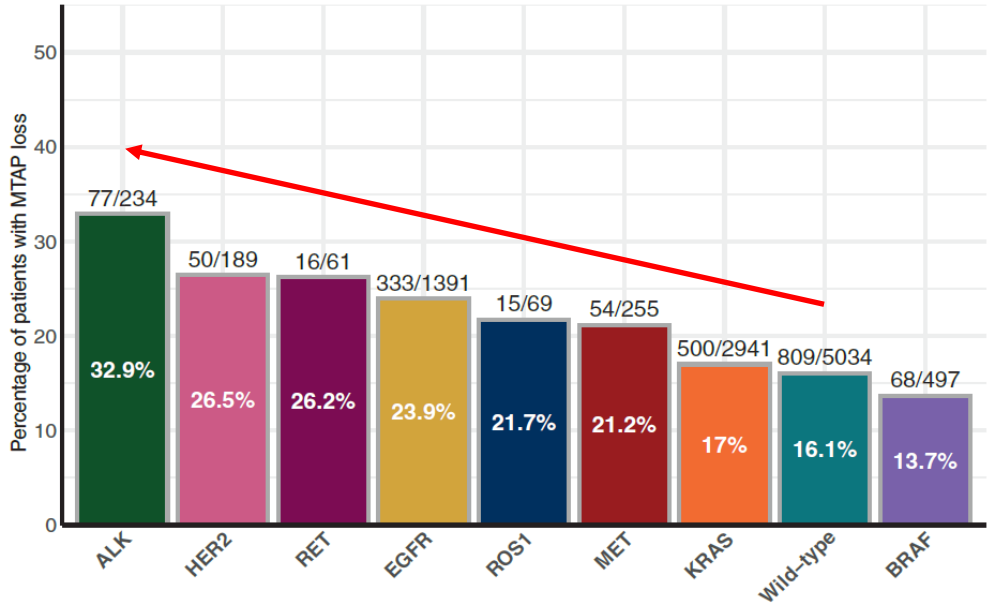


Overall survival and time to ICI failure are worse in MTAP deleted tumors

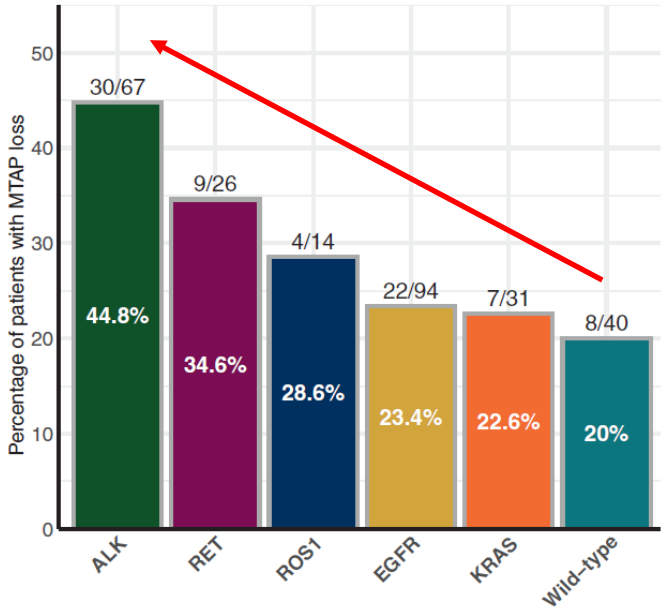
Han G, Nat Comm 2021; HSU J-M, Science 2025; Gjuka D, Cancer Cell 2023

MTAP Loss is often found in oncogene-driven NSCLC

MTAP deletion by tissue NGS (FoundationOne CDx)



MTAP loss by IHC



One out of three patients with ALK fusions may have an MTAP loss

Aldea M, Ann Oncol 2026

Synthetic lethality with PRMT5 inhibition

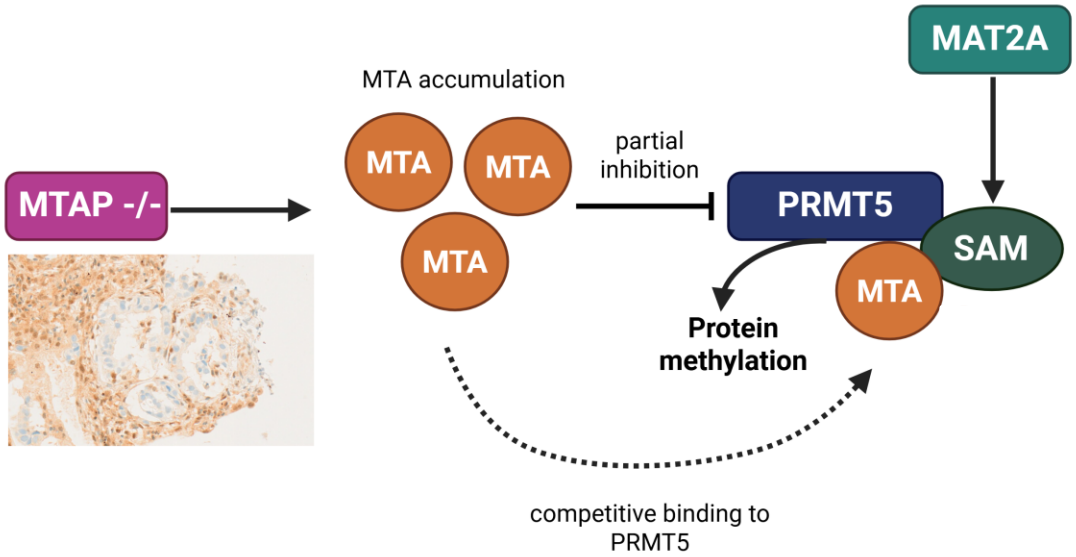


Figure created with BioRender

Gounder et al, Nat Commun 2025; Rodon J et al, Annals of Oncology 2024; Herzberg B et al, EORTC-NCI-AACR 2024

Synthetic lethality with PRMT5 inhibition

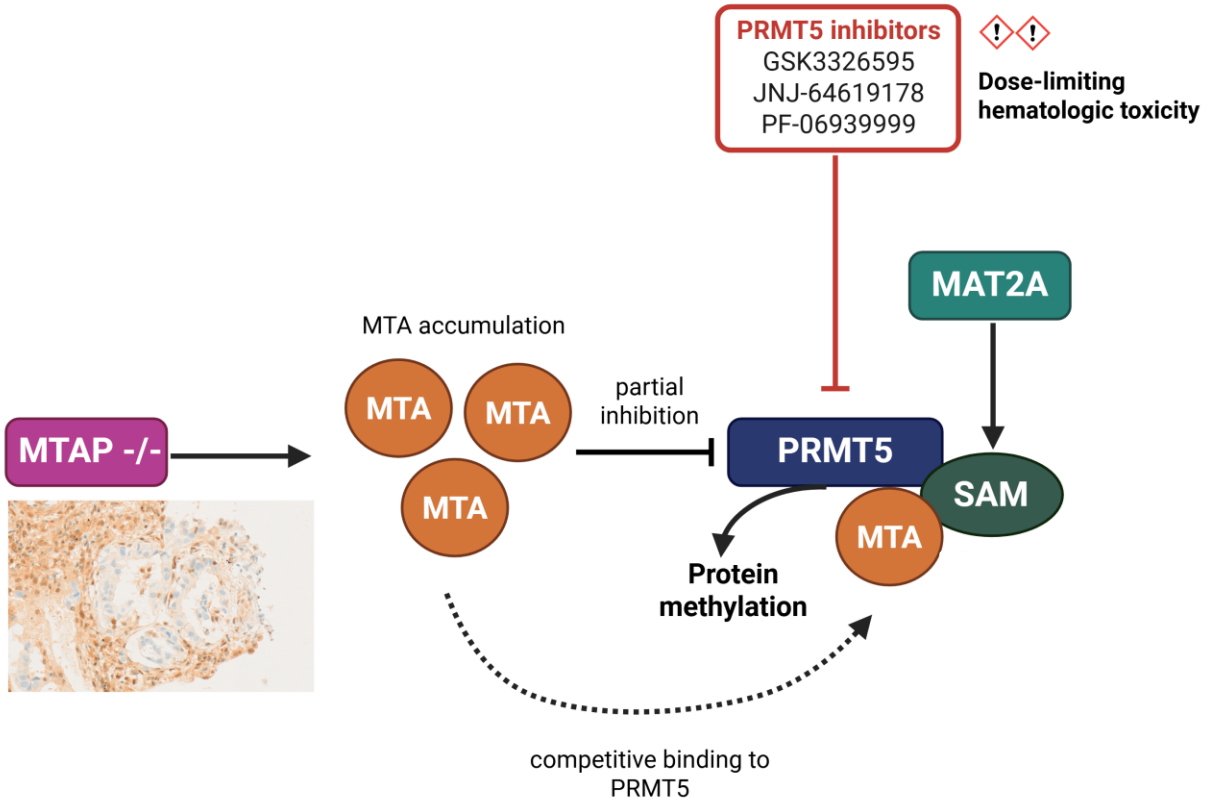


Figure created with BioRender

Gounder et al, Nat Commun 2025; Rodon J et al, Annals of Oncology 2024; Herzberg B et al, EORTC-NCI-AACR 2024

Synthetic lethality with PRMT5 inhibition

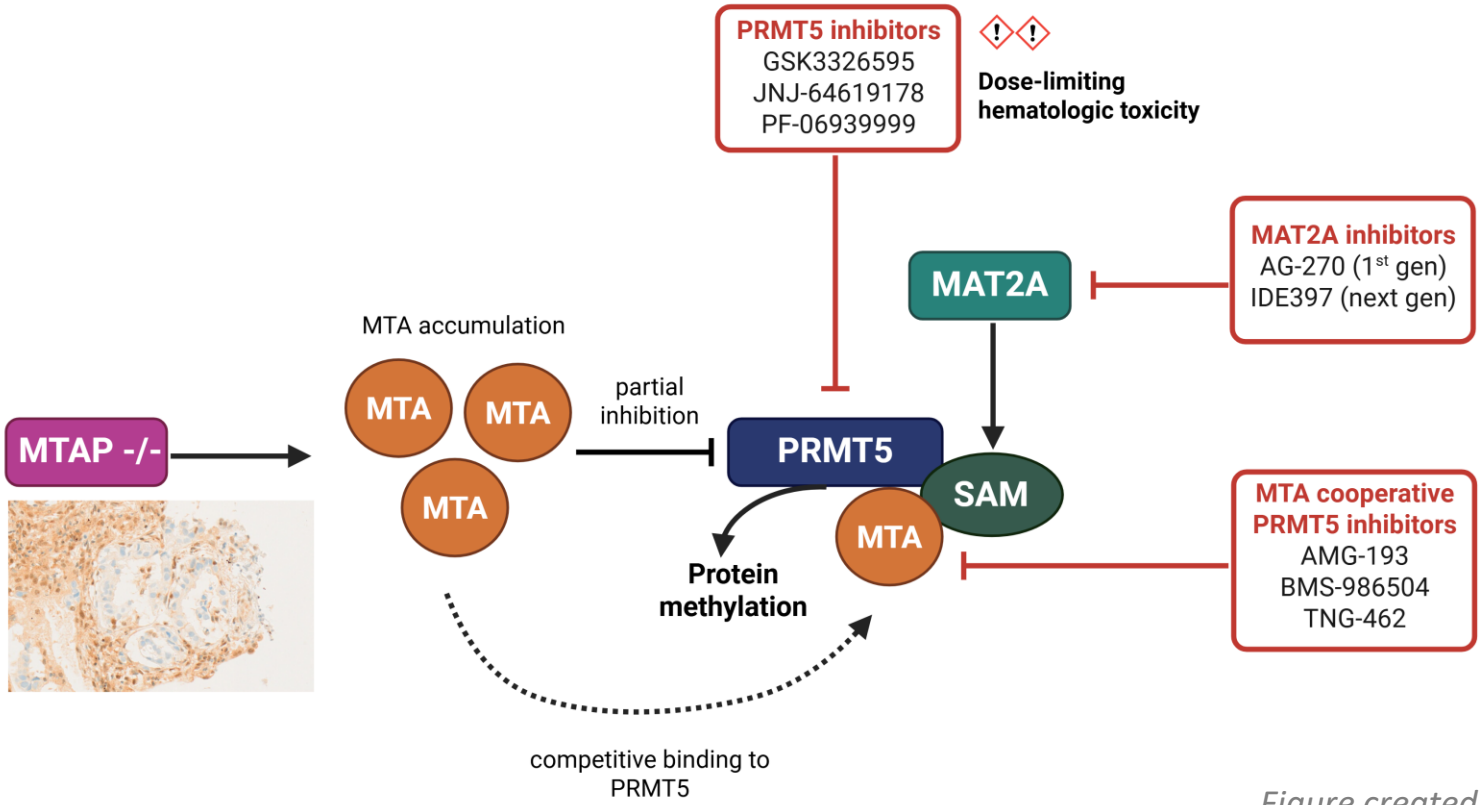
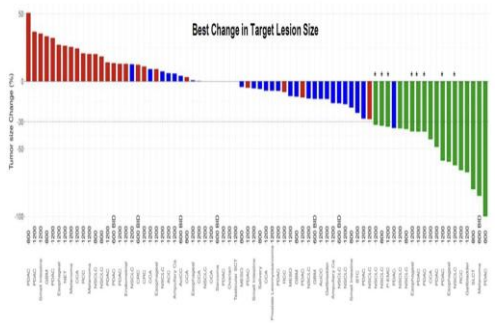


Figure created with BioRender

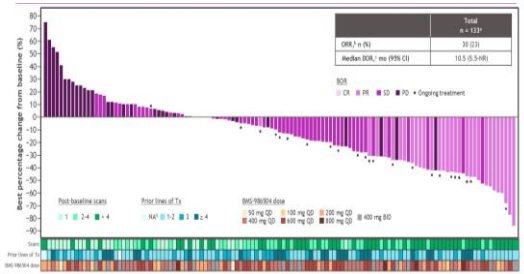
Gounder et al, Nat Commun 2025; Rodon J et al, Annals of Oncology 2024; Herzberg B et al, EORTC-NCI-AACR 2024

Clinical efficacy of MTA-PRMT5 inhibitors *across tumors*

AMG-193



BMS-98650



Pre-treated patients in the advanced setting

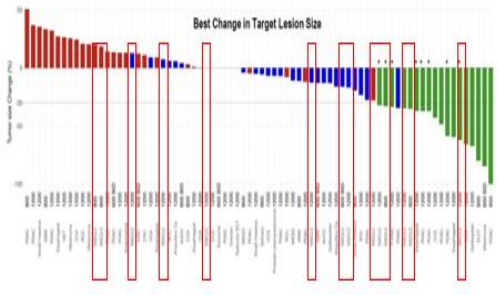
	AMG-193	BMS-986504	GTA-182	TNG-462
N	42	35	30	94
ORR	21.4%	30%	30%	27%
DCR	54.8%	70%	83.3%	78%
DOR	8.3m	10.5m	-	-
TTR	3.6m	5m	-	-
PFS	-	-	-	6.4m

discontinued **Ph 2**

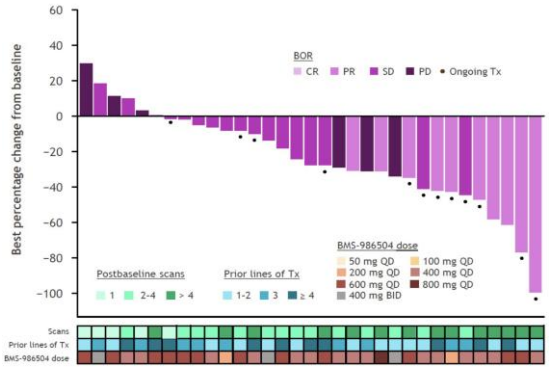
Rodon J, Ann Oncol. 2024; Arbour K, ASCO 2025; Shun Lu , ESMO Asia 2025; Press release from Tango Therapeutics, Oct 23, 2025

Clinical efficacy of MTA-PRMT5 inhibitors *in NSCLC*

AMG-193



BMS-98650



	AMG-193	BMS-986504	GTA-182	TNG-462
N	14	35	14	41
ORR	35%	29%	57%	-
DCR	78%	80%	85%	-
DOR	-	10.5m	-	-
mTTR	-	4.4m	-	-

Awaited in 2026

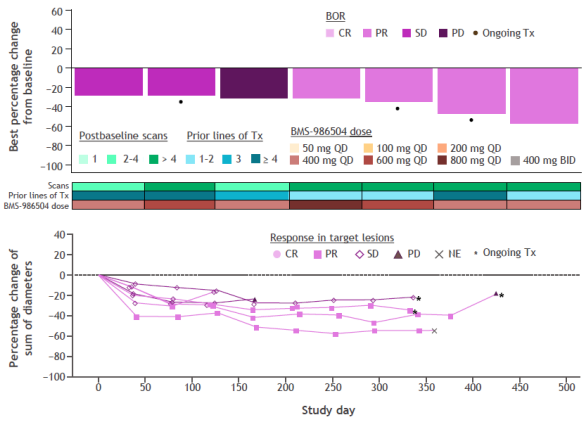
discontinued **Ph 2/3**

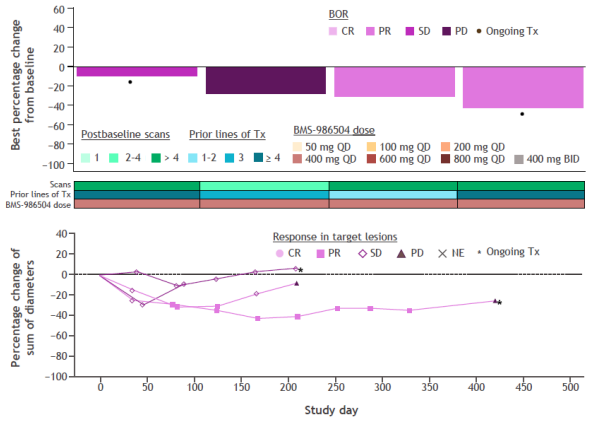
Rodon J, Ann Oncol. 2024; Jänne P, WCLC 2025; Shun Lu , ESMO Asia 2025; Press release from Tango Therapeutics, Oct 23, 2025

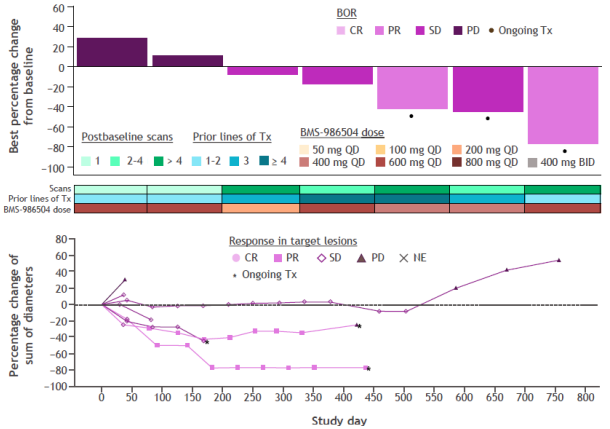
Clinical efficacy of MTA-PRMT5 inhibitors in *oncogene-driven* NSCLC

BMS-986504 – Navlimetostat (Phase I CA240-0007)

EGFR (N=7)	ALK (N=4)	KRAS (N=8)
ORR 57%, DOR 8.6 mo, TTR 5.4 mo	ORR 50%, DOR 7.1 mo, TTR 4.1 mo	ORR 25%, DOR 11.3 mo, TTR 4.4 mo







Jänne P, WCLC 2025

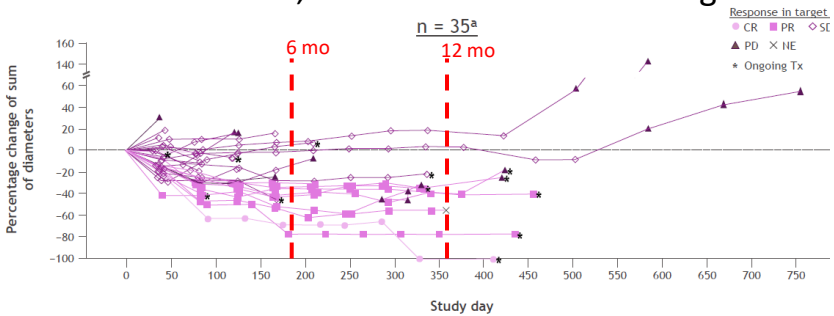
Durable efficacy of MTA-PRMT5 inhibitors

Long responses seen in patients with or without oncogenic drivers

NSCLC

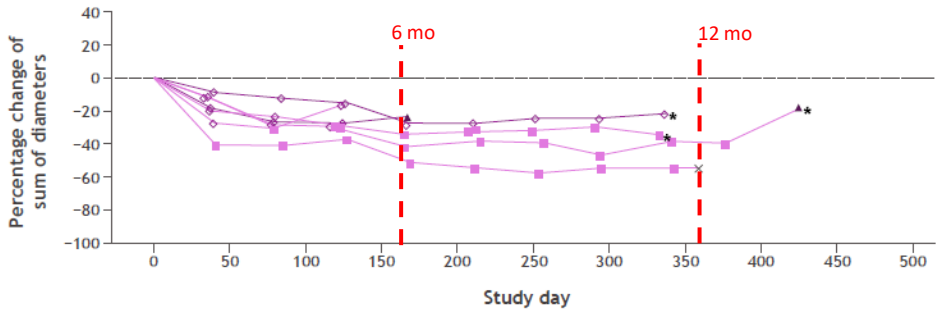
Navlimetostat (Ph 1) – all NSCLC

Median, n=2 lines in the M+ setting



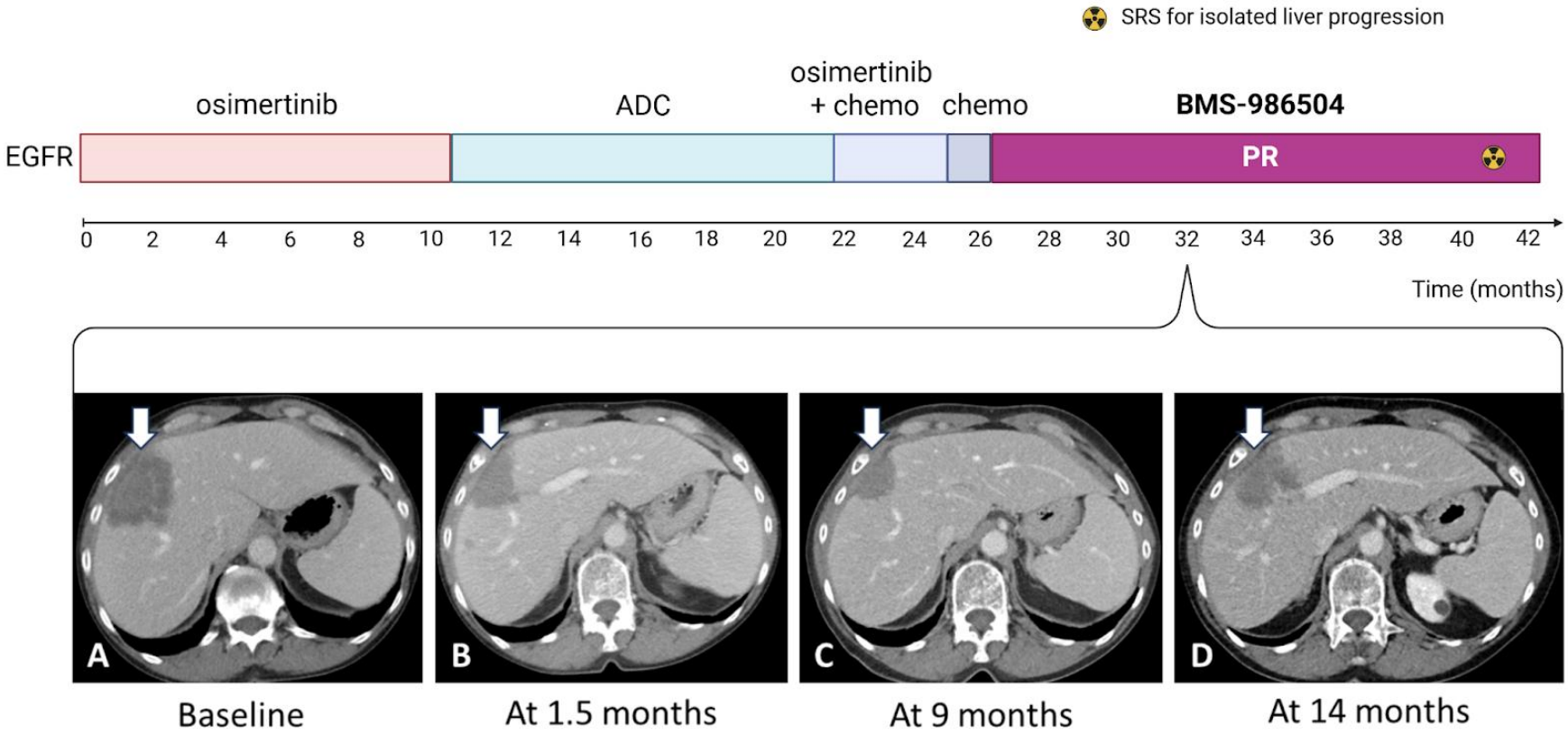
Navlimetostat (Ph 1) – *EGFR*-mutated NSCLC (N=7)

All pretreated with osimertinib



Arbour K et al, 3011 ASCO 2025; Janne P et al, OA08.01 – WCLC 2025

Clinical case



Aldea M, Ann Oncol 2026

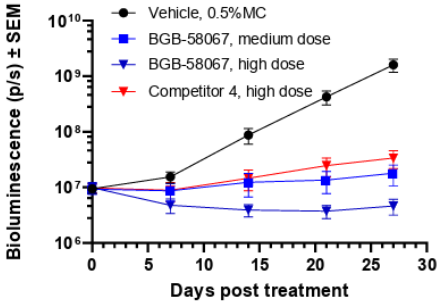
Brain penetrant MTA-PRMT5i

BGB-58067 (BeiGene)

Not a substrate of P-gp or BCRP

No reported clinical activity

Activity in MTAP del brain orthopic models

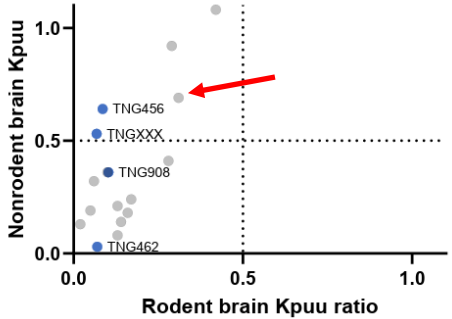


GTA-182 (Apeiron)

2/3 patients had CNS responses in the Ph I

TNG-456 (Tango)

No reported clinical activity



BAY 3713372 (Bayer)

No reported clinical activity

Jiang A, AACR 2026: P 3901 ; Shun Lu - ESMO ASIA 2025; Tsai A, SNO 2025; Briggs K, AACR 2025

Safety of MTA-PRMT5 inhibitors

Class effects: GI side effects & fatigue (mainly Gr 1–2); **Low heme tox → supports combos**

		AMG193	BMS-986504	TNG462
Class effects	**Nausea**	48.8%	Mainly G1–2†	26%
	Vomiting	30%	Mainly G1–2†	—
	Fatigue	31.3%	Mainly G1–2†	19%
	Decreased appetite	22%	Mainly G1–2†	—
Hematologic	**Anemia**	15%	8%	20%
	Neutropenia	3.8%	7%	—
	Thrombocytopenia	1.3%	6%	13%
	Grade ≥3	All TRAE 13.8%	14% TRAE	**G3 anemia 13%**
	Discontinuation	2.5%	2%	**0%** drug-related

GI, dizziness

Anemia

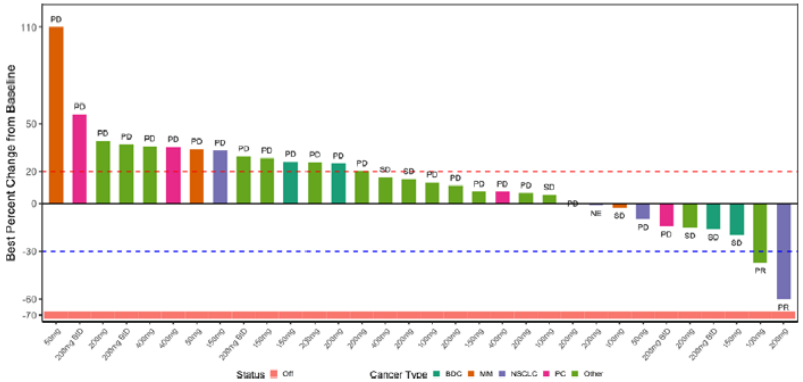
Rodon J et al, Ann Oncol 2024; Arbour K, ASCO 2025; Press release from Tango, https://www.globenewswire.com/; George B et al, 89O - ESMO TAT 2026; Von Hoff et al, NEJM 2013

The MAT2A inhibitor landscape

AG-270 / S095033 (Agios→ Servier)

First-in-class MAT2A inhibitor

Modest efficacy



UGT1A1 inhibition → reversible ↑ unconjugated bilirubin

Event, n (%)	All Grades	Grade 3
Patients with any TRAE	28 (70.0)	6 (15.0)
Blood bilirubin increased/hyperbilirubinemia[#]	10 (25.0)	4 (10.0)
Fatigue	10 (25.0)	0
Thrombocytopenia /platelet count decrease	7 (17.5)	3 (7.5)
Rash[a]	6 (15.0)	2 (5.0)
Anemia	4 (10.0)	1 (2.5)
Diarrhea	3 (7.5)	0
Nausea	3 (7.5)	0

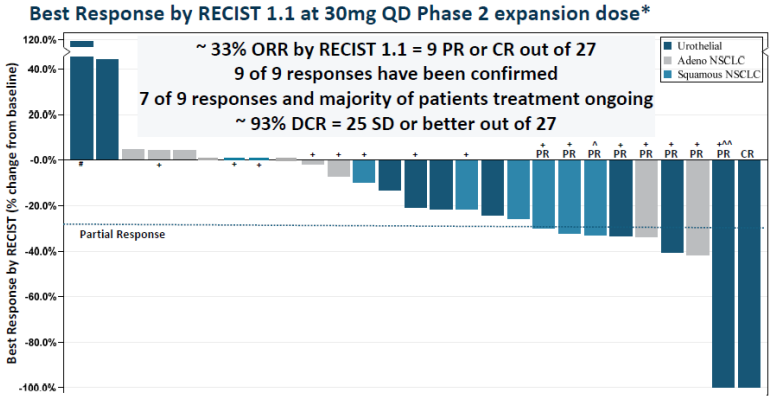
Programme discontinued for strategic reasons — proof-of-mechanism established the class

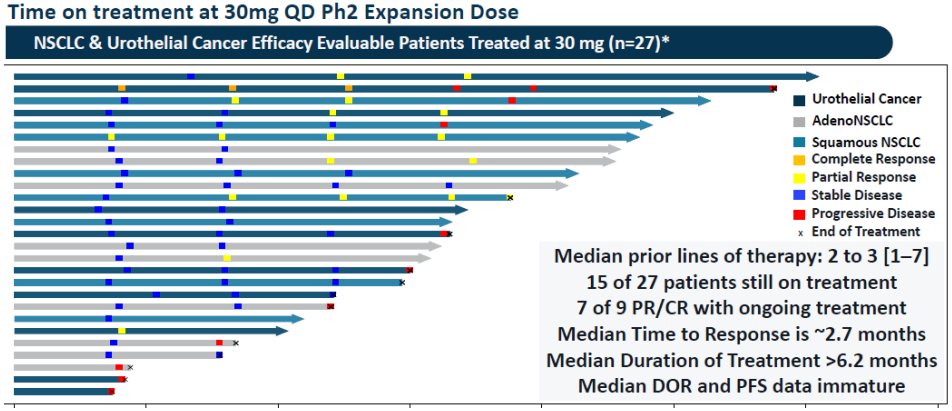
Gounder M, Nature Comm 2025

The MAT2A inhibitor landscape

IDE397 (IDEAYA)

Allosteric MAT2A inhibitor





Treatment Emergent & Treatment Related Adverse Events in Safety Population, n= 28

Preferred Term	TEAE (≥ 15%)		TRAE	
	All Grade, n (%)	Grade ≥ 3, n (%)	All Grade n (%)	Grade ≥ 3, n (%)
Any Event	23 (82%)	11 (39%)	15 (54%)	5 (18%)
Fatigue*	9 (32%)	1 (4%)	3 (11%)	0 (0%)
Peripheral Neuropathy**	8 (29%)	0 (0%)	7 (25%)	0 (0%)
Decreased Appetite	7 (25%)	0 (0%)	3 (11%)	0 (0%)
Constipation	6 (21%)	0 (0%)	1 (4%)	0 (0%)
Blood Creatinine Increase	5 (18%)	0 (0%)	3 (11%)	0 (0%)
Nausea	5 (18%)	0 (0%)	3 (11%)	0 (0%)
Asthenia	5 (18%)	1 (4%)	2 (7%)	1 (4%)

Herzberg B et al. ENA 2024 LBA501

The MAT2A inhibitor landscape

S095035 (Servier)

Next-gen AG-270 successor

- Designed to avoid UGT1A1 (bilirubin) liability
- NCT05312372

SYH2039 (CSPC → BeOne)

Licensed by BeOne (Dec 2024)

- Planned combo with BGB-58067 (in-house PRMT5i, brain-penetrant)

ISM3412 (Insilico Medicine)

AI-designed (Chemistry42)

- Preclinical: low-dose activity in MTAP-del xenografts; clean tox margin
- NCT06414460

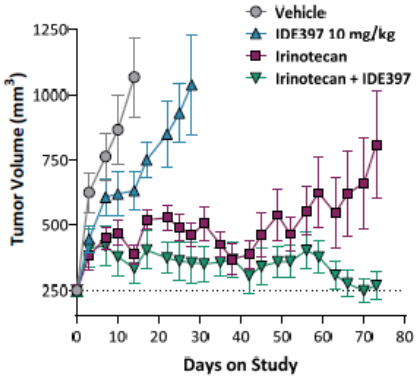
No clinical efficacy or safety data disclosed to date

Heist RS et al. AACR-NCI-EORTC 2019, Abstr PR03 · Herzberg B et al. ENA 2024 LBA501 · Garbett D et al. ENA 2024 PB204 · Insilico, AACR 2023 (poster); NCT06414460 · BeOne/CSPC press release, 12-Dec-2024

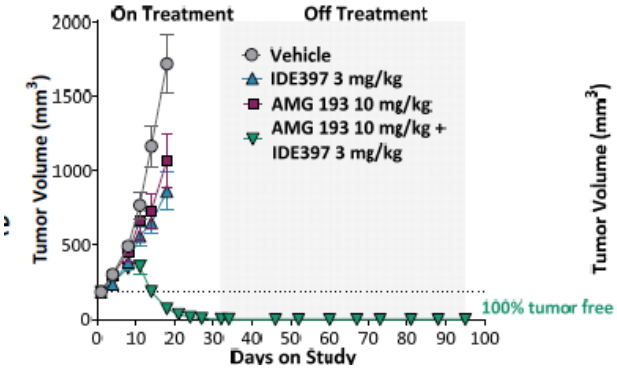
IDE892
SYH2039
GTA182
TNG456
~~AMG193~~
(disc. Apr 2026)
BGB-58067
AZD3470
Navlimetostat
Vopimetostat

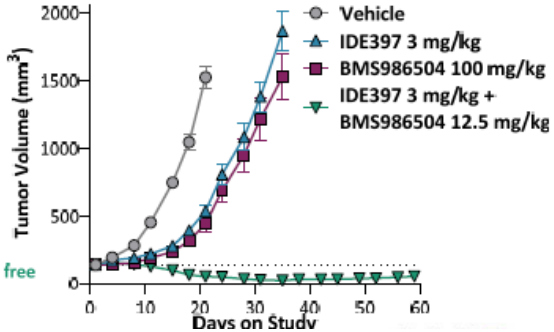
Combination strategies – Preclinical data

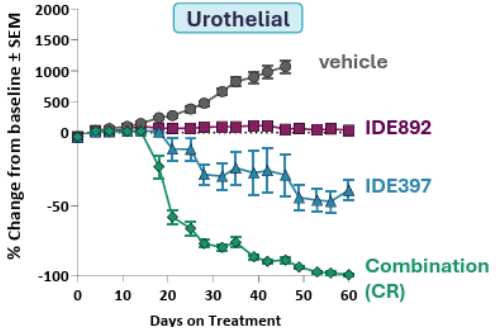
TOP1i combination

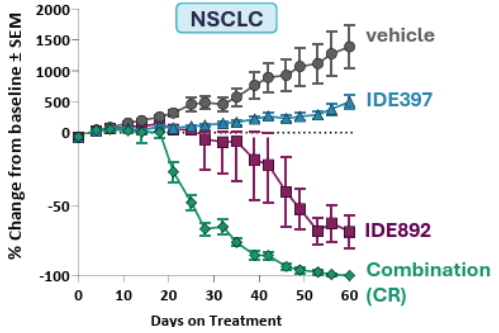


PRMT5i combination







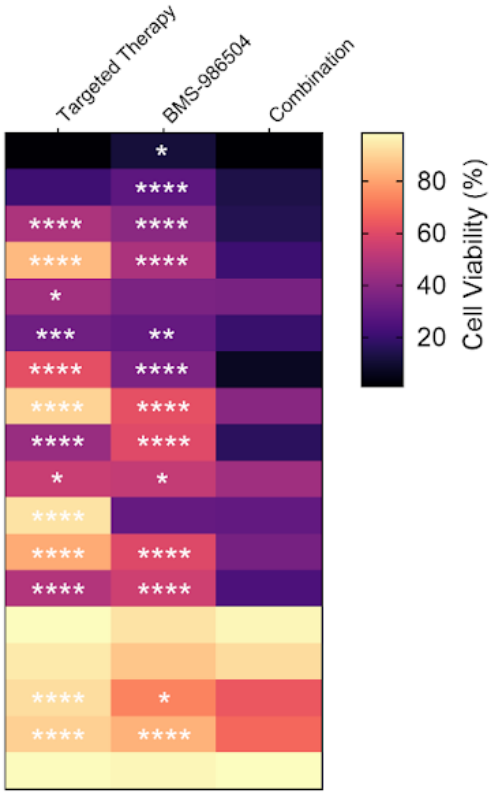


Herzberg B et al. ENA 2024 LBA501; Ideya Corporate Presentation

Combination strategies – Preclinical data

TKI combination

	BMS-986504	EGFR			KRAS			BRAF	HER2	MET		ALK	NRAS	TP53	Targeted Therapy naïve
Cell Line	IC50 (uM)	Exon 19del	L858R	T790M	G12C	G12D	Amp	V600E	Amp	Exon 14del	Amp	ALK fusion	Q61K	Mut	
H3122	0.02														Yes
H2228	0.04														Yes
HCC4006	0.04														Yes
DFCI161	0.04														No
DFCI76 MTAP KO	0.05														No
DFCI32	0.06														Yes
DFCI773	0.12														No
DFCI358	0.22														No
SNU2292	0.22														No
DFCI264	0.32														No
DFCI81	0.34														No
DFCI832	0.76														No
DFCI284	1.05														No
DFCI429	7.37														Yes
DFCI471	8.55														No
DFCI105	>10														Yes
DFCI298	>10														Yes
DFCI746	>10														No



Aldea M, Ann Oncol 2026

Combination strategies – focus on NSCLC

PRMT5i + MAT2Ai (dual-mechanism)

S095035 + vopimetostat (TNG462)

- S095035 + TNG462 – basket (Ph ½)

Other dual-mechanism programs (IDE892+IDE397, BGB-58067+SYH2039) not yet in NSCLC-specific trials.

PRMT5i + targeted / IO / chemo

BMS-986504 (navlimetostat)

+ pembro + chemo, 1L NSCLC (Ph 2/3, MountainTAP-29 N=590)

+ pumitamig + chemo, 1L NSCLC (Ph 1, MountainTAP-5)

Vopimetostat (TNG462)

+ pembrolizumab (Merck) — basket (Ph ½)

+ daraxonrasib (RMC-6236) or zoldonrasib (RMC-9805) – NSCLC/PDAC

BGB-58067 — BeOne Medicines

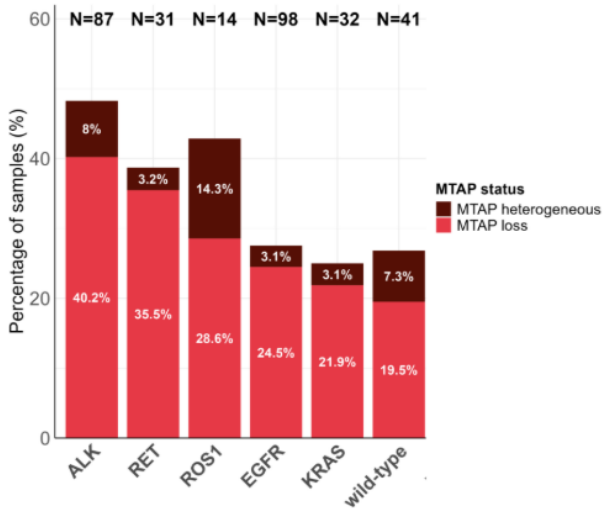
+ tislelizumab + chemo, 1L NSCLC

Sources: ClinicalTrials.gov NCT06188702 (S095035±TNG462); BMS MountainTAP-29/-5 (1L NSCLC); Tango/AstraZeneca and Tango/Merck collaborations; BeOne BGB-58067 1L NSCLC program. Trial status as of 2026.

Gaps and Perspectives

MTAP loss is heterogeneous in a small minority of cases

Underestimated? Combos needed for everyone?

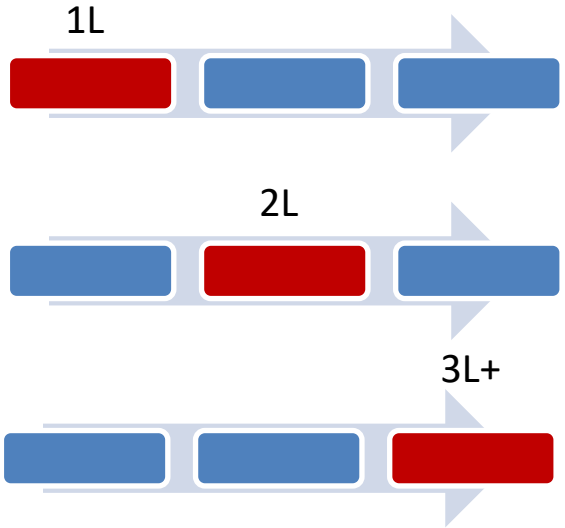


Aldea M, Ann Oncol 2026

Brain penetration ?

Added neuro tox?

Best therapeutic sequence and best combos?



Efficacy seems comparable, future strategy and safety will dictate the winner

Conclusion

- MTAP loss is a new target undergoing clinical validation.
- Start **screening for MTAP loss** even in patients with NSCLC, with or without (especially with!) oncogenic disease.
- These new drugs may offer additional prolonged benefit and chemo-free options for patients.
- Combinations are probably the future – how and when, TBD

KEEP
CALM
IT'S
ALMOST
EASY