Therapies of RAS and P53 and other “undruggable targets

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Disclosures

- Speaker fees: Amgen, Astra Zeneca, Bayer, Roche and Sanofi

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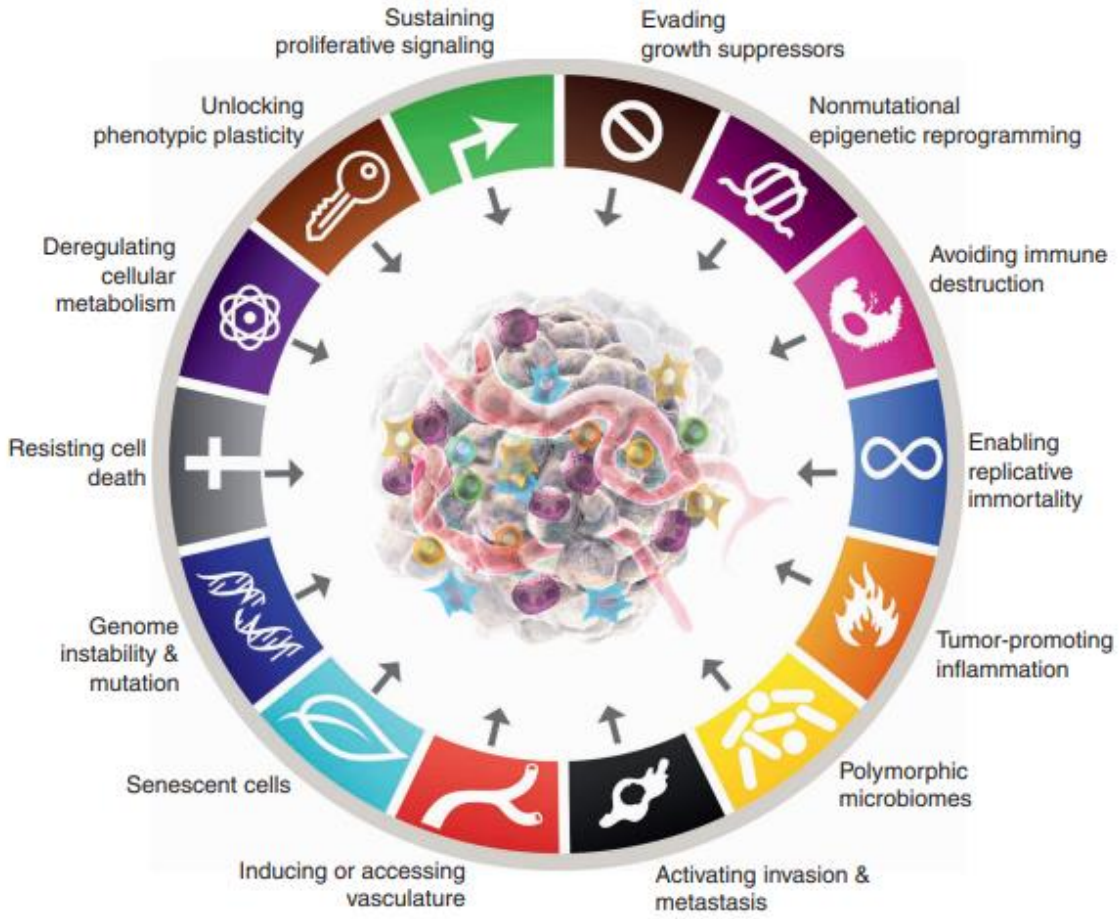

Figure 6. Hallmarks of Cancer—new additions. Depicted are the canonical and prospective new additions to the "Hallmarks of Cancer." This treatise raises the possibility, aiming to stimulate debate, discussion, and experimental elaboration, that some or all of the four new parameters will come to be appreciated as generic to multiple forms of human cancer and hence appropriate to incorporate into the core conceptualization of the hallmarks of cancer. The hallmarks of cancer graphic has been adapted from Hanahan and Weinberg (2).

Every cancer cell contains alterations that lead to the production of abnormal proteins responsible for uncontrolled cell growth and survival.

Douglas Hanahan, Cancer Discovery 2022

Currently only 15% of proteins are considered druggable

- For years, researchers have struggled to develop treatments that work on these so-called “undruggable” targets.

- Thanks to advances in
  - chemistry,
  - computational approaches,
  - and imaging
  - coupled with a deeper understanding of cancer biology

- New strategies to tackle these difficult targets !

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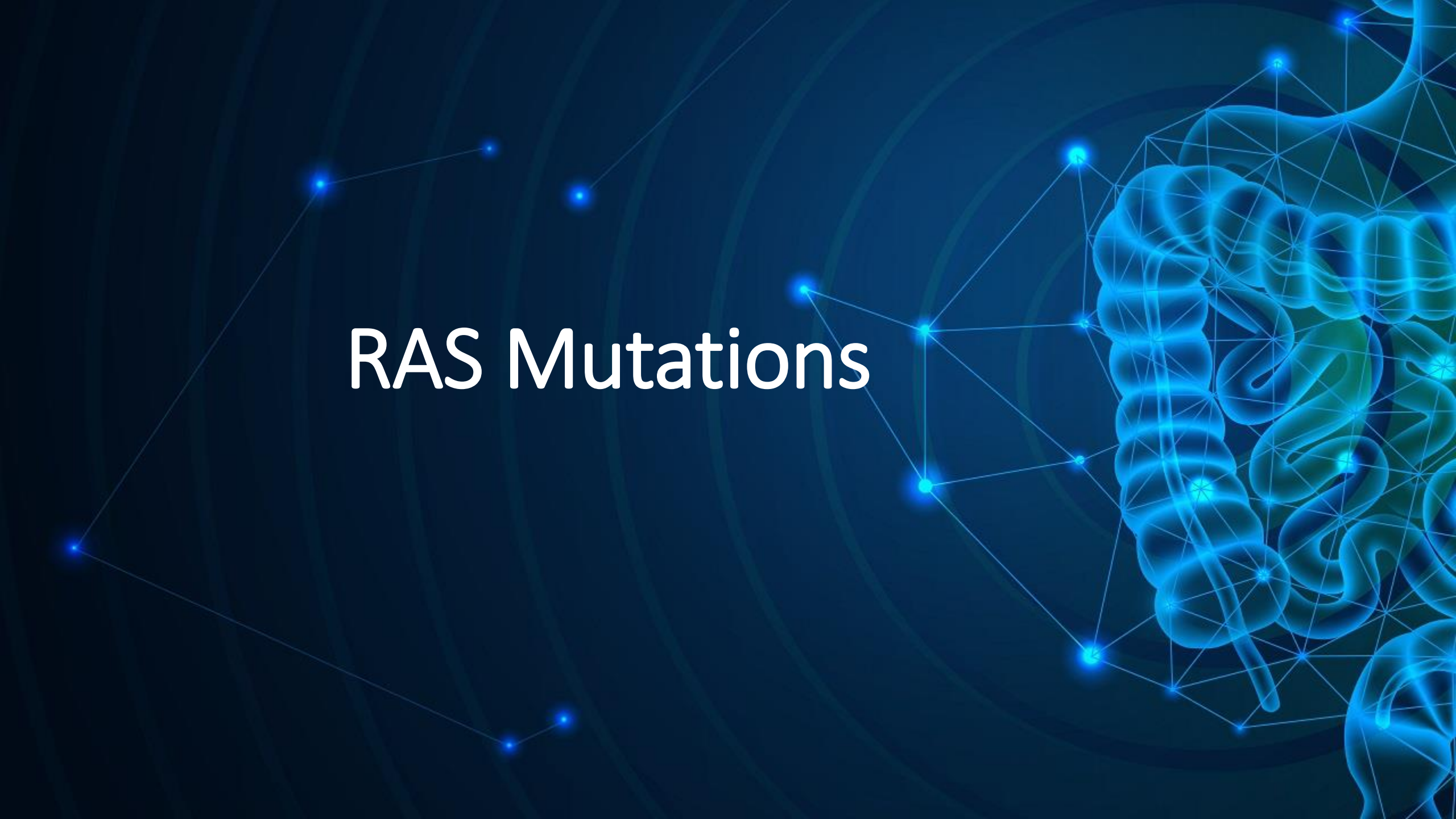
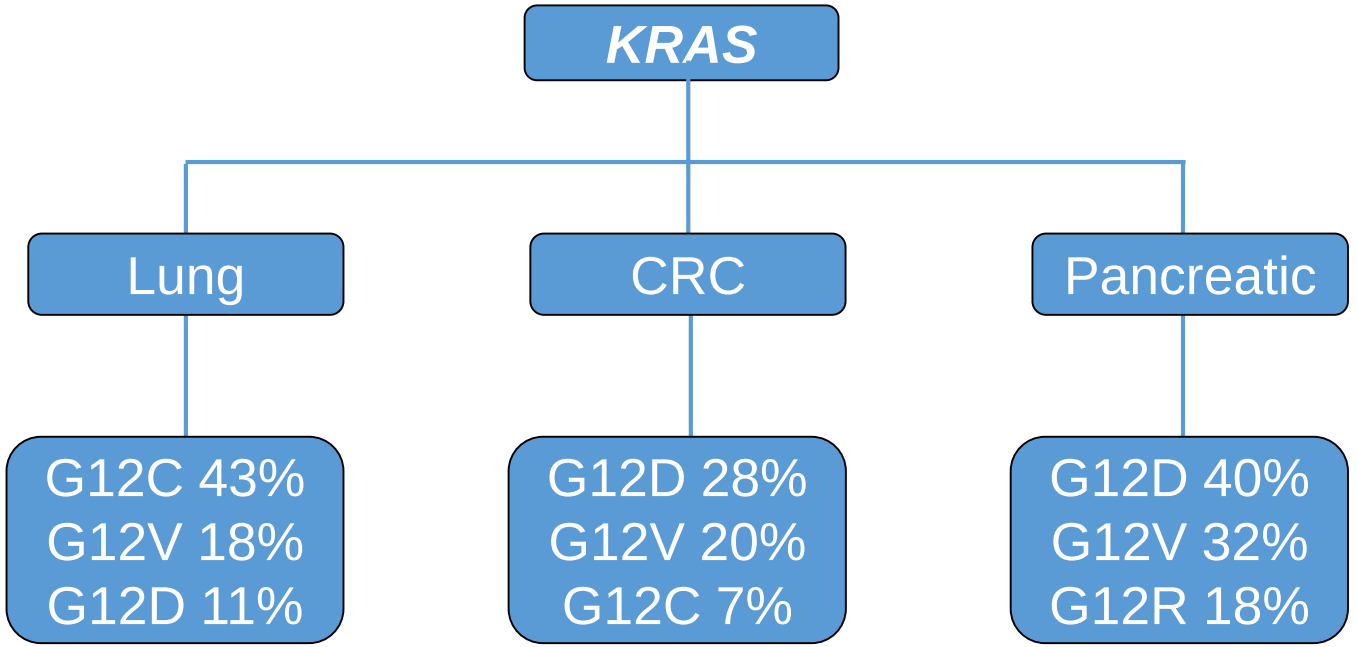
RAS Mutations



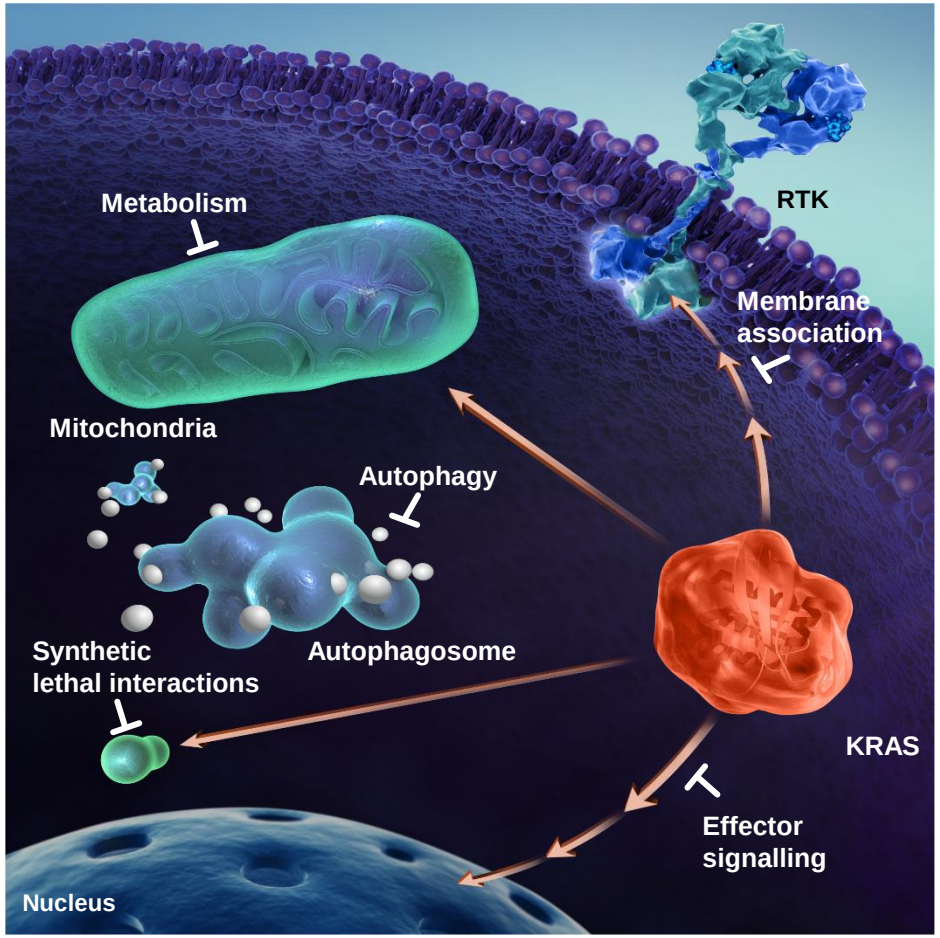
Frequency of KRAS mutation subtypes



KRAS has been one of cancer research's toughest challenges

- RAS proteins are relatively smooth, making tight binding of small molecules difficult[1]
- GTP binds with high affinity to KRAS, making competitive inhibition challenging[1,2]
- Risk of toxicities from nonselective binding to wild-type KRAS[2]
- Previous strategies have focused on pathways downstream of RAS (RAF-MAPK and PI3K)

Previous strategies to target KRAS[1,2]



1. Cox AD, et al. Nat Rev Drug Discov 2014;13:828–51;
2. Ryan MB, et al. Nat Rev Clin Oncol 2018;15:709–20.

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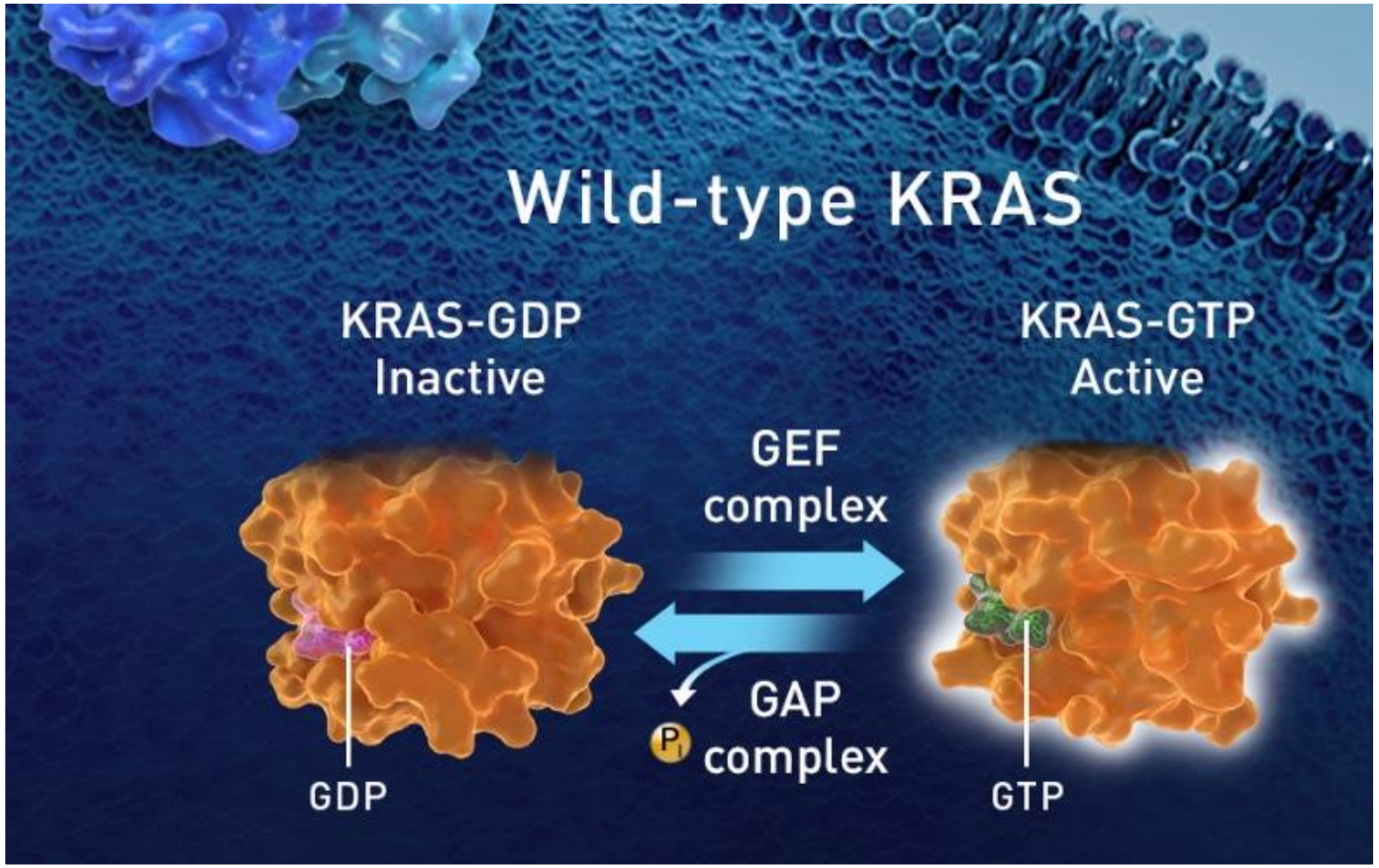
The KRAS protein cycles between an active GTP-bound state and an inactive GDP-bound



Sotorasib is a first-in-class, oral targeted therapy that selectively inhibits the KRAS^{G12C} protein

Sotorasib locks KRAS^{G12C} in an inactive state, preventing oncogenic signalling without affecting wild-type KRAS

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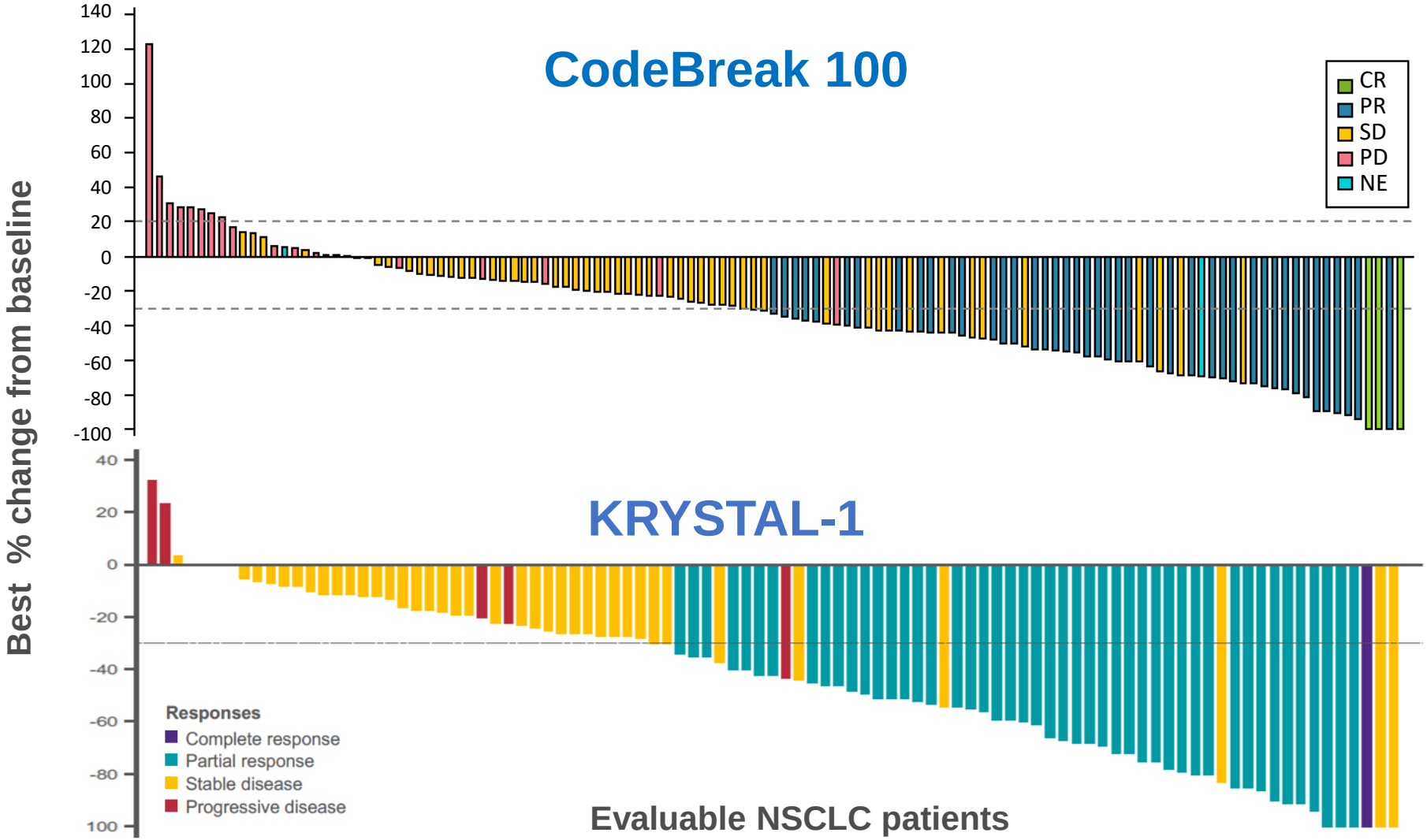
$KRAS^{G12C}$ inhibitors in development

Company	Drug	Phase	Tumour type
Amgen[1,2]	Sotorasib (AMG 510)	3	NSCLC, CRC, other tumour types
Mirati[3]	Adagrasib (MRTX849)	3	NSCLC, CRC, other tumour types
Novartis[4]	JDQ443	1/2	NSCLC, CRC
InventisBio[5]	D-1553	1/2	NSCLC, CRC
GenFleet Therapeutics[6]	GFH925	1/2	NSCLC, GI
Jacobio Pharmaceuticals[7]	JAB-21822	1/2	NSCLC, CRC, other tumour types
Roche/Genentech[8]	GDC-6036	1	NSCLC, CRC, other tumour types
Boehringer Ingelheim[9]	BI 1823911	1	Other tumour types
Eli Lilly[10]	LY3537982	1	NSCLC, other tumour types
Janssen[11]	JNJ-74699157	1	NSCLC, CRC, other tumour types

1. ClinicalTrials.gov Identifier: NCT04185883; (accessed June 2022); 2. LUMAKRAS™ Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf; (accessed June 2022); 3. ClinicalTrials.gov Identifier: NCT03785249 (accessed June 2022); 4. ClinicalTrials.gov Identifier: NCT04699188 (accessed June 2022); 5. ClinicalTrials.gov Identifier: NCT04585035 (accessed June 2022); 6. ClinicalTrials.gov Identifier: NCT05005234 (accessed June 2022); 7. ClinicalTrials.gov Identifier: NCT05002270 (accessed June 2022; 8. ClinicalTrials.gov Identifier: NCT04449874 (accessed June 2022); 9. ClinicalTrials.gov Identifier: NCT04973163 (accessed June 2022); 10. ClinicalTrials.gov Identifier: NCT04956640 (accessed June 2022); 11. ClinicalTrials.gov Identifier: NCT04006301 (accessed June 2022).

Information correct as of February 2022.
NSCLC, non-small cell lung cancer.

KRAS^{G12C} inhibitors have been most extensively evaluated in lung cancer



Sotorasib[1]
N=172* evaluable
FU=24.9 months
ORR=41%
SD= 43%
PD=13%
PFS=6.3 months
OS=12.5 months

Adagrasib[2]
N=112 evaluable
FU=12.9 months
ORR=43%
SD=37%
PD=5%
PFS=6.5 months
OS=12.6 months

*2 patients are not included in the efficacy set as they did not have measurable lesions at baseline and were ineligible for response assessment.

CR, complete response; FU, median follow-up; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Dy GK, et al. Presented at the American Association for Cancer Research (AACR) Annual Meeting, 2022;
2. Jänne PA, et al. N Engl J Med 2022. Epub ahead of print.

CodeBreak 100 – Phase 2 CRC cohorts
Study design and efficacy

Key eligibility

- Locally advanced or metastatic CRC with *KRAS G12C* mutation
- Received prior standard therapies
- At least one measurable lesion (RECIST v1.1)
- ECOG PS ≤1

Phase 2 (N=62)

- Sotorasib 960 mg QD

Primary endpoint

- ORR

Key secondary endpoints

- DoR, DCR, PFS, time to response, safety

Tumour response to sotorasib therapy	Sotorasib 960 mg (N=62)
Best response, n (%)	
Complete response	0
Partial response	6 (10%)
Stable disease	45 (73%)
Progressive disease	11 (18%)
ORR, n (%; 95% CI)**	6 (9.7%; 3.6–19.9)
DCR, n (%; 95% CI)†	51 (82.3%; 70.5–90.8)
Median PFS, months (95% CI)	4.0 (2.8–4.2)

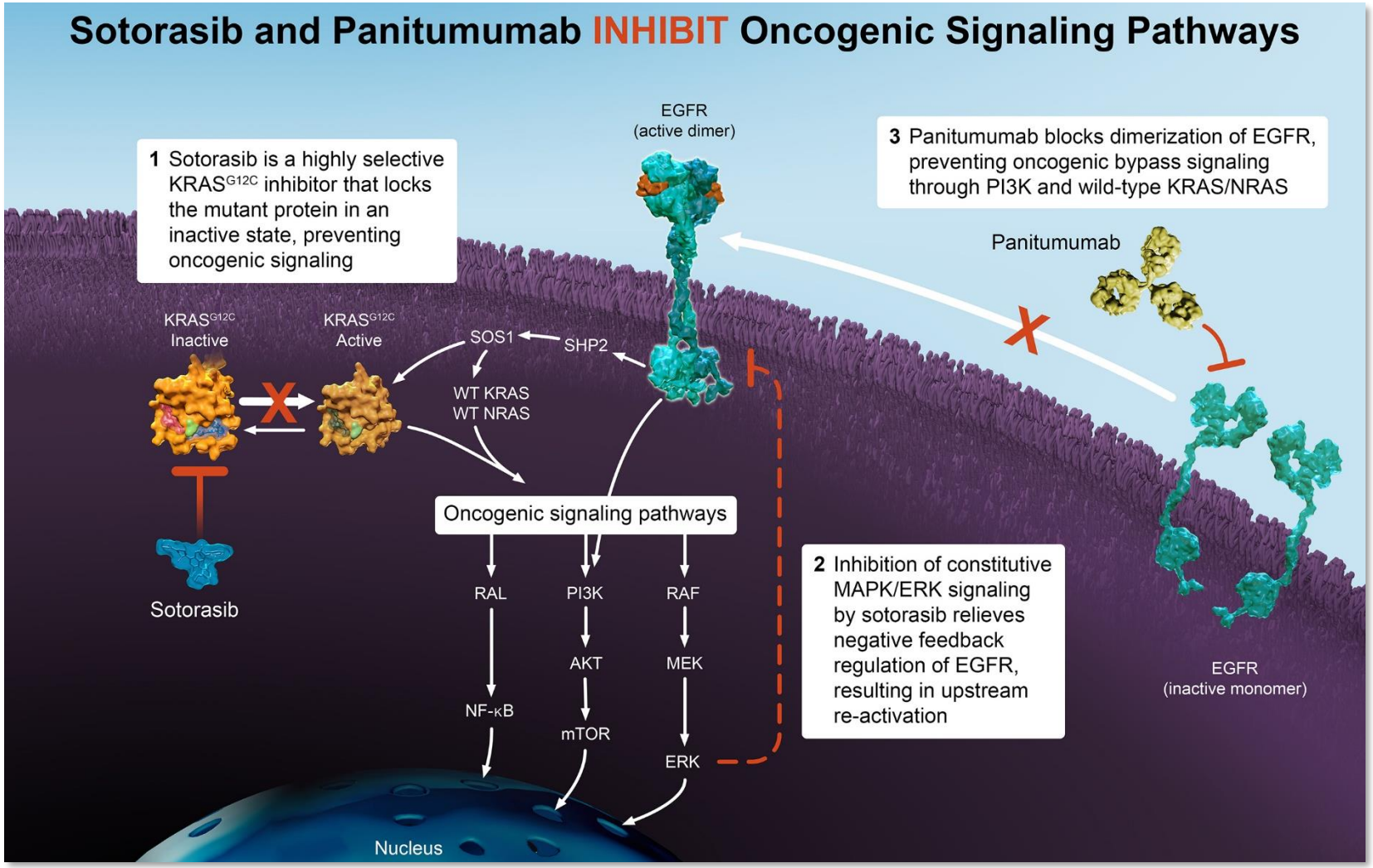
- Median follow-up: 11 months (range: 4.3–11.3 months)
- Five patients are continuing treatment;* 57 patients discontinued treatment
  - 52 due to disease progression, three requested by patients, one adverse event, one requirement for alternative therapy

*At the time of data cut-off for the colorectal cancer cohort, 1 March 2021.
**Objective response was defined as a complete or partial response.
†Disease control was defined as a complete response, partial response, or stable disease.

CI, confidence interval; DCR, disease control rate; DoR, duration of response; ECOG, eastern cooperative oncology group; PS, performance status; RECIST, response evaluation criteria in solid tumors; QD, daily.

Fakih MG, et al. Lancet Oncol 2022;23:115–24.

EGFR blockade reverts resistance to KRAS G12C inhibition in colorectal cancer



- Canon J, et al. Nature 2019;575:217–23; Berg M, Soreide K. Discov Med 2012;14:207–14; Freeman D, et al. J Clin Oncol 2008;26(suppl 15):Abstract14535.

CodeBreaK 101 – Phase 1b sotorasib + panitumumab in CRC

Response assessed by investigator	Part 1 Cohort A (n=8) sotorasib 960 mg/ Pmab 6 mg/kg	Part 2 Cohort A (n=18) sotorasib 960 mg/ Pmab 6 mg/kg	Part 1 + Part 2 combined cohort A (N=26)**
Disease control rate, n (%)	6 (75.0)	15 (83.3)	21 (80.8)
ORR, % (95% CI)			
Confirmed	12.5 (0.3–52.7)	16.7 (3.6–41.4)	15.4
Confirmed and unconfirmed†	12.5 (0.3–52.7)	33.3 (13.3–59.0)	26.9
Partial response, n (%)			
Confirmed	1 (12.5)	3 (16.7)	4 (15.4)
Confirmed and unconfirmed§	1 (12.5)	6 (33.3)	7 (26.9)
Stable disease, n (%)	5 (62.5)	12 (66.7)	17 (65.4)
Progressive disease, n (%)	1 (12.5)	2 (11.1)	3 (11.5)
Not done, n (%)	1 (12.5)	1 (5.6)	2 (7.7)

Overall, 27% achieved response (including unconfirmed response awaiting confirmation) and 81% achieved disease control

Fakih MG, et al. Ann Oncol 2021;32(suppl 5):S530–S582; Poster 424P.

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KRYSTAL-1 – Phase 1b/2 adagrasib + cetuximab in CRC

Key cligibility criteria

- Solid tumour with a *KRAS G12C* mutation*
- Unresectable or metastatic disease
- No available treatment with curative intent or available standard of care

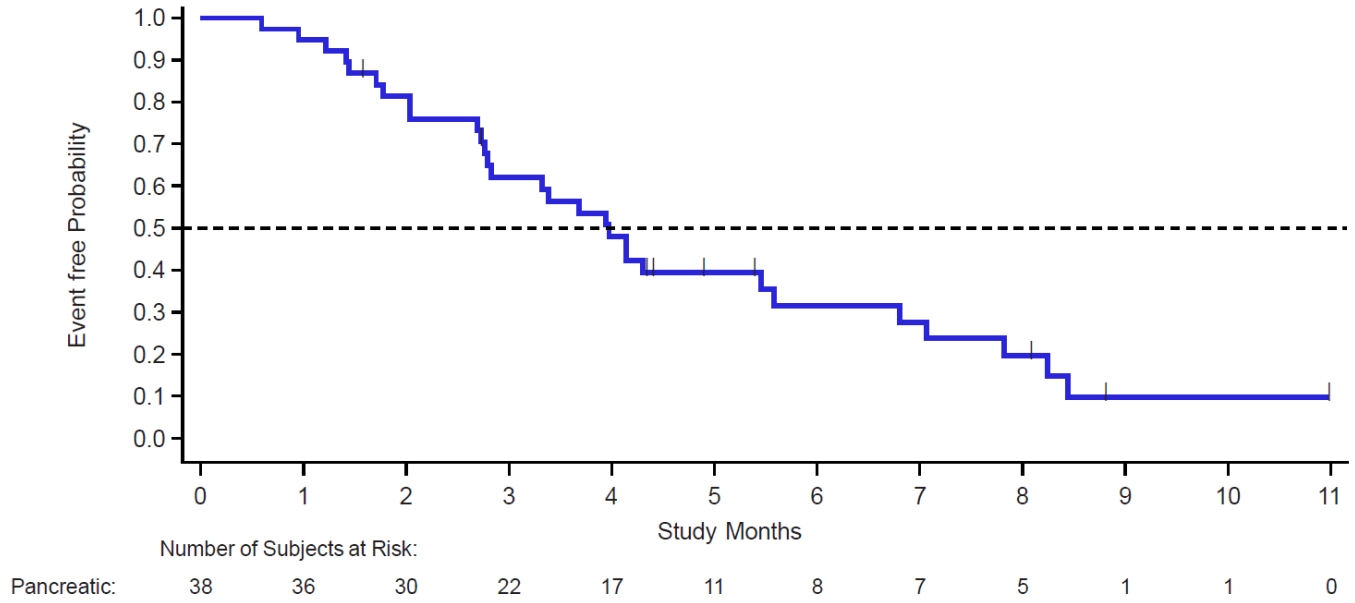
Efficacy outcomes††	Adagrasib monotherapy (n=46) ‡‡	Adagrasib + cetuximab (n=32) §§
Objective response rate, n (%)	10 (22)	12 (43)
Stable disease, n (%)	29 (64)	16 (57)
Disease control rate, n (%)	39 (87)	28 (100)
Median PFS, months (95% CI)	5.6 (4.1–8.3)	NA

*T.

Weiss J, et al. Presented at the European Society for Medical Oncology (ESMO) Congress, 2021.

CodeBreaK 100 – Phase 1/2 pancreatic cancer patients

PFS Kaplan–Meier estimates



Median follow-up: 16.8 months (range: 0.6–16.8)

	Combined Phase 1/2 (N=38)
ORR (CR+PR) Confirmed, n (%) 95% CI*	8 (21.1) (9.55–37.32)
DCR (CR+PR+SD) n (%) 95% Ci*	32 (84.2) (68.75–93.98)
Median PFS Months 95% CI	4.0 (2.8–5.6)
Median OS Months 95% CI	6.9 (5.0–9.1)

Strickler JH, et al. Presented at: ASCO Plenary Series; 2022; Virtual Meeting.

*Data cut-off date: 1 November 2021.

$KRAS^{G12C}$ inhibitor combinations: ongoing trials

$KRAS^{G12C}$ inhibitor combination strategy comparison

Combination	Amgen (sotorasib+)	Mirati (adagrasib+)	Novartis (JDQ433+)	Genentech (GDC6036+)
PD-1i	AMG-404[1] Pembrolizumab[1]	Pembrolizumab[3,4]	Spartalizumab[8]	–
SHP2i	TNO155[1] RMC-4630[1]	TNO155[5]	TNO155[8]	–
Anti-PD-L1 mAb	Atezolizumab[1]	–	–	Atezolizumab[9]
PD-1i + SHP2i	–	–	Spartalizumab + TNO155[8]	–
ALKi	–	–	–	Alectinib[10]
PI3Ki	–	–	–	Inavolisib[9]
Multi-TKI	–	–		Entrectinib[10]
EGFRi	–	–	–	Erlotinib[9]
Anti-EGFR mAb	Panitumumab[1]	Cetuximab[4]	–	Cetuximab[9]
Anti-VEGF mAb	–	–	–	Bevacizumab[9]
Pan-EGFR/Her2i	Afatinib[1]	Afatinib[4]	–	–
CDK4/6i	Palbociclib[1]	?[6]	–	–
SOS1i	BI 1701963[2]	BI 1701963[7]	–	
MEKi	Trametinib[1]	–	–	Cobimetinib, vemurafenib[10]
MEKi & EGFR mAb	Trametinib + panitumumab[1]	–	–	–
EGFR mAb + chemotherapy	Panitumumab + FOLFIRI[1]	–	–	–
VEGF mAb + chemotherapy	Bevacizumab + FOLFIRI/FOLFOX[1]	–	–	–
Chemotherapy	Carboplatin, pemetrexed, docetaxel[1]	–	–	Pemetrexed, cisplatin, carboplatin, gemcitabine, docetaxel[10]

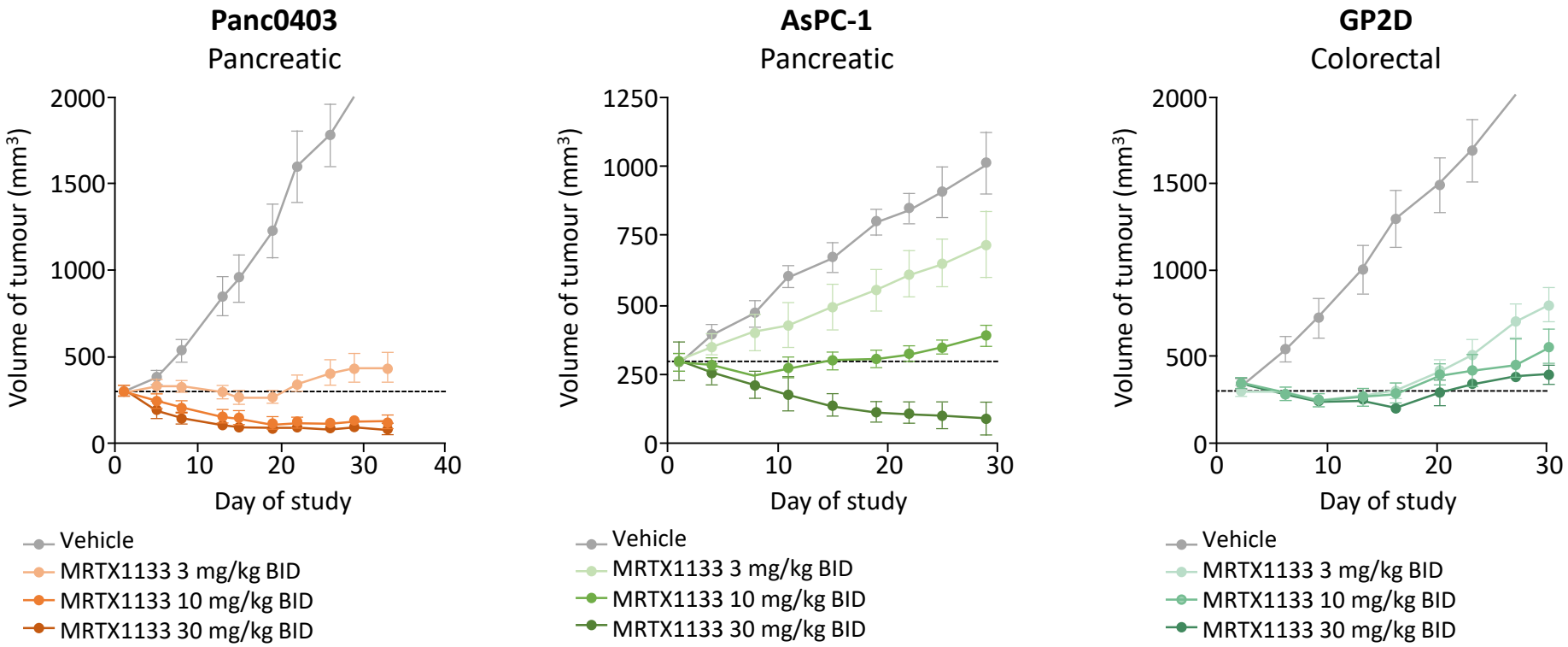
1. ClinicalTrials.gov Identifier: NCT04185883 (accessed June 2022); 2. Boehringer Ingelheim. Press release. Available at: https://www.boehringer-ingelheim.com/press-release/clinical-collaboration-amgen (accessed June 2022); 3 ClinicalTrials.gov Identifier: NCT04613596 (accessed June 2022); 4. ClinicalTrials.gov Identifier: NCT03785249 (accessed June 2022); 5. ClinicalTrials.gov Identifier: NCT04330664 (accessed June 2022; 6. Mirati Therapeutics. Pipeline. Available at: https://www.mirati.com/science/pipeline/ (accessed June 2022); 7. ClinicalTrials.gov Identifier: NCT04975256 (accessed September 2022); 8. ClinicalTrials.gov Identifier: NCT04699188 (accessed June 2022); 9. ClinicalTrials.gov Identifier: NCT04449874 (accessed September 2022). 10. ClinicalTrials.gov Identifier: NCT03178552 (accessed September 2022).

ALK, anaplastic lymphoma kinase; CDK, cyclin-dependant kinase; Her2, human epidermal growth factor receptor 2; i, inhibitor; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

KRAS^{G12D} inhibitors: MRTX1133 (preclinical models)

- MRTX1133 is an investigational, small molecule, KRAS^{G12D} inhibitor[1]

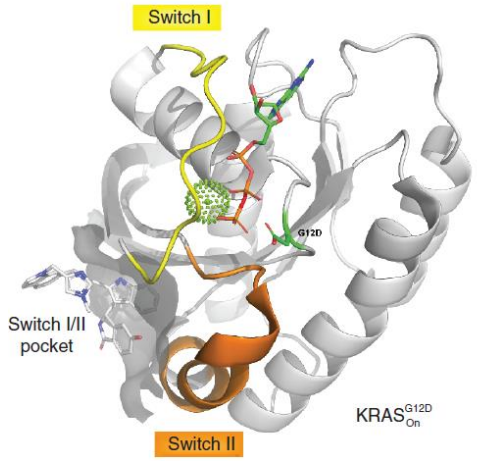
MRTX1133 exhibits anti-tumour activity in pancreatic and CRC preclinical models[2]



1. Wang X, et al. J Med Chem 2022;65:3123–3133; 2. Mirati Therapeutic. Presented at JP Morgan Healthcare Conference 2021; Exhibit 99.1.

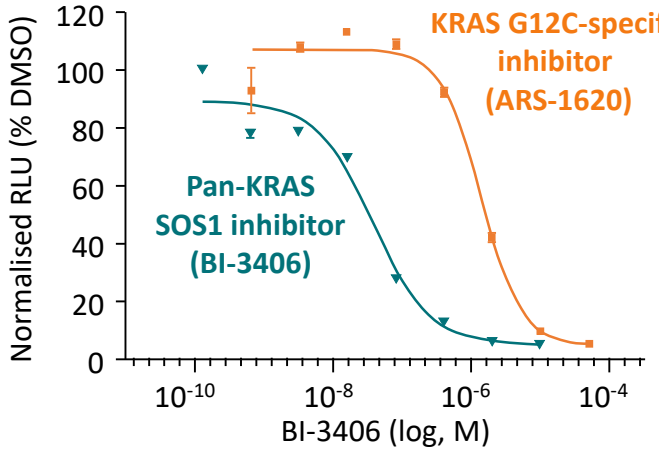
Pan-KRAS and pan-KRAS SOS1 inhibitors (preclinical models)

BI-2852 is a pan-KRAS inhibitor in preclinical development and targets all KRAS isoforms[1,2]

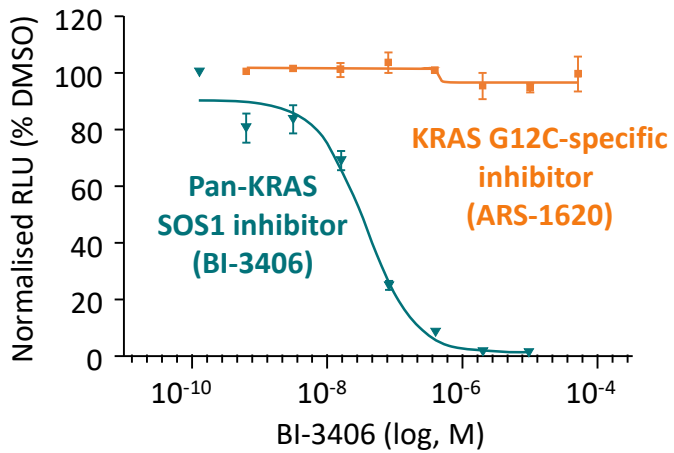


BI-3406 is a highly potent SOS1-specific inhibitor that can target multiple KRAS-mutant oncoproteins

Interaction between **SOS1** and **KRAS G12C**[3]



Interaction between **SOS1** and **KRAS G12D**[3]



Investigations are ongoing that combine inhibition of SOS1 with KRAS^{G12C} inhibitors[4–6]

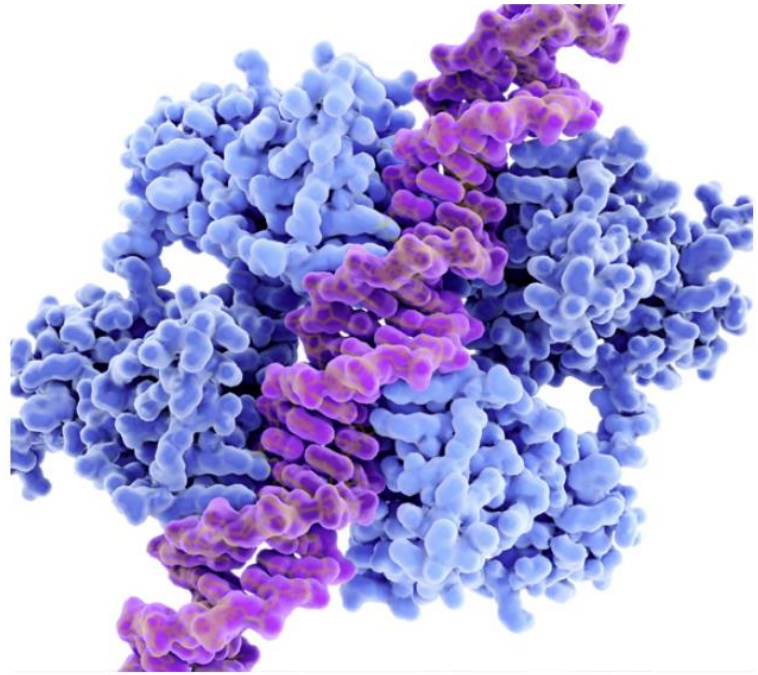
1. Kessler D, et al. Proc Natl Acad Sci USA 2019;116:15823–29; 2. Kessler D, et al. Future Med Chem. 2020;12:1911–23;
3. Hofmann MH, et al. Cancer Discov 2021;11:142–57; 4. ClinicalTrials.gov, NCT04699188. Available at:
https://clinicaltrials.gov/ct2/show/NCT04699188 (accessed June 2022); 5. Boehringer Ingelheim. Press release, 2021. Available at:
https://www.boehringer-ingelheim.com/press-release/clinical-collaboration-amgen (accessed June 2022); 6. ClinicalTrials.gov,
NCT04975256. (accessed June 2022).

DMSO, dimethyl sulphoxide; RLU, relative luminescence unit.

p53 Mutations

p53 Is the Most Frequently Mutated Gene in Cancer, but Can We Target It?

- *P53* is mutated / deleted in 50% of all cancers
- Dysfunction of p53 is a hallmark of many cancers (role in DNA repair, apoptosis, metabolism, cell cycle arrest,….)
- Particularly mutated in some of the most agressive cancers (SCLC, triple neg BC, ovarian cancer, …)



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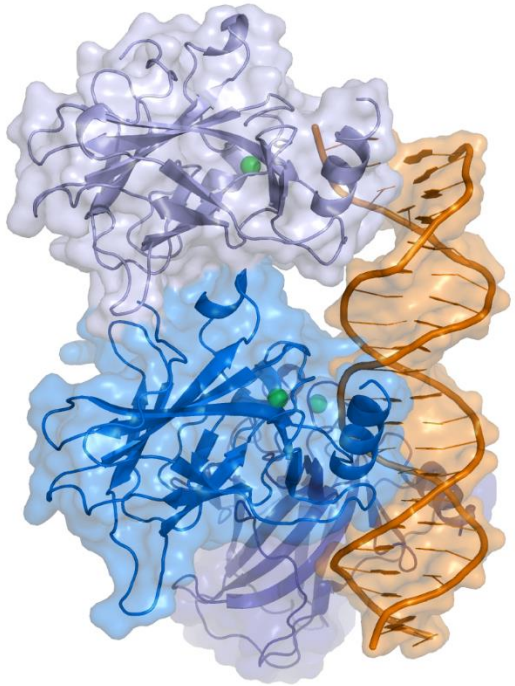
Targeting *p53*

- Challenges
  - Finding a suitable binding site for a Low Molecular Weight drug
  - Location of the mutant p53 (mostly in the nucleus)
  - Multiplicity of different mutations in *p53 (hundreds of diff mutations)*



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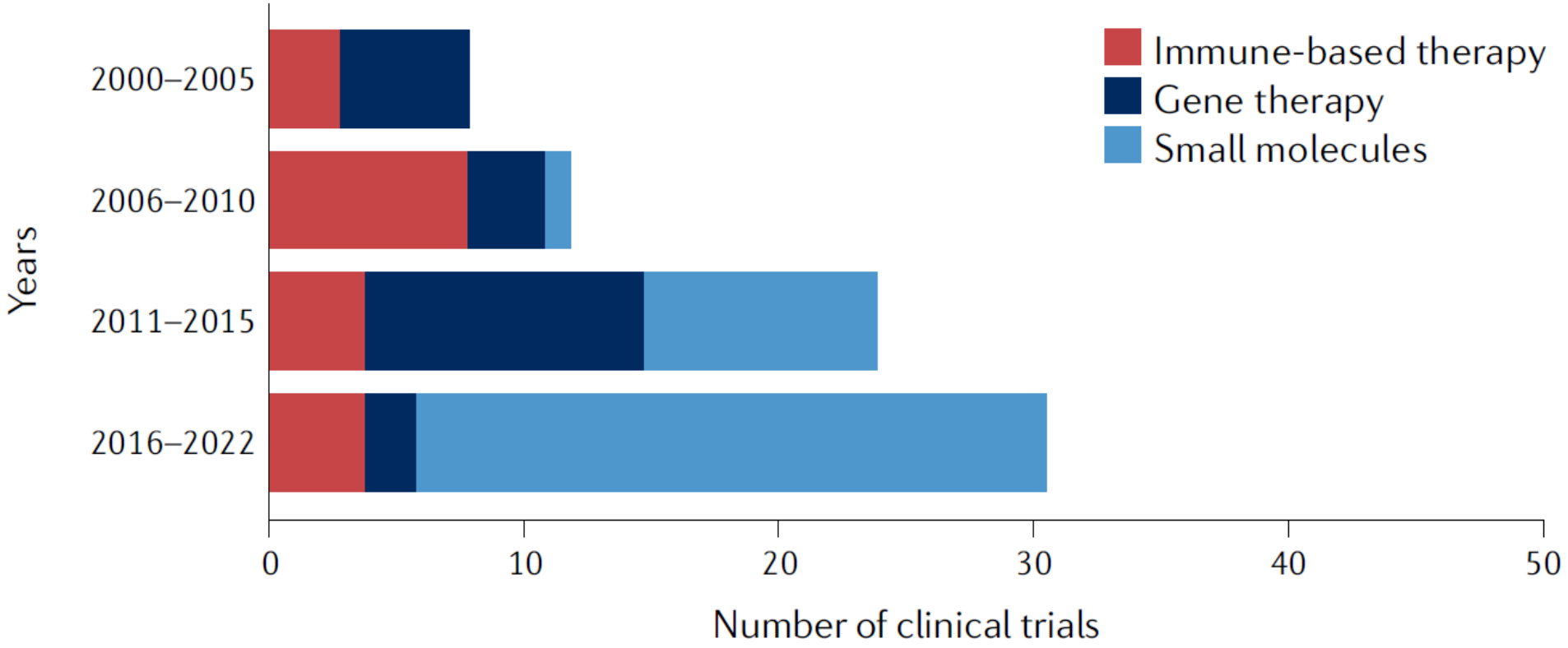


Fig. 2 | **Numbers of p53-targeted clinical trials by year and treatment category.**

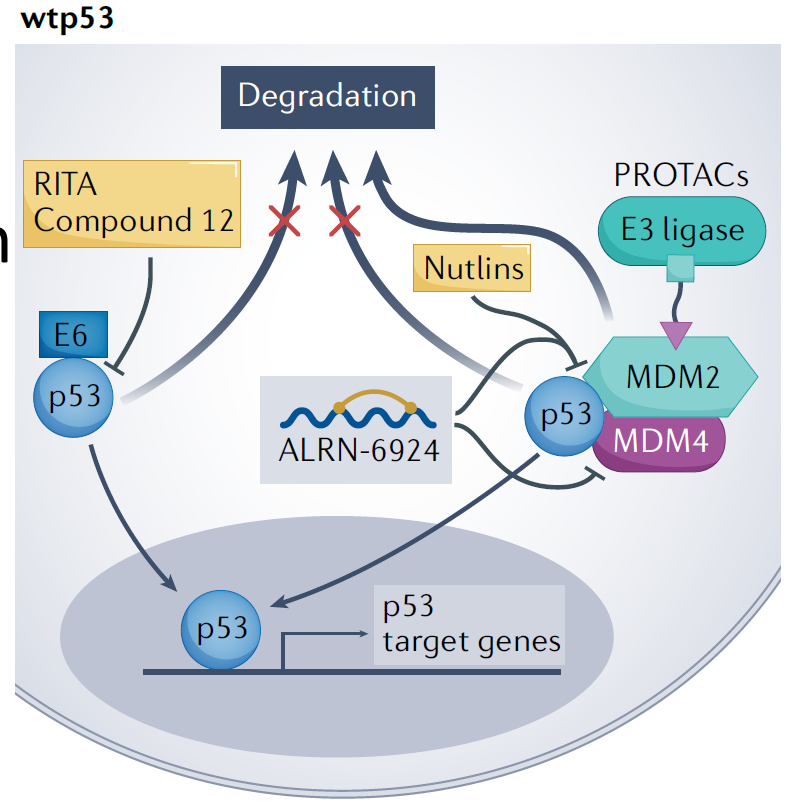
Exploring *p53* targeting strategies

- Prevention of degradation of the wild type p53 (maintaining tumor-suppressive status)
  - MDM2 inhibitors (neg regulator)
  - Dual MDM2-MDM4 inhibitor

- Restoring wild-type function of the mutant protein (Ex. Eprenetapopt (APR146))

- P53 based gene therapy

(wtp53 encoding DNA and RNA can be introduced in cancer cells by for example viruses)



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Exploring *p53* targeting strategies

- Mutant p53 targeting small molecules

2022 ASCO® ANNUAL MEETING

First-in-Human Study of PC14586, a Small Molecule Structural Corrector of Y220C Mutant p53, in Patients With Advanced Solid Tumors Harboring a *TP53* Y220C Mutation

Ecaterina E. Dumbrava,[1] Melissa L. Johnson,[2] Anthony W. Tolcher,[3] Geoffrey I. Shapiro,[4] John A. Thompson,[5] Anthony B. El-Khoueiry,[6] Andrae L. Vandross,[7] Shivaani Kummar,[8] Aparna R. Parikh,[9] Pamela N. Munster,[10] Erika Daly,[11] Laura DeLeon,[12] Megan Khaddar,[12] Kimberley LeDuke,[12] Kimberly Robell,[12] Lisa Sheehan,[12] Meagen St Louis,[12] Amy Wiebesiek,[12] Leila Alland,[12] Alison M. Schram[13]

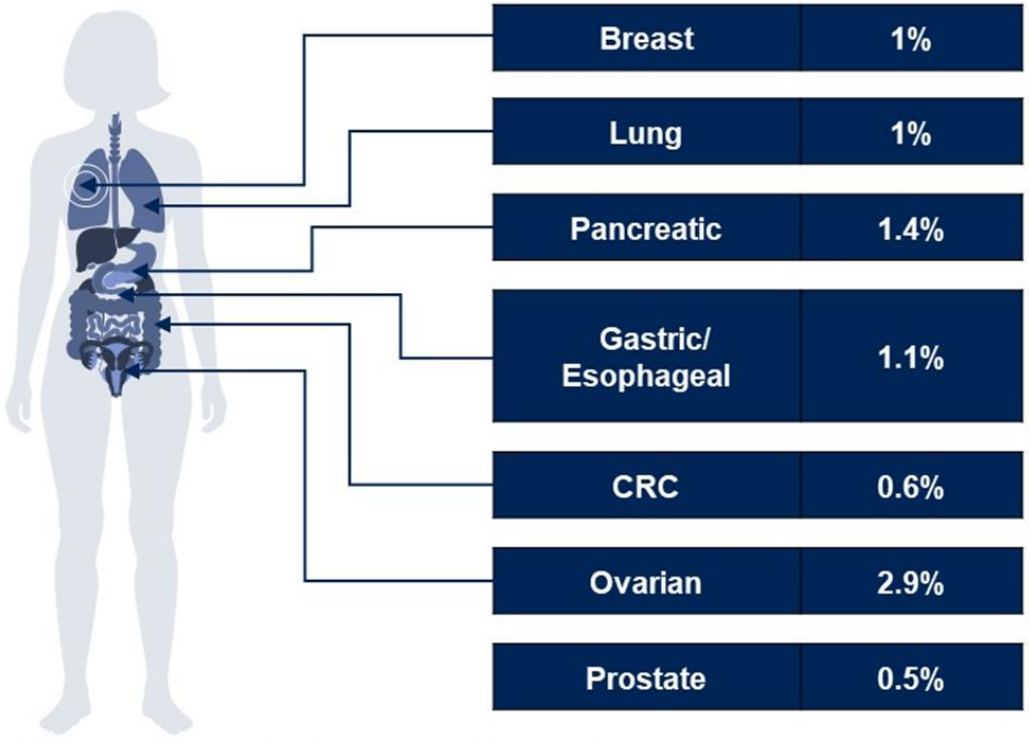
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Sarah Cannon Research Institute, Nashville, TN; [3]NEXT Oncology, San Antonio, TX; [4]Dana Farber Cancer Institute, Boston, MA; [5]Seattle Cancer Care Alliance, Seattle, WA; [6]USC Norris Cancer Center, Los Angeles, CA; [7]NEXT Oncology, Austin, TX; [8]OHSU Knight Cancer Institute, Portland, OR; [9]Massachusetts General Hospital, Boston, MA; [10]University of California, San Francisco, San Francisco, CA; [11]Cytel, Inc., Waltham, MA; [12]PMV Pharmaceuticals, Inc., Cranbury, NJ; [13]Memorial Sloan Kettering Cancer Center, New York, NY.

This work was supported by PMV Pharmaceuticals, Inc., Cranbury, New Jersey, USA

PC14586 is a p53 Y220C-Selective First-in-Class p53 Reactivator

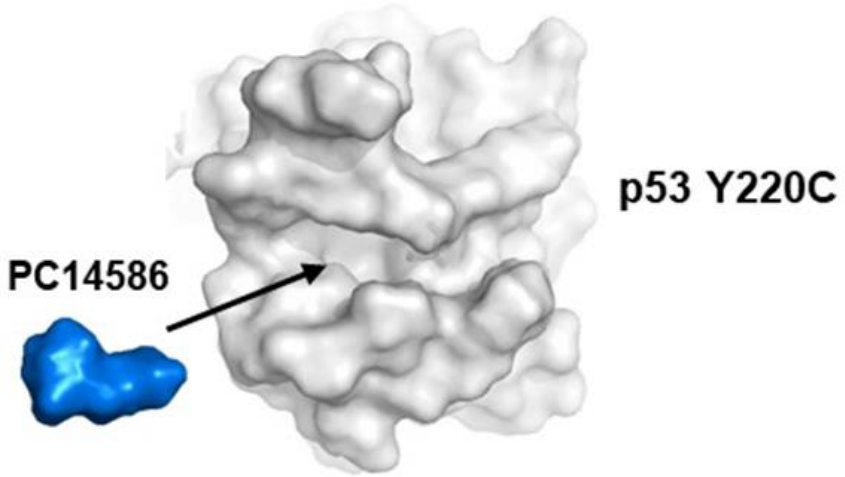
Frequency of *TP53 Y220C* Across Common Solid Tumors

Foundation Medicine Tissue and Heme assay test results collected between 1/1/12 and 12/31/2020



Breast	1%
Lung	1%
Pancreatic	1.4%
Gastric/ Esophageal	1.1%
CRC	0.6%
Ovarian	2.9%
Prostate	0.5%

Stabilizes p53 Y220C mutant in the WT p53 conformation



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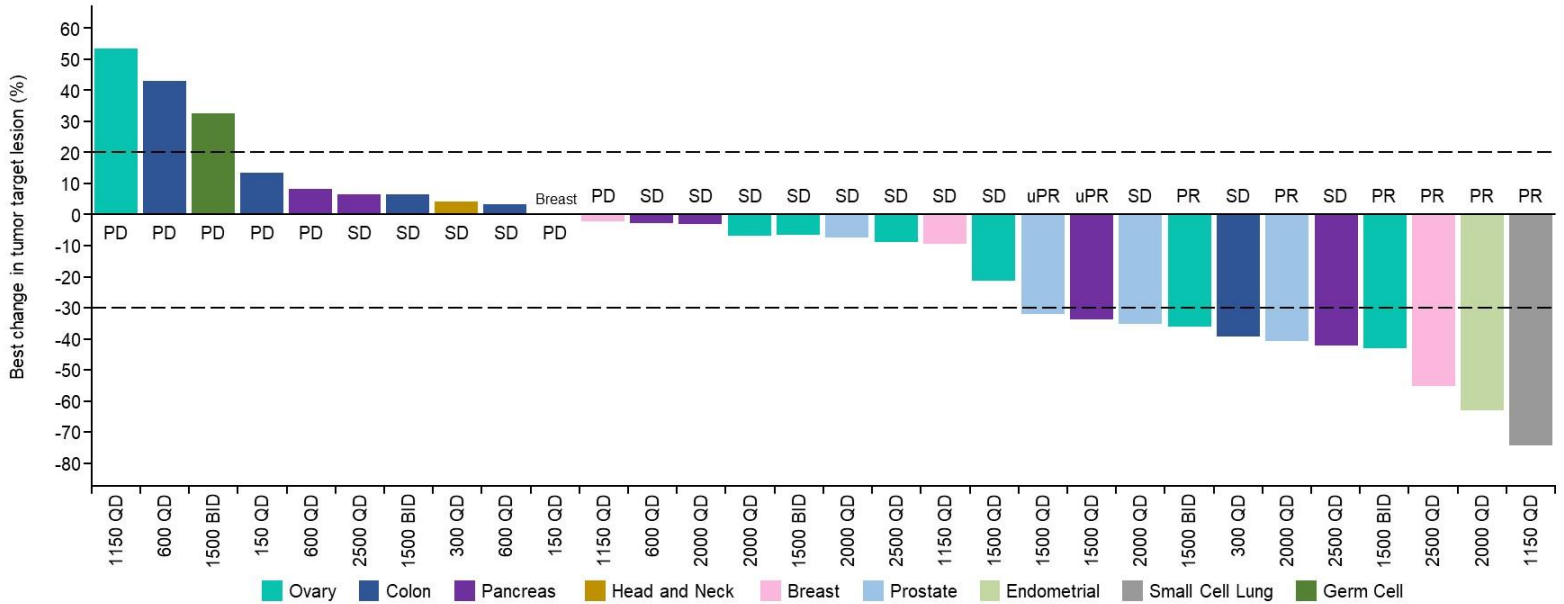
PC14586 is a p53 Y220C-Selective First-in-Class p53 Reactivator

Target Lesion Reduction Across Tumor Types

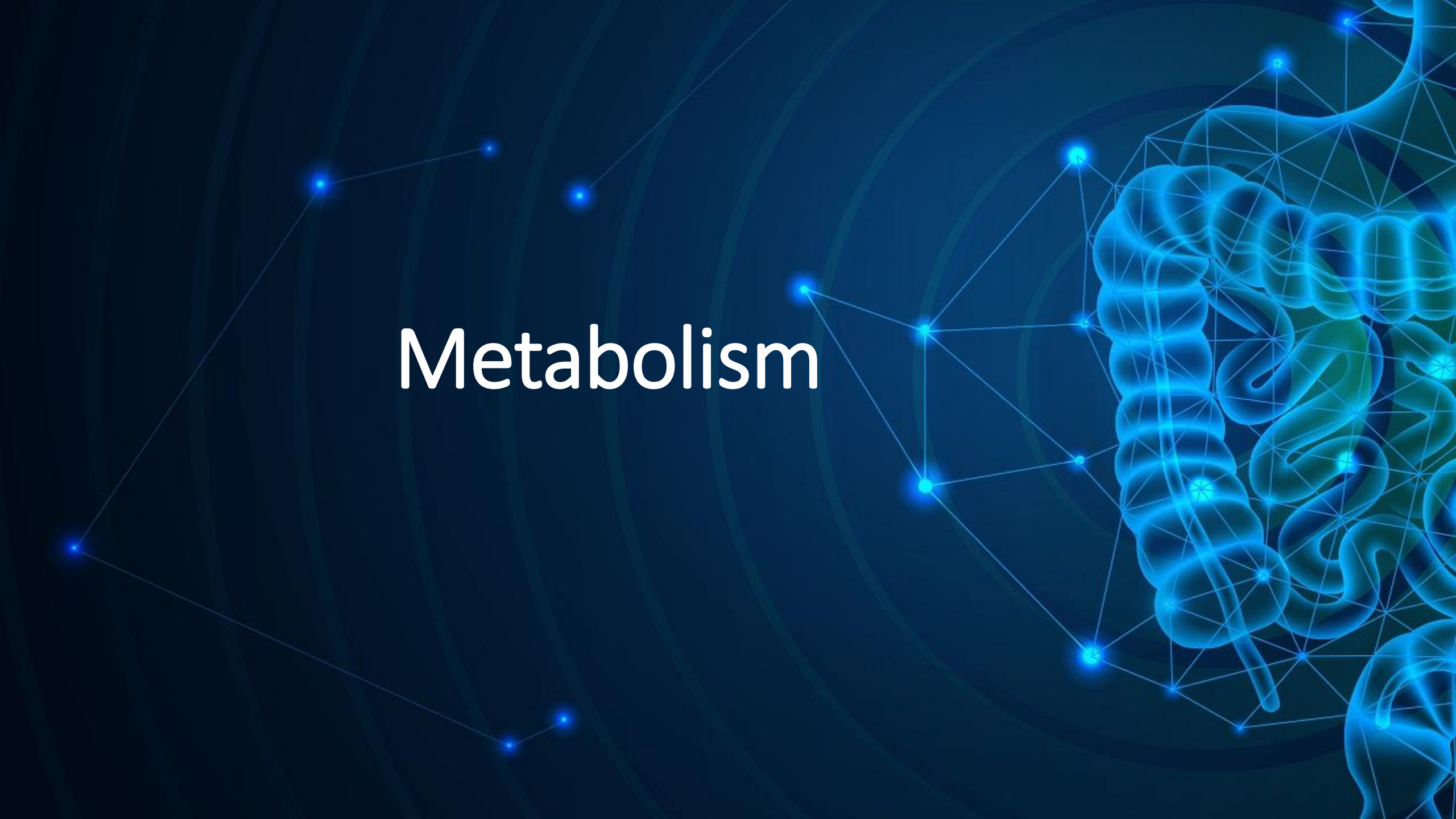


Includes patients with measurable disease and one post-baseline assessment. All doses are in mg. BID, twice daily; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed PR pending confirmation.

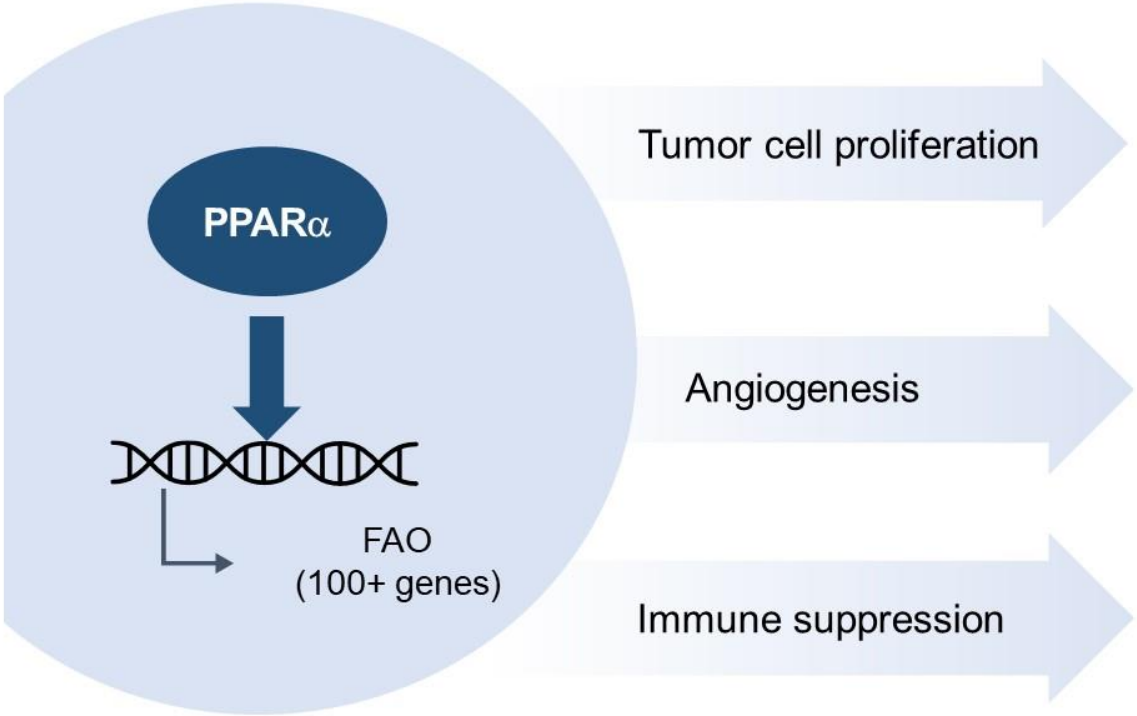
Data cut-off May 10, 2022

- Dose-limiting toxicities reported in 2 patients at 1500 mg BID
  - Grade 3 AST/ALT increase
  - Grade 3 acute kidney injury
- Maximum tolerated dose reached at 1500 mg BID
- RP2D not yet defined

Metabolism

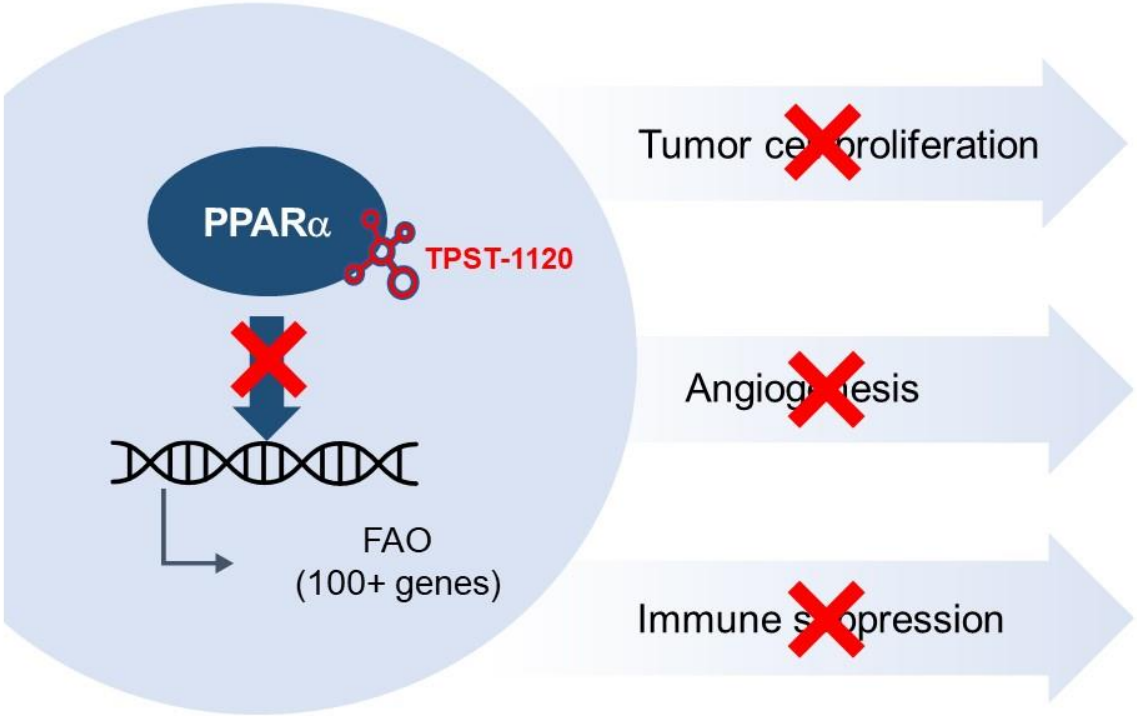


Fatty Acid Oxidation Supports Cancer Progression



- FAO is a key cancer metabolic adaptation that supports tumor growth and metastasis
- FAO is a principal metabolic pathway for immune suppressive cell types and FAO induces angiogenesis
- PPARα is a transcription factor and master regulator of FAO, controlling > 100 lipid metabolism genes
- Inhibiting PPARα to reduce FAO is a promising strategy to inhibit tumor growth and relieve immunosuppression

TPST-1120 – First-in-Class PPARα Antagonist



PPAR Inhibition* IC_{50} (μM)		
Isoform	**Species**	
PPAR-	Human	Mouse
α	**0.052**	**0.42**
β/δ	13	29
γ	33	30

**Luciferase Reporter*

Can we drug the “undruggable”

YES

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