

Targeting the Oncogenic State of RAS: Lessons from Tri-Complex Inhibitors

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Disclosure Information

AACR American Association for Cancer Research Annual Meeting April 17-22, 2026 SAN DIEGO
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Mallika Singh, PhD

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

RAS(ON) Proteins are Key Therapeutic Targets in RAS-Addicted Cancers

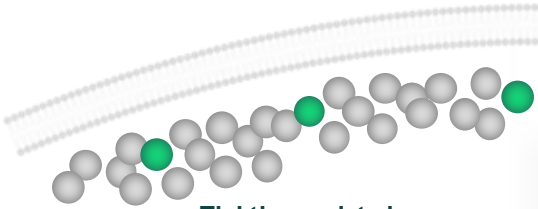
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RAS(OFF)

RAS(ON)

Normal

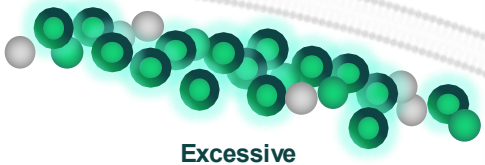
Cell Membrane



Tightly regulated
RAS(ON) proteins control cell growth

RAS-Mutant Cancers

RAS Cancer Mutations



Excessive
RAS(ON) signaling drives uncontrolled cell growth

Oncogenic mutations in **KRAS**, **NRAS** or **HRAS** are common at positions G12, G13 and Q61

>90%(1)
of PDAC

~50%
of CRC

~30%
of NSCLC

(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; PDAC = pancreatic ductal adenocarcinoma

RAS(ON) Multi-Selective Inhibition & Daraxonrasib (RMC-6236) Development

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Hu RAS oncogenes discovered

Discovery of first orally bioavailable RAS(ON) inhibitors

RMC-6236 Ph 1/1b First Patient Dosed

RMC-7977 & RMC-6236 publications

1980s | 1997 | 2013 | 2020 | 2022 | 2023 | 2024 | 2025-present

Discovery of first orally bioavailable RAS(OFF) inhibitors

Kras is essential for embryonic development

AACR: RAS(ON) multi-selective inhibition active and tolerable in nonclinical species

ESMO: Preliminary evidence of daraxonrasib activity and tolerability, first in patients with RAS mutant PDAC & NSCLC

Pivotal Studies

RASolute 302
2L PDAC

RASolve 301
2L NSCLC

RASolute 304
Resectable PDAC

RASolute 303
1L PDAC

RMC-7977 is a tool RAS(ON) multi-selective inhibitor

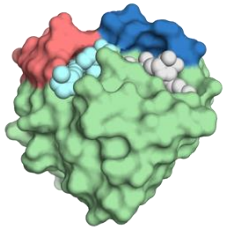
RASolute 302 met all primary and secondary endpoints, including progression free and overall survival, and with no new safety signals

Direct RAS Targeting Strategies

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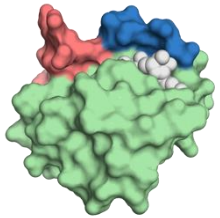
RAS(OFF) Inhibition

RAS^{MUT} (OFF)



SW II pocket binders

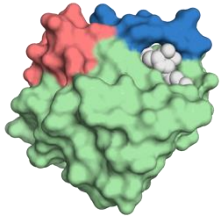
RAS^{MUT} (OFF)



exchange

GAP hydrolysis

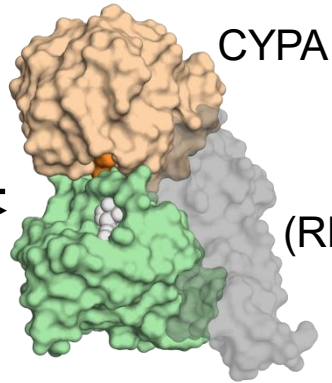
RAS^{MUT} (ON)



RAS(ON) Tri-Complex Acts by Steric Inhibition

RAS^{MUT}(ON) Tri-Complex

TCI



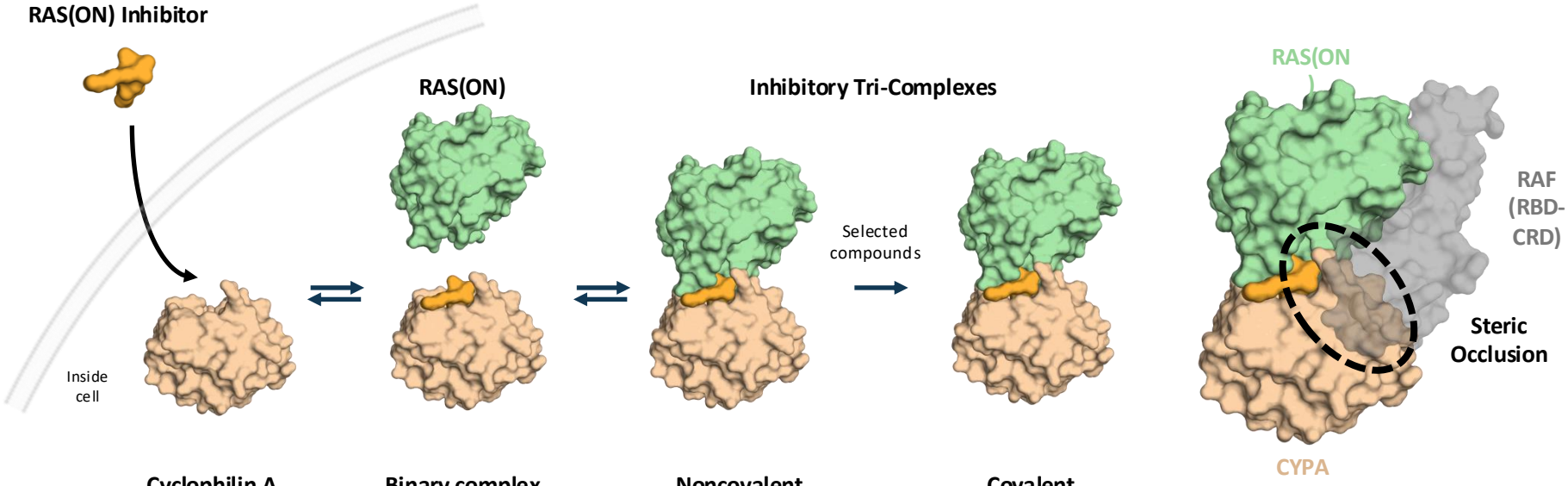
Daraxonrasib also Stimulates GTP Hydrolysis*

Ostrem et al., 2013 Nature
Canon et al., 2019 Nature
Hallin et al., 2020 Cancer Disc
Hallin et al., 2022 Nature Med
Kim et al., 2023 Nature
Maciag et al., 2025 Cancer Disc

Schulze et al., 2023 Science
Holderfield et al., 2024 Nature
Jiang et al., 2024 Cancer Disc
Weller et al., 2025 Science
Edwards et al,., 2025 AACR
*Cuevas-Navarro et al., 2025 Nature

Tri-Complex Platform Enables Selective Targeting of Oncogenic RAS(ON) Proteins

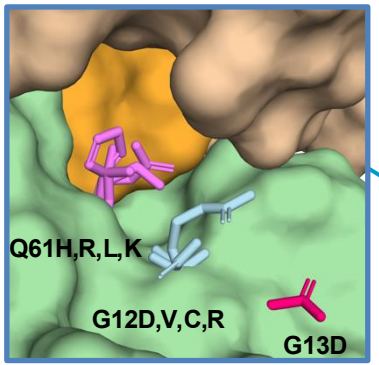
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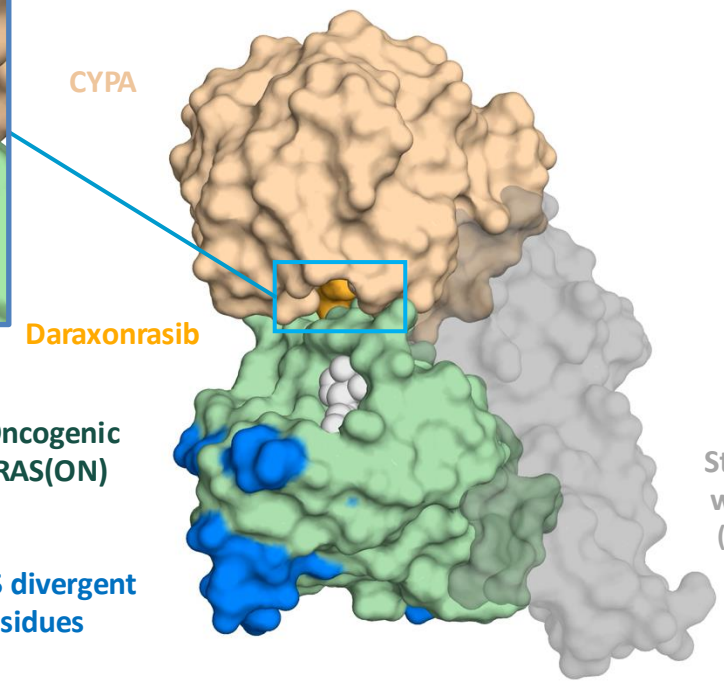


*Clinical stage

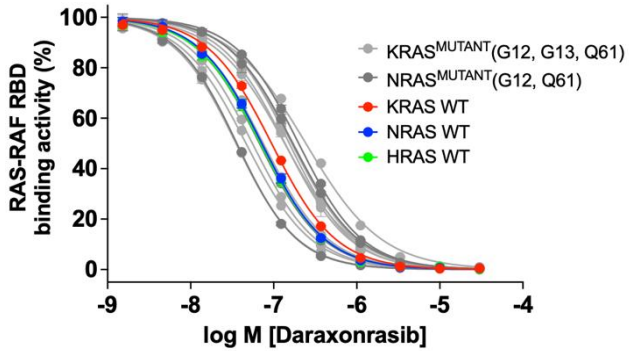
Daraxonrasib (RMC-6236): a RAS(ON) Multi-Selective, Noncovalent, Tri-Complex Inhibitor

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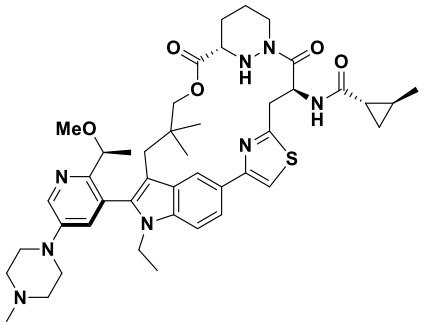




Biochemical (TR-FRET)*



*in presence of 25 µM CYPA

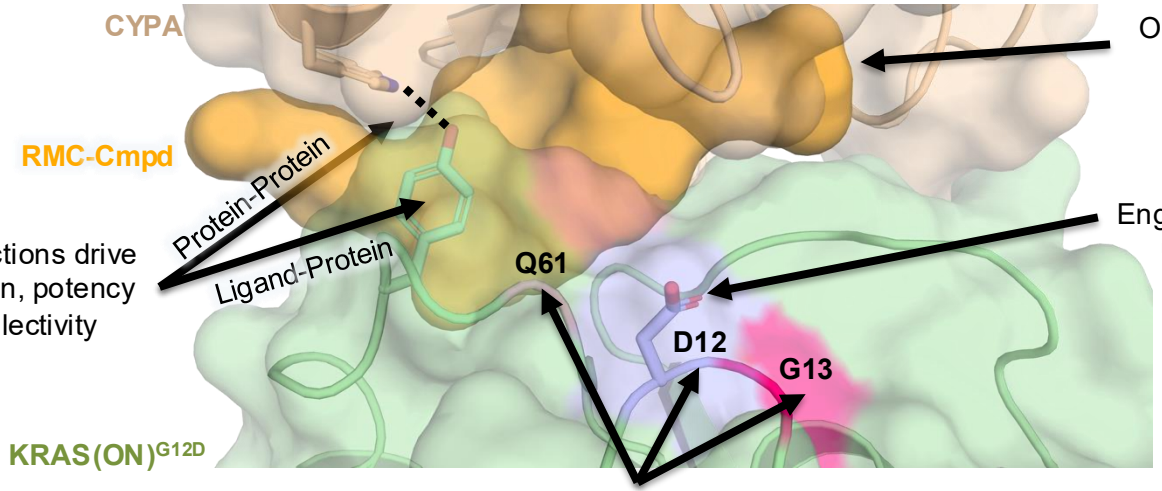


Jiang et al., 2024 Cancer Disc
Cregg et al., 2025 J Med Chem

Using Structure-Guided Design to Build a Diverse Library of RAS(ON) Tri-Complex Inhibitors

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Engineer Binding Site to Modify Potency, Reactivity and Selectivity



Optimize CYPA affinity to enhance potency

Noncovalent interactions drive tri-complex formation, potency and RAS(ON) selectivity

Engineer binding site to facilitate unprecedented covalency

Proximity to oncogenic hotspots to drive mutant-selectivity or accommodate multi-selective inhibitor

RAS(ON) G12C-selective: elironrasib

RAS(ON) G12D-selective: zoldonrasib

Covalent ⟷ **Noncovalent**

RAS(ON) multi-selective: daraxonrasib

RAS(ON) G12V-selective: RMC-5127

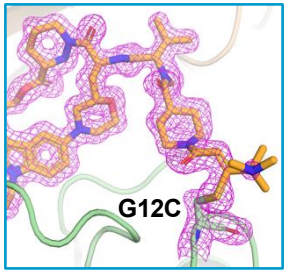
Schulze et al., Science 2023; Holderfield et al., Nature 2024; Jiang et al., Cancer Disc 2024; Weller et al., Science 2025; Cregg et al., J Med Chem 2025 x 2, Edwards et al., AACR 2025

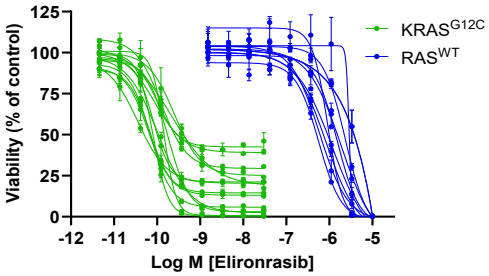
Complementary Investigational RAS(ON) Inhibitors Illustrate Spectrum of Mutant and Wild-Type RAS(ON) Selectivities

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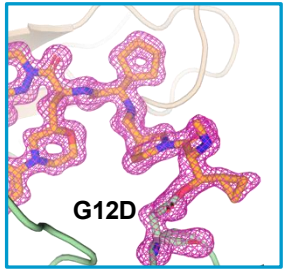
Covalent ← → Noncovalent

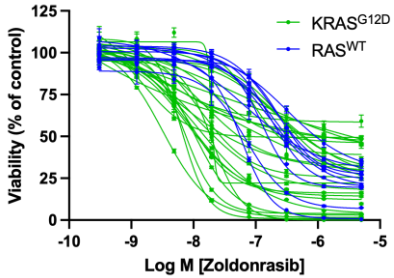
RAS(ON) G12C-selective: elironrasib



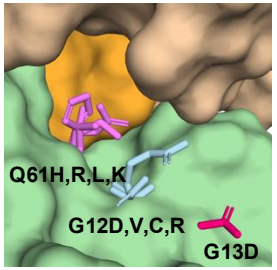


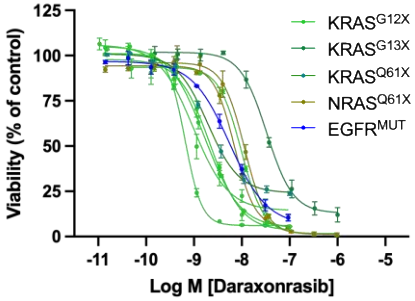
RAS(ON) G12D-selective: zoldonrasib



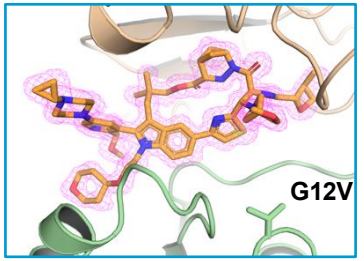


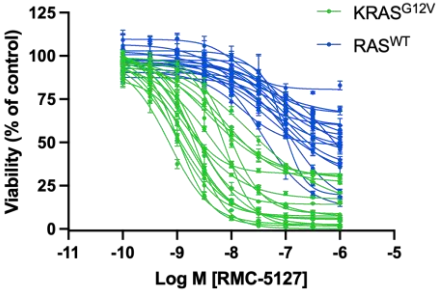
RAS(ON) multi-selective: daraxonrasib





RAS(ON) G12V-selective: RMC-5127

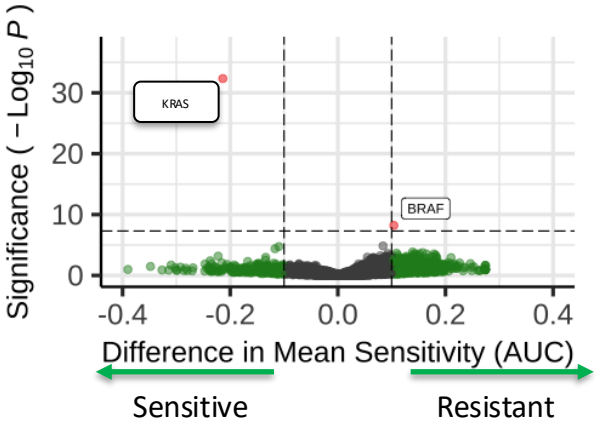




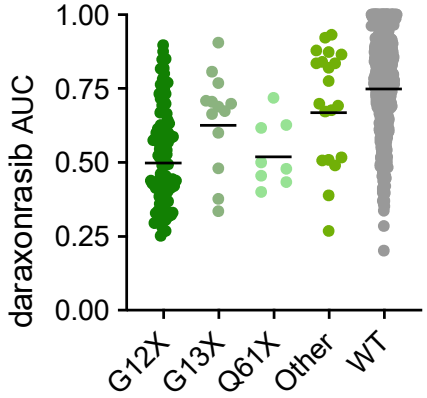
KRAS G12 Mutant Human Cancer Cells are Highly Addicted to KRAS and Sensitive to RAS(ON) Multi-Selective Inhibition

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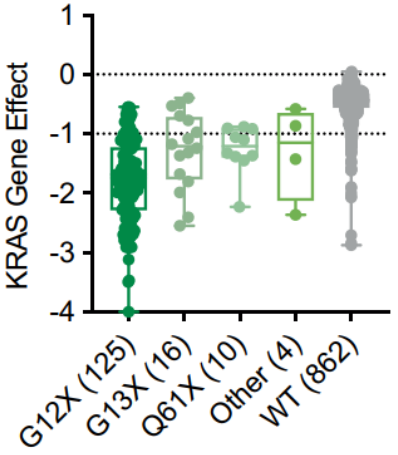
Genetic Features Associated with Daraxonrasib Sensitivity/Resistance



Sensitivity to Daraxonrasib by Mutated KRAS Codon



Genetic Dependency on KRAS, Data from DepMap

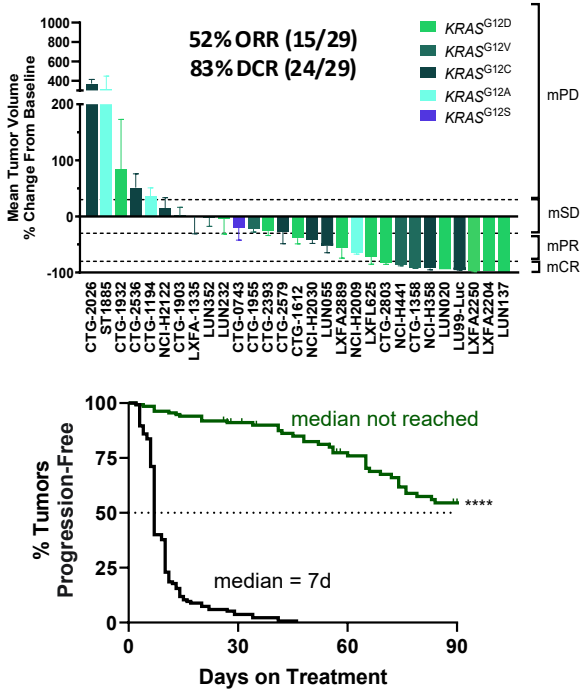


Holderfield et al., 2024 Nature
Jiang et al., 2024 Cancer Disc.

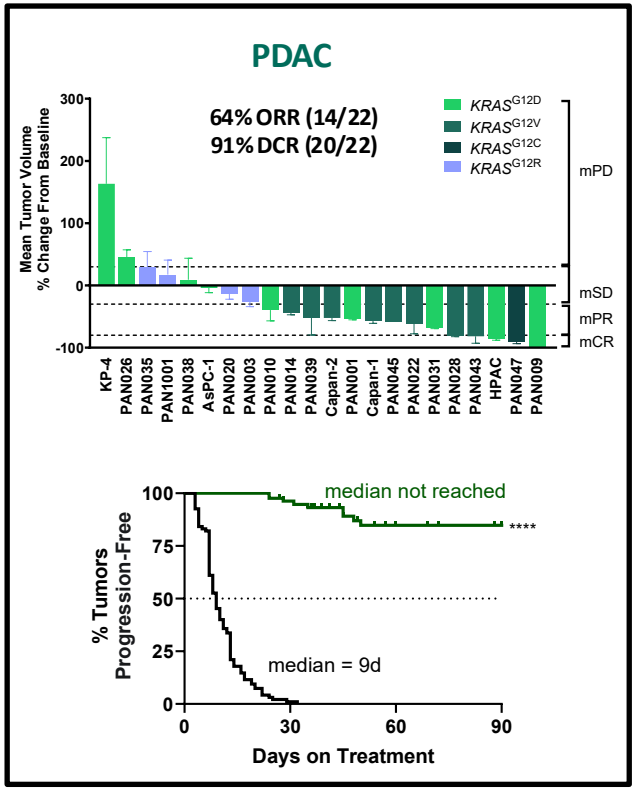
Daraxonrasib Drives Durable Responses and is Well-Tolerated in Models of Major Human Cancers with RAS G12 Mutant Drivers

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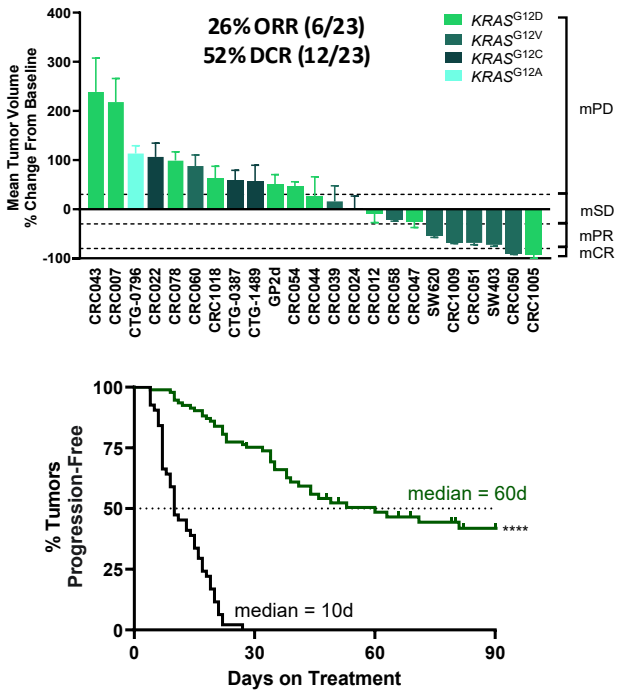
NSCLC



PDAC



CRC



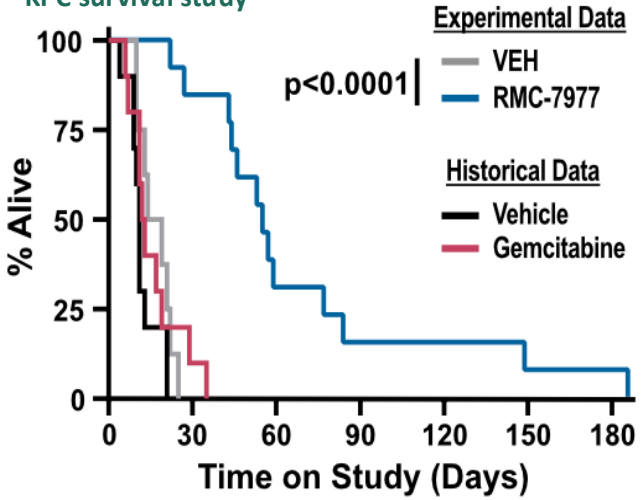
Daraxonrasib dosed at 25 mg/kg po qd; n=1-10/group; Progression defined as tumor doubling from baseline; Responses assigned according to mRECIST

Jiang et al., 2024 Cancer Disc

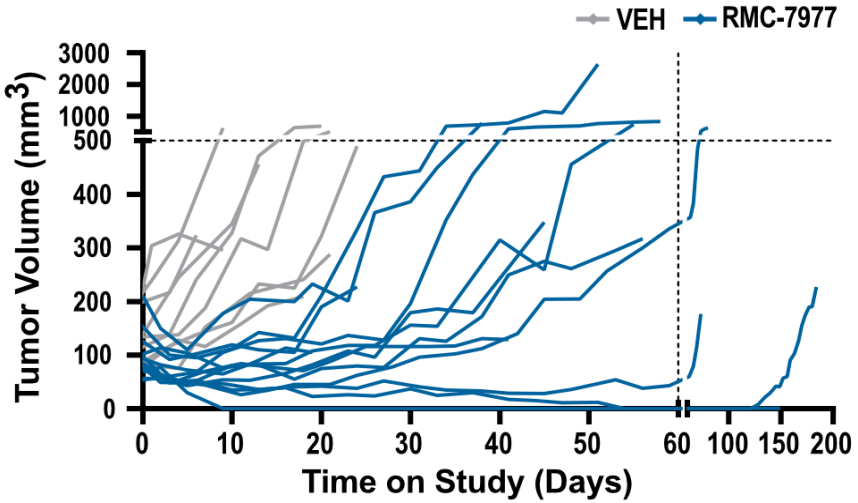
RMC-7977 Extends Overall Survival in the Chemo-Refractory KPC Autochthonous Model

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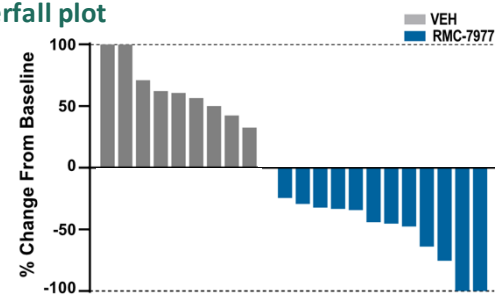
KPC survival study



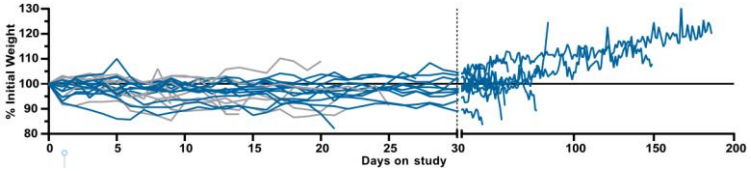
KPC tumor growth curves



KPC waterfall plot



KPC mouse weights



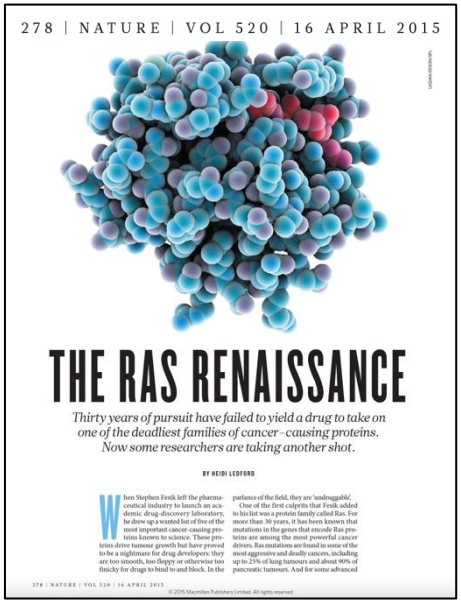
RMC-7977 is a tool RAS(ON) multi-selective inhibitor
Wasko, Jiang et al., 2024, Nature

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Dogma is a Moving Target, About Anti-RAS Therapeutic Strategies

Cambridge Dictionary

Dogma – a fixed belief that people are expected to accept without any doubt.



"Dogma is a moving target"

- Channing Der (2015)

nature chemical biology Volume 20 | October 2024 | 1238–1241

Direct RAS inhibitors turn 10

Jonathan M. L. Ostrem, Ulf Peters & Kevan M. Shokat

"If we are to drug the undruggable targets, it will be essential to continue looking at scientific dogma with a skeptical eye."

Slide Courtesy of Channing Der

Genetic Studies in Mouse Models Suggested that Blocking all RAS Function may be Intolerable

GENES & DEVELOPMENT 11:2468–2481 © 1997

K-*ras* is an essential gene in the mouse with partial functional overlap with N-*ras*

Leisa Johnson,[1] Doron Greenbaum,[1] Karen Cichowski,[1] Kim Mercer,[1,2] Elizabeth Murphy,[1,3] Eric Schmitt,[1] Roderick T. Bronson,[4] Heywood Umanoff,[5] Windfried Edelmann,[5] Raju Kucherlapati,[5] and Tyler Jacks[1,2,6]

Oncogene (1997) 15, 1151–1159

K-Ras is essential for the development of the mouse embryo

Keiko Koera[1], Kenji Nakamura[1], Kazuki Nakao[1], Jun Miyoshi[2], Kumao Toyoshima[2], Toshihisa Hatta[3], Hiroki Otani[3], Atsu Aiba[1] and Motoya Katsuki[1]

STEM CELLS 2016;34:1859–1871

Kras Is Required for Adult Hematopoiesis

ALISA DAMNERNSAWAD,[a] GUANGYAO KONG,[a] ZHI WEN,[a] YANGANG LIU,[a] ADHITHI RAJAGOPALAN,[b] XIAONA YOU,[a] JINYONG WANG,[a] YUN ZHOU,[a] ERIK A. RANHEIM,[c] HONGBO R. LUO,[d] QIANG CHANG,[e] JING ZHANG[a]

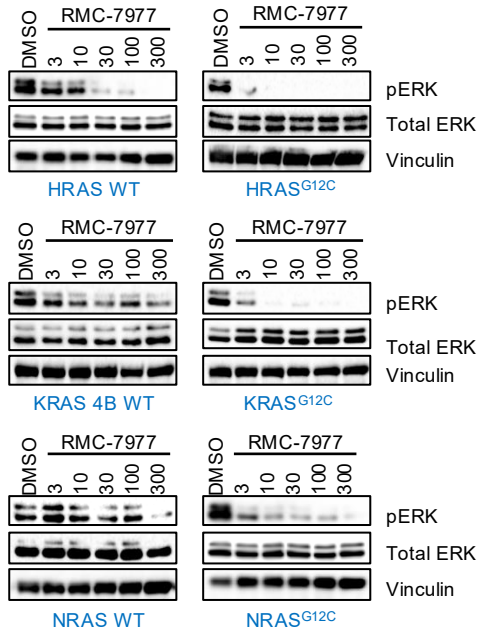
Cell Death and Disease (2019)10:838

Concomitant deletion of HRAS and NRAS leads to pulmonary immaturity, respiratory failure and neonatal death in mice

Rocío Fuentes-Mateos[1], David Jimeno[1], Carmela Gómez[1], Nuria Calzada[1], Alberto Fernández-Medarde[1] and Eugenio Santos[1]

RMC-7977 is a tool RAS(ON) multi-selective inhibitor

RMC-7977 inhibits all RAS isoforms



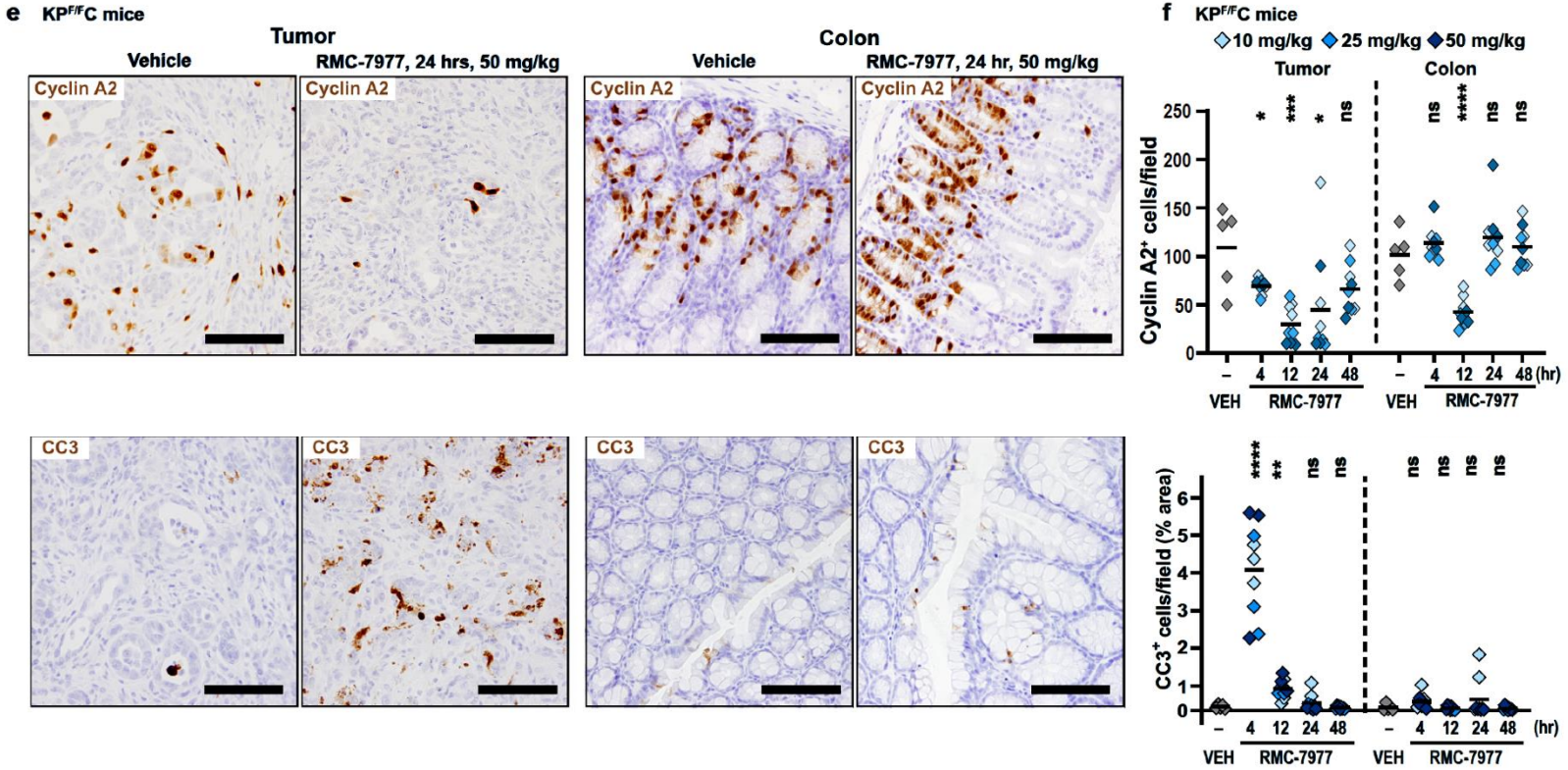
RAS-less MEFs (*Hras*/*Nras*/*Kras* null) ectopically expressing one specific human RAS protein

Holderfield et al., Nature 2024
Andrew Waters, U. Cincinnati

Slide Courtesy of Channing Der

The Dynamics of Cell Proliferation and Apoptosis Following RAS(ON) Inhibition are Different in Tumors & Normal Tissue

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RMC-7977 is a tool RAS(ON) multi-selective inhibitor

Wasko, Jiang et al., Nature 2024

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RMC-6236-001 Study

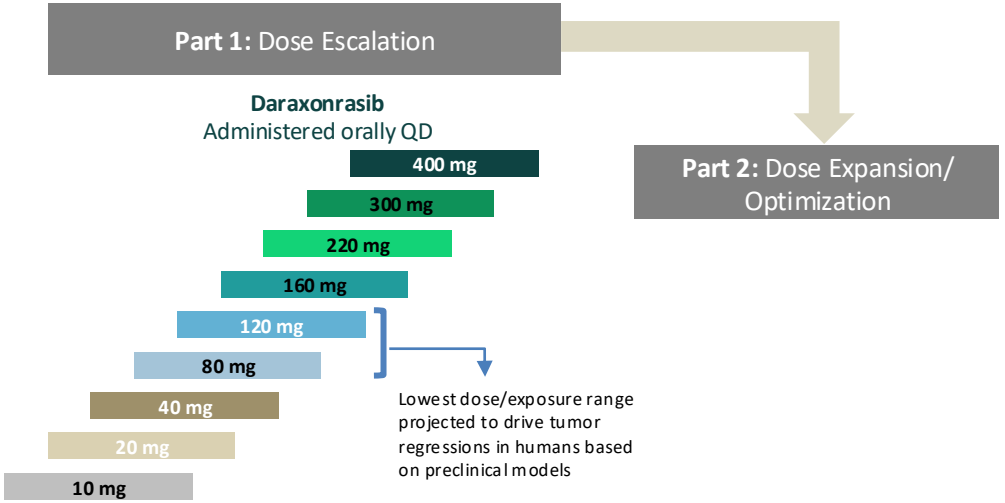
Phase 1/2, Multicenter, Open-Label Study of Daraxonrasib in Patients With Advanced Solid Tumors Harboring Specific RAS Mutations[1-3]

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Key Eligibility Criteria

- Adults (≥18 years) with histologically confirmed advanced solid tumor with specific *KRAS* G12 mutations[a] (dose escalation)
- Previously treated with standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- Adequate organ function

ClinicalTrials.gov: NCT05379985
Sponsor: Revolution Medicines, Inc.



Primary Endpoints

- DLT, safety
- RP2D

Secondary Endpoints

- ORR
- DOR
- DCR
- TTR
- PFS
- PK of daraxonrasib

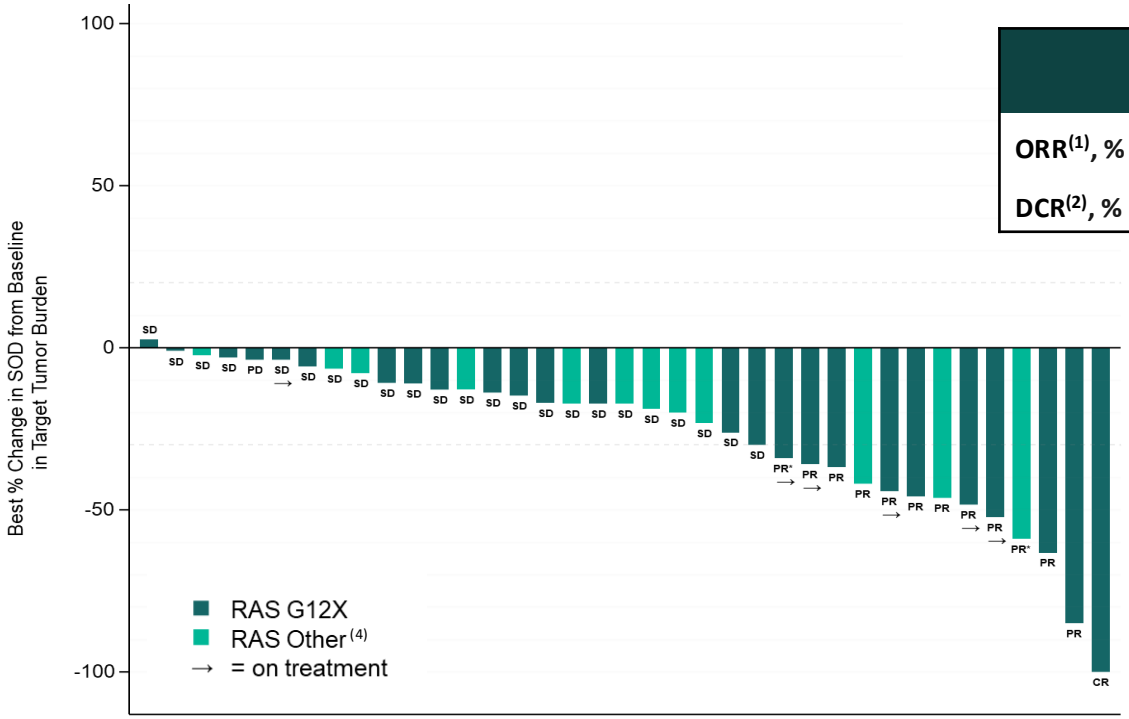
[a]*KRAS* G12 mutations are defined by nonsynonymous mutations in *KRAS* codon 12 (G12); patients with *KRAS* G12C mutations were not enrolled.[2,3]

CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma; mg, milligram; NSCLC, non-small cell lung cancer; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; QD, once daily; *RAS*, rat sarcoma; RP2D, recommended phase 2 dose; TTR, time to response; WT, wild type.

1. ClinicalTrials.gov. NCT05379985. Available at: https://clinicaltrials.gov/study/NCT05379985. Updated November 14, 2024. Accessed October 1, 2025. 2. Punekar SR, et al. Presented at: European Lung Cancer Congress; March 26–29, 2025; Paris, France. Abstract 6MO. 3. Garrido-Laguna I, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 23–25, 2025; San Francisco, CA. Abstract 722.

2L PDAC: Daraxonrasib at 300 mg; Antitumor Activity in Patients with RAS Mutant Tumors

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	RAS G12X N=26	RAS Mutant(4) N=38(3)
ORR(1), % (n)	35% (9)	29% (11)
DCR(2), % (n)	92% (24)	95% (36)

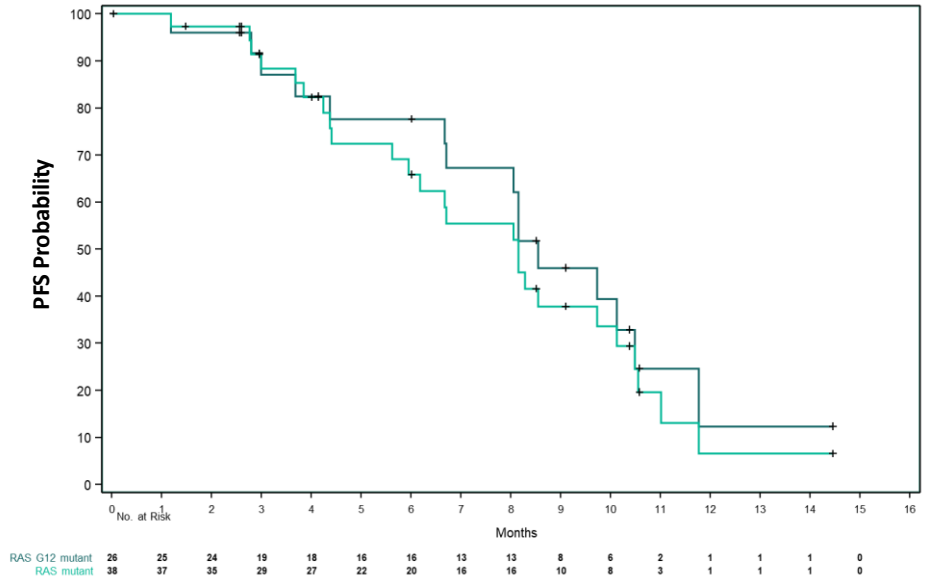
Median (range) follow-up is 16.7 (10.3, 24.6) months and 17.4 (10.3, 24.6) months for RAS G12X and RAS Mutant, respectively. Median duration of response (95% confidence interval) is 8.2 months (3.8, NE) and 8.2 months (3.8, 8.8), respectively. (1) Objective response rate (ORR) (per RECIST v 1.1) includes complete (CR) and partial responses (PR) that were confirmed or still had the potential to confirm. (2) Disease control rate (DCR) includes CR, PR and stable disease (SD). (3) One patient included in the denominator for ORR and DCR calculations is not displayed on waterfall and treated as a non-responder for purposes of the ORR and DCR calculations due to lack of post-baseline target lesion assessment. (4) RAS Mutant or RAS Other defined as patients with G12X, G13X or Q61X PDAC.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; PR*, unconfirmed partial response; RECIST, response evaluation criteria in solid tumors.

Data cutoff: June 30, 2025

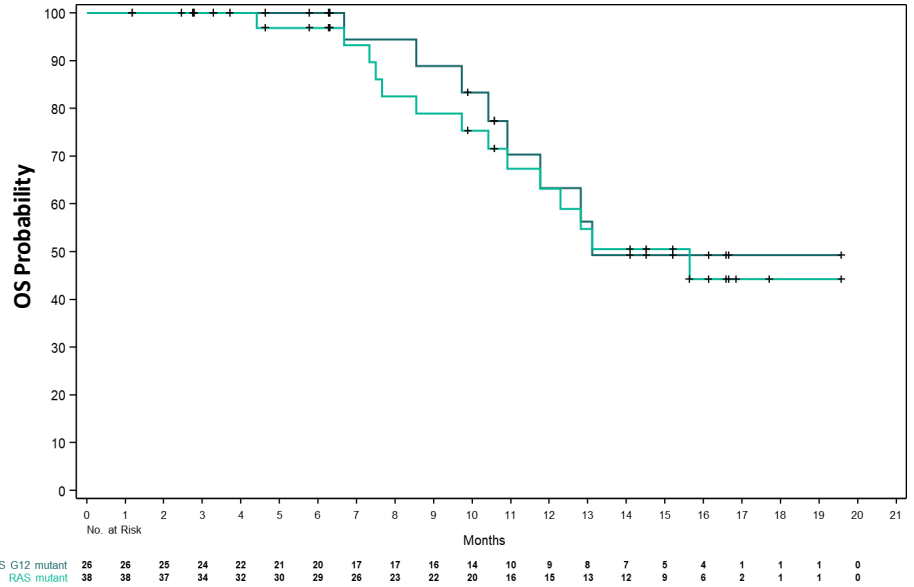
2L PDAC: Daraxonrasib at 300 mg; Progression-Free Survival and Overall Survival

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	Median PFS, Months (95% CI)
RAS G12X	8.5 (6.7, 10.5)
RAS Mutant	8.1 (5.9, 10.1)



	Median OS, Months (95% CI)
RAS G12X	13.1 (10.9, NE)
RAS Mutant	15.6 (10.9, NE)



Median (range) follow-up is 16.7 (10.3, 24.6) months and 17.4 (10.3, 24.6) months for RAS G12X and RAS Mutant, respectively. 2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not estimable.

Data cutoff: June 30, 2025

Safety Profile of Daraxonrasib at 300 mg Daily in Patients with 2L+ PDAC

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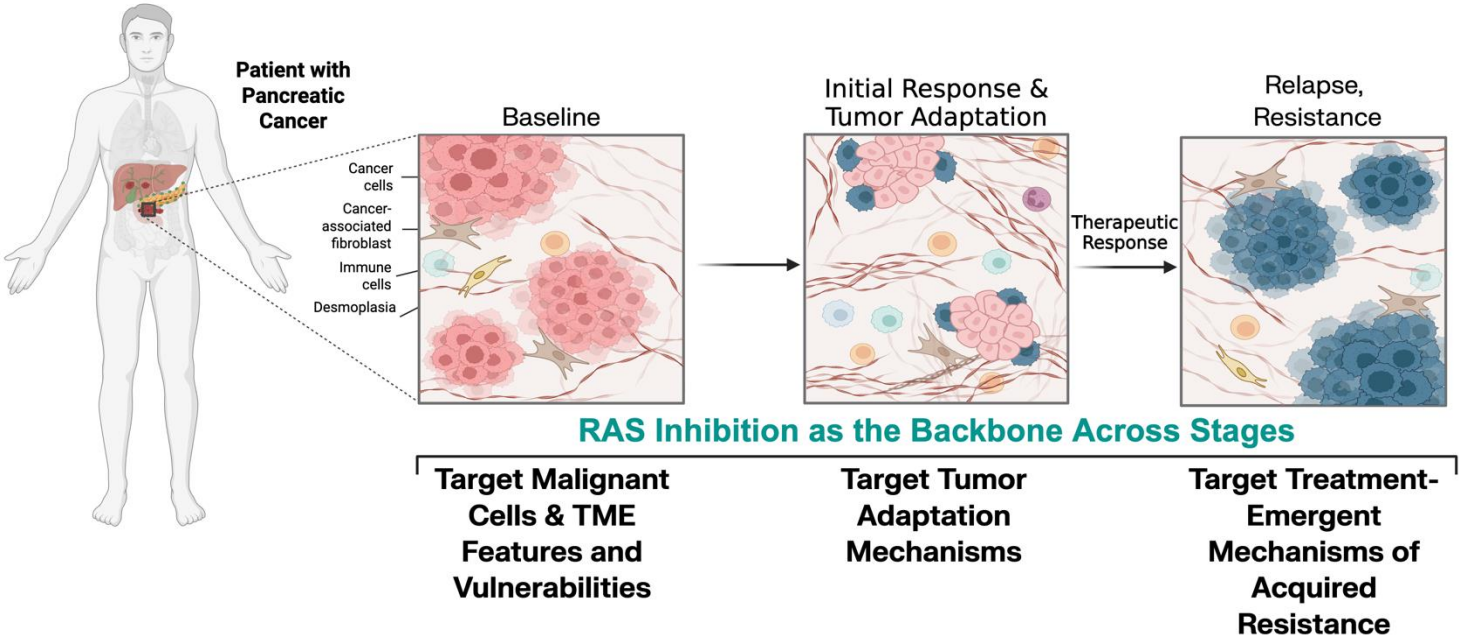
	N=83	
	Any Grade	**Grade ≥3**
Patients with Any TRAE, N (%)	80 (96%)	28 (34%)
TRAEs occurring in ≥15% of patients, N (%)		
Rash*	75 (90%)	6 (7%)
Stomatitis/mucositis*	45 (54%)	3 (4%)
Diarrhea	43 (52%)	3 (4%)
Nausea	32 (39%)	0
Vomiting	30 (36%)	0
Paronychia	15 (18%)	0
Fatigue	14 (17%)	1 (1%)
Other select TRAEs, N (%)		
Platelet count decreased	8 (10%)	3 (4%)
AST increased	8 (10%)	3 (4%)
Anemia	7 (8%)	6 (7%)
ALT increased	6 (7%)	2 (2%)
Neutrophil count decreased	5 (6%)	3 (4%)

*Bundled term comprising multiple MedDRA preferred terms (PTs).
2L+. second line and beyond; PDAC, pancreatic ductal adenocarcinoma; TRAE, treatment-related adverse event; ALT, alanine transaminase.; AST, aspartate transaminase.

Data cutoff: June 30, 2025

Key Combination Opportunities for Treating RAS-Driven Cancers

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Each stage of the treatment journey represents different and overlapping combination opportunities

Targeting concepts courtesy of Andy Aguirre

Figure created in BioRender

Doubling Down on RAS: Complementary RAS(ON) Inhibitors Designed for Monotherapy and Combination Strategies Against RAS-Addicted Cancers

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RAS Multi-Selective

- Monotherapy with broad potential for RAS-addicted cancers
- Backbone of RAS(ON) inhibitor doublets with mutant-selective RAS(ON) inhibitors
- Targeted agent for SOC combinations, including immunotherapies

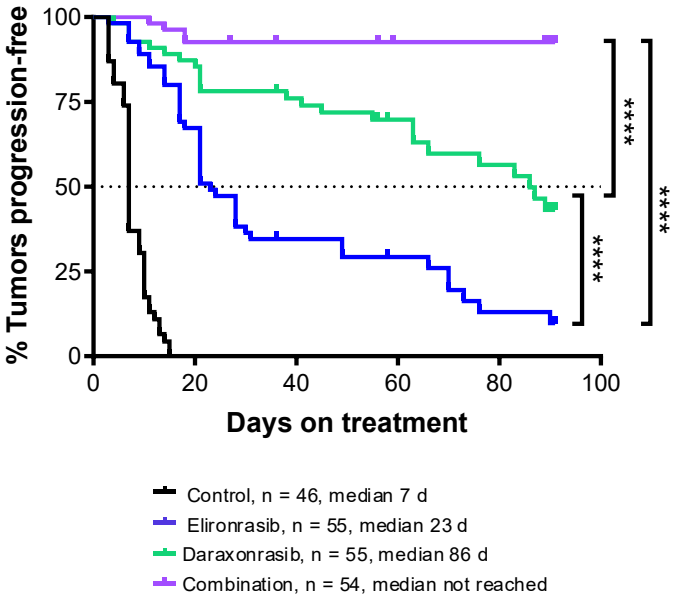
RAS Mutant-Selective

- Alternative monotherapy approaches
- Complementary to RAS multi-selective inhibitor in RAS(ON) inhibitor doublets
- Differentiated targeted agent profiles for SOC combinations, including immunotherapies

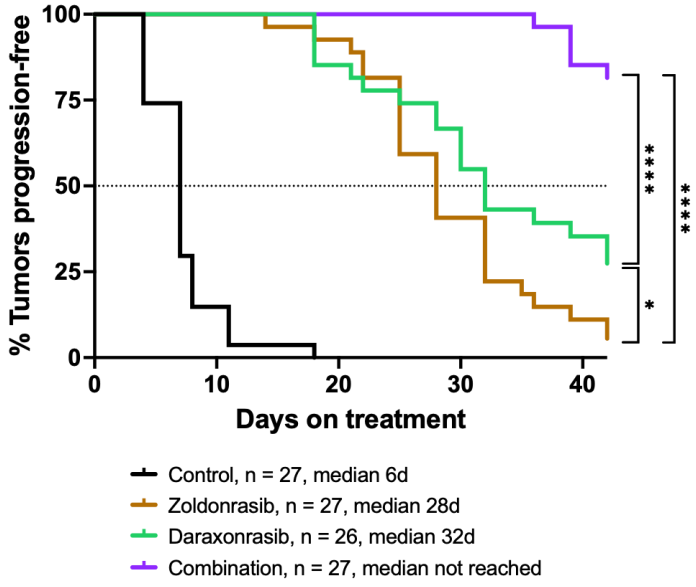
RAS(ON) Inhibitor Doublets with Daraxonrasib Provide Durable Responses in Preclinical Models

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KRAS^{G12C} NSCLC Xenograft Models



Kras^{G12D} PDAC Allograft Models



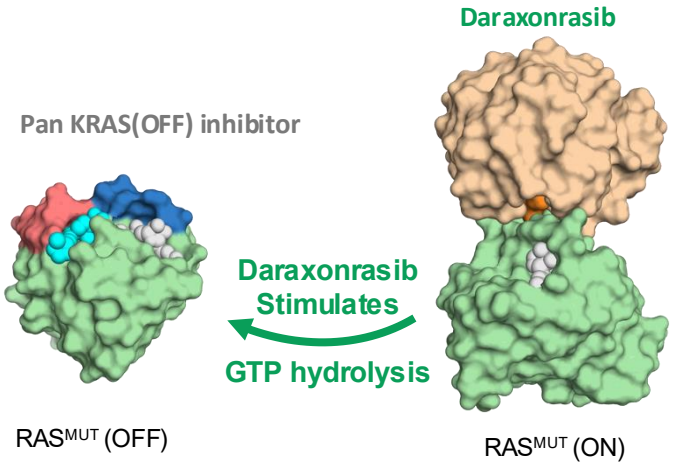
Wei et al., 2026, Cancer Discovery (left); ENA 2025 (right)
8 xenografted models with elironrasib dosed at 100 or 200 mg/kg PO QD; daraxonrasib dosed at 25 mg/kg PO QD; Combination: elironrasib 30, 100 or 200 mg/kg PO QD + daraxonrasib 25 mg/kg PO QD.
3 allograft models with Zoldonrasib dosed at 100 mg/kg PO QD; daraxonrasib dosed at 25 mg/kg PO QD; combination: zoldonrasib 100 mg/kg PO QD + daraxonrasib 25 mg/kg PO QD.
Log-rank test *P < 0.05; ****P < 0.0001

Foundation for the 1L PDAC trial RASolute 309 Daraxonrasib + Zoldonrasib

RAS(ON) Multi-Selective and pan KRAS(OFF) Inhibitor: Cooperative Trapping Drives Deep and Durable Responses in Preclinical Models

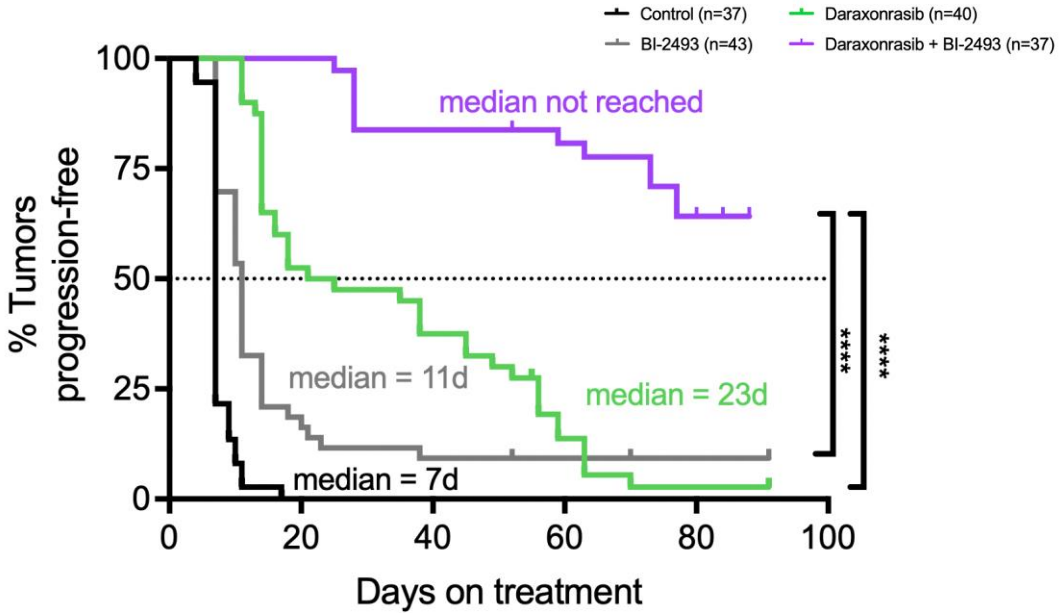
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Complementary Mechanisms of Action



In collaboration w Ryan Corcoran and lab

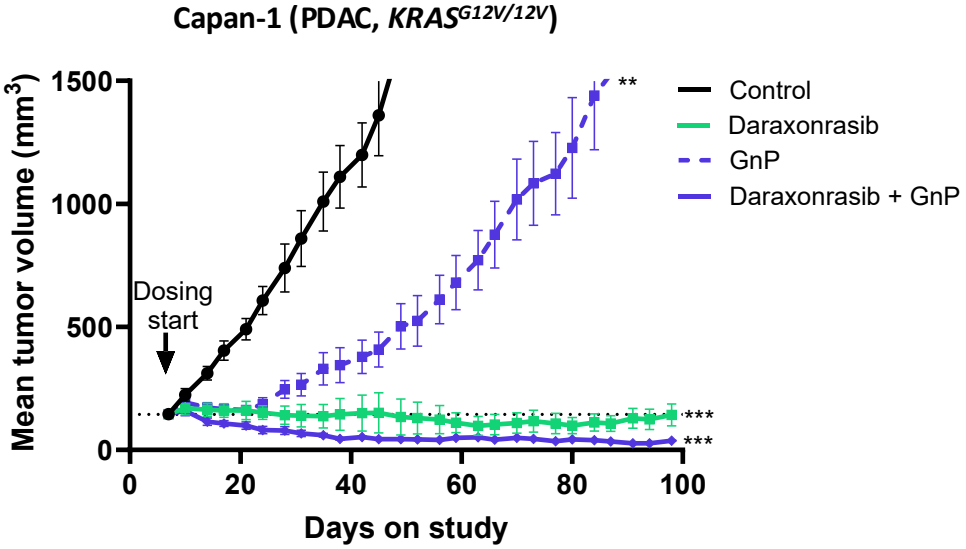
Durability in KRAS G12 Models Including KRAS amp

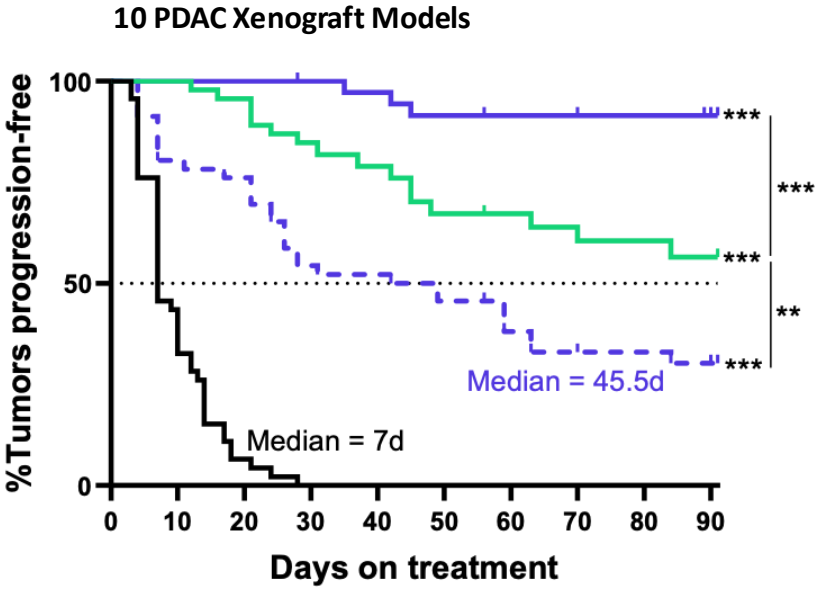


- 8 xenograft models tested with KRAS G12D, V, R and C mutations. Log-rank test ****P < 0.0001
- BI-2493 is a panKRAS(OFF) inhibitor dosed at 90 mg/kg po bid as a monotherapy and 30 mg/kg po bid in combination
- HPAF-II study (9 mice) dosed with daraxonrasib 5 mg/kg in combo; all others at 10 mg/kg
- See also Pfaff & Shokat, 2026, bioRxiv

Foundation for 1L PDAC Trial RASolute 303: Daraxonrasib alone or with GnP Improved Depth & Durability of Responses in Preclinical Models

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Daraxonrasib was dosed at 25 mg/kg PO QD; GnP: gemcitabine 50 mg/kg ip q3d + nab-paclitaxel 250 mg/kg iv qw;
Right panel: ** p<0.01, *** p<0.001 , two-way ANOVA repeat measures
Left pane: 10 PDAC models (7 KRASG12X, 3 KRASWT) were included in the K-M plot. Log-rank test **P < 0.01; ***P < 0.001

Key Themes

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- Direct RAS(ON) inhibitors are in development with potential as therapeutic backbone(s) for RAS-addicted cancer treatment
- Investigational RAS(ON) inhibitors, as monotherapy and in combinations, are being evaluated in earlier lines of therapy
- Tumor adaptation and acquired monotherapy resistance to RAS(ON) inhibition converge on RAS pathway reactivation thus far
- Preclinical data demonstrate that combinations with RAS(ON) inhibitors as a backbone can abrogate resistance via deeper pathway inhibition, targeting emergent vulnerabilities, maximizing cytotoxicity, and engaging the immune system
- Additional modalities and combination candidates such as T-cell engagers for covalent-haptenated peptides, bi-specifics, ADCs and KRAS degraders are emerging

Acknowledgements

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- The patients, their families, and investigators who are making clinical evaluation of RAS(ON) inhibitors possible

- Key research collaborators
  - Ken Olive and colleagues, Columbia University
  - Andy Aguirre and colleagues, DFCI and Broad PRISM Team, Broad Institute
  - Ben Stanger, Bob Vonderheide, Timour Baslan, U Penn
  - Kian-Huat Lim, Wash U
  - Channing Der and colleagues, UNC

- Revolution Medicines Research and Development Teams

Revolution Medicines Presentations

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Title	Presenter	Day	Time	Session
Preclinical Disclosures				
RAS(ON) Inhibition in both Cancer and Immune Cells by Daraxonrasib Drives Anti-Tumor Immunity	Nataliya Shifrin	Monday, April 20th	2:00 PM–5:00 PM	Immune Mechanisms Invoked by Other Therapies and Exposures
Discovery of a New Class of Mutant-Targeted Catalytic RAS(ON) Inhibitors with Retained Antitumor Activity in Setting of Emergent Resistance due to Elevated RAS Flux	Jan Smith	Tuesday, April 21st	2:30 PM–4:30 PM	Targeted Protein Degradation and Non-canonical Oncogenic Signaling
RAS(ON) Multi-Selective Inhibitors Stimulate the Hydrolysis of RAS-GTP to RAS-GDP and Drive Synergistic Combination Benefit with KRAS(OFF) Inhibitors in G12 Mutant Tumors	Kyle Seamon	Tuesday, April 21st	2:00 PM–5:00 PM	Mechanisms of Anticancer Drug Action
Clinical Disclosures				
Preliminary Safety and Clinical Activity of Zoldonrasib (RMC-9805), an Oral, RAS(ON) G12D-Selective, Tri-complex Inhibitor in Patients with KRAS G12D Non-Small Cell Lung Cancer (NSCLC)	Jonathan Riess	Sunday, April 19th	1:00 PM–3:00 PM	Clinical Trials Plenary 1: New Frontiers in Precision Oncology
Daraxonrasib plus Chemotherapy (CT) as First-Line (1L) Treatment for Patients (Pts) with Metastatic Pancreatic Adenocarcinoma (mPDAC)	Brian Wolpin	Tuesday, April 21st	2:00 PM–5:00 PM	Late-Breaking Research: Clinical Research 3
Daraxonrasib Monotherapy as First-Line (1L) Treatment for Patients with Metastatic Pancreatic Adenocarcinoma (mPDAC)	Eileen O'Reilly	Tuesday, April 21st	2:00 PM–5:00 PM	Late-Breaking Research: Clinical Research 3
RASolve 301: A Phase 3 Study of Daraxonrasib (RMC-6236) vs. Docetaxel in patients with previously treated RAS-mutant NSCLC	Ferdinandos Skoulidis	Tuesday, April 21st	9:00 AM–12:00 PM	Late-Breaking Research

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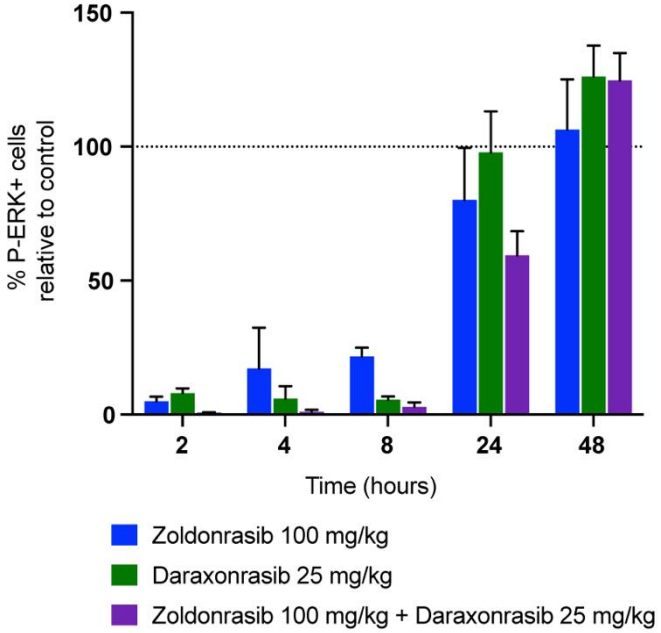
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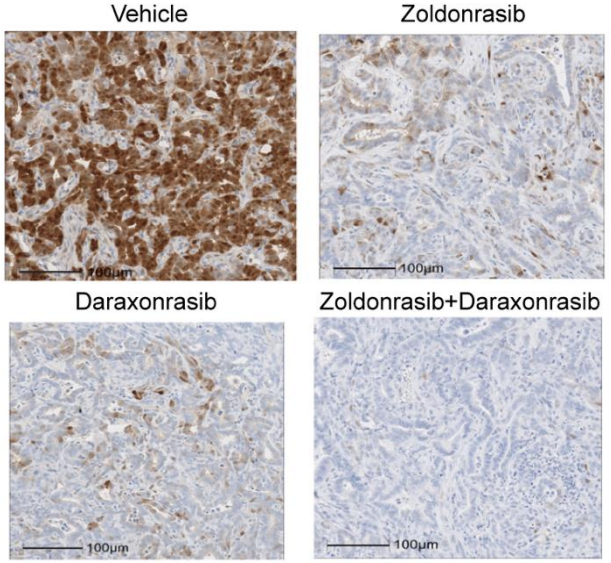
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Deep RAS Pathway Suppression with RAS(ON) Inhibitor Doublet in a GEMM-Derived Model of KRAS G12D Mutant PDAC

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KPCYc3 (*Kras^{G12D}*, *Trp53^{R172H}*, PDAC)

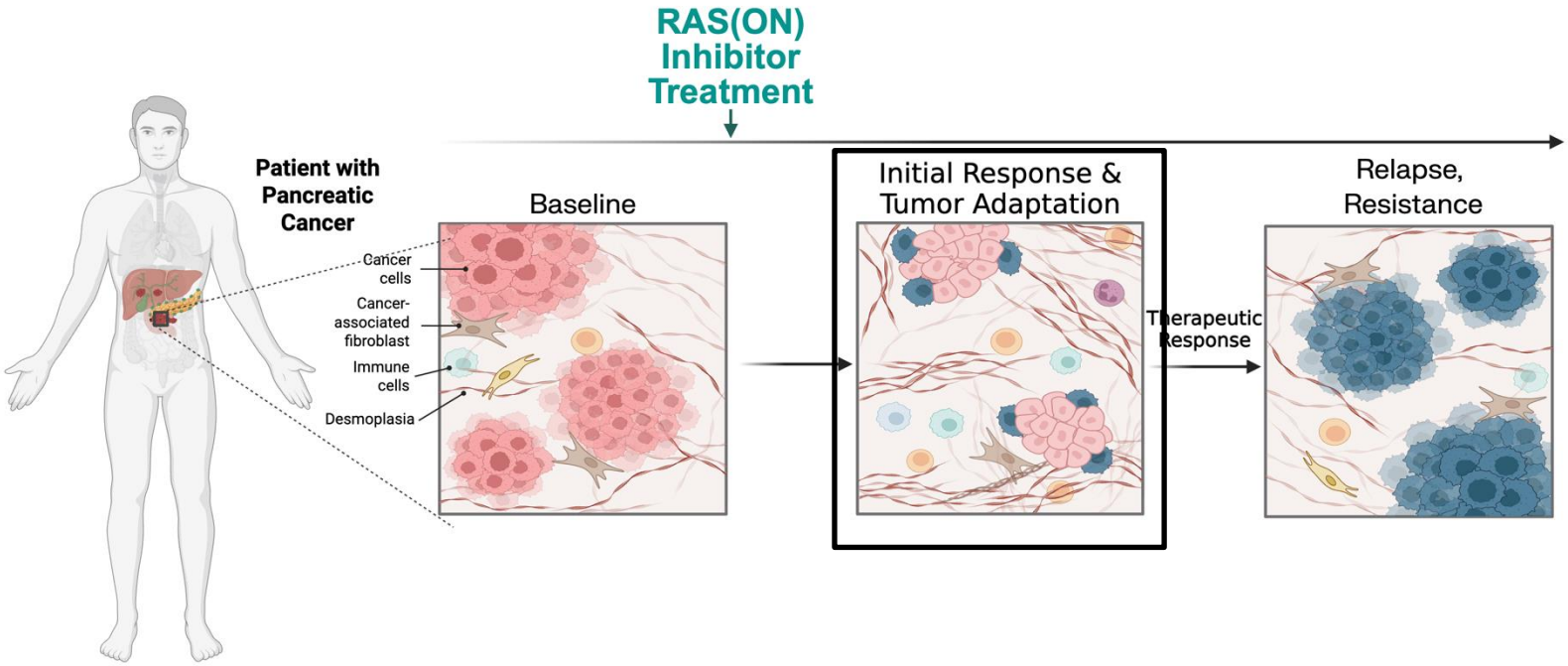




p-ERK 4h post-dose

A Conceptual Framework for Tumor Adaptation and Acquired Resistance to RAS Inhibition in PDAC

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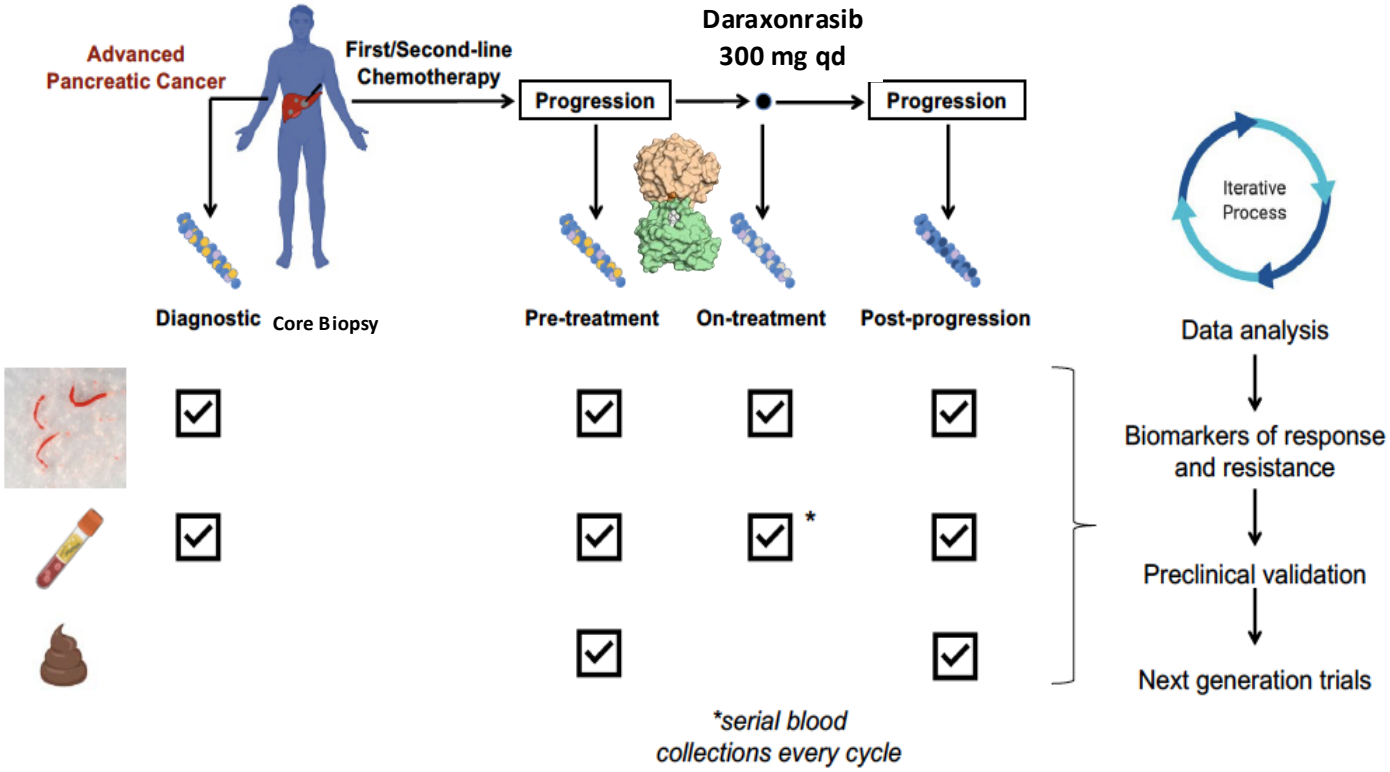


Each stage of the treatment journey represents different and overlapping combination opportunities

Figure created in BioRender

A Translational Platform to Interrogate the Effects of RAS(ON) Inhibition in Tumors

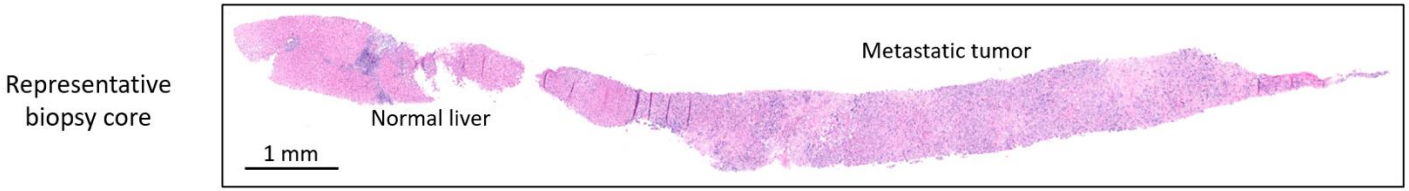
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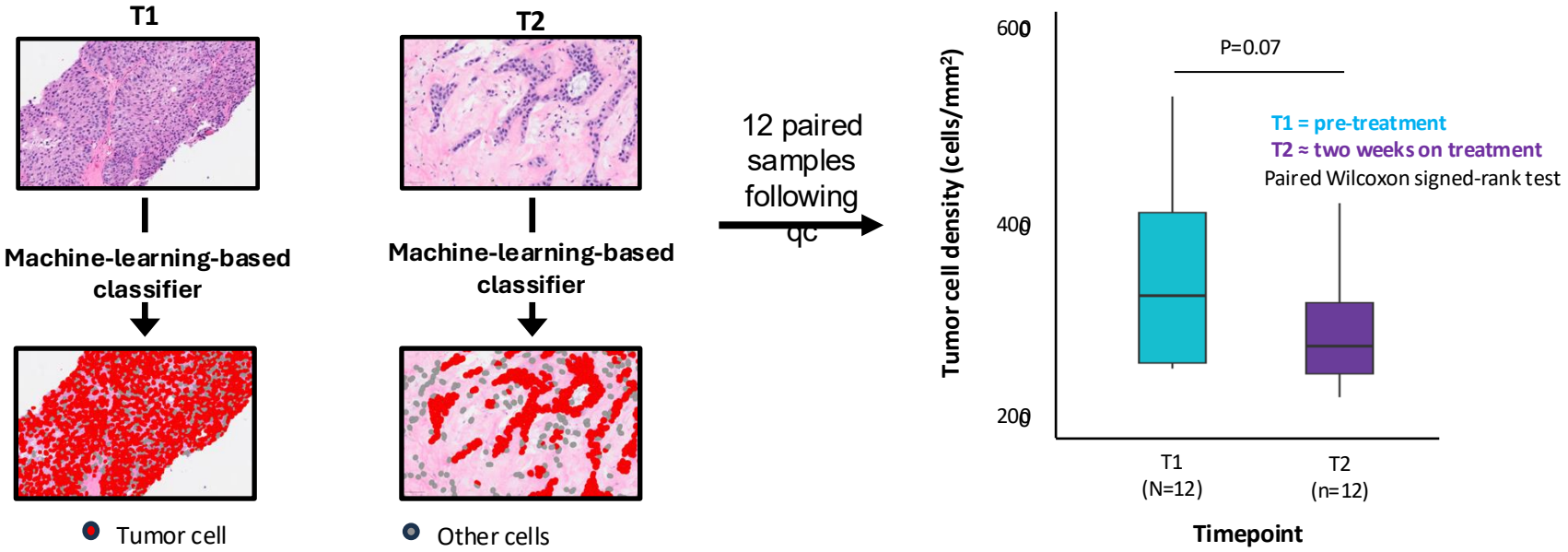


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Reduction in Tumor Cell Density in Liver Metastases Following ~2 Weeks of Daraxonrasib Treatment

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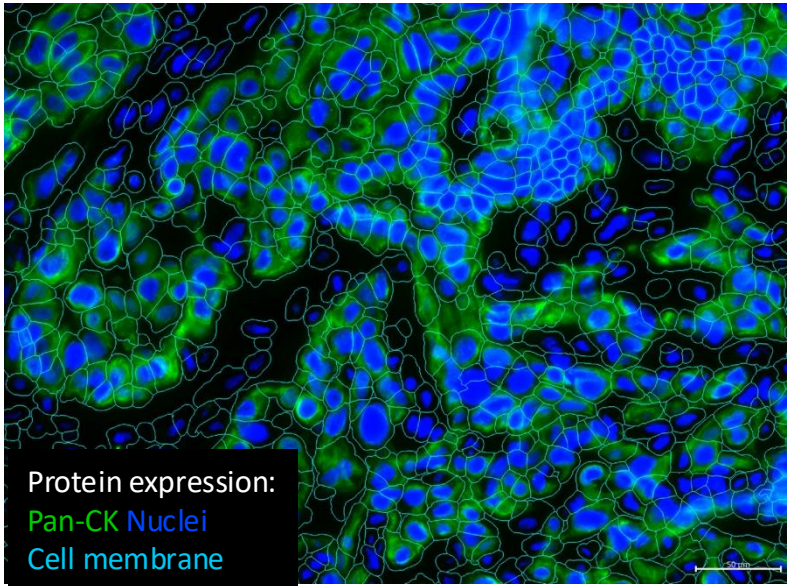


Väyrynen et al., 2020 Clin Cancer Res

Transcriptional RAS Signaling Output Decreases in Tumor Cells Following Daraxonrasib Treatment

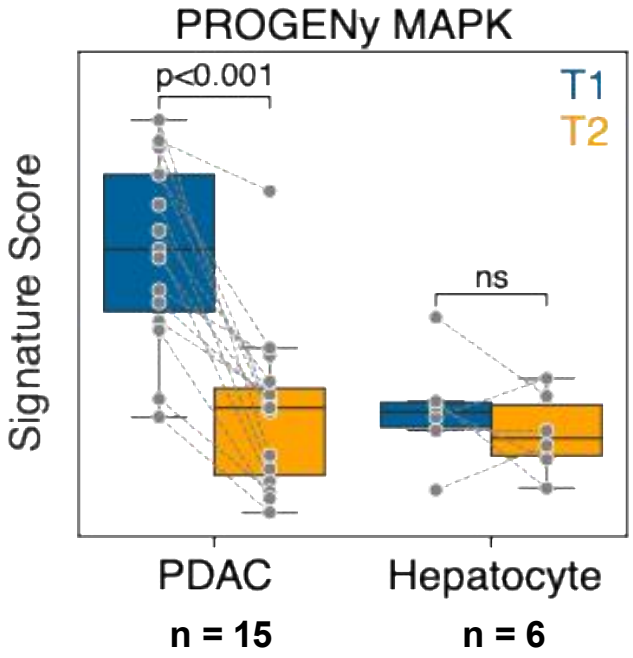
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Spatial Transcriptomics via CosMx



13 PROGENy transcripts represented in CosMx

T1 = Pre-treatment
T2 ≈ Two weeks on treatment

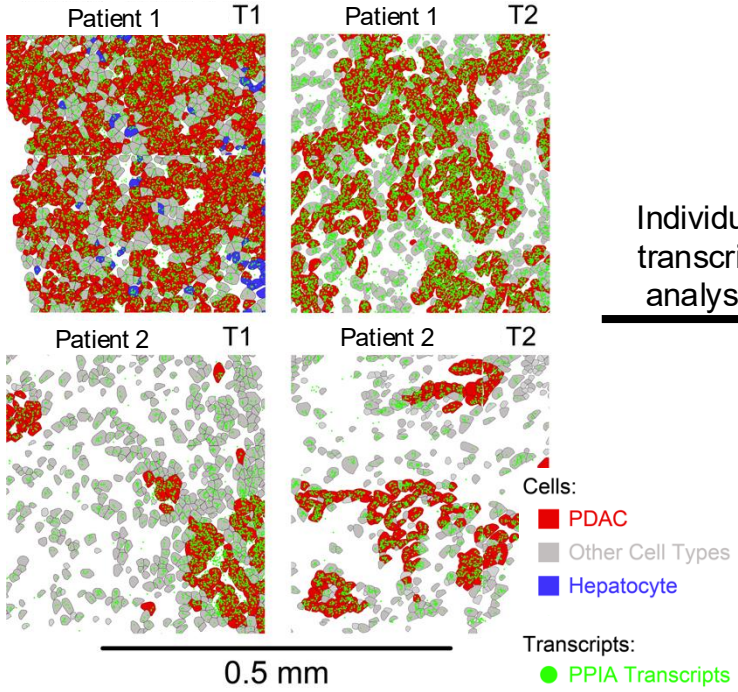


Paired Wilcoxon signed-rank test

Cyclophilin A (PPIA) Expression is Maintained in Tumor Cells Following Daraxonrasib Treatment

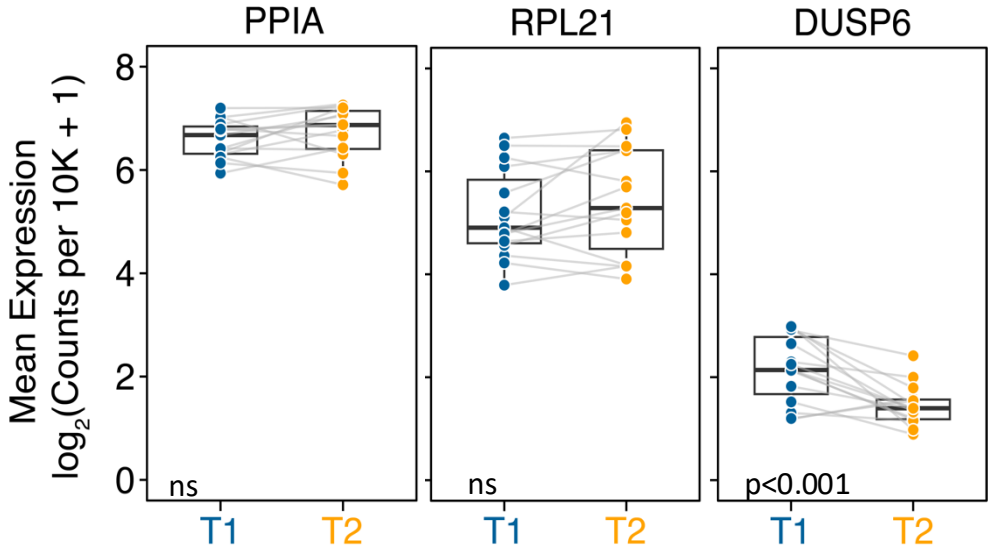
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Spatial Transcriptomics via CosMx



Individual transcript analysis

Individual Transcript Changes



T1 = pre-treatment
T2 ≈ two weeks on treatment

N = 15, Paired Wilcoxon signed-rank test

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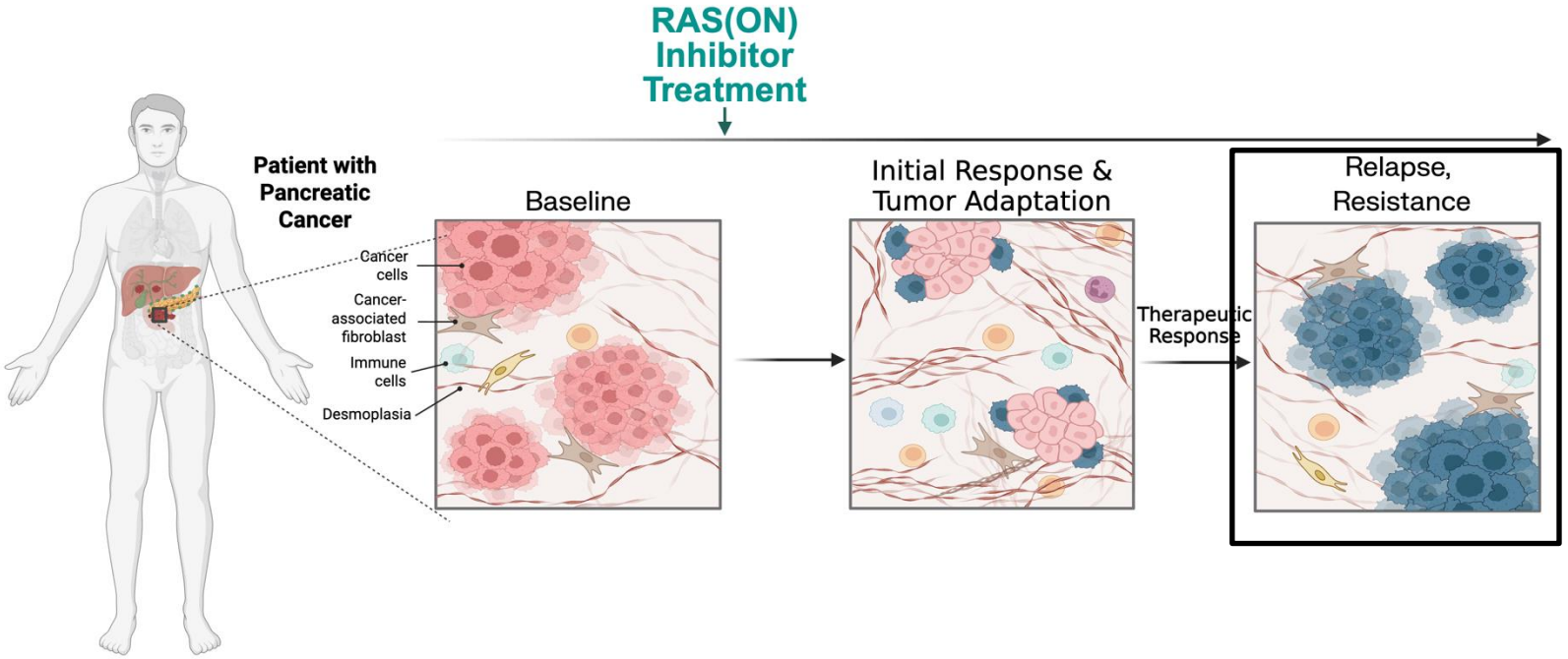
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A Conceptual Framework for Tumor Adaptation and Acquired Resistance to RAS Inhibition in PDAC

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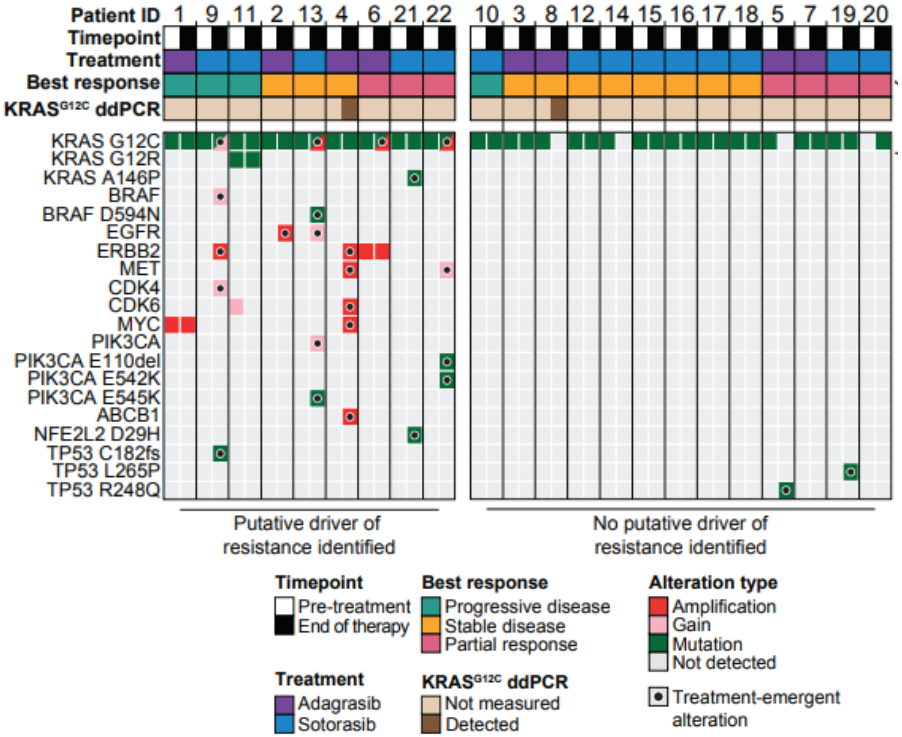
Each stage of the treatment journey represents different and overlapping combination opportunities

Figure created in BioRender

Clinical Resistance Mechanisms to RAS(OFF) Inhibitors in KRAS G12C Mutant PDAC Highlight Potential Advantage of Maximizing RAS(ON) Inhibition

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Genetic alterations associated with acquired resistance to $KRAS^{G12C}$ inhibition in patients with PDAC



Genomic Mechanisms of Resistance

RAS Pathway Reactivation

- Upstream RTK activation
- Retention of $KRAS^{G12C}$ allele with or without amplification
- Secondary KRAS mutation
- Downstream RAS-MAPK pathway mutations

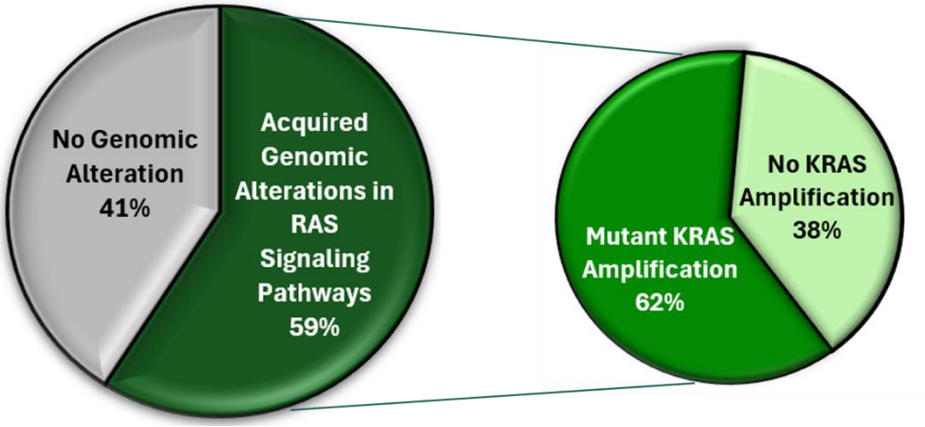
Orthogonal Pathway Mutations

Majority of patients with no genomic mechanisms of resistance identified

From Dilly et al., 2024, Cancer Discovery

Acquired Resistance Alterations in ctDNA from Patients with PDAC Treated with Daraxonrasib in 2L+

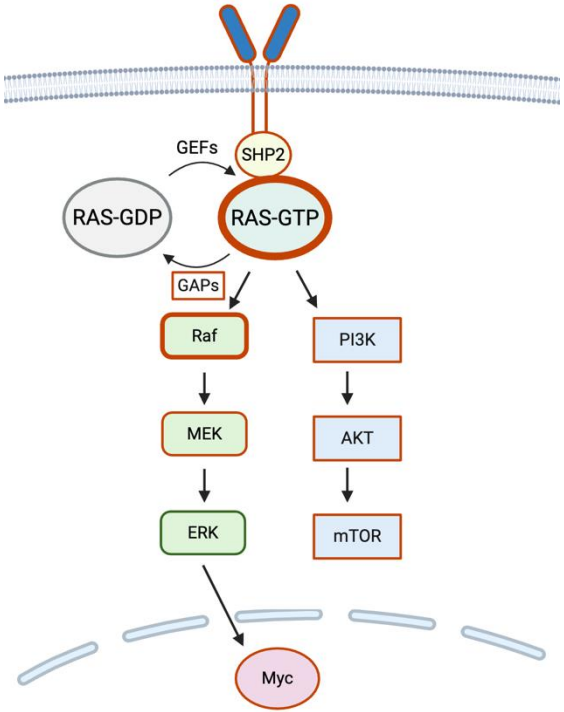
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44 patients treated with 160 to 300 mg of daraxonrasib with PFS > 3 months who subsequently progressed and had paired baseline and EOT sequenced successfully

26 patients with acquired oncogenic alteration in RAS signaling pathways (RAS, MAPK, PI3K, MYC, RTK)

16 patients with acquired mutant allele *KRAS*^{amp}

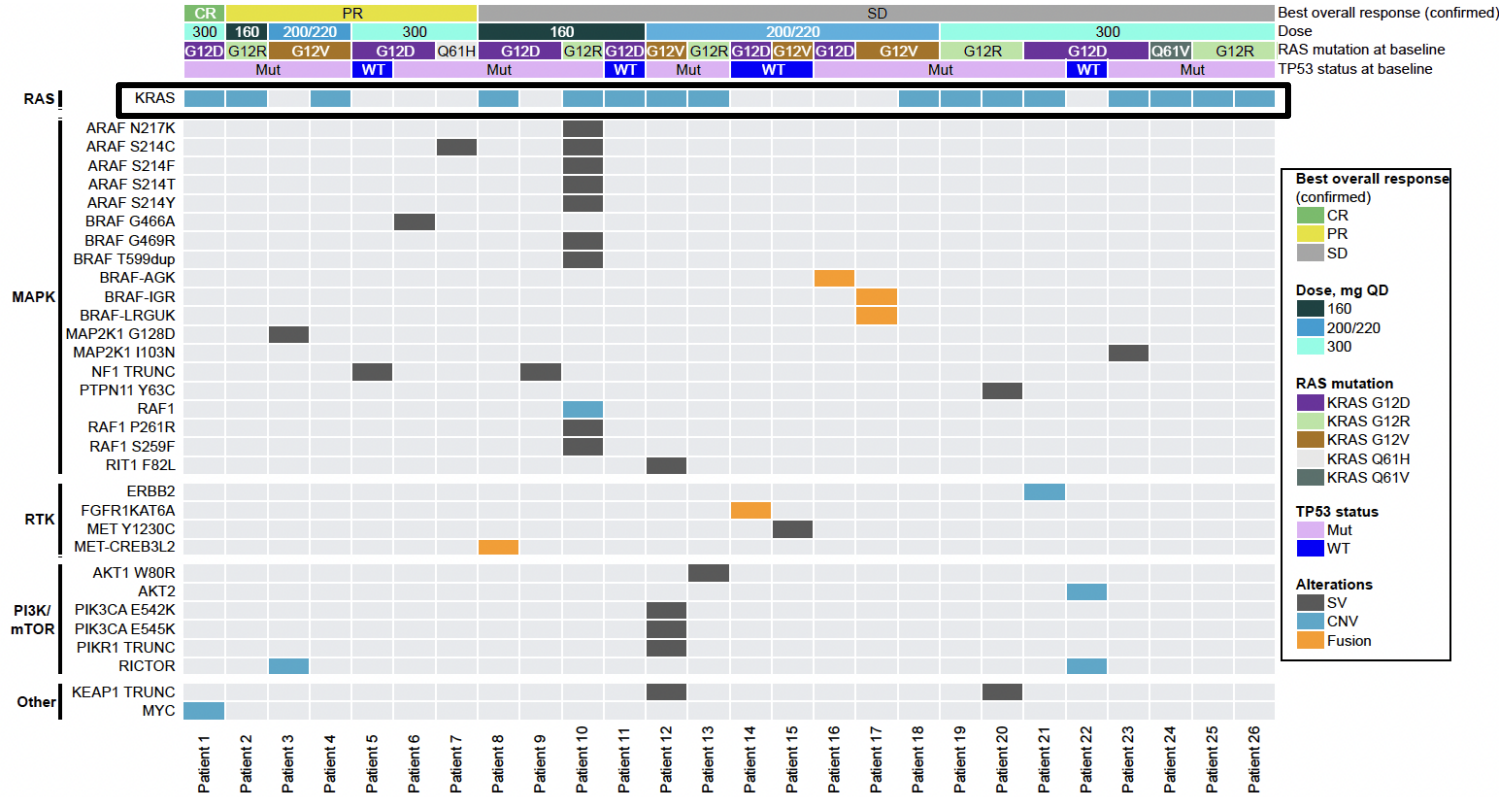


Genes alterations found in end-of-treatment ctDNA samples (Red outline). Line thickness reflects frequency of alterations.

Data cutoff: June 30, 2025

RAS Pathway Reactivation in Acquired Resistance to Daraxonrasib

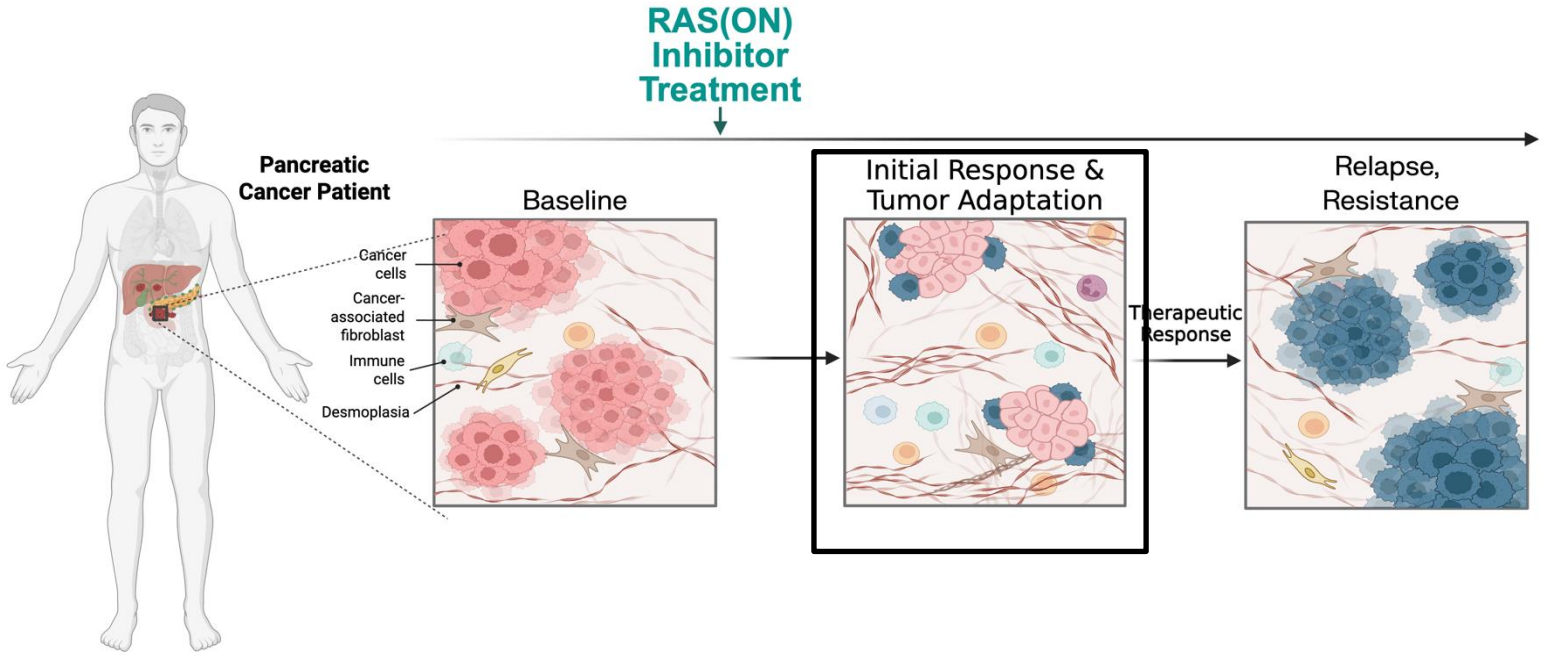
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Aronchik, Kar et al., ENA 2025

A Conceptual Framework for Tumor Adaptation and Acquired Resistance to RAS Inhibition in PDAC

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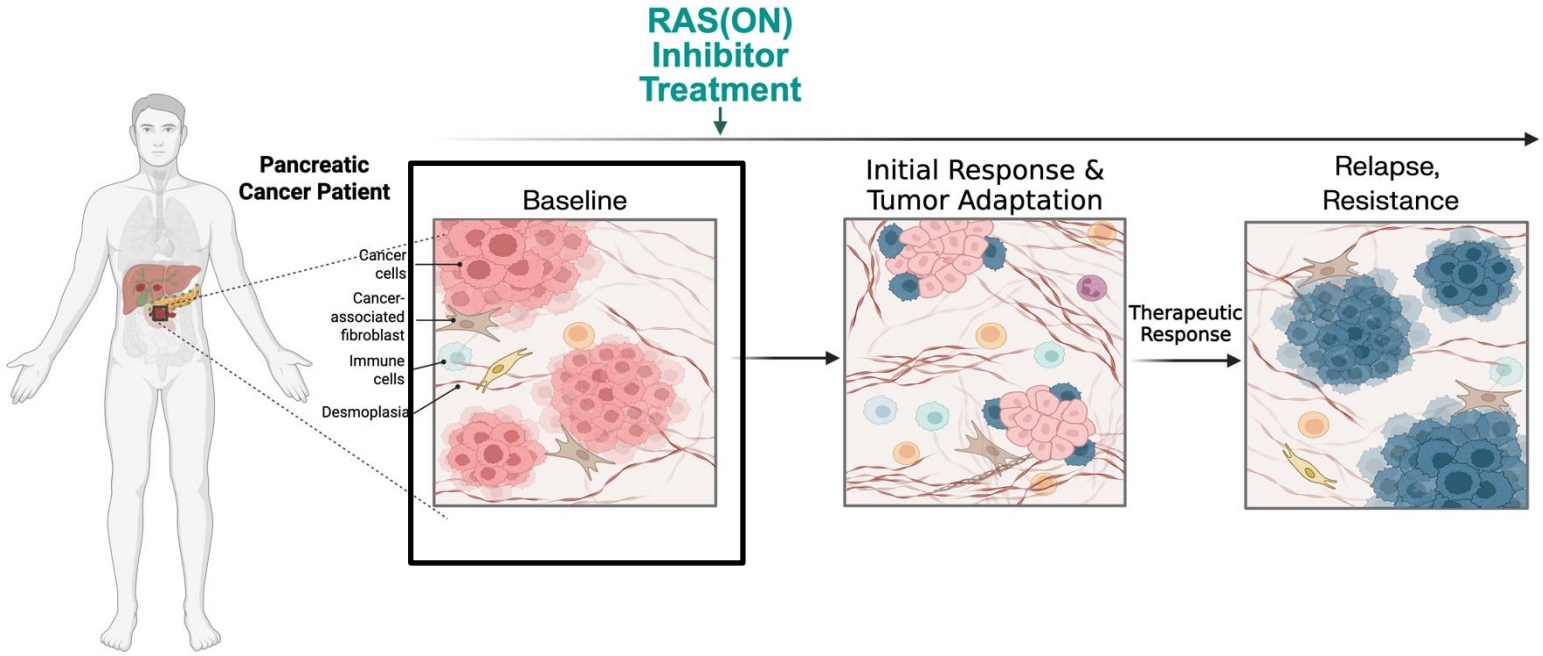


Each stage of the treatment journey represents different and overlapping combination opportunities

Figure created in BioRender

A Conceptual Framework for Tumor Adaptation and Acquired Resistance to RAS Inhibition in PDAC

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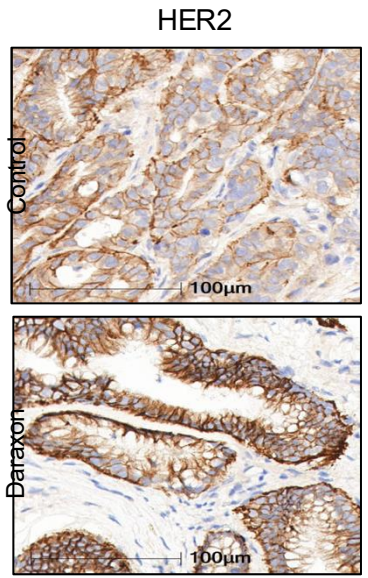


Each stage of the treatment journey represents different and overlapping combination opportunities

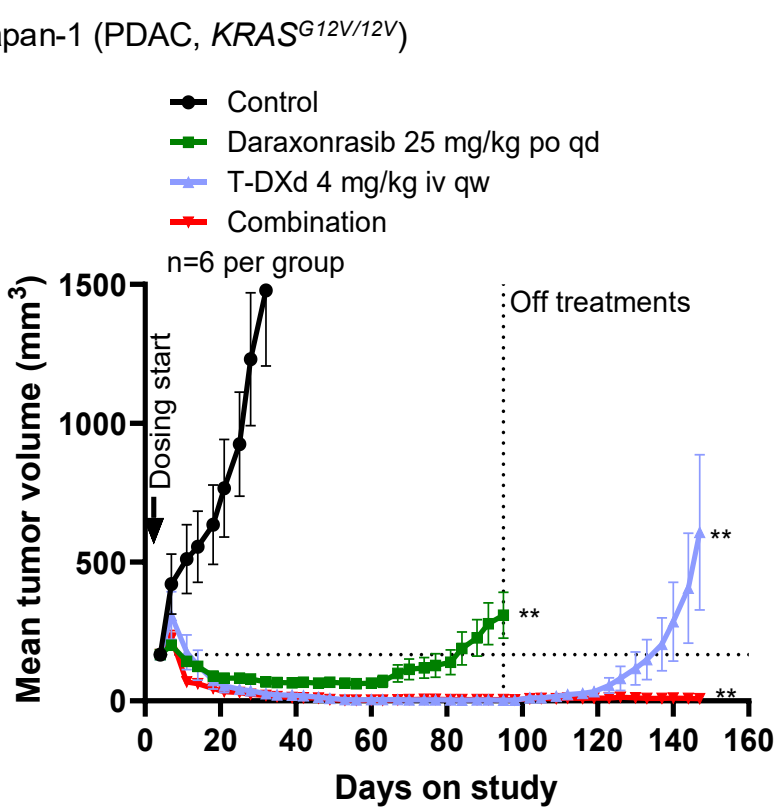
Figure created in BioRender

RAS(ON) Inhibition in Combination with Trastuzumab Deruxtecan (T-DXd) in the Treatment-Naïve Setting

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4h post-last dose
on day 7

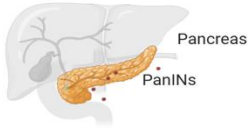


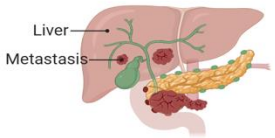
**P < 0.01, control and treatment groups were compared by two-way RM ANOVA on the last day of the control

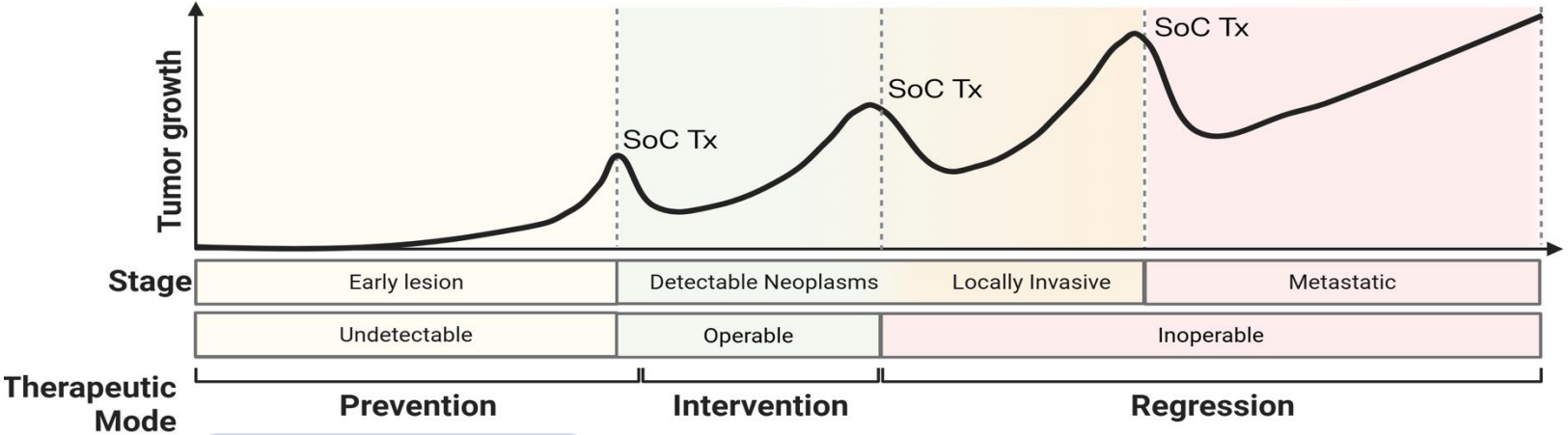
Bulle et al., 2024, Nat Communications
Han et al., 2023, Genes & Dev

RAS(ON) Inhibition and Stages of PDAC Development
Can RAS(ON) Inhibition be Deployed in Interception & Prevention?

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Exploratory Collaboration

Johns Hopkins Medicine · Revolution Medicines · UC Davis · Dana-Farber Cancer Institute

RASolute 304
Resectable PDAC

RASolute 302 2L PDAC, Daraxonrasib
RASolute 303 1L PDAC, Daraxonrasib +/- GnP
RASolute 305 1L PDAC, Zoldonrasib + Chemo
RASolute 309 1L PDAC, Daraxonrasib+Zoldonrasib[1]

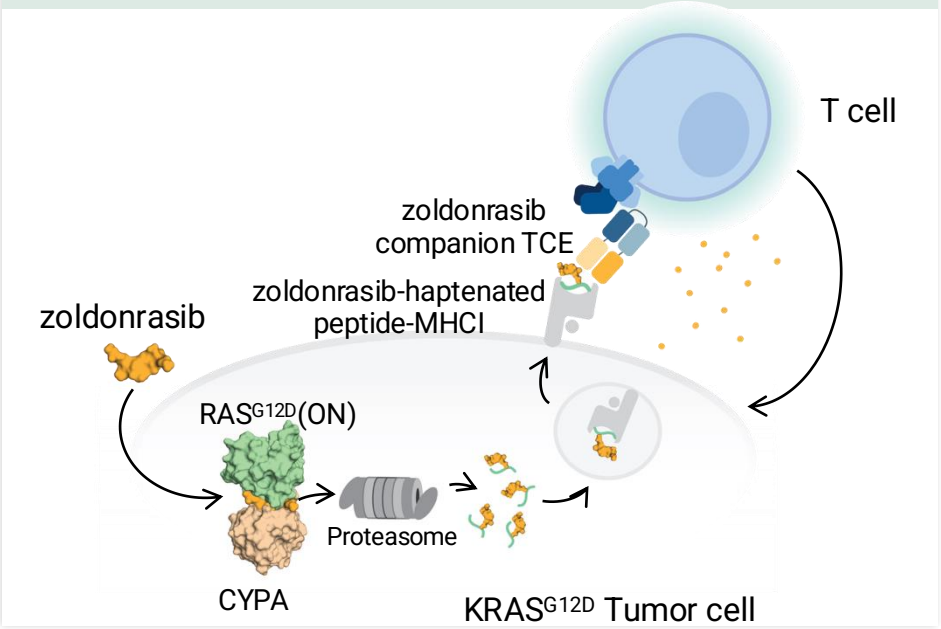
The Mark Foundation for Cancer Research · AACR · Lustgarten Foundation Pancreatic Cancer Research

[1]Start-up activities ongoing
Illustrative figure created in BioRender

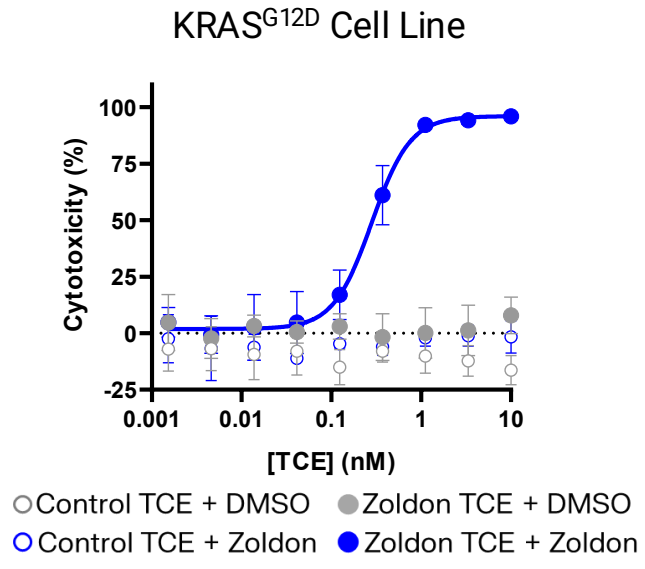
Using RAS(ON) Mutant-Selective Covalent Inhibitors to Direct Immune-Mediated Cell Killing of RAS Mutant Tumors

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T cell engagers (TCE) to target zoldonrasib–haptenated KRAS G12D peptides



T cell-mediated cell killing *in vitro* with zoldonrasib companion TCE



RESEARCH

CANCER

Chemical remodeling of a cellular chaperone to target the active state of mutant KRAS

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Article

Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer

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Urszula N. Wasko[1,2,29], Jingjing Jiang[3,29], Tanner C. Dalton[1,2], Alvaro Curiel-Garcia[1,2], A. Cole Edwards[4], Yingyun Wang[3], Bianca Lee[3], Margo Orlen[3], Sha Tian[4], Clint A. Stalnecker[7,8], Kristina Drizyte-Miller[7], Marie Menard[3], Julien Dilly[9,10], Stephen A. Sastra[1,2], Carmine F. Palermo[1,2], Marie C. Hasselluhn[1,2], Amanda R. Decker-Farrell[1,2], Stephanie Chang[3], Lingyan Jiang[3], Xing Wei[3], Yu C. Yang[3], Ciara Helland[3], Haley Courtney[3], Yevgeniy Gindin[3], Karl Muonio[3], Ruiping Zhao[3], Samantha B. Kemp[5], Cynthia Clendenin[11], Rina Sor[11], William P. Vostrejs[8], Priya S. Hibshman[4], Amber M. Amparo[7], Connor Hennessey[9,10], Matthew G. Rees[12], Melissa M. Ronan[12], Jennifer A. Roth[12], Jens Brodbeck[3], Lorenzo Tomassoni[2,13], Basil Bakir[1,2], Nicholas D. Socci[14], Laura E. Herring[15], Natalie K. Barker[16], Junning Wang[9,10], James M. Cleary[9,10], Brian M. Wolpin[9,10], John A. Chabot[16], Michael D. Kluger[16], Gulam A. Manji[1,2], Kenneth Y. Tsai[17,18], Miroslav Sekulic[19], Stephen M. Lagana[19], Andrea Califano[1,2,13,20,21,22,23,24], Elsa Quintana[3], Zhengping Wang[3], Jacqueline A. M. Smith[3], Matthew Holderfield[3], David Wildes[3], Scott W. Lowe[6,25], Michael A. Badgley[1,2], Andrew J. Aguirre[9,10,12,26], Robert H. Vonderheide[5,11,27], Ben Z. Stanger[5,11], Timour Baslan[28], Channing J. Der[7,8], Mallika Singh[3]✉ & Kenneth P. Olive[1,2]✉

Article

Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy

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Matthew Holderfield[1], Bianca J. Lee[1], Jingjing Jiang[1], Aidan Tomlinson[1], Kyle J. Seamon[1], Alessia Mira[2], Enrico Patrucco[2], Grace Goodhart[3], Julien Dilly[4], Yevgeniy Gindin[1], Nuntana Dinglasan[1], Yingyun Wang[1], Lick Pui Lai[1], Shurui Cai[1], Lingyan Jiang[1], Nicole Nasholm[1], Nataliya Shifrin[1], Cristina Blaj[1], Harshit Shah[1], James W. Evans[1], Nilufar Montazer[1], Oliver Lai[1], Jade Shi[1], Ethan Ahler[1], Elsa Quintana[3], Stephanie Chang[1], Anthony Salvador[1], Abby Marquez[1], Jim Cregg[1], Yang Liu[1], Anthony Milin[1], Anqi Chen[1], Tamar Bar Ziv[1], Dylan Parsons[1], John E. Knox[1], Jennifer E. Klomp[5], Jennifer Roth[6], Matthew Rees[6], Melissa Ronan[6], Antonio Cuevas-Navarro[7], Feng Hu[7], Piro Lito[7,8], David Santamaria[9], Andrew J. Aguirre[4,6,10,11], Andrew M. Waters[3,5,12,13], Channing J. Der[5,12], Chiara Ambrogio[2], Zhengping Wang[1], Adrian L. Gill[1], Elena S. Koltun[1], Jacqueline A. M. Smith[1]✉, David Wildes[1]✉ & Mallika Singh[1]✉

Science 24 JULY 2025

DRUG DEVELOPMENT

A neomorphic protein interface catalyzes covalent inhibition of RAS^{G12D} aspartic acid in tumors

Caroline Weller[1]†, G. Leslie Burnett[1]†, Lingyan Jiang[1]†, Sujata Chakraborty[1], Dongyu Zhang[1], Nicole A. Vita[1], Julien Dilly[2], Eejung Kim[2], Benjamin Maldonato[1], Kyle Seamon[1], Diane F. Eilerts[1], Anthony Milin[1], Abby Marquez[1], Jessica Spradlin[1], Ciara Helland[1], Andrea Gould[1], Tamar Bar Ziv[1], Phuong Dinh[1], Shelby L. Steele[1], Zhican Wang[1], Yunming Mu[1], Seema Chugh[2], Hanrong Feng[2], Conner Hennessey[2], Junning Wang[2], Jennifer Roth[3], Matthew Rees[3], Melissa Ronan[3], Brian M. Wolpin[2], William C. Hahn[2], Matthew Holderfield[1], Zhengping Wang[1], Elena S. Koltun[1], Mallika Singh[1], Adrian L. Gill[1], Jacqueline A. M. Smith[1], Andrew J. Aguirre[2,3], Jingjing Jiang[1]*, John E. Knox[1]*, David Wildes[1]*

RESEARCH ARTICLE

Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers

Jingjing Jiang[1], Lingyan Jiang[1], Benjamin J. Maldonato[1], Yingyun Wang[1], Matthew Holderfield[1], Ida Aronchik[1], Ian P. Winters[1,2], Zeena Salman[1], Cristina Blaj[1], Marie Menard[1], Jens Brodbeck[1], Zhe Chen[1], Xing Wei[1], Michael J. Rosen[2], Yevgeniy Gindin[1], Bianca J. Lee[1], James W. Evans[1], Stephanie Chang[1], Zhican Wang[1], Kyle J. Seamon[1], Dylan Parsons[1], James Cregg[1], Abby Marquez[1], Aidan C.A. Tomlinson[1], Jason K. Yano[1], John E. Knox[1], Elsa Quintana[1], Andrew J. Aguirre[3,4,5,6], Kathryn C. Arbour[7], Abby Reed[8], W. Clay Gustafson[1], Adrian L. Gill[1], Elena S. Koltun[1], David Wildes[1], Jacqueline A.M. Smith[1], Zhengping Wang[1], and Mallika Singh[1]

Journal of Medicinal Chemistry

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Drug Annotation

Discovery of Elironrasib (RMC-6291), a Potent and Orally Bioavailable, RAS(ON) G12C-Selective, Covalent Tricomplex Inhibitor for the Treatment of Patients with RAS G12C-Addicted Cancers

James Cregg,* Kristof Pota, Aidan C. A. Tomlinson, Jason Yano, Abby Marquez, Yang Liu, Christopher J. Schulze, Kyle J. Seamon, Matthew Holderfield, Xing Wei, Yongxian Zhuang, Yu Chi Yang, Jingjing Jiang, Yue Huang, Ruiping Zhao, Yun Ling, Zhican Wang, Michael Flagella, Zhengping Wang, Mallika Singh, John E. Knox, Robert Nichols, David Wildes, Jacqueline A. M. Smith, Elena S. Koltun, and Adrian L. Gill*

Journal of Medicinal Chemistry

Editors' Choice

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Drug Annotation

Discovery of Daraxonrasib (RMC-6236), a Potent and Orally Bioavailable RAS(ON) Multi-selective, Noncovalent Tri-complex Inhibitor for the Treatment of Patients with Multiple RAS-Addicted Cancers

James Cregg,* Anne V. Edwards, Stephanie Chang, Bianca J. Lee, John E. Knox, Aidan C. A. Tomlinson, Abby Marquez, Yang Liu, Rebecca Freilich, Naing Aay, Yingyun Wang, Lingyan Jiang, Jingjing Jiang, Zhican Wang, Michael Flagella, David Wildes, Jacqueline A.M. Smith, Mallika Singh, Zhengping Wang, Adrian L. Gill, and Elena S. Koltun*

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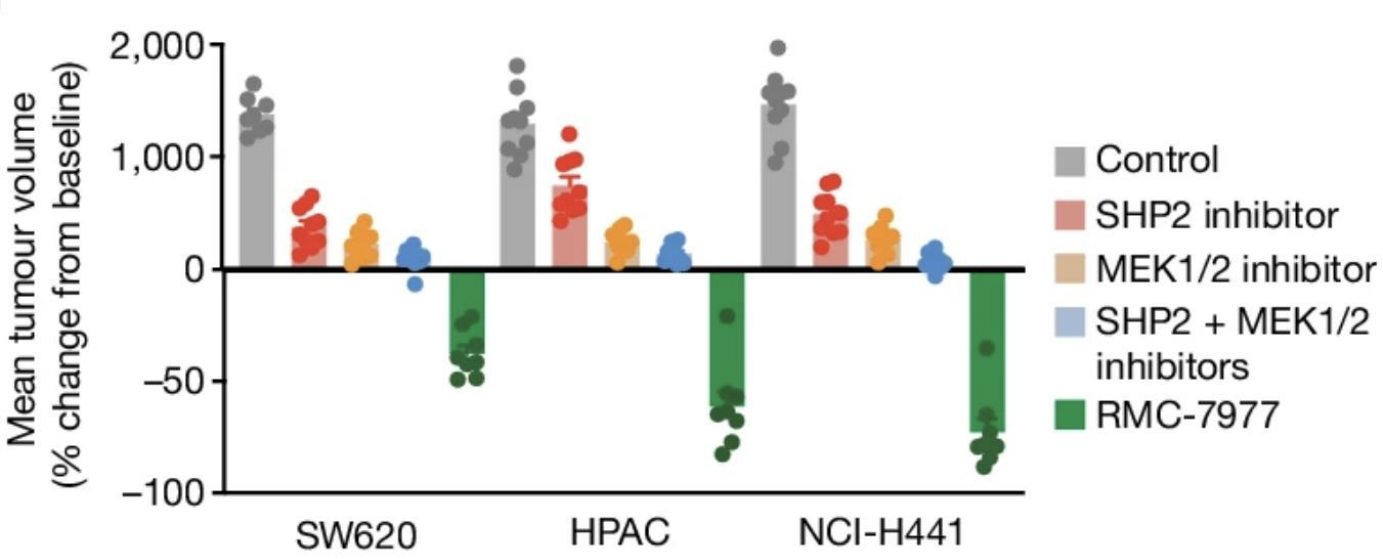
Lessons Learned: Revision of RAS Concepts Once Considered Dogma

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Original dogma	New findings leading to revisions of dogma
The three RAS proteins are identical	KRAS and NRAS, but not HRAS, can undergo alternative prenylation by geranylgeranylation and thereby escape farnesyltransferase inhibitor treatment
RAS effector signaling pathways are linear and unidirectional	Inhibition of KRAS-ERK signaling impairs ERK-dependent negative feedback mechanisms, leading to compensatory ERK reactivation and driving resistance to RAS inhibitors; RAS effector pathways are complex multi-directional networks
Mice are small people	The potent anti-tumor activities of inhibitors of the RAS-ERK MAPK pathway occur at concentrations that are well-tolerated in mice but highly toxic in humans; mice better tolerate ERK inhibition compared with humans
Lacking druggable binding pockets, RAS is undruggable	The RAS switch II region contains a druggable pocket; RAS is druggable
Unlike WT RAS, mutant RAS proteins are chronically GTP-bound and do not undergo GDP-GTP cycling	Sotorasib and adagrasib selectively recognize inactive OFF-state GDP-bound $KRAS^{G12C}$ and prevent cycling to the active ON state of GTP-bound $KRAS^{G12C}$; to varying degrees, all mutant RAS proteins retain GDP-GTP cycling
All RAS mutations cause the same changes to RAS	Missense mutations at G12 and Q61 result in distinct biochemical and structural consequences, exhibit distinct biological and signaling properties, and differential sensitivities to different RAS inhibitors; unlike other $KRAS^{G12X}$ mutants, $KRAS^{G12R}$ fails to engage PI3K
Targeting all RAS proteins simultaneously will be intolerably toxic	**Pan-RAS inhibitors exhibit potent anti-tumor activity and yet limited toxicity compared with standard-of-care cytotoxic drugs**

Cox & Der (2026) Annu Rev Cancer
Slide courtesy of Channing Der

Directly Targeting RAS in KRAS-Driven Tumors is Distinct from Pathway "Clamping"



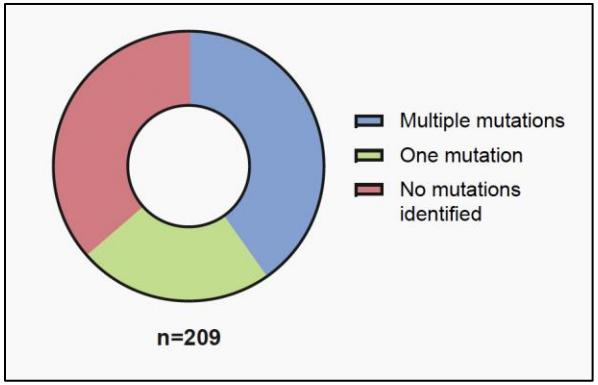
- Inhibitors dosed based on translatable exposures
- All regimens were tolerated

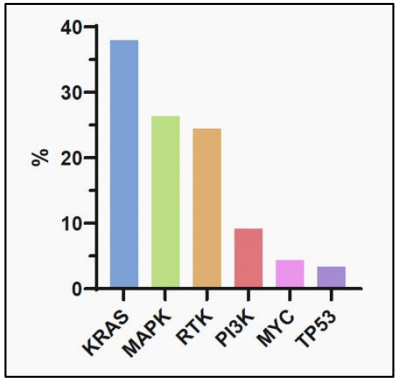
RMC-7977 is a tool RAS(ON) multi-selective inhibitor

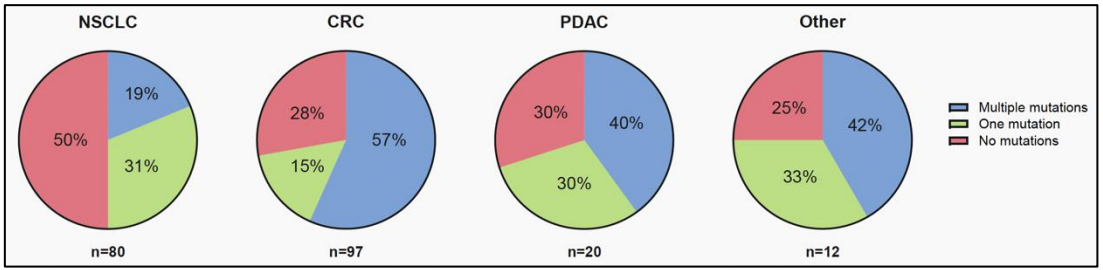
Holderfield et al., Nature 2024

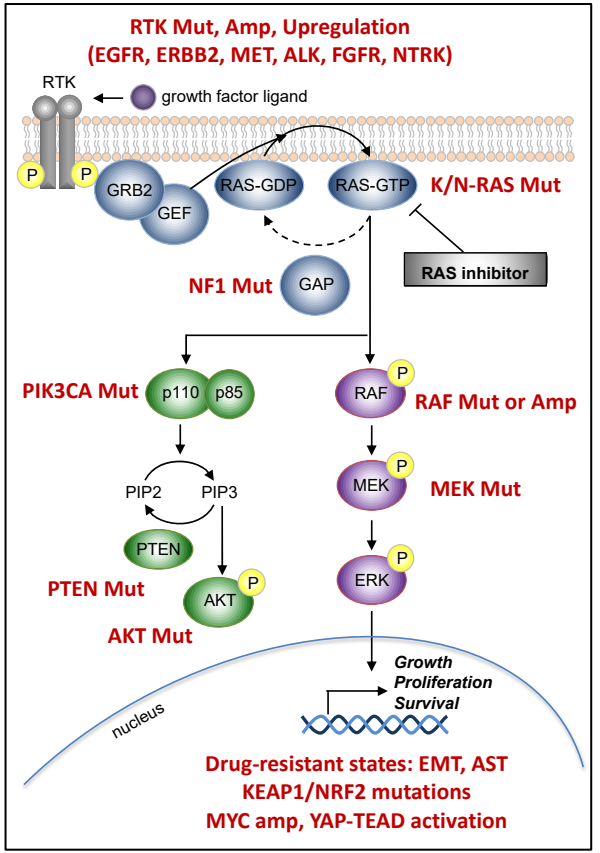
Current Understanding of KRAS G12C(OFF) Inhibitor Resistance Mechanisms

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From Ebright et al., Cancer Discovery 2025

RAS(ON) Inhibitors are Generally Well Tolerated in Patients Across Patient Populations

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- Daraxonrasib monotherapy was generally well tolerated at the doses selected for ongoing Phase 3 studies, with anticipated on target TRAEs.
- Daraxonrasib + GnP in combination demonstrated acceptable safety/tolerability
  - TRAEs were manageable with routine clinical interventions
  - The most common TRAEs were rash and GI-related toxicities that were primarily Grade 1 or 2 in severity
  - Mean dose intensity was favorable with few treatment discontinuations due to TRAEs
- Zoldonrasib monotherapy demonstrated an encouraging safety profile and was generally well tolerated at clinically active doses
  - TRAEs were primarily low grade and manageable with routine clinical interventions
  - No Grade 4 or 5 TRAEs were observed
  - Mean dose intensities were favorable with few treatment discontinuations due to TRAEs
  - Safety/tolerability profiles well suited for evaluation across range of combination settings

RAS(ON) Inhibitors are Generally Well Tolerated in Patients Across Patient Populations

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- Daraxonrasib monotherapy at Phase 3 relevant doses results in expected, on mechanism TRAEs; the majority of these are ≤ Grade 3 and manageable with few overall treatment discontinuations
- At 120–220 mg qd in NSCLC
  - Rash (7%) was the only G3 TRAE in ≥ 5% patients; no G4 or 5 TRAEs were observed
  - GI events such as diarrhea; G3 TRAEs are infrequent
  - Mucosal such as stomatitis not observed
  - 91% dose intensity
- Elironrasib and zoldonrasib monotherapies result in ≤ 10% Grade 3 TRAEs, which are primarily GI events such as nausea and diarrhea
- Daraxonrasib + elironrasib RAS(ON) doublet is generally well tolerated in 2L+ NSCLC patients previously treated with G12C(OFF) inhibitors