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Targeting KRAS in Pancreatic Cancer: A Long But Successful Climb

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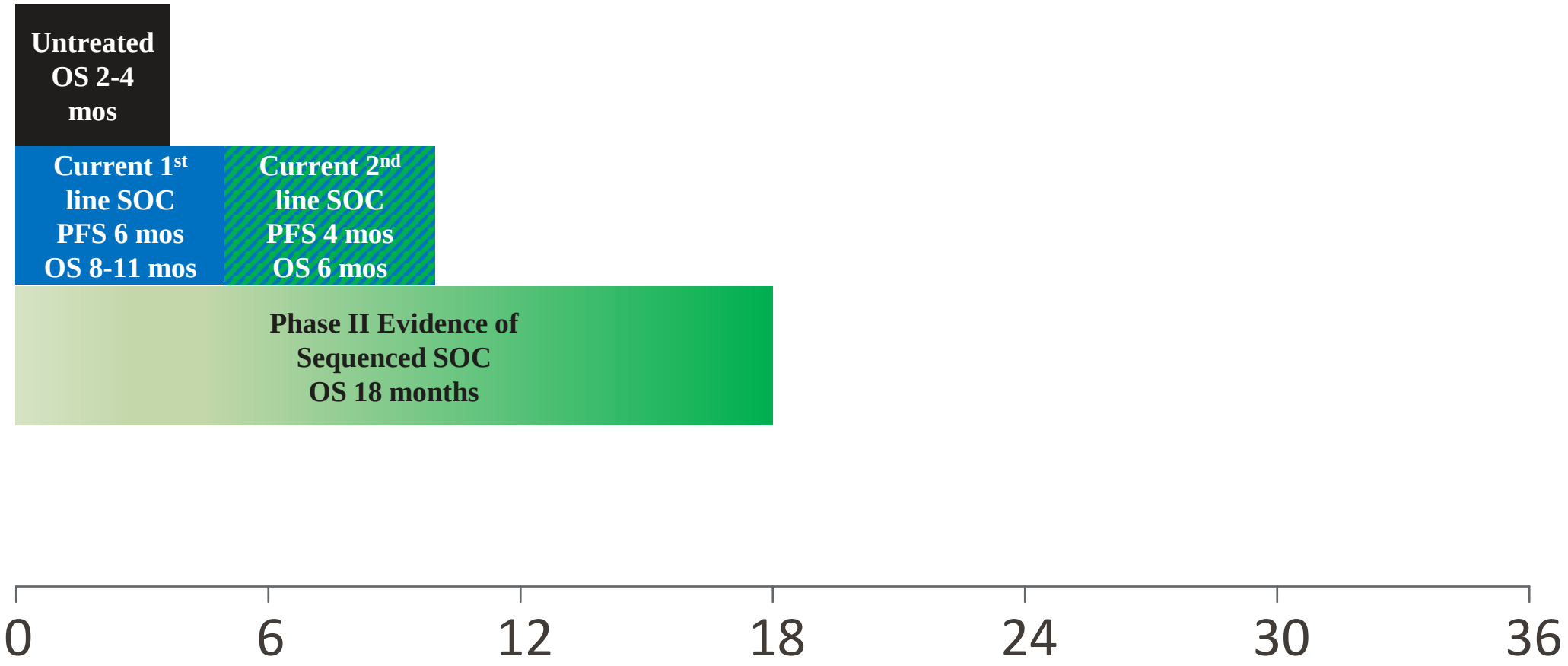
Disclosures

- Consulting: Tempus, BMS/Mirati, Revolution Medicine, Lilly/Loxo, Agenus, GSK, AstraZeneca, Incyte, Taiho

- Research grants: Compass, BMS, Pfizer, Revolution Medicine, Agenus, AstraZeneca, Agenus, Syndax, Taiho

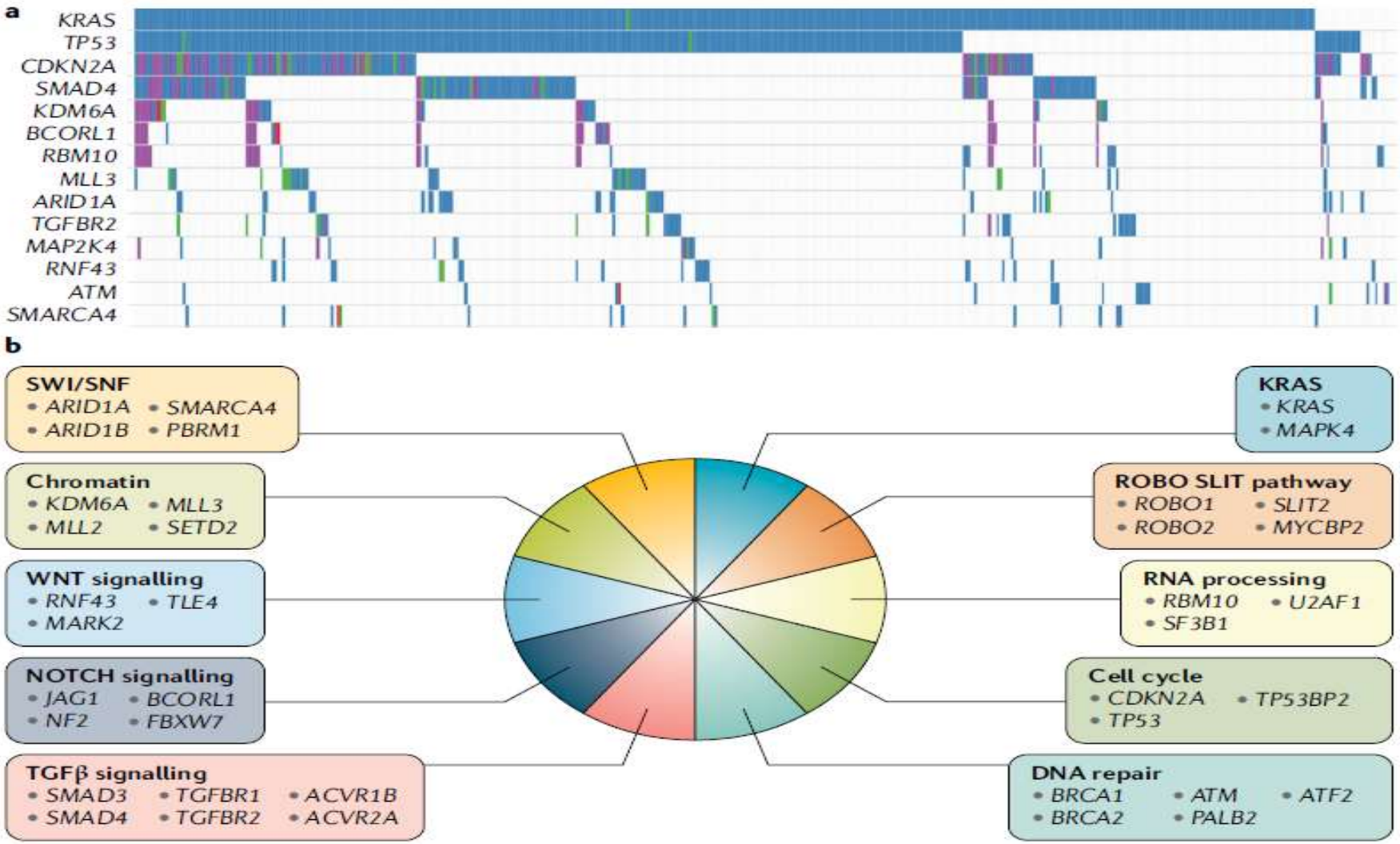
- Ownership shares: Quest/Haystack, Cage Pharma

Metastatic Pancreatic Cancer Survival



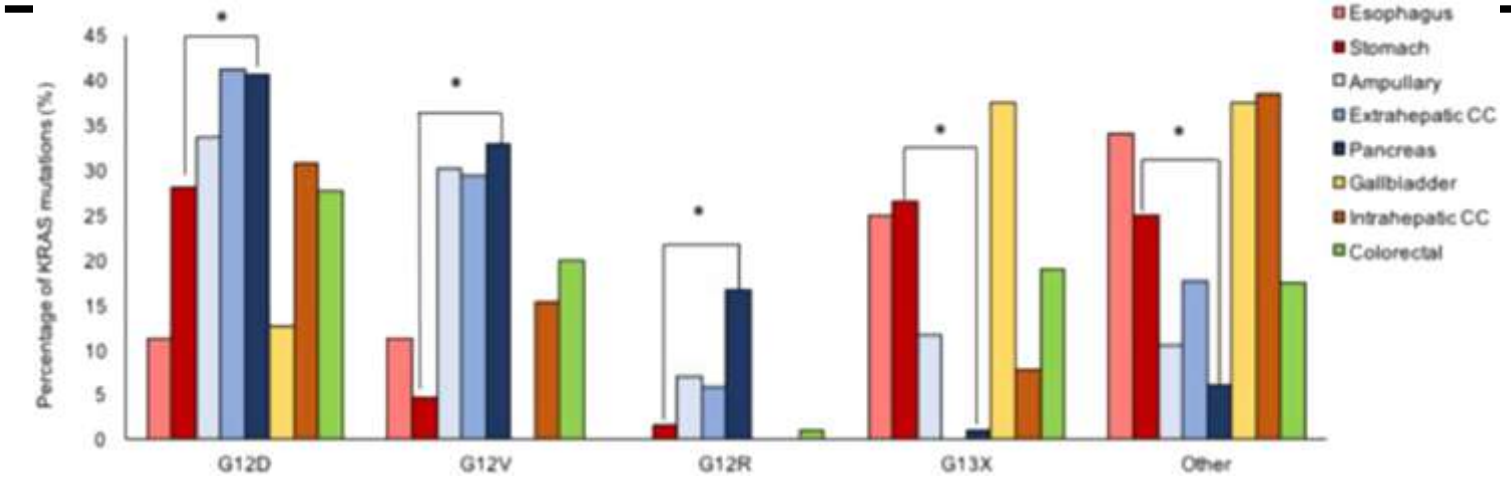
Burris, JCO, 1997, 15(6): 2403-2413; Conroy, NEJM, 2011, 364(19): 1817-1825; Von Hoff, NEJM, 2013, 369(18): 1691-1703; Ramanathan, R., 2013, JCO; Portal, A, Br J Cancer, 2015; Weinberg, B, 2015, Oncology

Molecular profiling has made targeted therapy a reality



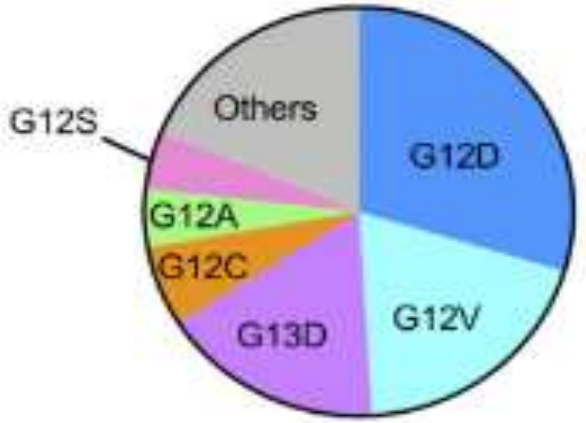
Collisson EA, et al, Nat Rev Gastro Hep, 2019
Bailey P, et al. Nature. 2016;531:47-52
Jones S, et al, Science. 2008;321:1801-1806

KRAS mutations are common in solid tumors, especially GI cancers

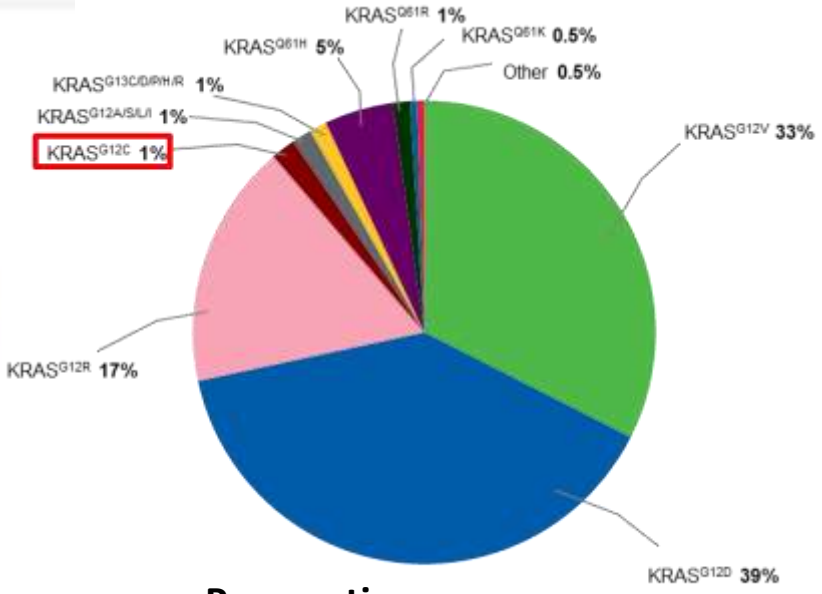


A

Organ	# Studies	Total Cases	KRAS Mutant Cases	% KRAS Mutant
Esophagus	7	663	36	5.4%
Stomach	9	1611	140	8.7%
Ampulla	1	160	88	55.0%
Extrahepatic CC	4	61	18	29.5%
Intrahepatic CC	6	380	29	7.6%
Gallbladder	2	135	8	5.9%
Pancreas	7	954	811	85.0%
Colorectal	10	3418	1393	40.8%

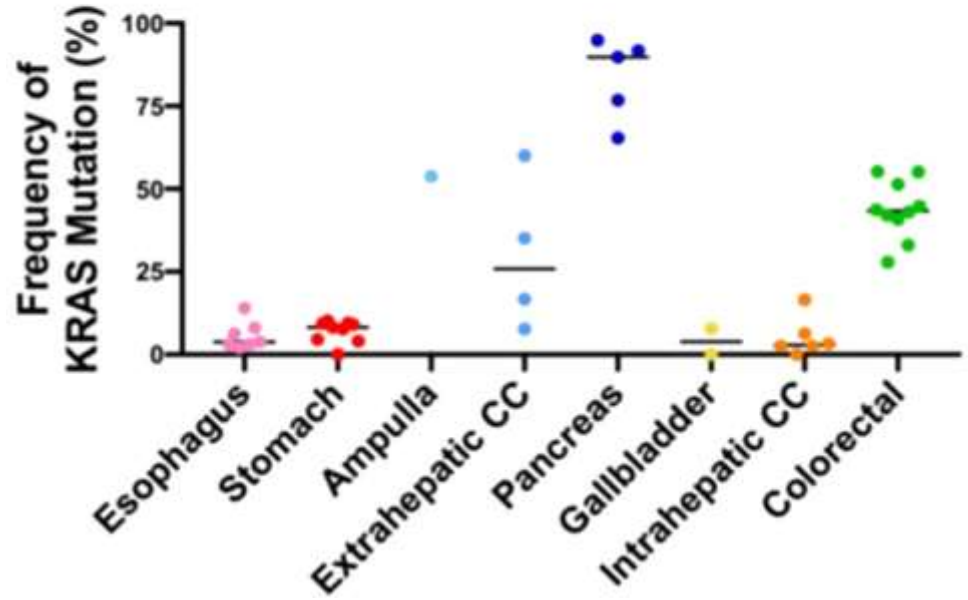


Colorectal cancer



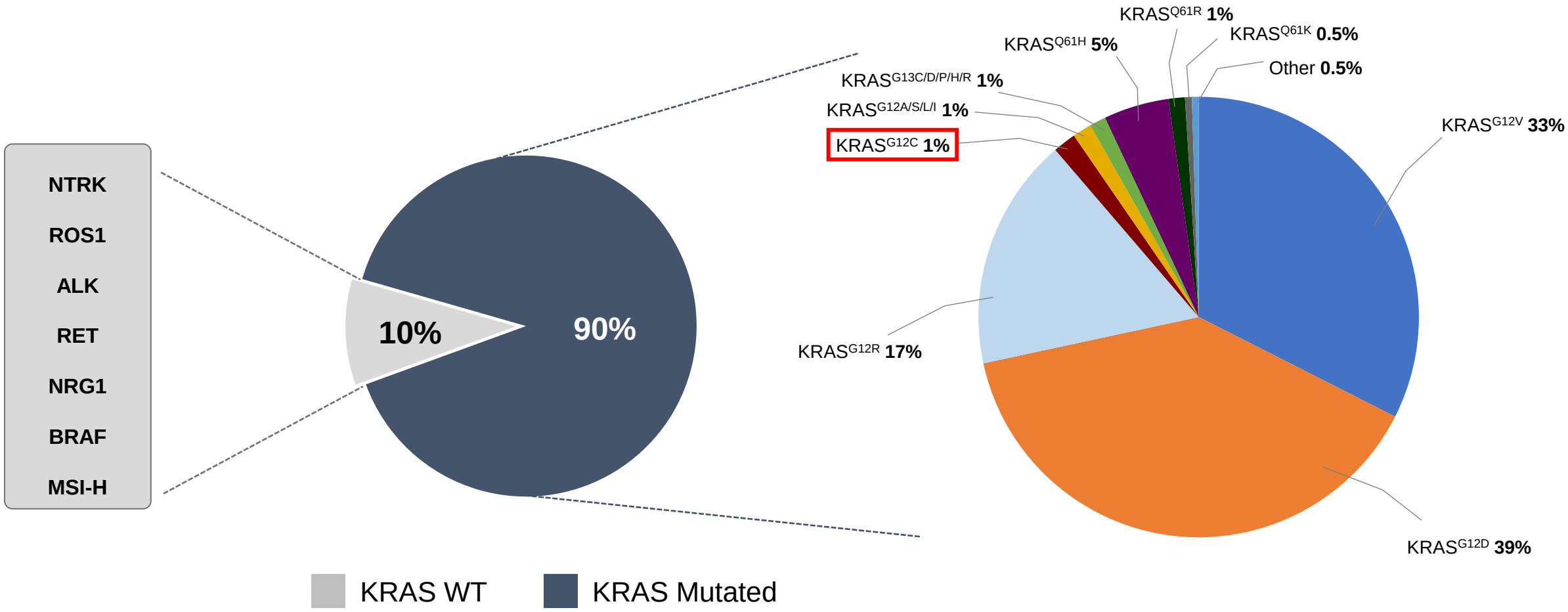
Pancreatic cancer

B



Wang et al. Modern Pathology 2023; Sunaga et al. Cancers 2021.

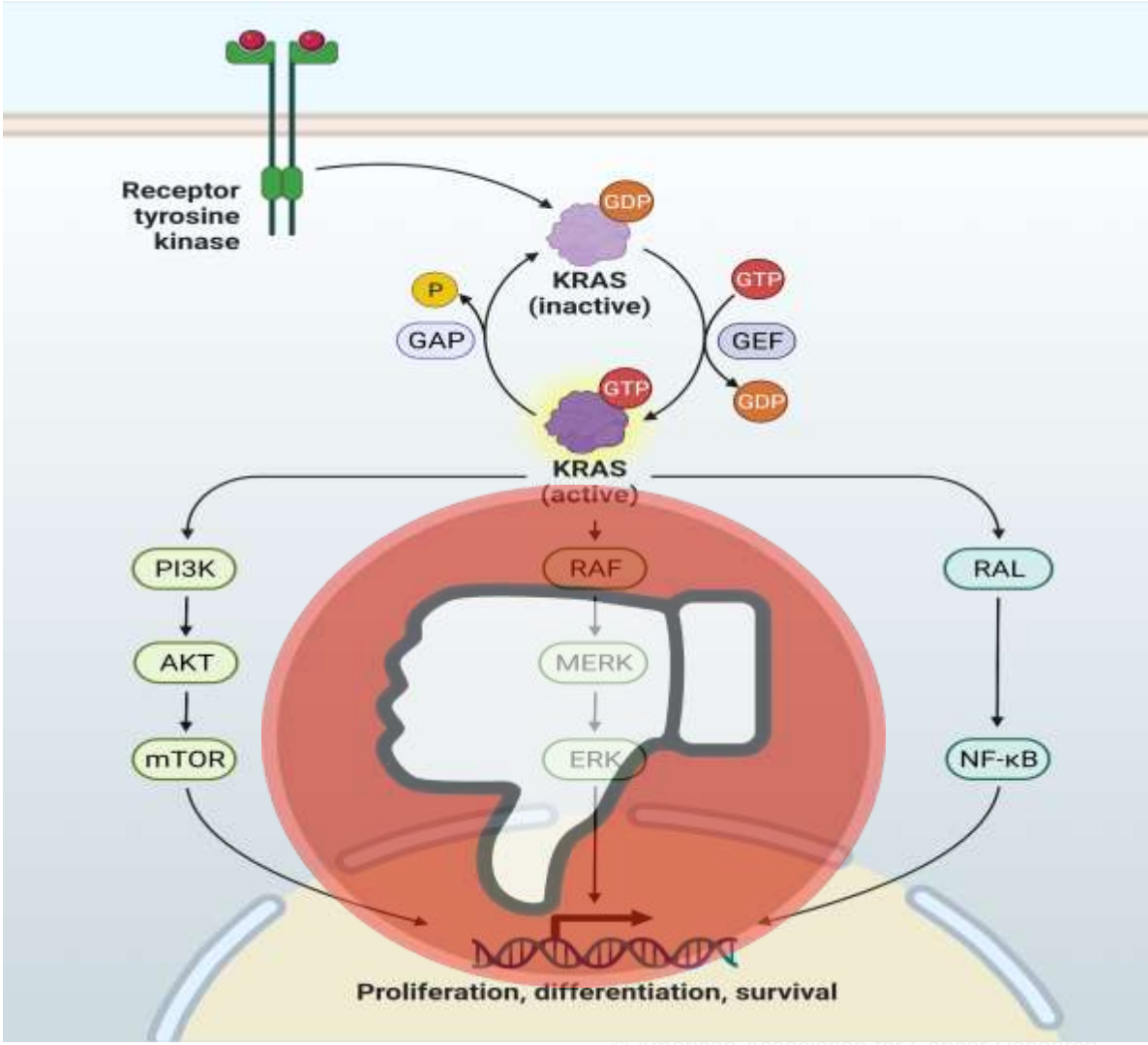
KRAS Mutations are a hallmark of PDAC



Zehir A, et al. Nat Med 2017. Salem ME, et al. JCO Precis Oncol 2022. Luo J. Semin Oncol 2021 [data analyzed using cBio Cancer Genomics Portal (http://cbioportal.org); Cerami E, et al. Cancer Discov. 2012; Gao J, et al. Sci Signal. 2013]. Hosein AN, et al. Nat Cancer 2022

KRAS was considered undruggable for decades

- *KRAS* gene and mutations identified in 1982-3, a GTPase that cycled between active state (GTP-bound) vs inactive state (GDP-bound)
- KRAS mutations resulted in a KRAS protein that was constitutively active with impaired GTPase activity
- 40 years of targeting KRAS downstream and parallel signaling was ineffective



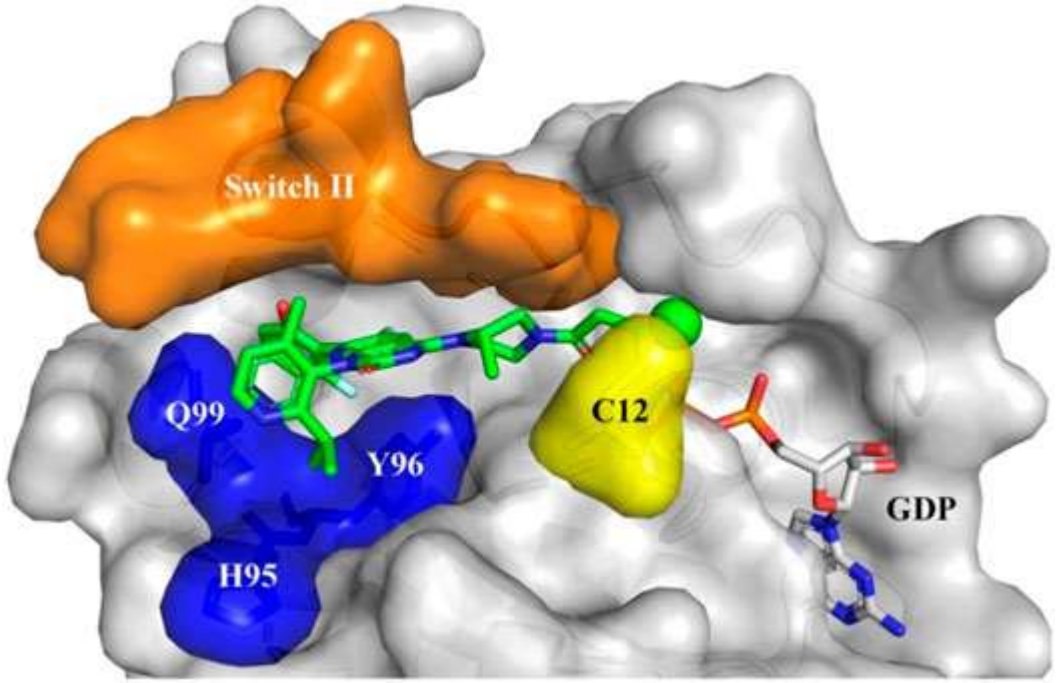
Jancik et al J Biomed Biotech 2010; Huang et al Sig Transd Targeted Ther 2021

https://bpsbioscience.com/research-areas/ras

We are in a new era of direct KRAS targeting now

- In 2013, the Shokat lab found that we could target the cysteine residues of the KRAS G12C novel binding pocket in the inactive form

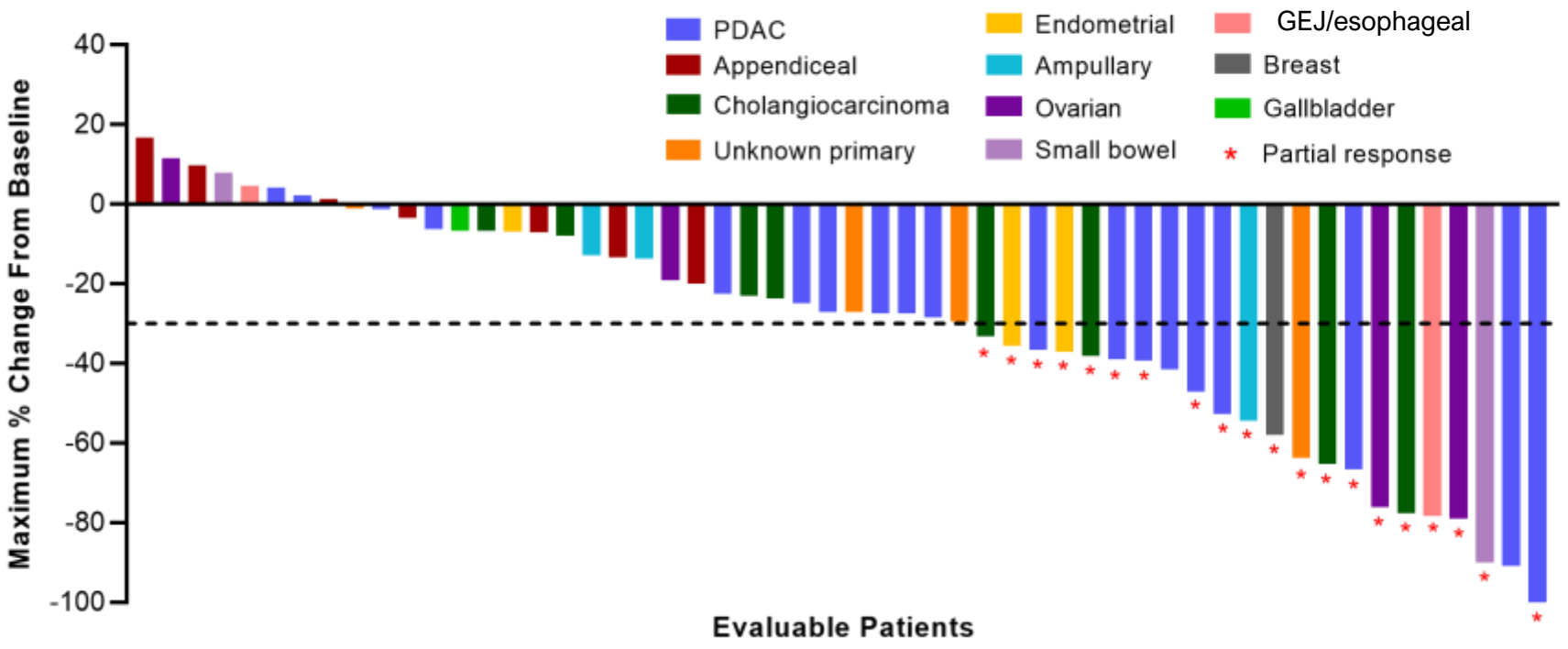
- ~ Prevalence of KRAS G12C mutations
  - NSCLC 9%
  - CRC 3%
  - Appendiceal 4%
  - Pancreatic 1%



https://bpsbioscience.com/research-areas/ras

Jancik et al J Biomed Biotech 2010; Huang et al Sig Transd Targeted Ther 2021, Salem et al JCO PM 2022

G12Ci – first to the party: adagrasib in active in patients with KRAS G12C mutations

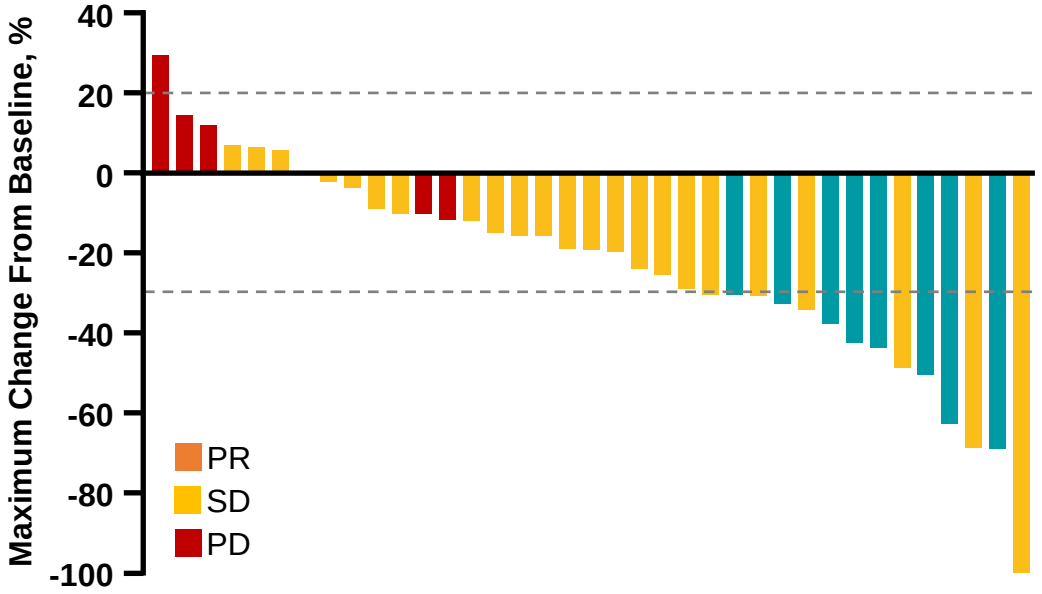


Tumor Type	ORR, n (%)
All patients (n=57)	**20 (35)**
PDAC (n=21)	**7 (33)**
BTC (n=12)	**5 (42)**
Other GI (n=12)	**2 (17)**
Appendiceal (n=7)	0 (0)
Small bowel (n=2)	1 (50)
GEJ/esophageal (n=3)	1 (33)
Gynecological tumors (n=7)	**4 (57)**
Ovarian (n=4)	2 (50)
Endometrial (n=3)	2 (67)
Other tumors (n=5)	**2 (40)**
Unknown primary (n=4)	1 (25)
Breast (n=1)	1 (100)

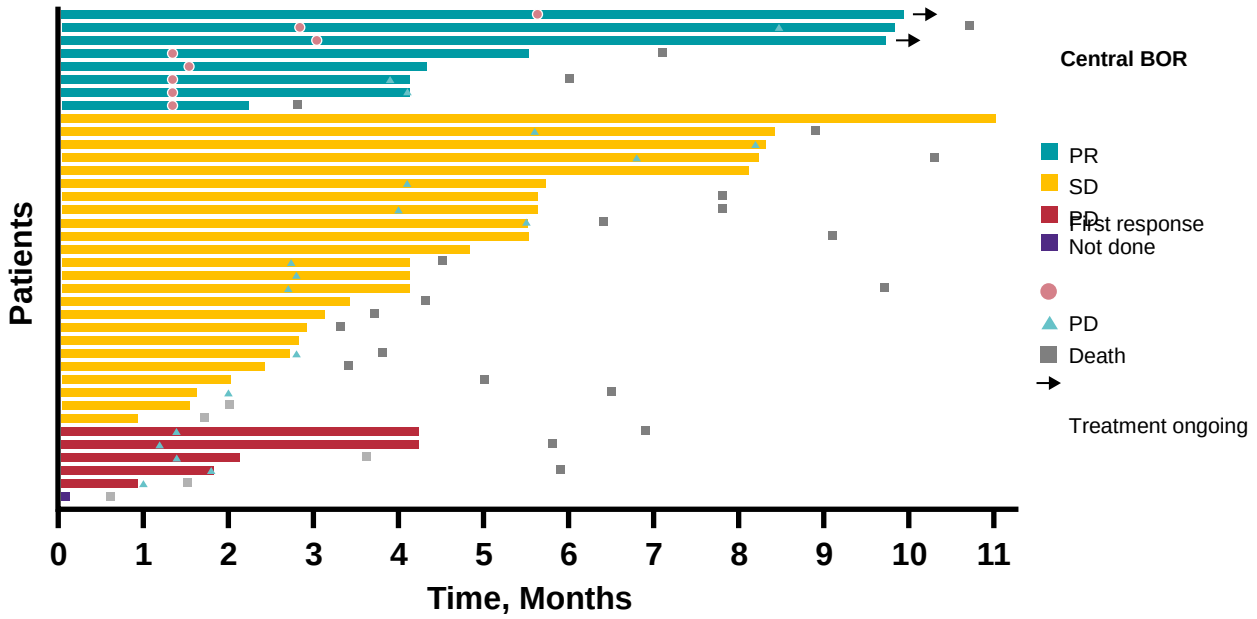
- Confirmed objective responses were observed in 20/57 patients (35%)
- Disease control was observed in 49/57 patients (86%)

G12Ci – first to the party: sotarasib in active in patients with KRAS G12C mutations

Best Tumor Change (n=38)



Duration of Response (n=38)

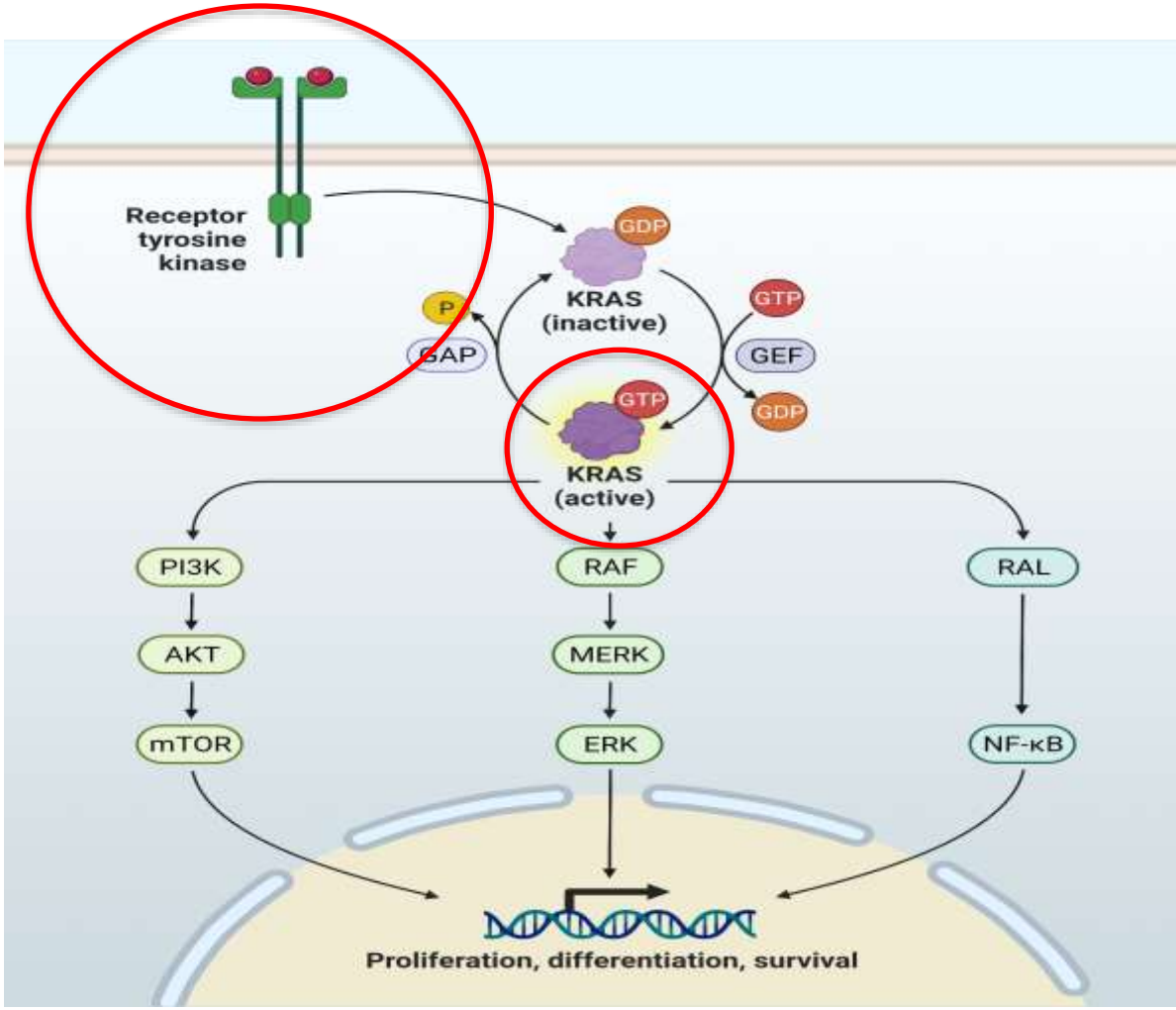


ORR: 21% DCR: 84%

Median DOR was 6 months

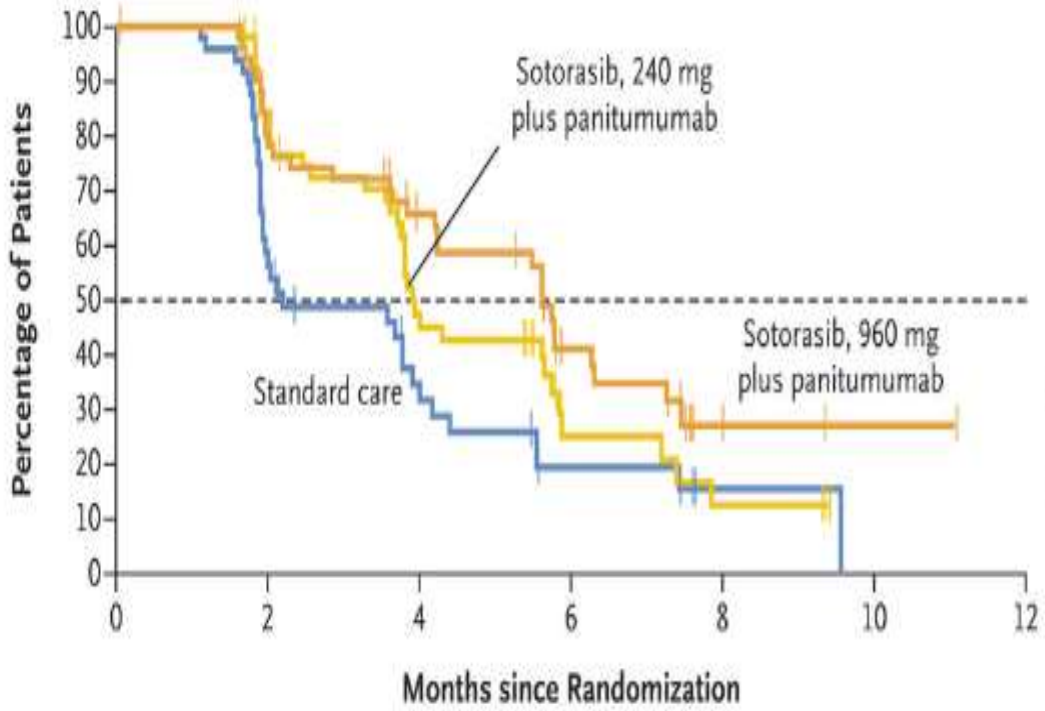
Median PFS = 4.0 m
Median OS = 6 months

Combination strategy: RTKi + mKRASi being explored clinically



Sotorasib activity magnified by addition of an EGFR inhibitor

A Progression-free Survival (Intention-to-Treat Population)



No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

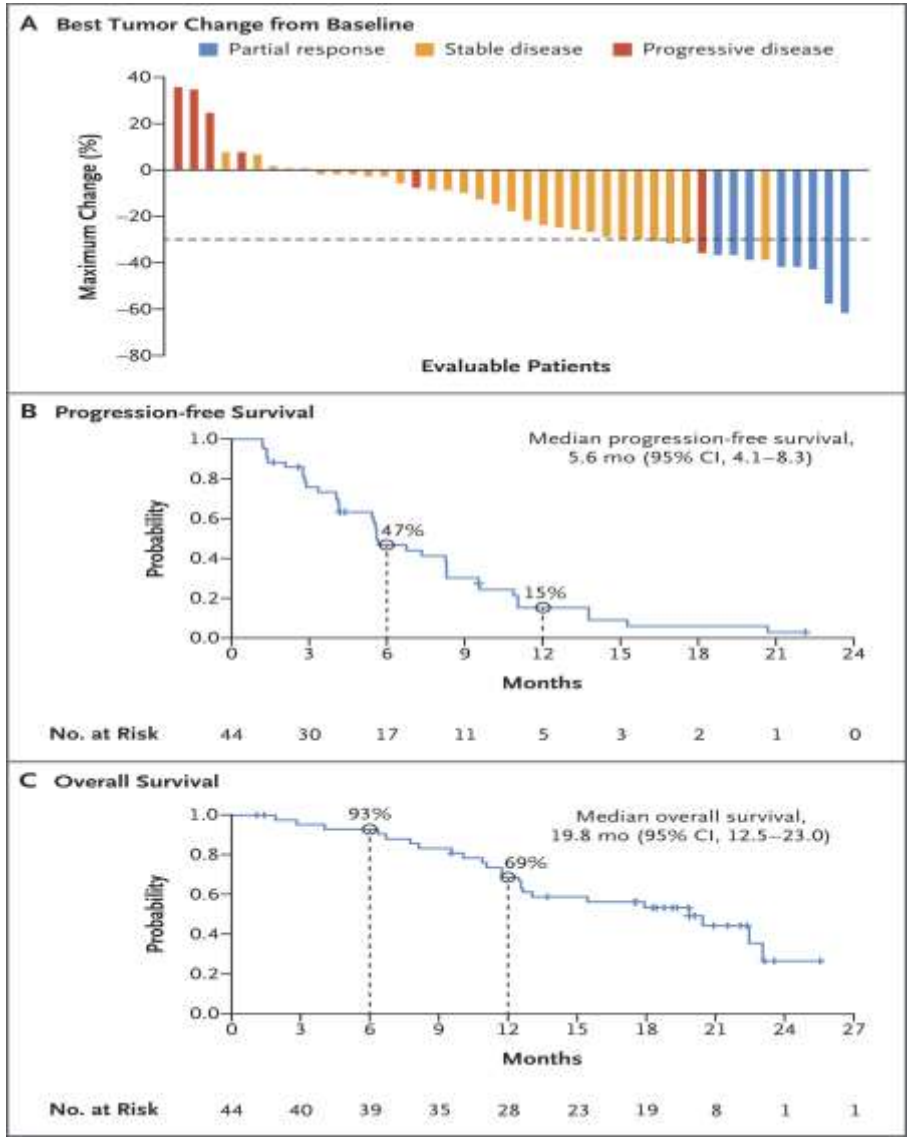
ORR 26.4% vs 5.7% vs 0%

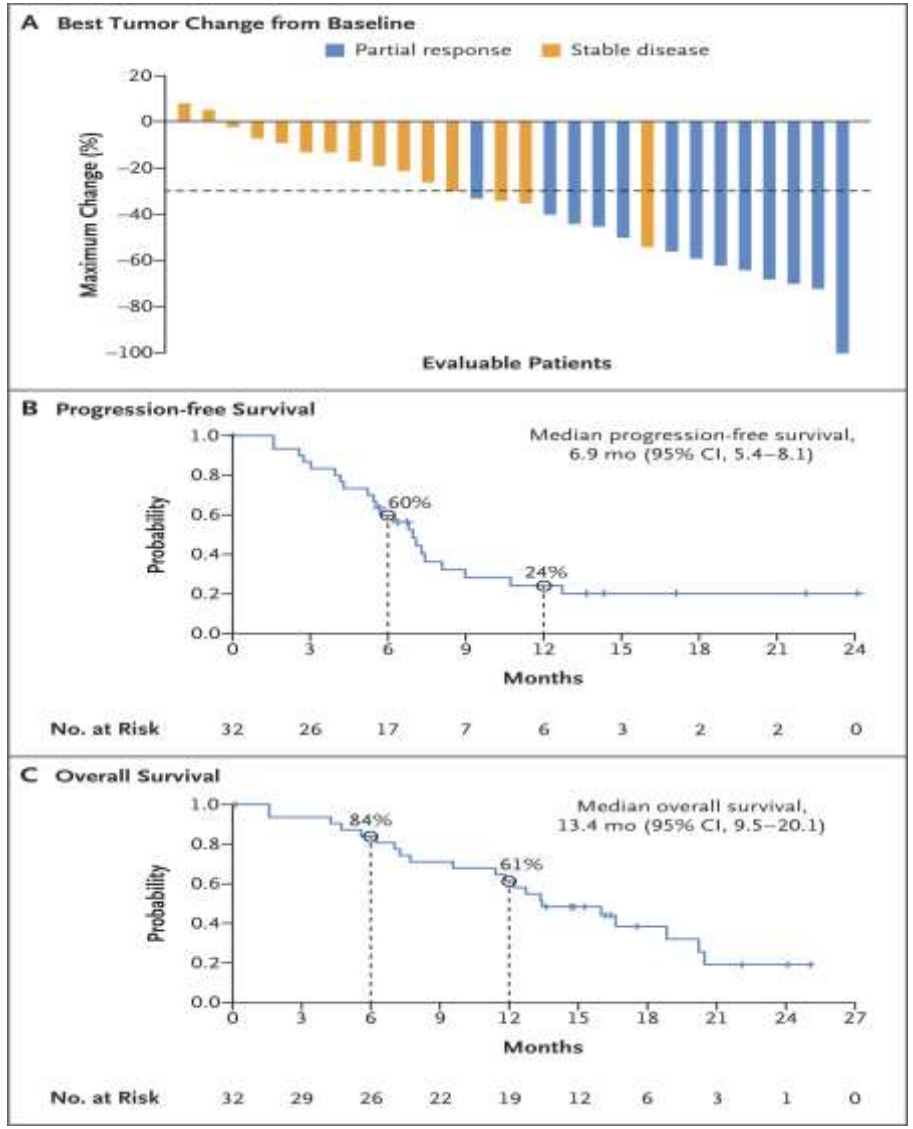
Phase I expansion 7% ORR single agent

Fakih et al. NEJM 2023

Adagrasib activity magnified by addition of an EGFR inhibitor

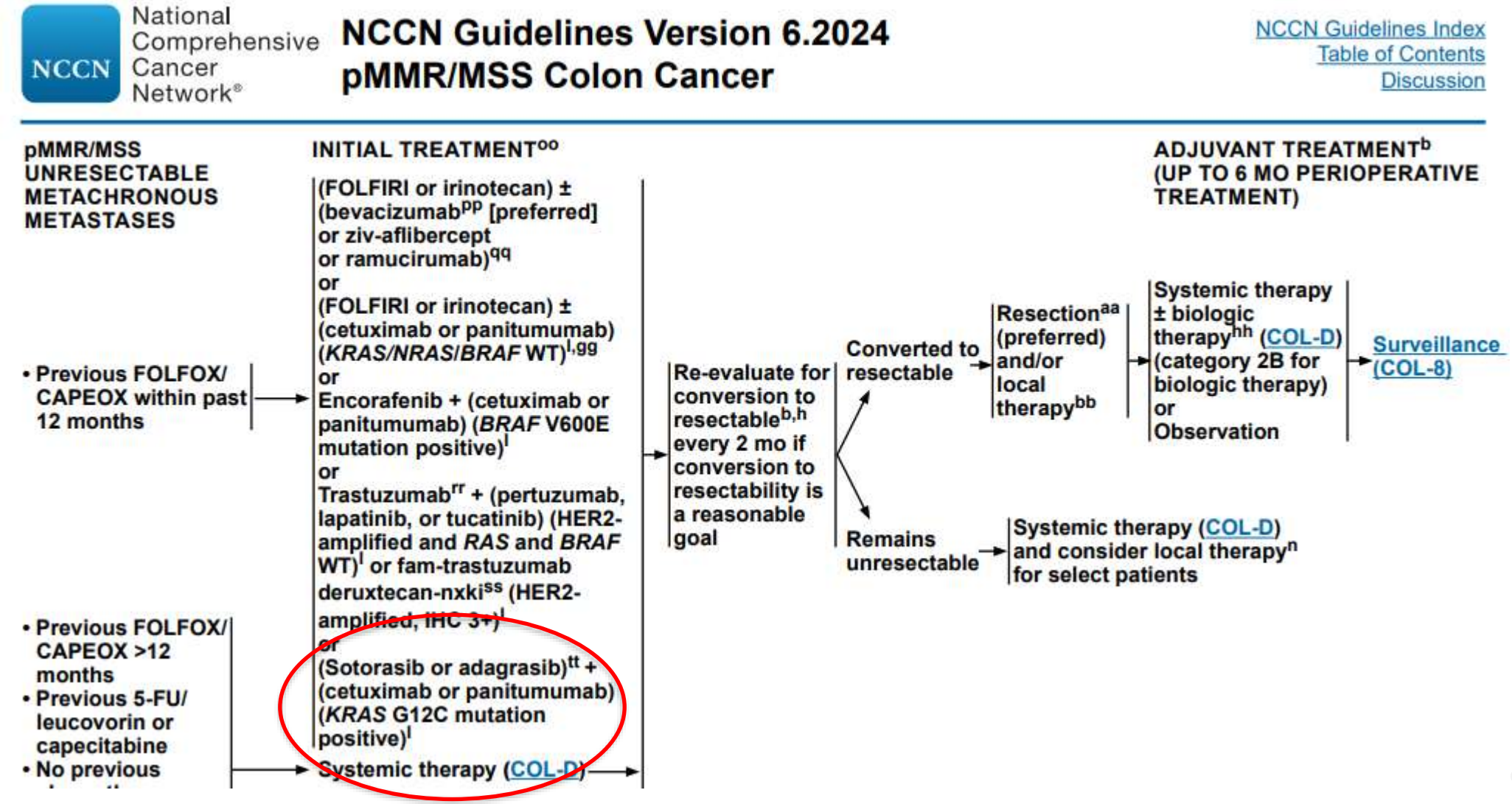
- ORR 19% vs 46%
- PFS 5.6 vs 6.9.
- DOR 4.3 vs 7.6m





Yaeger et al. NEJM 2023

Guidelines now support G12Ci treatment in CRC



NCCN compendia allow for G12Ci therapy in multiple entities

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NCCN Drugs & Biologics Compendium®

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Disease Information	
Guideline Name:	Small Bowel Adenocarcinoma 2.2025
Disease:	Small Bowel Adenocarcinoma
Agent:	Adagrasib

Disease:	Appendiceal Adenocarcinoma
Agent:	Adagrasib

Disease:	Ampullary Adenocarcinoma
Agent:	Adagrasib

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Disease Information	
Guideline Name:	Biliary Tract Cancers 6.2024
Disease:	Extrahepatic Cholangiocarcinoma
Agent:	Adagrasib

Guideline Name:	Biliary Tract Cancers 6.2024
Disease:	Intrahepatic Cholangiocarcinoma
Agent:	Adagrasib

☐ Small Bowel Adenocarcinoma - Small Bowel Adenocarcinoma Guideline Panel Disclosure	Sotorasib	Lumakras®	KRAS G12C-directed tyrosine kinase inhibitor	Adenocarcinoma

Pancreatic Adenocarcinoma - Pancreatic Adenocarcinoma Guideline Panel Disclosure	Sotorasib	Pancreatic Adenocarcinoma 2.2 Pancreatic Adenocarcinoma Adagrasib Adagrasib is indicated

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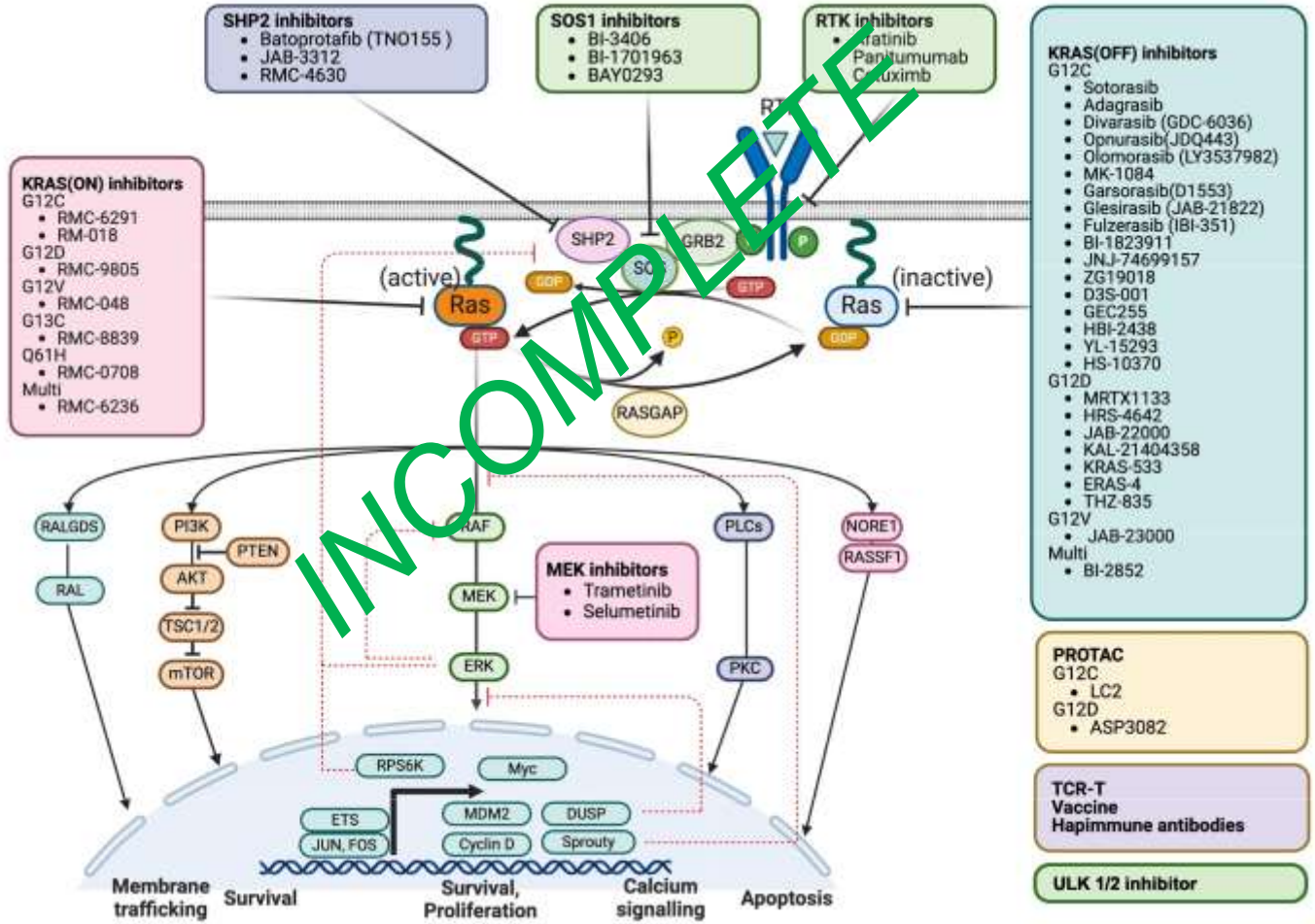
Disease Information	
Guideline Name:	Biliary Tract Cancers 6.2024
Disease:	Gallbladder Cancer
Agent:	Adagrasib

Combination strategy: does vertical inhibition of signaling cascade improve outcomes?

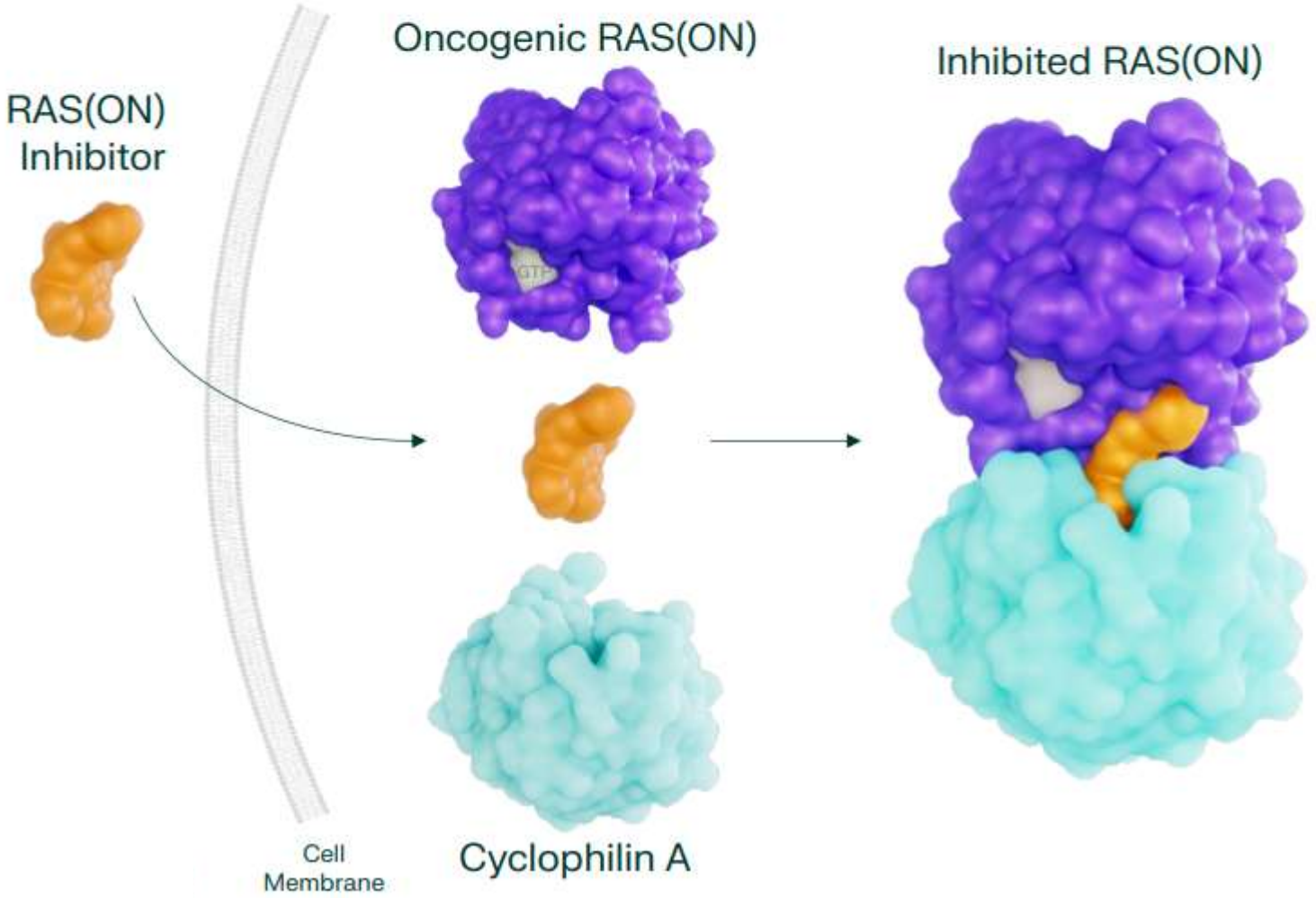
The party becomes a rager: multiple agents for KRAS inhibition

- Direct inhibition with small molecules
- KRAS vaccines
- Pan-KRAS degraders (PROTACs)
- Indirect inhibition by targeting effector molecules and/or their interaction with KRAS (e.g. SOS1 or SHP2 inhibitors)



Oya et al 2024

Pioneering Tri-Complex RAS(ON) Inhibitors Designed to Deliver Robust and Durable Antitumor Activity



RMC-6236

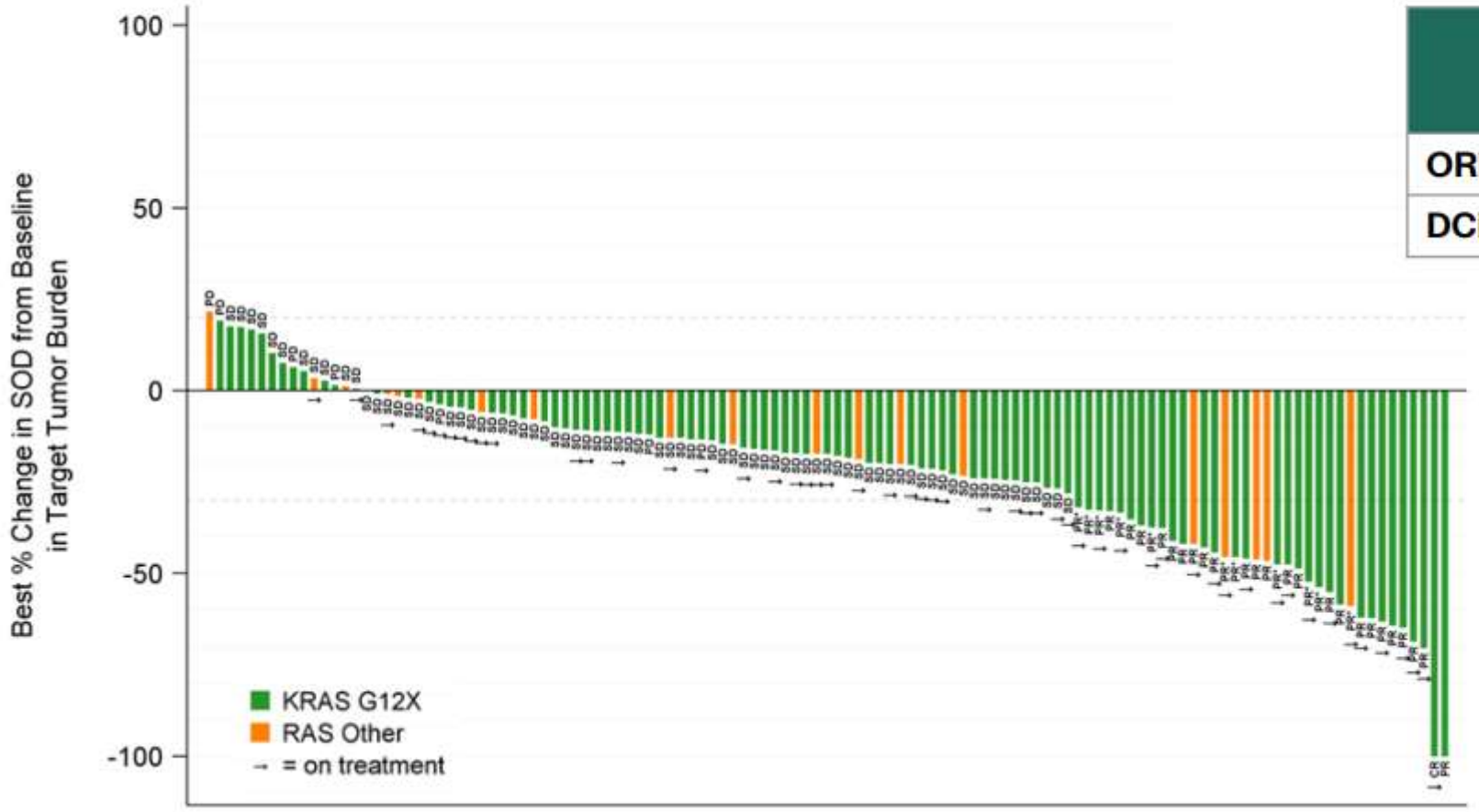
- **Oral RAS(ON) multi-selective inhibitor**
- **Clinically validated across diverse oncogenic RAS variants, including G12D**

RMC-9805

- **Oral RAS(ON) G12D-selective covalent inhibitor**
- **Clinically validated against oncogenic RAS G12D**

RMC-6236 Current Data

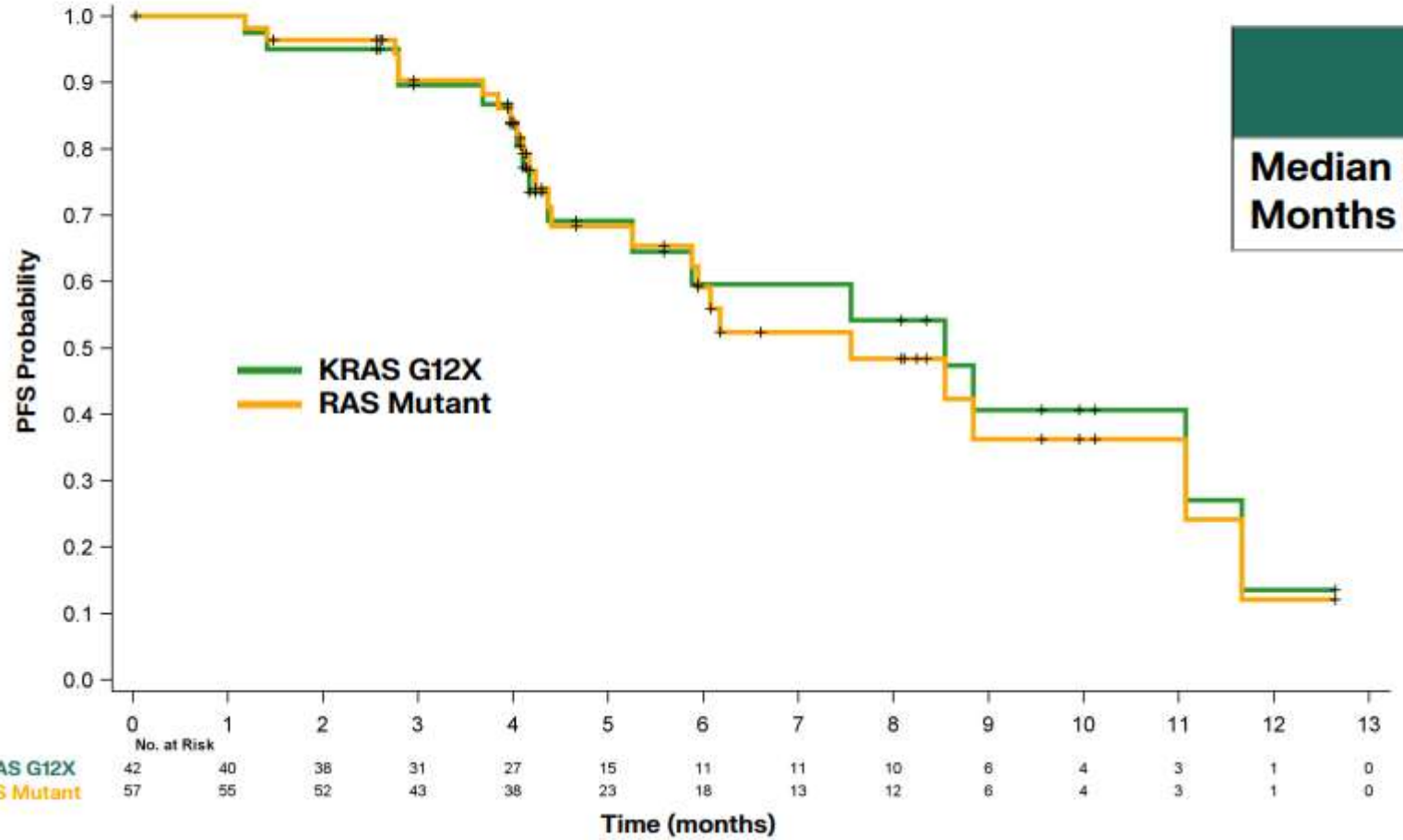
ORR and DCR in PDAC Patients Treated with RMC-6236 160-300 mg



	KRAS G12X[a], 160-300 mg	
	2L (N = 42)	3L+ (N = 63)
ORR[b]	29%	22%
DCR[b]	91%	89%

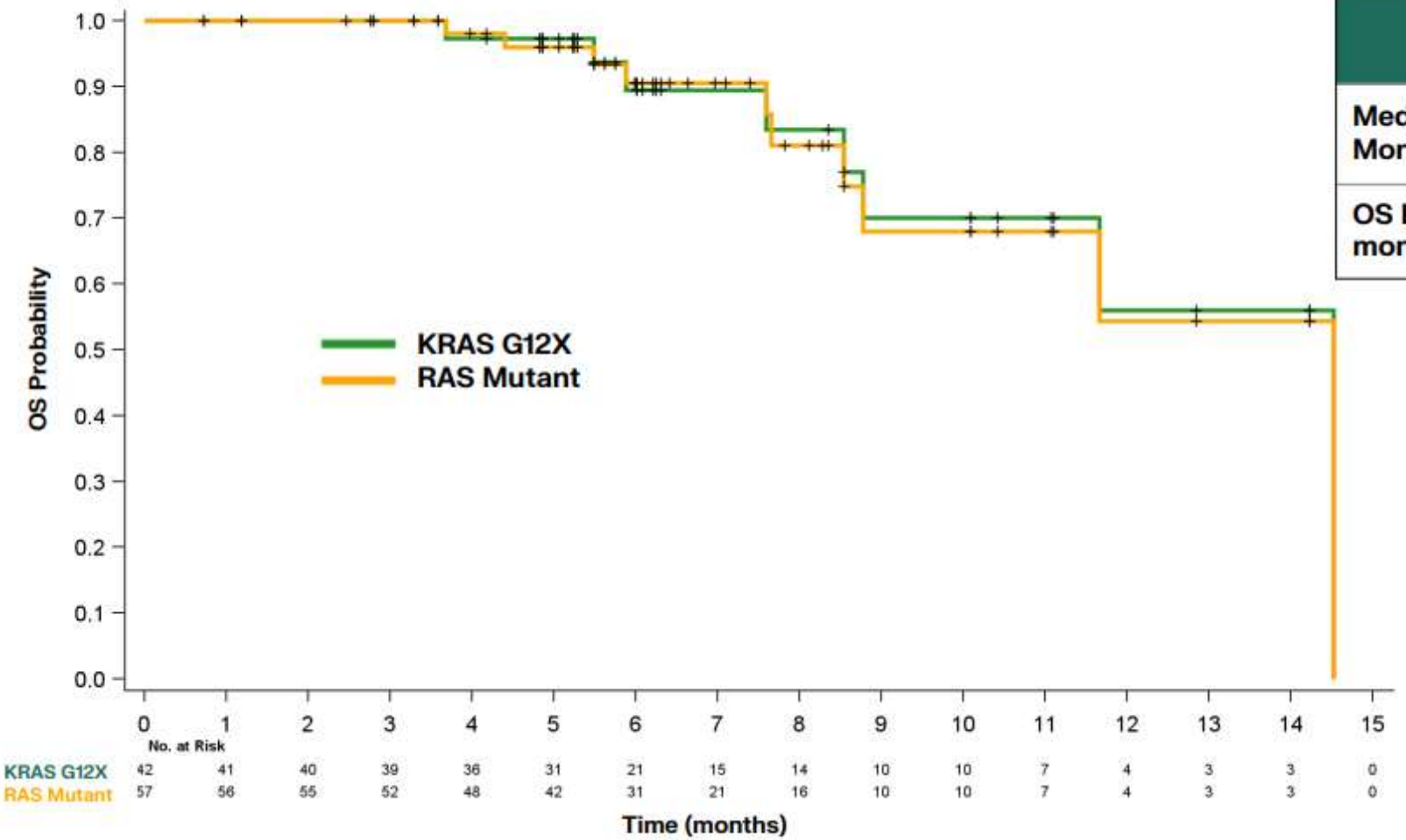
Data cutoff: July 23, 2024.
Among patients with an objective response (confirmed or unconfirmed), 50% of initial response occurred after 2 months of RMC-6236 treatment.

Compelling PFS in PDAC Patients Treated with RMC-6236 160-300 mg as 2L Therapy



	KRAS G12X[a] (N = 42)	RAS Mutant[b] (N = 57)
Median PFS, Months (95% CI)	**8.5** (5.3-11.7)	**7.6** (5.9-11.1)

Compelling OS in PDAC Patients Treated with RMC-6236 160-300 mg as 2L Therapy



	KRAS G12X[a] (N = 42)	RAS Mutant[b] (N = 57)
Median OS, Months (95% CI)	**14.5** (8.8, NE)	**14.5** (8.8, NE)
OS Rate at 6 months, % (95% CI)[c]	**89** (70, 97)	**91** (77, 96)

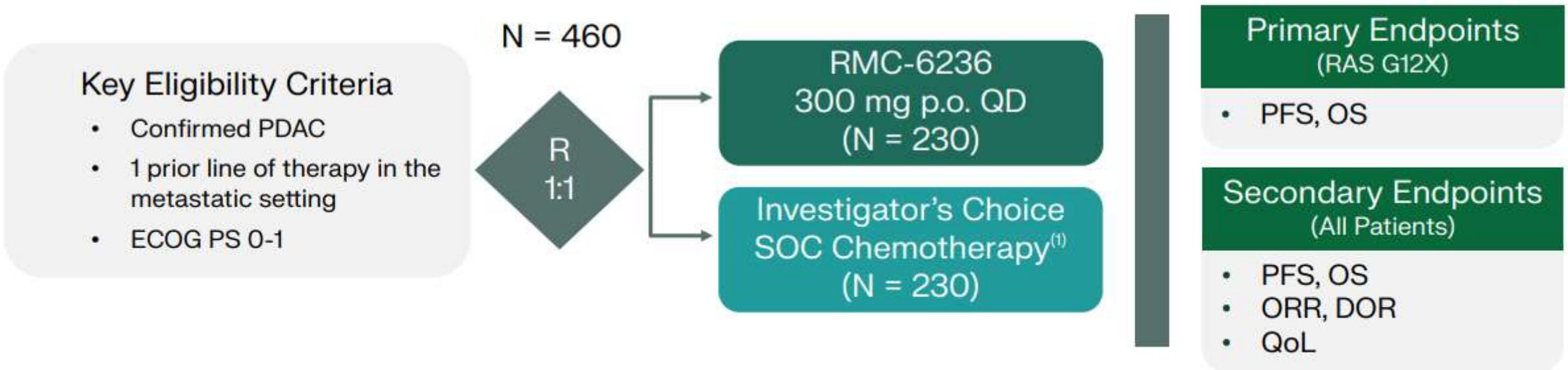
Treatment-Related Adverse Events: PDAC (160-300 mg)

	N = 127	
Maximum Severity of Treatment-Related AEs (TRAEs)	**Any Grade**	**Grade ≥3**
Any TRAE	122 (96%)	28 (22%)
TRAEs occurring in ≥10% of patients, n (%)		
Rash[1]	111 (87%)	8 (6%)
Diarrhea	58 (46%)	2 (2%)
Nausea	54 (43%)	0 (0%)
Stomatitis/mucositis	48 (38%)	3 (2%)
Vomiting	36 (28%)	0 (0%)
Fatigue	21 (17%)	1 (1%)
Paronychia	13 (10%)	0 (0%)
Other select TRAEs, n (%)		
ALT elevation	6 (5%)	0 (0%)
AST elevation	8 (6%)	0 (0%)
Electrocardiogram QT prolonged	1 (1%)	1 (1%)
Neutropenia/neutrophil count decreased	6 (5%)	1 (1%)
Thrombocytopenia/platelet count decreased	14 (11%)	3 (2%)

(1) Includes preferred terms of dermatitis acneiform, eczema, erythema, rash, rash erythematous, rash maculopapular, rash pruritic and rash pustular; multiple types of rash may have occurred in the same patient.
ALT, alanine transaminase; AST, aspartate transferase

5/11/24 data cutoff

Trial Design for RASolute 302: 2L Metastatic PDAC



RMC-9805 Current Data

RMC-9805-001 Phase 1 Study Design (RMC-9805 Monotherapy)

Key Eligibility Criteria

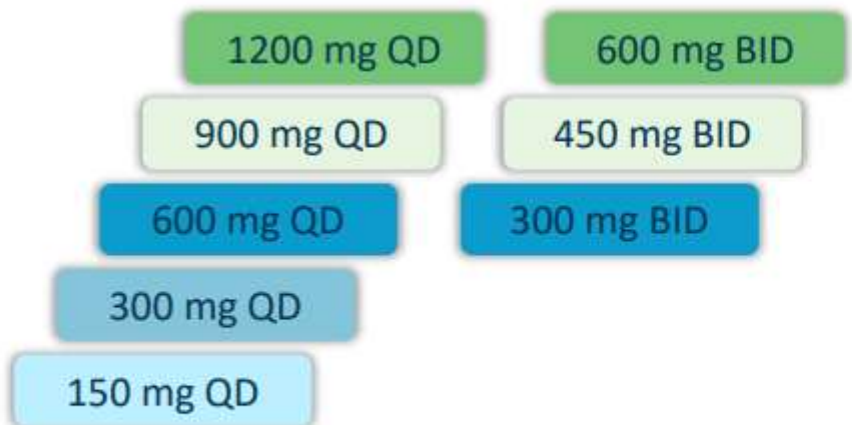
- Advanced solid tumors with KRAS G12D mutations
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

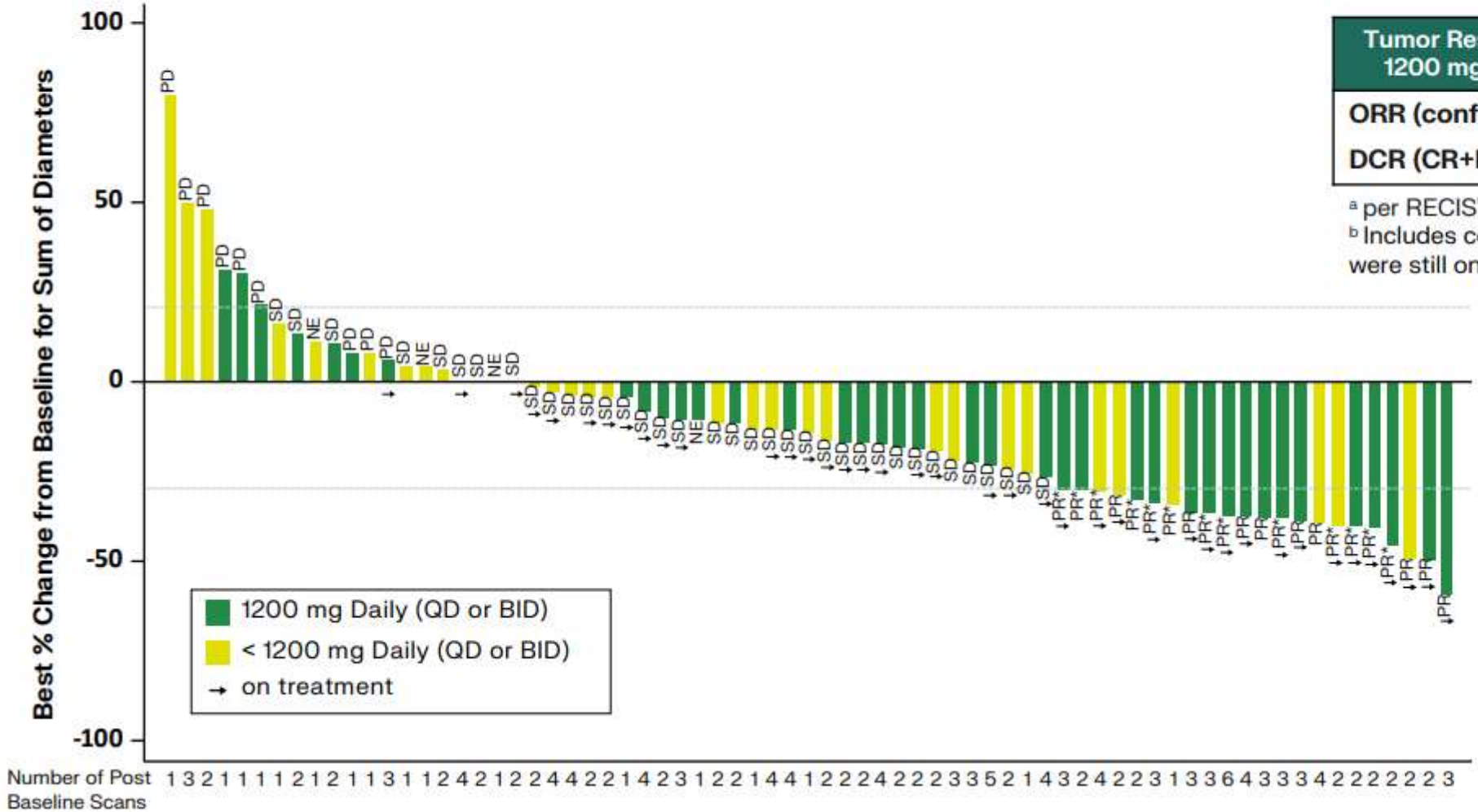
Part 1: Dose Escalation

RMC-9805 administered orally QD or BID, 21-day treatment cycle



Part 2: Expansion and Dose Optimization in PDAC

Encouraging Initial Antitumor Activity in PDAC Patients Treated with RMC-9805



Tumor Response for PDAC Patients Treated with 1200 mg Daily Dose (QD, N=20 or BID, N=20)[a]	
ORR (confirmed or pending)[b], % (n)	30% (12)
DCR (CR+PR+SD), % (n)	80% (32)

[a] per RECIST v1.1 ;
[b] Includes confirmed PRs and unconfirmed PRs who were still on treatment and may yet be confirmed

Meaningfully different tolerability between two agents

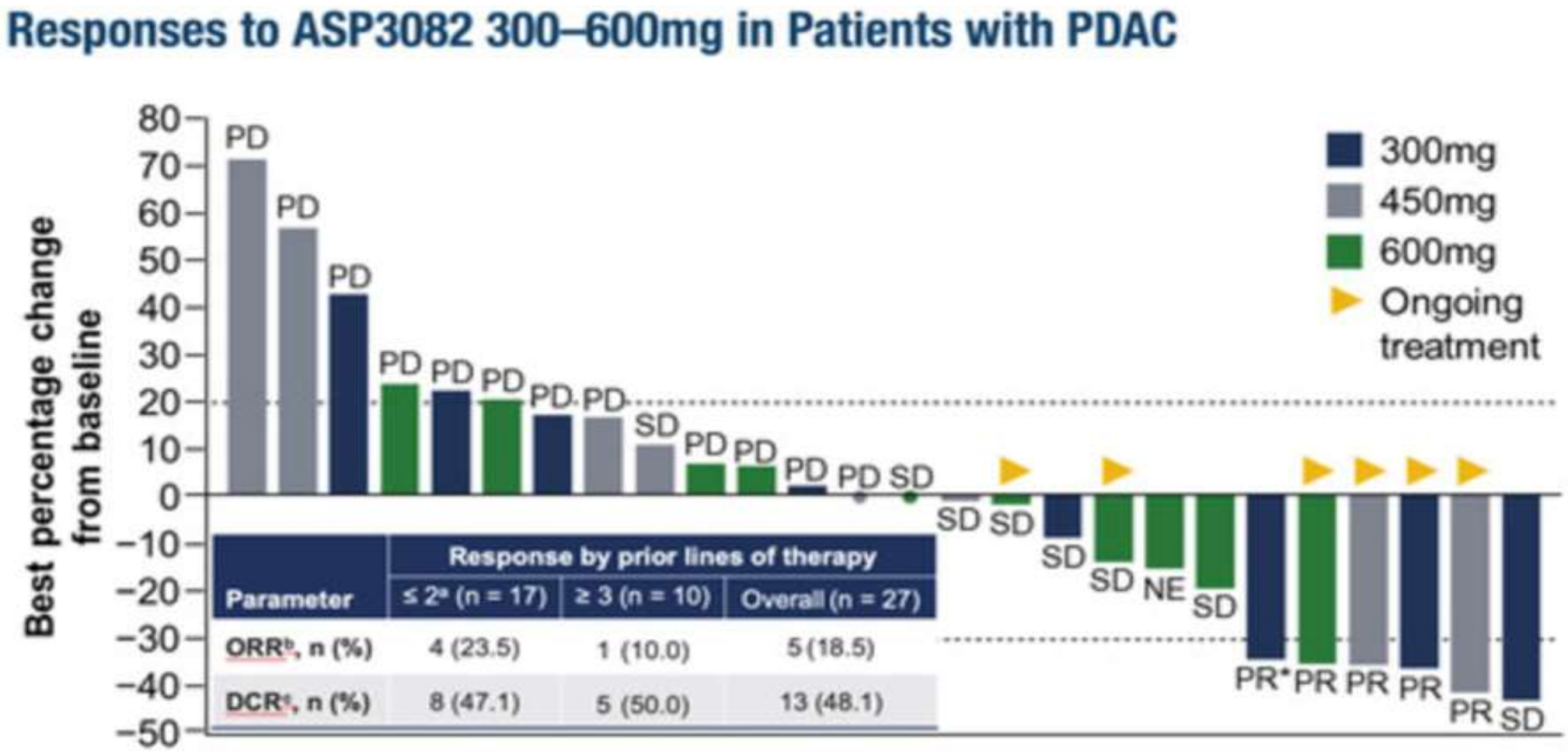
Maximum severity of treatment-related AEs (TRAEs)	RMC-6236 160-300 mg QD (N =127)	
	Any Grade	Grade ≥ 3
Any TRAE	124 (98)	37 (29)
TRAEs occurring in ≥ 10% of patients, n (%)		
Rash[a]	115 (91)	10 (8)
Diarrhea	61 (48)	3 (2)
Nausea[b]	54 (43)	0 (0)
Vomiting[b]	39 (31)	0 (0)
Stomatitis	39 (31)	4 (3)
Fatigue	25 (20)	1 (1)
Paronychia	17 (13)	0 (0)
Mucosal inflammation	16 (13)	1 (1)
Thrombocytopenia/platelet count decreased	14 (11)	3 (2)
Decreased appetite	14 (11)	1 (1)
Peripheral edema	13 (10)	0 (0)
Other select TRAEs, n (%)		
Anemia	11 (9)	7 (6)
ALT elevation	10 (8)	3 (2)
AST elevation	9 (7)	2 (2)
Neutropenia/neutrophil count decreased	7 (6)	2 (2)

	RMC-6236 160–300 mg QD (N = 127)
TRAEs leading to dose modification, n (%)	45 (35)
Dose interruption	43 (34)
Dose reduction	24 (19)
Dose discontinuation	0 (0)
Specific TRAEs leading to dose reduction in >10% patients, n (%)	
Rash[a]	14 (11)
Mean dose intensity	92%

Patients Treated with RMC-9805 1200 mg Daily (1200 mg QD, N=60 or 600 mg BID, N=39)				
Maximum Severity of Treatment-Related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	23 (23%)	4 (4%)	0	27 (27%)
Diarrhea	16 (16%)	4 (4%)	0	20 (20%)
Vomiting	13 (13%)	2 (2%)	0	15 (15%)
Rash[a]	10 (10%)	0	0	10 (10%)
Other select TRAEs, n(%)				
ALT elevation	5 (5%)	0	1 (1%)	6 (6%)
AST elevation	3 (3%)	1 (1%)	0	4 (4%)
Stomatitis	0	0	0	0
TRAEs leading to dose reduction, n (%)	4 (4%)	0	0	4 (4%)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0

- No treatment-related Grade 4 or 5 AEs or SAEs have been reported

Activity seen in KRAS G12D degrader



Parameter	Response by prior lines of therapy		
	≤ 2[a] (n = 17)	≥ 3 (n = 10)	Overall (n = 27)
ORR[b], n (%)	4 (23.5)	1 (10.0)	5 (18.5)
DCR[c], n (%)	8 (47.1)	5 (50.0)	13 (48.1)

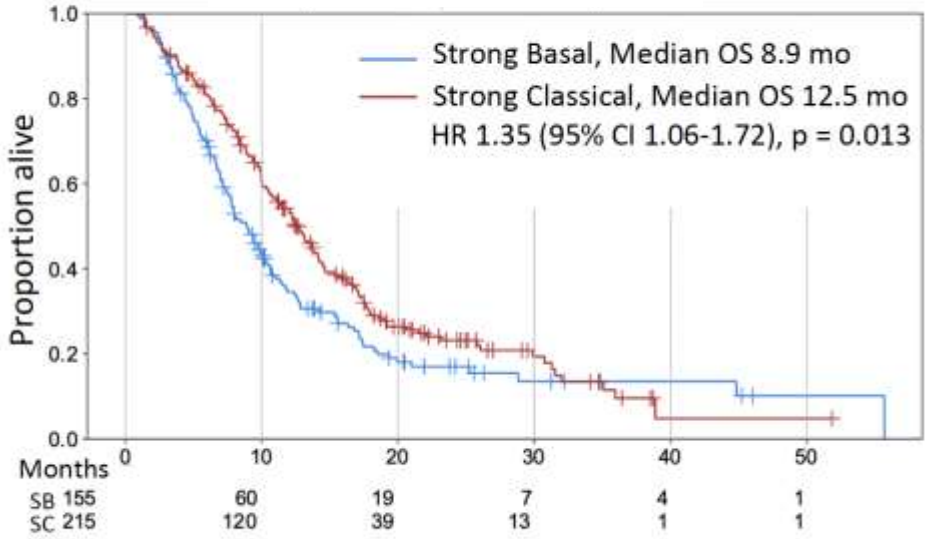
Park et al. ESMO 2024

Combination strategy: is combining with chemotherapy additive or synergistic?

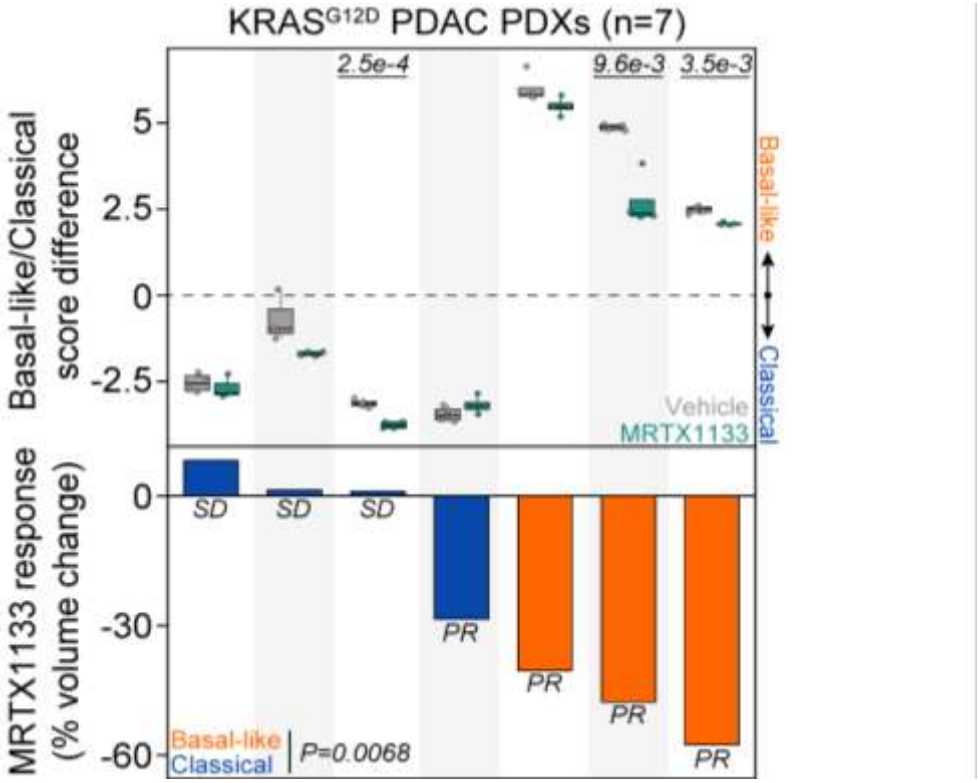
RAS inhibitors may preferentially target a chemo-resistant (basal) phenotype in PDAC

Basal type pancreatic cancer is more chemotherapy resistant

FOLFIRINOX



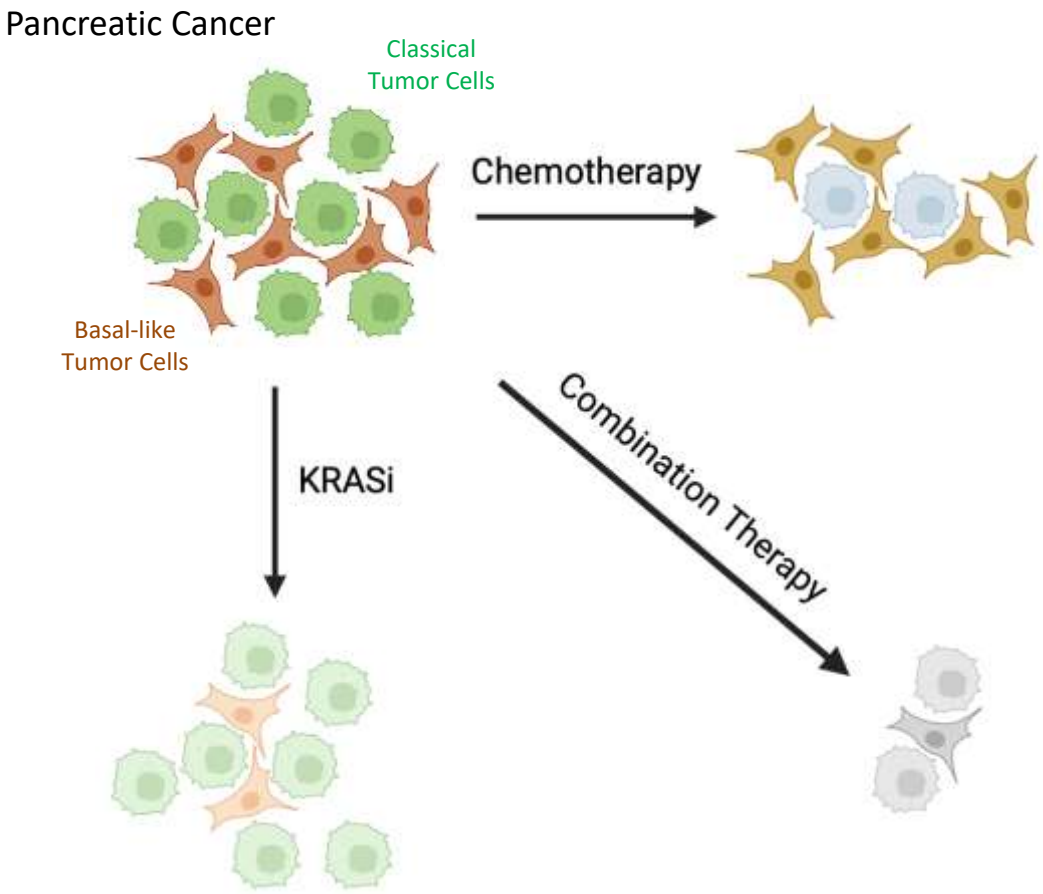
. . . but responds better to KRAS inhibition.



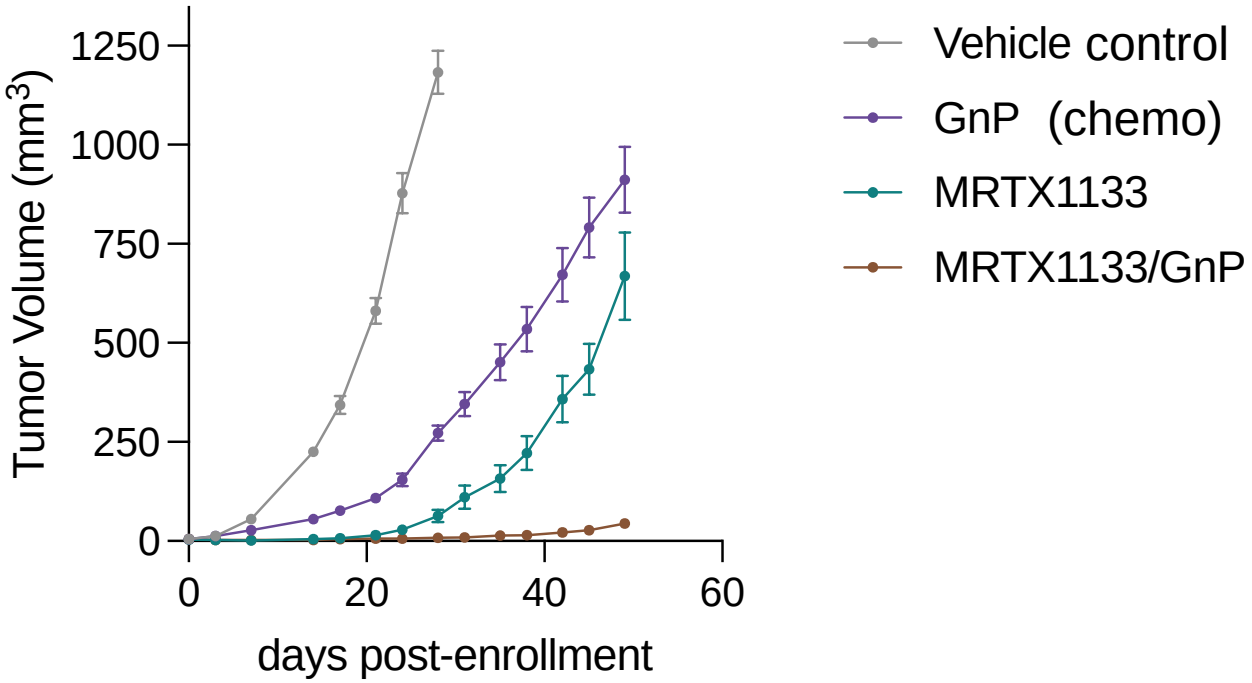
Aguirre et al AACR 2024

Breakthrough Cancer Foundation: MDACC, DFCI, MSK

Combination chemo+KRASi therapy could target both subtypes of pancreatic cancer



Mouse model of pancreatic cancer treated with chemotherapy + KRAS inhibition



Further detail:
AACR Tuesday session: Advances in Organ Site Research - Unwrapping heterogeneity in pancreatic cancer
Mechanisms of resistance of KRAS inhibition in pancreatic cancer
Andy Aguirre

Much more coming in this space

Clinical Development Pipeline

APPROACH	FOCUS	EARLY CLINICAL DEVELOPMENT[1]	REGISTRATIONAL TRIAL
RMC-6236 (MULTI: G12X, G13X, Q61X)			
Monotherapy	PDAC		
	NSCLC		
	Other solid tumors		
Combination	+ Chemotherapy, PDAC and CRC		
	+ Pembrolizumab, NSCLC		
	+ anti-EGFR, CRC		
RMC-6291 (G12C)			
Monotherapy	Solid tumors		
Combination	+ Pembrolizumab, NSCLC		
	+ RMC-6236, solid tumors		
RMC-9805 (G12D)			
Monotherapy	Solid tumors		
Combination	+ RMC-6236, solid tumors		

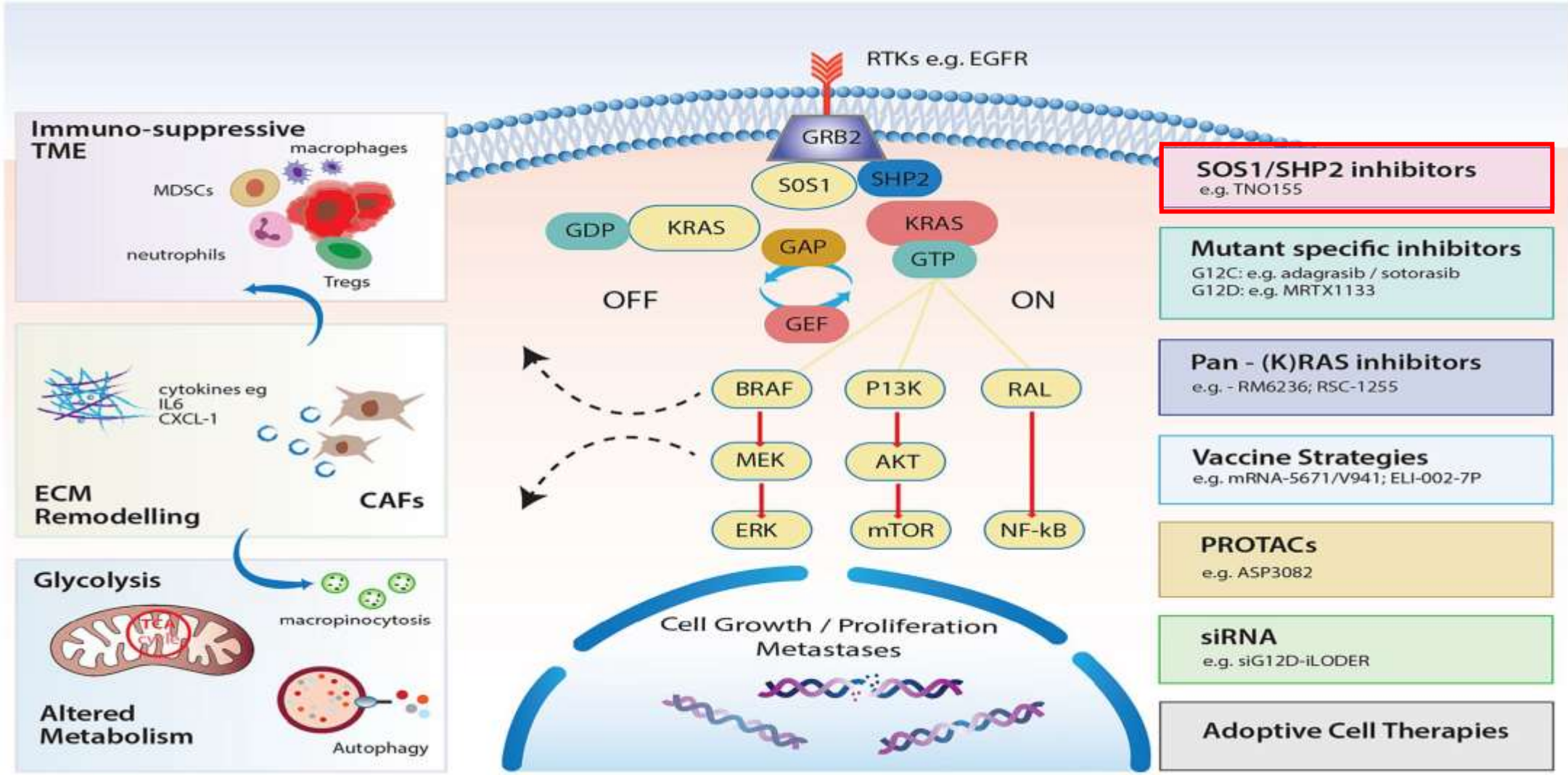
(1) Long bar indicates that registrational intent has been announced.

Phase I this year

BMS/Mirati – G12D
Incyte – G12D
Beigene – multi-Ras and G12D
Jazz – multi-RAS
Pfizer – multi-RAS
Lilly/Loxo -multi-Ras and G12D
BI – multi-RAS

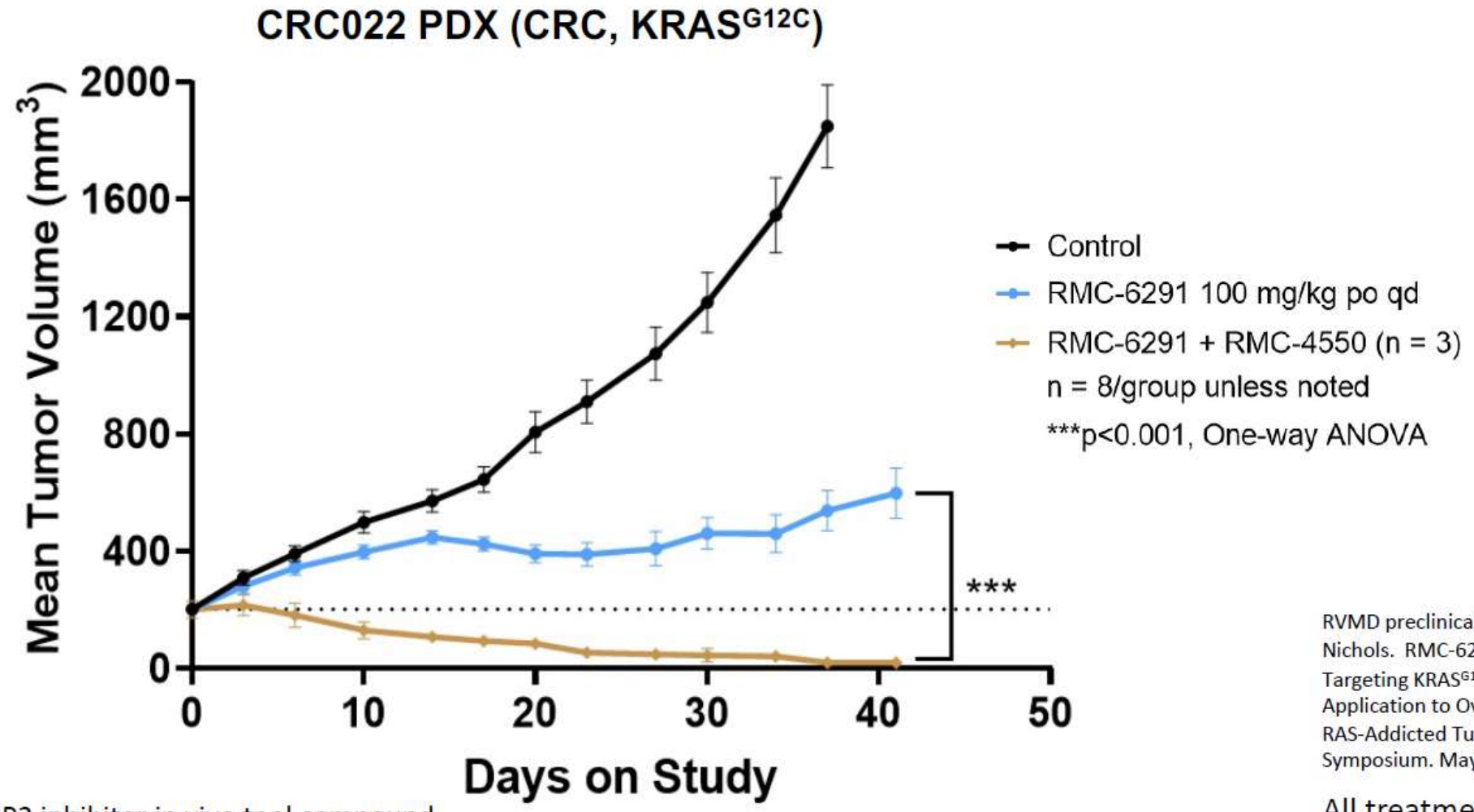
Combination strategy: does vertical inhibition of signaling cascade improve outcomes?

Combination strategy: Vertical inhibition with SOS1/SHP2+KRASi



Linehan et al Front Med 2024

KRAS G12Ci+SHP2i is active preclinically in resistant CRC models



RMC-4550 is a SHP2 inhibitor in vivo tool compound

RVMD preclinical research
Nichols. RMC-6291: Biological Features of Targeting KRASG12C(ON) and Potential Application to Overcoming Drug Resistance in RAS-Addicted Tumors. The Third RAS Initiative Symposium. May 24 – 26, 2021.

All treatments well tolerated

Kindly provided by Mallika Singh

Combination strategy: how do we deal with suboptimal durability/resistance?

Many mechanisms of KRASi resistance are emerging

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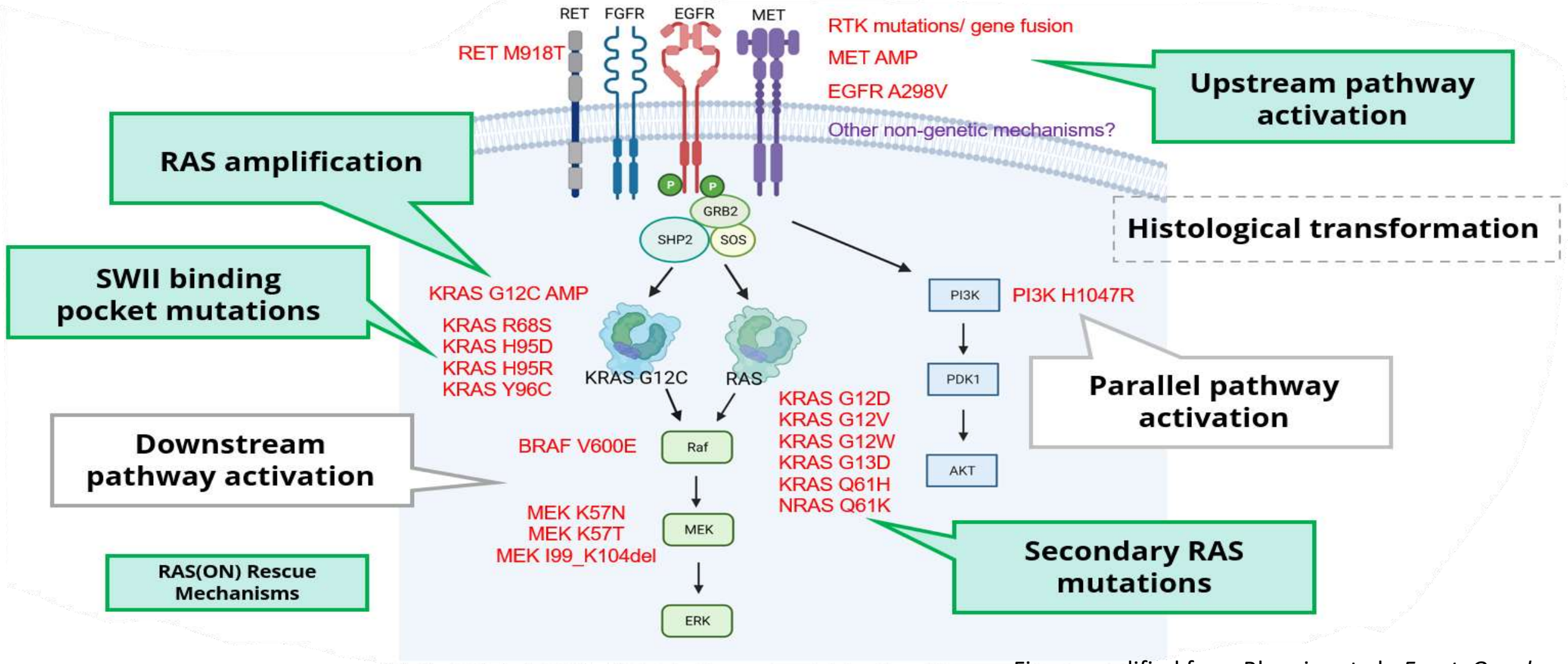


Figure modified from Blaquier et al., *Front. Oncol.*

Multiple mechanisms of resistance emerge on therapy with KRASi

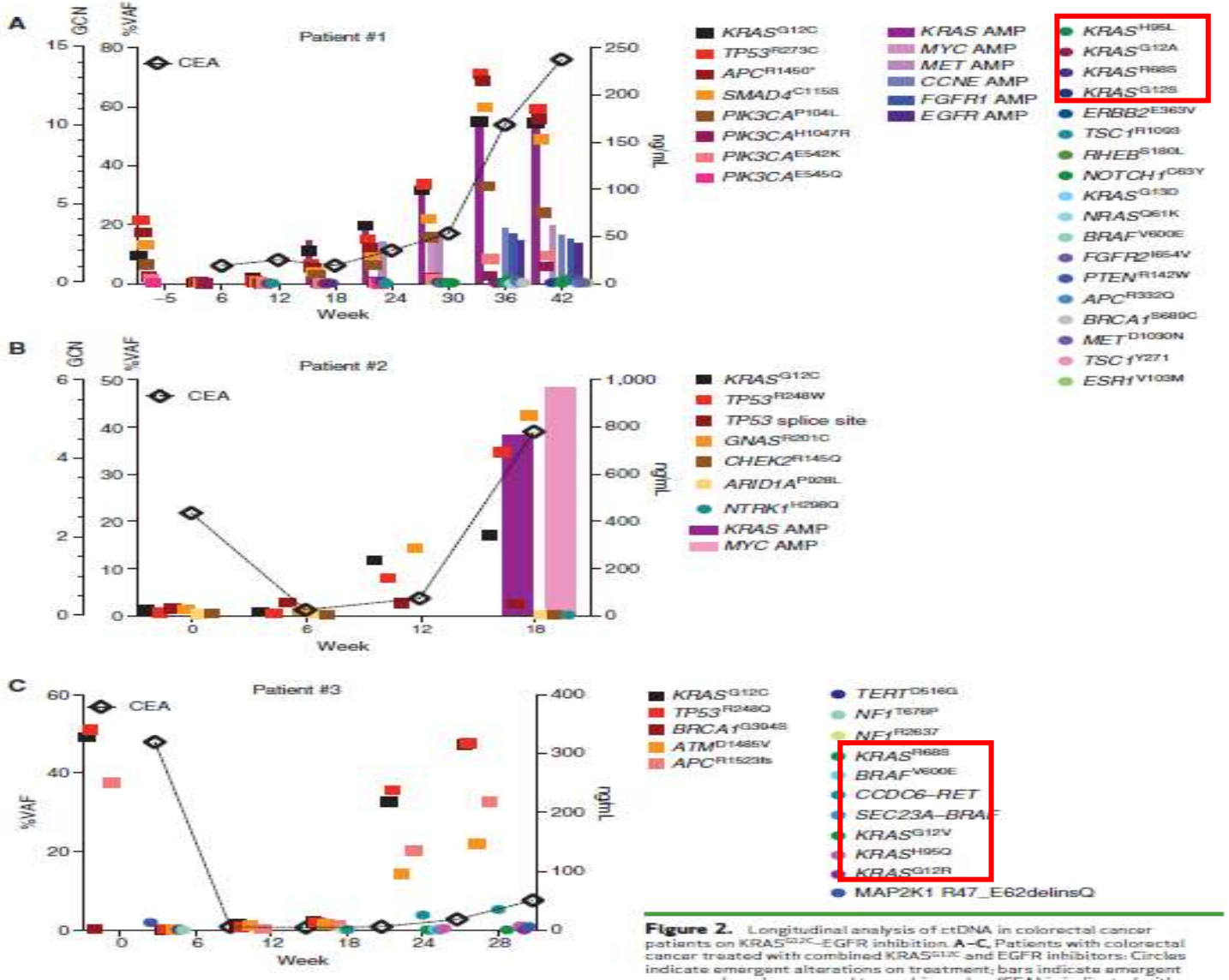


Figure 2. Longitudinal analysis of ctDNA in colorectal cancer patients on KRAS^{G12C}–EGFR inhibition. **A–C,** Patients with colorectal cancer treated with combined KRAS^{G12C} and EGFR inhibitors: Circles indicate emergent alterations on treatment; bars indicate emergent

Yaeger …Misale. Cancer Discovery 2023

Multi RAS inhibitors have potency against emerging KRAS mutations

$KRAS^{G12}$	G12A	G12C	G12D	G12E	G12F	G12H	G12I	G12K	G12L	G12M	G12N	G12P	G12Q	G12R	G12S	G12T	G12V	G12W	G12Y
Clinical resistance		■			■									■			■	■	
RMC-6236	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

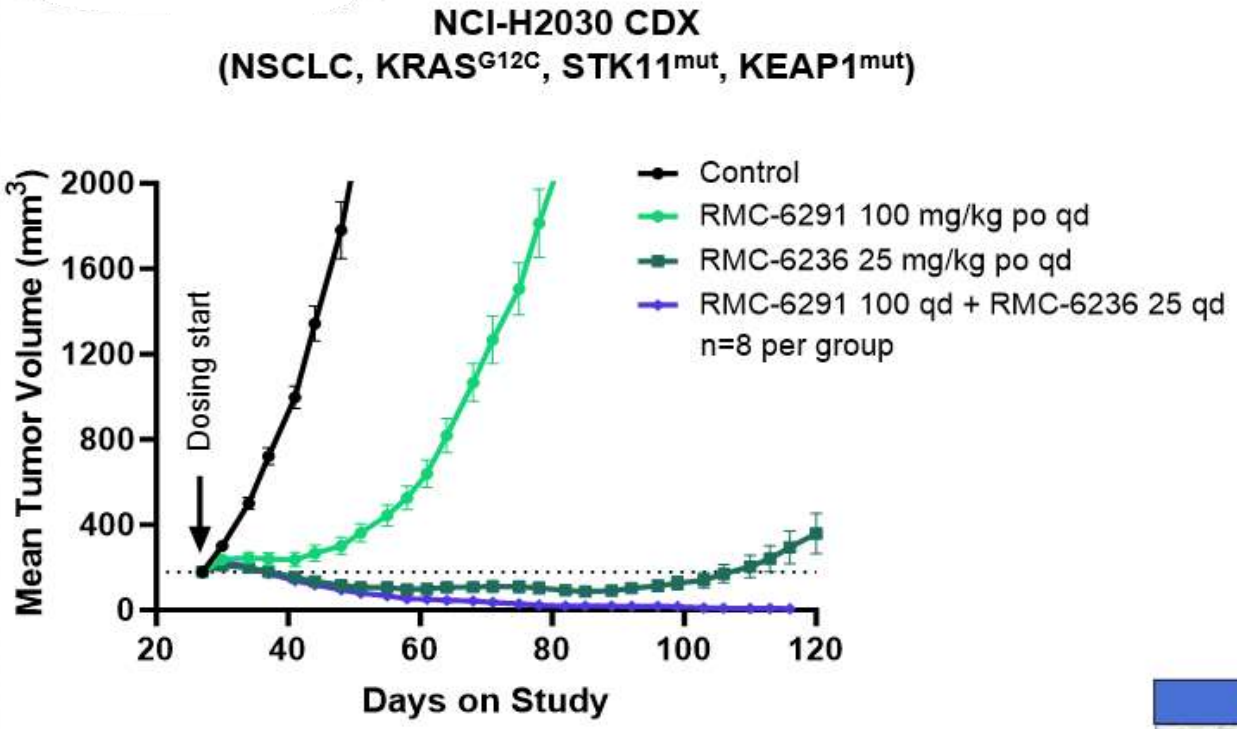
$KRAS^{G13}$	G13	G13D
Clinical resistance		■
RMC-6236	+	+

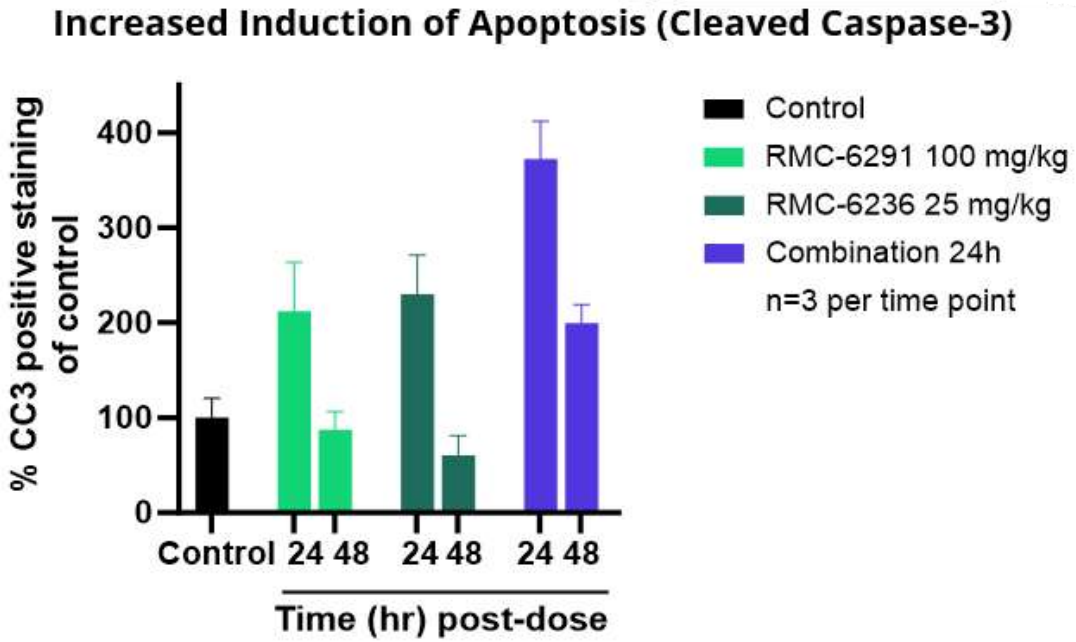
$NRAS^{Q61}$	Q61	Q61K
Clinical resistance		■
RMC-6236	+	+

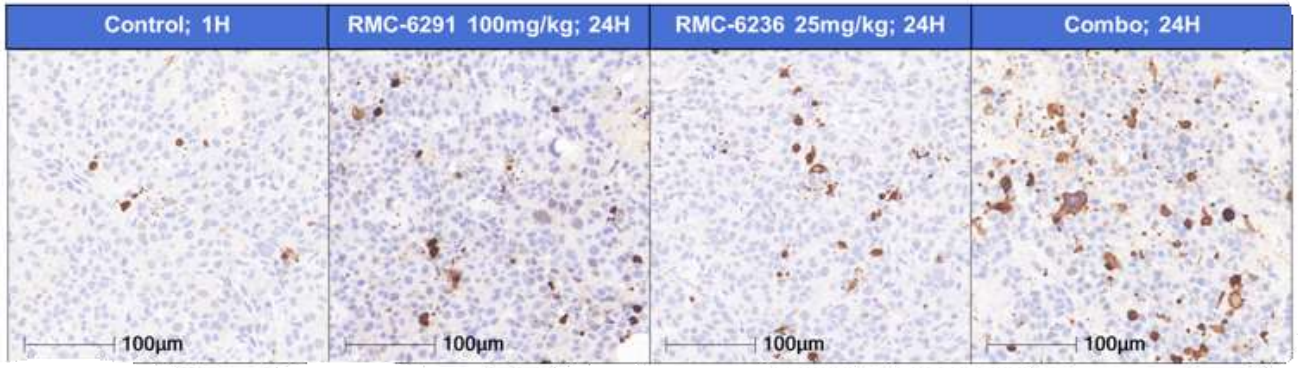
+ Active against mutation

■ Resistance mutation reported in clinic

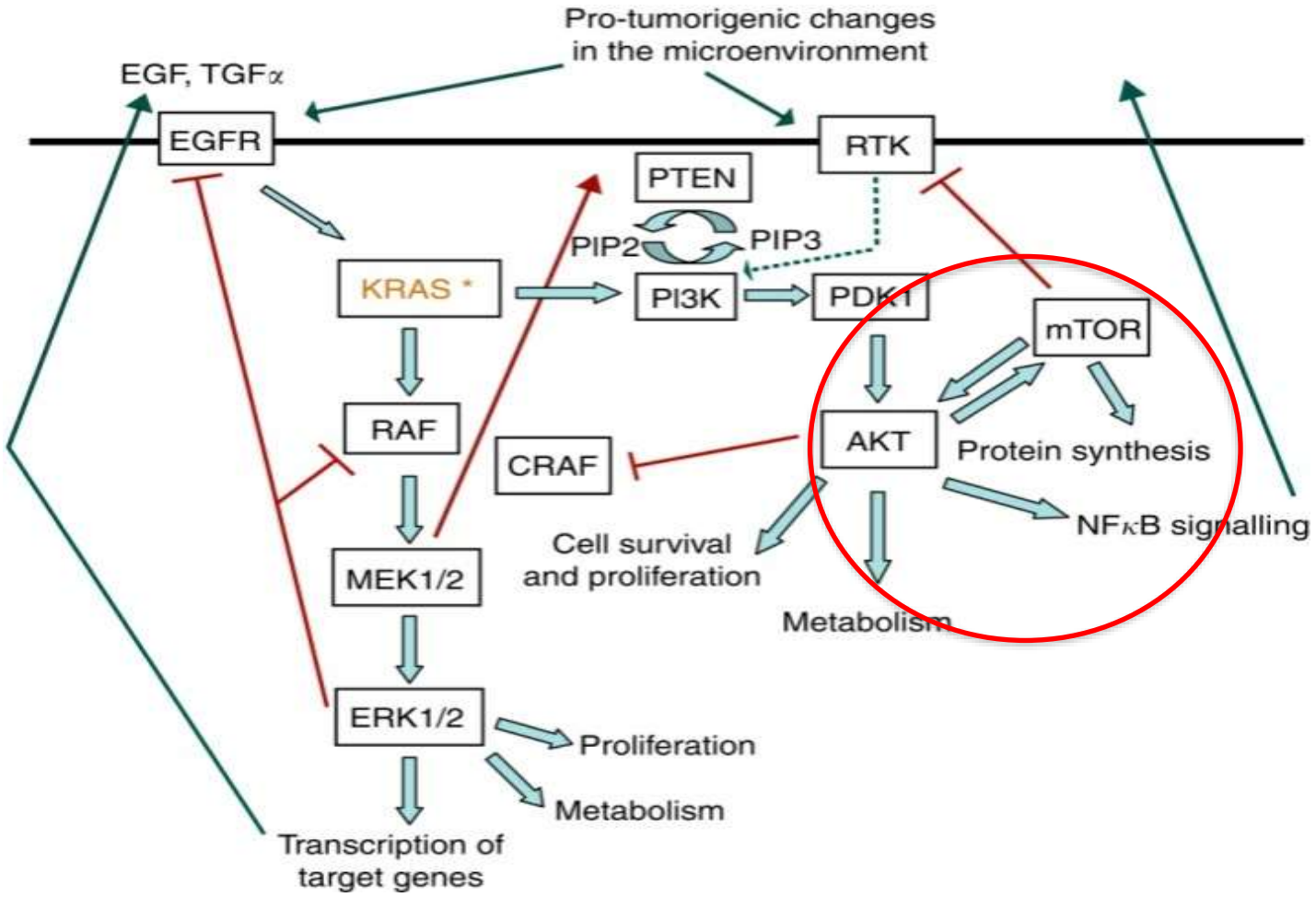
Can combination dual KRAS inhibition overcome resistance?







Example: where would we expect to see compensatory upregulation?



Eser *et al.*
British Journal of Cancer (2014) 111, 817-822 doi:10.1038/bjc.2014.215

KRASi results in compensatory, therapeutically targetable AKT/mTOR activation

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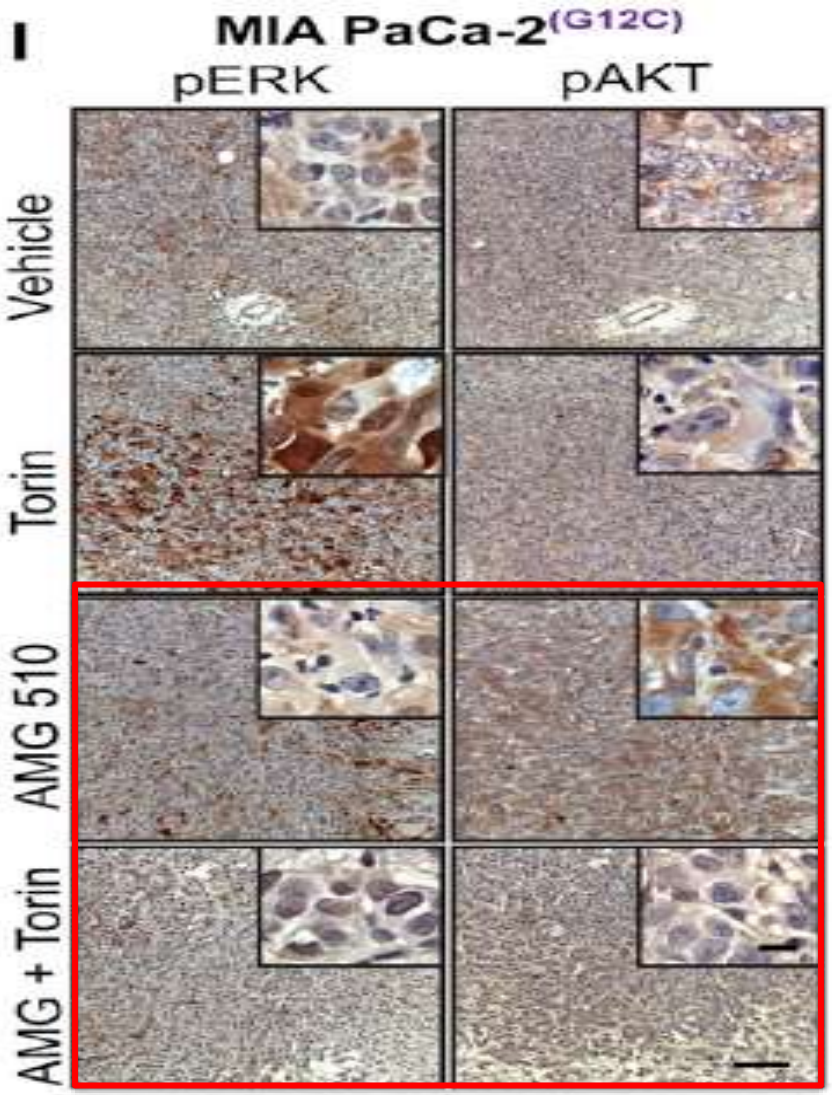
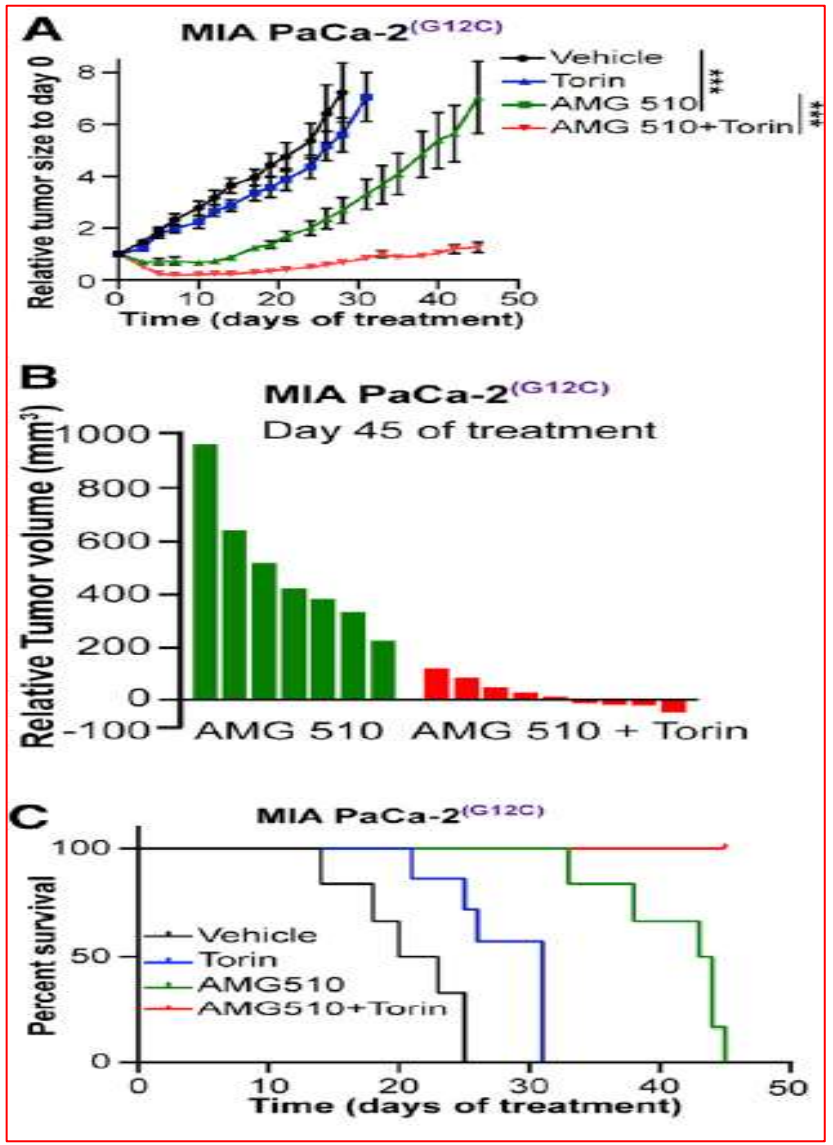


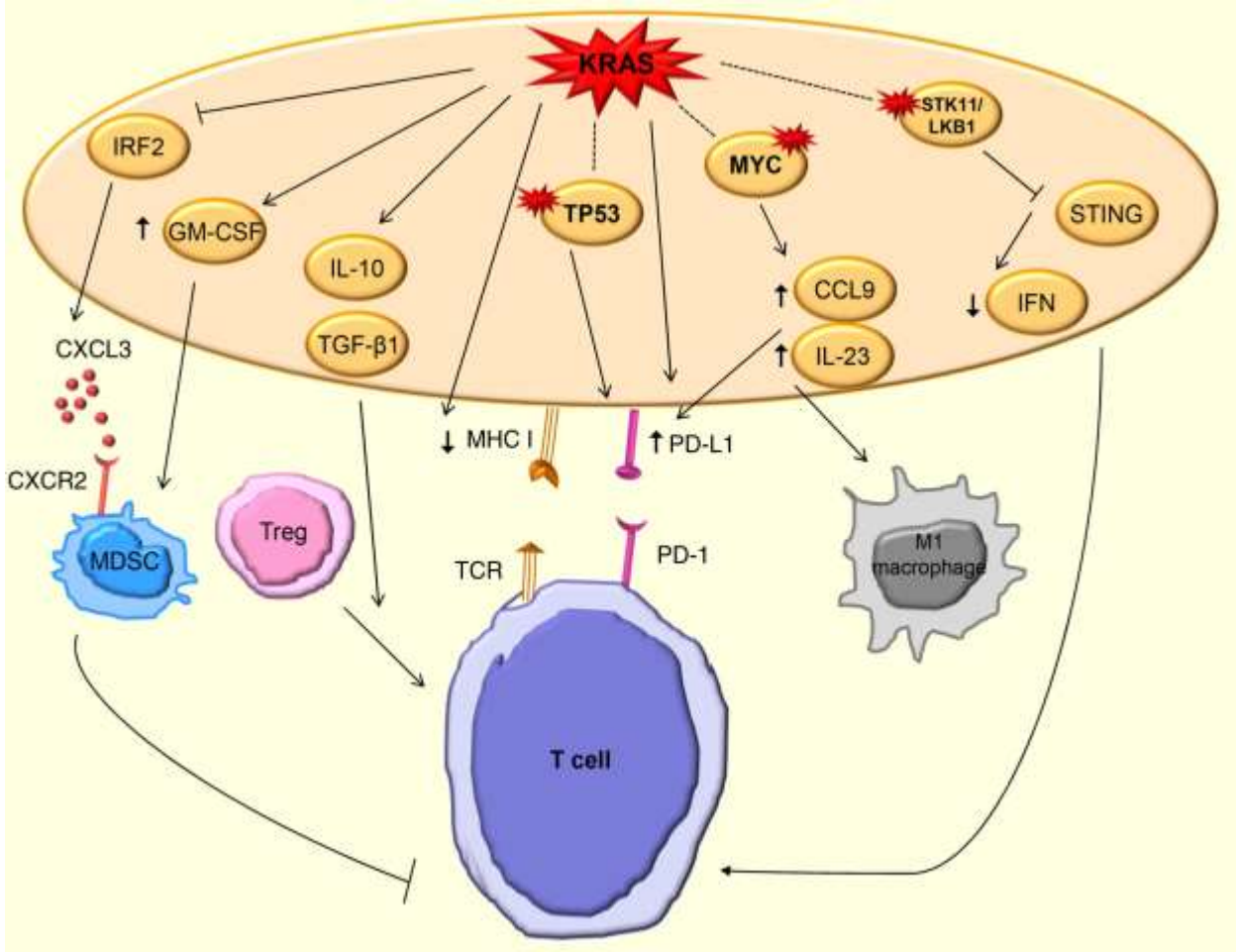


Brown et al. Cell Reports Medicine 2020

Combination strategy: KRAS inhibitors as immunomodulators

KRAS mutations have known immunosuppressive effects

- Including:
  - Decreased MHC I expression
  - Recruitment of MDSCs and Tregs to TME
  - Upregulation of PD-L1
  - Decreased tumor-specific T cell function



Hamarsheh et al Nature Comm 2024

KRAS G12Di has immunomodulatory impact on tumor and immune cell populations

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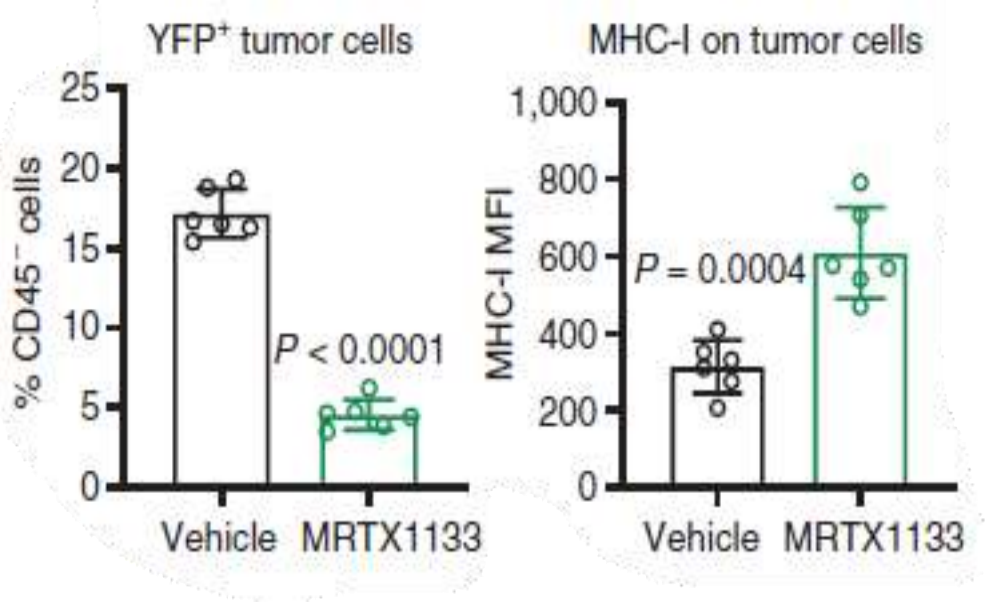

TUMOR CELLS

Decreased viability and increased MHC-1 expression on surviving cells

Kemp et al Cancer Discovery 2023

KRAS G12Di has immunomodulatory impact on tumor and immune cell populations

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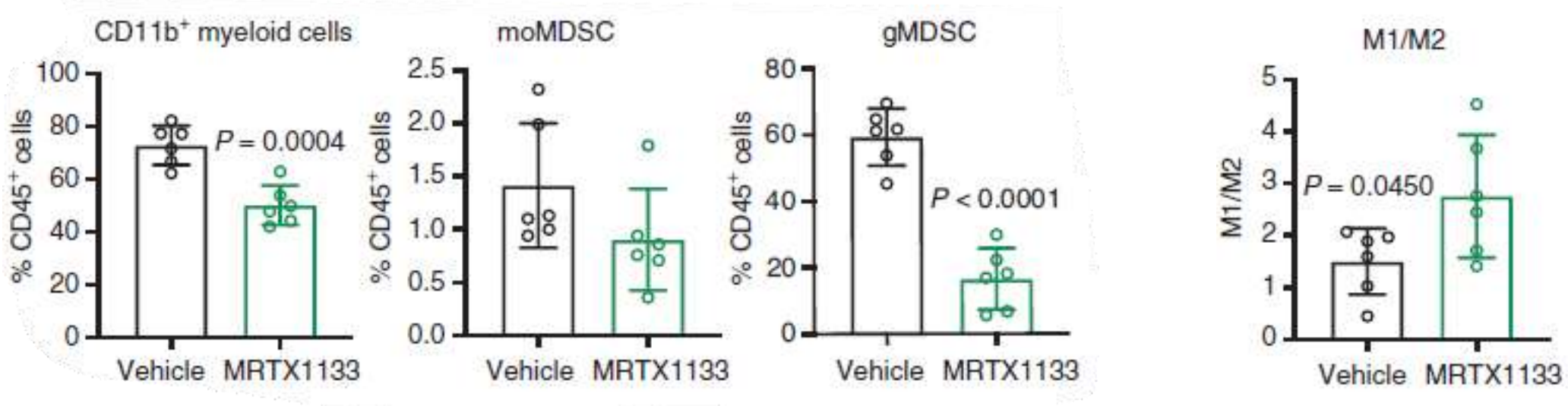

MYELOID CELLS

Decreased immunosuppressive myeloid cells

Kemp et al Cancer Discovery 2023

KRAS G12Di has immunomodulatory impact on tumor and immune cell populations

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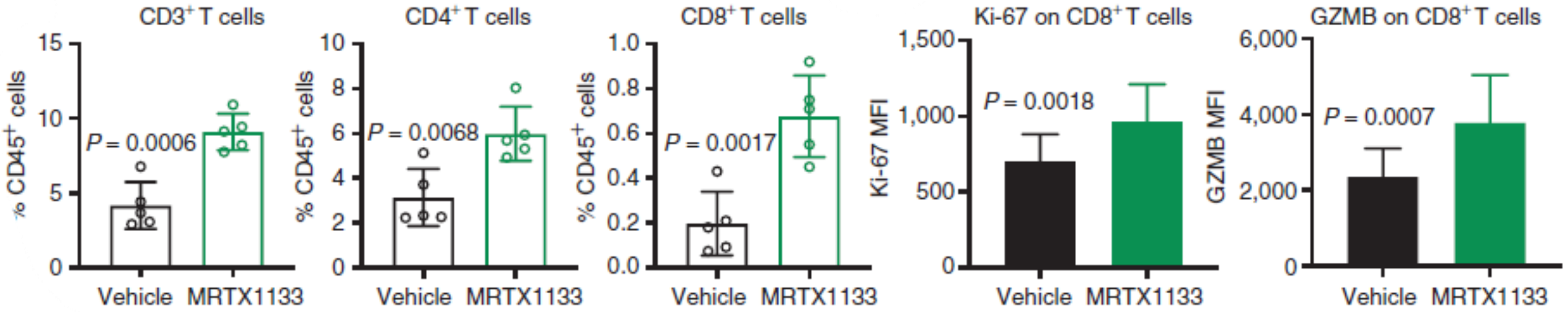

CD8/CD4 cells

Increased cytotoxic CD8+ and CD4+ TILS

Kemp et al Cancer Discovery 2023

KRAS G12Di requires CD8/CD4 lymphocytes for anti-tumor effect

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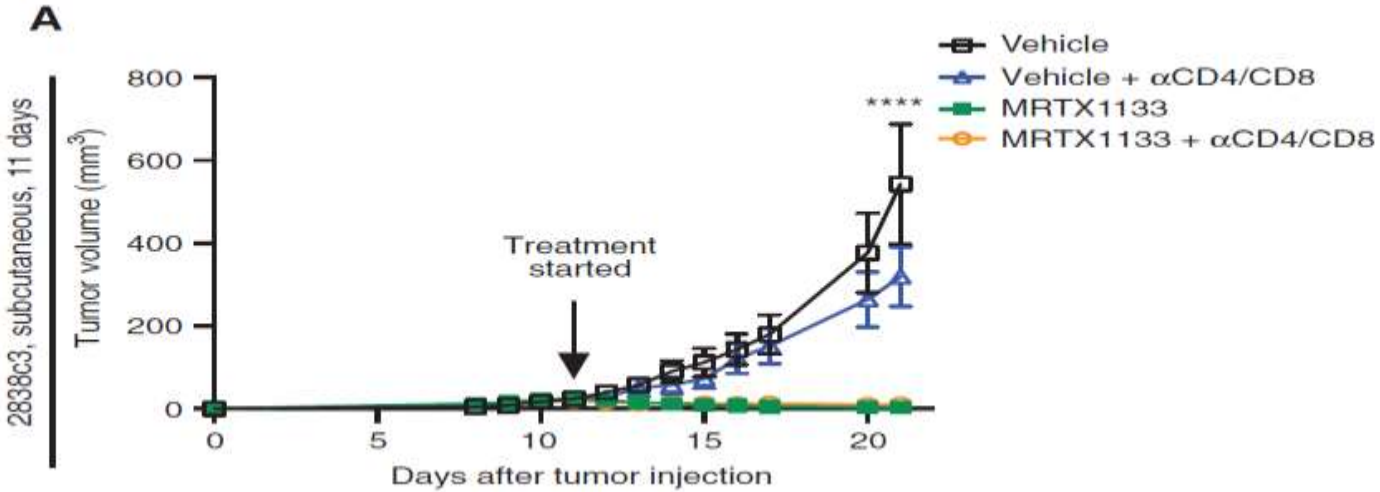

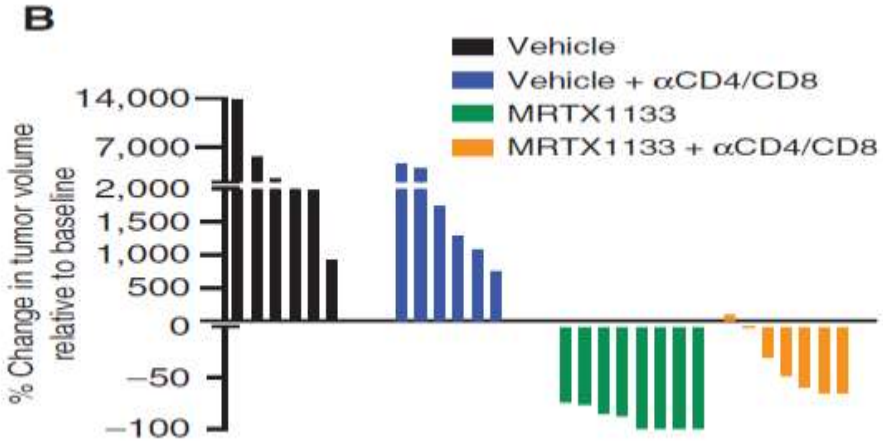

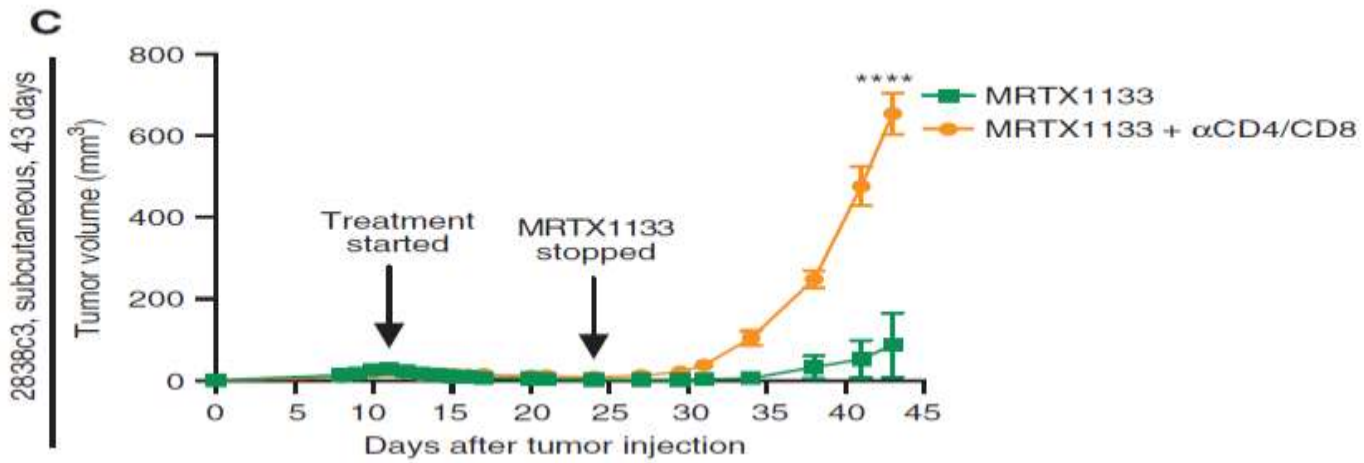

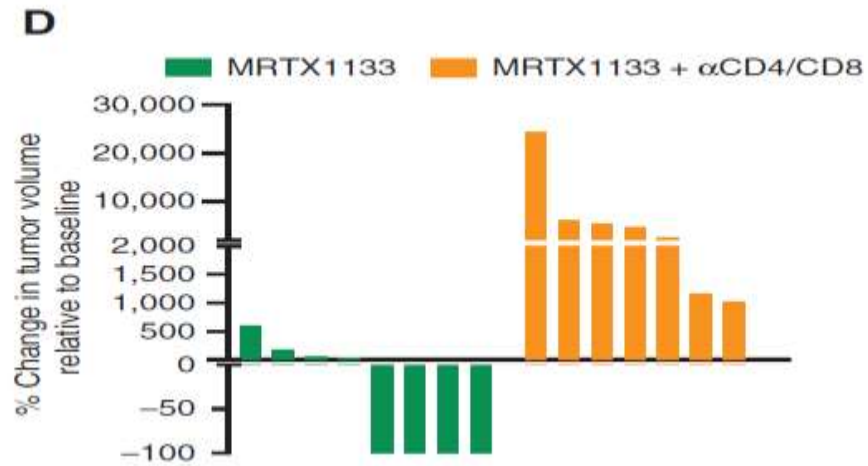

Kemp et al Cancer Discovery 2023

Confirmation: KRAS G12Di requires CD8+ cells for anti-tumor effect

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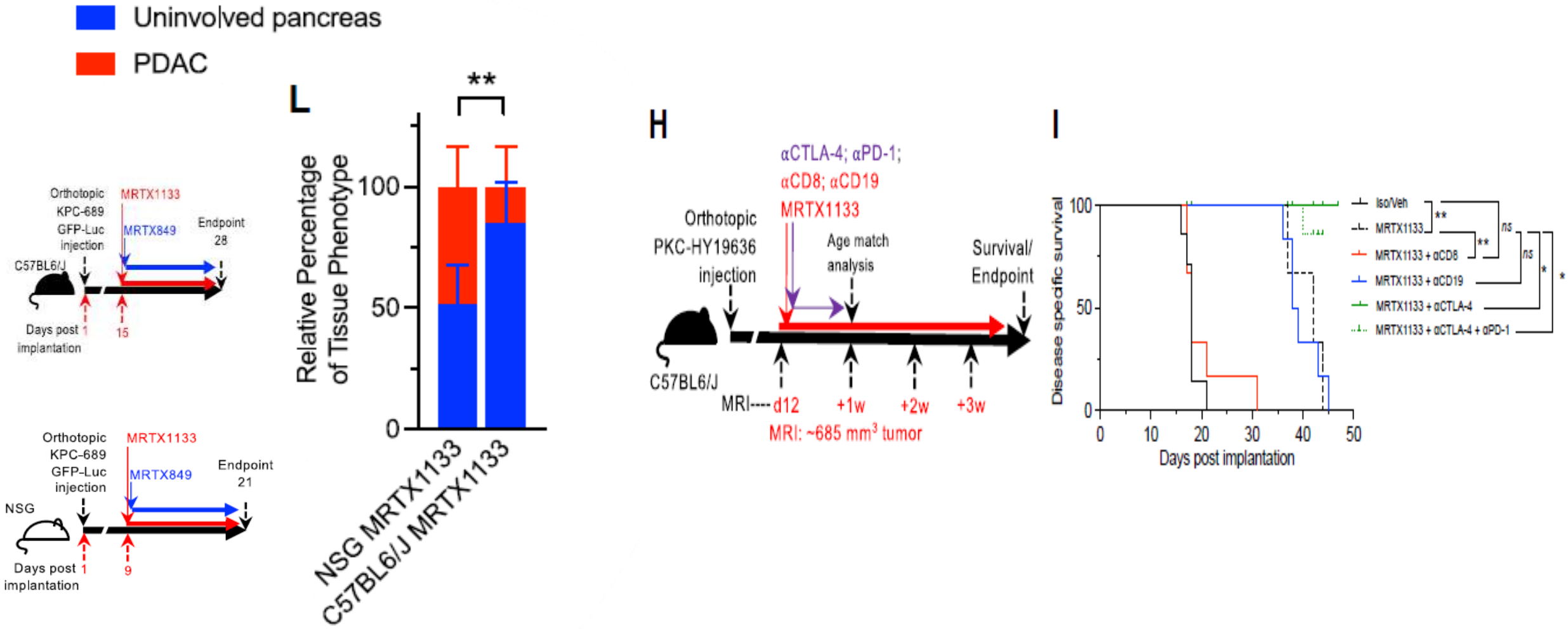
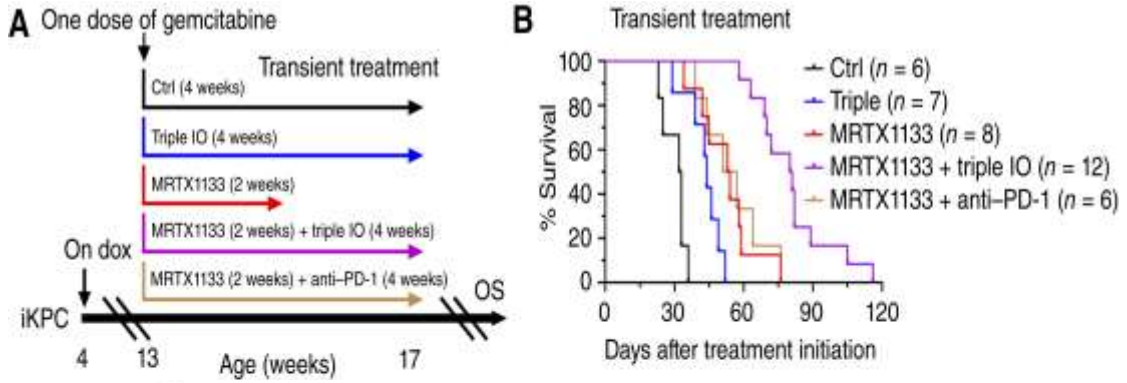
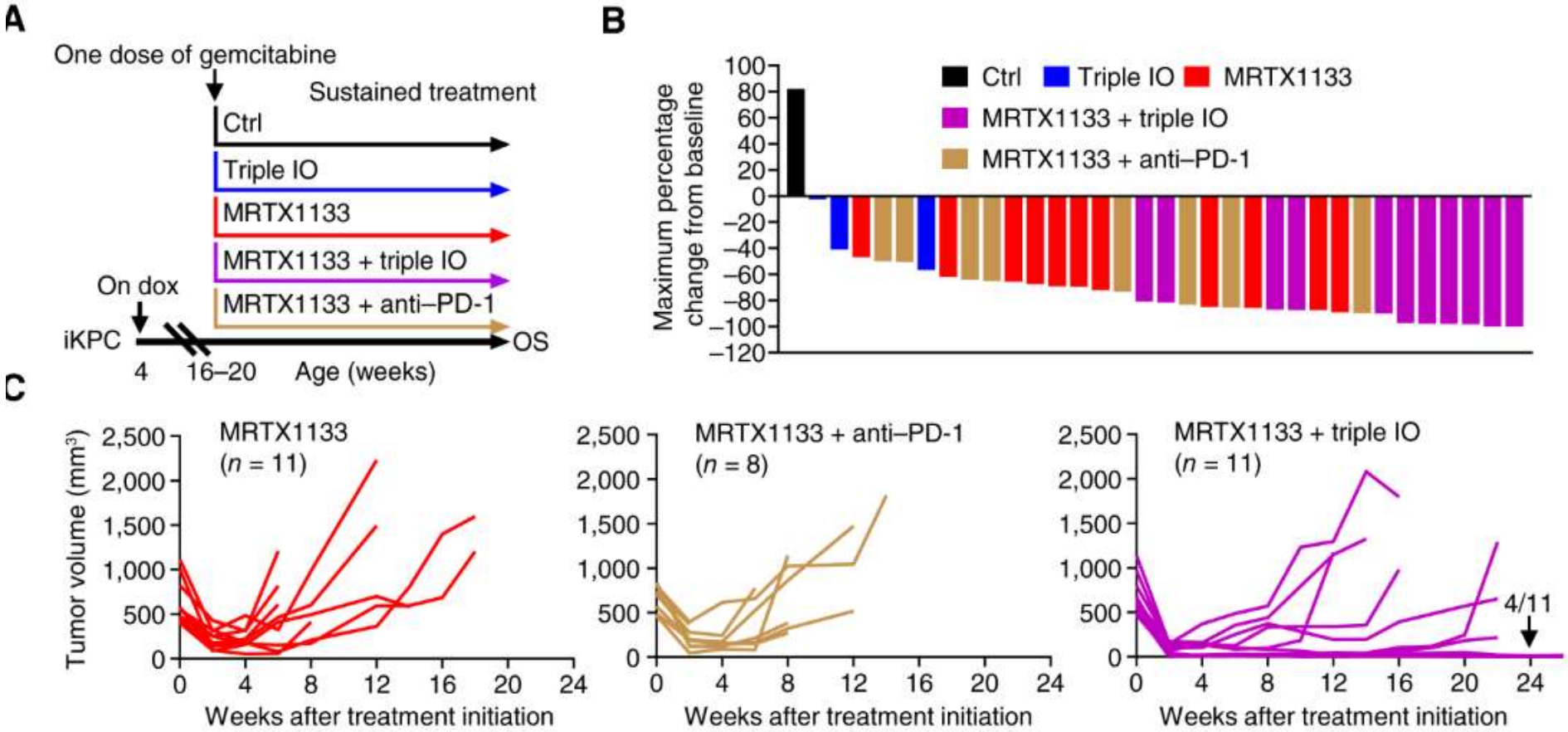


Mahadevan et al Cancer Cell 2023

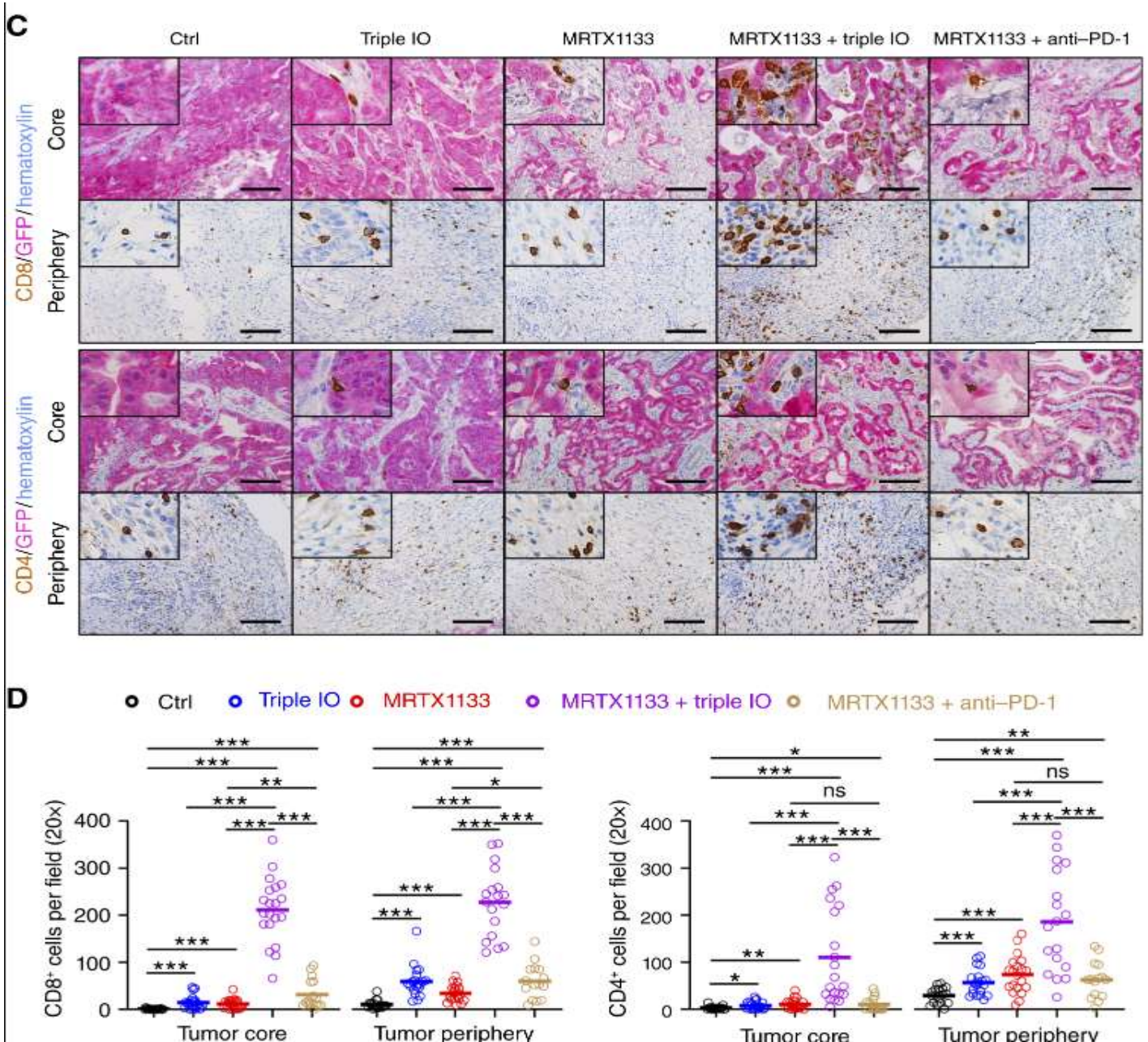
Optimal immune combination therapy may involve multiple IO agents

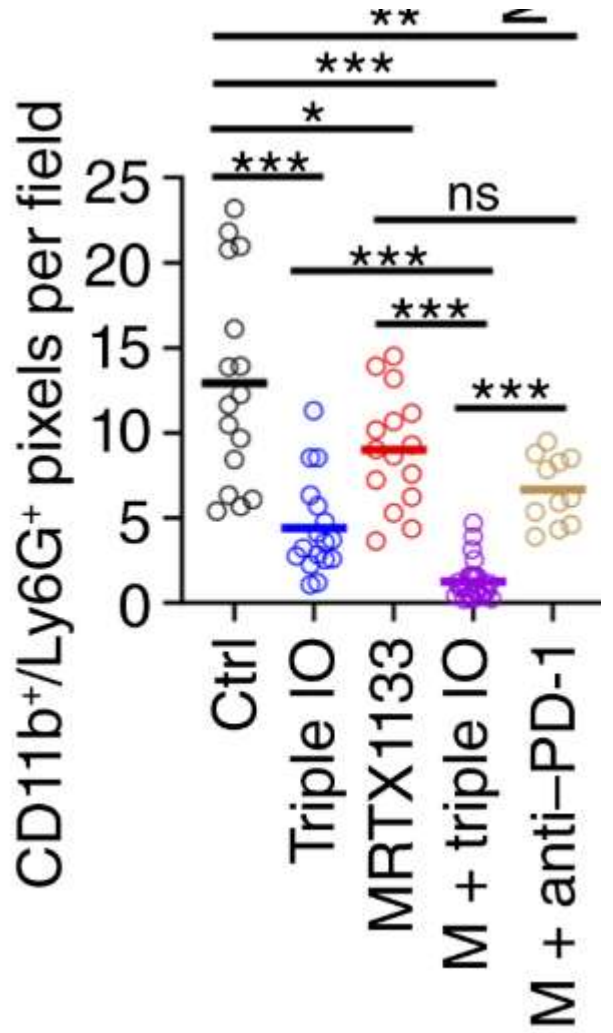




Liu et al. Cancer Discovery 2025

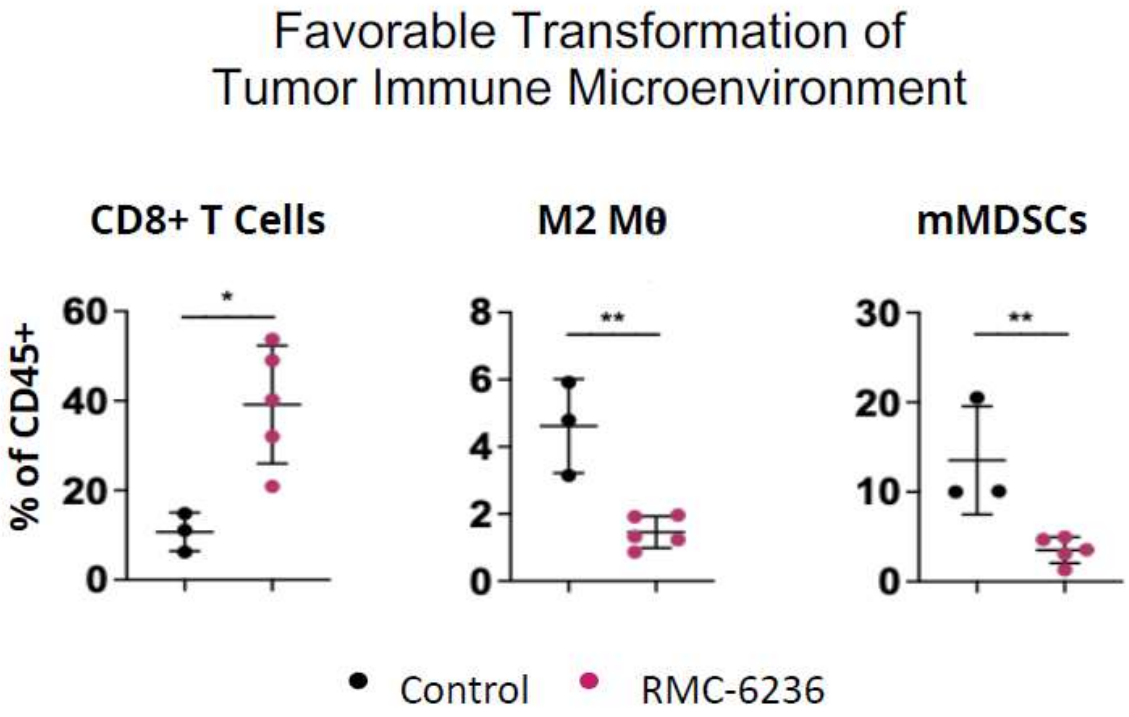
KRASi appears to jumpstart or drive TME remodeling

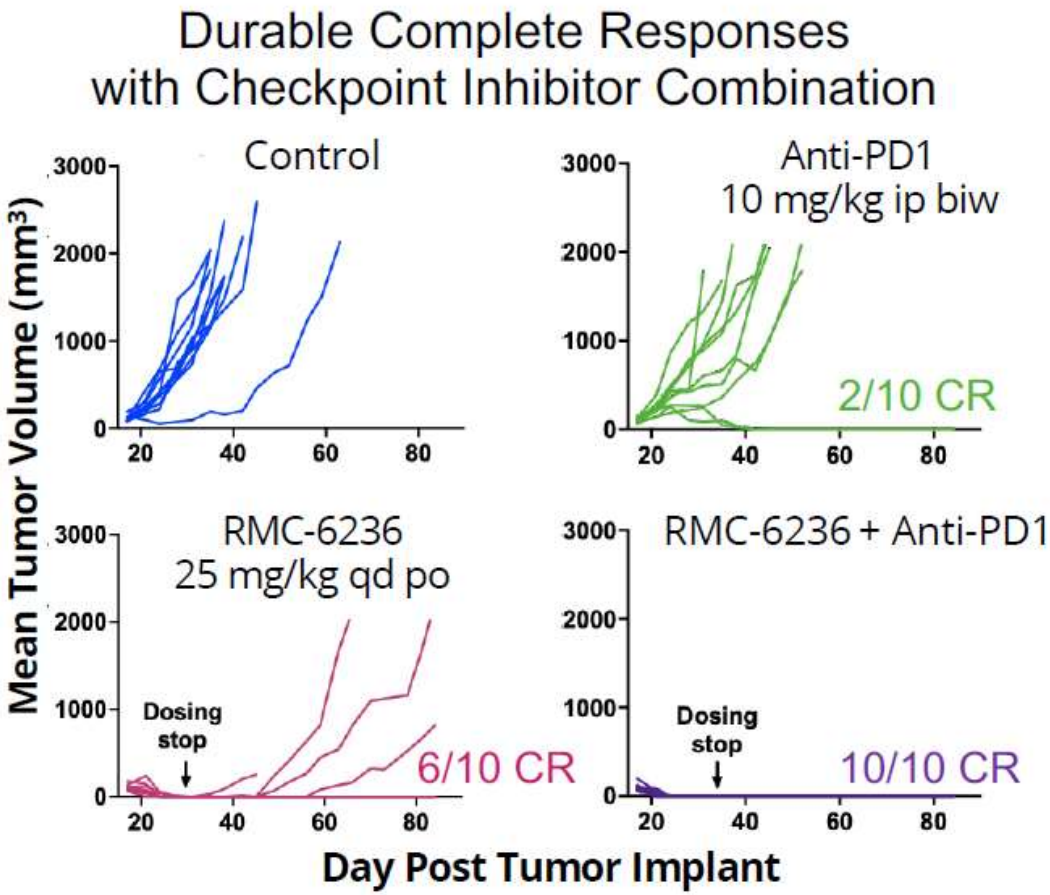




Liu et al. Cancer Discovery 2025

Multi-RASi also alters TME and has benefit with combined with anti-PD1 therapy





RVMD preclinical research
Syngeneic tumor model with CT26 cell line engineered to express $KRAS^{G12C}$
M2 Mθ = M2 macrophages; mMDSCs = Monocytic myeloid derived suppressor cells

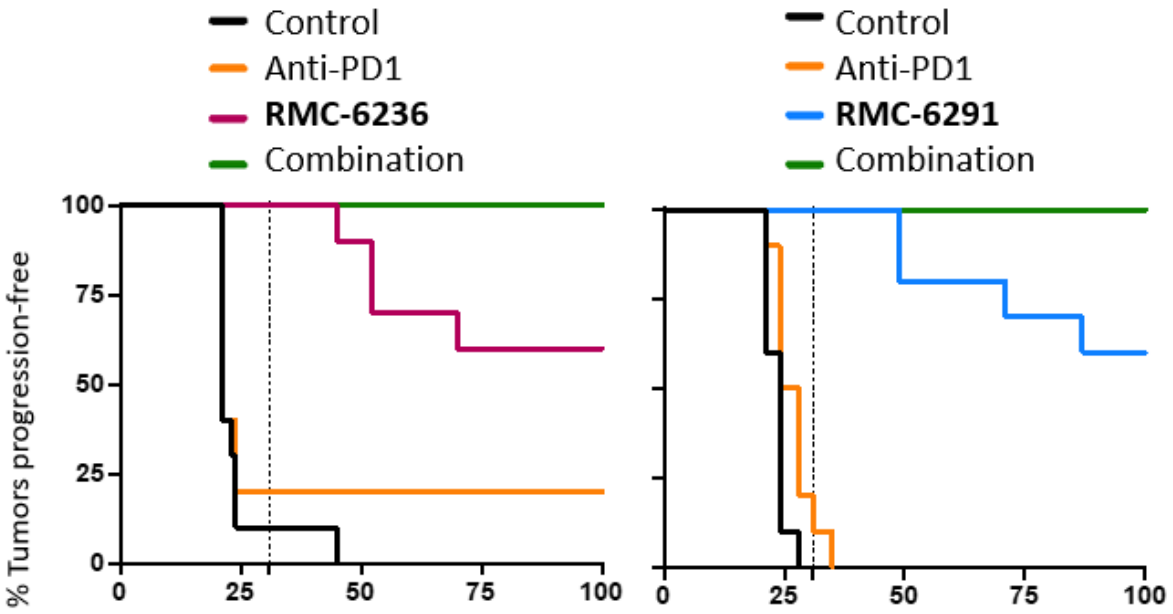
Re-challenge experiments demonstrated RMC-6236 treatment induced long lasting immunological memory

Singh et al AACR 2022

Combination therapy clinical trial to test the hypothesis now ongoing

Phase 1b Combos: RAS(ON) Inhibitor Combinations with Pembrolizumab to Inform Potential Evaluation in 1L NSCLC

Preclinical Validation[1]



RMC-LUNG-101 Clinical Trial: Pembrolizumab[2]

Objectives: evaluate safety, tolerability and preliminary activity of RMC-6236 and RMC-6291 each combined with pembrolizumab

Patient Population: RMC-6236 in KRAS-mutant NSCLC, RMC-6291 in KRAS G12C NSCLC

Study Status: Recruiting

RMC-LUNG-101 Clinical Trial: https://www.clinicaltrials.gov/study/NCT06162221

Vaccines approaches

ELI-002 Personalized mKRAS vaccine (Amplify-201)

nature medicine

Article

https://doi.org/10.1038/s41591-023-02760-3

Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial

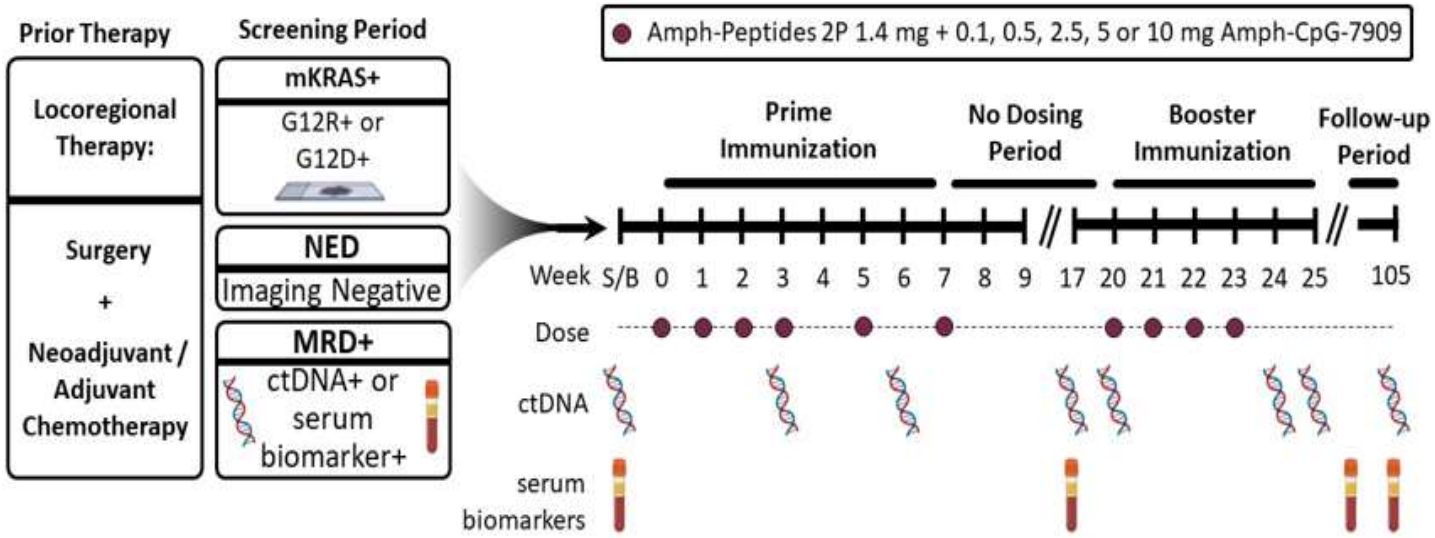
Received: 25 July 2023

Accepted: 11 December 2023

Published online: 09 January 2024

A list of authors and their affiliations appears at the end of the paper

Pancreatic and colorectal cancers are often KRAS mutated and are incurable when tumor DNA or protein persists or recurs after curative intent therapy

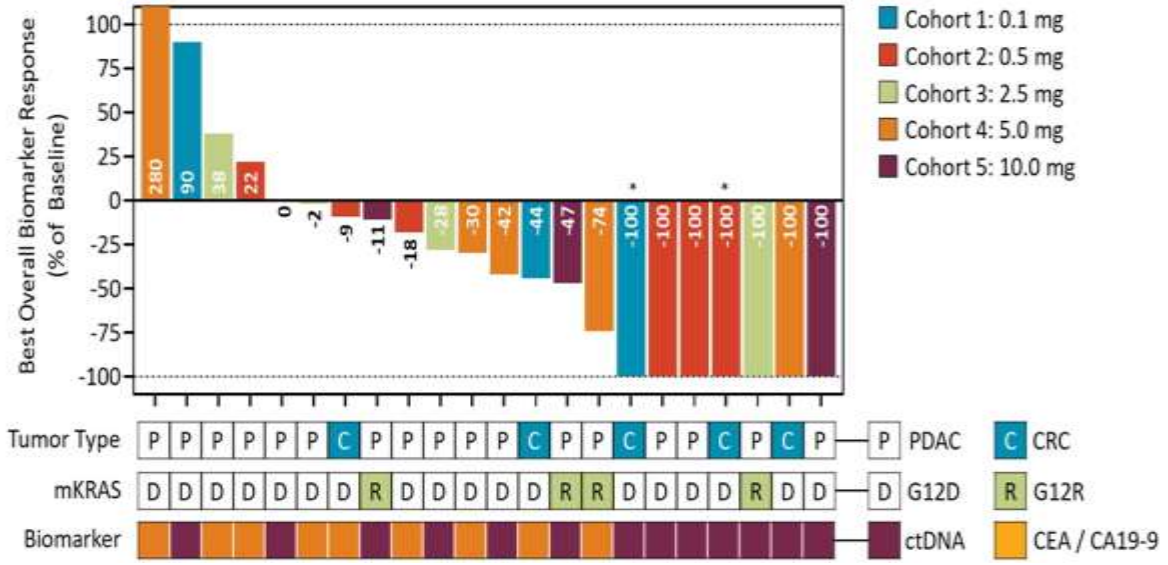


***Reduction** = % decrease from baseline*

- *17/22 (77%)*

***Clearance** = 0 MTM/mL on ctDNA assay*

- *7/22 (32%)*



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Safety and immunogenicity of a first-in-human mutant KRAS long peptide vaccine combined with ipilimumab/nivolumab in resected pancreatic cancer: preliminary analysis from a phase I study

Daniel Haldar, MD


Amanda Huff, PhD


Hao Wang, PhD


Elizabeth Jaffee, MD


Nilofer Azad, MD


Neeha Zaidi, MD


mKRAS vaccines now in clinic

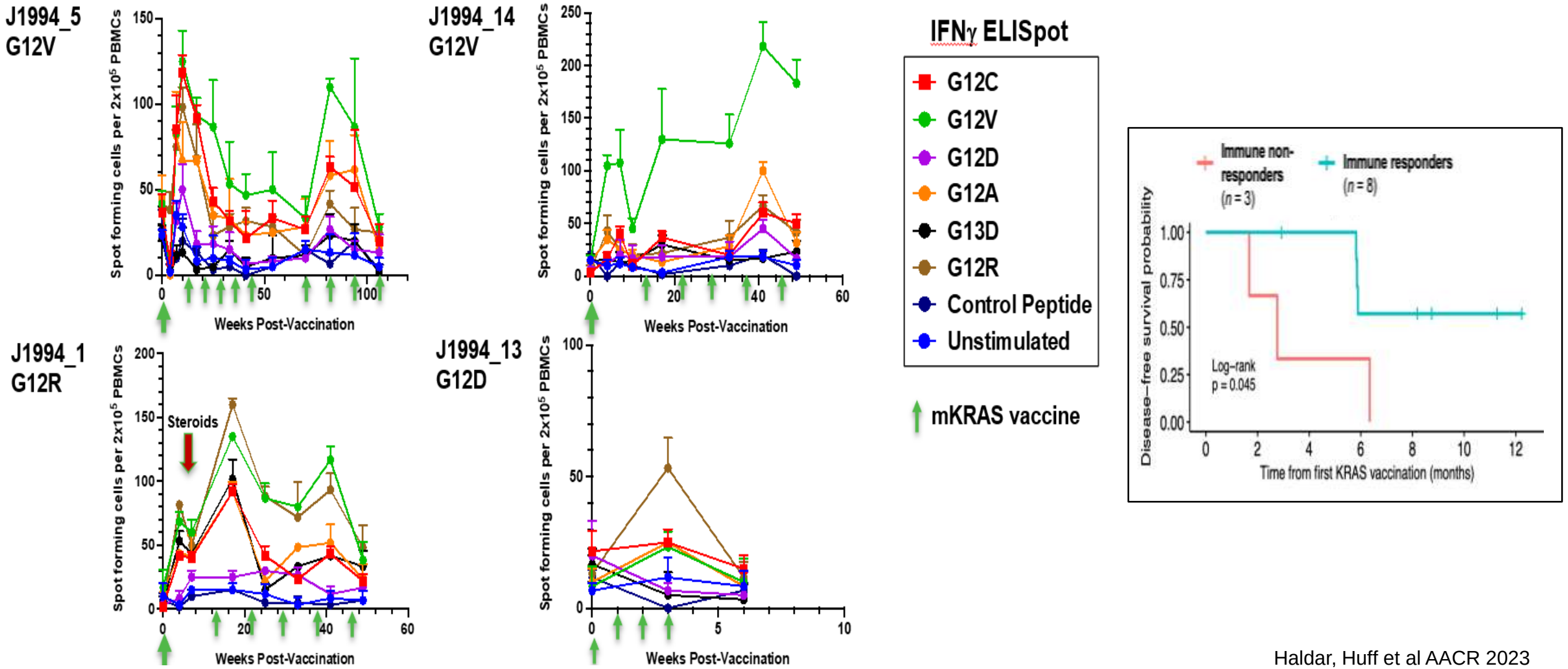
Pooled long peptide mKRAS vaccine + ipilimumab/ nivolumab in resected PDAC and advanced CRC patients

Vaccine Design

Schema: First-In-Human Pilot Study

Haldar, Huff et al AACR 2023

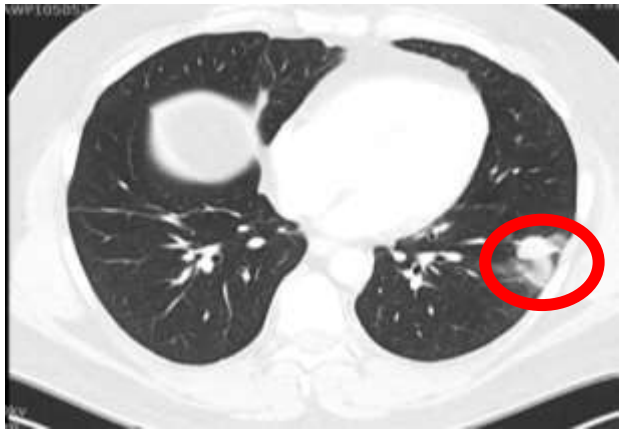
mKRAS-specific immune responses seen and correlated with DFS



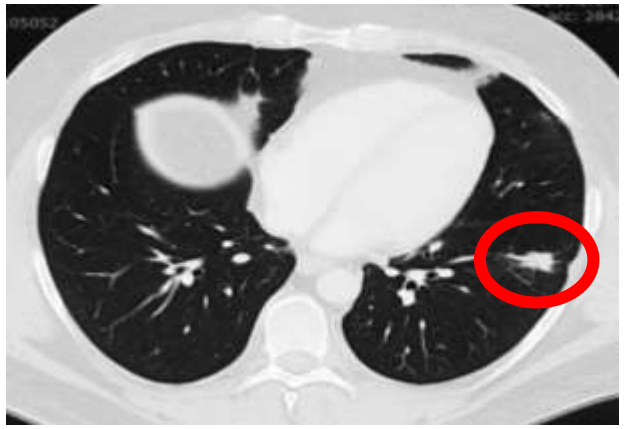
Haldar, Huff et al AACR 2023

ACTIVITY NOTED IN PRETREATED MCRC

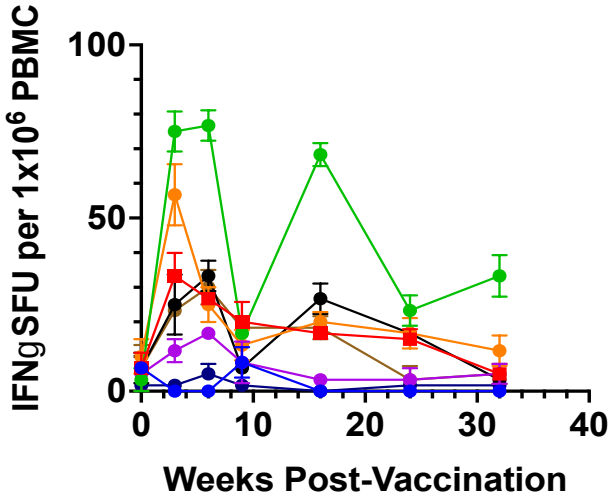
KRAS G12D



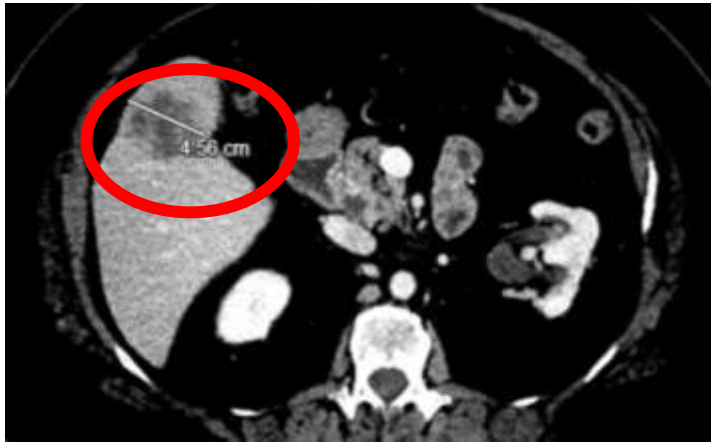
Pre-vaccine + αPD1/αCTLA-4



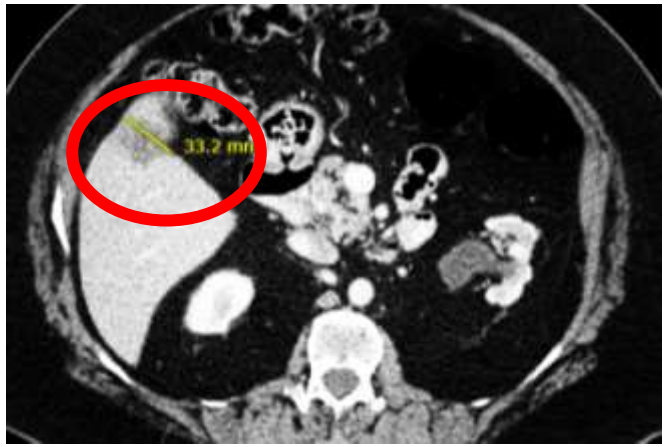
2 months post-treatment



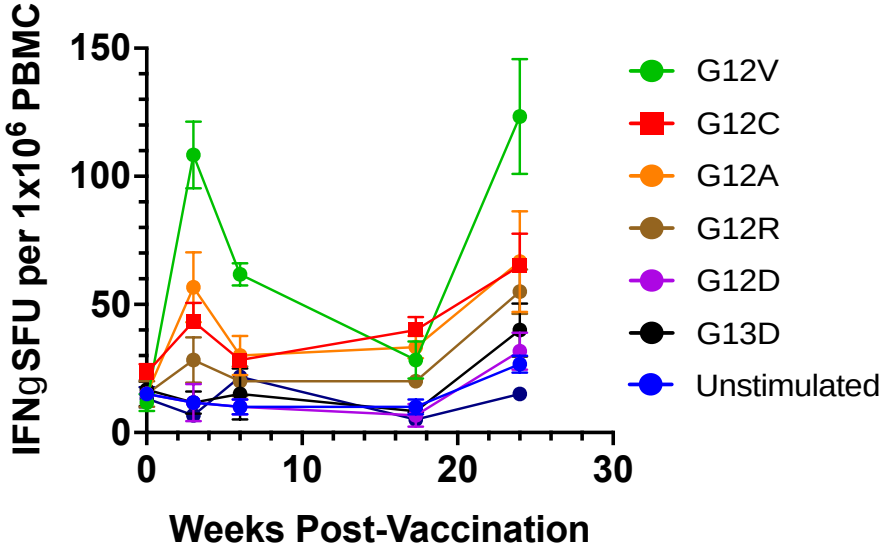
KRAS G12D



Pre-vaccine + αPD1/αCTLA-4



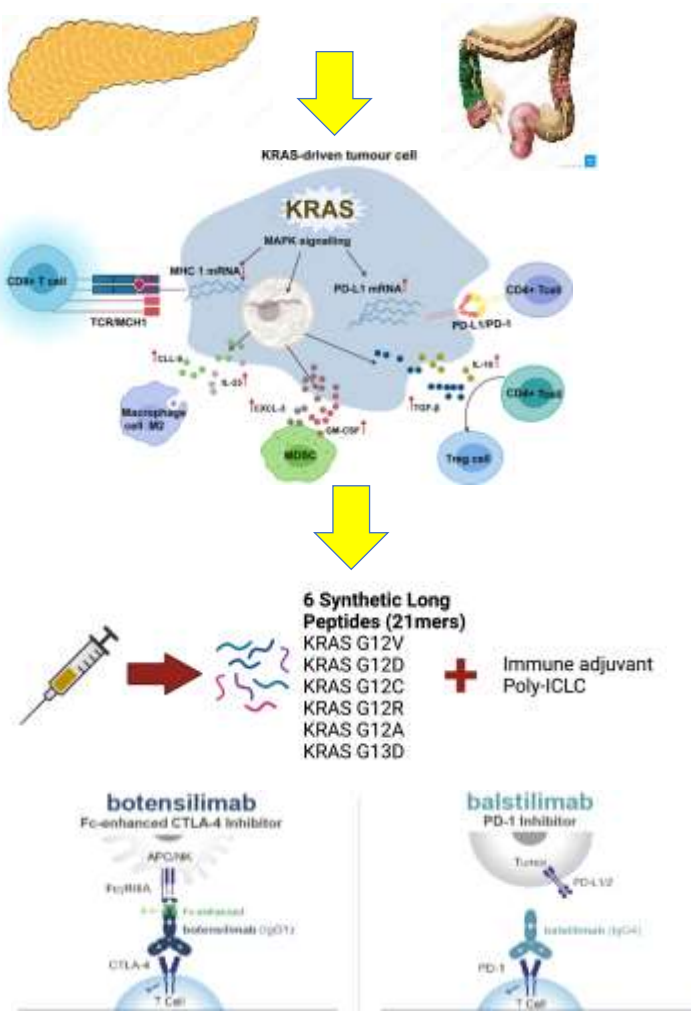
2 months post-treatment



Do not post.

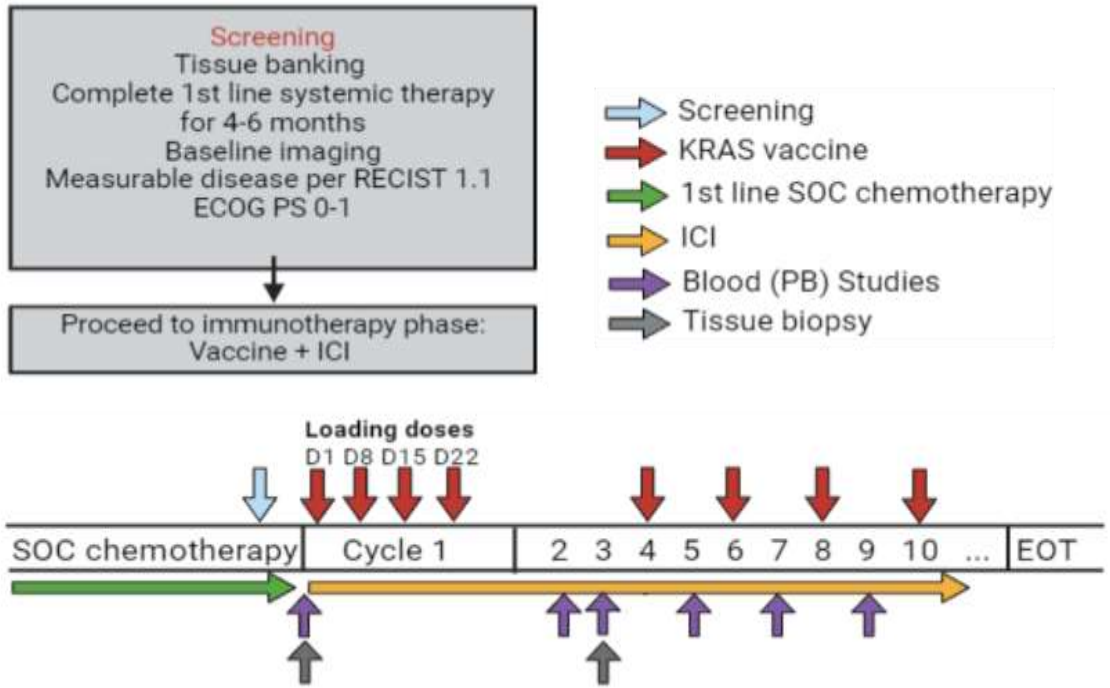
Dr. Daniel Haldar, Dr. Nilo Azad

Moving strategy earlier in care



Eligibility Criteria:

- Histologically or cytologically proven unresectable MSS CRC or PDAC
- Have one of the six KRAS mutations included in the vaccine
- Have received 4-6 months of 1st line chemotherapy +/- VEGFi or EGFRi



Rationale for anti-cancer vaccines + KRAS inhibitors

- KRAS mutations decrease MHC I expression needed for antigen presentation
  - KRAS inhibitors result in increased MHC 1 expression
- KRAS mutations result in T cell inactivation/exhaustion
  - Immune checkpoint inhibitors activate T cells
- Common GI cancers have low #s of TILs and neoantigens
  - We now have mKRAS-specific vaccines

KRAS inhibitor

+

ICI inhibition

+

mKRAS specific vaccine

=

?Durable Clinical Benefit?

Prediction: PDAC patients in the next few years will ubiquitously receive KRAS inhibitors as part of their therapy

Conclusions

- We need to be working, now, on trial designs that explore:
  - Sequencing of direct KRAS inhibitors
  - Combination approaches for MAPK signaling and more broadly
  - Understanding and overcoming resistance
  - Exploring the effect of KRASi on the stroma and TME to develop other classes of agents

- Pharmaceutical companies and investigators need to work together to answer these questions quickly and together

Targeting KRAS in Pancreatic Cancer: A Long But Successful Climb

JOHNS HOPKINS
SCHOOL of MEDICINE

THIS IS THE BEST TIME EVER TO BE IN DRUG DEVELOPMENT FOR CANCER