RMC-6236, a Novel, First in Class, Tri-complex RAS^{MULTI}(ON) Inhibitor: Preliminary Clinical Results & Learnings

Hanson Wade Meeting: RAS-Targeted Drug Development

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September 28, 2023

Dana-Farber Cancer Institute | Hale Family Center for Pancreatic Cancer Research

Disclosure Information

- *Research support to institution*: AstraZeneca, BreakThrough Cancer, Celgene/BMS, Eli Lilly, Hale Family Center for Pancreatic Cancer Research, Lustgarten Foundation, NIH/NCI, Novartis, Pancreatic Cancer Action Network, Revolution Medicines, Stand Up to Cancer

- *Paid advisory roles*: Celgene/BMS, GRAIL, Ipsen, Lustgarten Foundation, Mirati, Third Rock Ventures

RMC-6236-001 Trial

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in *KRAS*

REVOLUTION MEDICINES

The Christ Hospital Cancer Center

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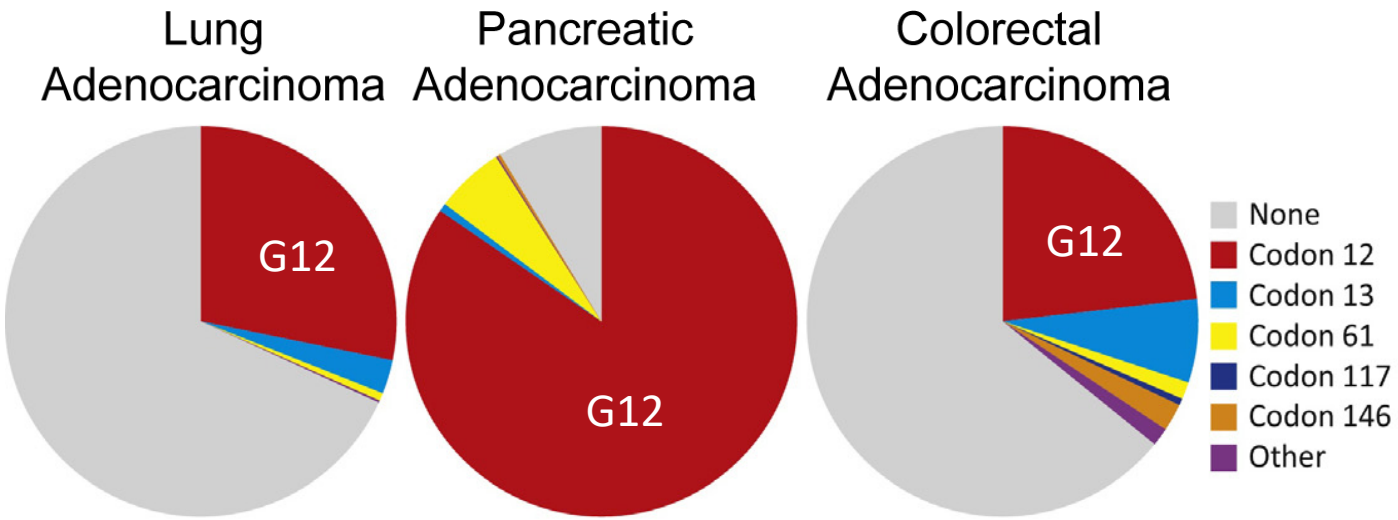
Outline

- Background
- Preclinical data for RMC-6236
- Clinical trial design and initial toxicity and efficacy data for RMC-6236-001 trial
- Future directions for RAS inhibition in pancreatic cancer

KRAS mutant alleles by cancer type

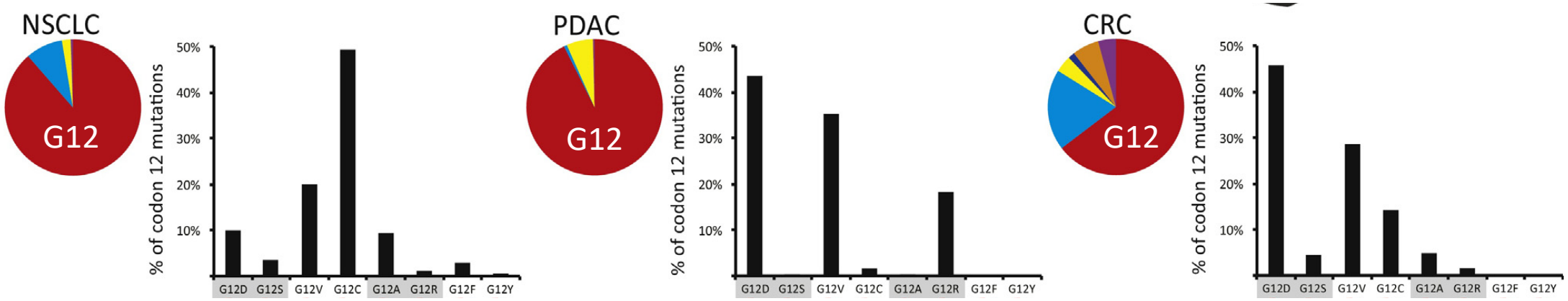


KRAS mutations are most common in the three leading causes of cancer death in US:

NSCLC + PDAC + CRC = 230,170 deaths = 38% of all est. US cancer deaths in 2023

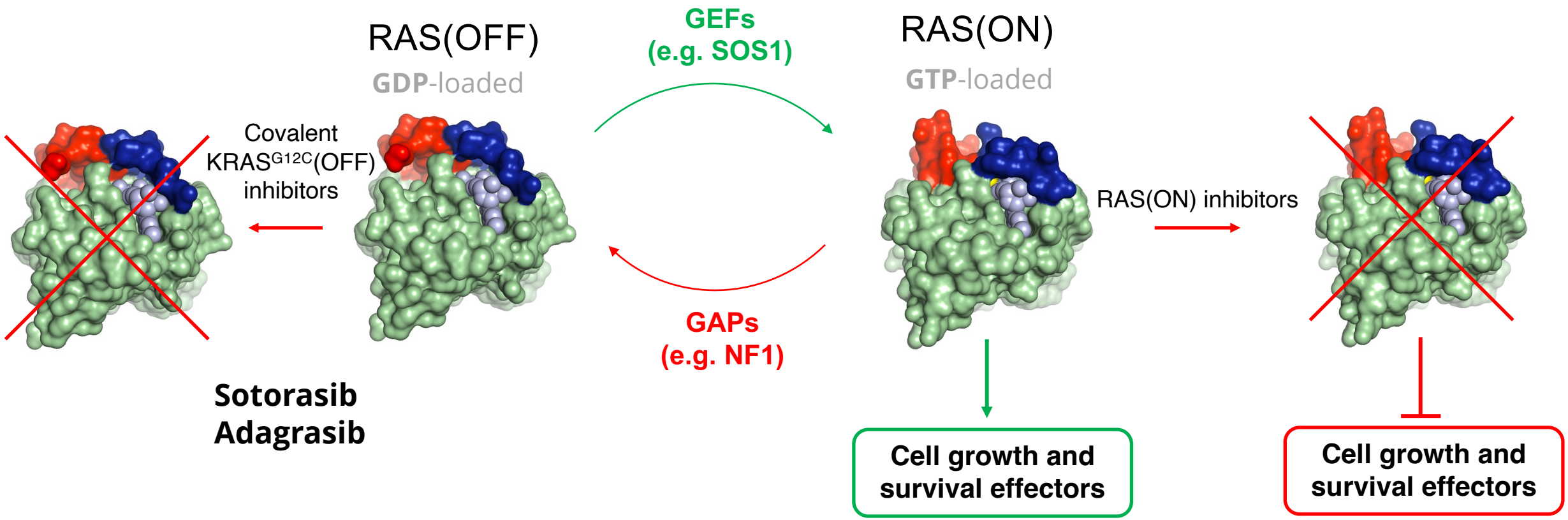
32% NSCLC [76,269 est. new cases in 2023]
92% PDAC [58,926 est. new cases in 2023]
45% CRC [68,400 est. new cases in 2023]

Percent and allele for codon 12 KRAS mutations by cancer type:



Haigis, Trends in Cancer 2017.

Targeting RAS(ON) Directly Disrupts Oncogenic Signaling but has Historically Proved Challenging



GEFs: Guanine nucleotide exchange factors
GAPs: GTPase activating proteins

Natural Compounds Use Abundant Cellular Chaperones to Form Tri-Complexes with Distinct Biological Targets

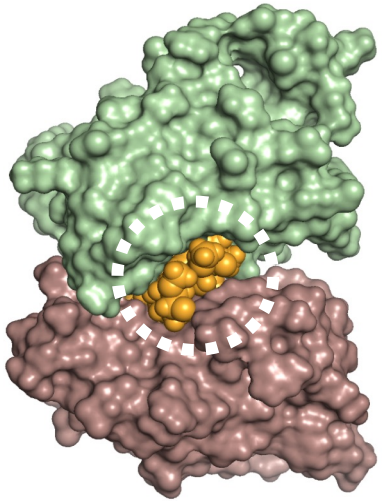
Target protein

Drug

Chaperone

Rapamycin

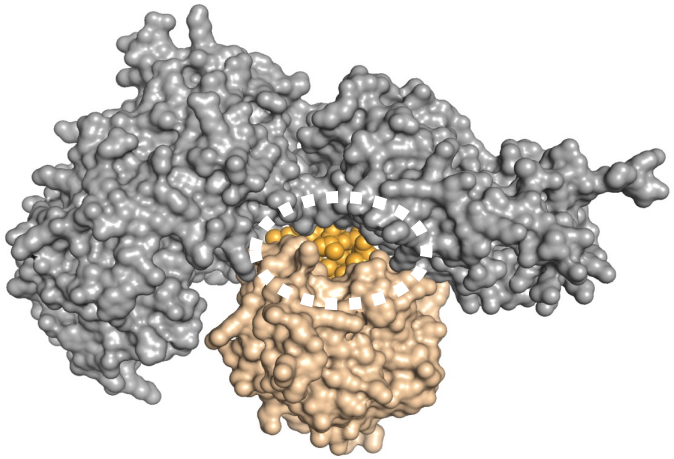
mTOR



FKBP12

Cyclosporine

Calcineurin



Cyclophilin A

This mechanism may be adapted to difficult-to-drug targets like RAS(ON)

Science **381**, 794–799 (2023) 18 August 2023

CANCER

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

Christopher J. Schulze[1]†, Kyle J. Seamon[1]†, Yulei Zhao[2]†, Yu C. Yang[1], Jim Cregg[3], Dongsung Kim[2], Aidan Tomlinson[3], Tiffany J. Choy[1], Zhican Wang[4], Ben Sang[2], Yasin Pourfarjam[2], Jessica Lucas[2], Antonio Cuevas-Navarro[2], Carlos Ayala-Santos[2], Alberto Vides[2], Chuanchuan Li[2], Abby Marquez[3], Mengqi Zhong[3], Vidyasiri Vemulapalli[1], Caroline Weller[1], Andrea Gould[1], Daniel M. Whalen[3], Anthony Salvador[3], Anthony Milin[3], Mae Saldajeno-Concar[3], Nuntana Dinglasan[1], Anqi Chen[3], Jim Evans[1], John E. Knox[3], Elena S. Koltun[3], Mallika Singh[1], Robert Nichols[1], David Wildes[1], Adrian L. Gill[3], Jacqueline A. M. Smith[1]*, Piro Lito[2,5,6]*

CANCER

Targeting cancer with molecular glues

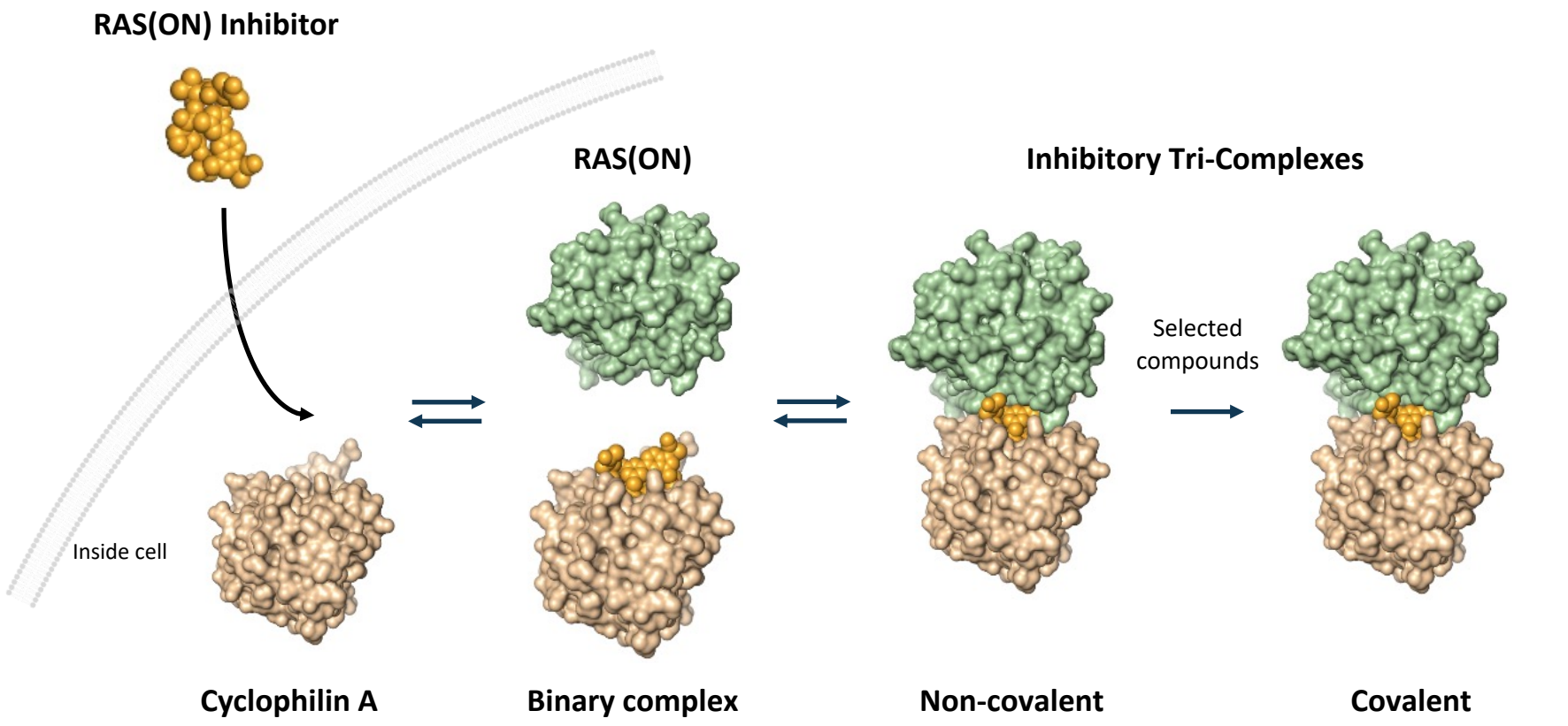
Molecular glues suppress the active form of the oncogenic protein KRAS

By **Jun O. Liu[1,2,3]**

SCIENCE

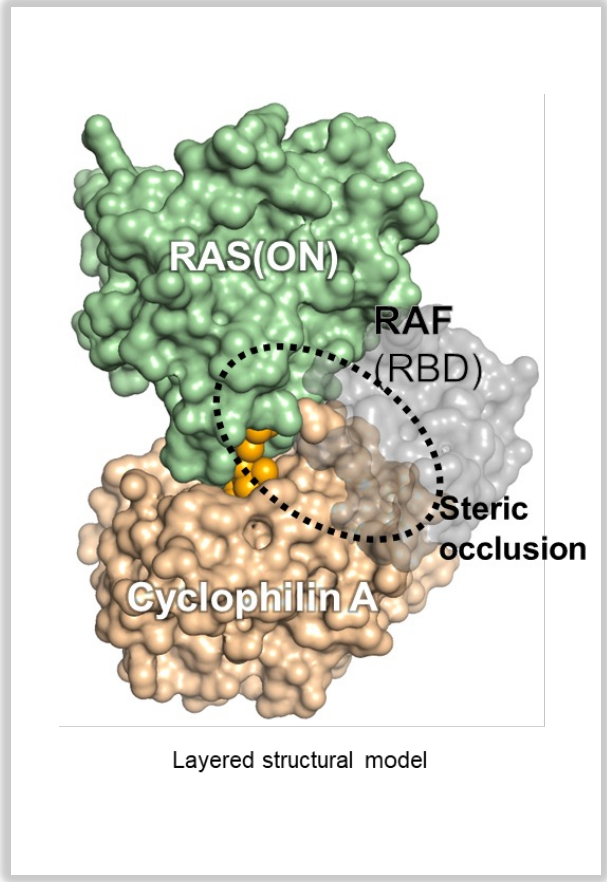
18 AUGUST 2023 • VOL 381 ISSUE 6659

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



RMC-6236 RAS^{MULTI}
RMC-0708 KRAS^{Q61H}

RMC-6291 KRAS^{G12C}
RMC-9805 KRAS^{G12D}
RMC-8839 KRAS^{G13C}

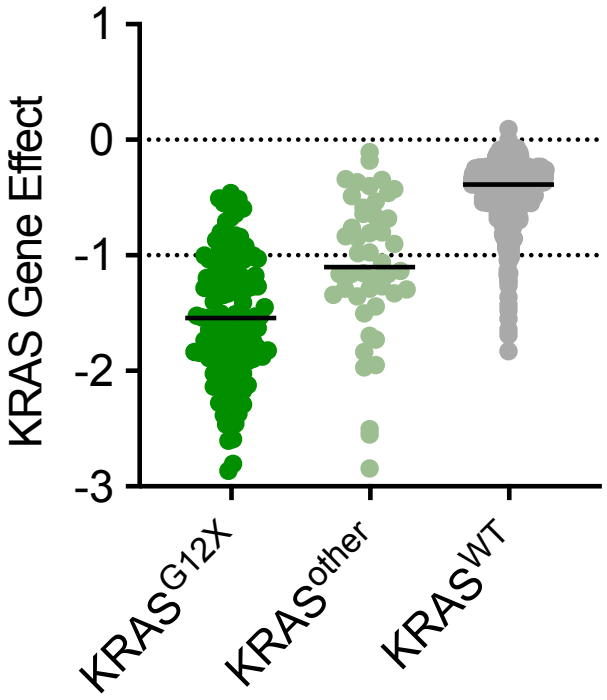


Layered structural model

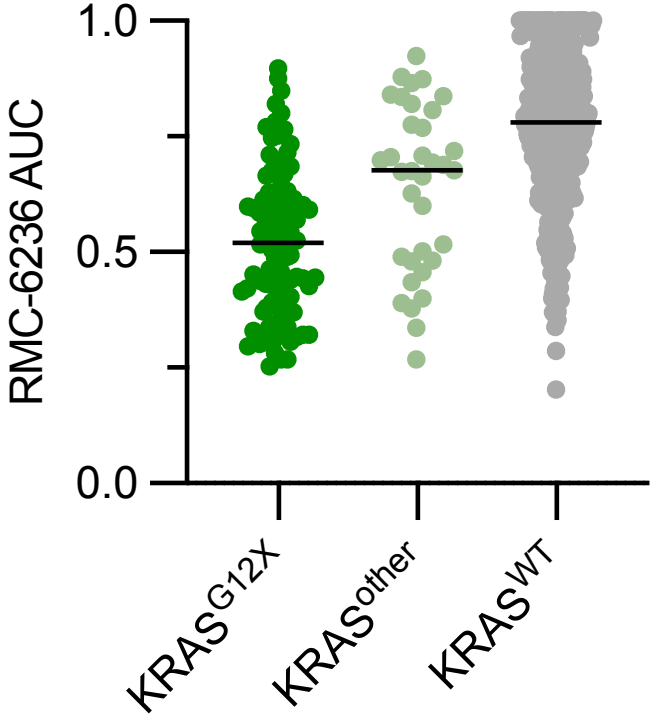
Tri-complex with cyclophilin A and mutant or wild-type KRAS, NRAS, and HRAS

$KRAS^{G12X}$ Mutated Cancer Cell Lines are Highly Addicted to KRAS

Genetic Dependency on KRAS, data from DepMap

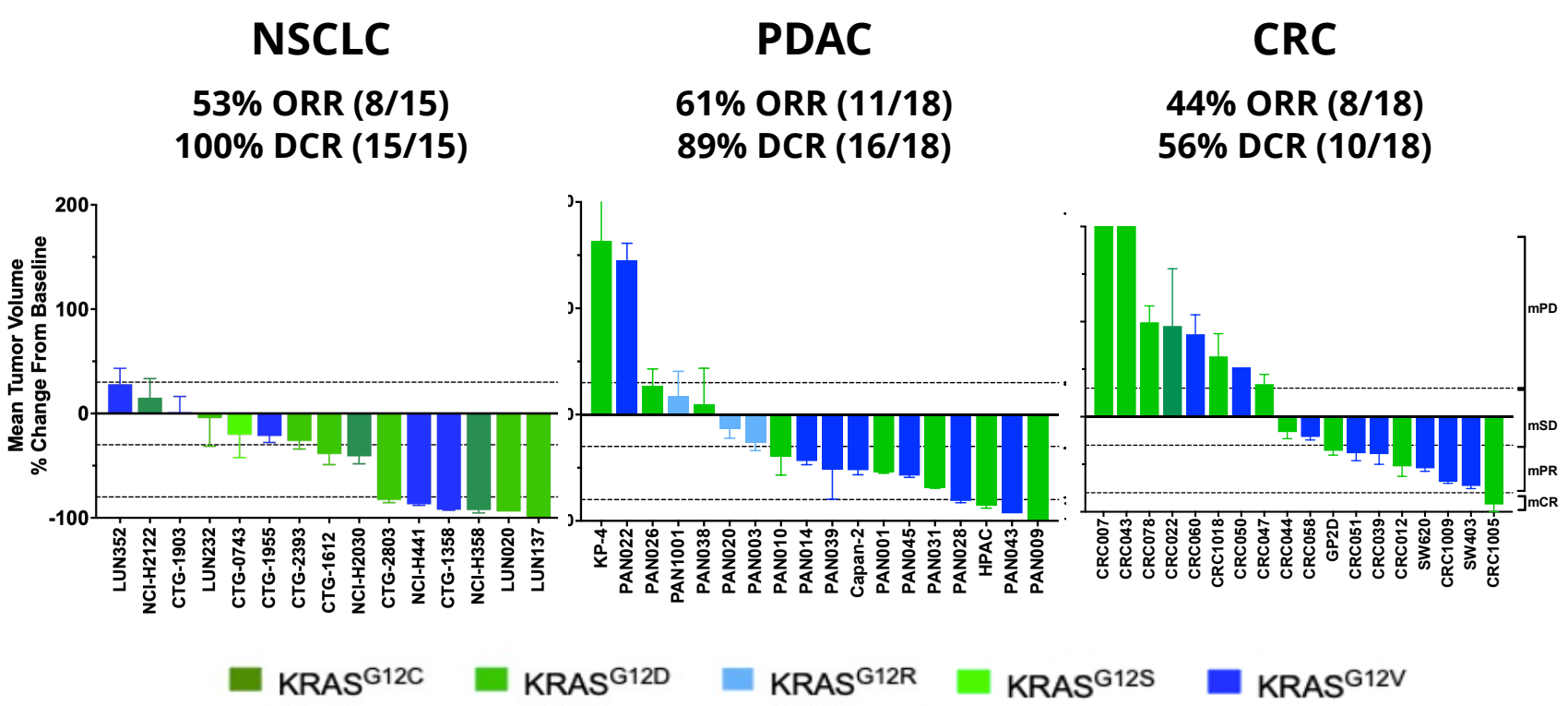


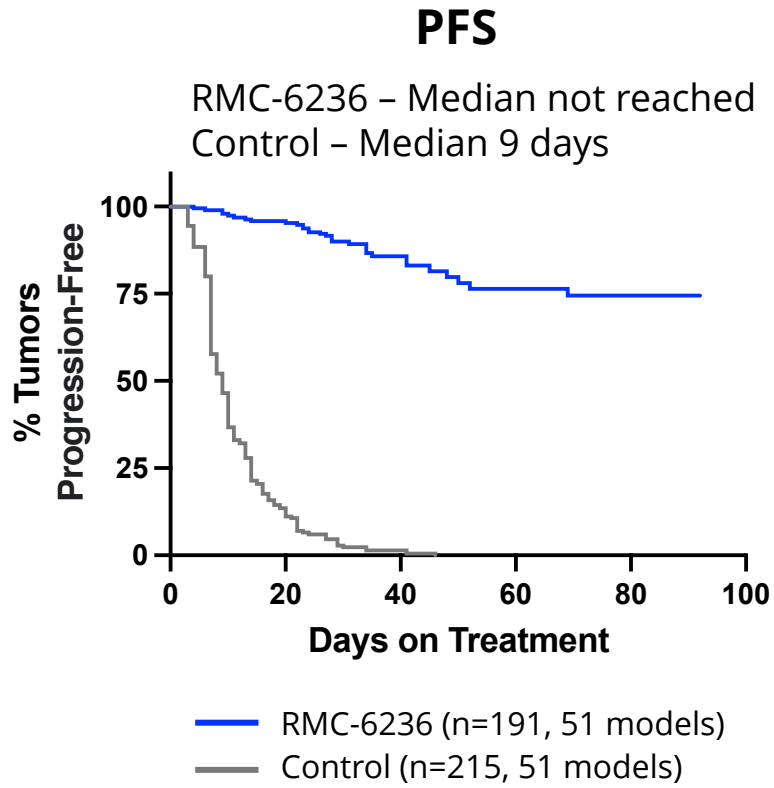
Inhibition of Proliferation, PRISM screen



PRISM data generated in collaboration with **Dr. Andrew Aguirre (DFCI)** and Broad PRISM platform
KRAS Gene effect data acquired from DepMap.org (Public 22Q4, Chronos score)
RAS^{MULTI}(ON) inhibition phenocopies KRAS knockout via CRISPR

RMC-6236: Highly Active with Durable Benefit Across *in Vivo* Models of Major Human Cancers with KRAS^{G12X} Drivers





RMC-6236 dosed at 25 mg/kg po qd; n=1-10/group
ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival
Progression defined as tumor doubling from baseline. Responses assigned according to mRECIST
NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma; CRC = colorectal cancer

RMC-6236-001 Phase 1/1b Study Design

Key Eligibility Criteria

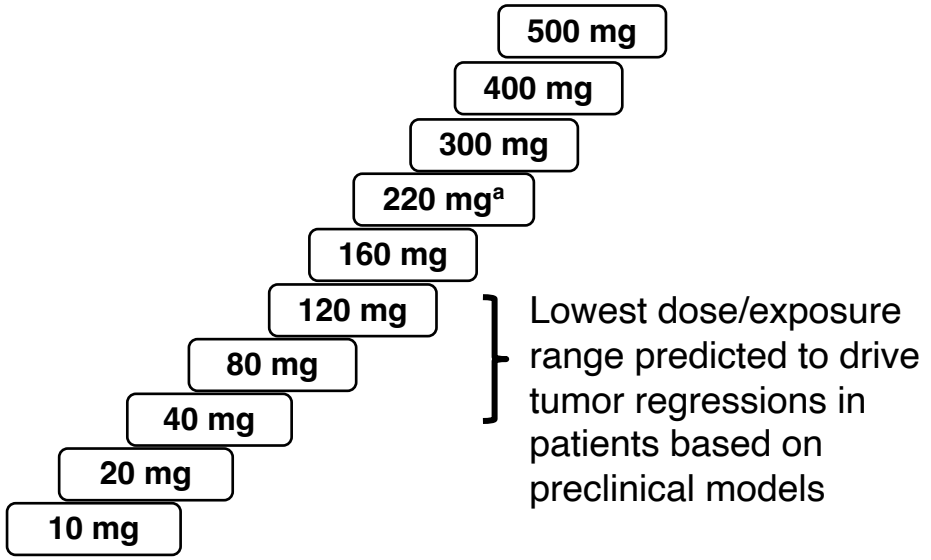
- Advanced solid tumors with $KRAS^{G12}$ mutations (currently excluding $KRAS^{G12C}$)
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Preliminary anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD



Dose Expansion / Optimization

RMC-6236-001: Treatment-Related AEs Occurring in ≥10% of All Patients

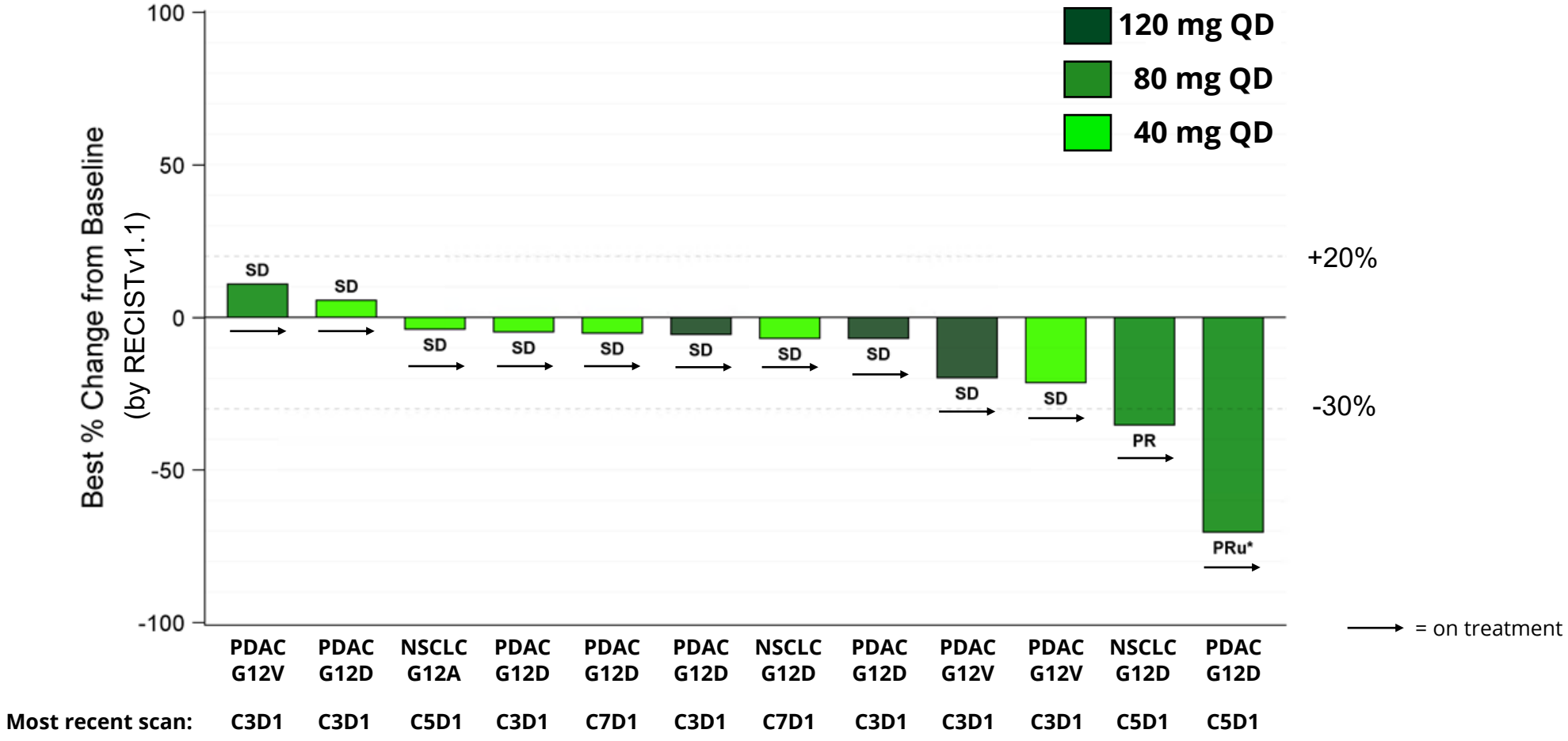
	10 mg QD (N=3)		20 mg QD (N=13)		40 mg QD (N=9)		80 mg QD (N=7)		120 mg QD (N=4)		Overall (N=36)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Rash (CMQ)*	0	0	2 (15.4%)	0	4 (44.4%)	0	6 (85.7%)	0	4 (100%)	0	16 (44.4%)	0
Nausea	1 (33.3%)	0	2 (15.4%)	0	6 (66.7%)	0	2 (28.6%)	0	1 (25.0%)	0	12 (33.3%)	0
Diarrhea	0	0	1 (7.7%)	0	2 (22.2%)	0	1 (14.3%)	0	2 (50.0%)	0	6 (16.7%)	0
Fatigue	0	0	0	0	2 (22.2%)	0	0	0	2 (50.0%)	0	4 (11.1%)	0
Vomiting	0	0	1 (7.7%)	0	2 (22.2%)	0	0	0	1 (25.0%)	0	4 (11.1%)	0

One related grade 4 adverse event of bowel perforation (also considered a serious adverse event) was reported in a patient receiving 80 mg daily. The likely cause of the perforation was considered to be shrinkage of metastatic $KRAS^{G12V}$ pancreatic cancer at the site of full-thickness bowel infiltration.

EDC data as of 02/17/2023. CMQ = Customized MedDRA Query

*Consists of dermatitis acneiform, dermatitis psoriasiform, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, and rash pustular.

RMC-6236-001: Change in Tumor Burden from Patients with KRAS^{G12X} NSCLC or Pancreatic Cancer Treated at ≥40 mg Daily



EDC data as of 02/17/2023; efficacy evaluable patients defined as those in this data set with at least one post baseline response assessment or who have died or have experienced clinical progression prior to the first post baseline scan (n=12). Cycle time is 21 days. SD = stable disease, PR = partial response. NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma. *PR subsequently confirmed as of 03/16/23.

RMC-6236-001 Case Report: Patient with KRAS^{G12V} Metastatic Pancreatic Cancer

- 52 year-old male
- Pancreas mass and peritoneal metastases identified October 2022
- Biopsy of peritoneal nodule: pancreatic adenocarcinoma
- Oct-2022 to Apr-2023 Gemcitabine/Nab-paclitaxel + investigational agent: Stable disease x 6 months
- Apr-2023 to May-2023 5-fluorouracil / folinic acid / nanoliposomal irinotecan: Progressive disease

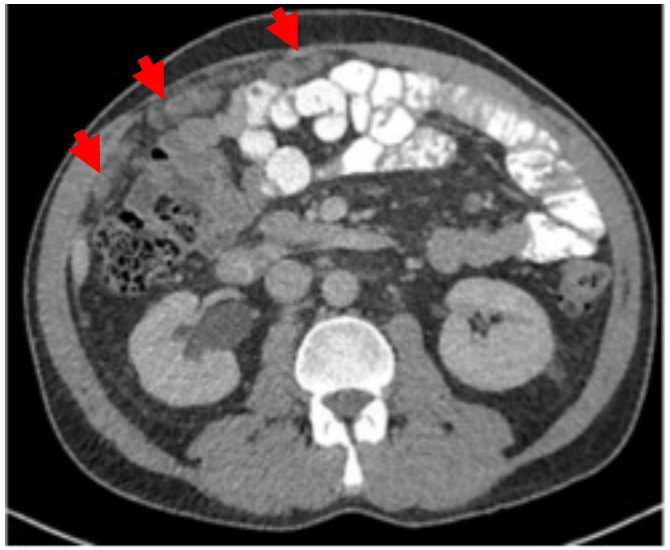
- Progression of peritoneal metastases
- Somatic NGS: KRAS^{G12V} with co-occurring TP53 and SMAD4 mutations from peritoneal biopsy
- Treated with RMC-6236 at 160 mg daily (dose level 6)
- Partial response identified at 6 weeks (RECISTv1.1, -35%), which is ongoing after 4 months
- Normalization of serum CA19-9
- Grade 1 rash, nausea, and diarrhea

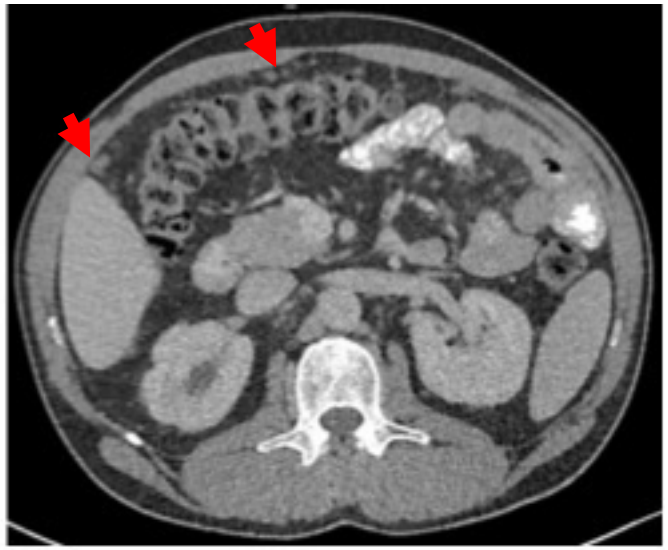
Data as of 09/21/2023

Case Report: Confirmed Partial Response by CT imaging

Peritoneal Disease | **Peritoneal Disease**

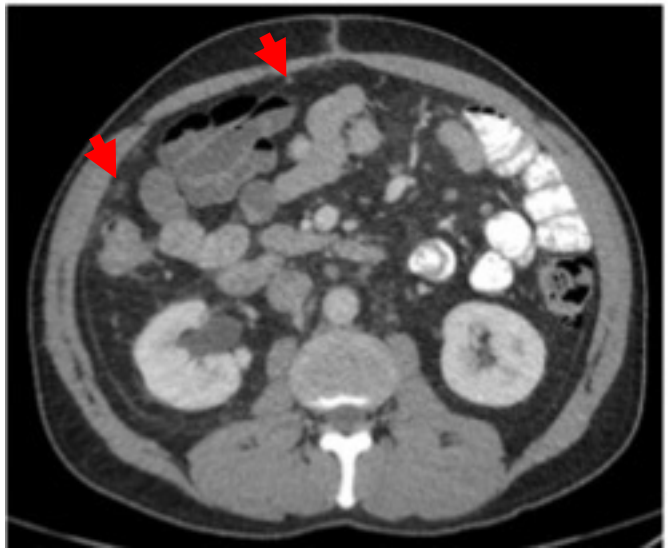
Baseline

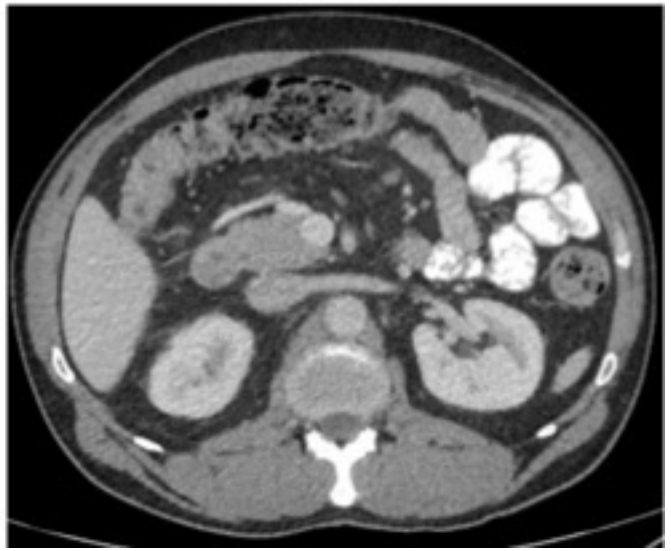




SLD: 65.9 mm

On Treatment RMC-6236, C5D1





SLD: 24.9 mm
Partial Response: -62%

SLD = sum of longest diameters per RECIST 1.1

Images courtesy of RMC-6236-001 study site with additional annotation by RVMD
(SLD values and red arrows highlighting detectable lesions)

Data as of 09/21/2023

Further data in PDAC, NSCLC, and other histologies to be presented at…

AACR-NCI-EORTC INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 11-15, 2023
Oral Presentation
Alex Spira, MD

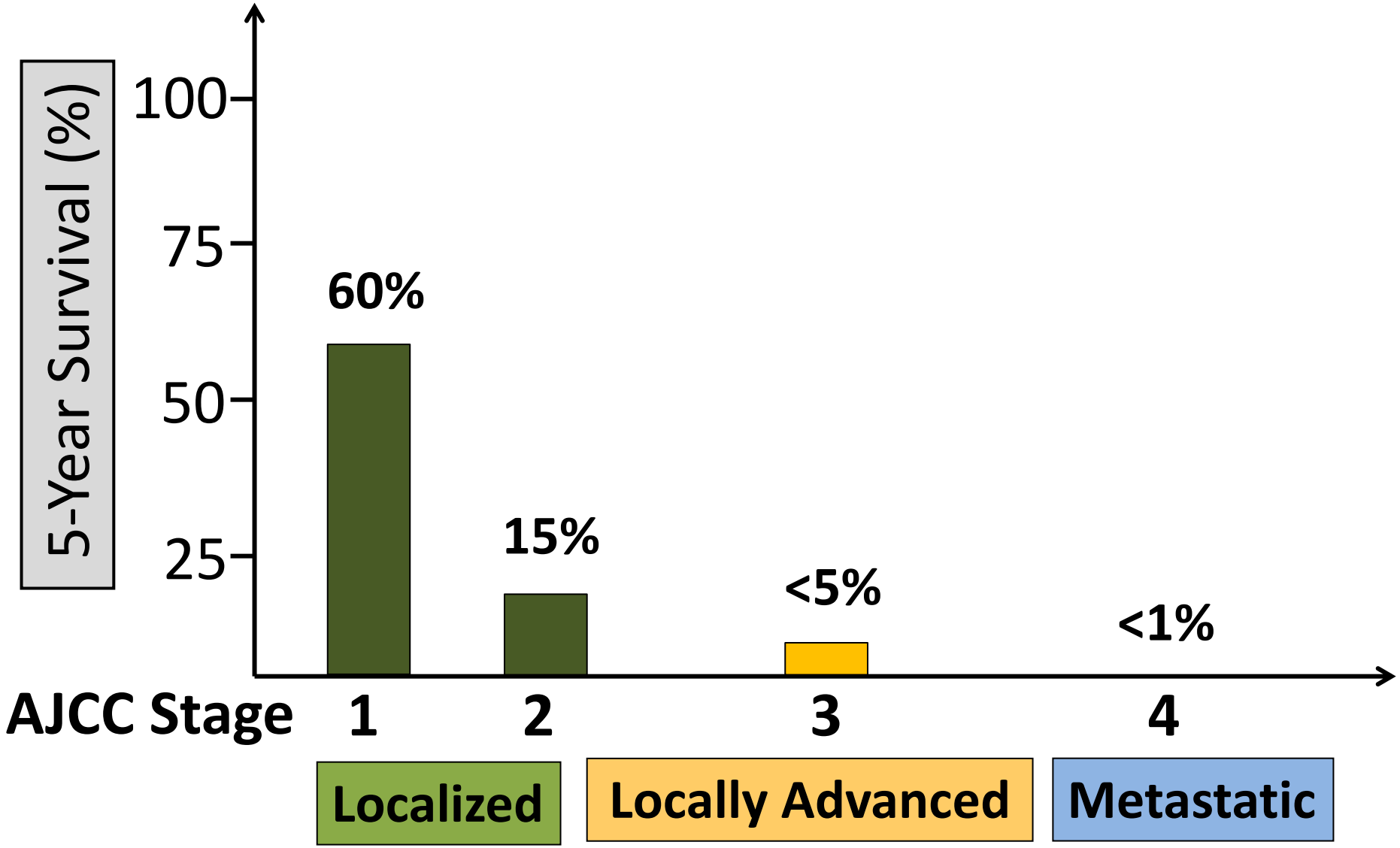
Preliminary safety and pharmacokinetic profiles of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS^{MULTI}(ON) inhibitor in patients with KRAS mutant solid tumors on the Phase 1 trial RMC-6236-001

MADRID 2023 ESMO congress

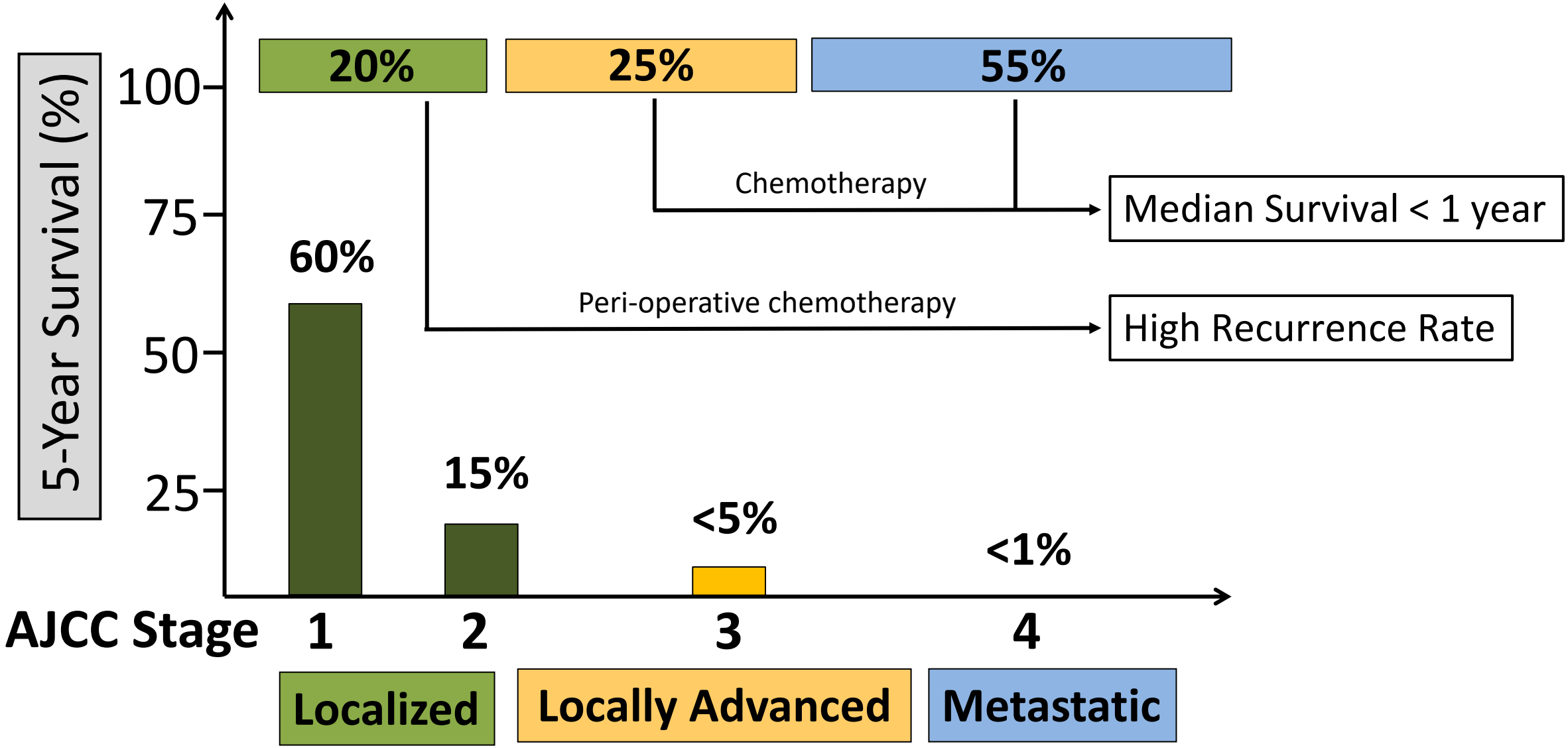
October 20-24, 2023
Oral Presentation
Kathryn Arbour, MD

Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC)

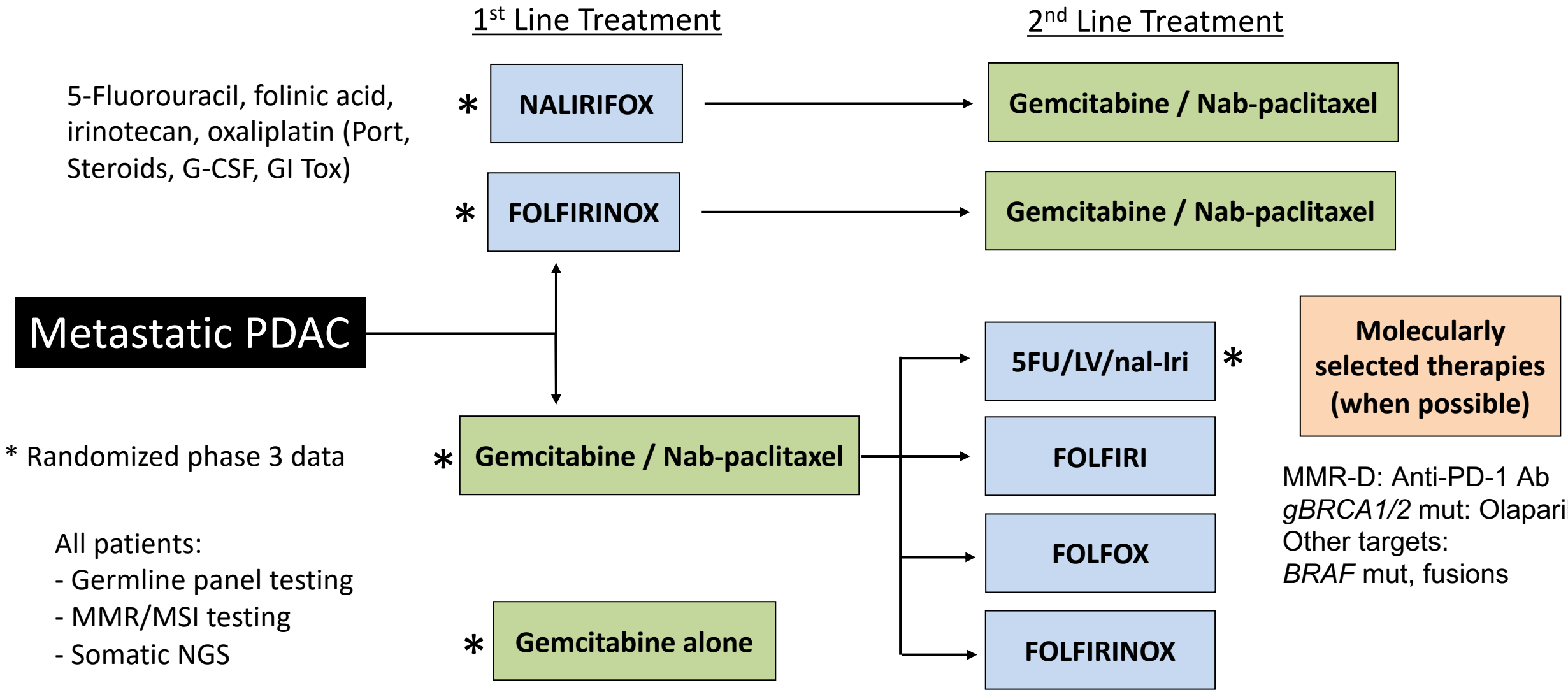
Pancreatic Cancer Survival



Pancreatic Cancer Survival

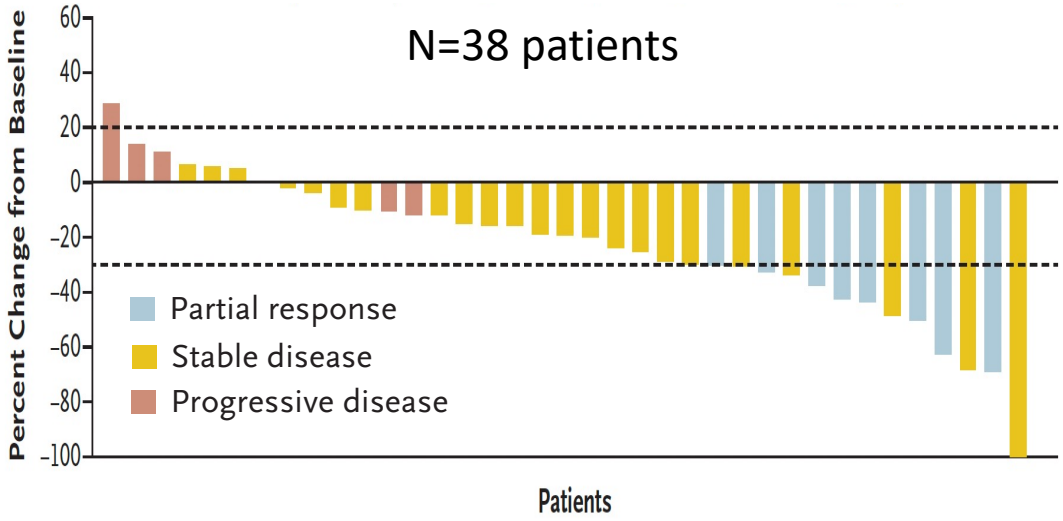


Current treatment paradigm for metastatic pancreatic cancer



For the 1%: KRAS^{G12C} inhibitors in pancreatic cancer

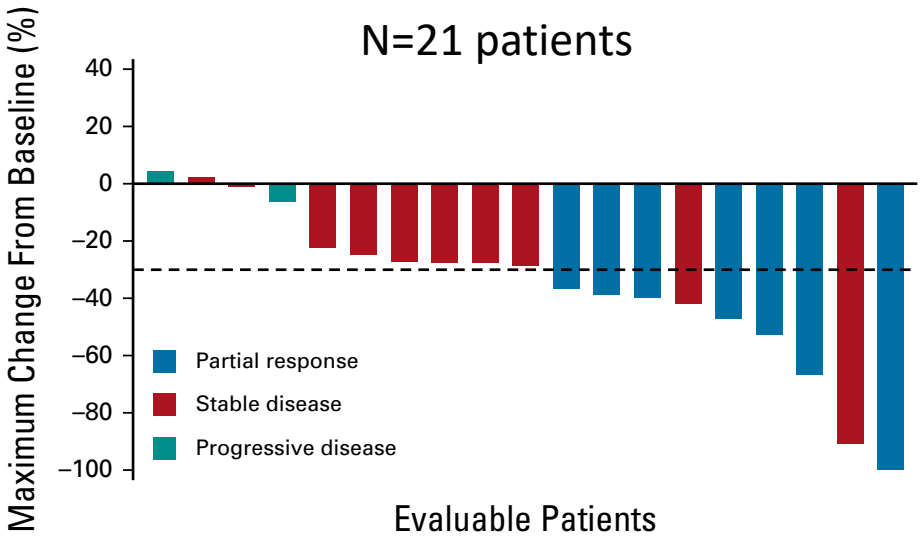
Sotorasib in advanced, previously-treated PDAC



ORR: 21% (8/38)
DCR: 84% (32/38)
mPFS: 4.0 mos
mOS: 6.9 mos

Strickler et al. NEJM 2023

Adagrasib in advanced, previously-treated PDAC

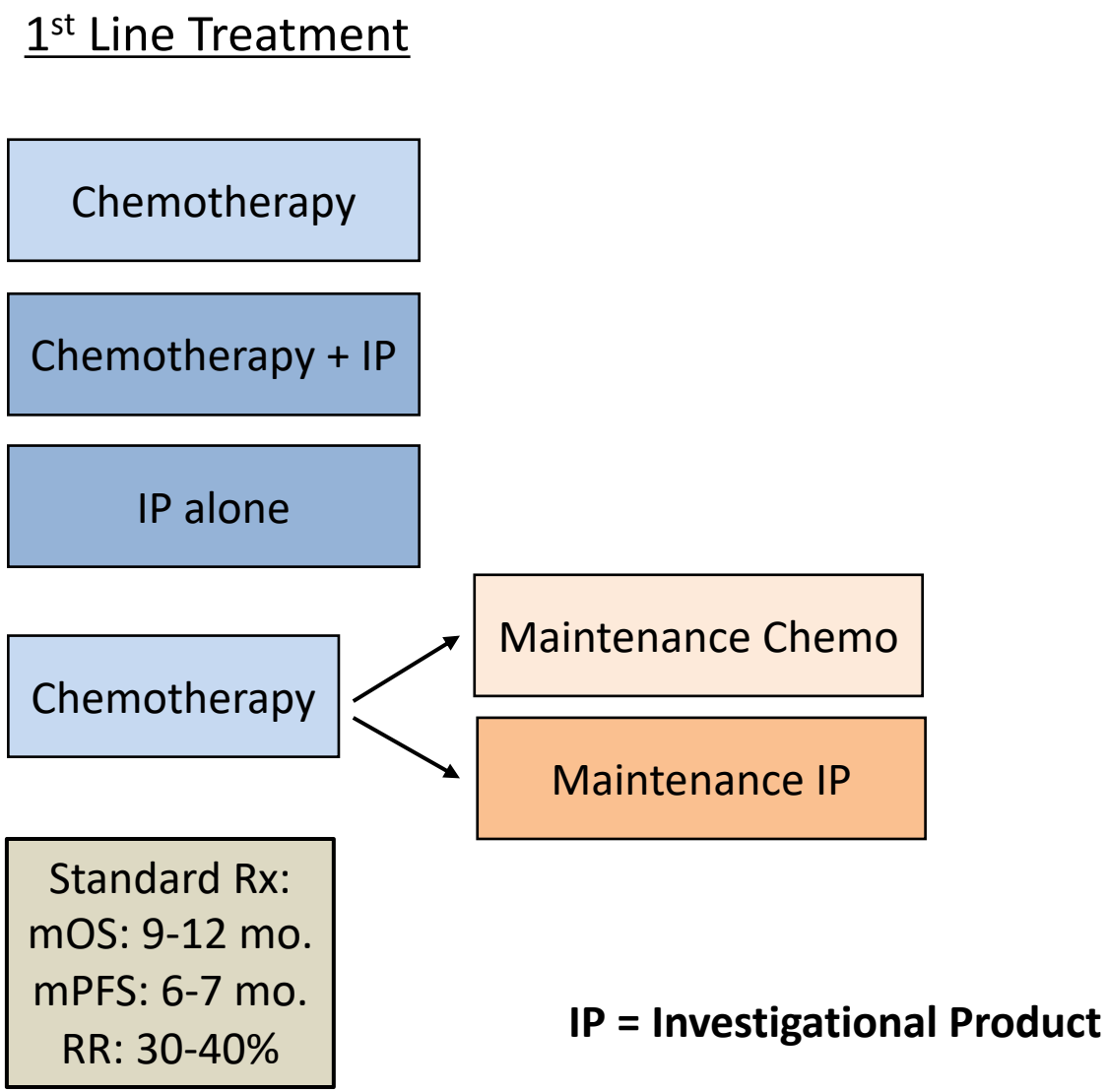


ORR: 33% (7/21)
DCR: 81% (17/21)
mPFS: 5.4 mos
mOS: 8.0 mos

Bekaii-Saab et al. JCO 2023

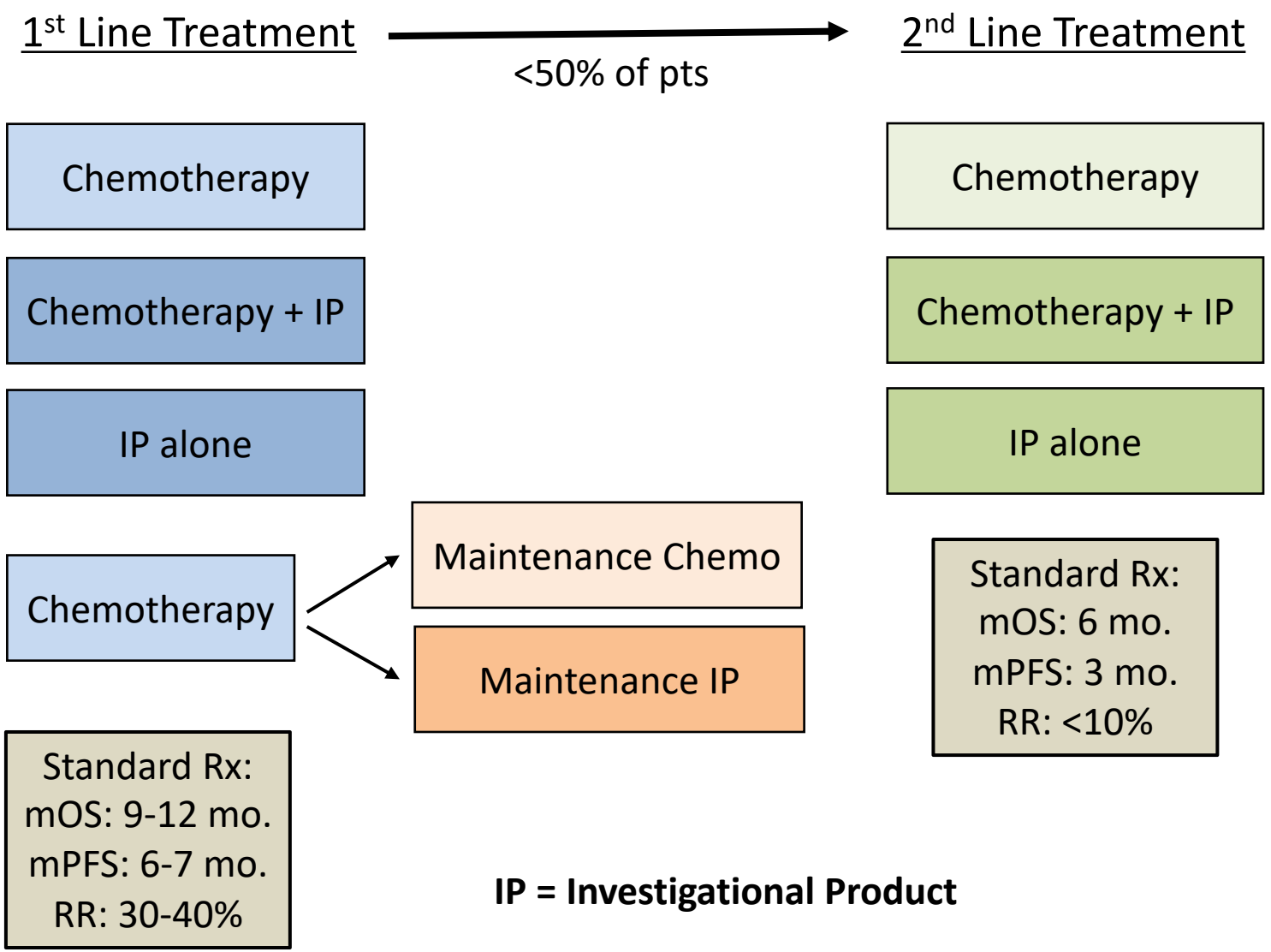
Divarasib in advanced, previously-treated PDAC:
ORR 43% (3/7); DCR 100% (7/7) Sacher et al. NEJM 2023

Evaluating new therapies in metastatic pancreatic cancer



IP = Investigational Product

Evaluating new therapies in metastatic pancreatic cancer



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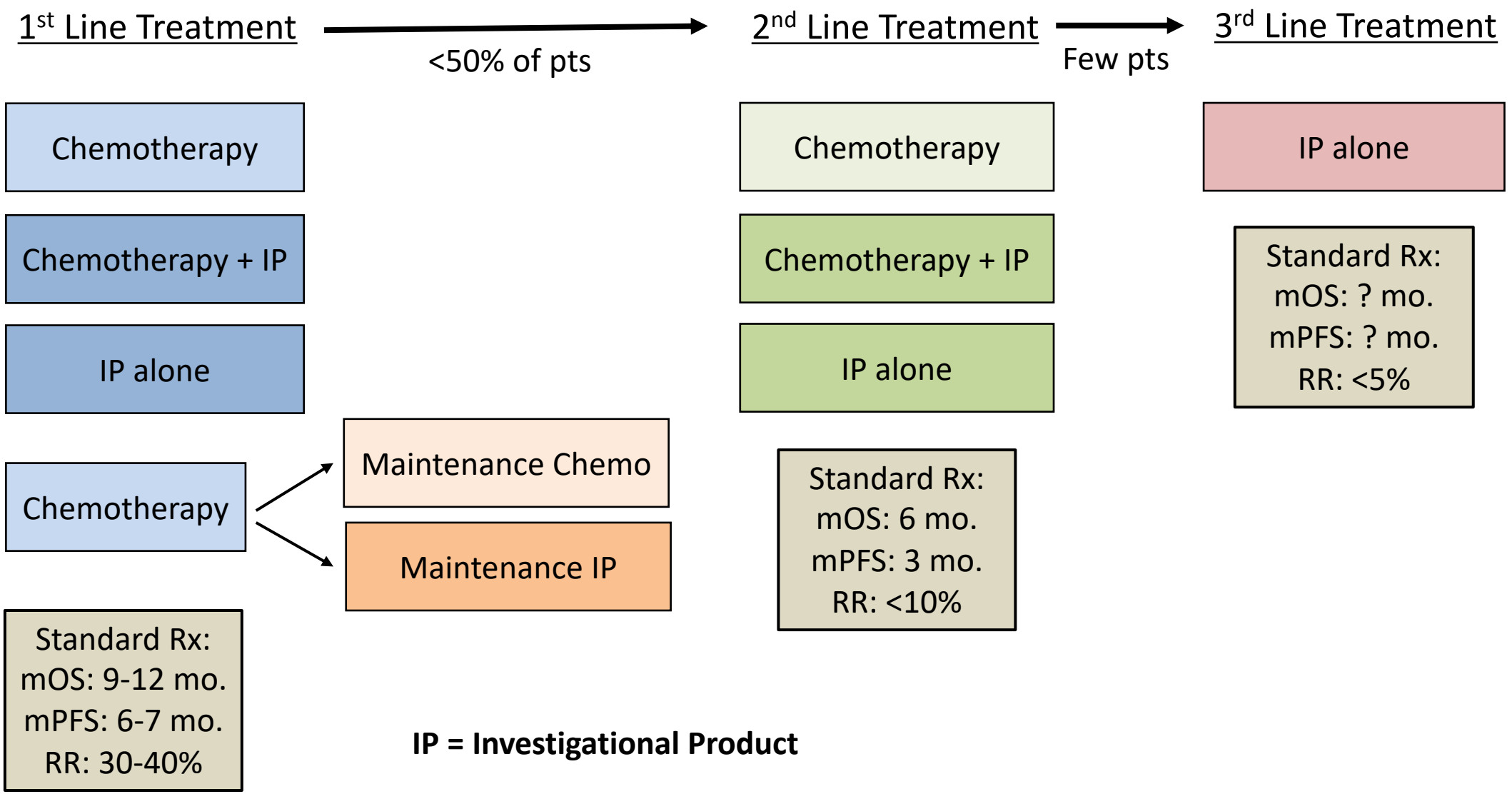


IP = Investigational Product

Practicalities for General Trial Design in Pancreatic Cancer

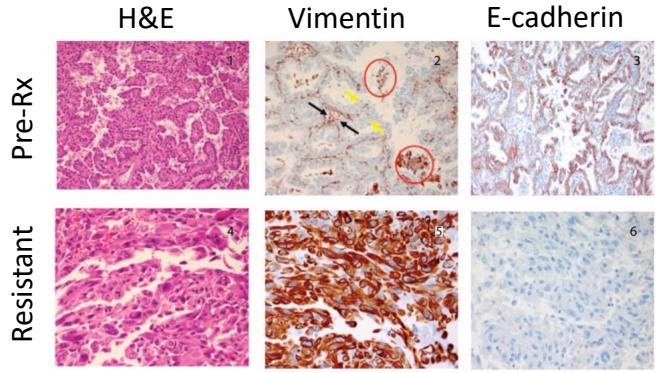
- Rationale for IP plus chemotherapy combinations.
- Chemotherapy and overlapping toxicities.
- Patients often with multiple symptoms and complications from the disease.
- 1st line molecularly-selected trials need rapid turn-around for assay results.
- Maintenance trials are of growing interest.
- Rapid movement of effective drugs to earlier treatment settings.
- KRAS inhibitors should have large role to play!
- Get research tissue.

Histologic transformation and changes to the TME as mechanisms of resistance

Adeno-Squamous Transition (AST): Transition to squamous cell carcinoma upon adagrasib resistance observed in 2 of 9 (22%) NSCLC cases with paired pre-/post-treatment tissue biopsies.

Awad,…, Aguirre et al. NEJM 2022

Epithelial-mesenchymal transition (EMT)



NCSLC: Rapid autopsy s/p sotorasib

Tsai,..., Pecot et al. JCI 2022

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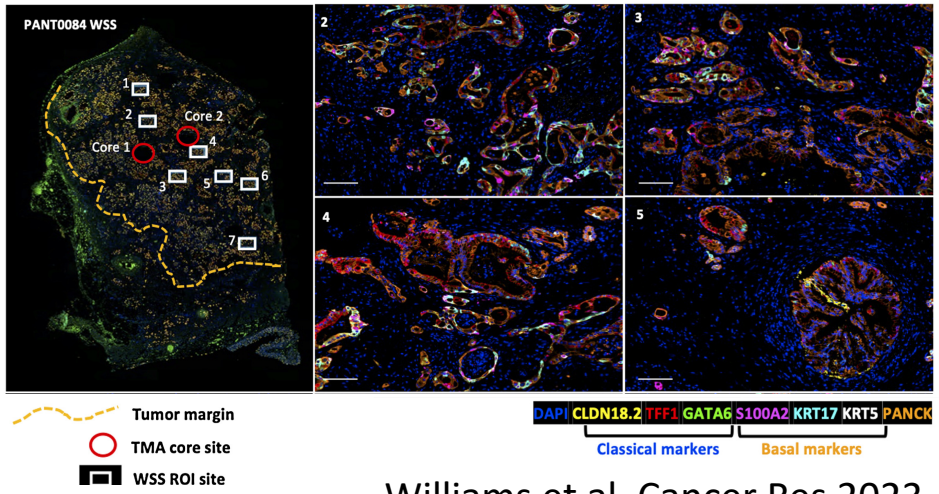
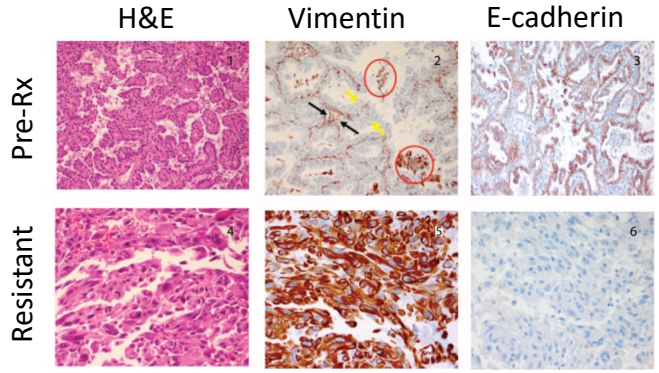


Williams et al. Cancer Res 2023
Raghavan et al. Cell 2021

Epithelial-mesenchymal transition (EMT)



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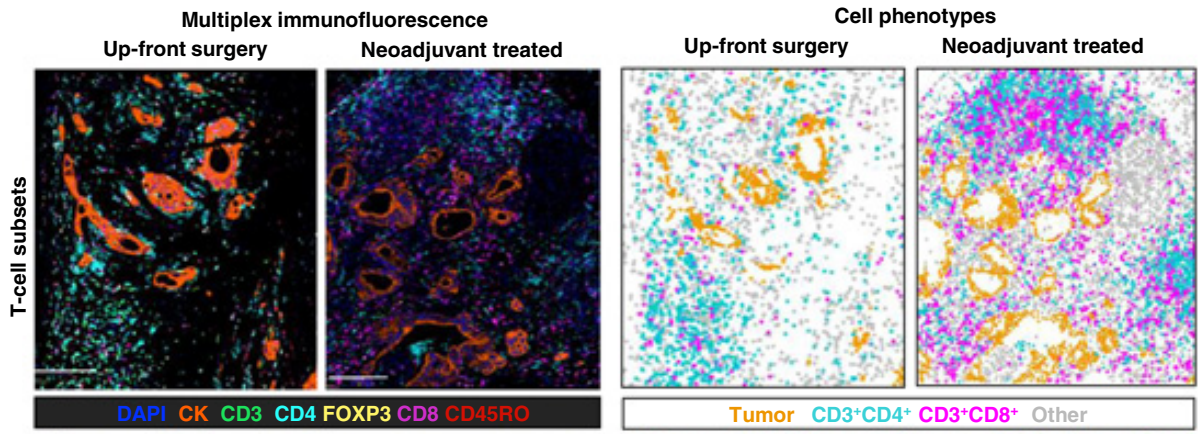
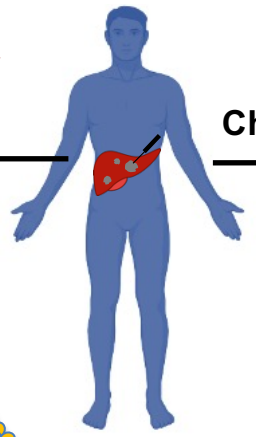


Dias Costa et al. Clin Cancer Res 2022

Translational platform for clinical trials of KRAS inhibition

BREAK THROUGH CANCER
Collaborating for Cures

Advanced Pancreatic Cancer

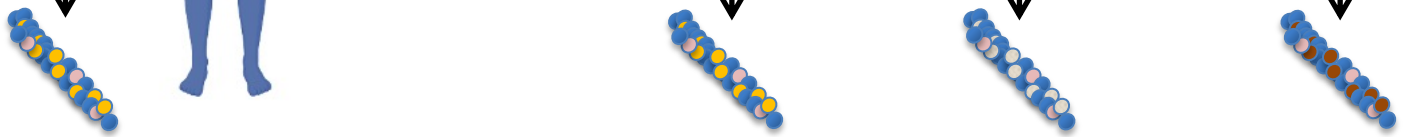


First-line Chemotherapy

KRAS Inhibitor

Progression * **Progression** * * * Serial QOL Assessment

Serial blood and tissue biopsies



	Diagnostic	Pre-treatment	On-treatment	Post-progression
DNA, RNA Seq	✓	✓		✓
Single-cell/-nuc multi-omics	✓	✓	✓	✓
Histopathology & Spatial Profiling	✓	✓	✓	✓
Organoids & PDX	✓	✓		✓
Rapid Biomarker Assays	✓	✓		✓
Serial ctDNA and blood biomarkers	✓	✓	✓	✓

Data analysis

↓

Biomarkers of response and resistance

↓

Preclinical validation

↓

Next generation trials

Summary

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in *KRAS*

- RMC-6236 is a tri-complex, $KRAS^{MULTI}$(ON) inhibitor with strong preclinical data in multiple *KRAS*-mutant malignancies across different *KRAS* variants
- Trial enrollment is ongoing at 10 U.S. sites
- Toxicity profile thus far has consisted primarily of rash, nausea/vomiting, and diarrhea.
- Early efficacy signals have been seen, with partial responses by RECISTv1.1 in patients with *KRAS*-mutant NSCLC and PDAC
- Additional data to be presented next month at AACR-NCI-EORTC Conference (Boston) and ESMO Congress (Madrid).

Thank you.

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in *KRAS*

Enrolling patients and their families
Investigators and staff at the 10 enrolling centers
Revolution Medicines study team

Virginia
San Antonio