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RMC-6236: Pancreatic Cancer Update to Support Pivotal Phase 3 Trial

July 15, 2024

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For a further description of the risks and uncertainties that could cause actual results to differ from those anticipated in these forward-looking statements, as well as risks relating to the business of Revolution Medicines in general, see Revolution Medicines' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 8, 2024, and its future periodic reports to be filed with the Securities and Exchange Commission.

This presentation concerns product candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). These product candidates are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are is being investigated.

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Mission: to revolutionize treatment for patients with RAS-addicted cancers through the discovery, development and delivery of innovative, targeted medicines.

- RMC-6236, our most advanced investigational drug, is a groundbreaking RAS(ON) multi-selective inhibitor with encouraging clinical safety profile and antitumor activity across multiple RAS solid tumors
- Updated clinical data from first-in-human study indicate promising progression-free survival (PFS) with RMC-6236 in patients with previously treated pancreatic ductal adenocarcinoma (PDAC)
- Totality of evidence supports initiating RASolute 302, a global, randomized Phase 3 trial in 2L metastatic PDAC patients

Unmet Medical Needs in Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC is a Devastating, RAS-Driven Disease with Major Unmet Medical Needs

60K new cases estimated to be diagnosed in the US in 2024[1]

- 3rd leading cause of cancer deaths[1]

Most patients diagnosed with metastatic disease[2]

- 5-year survival is 3%[2]

Multi-agent chemotherapy is the primary treatment for most patients[3]

- Current targeted therapies benefit minority of patients[3]

Pancreatic cancer is the most RAS-addicted of all major cancers

- Over 90% of patients with PDAC have RAS mutant tumors[4]

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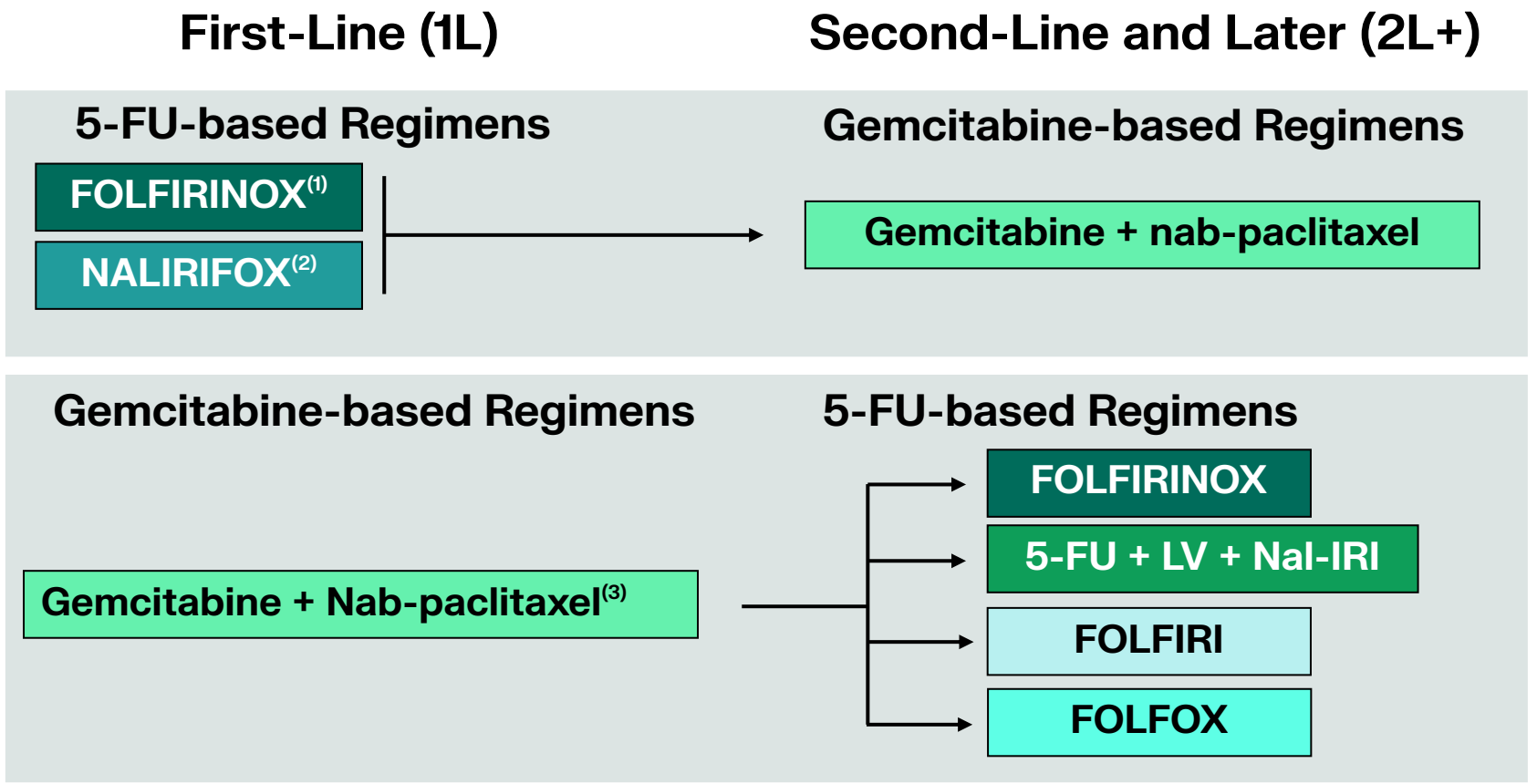
(1) Incidence from ACS Cancer Facts and Figures 2024, adjusted for PDAC only. Includes all stages of disease. (2) ACS Cancer Facts and Figures 2024 adjusted for metastatic stage only. (3) CancerMPact 2022. (4) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.

Current Treatment Paradigm for Metastatic PDAC



Supportive care measures: IV port-a-cath, steroids, G-CSF, GI toxicity management

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5-FU, fluorouracil; LV, leucovorin; Nal-IRI, nanoliposomal irinotecan; GI, gastrointestinal

(1) Conroy T, et al. *NEJM* 2011;364:1817-25. (2) Wainberg AZ, et al. *Lancet* 2023;402:1272–81; (3) Von Hoff DD, et al. *NEJM* 2013;369:1691-703.

Chemotherapy in Previously Treated Metastatic PDAC Provides Limited Clinical Benefit with Significant Toxicity

Reported Efficacy

Study	Regimen	Treatment line	No. of patients	ORR (%)	Median PFS (months)	Median OS (months)
NAPOLI 1[1]	**5-FU+LV+Nal-IRI**	2L+	117	8	**3.1**	**6.1**
SWOG S1513[2]	**FOLFIRI**	2L	58	10	**2.9**	**6.5**
SWOG S1115[3]	**FOLFOX**	2L	62	7	**2.0**	**6.7**
SEQUOIA[4]	**FOLFOX**	2L	284	6	**2.1**	**6.3**
QUILT-3.010[5]	**Gemcitabine + nab-paclitaxel**	2L	40	3	**2.7**	**6.6**
Trybeca-1[6]	**Gemcitabine + nab-paclitaxel**	2L	148	NA	**3.5**	**6.9**
GEMPAX[7]	**Gemcitabine + paclitaxel**	2L	140	17	**3.1**	**6.4**
Gupta et al.[8]	**5-FU+LV+Nal-IRI**	3L+	30	3	**1.9**	**5.0**
Enzler et al.[9]	**CBP501+cisplatin+nivolumab**	3L+	36	6	**1.9**	**5.1**

Reported Safety and Dose Modifications

- 5-FU/LV/Nal-IRI dose interruptions required in 62% of patients, dose reductions in 33%, and discontinuations in 11%[1]
- Gemcitabine + nab-paclitaxel dose modifications required in 63%[6]

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NA, not available.

(1) Onivyde USPI; (2) Chiorean EG, et al. Clin Cancer Res 2021:27:6314–33; (3) Chung V, et al. JAMA Oncol 2017;3:516–22; (4) Hecht JR, et al. J Clin Oncol 2021;39:1108–18; (5) Huffman BM, et al. JAMA Network Open 2023;6:e2249720. (6) Hammel P, et al. ASCO GI 2022; (7) Fouchardiere C, et al. J Clin Oncol 2024;42:1055-1066; (8) Gupta A, et al. Frontiers Oncol 2023: 13:1250136; (9) Enzler T, et al. Eur J Cancer 2024: 113950, means of median PFS and median OS from four experimental regimens provided

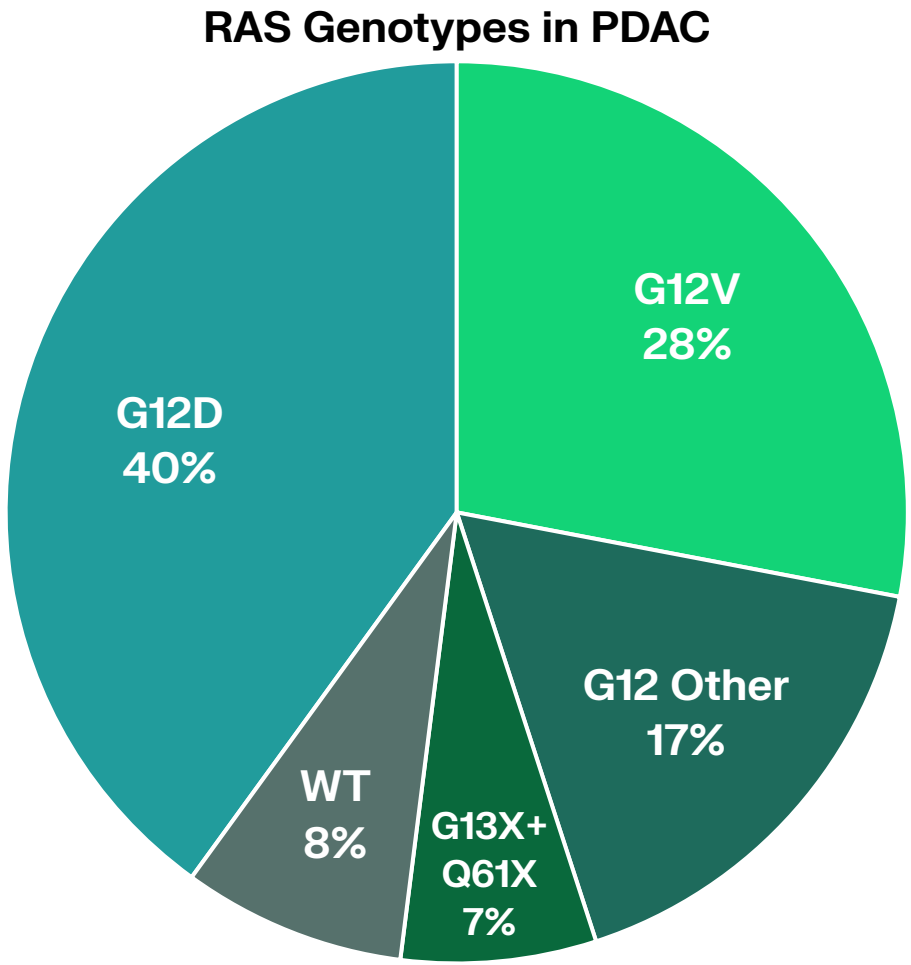
RMC-6236 – RAS(ON) Multi-Selective Inhibitor

RAS-Targeted Therapies Have the Potential to Address Large Unmet Needs and Transform Treatment for PDAC

60,000
new PDAC cases per year (U.S.)[1]

92%
have RAS driver mutations[2]

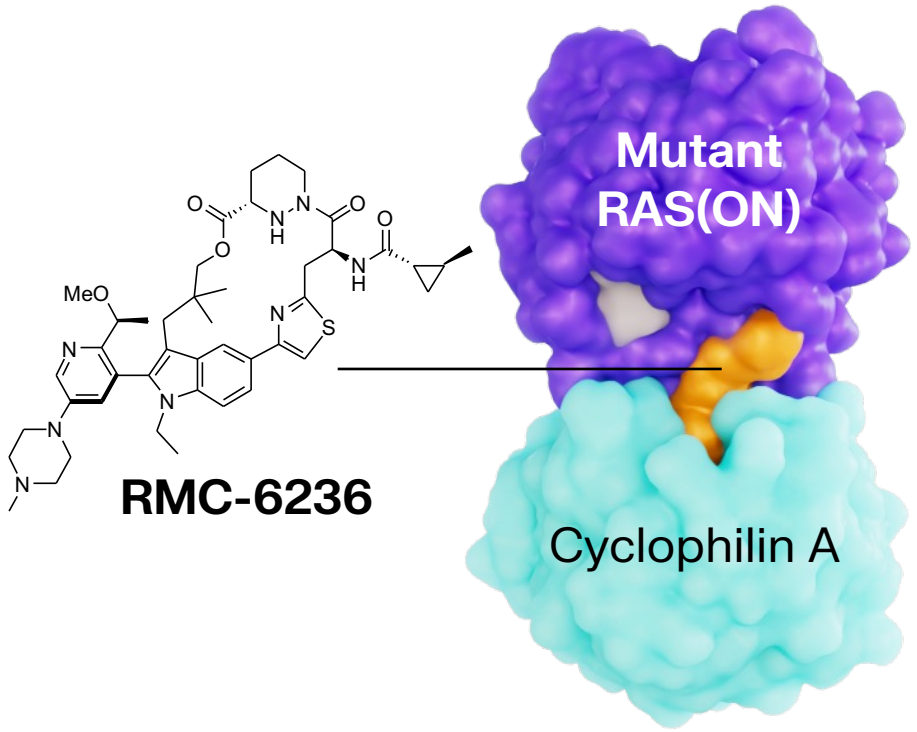
85%
have RAS G12X driver mutations, <2% are G12C[2]



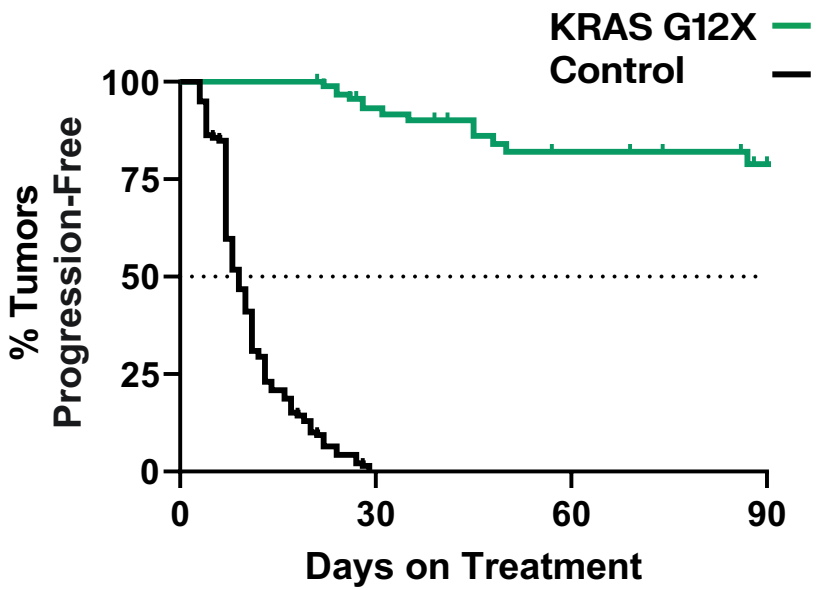
WT, wild type
(1) ACS Cancer Facts and Figures 2024 adjusted for PDAC only.
(2) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.
RAS G12X, non-synonymous mutations in KRAS, HRAS or NRAS at codon 12 (G12). G13X and Q61X, non-synonymous mutations in KRAS, HRAS or NRAS at codons 13 and 61, respectively.

RMC-6236: RAS(ON) Multi-Selective Inhibitor Designed to Directly Inhibit Oncogenic State of Common RAS Drivers of PDAC

Pioneering Drug Design and Mechanism of Action



Induces Durable Progression-Free Survival in RAS G12X PDAC Models[1]



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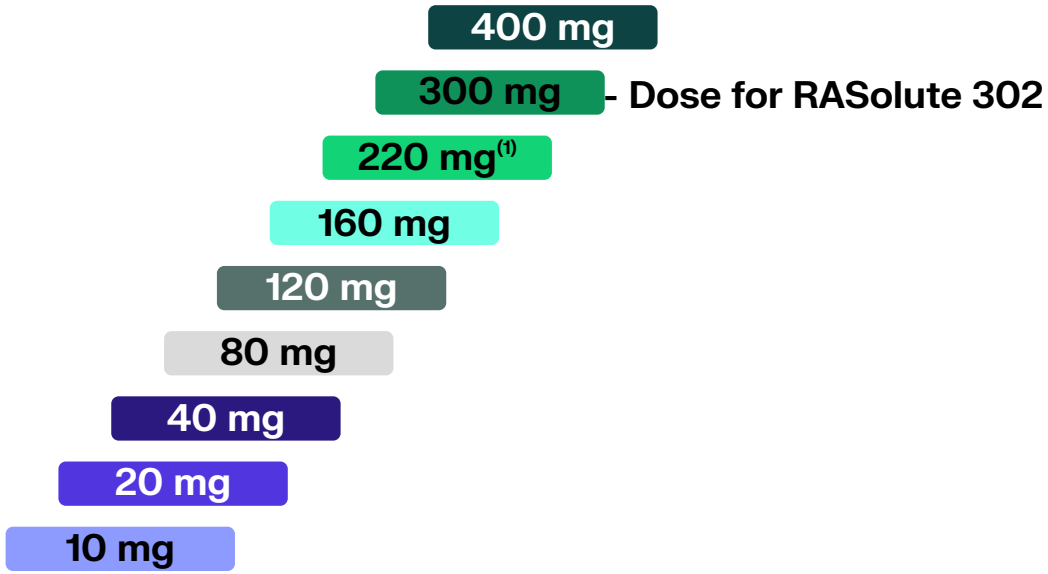
(1) RVMD preclinical data, Jiang et. al. Cancer Discovery 2024:14:1-24.

Clinical Experience in Patients with PDAC: RMC-6236-001 First-in-Human Trial

RMC-6236 has been Evaluated Across a Large Number of Patients with Advanced RAS Mutant Solid Tumors in the First-in-Human Trial

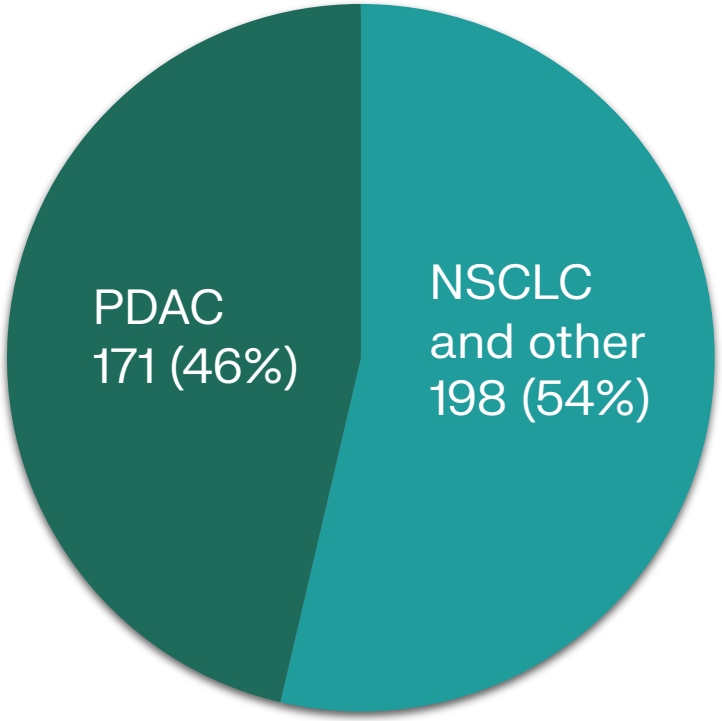
Dose Escalation in Solid Tumors

RMC-6236 administered orally QD



Tumor Types in FIH Trial

N = 369



RMC-6236-001 Clinical Trial: https://clinicaltrials.gov/study/NCT05379985
(1) 220 mg cleared dose limiting toxicity (DLT) evaluation and a dose of 200 mg was selected for further expansion/optimization.
FIH, first-in-human; QD, once daily.

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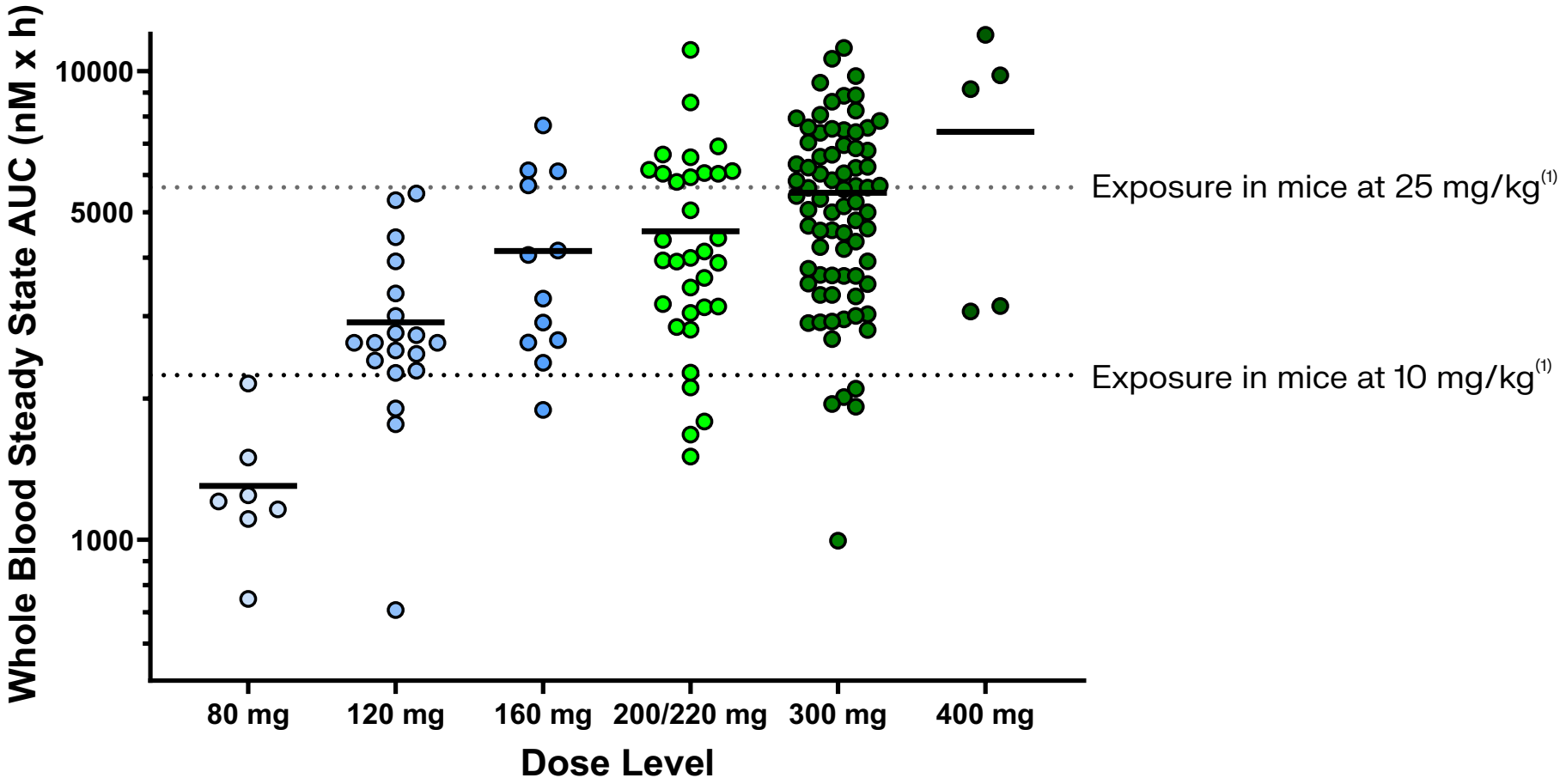
5/11/24 data cutoff

Dose Levels of 160-300 mg QD Achieved Target Exposures in Almost All Patients



(1) Exposures corrected with cross-species protein binding and blood/plasma partitioning. 10 mg/kg/day induces tumor regressions in sensitive preclinical models while 25 mg/kg/day induces regressions in the majority of preclinical models (Jiang et. al. Cancer Discovery 2024:14:1-24).

3/26/24 data cutoff

Patient Demographics and Baseline Characteristics: PDAC (160–300 mg)

Baseline Characteristics	N=127
Age, median (range), years	64 (30-86)
Male, n (%)	71 (56%)
ECOG PS 1, n (%)	82 (65%)
Number of prior anti-cancer therapies, median (range)	2 (1-11)
Select type of prior anti-cancer regimens, n (%)	
(m)FOLFIRINOX	95 (75%)
Gemcitabine + nab-paclitaxel	91 (72%)
Number of prior anti-cancer therapies in metastatic setting, median (range)	2 (0-5)
Number of prior anti-cancer therapies in metastatic setting[(1)]	
0	2 (2%)
1	56 (44%)
2+	68 (54%)
Liver metastases at baseline	86 (68%)
Metastatic at diagnosis (Stage IV)	67 (53%)

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(1) First-in-human study enrolled patients with locally advanced or metastatic PDAC; 1 prior line of therapy in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose; 1 patient with data missing for line of therapy
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

5/11/24 data cutoff

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%)

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(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

Treatment-Related Adverse Events Leading to Dose Modifications: RAS Mutant PDAC (160–300 mg)

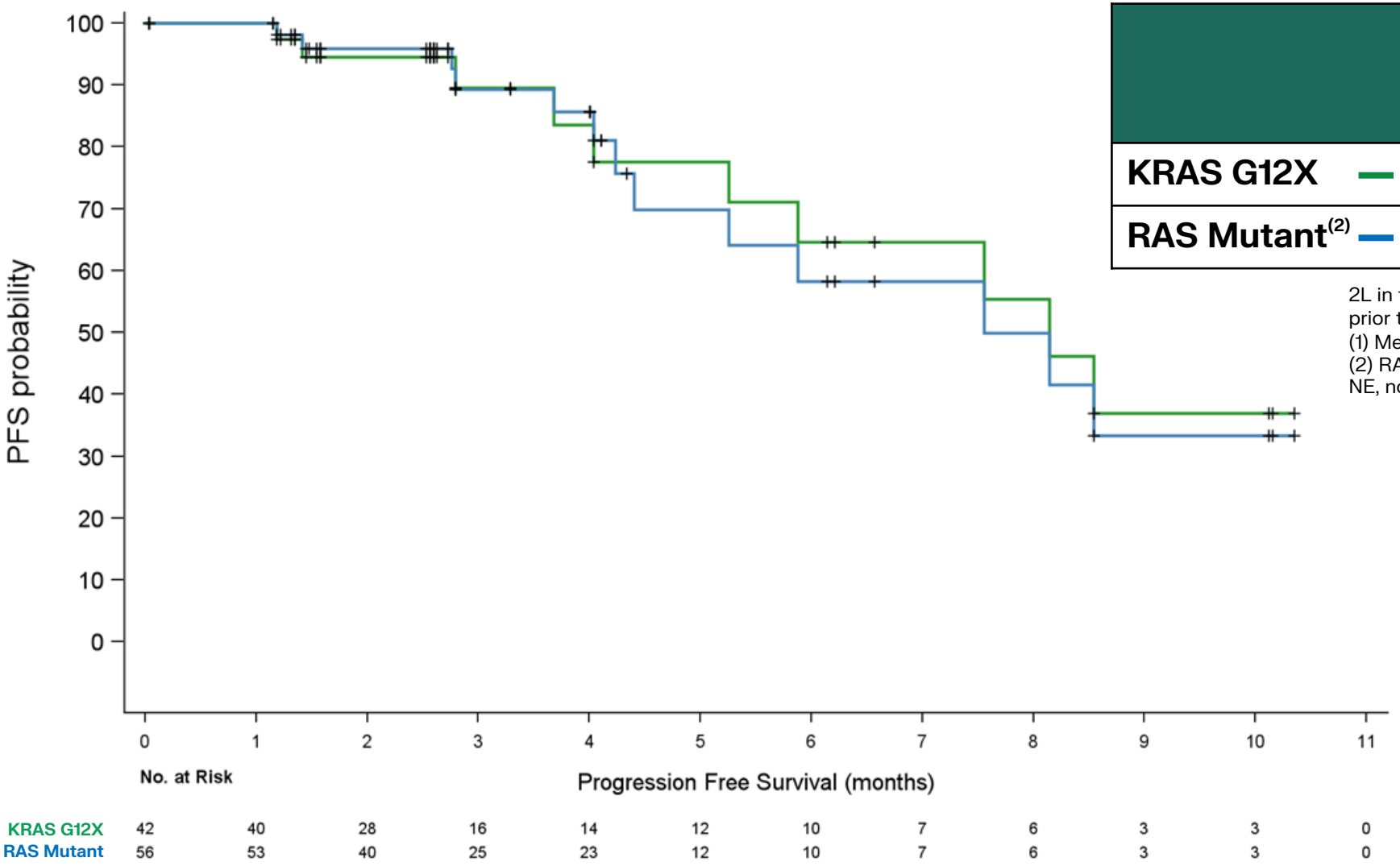
	N = 127
TRAEs leading to dose modification, n (%)	35 (28%)
Dose interruption	34 (27%)
Dose reduction	14 (11%)
Dosing discontinuation	0 (0%)
Specific TRAEs leading to dose reduction (≥2 patients) by preferred term	
Rash[1]	7 (6%)
Stomatitis/mucositis	4 (3%)
Decreased appetite	2 (2%)
Diarrhea	2 (2%)
Platelet count decreased	2 (2%)

- Dose intensity was ≥ 92% at each dose level with an average of 94% across the 160-300 mg cohorts

(1) Includes preferred terms of dermatitis acneiform and rash maculopapular; multiple types of rash may have occurred in the same patient.

5/11/24 data cutoff

Observed PFS in 2L Metastatic PDAC on RMC-6236 (160-300 mg)



	Median PFS Months (95% CI)	Benchmark Median PFS[1] Months
KRAS G12X	**8.1** (5.9-NE)	2.0-3.5
RAS Mutant[2]	**7.6** (5.3-NE)	

2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose
(1) Median PFS benchmark from published reports (see slide 7)
(2) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.
NE, not estimable.

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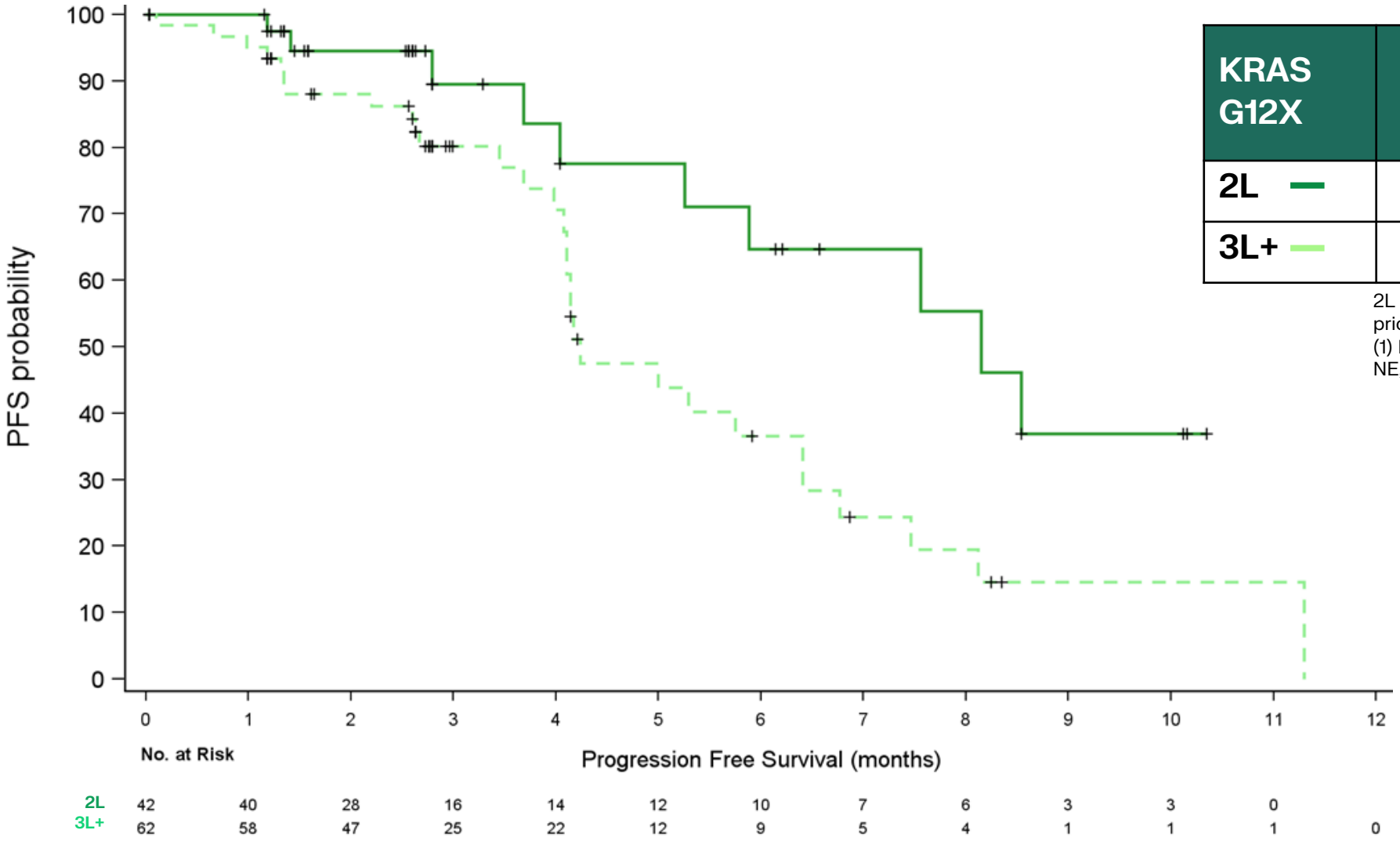
5/11/24 data cutoff

Observed PFS in 2L vs. 3L+ Metastatic PDAC on RMC-6236 (160-300 mg)



KRAS G12X	Median PFS Months (95% CI)	Benchmark Median PFS[1] Months
2L	8.1 (5.9-NE)	2.0-3.5
3L+	4.2 (4.1-6.4)	1.9

2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose
(1) Median PFS benchmark from published reports (see slide 7)
NE, not estimable

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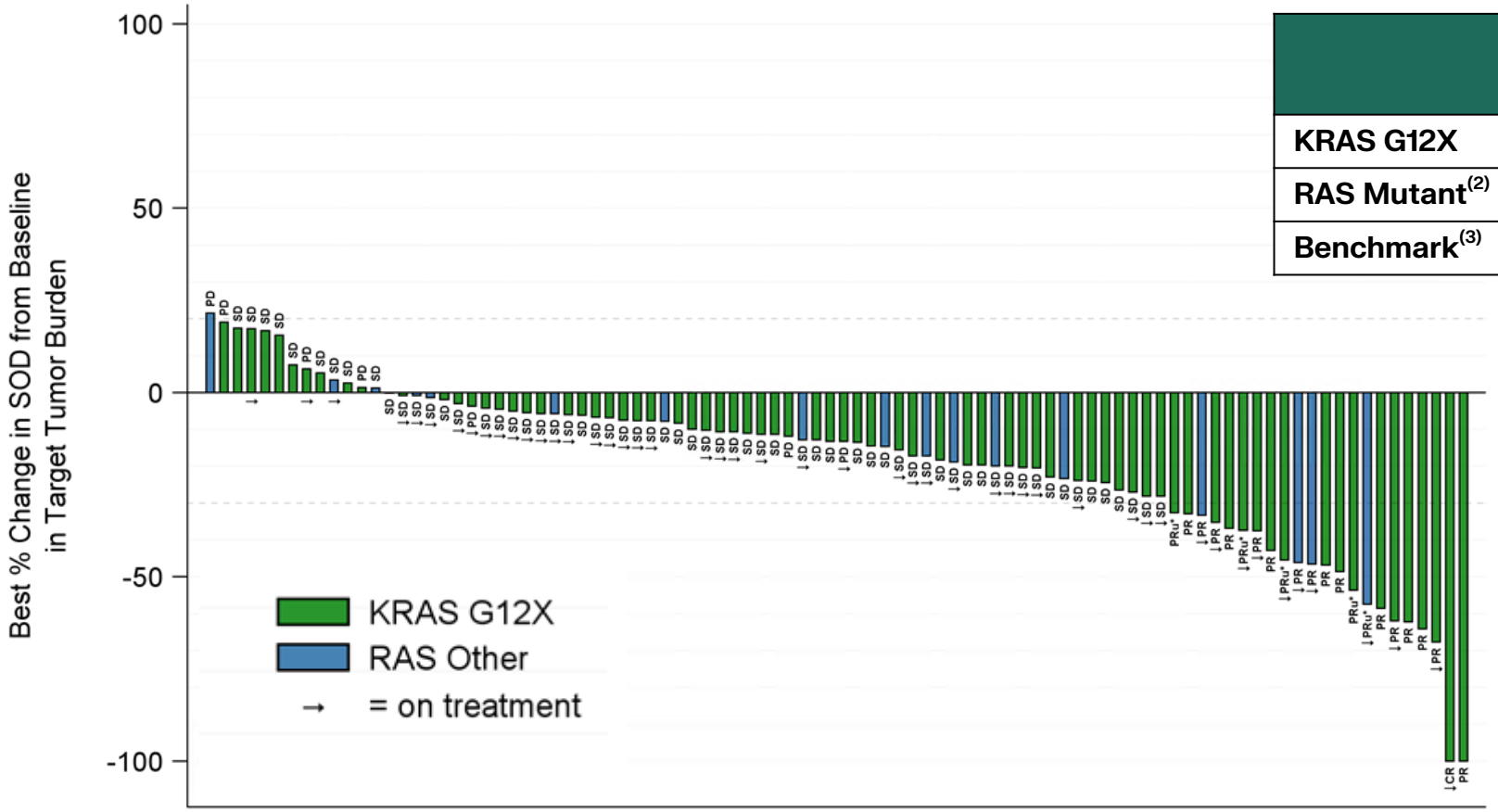
5/11/24 data cutoff

Best Percentage Change in Tumor Size from Baseline and Objective Response Rate in 2L+ PDAC (RMC-6236 160-300 mg)

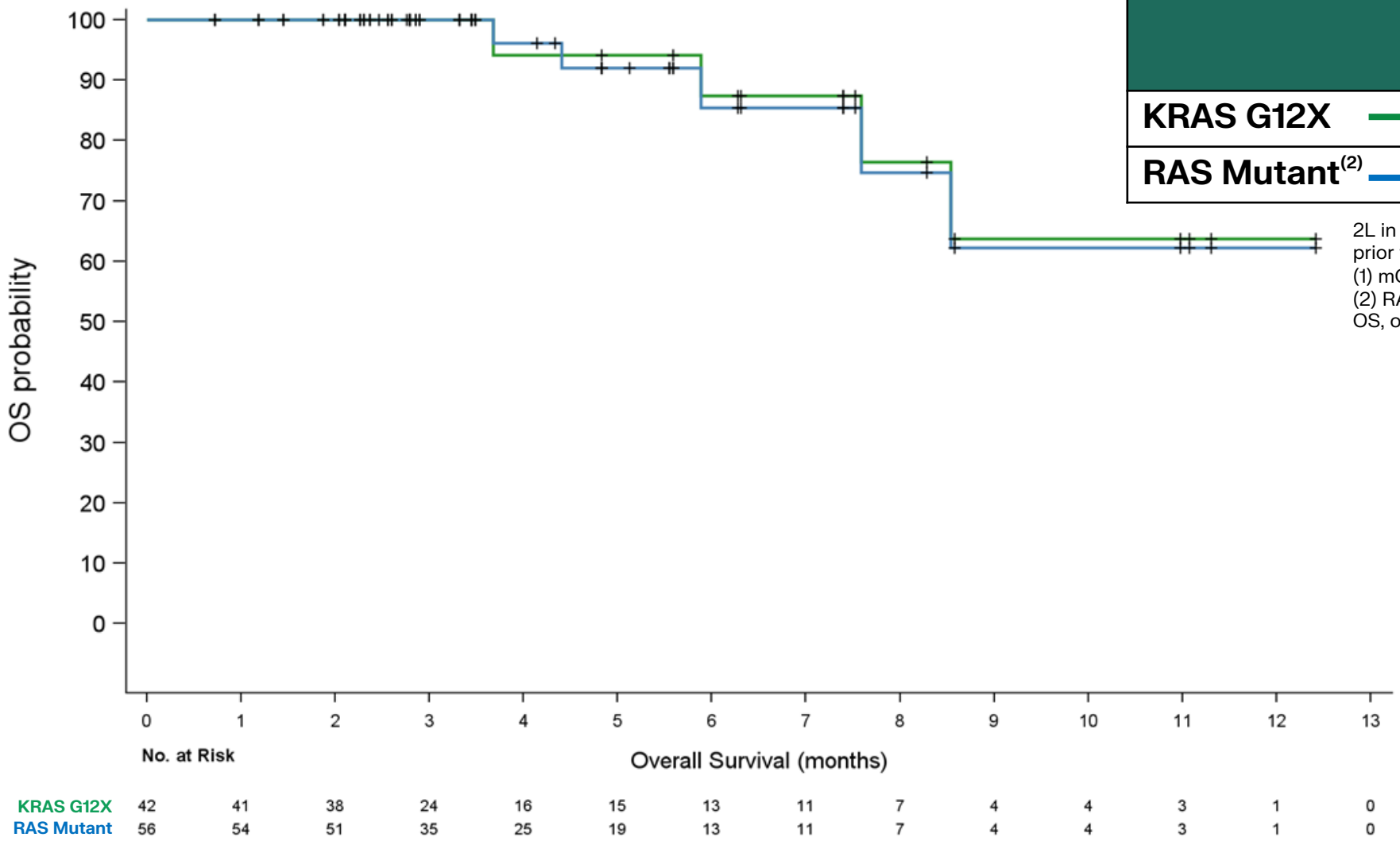


	ORR 14+ week[1]	ORR 20+ week[1]	DCR 14+ week[1]
KRAS G12X	20% (16/79)	27% (13/48)	87% (69/79)
RAS Mutant[2]	21% (20/97)	26% (16/61)	88% (85/97)
Benchmark[3]	9%		NA

(1) "ORR 14+ week" and "DCR 14+ week" analyses include all patients who received first dose of RMC-6236 at least 14 weeks prior to data cutoff date (to allow 2 potential scans). "ORR 20+ week" analysis is similarly defined to allow 3 potential scans. 5 patients included in the denominator of the '14+ week' analyses are not displayed on waterfall due to lack of post-baseline target lesion assessment (4 patients discontinued treatment without post-baseline scans: 3 due to death, 1 due to subject request to withdraw from treatment, and 1 patient had documented PD due to new lesion without target lesion assessment); *Unconfirmed PRs (PRu) with treatment discontinued (will never confirm) are not considered responders but remain in the denominator (n=5); ORR (by RECISTv1.1) includes confirmed CRs/PRs and unconfirmed CRs/PRs who are still on treatment and may yet confirm; 2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose; ORR, objective response rate; DCR, disease control rate; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; RAS Other, non-G12X RAS mutations.
(2) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.
(3) Benchmark mean ORR derived from published reports (see slide 7); NA, not available.

5/11/24 data cutoff

Interim Observed OS in 2L Metastatic PDAC on RMC-6236 (160-300 mg)



	Median OS Months (95% CI)	Benchmark Median OS[1] Months
KRAS G12X	NE (8.5, NE)	6.1-6.9
RAS Mutant[2]	NE (8.5, NE)	

2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose
(1) mOS benchmark from published reports (see slide 7)
(2) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.
OS, overall survival; NE, not estimable

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5/11/24 data cutoff

RASolute 302 Phase 3 Trial

Global, randomized, controlled Phase 3 trial comparing RMC-6236 to chemotherapy in 2L treatment of patients with metastatic PDAC

Trial Design for RASolute 302: 2L Metastatic PDAC

Key Eligibility Criteria

- Confirmed PDAC
- 1 prior line of therapy in the metastatic setting
- ECOG PS 0-1

N = 460

R
1:1

- RMC-6236 300 mg p.o. QD (N = 230)
- Investigator's Choice SOC Chemotherapy[1] (N = 230)

Primary Endpoints
(RAS G12X)

- PFS, OS

Secondary Endpoints
(All Patients)

- PFS, OS
- ORR, DOR
- QoL

SOC, standard of care; WT, wild type; p.o., oral administration; QD, once daily, DOR, duration of response; QoL, quality of life.
Trial design and dose selection based on FDA meeting. Finalization of design details pending final protocol submission.
(1) SOC chemotherapy options: Gemcitabine + nab-paclitaxel, modified FOLFIRINOX, NAL-IRI+5-FU+LV, or FOLFOX

Nested Trial Design with Hierarchical Testing Aims to Maximize Probability of Success and Potentially Enable Broad Label

Primary Analysis: ***Core study population***

RAS G12X patients

Secondary Analysis: ***Expanded study population***

RAS G12X, G13X and Q61X patients

+

RAS WT patients who do not have other non-RAS, 'actionable' mutations[1]

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WT, wild type

(1) RAS(ON) multi-selective inhibitors exhibit anti-tumor activity In preclinical models of PDAC with RAS WT (Wasko et. al, Nature 2024: 629: 927-936)

Estimated Timeline for RASolute 302 Phase 3 Trial

2024		2025		2026		2027	
1H	2H	1H	2H	1H	2H	1H	2H

Anticipated study initiation

Anticipated Primary Endpoint PFS read-out

Anticipated Primary Endpoint OS read-out

Implications

Key Takeaways

RMC-6236 is the first targeted investigational drug designed to directly inhibit all major forms of oncogenic RAS, the major drivers of PDAC

RMC-6236 has shown compelling anti-tumor activity and a favorable safety profile in a broad population of patients with previously treated PDAC, and has potential to become an important new treatment option

Extensive efforts are ongoing toward launching *RASolute 302*, a global, randomized Phase 3 clinical trial comparing **RMC-6236** to chemotherapy as 2L treatment of patients with metastatic PDAC

Financial Information

Financial Position	
Cash, cash equivalents and marketable securities as of March 31, 2024	$1.7 billion

2024 GAAP Net Loss Guidance
2024 GAAP Net Loss of $560 million to $600 million[(1)]

(1) Includes non-cash stock-based compensation expense of approximately $70 million to $80 million.

- **Updated GAAP Net Loss Guidance**
  - Progress and increased confidence in RMC-6236 drive additional investments, including:
    - Acceleration of PDAC Phase 3 trial (RASolute 302)
    - Scaling for commercial supply
    - Investigation in earlier lines of PDAC treatment
- **Reiterating Cash Runway Guidance**
  - With current cash, cash equivalents and marketable securities, the company projects it can fund planned operations into 2027, based on its current operating plan.

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On Target to Outsmart Cancer™