Revolution Medicines

Pancreatic Cancer Update

- RMC-6236: RAS(ON) Multi-Selective Inhibitor
- RMC-9805: RAS(ON) G12D-Selective Inhibitor

October 25, 2024

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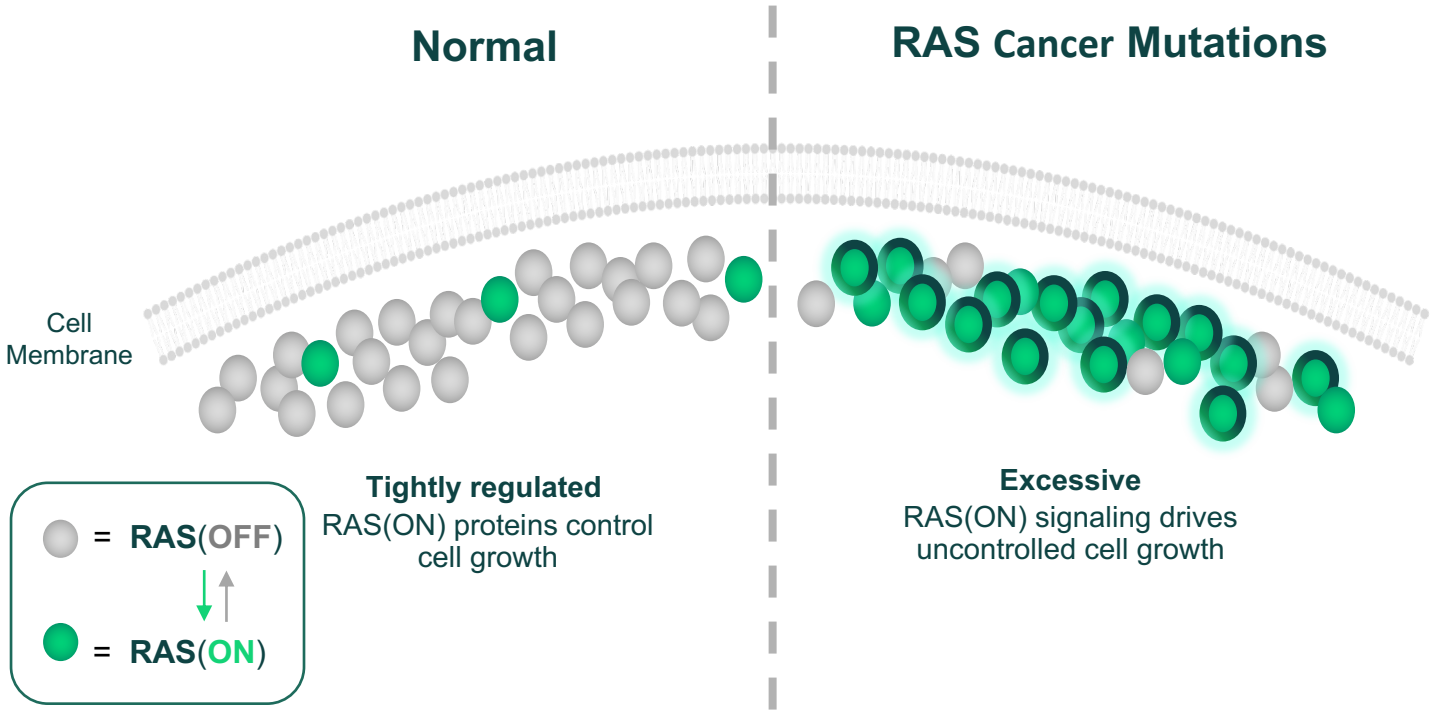
Revolution Medicines

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

- Portfolio of multiple clinical-stage RAS(ON) inhibitors with proof-of-concept in patients with difficult to treat tumors
- RMC-6236 is a RAS(ON) multi-selective inhibitor with compelling safety and antitumor activity across multiple RAS solid tumors
  - Updated clinical data demonstrate promising progression-free survival (PFS) and overall survival (OS) in patients with previously treated pancreatic ductal adenocarcinoma (PDAC)
  - RASolute 302, a global, randomized Phase 3 trial in second line metastatic PDAC patients is ongoing
- RMC-9805 is a RAS(ON) G12D-selective inhibitor with encouraging initial clinical proof-of-concept in patients with previously treated PDAC

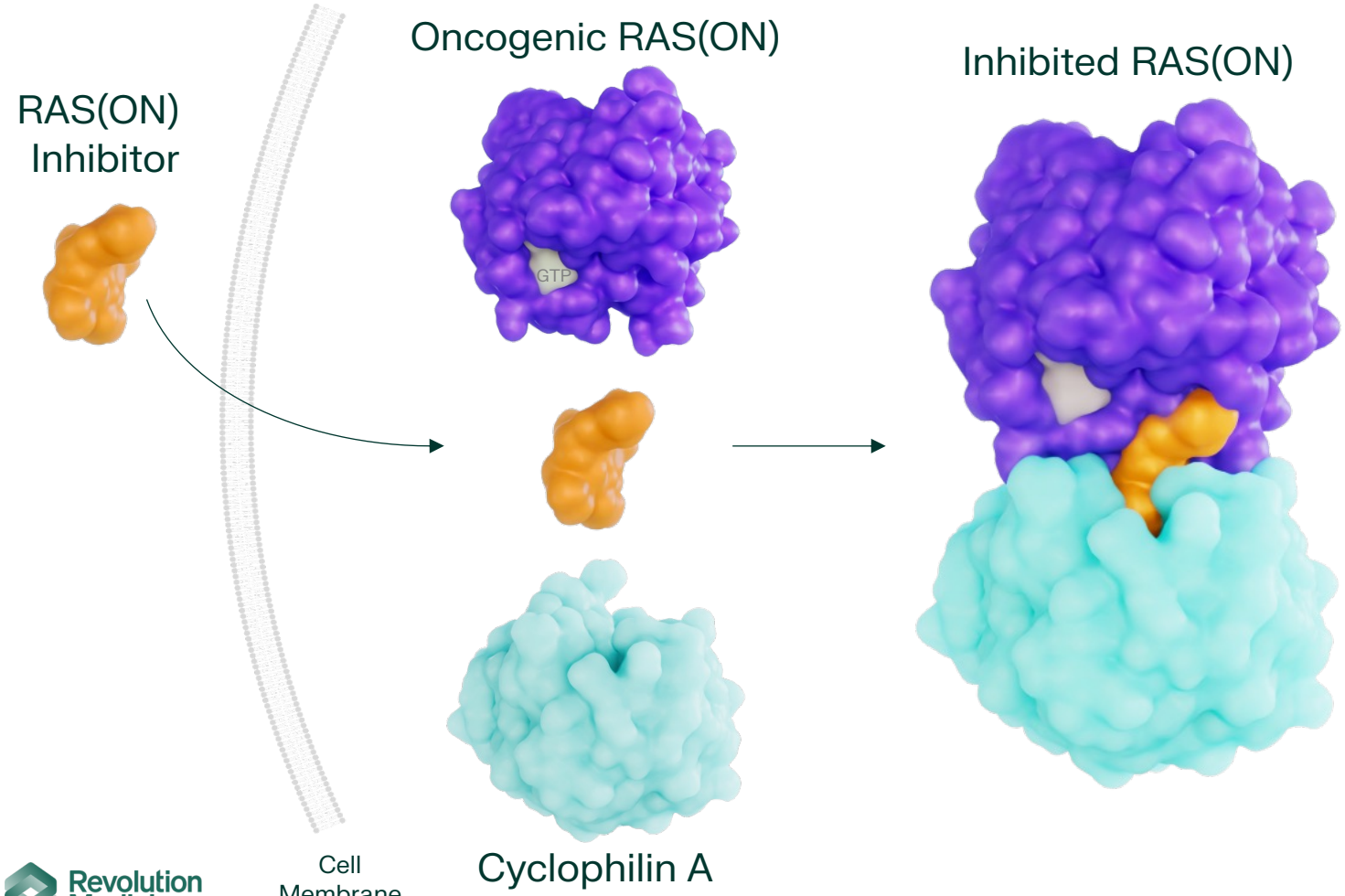
Uncontrolled RAS(ON) Signaling Drives RAS-Addicted Cancers, Including Pancreatic Cancer



- **Pancreatic cancer is third leading cause of cancer mortality in US[1]**
  - **~60,000 people expected to be diagnosed in 2024[1]**
  - **~50,000 people expected to die in 2024[1]**
- **>90% of PDAC tumors harbor an oncogenic RAS mutation[2]**
  - **RAS G12D is the single most common (~40%)**

[1] Incidence from ACS Cancer Facts and Figures 2024, adjusted for PDAC only; includes all stages of disease.
[2] Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.
PDAC, pancreatic ductal adenocarcinoma.

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**

Significant Need for Treatment(s) with Improved Efficacy and Tolerability for Patients with Previously Treated Metastatic PDAC

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]

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

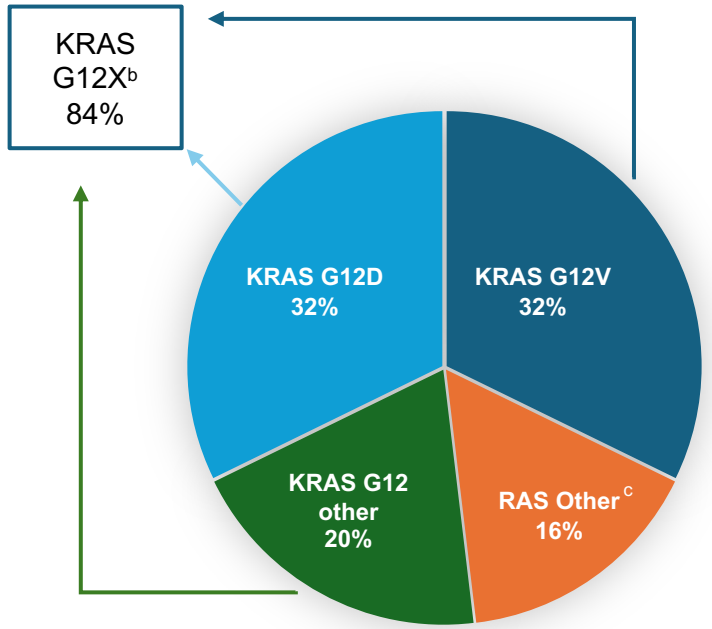
RMC-6236:

Oral RAS(ON) Multi-Selective Inhibitor

Phase 1 Study Demographics and Baseline Characteristics in PDAC Patients Representative of Phase 3 Study Population

PDAC Patients, RMC-6236 160–300 mg QD (N = 127)	
Age, years, median (range)	64 (30–86)
Male, n (%)	71 (56)
ECOG PS 1, n (%)	81 (64)
Number of prior anticancer therapies, median (range)	2 (1-11)
Number of prior anticancer therapies in metastatic setting, n (%)[a]	
0	2 (1)
1	57 (45)
2+	68 (54)
Liver metastases at baseline, n (%)	85 (67)
Metastatic at diagnosis [Stage IV], n (%)	66 (52)

RAS Genotypes Among Patients with PDAC 160–300 mg



Data cutoff: July 23, 2024.

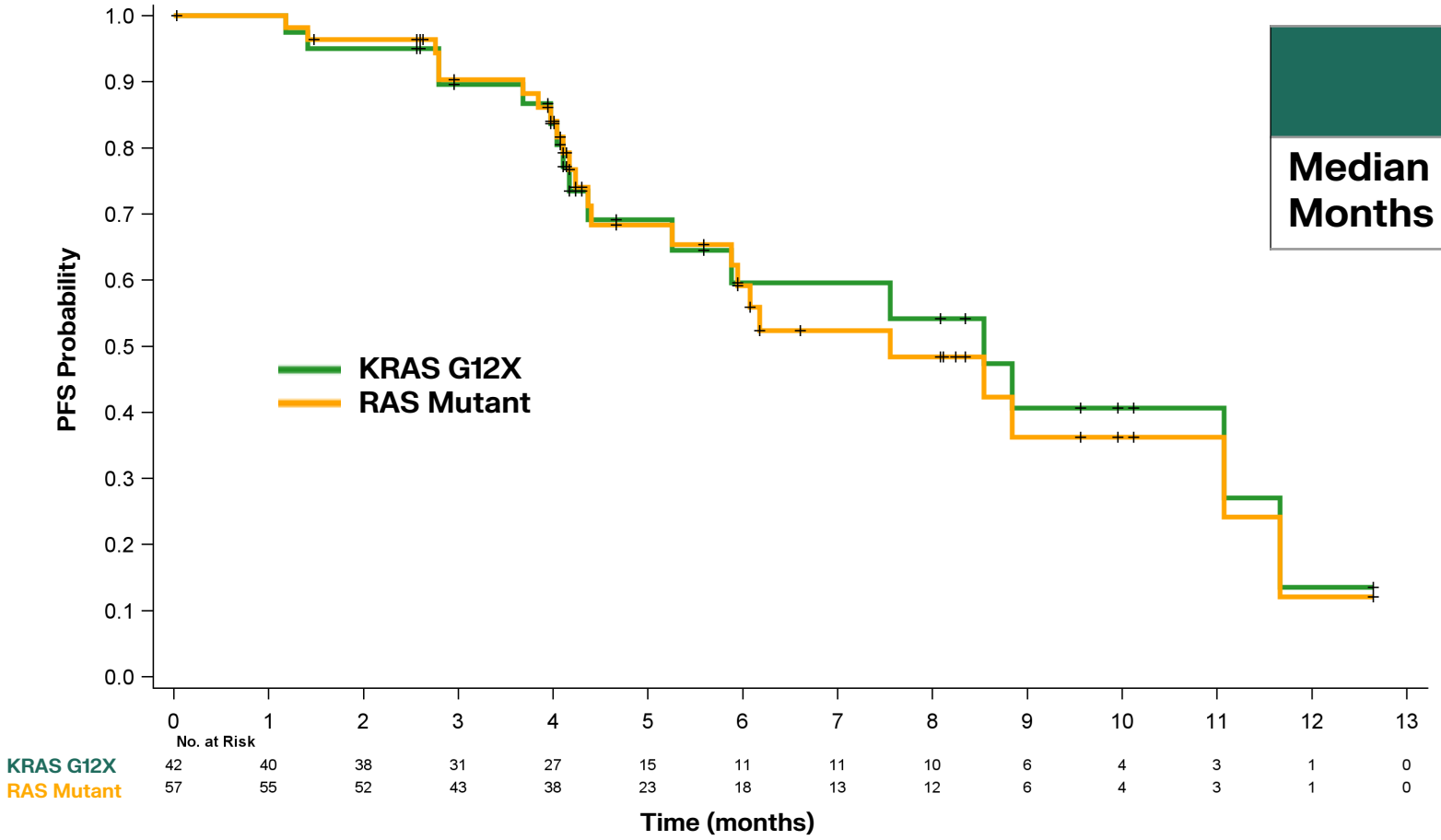
[a]Patients with locally advanced or metastatic PDAC; 1 prior line of therapy in the metastatic setting included patients who progressed on prior therapy in an earlier setting within 6 months of last dose.

[b]KRAS G12X mutations are defined by nonsynonymous mutations in KRAS codon 12 (G12).

[c]RAS Other includes mutations in KRAS G13X, KRAS Q61X, or mutations in HRAS or NRAS at codons G12X, G13X, or Q61X.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PDAC, pancreatic ductal adenocarcinoma; QD, daily.

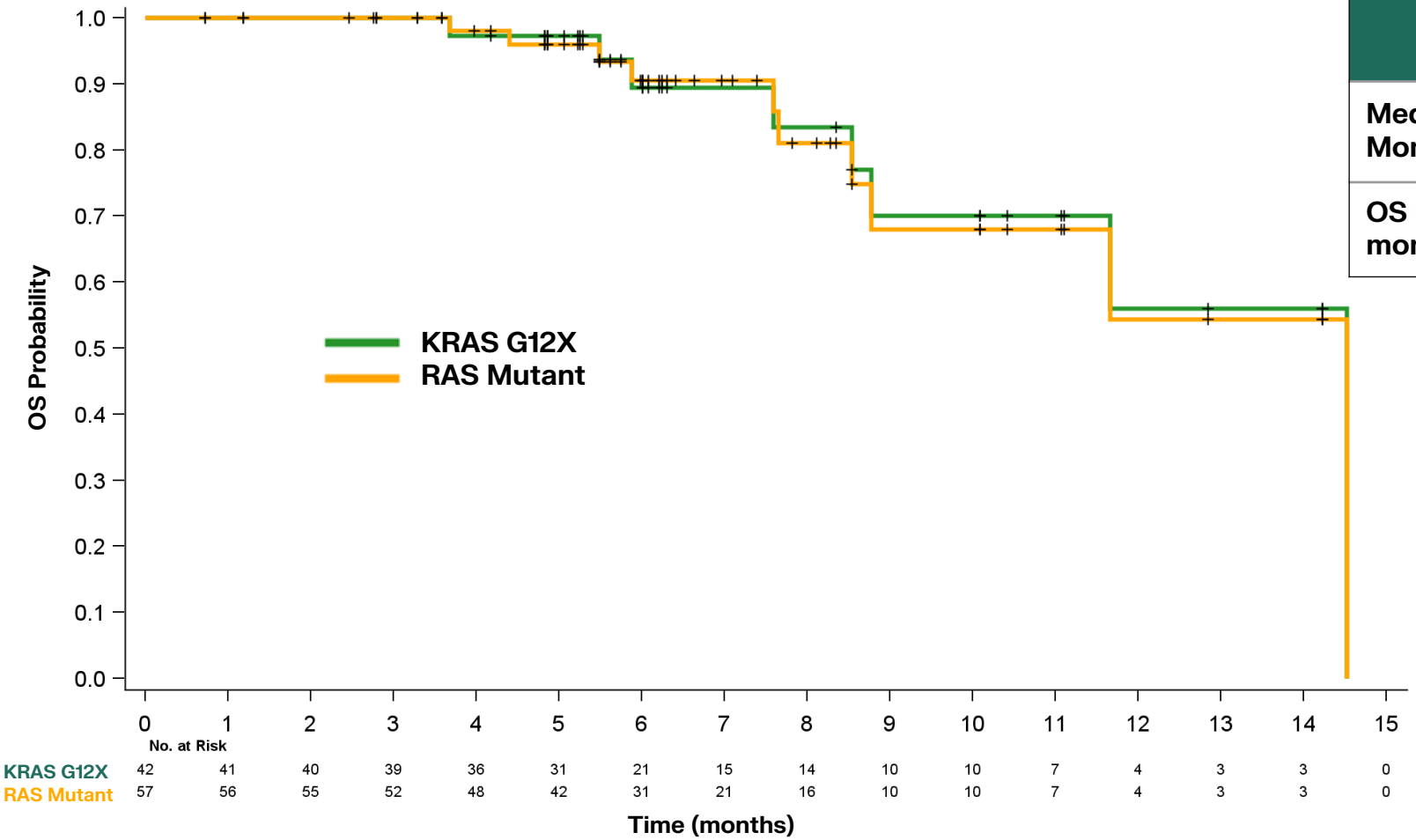
Compelling PFS in PDAC Patients Treated with RMC-6236 160-300 mg as 2L Therapy



	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)

Data cutoff: July 23, 2024.
2L in the metastatic setting includes patients who progressed within 6 months of the last dose of a prior therapy in an earlier setting.
Median follow-up is 6 months for KRAS G12 and 6.2 months for RAS mutant.
[a]KRAS G12X mutation includes any KRAS mutation where glycine (G) at position 12 is substituted by any other amino acid.
[b]RAS mutant includes any G12, G13, or Q61 substitution mutation in metastatic PDAC.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival.

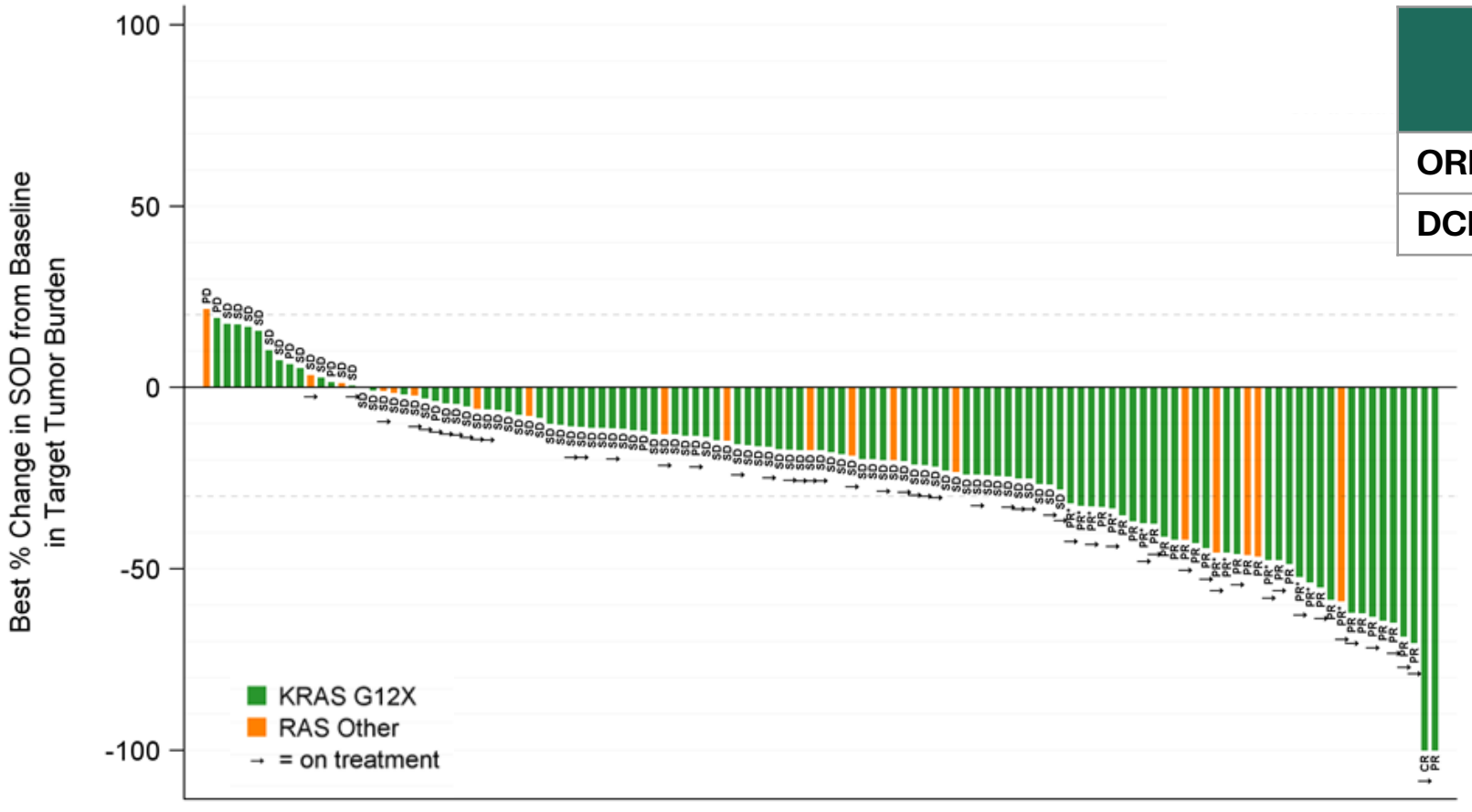
Compelling OS in PDAC Patients Treated with RMC-6236 160-300 mg as 2L Therapy



	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)

Data cutoff: July 23, 2024.
Median follow-up is 6 months for KRAS G12X and 6.2 months for RAS mutant.
[a]KRAS G12X mutation includes any KRAS mutation where glycine (G) at position 12 is substituted by any other amino acid.
[b]RAS mutant includes any G12, G13, or Q61 substitution mutation in metastatic PDAC.
[c]OS rate at 6 months and 95% CI are from Kaplan-Meier analysis.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; NE, not evaluable; OS, overall survival.

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.

[a]KRAS G12X mutation includes any KRAS mutation where glycine (G) at position 12 is substituted by another amino acid. RAS Other includes mutations in KRAS G13X, KRAS Q61X, or mutations in HRAS or NRAS at codons G12X, G13X, or Q61X.

[b]ORR and DCR analyses included all patients who received first dose of RMC-6236 at least 14 weeks prior to data cutoff date (to allow 2 potential scans). Unconfirmed PRs (PR*) with treatment discontinued (will never confirm) were not considered responders but remained in the denominator; ORR (by RECIST v1.1) included confirmed CRs/PRs and unconfirmed CRs/PRs who were still on treatment and may yet be confirmed; 2L in the metastatic setting included patients who progressed on prior therapy in an earlier setting within 6 months of last dose.

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; SD, stable disease; SOD, sum of diameters.

RMC-6236 Generally Well Tolerated in Patients with PDAC

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)

- Majority of TRAEs were Grade 1 - 2
- One Grade 4 TRAE observed (platelet count decreased); no Grade 5 TRAEs

Data cutoff: July 23, 2024.

[a]Includes preferred terms of dermatitis, 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.

[b]No prophylaxis for nausea or vomiting was administered.

Median duration of treatment is 5.3 months in 160-300mg population.

AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; TRAE, treatment-related adverse event.

RMC-6236 Achieves High Dose Intensity at Therapeutic Doses in Patients with PDAC

	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%

Data cutoff: July 23, 2024.
[a]Includes preferred terms of dermatitis acneiform, rash, rash maculopapular.
Median duration of treatment is 5.3 months in 160-300 mg population.
PDAC, pancreatic ductal adenocarcinoma. QD, daily. TRAE, treatment-related adverse event.

Design of Ongoing RASolute 302 Study: 2L Metastatic PDAC

Key Eligibility Criteria

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

NCT06625320

N = 460

R
1:1

- RMC-6236 300 mg PO 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

(1) SOC chemotherapy options: Gemcitabine + nab-paclitaxel, modified FOLFIRINOX, NAL-IRI+5-FU+LV, or FOLFOX.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R, randomized; PO, oral administration; QD, once daily; SOC, standard of care; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of response;. QoL, quality of life.

Highlights of RMC-6236 Program

- RMC-6236 is the first targeted investigational drug designed to directly inhibit all major forms of oncogenic RAS(ON), the common drivers of PDAC
- RMC-6236 exhibited a manageable safety profile, favorable dose intensity and compelling survival measures (median PFS and median OS) in a broad population of previously treated patients with RAS mutant metastatic PDAC
- These data support our ongoing global, randomized Phase 3 clinical study (RASolute 302) of RMC-6236 as 2L treatment versus SOC chemotherapy in patients with previously treated metastatic PDAC

2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; OS, overall survival; SOC, standard of care.

Need and Opportunity for Improved Outcomes in 1L Metastatic PDAC

Treatment	Trial	Median Survival
FOLFIRINOX	Conroy et al. (*Prodige-4 Intergroup trial*)	11.1 months
Gemcitabine plus nab-paclitaxel	Von Hoff et al. (*MPACT trial*)	8.5 months
NALIRIFOX	Wainberg et al. (NAPOLI-3)	11.1 months

- Currently designing Phase 3 study of RMC-6236 in 1L treatment of patients with metastatic PDAC

Gemcitabine: 1000 mg/m^2 weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks (days 1, 8, and 15).
FOLFIRINOX: oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m2 given as a bolus followed by 2400 mg/m2 given as a 46-hour continuous infusion, every 2-weeks.
(m)FOLFIRINOX: irinotecan 150 mg/m^2 day-1, oxaliplatin 85 mg/m^2 day-1, leucovorin 400 mg/m^2 day-1, 5-fluorouracil (5-FU) 2,400 mg/m^2 over 46 hours every 2 weeks.
Gemcitabine plus nab-paclitaxel: nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks.
NALIRIFOX: liposomal irinotecan 50 mg/m2, oxaliplatin 60 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2400 mg/m^2 administered sequentially as a continuous IV infusion over 46-hour, every 2-weeks (days 1 and 15).

RMC-9805:

Oral, Covalent RAS(ON) G12D-Selective Inhibitor

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

Key Eligibility Criteria

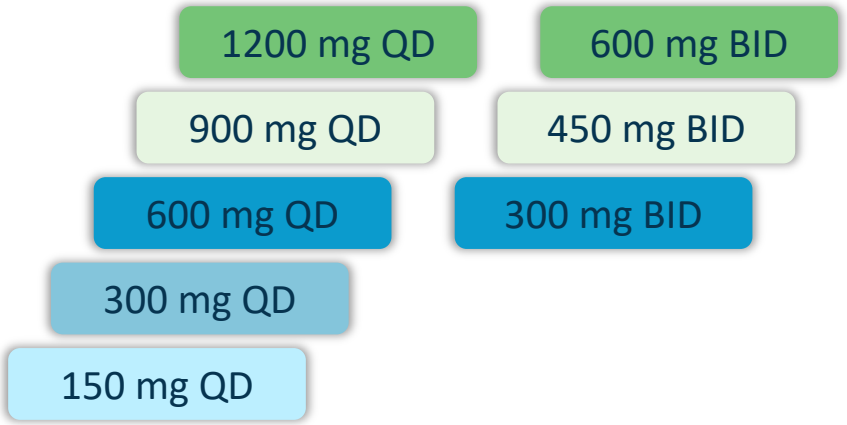
- Advanced solid tumors with KRAS G12D mutations
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Part 1: Dose Escalation

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

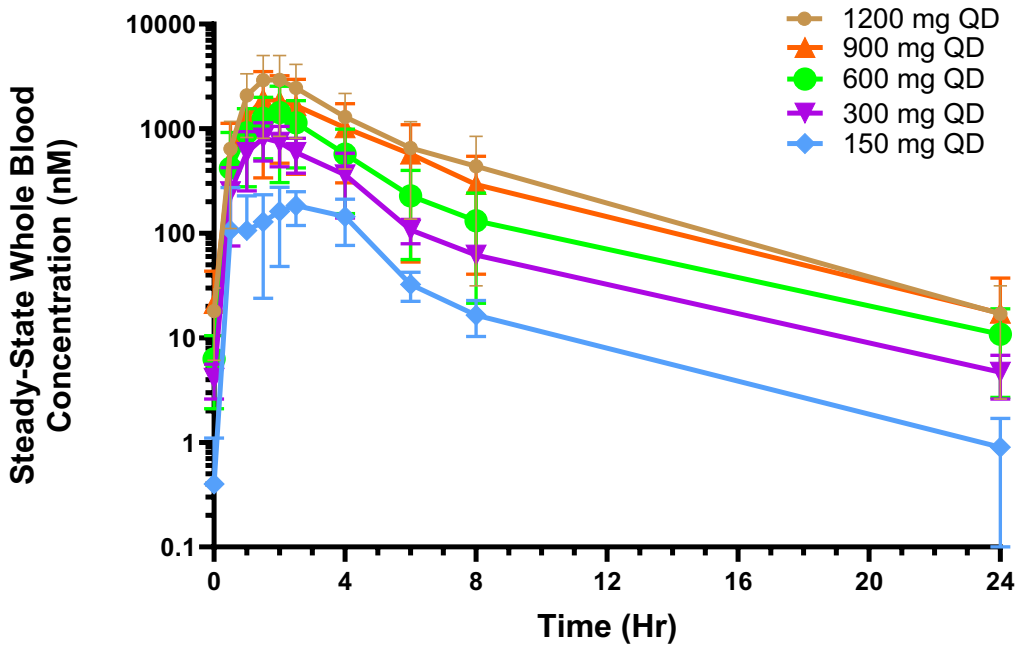


Part 2: Expansion and Dose Optimization in PDAC

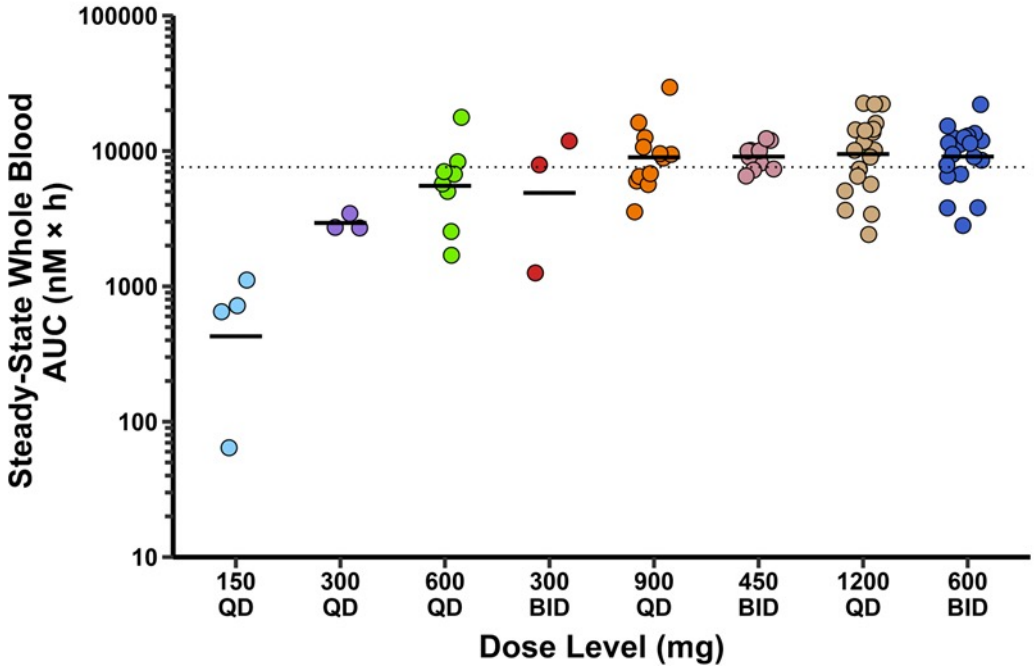
ECOG PS, Eastern Cooperative Oncology Group Performance Status; PDAC, pancreatic ductal adenocarcinoma; QD, once daily; BID, twice daily.

Dose-Dependent Exposure Increases for RMC-9805 Reach Levels Predicted to Induce Tumor Regressions

Mean Steady-State Blood PK Profiles



Individual Steady-State Blood AUC



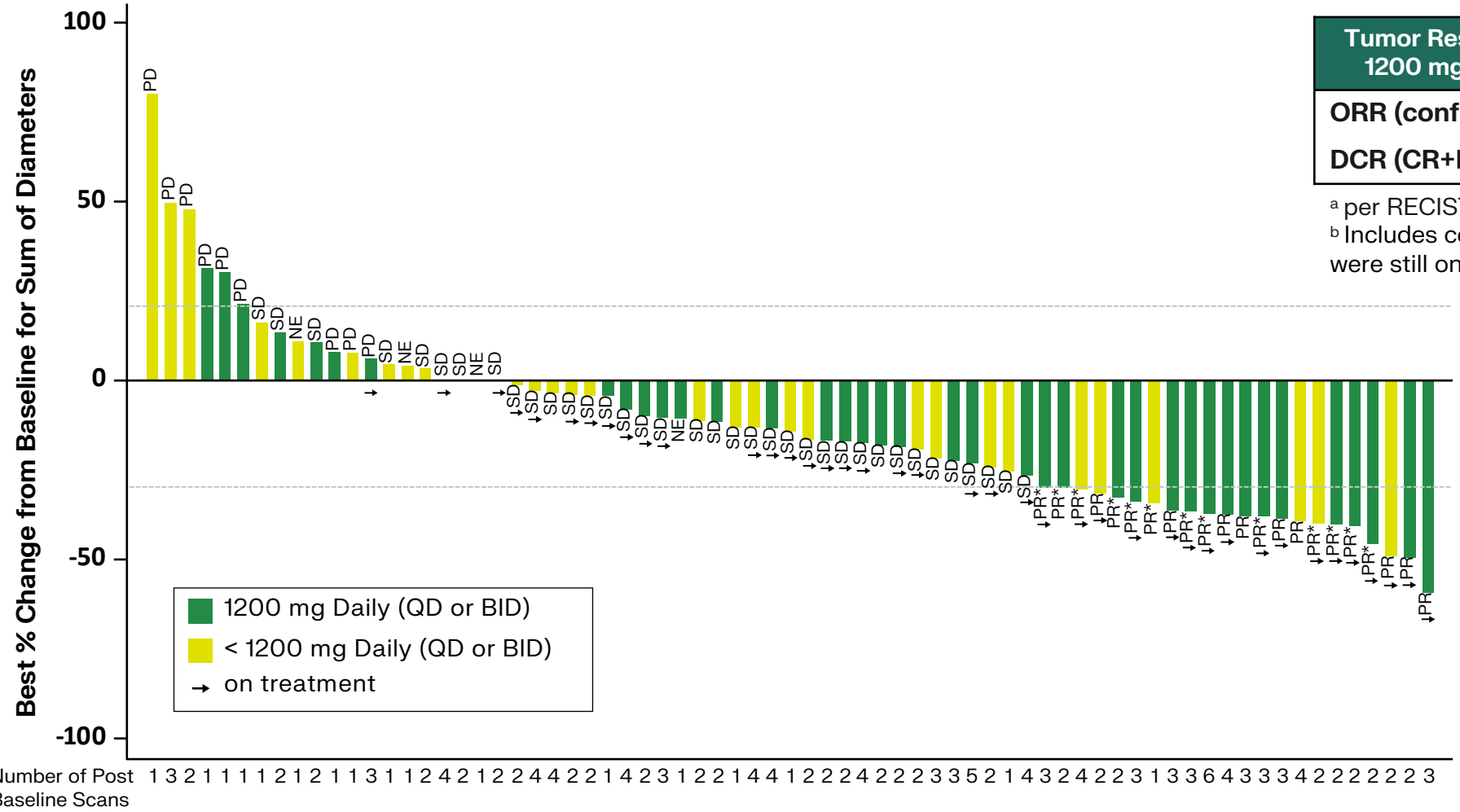
Exposure in mice at 100 mg/kg

- Dose that induces tumor regressions in majority of preclinical PDAC models

- PK supports 1200 mg QD as a candidate RP2DS in PDAC

PK data as of July 16, 2024.
Left: steady-state concentrations from Cycle 1 Day 15; Error bars represent standard deviation; Right: steady-state AUC in Cycle 1 Day 15; Each circle represents an individual patient AUC.
AUC, area under the curve; QD, once daily; BID, twice daily; PDAC, pancreatic ductal adenocarcinoma; PK, Pharmacokinetics; RP2DS, recommended Phase 2 dose and schedule.

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

Data cutoff: September 2, 2024. All treated patients with PDAC who received a first daily dose at least 14 weeks prior to data cutoff date (applies to Waterfall plot and ORR table);
3 additional patients (N=2 at 1200 mg daily; N=1 at < 1200 mg daily) are not displayed on the Waterfall plot due to withdrawal of consent or clinical progression; among patients with a response (confirmed or unconfirmed), 55% of first responses occurred after 2 months of RMC-9805 treatment (all dose levels); CR, complete response; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; PR*, unconfirmed partial response; SD, stable disease; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors.

RMC-9805 Generally Well Tolerated at 1200 mg Daily

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

Data cutoff: September 2, 2024.
Mmedian time on treatment was 2.8 months (range: 0.2–6.7).
[a]Includes preferred terms of dermatitis, dermatitis acneiform, dermatitis psoriasiform, eczema, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; SAE, serious adverse event; TRAE, treatment-related adverse event; QD, once daily; BID, twice daily.

Highlights of RMC-9805 Program

- RMC-9805 has demonstrated promising initial clinical profile in patients with KRAS G12D PDAC
  - Orally administered and well tolerated
  - Encouraging antitumor activity as demonstrated by tumor regressions
  - Durability assessment pending longer follow-up
- Dose optimization in KRAS G12D PDAC and other solid tumors is ongoing – 1200 mg QD identified as a candidate RP2DS in PDAC
- Observations to date support ongoing development as a single agent and in combination with other therapies, including the RAS(ON) multi-selective inhibitor RMC-6236

PDAC, pancreatic ductal adenocarcinoma; QD, once daily; RP2DS, recommended Phase 2 dose and schedule.

Takeaways

Concurrent Development of RMC-6236 and RMC-9805 with Goal of Providing New Treatment Options for Patients with Pancreatic Cancer

- Metastatic PDAC is a devastating disease demanding treatment options with improved efficacy and toxicity
- PDAC is largely a RAS disease, with nearly all tumors driven by RAS mutations
  - Vast majority are KRAS G12X (~85%), including KRAS G12D (~40%)
- **RMC-6236**: Preliminary evaluation in patients with PDAC, including KRAS G12D PDAC, shows acceptable tolerability and a compelling efficacy profile, driving the ongoing randomized Phase 3 trial in 2L PDAC
- **RMC-9805**: Preliminary evaluation in patients with KRAS G12D PDAC shows acceptable tolerability and encouraging initial antitumor activity, with durability assessment pending longer follow-up
- **While likely to serve partially overlapping patient populations with RAS G12D tumors, these investigational drugs have distinct and complementary profiles that could ultimately enable multiple treatment options for patients across a range of tumor types, stages of disease and lines of therapy**
- Investigation of multiple rational treatment strategies for KRAS G12D PDAC is ongoing, including:
  - Monotherapies
  - RAS(ON) inhibitor doublets
  - Combinations with non-RAS-directed therapies

PDAC, pancreatic ductal adenocarcinoma; 2L, second line.

Revolution Medicines

On Target to Outsmart Cancer™

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