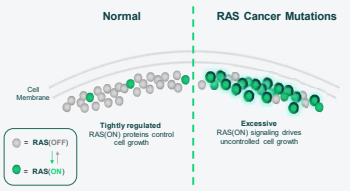
Updated Safety and Efficacy from a Phase 1 Study of RMC-6236, a RAS(ON) Multi-Selective, Tri-Complex Inhibitor, in Patients with RAS Mutant Pancreatic Ductal Adenocarcinoma (PDAC)

Brian Wolpin[1], David S. Hong[2], Alex Spira[3], Alexander Starodub[4], Wungki Park[5], David Sommerhalder[6], Jennifer Valerin[7], Minal Barve[8], Salman Punekar[9], Meredith Pelster[10], Benjamin Herzberg[11], Nilofer Azad[12], Kyaw Aung[13], J. Randolph Hecht[14], Li Cheng[15], Rashmi Vora[15], Zeena Salman[15], Ying Zhang[15], Tong Lin[15], Ignacio Garrido-Laguna[16]

[1]Dana-Farber Cancer Institute, Gastrointestinal Cancer Center, Boston, USA; [2]The University of Texas MD Anderson Cancer Center, Dept of Investigational Cancer Therapeutics, Houston, USA; [3]NEXT Oncology Virginia, Virginia Cancer Specialists Research Institute, Fairfax, USA; [4]The Christ Hospital Health Network, Parkview Physician Group - Parkview Cancer Institute, Cincinnati, USA; [5]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, USA; [6]NEXT Oncology, Feist-Weiller Cancer Center, Shreveport, USA; [7]University of California Irvine, Division of Hematology/Oncology - Medicine, Orange, USA; [8]Mary Crowley Cancer Research, Texas Oncology, Dallas, USA; [9]NYU Langone Health, Perlmutter Cancer Center, New York, USA; [10]Sarah Cannon Research Institute, Texas Oncology, Nashville, USA; [11]Columbia University Irving Medical Center, Medical Oncology, New York, USA; [12]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Medical Oncology, Baltimore, USA; [13]University of Texas Health, Medical Oncologist - Gastrointestinal Cancer - Livestrong Cancer Institutes, Austin, USA; [14]UCLA Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, USA; [15]Revolution Medicines, Redwood City, USA; [16]University of Utah, Huntsman Cancer Institute, Salt Lake City, USA.

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Introduction

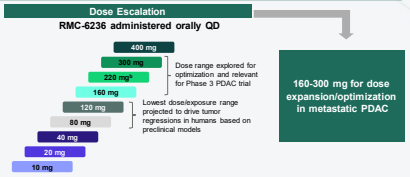


- RMC-6236 is a RAS(ON) multi-selective, tri-complex RAS inhibitor designed to directly inhibit uncontrolled RAS(ON) signaling in PDAC
- Unmet need in PDAC is significant given high mortality rate
- Outcomes for patients with 2L PDAC treated with standard of care chemotherapy are:
  - Median PFS ~2–3.5 months[1-9]
  - Median OS ~6.1–6.9 months[1-9]
- >90% of PDAC tumors harbor an oncogenic RAS mutation

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

Materials and Methods

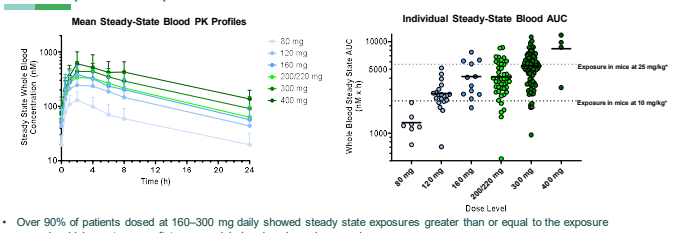
- RMC-6236 is being investigated in an ongoing Phase 1 monotherapy study in patients with advanced RAS mutant tumors (NCT05379985)
- Eligible patients were ≥18 years old with ECOG PS 0–1 and advanced solid tumors with KRAS G12X mutations[a] (initially excluding KRAS G12C), who had received prior standard therapy appropriate for tumor type and stage, and who had no active brain metastases
- Patients received escalating doses of single agent RMC-6236
- Additional patients with RAS mutant PDAC were enrolled for dose optimization and expansion
- Objectives included assessment of safety/tolerability, pharmacokinetics, and antitumor activity



Data cutoff 23 Jul 2024.
[a]KRAS G12X mutations are defined by nonsynonymous mutations in KRAS codon 12 (G12). RAS mutant includes patients with G12, G13, or Q61 mutant metastatic PDAC.
[b]220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization.
DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PDAC, pancreatic ductal adenocarcinoma; QD, once daily.

Key Results

Dose-Dependent Exposure Increases for RMC-6236



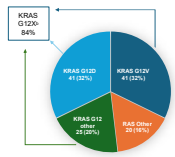
- Over 90% of patients dosed at 160–300 mg daily showed steady state exposures greater than or equal to the exposure range in which most xenograft tumor models in mice showed regressions

Data cutoff 26 Apr 2024.
*10 mg/kg QD induces tumor regressions in sensitive models, 25 mg/kg QD induces tumor regressions in the majority of models. Exposure corrected with cross-species protein binding and blood/plasma partitioning.
Left: steady-state concentrations from Cycle 1 Day 15; error bars represent standard deviation. Right: steady-state AUC from Cycle 1 Day 15, each circle represents an individual patient
Treated patients from 60–400 mg were included in the analyses.
AUC, horizontal bars represent mean AUC for each dose level.
AUC, area under the curve; PK, pharmacokinetic; QD, once daily.

RMC-6236 Demographics and Baseline Characteristics for Patients with PDAC

	160–300 mg (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 (N = 127)



Data cutoff 23 Jul 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.

RMC-6236 Treatment-Related Adverse Events (TRAEs) and TRAEs leading to Dose Modifications in Patients with PDAC

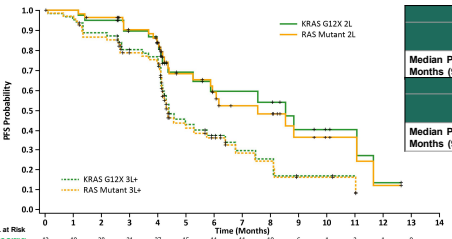
Maximum severity of TRAEs	160–300 mg (N=127) Any Grade	Grade ≥3
Any TRAE	124 (98)	37 (29)
TRAEs occurring in ≥10% of patients, n (%)		
Rash[a]	115 (91)	10 (8)
Diarrhea	61 (48)	3 (2)
Nausea[b]	54 (43)	0 (0)
Vomiting[b]	39 (31)	0 (0)
Stomatitis	39 (31)	4 (3)
Fatigue	25 (20)	1 (1)
Paronychia	17 (13)	0 (0)
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)

	160–300 mg (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[c]	14 (11)
Mean dose intensity	92%

- Majority of TRAEs were Grade 1–2
- Rash (bundled term) was the most common TRAE and was predominantly acneiform
- One Grade 4 TRAE observed (platelet count decreased)
- No Grade 5 TRAEs
- Rash was the most common TRAE leading to dose reduction
- No TRAEs resulted in treatment discontinuation
- Mean dose intensity was 92%

Data cutoff 23 Jul 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.
[c]Includes preferred terms of dermatitis acneiform, rash, rash maculopapular.
Median duration of treatment is 5.3 months in 160-300 mg population.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; TRAE, treatment-related adverse event

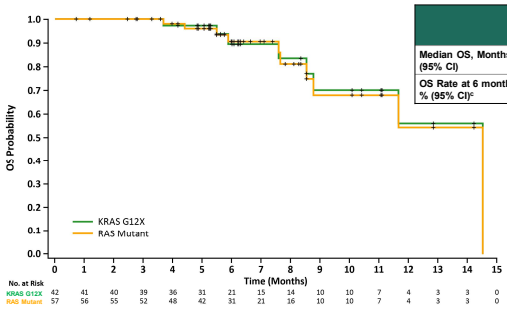
RMC-6236 Progression-Free Survival in Patients with 2L+ PDAC



	2L 160-300mg 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)
	3L+ 160-300mg KRAS G12X[a] (N=63)	RAS Mutant[b] (N=68)
Median PFS, Months (95% CI)	4.4 (4.2, 6.4)	4.4 (4.1, 5.7)

Data cutoff 23 Jul 2024.
2L+ the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose.
3L+ includes patients with more than 1 prior line of therapy (metastatic setting).
Median follow-up is 6 months for KRAS G12 and 6.2 months for RAS mutant in the 2L setting. Median follow-up is 5.7 months for both KRAS G12 and RAS mutant in the 3L+ setting.
[a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12) mutant metastatic PDAC.
[b]RAS mutant is defined as patients with G12, G13, or Q61 mutant metastatic PDAC.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival.

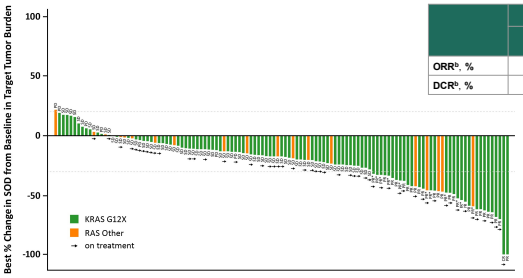
RMC-6236 Overall Survival in Patients with 2L PDAC



	KRAS G12X[a] 160-300mg (N=42)	RAS Mutant[b] 160-300mg (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 23 Jul 2024.
Median follow-up is 6 months for KRAS G12X and 6.2 months for RAS mutant.
[a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12).
[b]RAS mutant is defined as patients with G12, G13, or Q61 mutant 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.

RMC-6236 Best Response in Patients with 2L+ PDAC



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

Data cutoff 23 Jul 2024.
Among patients with a response (confirmed or unconfirmed), 50% of first response occurred after 2 months of RMC-6236 treatment.
[a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12), 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 1.1) 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; PR*, unconfirmed PR; SD, stable disease; SOD, sum of diameters.

Conclusion

- 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 encouraging survival measures (median PFS and median OS) in a broad population of previously treated patients with RAS mutant PDAC
- RASolute 302, a global, randomized, Phase 3 clinical trial of RMC-6236 as 2L treatment versus chemotherapy has been initiated in patients with previously treated metastatic PDAC (ClinicalTrials.gov Identifier: NCT06625320)

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- This study was sponsored by Revolution Medicines, Inc. (ClinicalTrials.gov identifier: NCT05379985).

Revolution Medicines

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Contact: Li Cheng at lcheng@revmed.com