Revolution Medicines

Clinical Updates on RAS(ON) Inhibitors: Monotherapy and Combinations

December 2, 2024

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This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are based on our current expectations, estimates and projections about our industry and our Company, management's beliefs and certain assumptions we have made. The words "plan," "anticipate," "believe," "continue," "estimate," "expect," "intend," "may," "will" and similar expressions are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, prospective products, availability of funding, ability to manage existing collaborations and establish new strategic collaborations, licensing or other arrangements, the scope, progress, results and costs of developing our product candidates or any other future product candidates, conducting clinical trials, the potential market size and size of the potential patient populations for our product candidates, the timing and likelihood of success of obtaining product approvals, plans and objectives of management for future operations, the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates, future results of anticipated products and the impact of global events and other macroeconomic conditions on our business are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. The information included in these materials is provided as of December 2, 2024, unless specified elsewhere herein, and is qualified as such. Except as required by applicable law, we undertake no obligation to update any forward-looking statements or other information contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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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.

This presentation includes certain information regarding publicly available results from clinical trials by third parties evaluating other product candidates. Such trials were not head-to-head trials with any of Revolution Medicines' product candidates and include differences in study protocols, patient populations and reporting standards, and caution should be exercised when comparing data across trials.

Three Pioneering RAS(ON) Inhibitors Show Compelling Clinical Promise

- **Advancing RMC-6236 into first Phase 3 registrational trials**
  - RASolute 302 in patients with 2L metastatic PDAC ongoing
  - RASolve 301 in patients with previously treated NSCLC expected to initiate in Q1 2025
- **Expanding the reach of RMC-6236**
  - Compelling PDAC 2L monotherapy data substantiate opportunity in 1L
  - Initial data indicate combinability with immune checkpoint inhibitor
- **Moving mutant-selective inhibitors RMC-6291 (G12C) and RMC-9805 (G12D) toward late-stage development**
  - Encouraging clinical profile of RMC-9805 monotherapy in PDAC
  - Initial validation of RAS(ON) inhibitor doublet, RMC-6291 with RMC-6236

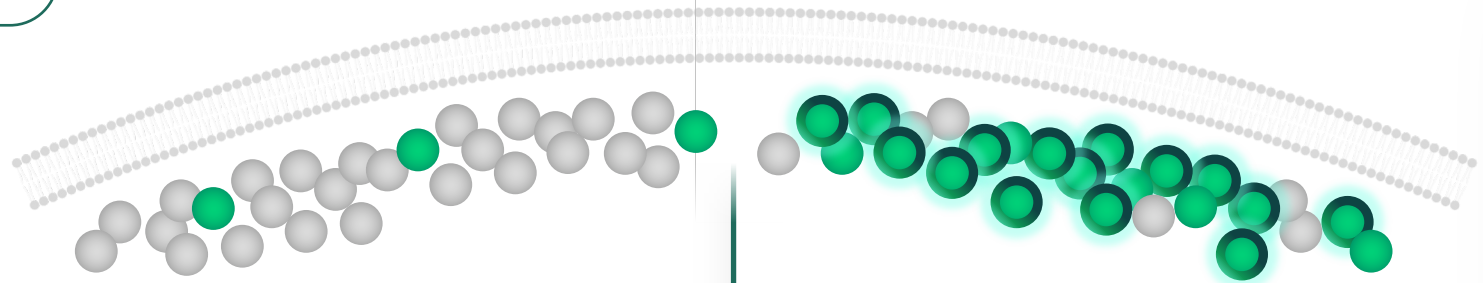
PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; 2L, second line; 1L, first line.

Portfolio of RAS(ON) Inhibitors Designed to Target Significant Number of Human Cancers

RAS(OFF)

RAS(ON)

Normal



Tightly regulated
RAS(ON) proteins control cell growth

RAS-Mutant Cancers

RAS Cancer Mutations

Excessive
RAS(ON) signaling drives uncontrolled cell growth

Oncogenic mutations in **KRAS**, **NRAS** or **HRAS** are common at positions G12, G13 and Q61

New patients per year (U.S.)[1]

>200,000
including

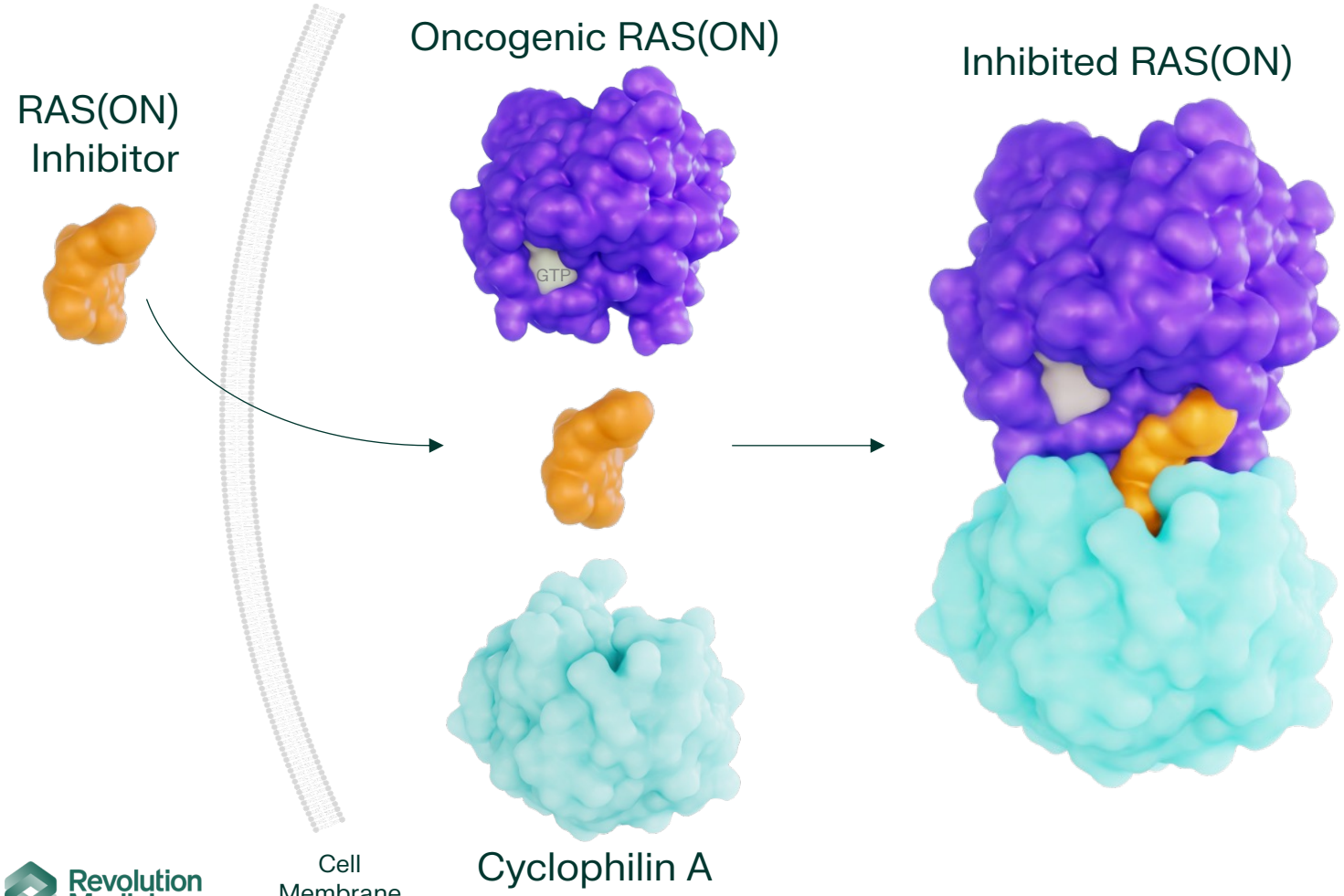
60,000
Lung cancer
(~30% of NSCLC)

75,000
Colorectal cancer
(~49% of CRC)

53,000
Pancreatic cancer
(~92% of PDAC)

(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023 (see appendix for additional detail).

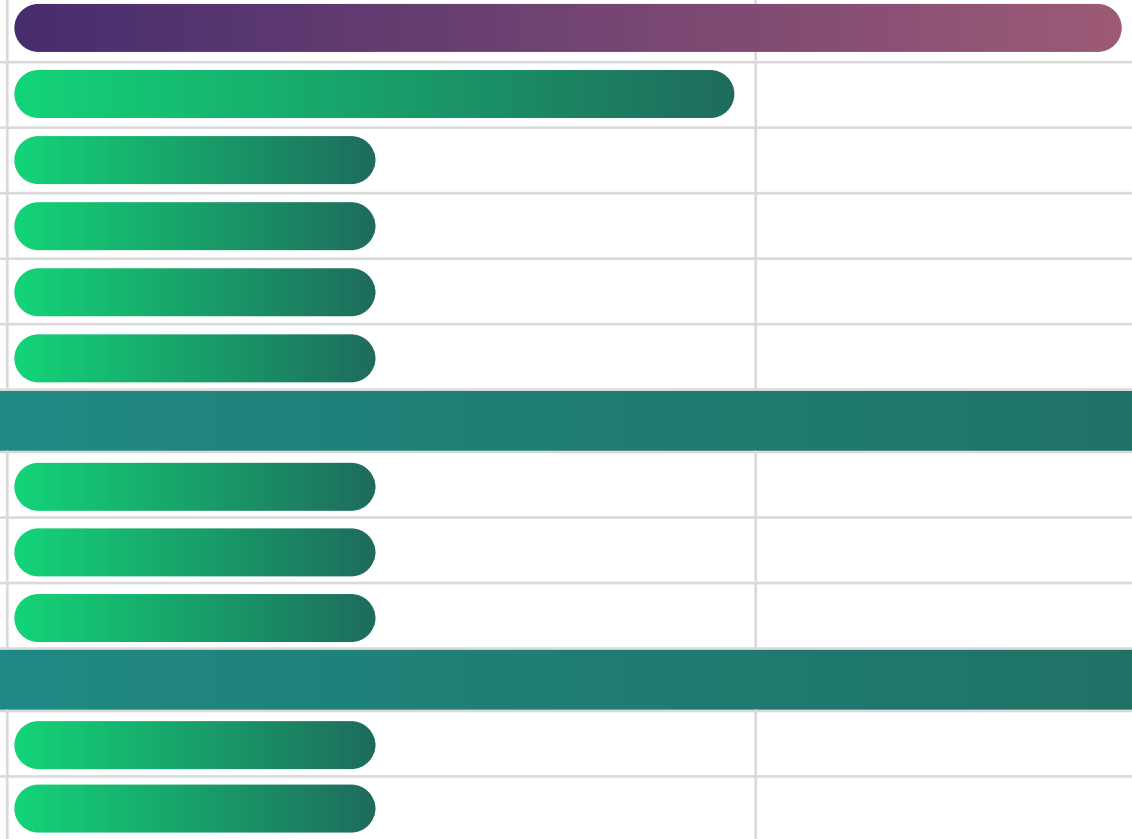
Pioneering Tri-Complex RAS(ON) Inhibitors Designed to Deliver Robust and Durable Antitumor Activity



- **Direct inhibition of RAS(ON) cancer drivers aiming to defy common drug resistance mechanisms**
- **Clinical validation of first three RAS(ON) inhibitors studied as single agents**
- **Initial clinical evidence indicates combinability of RAS(ON) inhibitors with immunotherapy and in RAS(ON) inhibitor doublet**

RAS(ON) Inhibitor Clinical Development Pipeline

APPROACH	FOCUS	EARLY CLINICAL DEVELOPMENT[1]	REGISTRATIONAL TRIAL
RMC-6236 (MULTI: G12X, G13X, Q61X)			
Monotherapy	PDAC RASolute		
	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.

Additional Clinical Development Opportunities (next steps subject to portfolio priority decisions):

- **RAS(ON) Mutant-Selective Inhibitors**: RMC-5127 (G12V), RMC-0708 (Q61H) and RMC-8839 (G13C)
- **RAS Companion Inhibitors**: RMC-4630 (SHP2) and RMC-5552 (mTORC1/4EBP1)

NSCLC, non-small cell lung cancer. PDAC, pancreatic ductal adenocarcinoma. CRC, colorectal cancer.

RMC-6236 Monotherapy
in Pancreatic Ductal Adenocarcinoma

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**

- 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.

PDAC, pancreatic ductal adenocarcinoma; 5-FU+LV+Nal-IRI, 5-fluorouracil, Leucovorin, Liposomal irinotecan; FOLFOX, Leucovorin, 5-fluorouracil, Oxaliplatin; FOLFIRI, Leucovorin, 5-fluorouracil, irinotecan; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NA, not available.

Patients with PDAC Treated with RMC-6236 at 300 mg Daily

	(N=76)
Age, years, median (range)	65 (31-83)
Male, n (%)	44 (58%)
ECOG PS 1, n (%)	50 (66%)
Number of prior anti-cancer therapies, median (range)	2 (1-7)
Number of prior anti-cancer therapies in metastatic setting, n (%)[1]	
0	0 (0%)
1	37 (49%)
2+	39 (51%)
Liver metastases at baseline, n (%)	51 (67%)
Metastatic at diagnosis [stage IV], n (%)	41 (54%)

(1) Patients with 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.
PDAC, pancreatic ductal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

RMC-6236 Generally Well Tolerated in Patients with PDAC at 300 mg Daily

Maximum Severity of TRAEs	(N=76)	
	Any Grade	Grade ≥ 3
Any TRAE	73 (96%)	26 (34%)
TRAEs occurring in ≥ 10% of patients, n (%)		
Rash [1]	69 (91%)	6 (8%)
Diarrhea	40 (53%)	3 (4%)
Nausea [2]	29 (38%)	0 (0%)
Vomiting [2]	27 (36%)	0 (0%)
Stomatitis	26 (34%)	3 (4%)
Mucosal inflammation	13 (17%)	1 (1%)
Fatigue	12 (16%)	1 (1%)
Decreased appetite	10 (13%)	0 (0%)
Paronychia	10 (13%)	0 (0%)
Oedema peripheral	10 (13%)	0 (0%)
Platelet count decreased	8 (11%)	3 (4%)
Dry skin	8 (11%)	0 (0%)
Other select TRAEs, n (%)		
Anemia	6 (8%)	5 (7%)
ALT increased	5 (7%)	3 (4%)
Neutrophil count decreased	5 (7%)	2 (3%)
AST increased	4 (5%)	1 (1%)

One Grade 4 TRAE observed (platelet count decreased); no Grade 5 TRAEs

(1) 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. (2) No prophylaxis for nausea or vomiting was administered.
Median duration of treatment is 5.2 months.
PDAC, pancreatic ductal adenocarcinoma; TRAE, treatment-related adverse event; ALT, alanine transaminase; AST, aspartate transferase.

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ENA 2024 data set
(Data cutoff: Jul 23, 2024)

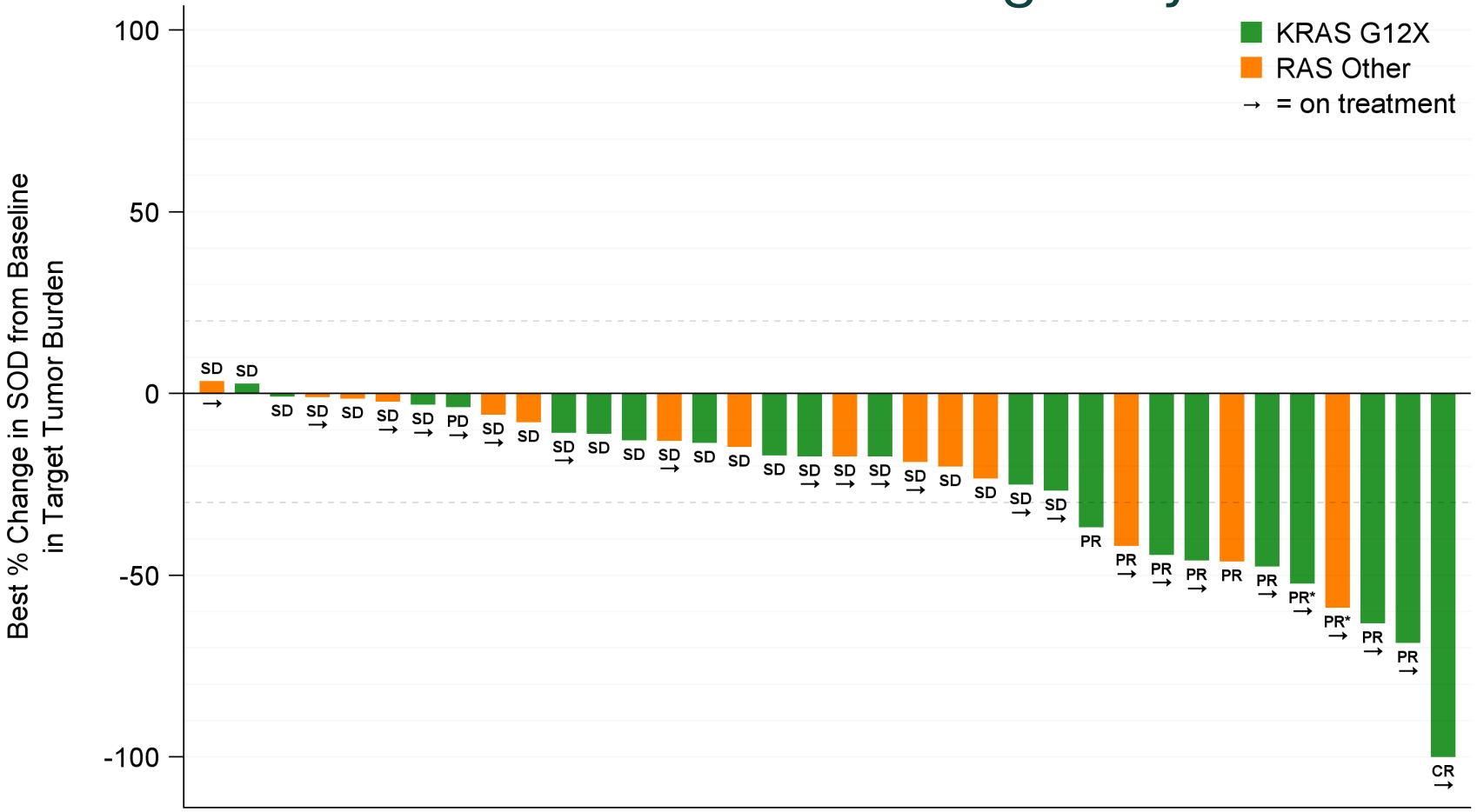
Favorable Dose Intensity Achieved in Patients with PDAC Receiving RMC-6236 at 300 mg

	(N=76)
TRAEs leading to dose modification, n (%)	32 (42%)
Dose interruption	30 (40%)
Dose reduction	19 (25%)
TRAEs leading to dose discontinuation, n (%)	0 (0%)
Specific TRAEs leading to dose reduction in >10% patients, n (%)	
Rash (1)	10 (13%)
Mean dose intensity	89%

(1) Includes preferred terms of dermatitis acneiform, rash and rash maculopapular.
PDAC, pancreatic ductal adenocarcinoma; TRAE, treatment-related adverse event.

ENA 2024 data set
(Data cutoff: Jul 23, 2024)

Encouraging Objective Response Rates in 2L Patients with PDAC Treated with RMC-6236 at 300 mg Daily



	ORR
KRAS G12X	**36%** (8/22)
RAS Mutant[(1)]	**27%** (10/37)

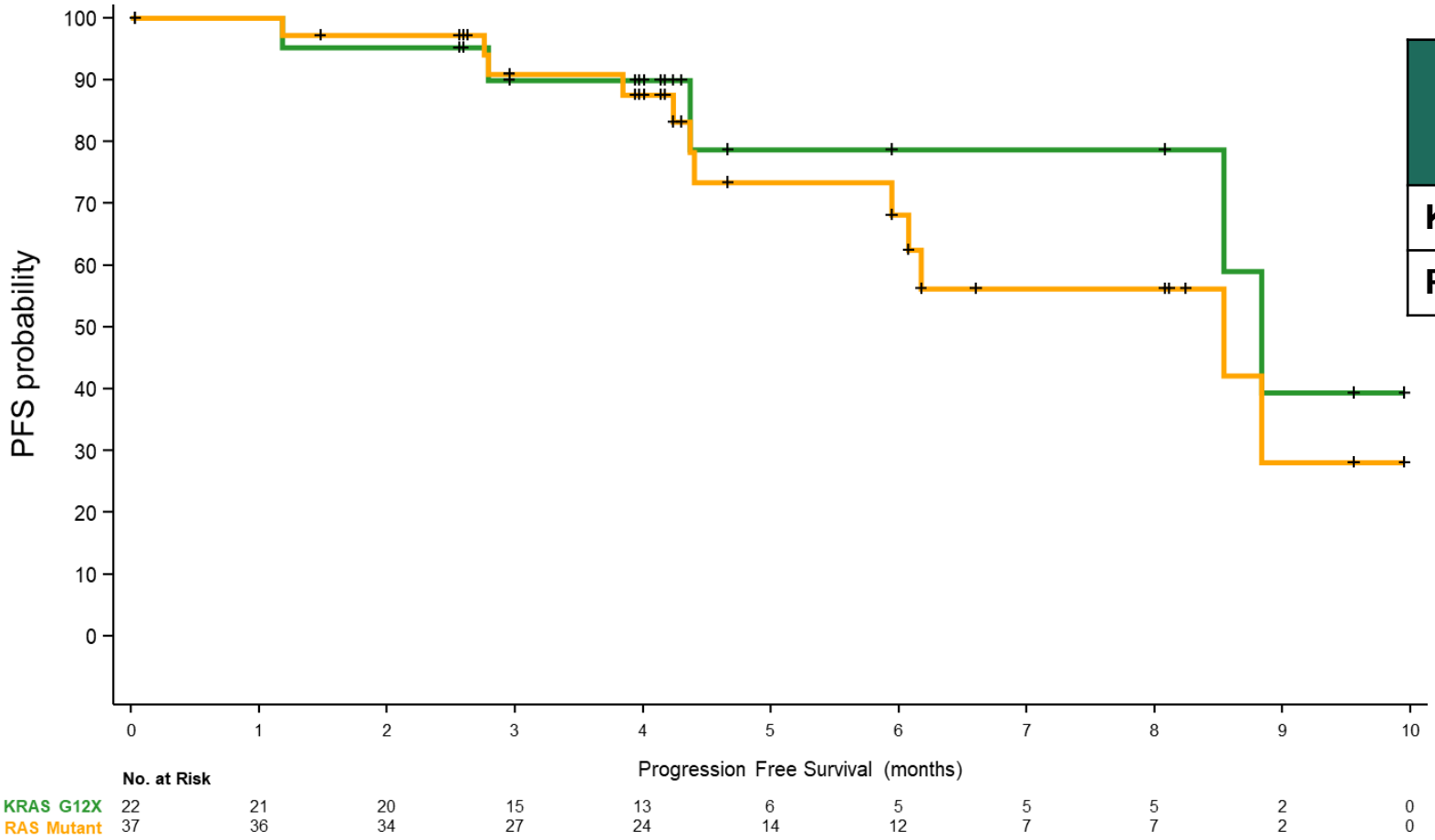
(1) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.

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. Among patients with a response (confirmed or unconfirmed), 46% of first response occurred within 2 months of RMC-6236 treatment. 2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose. ORR 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 remain in the denominator; ORR (by RECIST v1.1) includes confirmed CRs/PRs and unconfirmed CRs/PRs who were still on treatment and may yet be confirmed. One patient included in the denominator of the ORR analyses is not displayed on waterfall due to lack of post-baseline target lesion assessment (patient withdrew consent).

2L, second line; PDAC, pancreatic ductal adenocarcinoma; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; PR*, unconfirmed PR; SD, stable disease; SOD, sum of diameters.

ENA 2024 data set
(Data cutoff: Jul 23, 2024)

Encouraging Progression-Free Survival in 2L Patients with PDAC Treated with RMC-6236 at 300 mg Daily



	Median PFS, months (95% CI)
KRAS G12X	**8.8** (8.5, NE)
RAS Mutant[(1)]	**8.5** (5.9, NE)

(1) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.
2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose.
Median follow-up is 6.1m and 6.6m for KRAS G12 and RAS mutant in the 2L setting at 300mg, respectively.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; CI, confidence interval; NE, not estimable.

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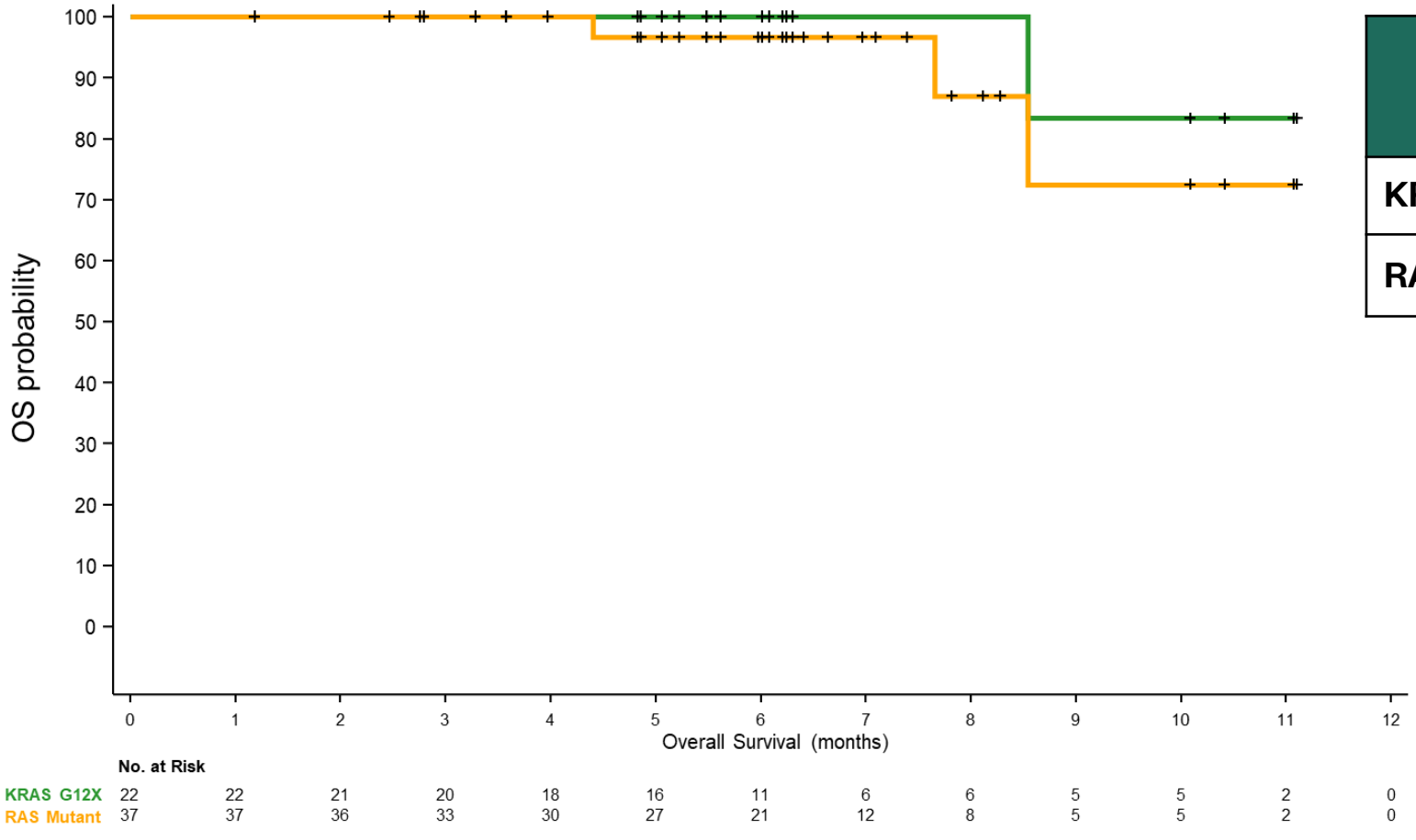
ENA 2024 data set
(Data cutoff: Jul 23, 2024)

Encouraging Overall Survival in 2L Patients with PDAC Treated with RMC-6236 at 300 mg Daily



	Median OS Months (95% CI)	OS Rate at 6 months, % (95% CI)
KRAS G12X	**NE** (NE, NE)	**100** (100, 100)
RAS Mutant[(1)]	**NE** (8.5, NE)	**97** (79, 100)

(1) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC.
2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose. Median follow-up is 6.1m and 6.6m for KRAS G12 and RAS mutant in the 2L setting at 300mg, respectively. OS rate at 6 months and 95% CI are from Kaplan-Meier analysis.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; OS, overall survival; CI, confidence interval; NE, not estimable.

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ENA 2024 data set
(Data cutoff: Jul 23, 2024)

RMC-6236 Monotherapy Shows Compelling Profile at Phase 3 Dose in Patients with RAS Mutant Metastatic 2L PDAC

- RMC-6236 is the first targeted investigational drug designed to directly inhibit all major forms of oncogenic RAS(ON), the common drivers of PDAC
- At the Phase 3 dose of 300 mg QD, RMC-6236 exhibited a manageable safety profile, favorable dose intensity and encouraging PFS and OS
- Data support RASolute 302, the ongoing global, randomized Phase 3 study of RMC-6236 vs. SOC chemotherapy as 2L treatment for patients with metastatic PDAC
- Aim to progress RMC-6236 into earlier lines of therapy for patients with metastatic PDAC

2L, second line; PDAC, pancreatic ductal adenocarcinoma; QD, once daily; SOC, standard of care.

RMC-6236 Monotherapy
in Non-Small Cell Lung Cancer

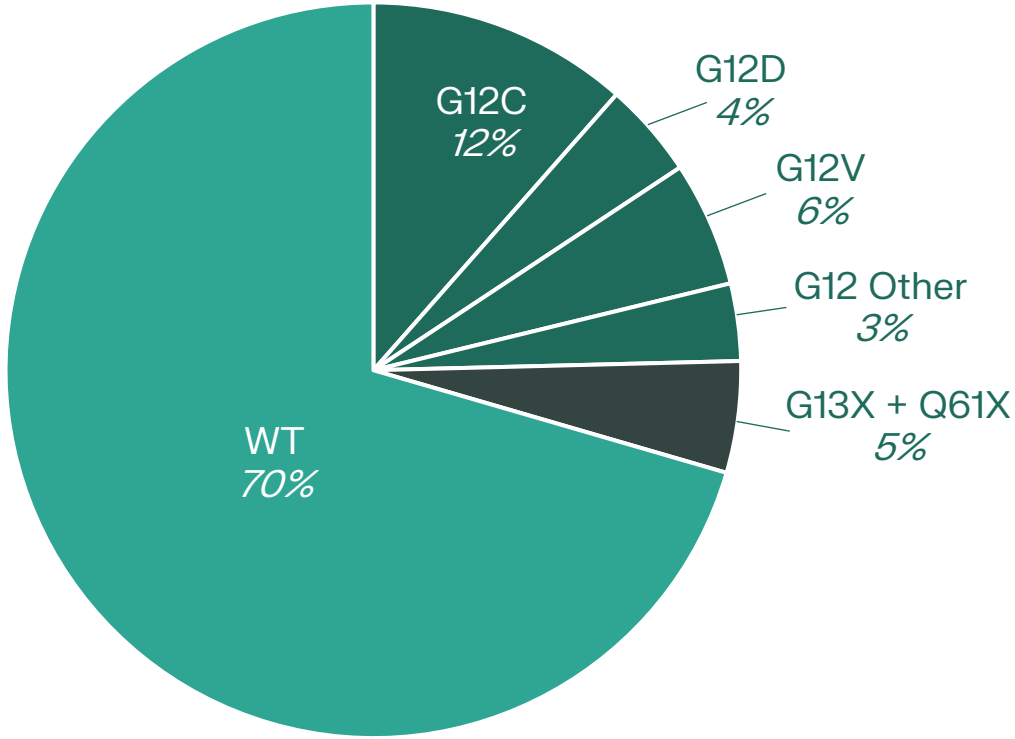
RAS-Targeted Therapies Have the Potential to Address Large Unmet Needs and Transform Treatment for RAS Mutant NSCLC

~200,000
new NSCLC cases per year (U.S.)[1]

30%
have RAS driver mutations[2]

25%
have RAS G12X driver mutations[2]

RAS Genotypes in NSCLC[3]



(1) ACS Cancer Facts and Figures 2024 adjusted for NSCLC only. (2) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022. (3) Numbers in the chart are rounded for presentation purposes. 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. NSCLC, non-small cell lung cancer; WT, wild-type.

Significant Need for Improved Treatment(s) for Patients with Previously Treated Locally Advanced or Metastatic NSCLC

Study	Timing relative to CPI approval in 1L	Treatment arm	No. of patients	ORR (%)	Median PFS (months)	Median OS (months)
REVEL[1]	prior	Docetaxel, 2L+	625	14%	**3.0**	**9.1**
CheckMate 057[2]	prior	Docetaxel, 2L+	290	12%	**4.2**	**9.4**
OAK[3]	prior	Docetaxel, 2L+	425	13%	**4.0**	**9.6**
POPLAR[4]	prior	Docetaxel, 2L+	143	14.7%	**3.0**	**9.7**
CodeBreak 200[5]	after	Docetaxel, 2L+	174	13.2%	**4.5**	**11.3**
TROPION-Lung-01[6]	after	Docetaxel, 2L+	305	13%	**3.7**	**11.8**
KRYSTAL-12[7]	after	Docetaxel, 2L+	152	9.2%	**3.8**	**NA**

Dose interruptions required in 15% of patients, dose reductions in 27%, and discontinuations in 11%[5]

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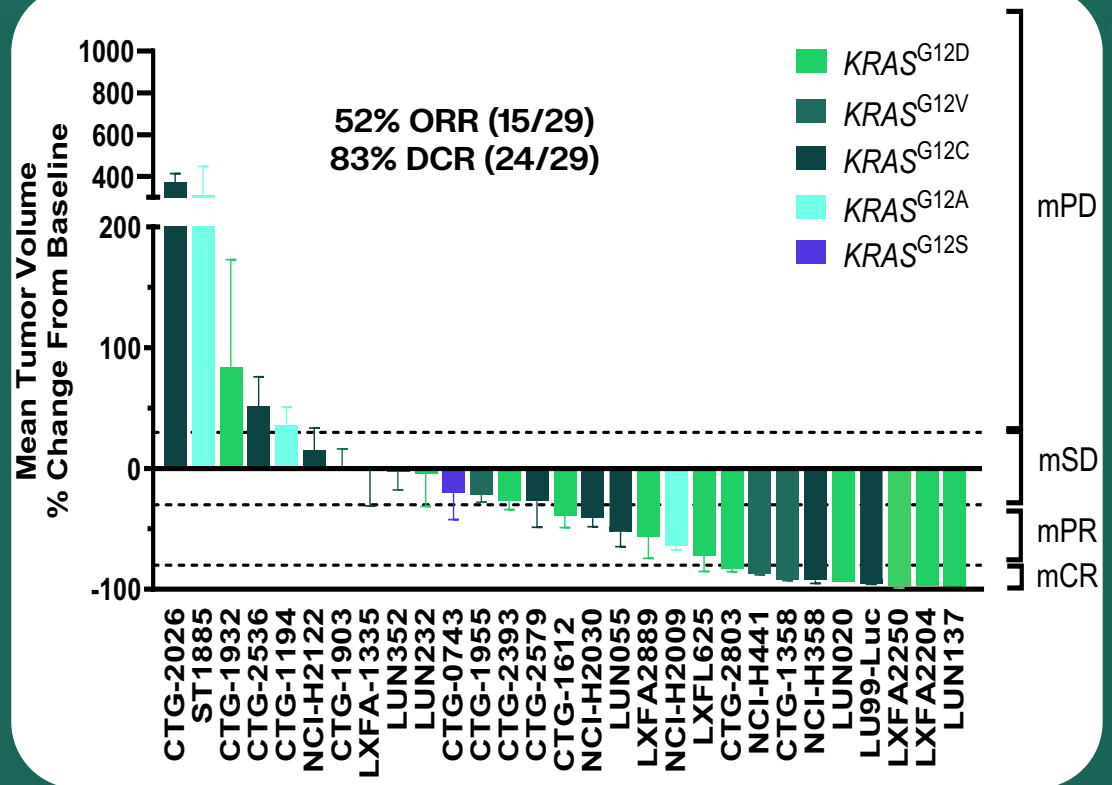
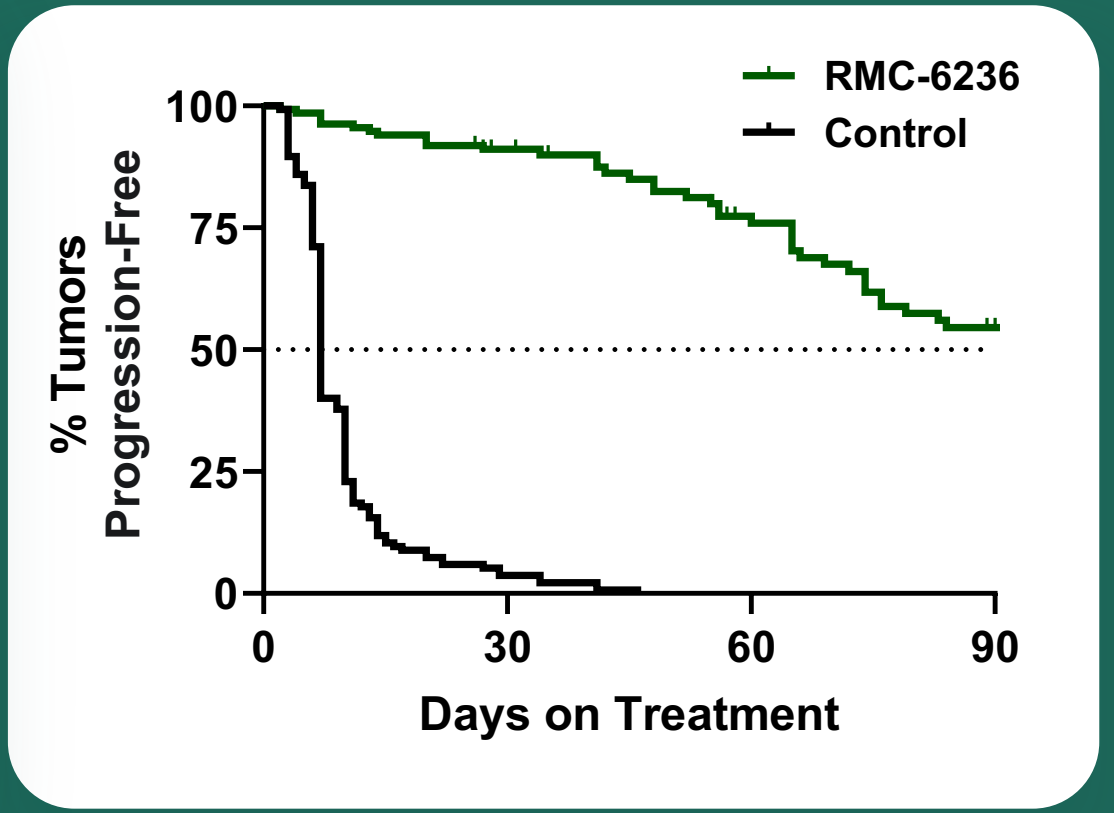
(1) Garon EB, et al. Lancet 2014;384:665-673; (2) Borghaei H, et al. N Engl J Med 2015; 373:1627-1639; (3) Rittmeyer A, et al. Lancet 2017;389:255-265; (4) Fehrenbacher L, et al. Lancet 2016;387:1837-1846; (5) de Langen AJ, et al. Lancet 2023;401:733-746; (6) Ahn MJ, J Clin Oncol. 2024 Sep 9:JCO2401544. doi: 10.1200/JCO-24-01544. ; (7) Mok TS, J Clin Oncol. 2024;42(17_suppl):LBA8509.
NSCLC, non-small cell lung cancer; CPI, check point inhibitor; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; 1L, first line; 2L, second line.

RMC-6236 Induces Frequent Responses and Durable Progression-Free Survival in Preclinical Models of RAS G12X NSCLC





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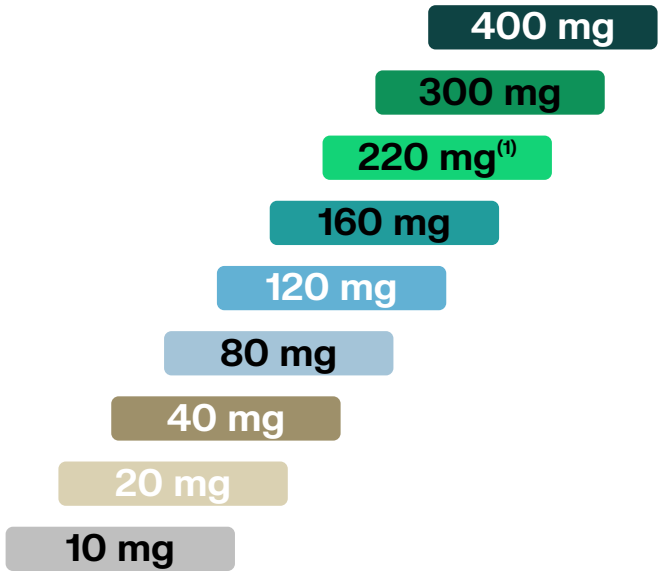
RVMD preclinical data, Jiang et. al. Cancer Discovery 2024:14:1-24.
NSCLC, non-small cell lung cancer; mPD, median progressive disease; mSD, median stable disease; mPR, median partial response; mCR, median complete response.

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

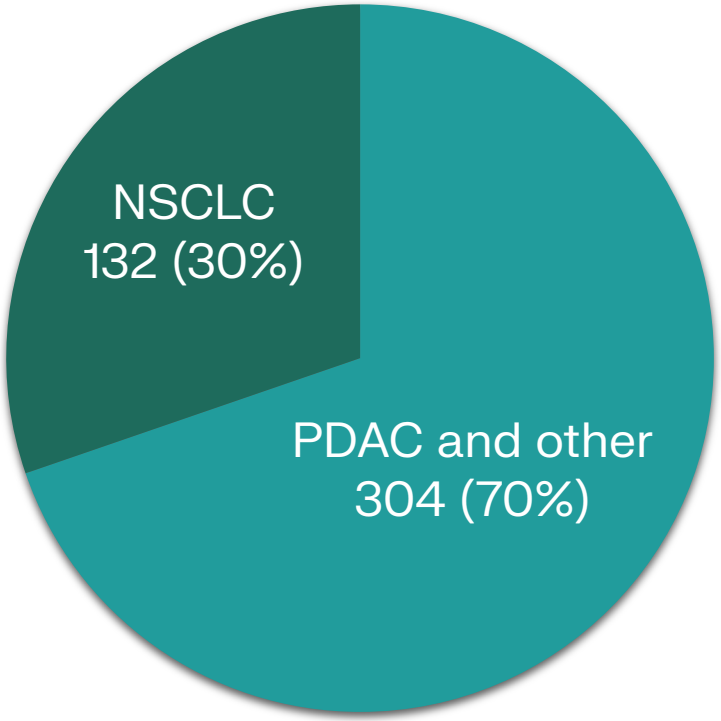
Dose Escalation in Solid Tumors

RMC-6236 administered orally QD



Tumor Types in FIH Trial

N=436

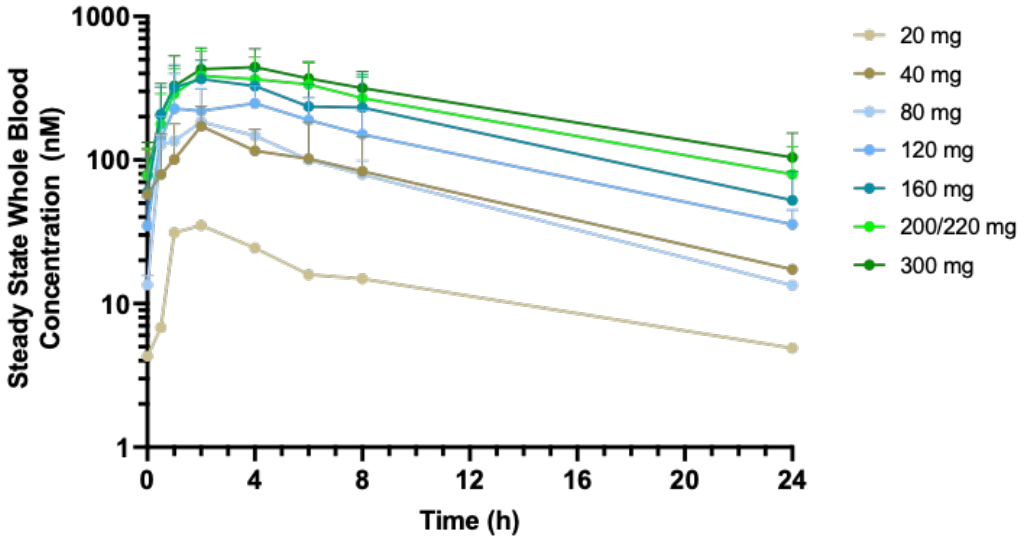


(1) 220 mg was explored in escalation phase, while 200 mg was selected for further expansion/optimization.
RMC-6236-001 Clinical Trial: https://clinicaltrials.gov/study/NCT05379985
FIH, first-in-human; QD, once daily; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

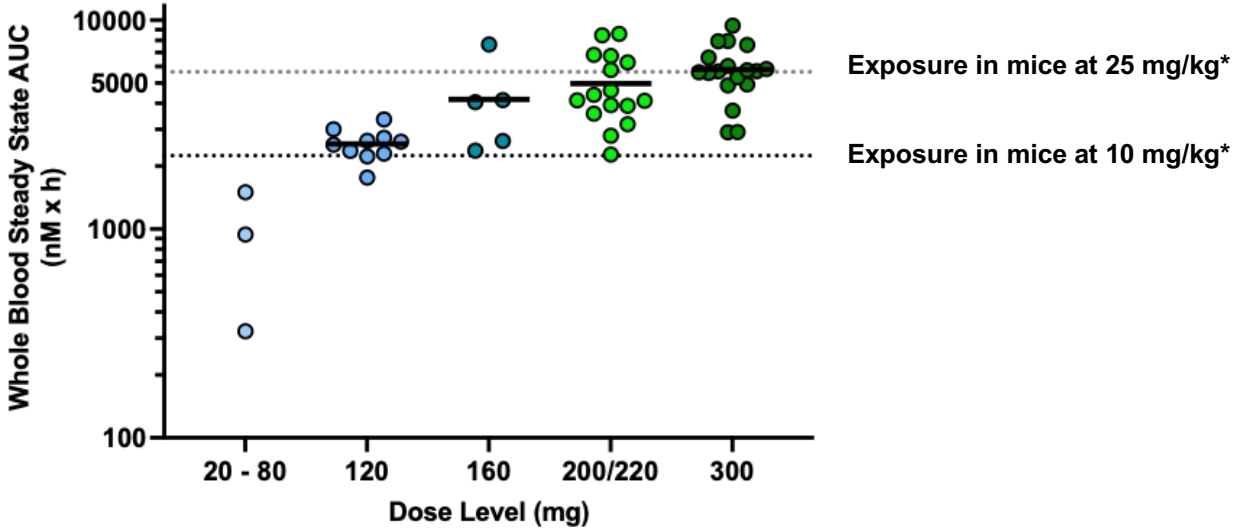
Data cutoff: Sept 30, 2024.

RMC-6236 120-300 mg Daily Provided Exposures in Patients with NSCLC Consistent with Tumor Regressions in Preclinical Models

Mean Steady-State (C1 D15) Blood PK Profiles



Individual Steady-State (C1 D15) Blood AUC



10 mg/kg in mice was associated with tumor regressions in most sensitive models of NSCLC;
25 mg/kg was associated with tumor regressions in most NSCLC models tested

* Exposure corrected with cross-species protein binding and blood/plasma partitioning.
Left: error bars represent standard deviation. Right: each circle represents an individual patient .
Treated patients from 20-300 mg were included in the analyses. AUC, horizontal bars represent mean AUC for each dose level.
NSCLC, non-small cell lung cancer; AUC, area under the curve; PK, pharmacokinetics.

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Data cutoff: Apr 26, 2024.

Patients with Locally Advanced or Metastatic RAS Mutant NSCLC Treated with RMC-6236 at 120-300 mg Daily

Baseline Characteristics	N=124[1]
Age, years, median (range)	67 (31, 89)
Male, n (%)	49 (40%)
ECOG PS 1, n (%)	100 (81%)
Number of prior anti-cancer therapies, median (range)	2 (1, 6)
Number of prior anti-cancer therapies in metastatic setting, n (%)	
0	9 (7%)
1	46 (37%)
2	36 (29%)
3+	33 (27%)
Smoking current/past, n (%)	94 (76%)
Brain metastases at baseline, n (%)	36 (29%)
Metastatic at diagnosis [stage IV], n (%)	70 (57%)

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(1) Additional 7 patients were treated at doses from 20-80 mg daily and 1 patient treated at 400mg daily.
NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Data cutoff: Sept 30, 2024.

RMC-6236 Generally Well Tolerated in Patients with NSCLC Treated at 120-220 mg Daily

	120-300 mg (N=124)		120-220 mg (N=73)		300 mg (N=51)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TRAE	121 (98%)	33 (27%)	71 (97%)	12 (16%)	50 (98%)	21 (41%)
TRAEs in ≥ 10% of patients, n (%)						
Rash [(1)]	110 (89%)	9 (7%)	66 (90%)	5 (7%)	44 (86%)	4 (8%)
Diarrhea	87 (70%)	10 (8%)	46 (63%)	1 (1%)	41 (80%)	9 (18%)
Nausea	68 (55%)	0 (0%)	36 (49%)	0 (0%)	32 (63%)	0 (0%)
Vomiting	55 (44%)	3 (2%)	29 (40%)	2 (3%)	26 (51%)	1 (2%)
Stomatitis	47 (38%)	3 (2%)	25 (34%)	0 (0%)	22 (43%)	3 (6%)
Paronychia	26 (21%)	0 (0%)	14 (19%)	0 (0%)	12 (24%)	0 (0%)
Fatigue	20 (16%)	0 (0%)	8 (11%)	0 (0%)	12 (24%)	0 (0%)
Dry skin	19 (15%)	0 (0%)	9 (12%)	0 (0%)	10 (20%)	0 (0%)
AST increased	17 (14%)	2 (2%)	11 (15%)	0 (0%)	6 (12%)	2 (4%)
ALT increased	15 (12%)	3 (2%)	10 (14%)	0 (0%)	5 (10%)	3 (6%)
Decreased appetite	14 (11%)	0 (0%)	4 (6%)	0 (0%)	10 (20%)	0 (0%)
Dysgeusia	12 (10%)	0 (0%)	3 (4%)	0 (0%)	9 (18%)	0 (0%)
Other select TRAEs, n (%)						
Anemia	9 (7%)	3 (2%)	4 (6%)	2 (3%)	5 (10%)	1 (2%)

- One Grade 4 pneumonitis (possibly related) observed at 300 mg dose level in patient with concomitant pneumocystis pneumonia
- No other Grade 4 TRAEs. No Grade 5 TRAEs

Revolution Medicines

(1) Includes preferred terms of rash pustular, Rash papular, Rash maculopapular, Rash macular, Rash, Erythema, Dermatitis acneiform. Multiple types of rash may have occurred in the same patient.
TRAE, treatment-related adverse event; NSCLC, non-small cell lung cancer; ALT, alanine transaminase; AST, aspartate transferase.

Data cutoff: Sept 30, 2024.

RMC-6236 Favorable Dose Intensity Maintained at 120-220 mg

	120-300 mg (N=124)	120-220 mg (N=73)	300 mg (N=51)
TRAEs leading to dose modification, n (%)	64 (52%)	30 (41%)	34 (67%)
Dose interruption	59 (48%)	25 (34%)	34 (67%)
Dose reduction	34 (27%)	15 (21%)	19 (37%)
TRAEs leading to dose discontinuation, n (%)	7 (6%)	3 (4%)	4 (8%)
TRAEs leading to dose reductions in ≥ 10% patients			
Diarrhea	12 (10%)	4 (6%)	8 (16%)
Rash (1)	13 (11%)	6 (8%)	7 (14%)
Mucositis/stomatitis	6 (5%)	1 (1%)	5 (10%)
Mean dose intensity	81%	88%	72%

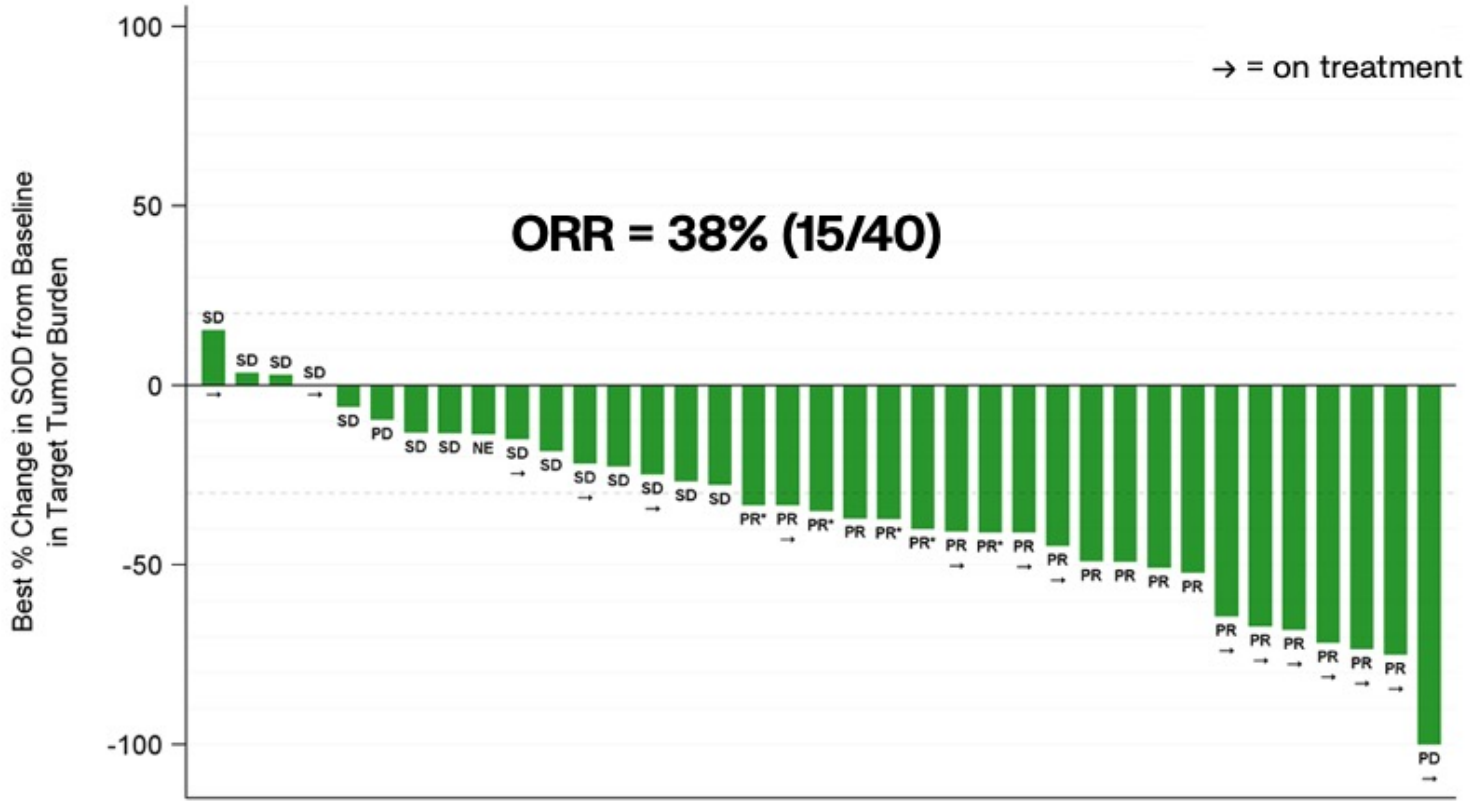
- For the 120–220 mg cohort, median treatment duration was 5.5 months
- Median cumulative duration of dose interruption was 8.5 days

Revolution Medicines

(1) Includes preferred terms of Rash pustular, Rash maculopapular, Rash, Dermatitis acneiform. Multiple types of rash may have occurred in the same patient.
TRAE, treatment-related adverse event.

Data cutoff: Sept 30, 2024.

Encouraging Objective Response Rate in 2L/3L Patients with RAS G12X NSCLC Treated with RMC-6236 at 120-220 mg Daily

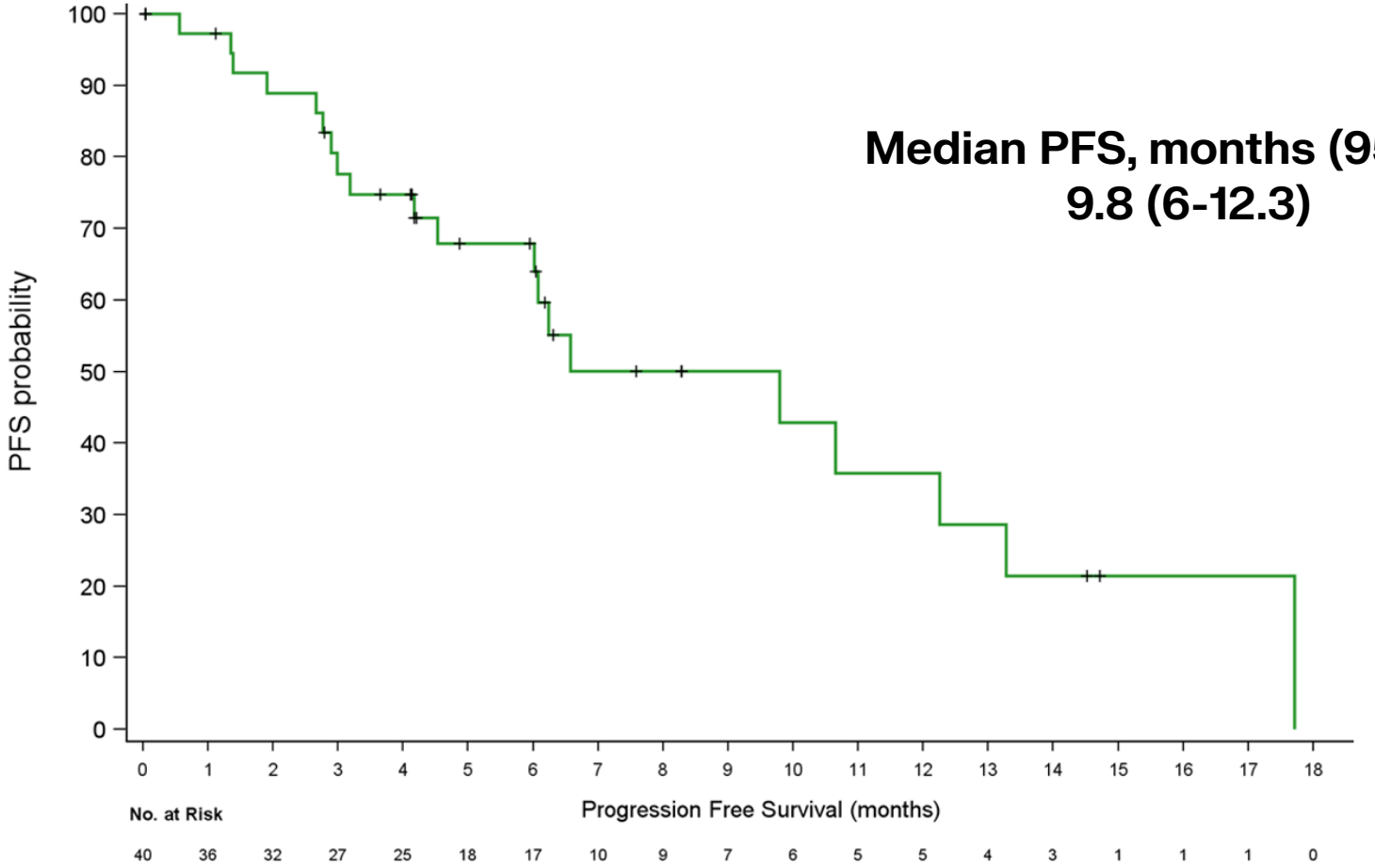


Population includes patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy which include prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially, and have not received docetaxel previously. Adjuvant therapy or multimodal therapy with curative intent is considered prior therapy if disease progression occurred or treatment completion was within 6 months of first dose of RMC-6236. Among patients with a response (confirmed or unconfirmed), 65% of first response occurred within 2 months of RMC-6236 treatment. ORR 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). ORR (by RECIST v1.1) included confirmed CRs/PRs and unconfirmed CRs/PRs who were still on treatment and may yet be confirmed; Unconfirmed PRs (PR*) with treatment discontinued (will never confirm) were not considered responders but remain in the denominator. 3 patients included in the denominator of the ORR analyses are not displayed on waterfall due to lack of post-baseline target lesion assessment (2 due to patient request to withdraw from treatment, and 1 due to patient withdrawal of consent); patient with 100% reduction in SOD from baseline was deemed as PD due to new lesion, treatment is ongoing post progression.

NSCLC, non-small cell lung cancer; SOD, sum of diameter; ORR, objective response rate; SD, stable disease; PD, progressive disease; NE, not evaluable; PR, partial response; CR, complete response.

Data cutoff: Sept 30, 2024.

Encouraging Progression-Free Survival in 2L/3L Patients with RAS G12X NSCLC Treated with RMC-6236 120-220 mg Daily

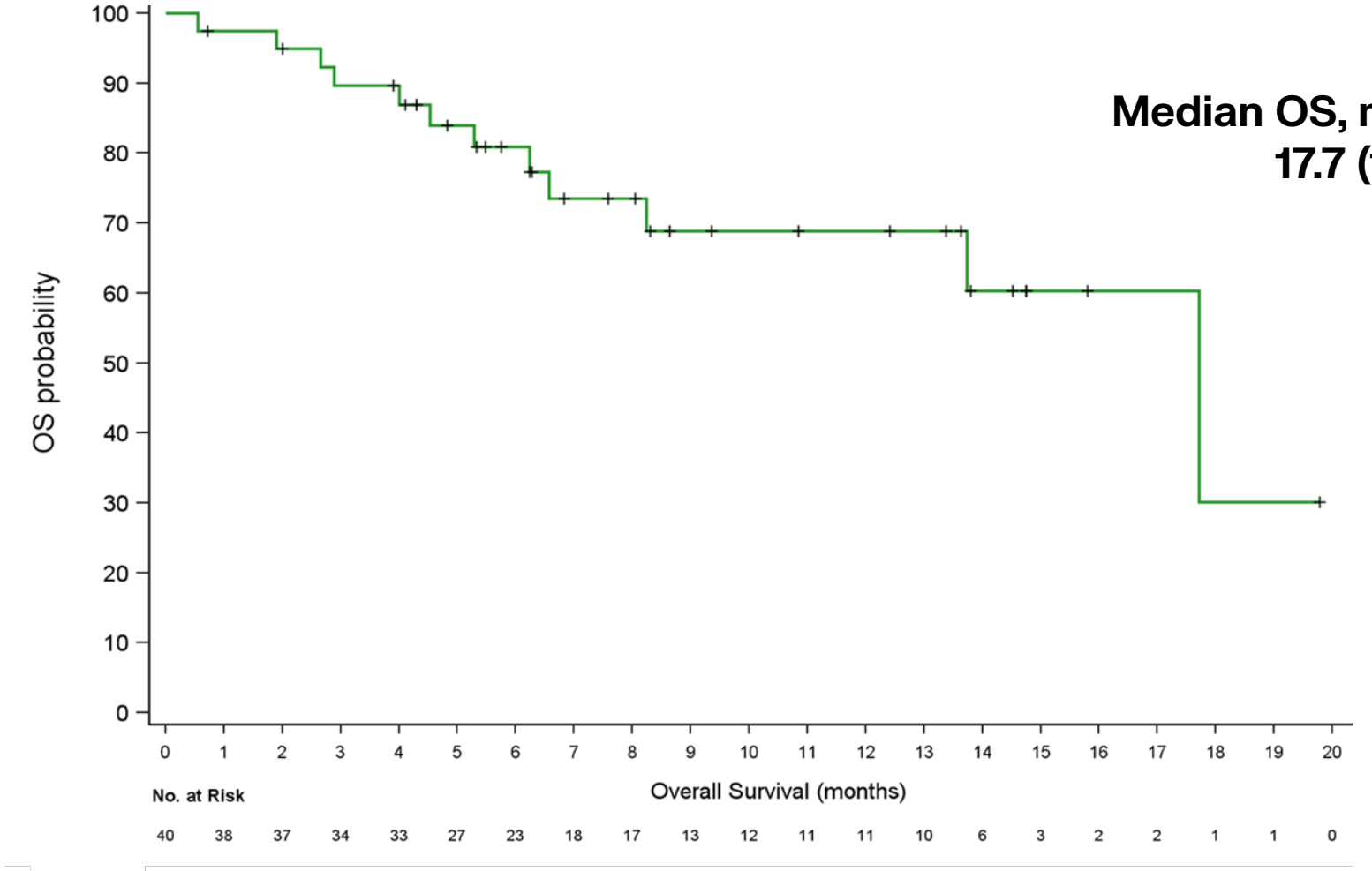


Median PFS, months (95% CI)
9.8 (6-12.3)

Population includes patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy which must include prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially, and have not received docetaxel previously. Adjuvant therapy or multimodal therapy with curative intent is considered prior therapy if disease progression occurred or treatment completion was within 6 months of first dose of RMC-6236. Median follow-up is 10.8 months.
NSCLC, non-small cell lung cancer; PFS, progression-free survival; CI, confidence interval.

Data cutoff: Sept 30, 2024.

Encouraging Interim Overall Survival in 2L/3L Patients with RAS G12X NSCLC Treated with RMC-6236 120-220 mg Daily



Median OS, months (95% CI)
17.7 (13.7-NE)

Population includes patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy which must include prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially, and have not received docetaxel previously. Adjuvant therapy or multimodal therapy with curative intent is considered prior therapy if disease progression occurred or treatment completion was within 6 months of first dose of RMC-6236. Median follow-up is 10.8 months.
NSCLC, non-small cell lung cancer; OS, overall survival; CI, confidence interval; NE, not estimable.

Data cutoff: Sept 30, 2024.

RASolve 301: Proposed Global Randomized Phase 3 Trial in Patients with Previously Treated RAS Mutant NSCLC

Trial Design[1]

R

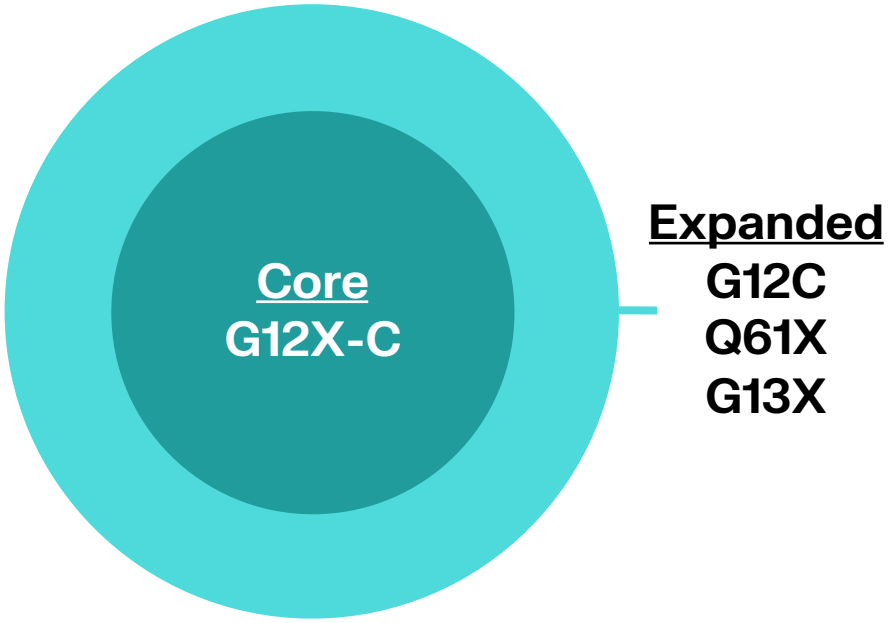
- **RMC-6236**
- **Docetaxel**

Endpoints

PFS
OS
ORR
Patient Reported Outcomes

- **N** = ~400 patients
- **Prior therapies**: 1 or 2 prior lines of therapy which must include immunotherapy and platinum chemotherapy administered concurrently or sequentially; no prior docetaxel; no prior RAS inhibitor
- **RAS genotypes**: RAS G12X-C, G12C, G13X or Q61X
- **Study Initiation**: Expected Q1 2025

Proposed Patient Populations[1,2]



Nested trial design[1] to enable hierarchical evaluation of Core and Core + Expanded populations

(1) Study design subject to change based on regulatory authority feedback
(2) Percentages of all NSCLC patients with tumors bearing RAS G12X-C, G12C, G13X, or Q61X genotypes are shown on slide 16.
NSCLC, non-small cell lung cancer; R, randomize; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; Q1, first quarter.

RMC-6236 Monotherapy Shows Promising Benefit/Risk in Patients with Previously Treated RAS Mutant NSCLC

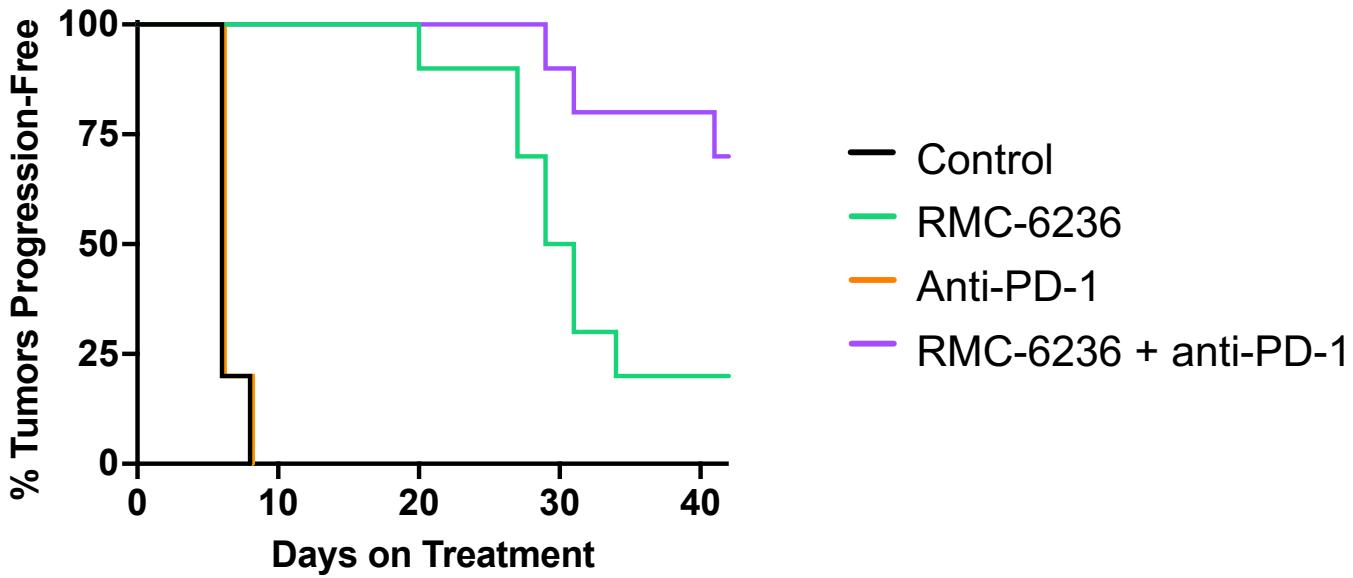
- Updated RMC-6236 monotherapy results demonstrate manageable safety/tolerability profile, favorable dose intensity and encouraging PFS and OS at clinically active dose range of 120–220 mg daily
- Data support initiation of a global, randomized Phase 3 study (RASolve 301) of RMC-6236 vs. docetaxel in patients with previously treated, locally advanced or metastatic NSCLC

NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival.

Safety Evaluation of RMC-6236 + Pembrolizumab Combination

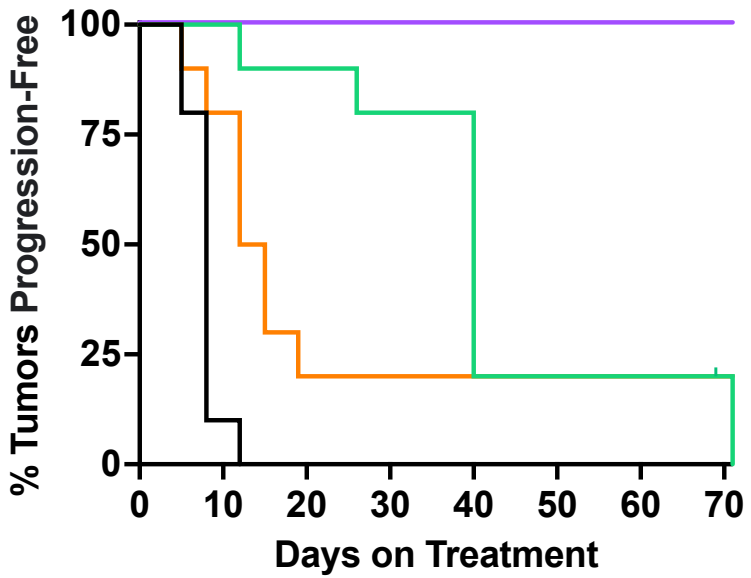
RMC-6236 Enhances Response to Anti-PD-1 in RAS Mutant Preclinical Cancer Models

KRAS G12D PDAC Allograft Model



RMC-6236 dosed at 25 mg/kg PO QD. Anti-PD-1 clone RMP1-14 dosed at 10 mg/kg IP BIW for a total of 6 doses.
Model: KPCYc3 (*KRAS*$^{G12D/+}$, *Trp53*$^{R172H/+}$) derived as described in Li et al. Immunity 2018

KRAS G12D MSS CRC Allograft Model



RMC-6236 dosed at 25 mg/kg PO QD. Anti-PD-1 clone RMP1-14 CP151 dosed at 10 mg/kg IP BIW for the duration of the study.
Model: eCMT93 (*KRAS*$^{G12D/G12D}$)

PDAC, pancreatic ductal adenocarcinoma; MSS, microsatellite stable; CRC, colorectal cancer; QD, once daily; BIW, twice weekly; IP, intraperitoneal

Exploration of Safety of RMC-6236 + Pembrolizumab in Previously Treated Patients with RAS Mutant NSCLC

Baseline Characteristics	N=20
Age, median (range), years	67 (36, 80)
Male, n (%)	6 (30%)
ECOG PS 1, n (%)	17 (85%)
Number of prior anti-cancer therapies, median (range)	1 (1, 5)
Previously treated with immune checkpoint inhibitor	17 (85%)
Brain metastasis at baseline	6 (30%)

NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Data cutoff: Oct 28, 2024.

Initial Data Support Combinability of RMC-6236 200 mg QD and Pembrolizumab 200 mg Q3W

	N=20				
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
Any TRAE	6 (30%)	7 (35%)	4 (20%)	1 (5%)	18 (90%)
TRAEs occurring in ≥15% of patients, n (%)					
Rash[1]	10 (50%)	3 (15%)	1 (5%)	0 (0%)	14 (70%)
Vomiting	3 (15%)	5 (25%)	1 (5%)	0 (0%)	9 (45%)
Diarrhea	7 (35%)	1 (5%)	0 (0%)	0 (0%)	8 (40%)
Nausea	8 (40%)	0 (0%)	0 (0%)	0 (0%)	8 (40%)
Mucositis/Stomatitis	6 (30%)	2 (10%)	0 (0%)	0 (0%)	8 (40%)
Anemia	2 (10%)	1 (5%)	0 (0%)	0 (0%)	3 (15%)
AST increased	2 (10%)	1 (5%)	0 (0%)	0 (0%)	3 (15%)
Neutrophil count decreased	3 (15%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Paronychia	2 (10%)	1 (5%)	0 (0%)	0 (0%)	3 (15%)
Other select TRAEs, n (%)					
ALT increased	1 (5%)	0 (0%)	1 (5%)	0 (0%)	2 (10%)
Pneumonitis	0 (0%)	1 (5%)	1 (5%)	0 (0%)	2 (10%)
TRAEs leading to RMC-6236 dose interruption, n (%)	1 (5%)	2 (10%)	2 (10%)	1 (5%)	6 (30%)
TRAEs leading to RMC-6236 dose reduction[2], n (%)	0 (0%)	0 (0%)	2 (10%)	0 (0%)	2 (10%)
TRAEs leading to RMC-6236 discontinuation, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TRAEs leading to pembrolizumab discontinuation[3], n (%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)

- Median duration of treatment at the time of data cutoff was 2.3 months, 12 patients (60%) have been on RMC-6236 treatment for ≥60 days, and the mean relative dose intensity of RMC-6236 was 97%; one Grade 4 TRAE (thrombocytopenia); no Grade 5 TRAEs

(1) Rash bundled term includes dermatitis acneiform, rash maculopapular, rash, rash pustular, erythema.
(2) RMC-6236 dose was reduced to 140 mg QD due to Grade 3 rash in two patients.
(3) Pembrolizumab was discontinued due to pembrolizumab-related Grade 2 pneumonitis in one patient.
QD, once daily; Q3W, once every three weeks; TRAE, treatment-related adverse event; ALT, alanine transaminase; AST, aspartate transferase.

Revolution Medicines

Data cutoff: Oct 28, 2024.

Combination of RMC-6236 + Pembrolizumab in Patients with NSCLC Appears to be Generally Well Tolerated

- Initial safety data encouraging for patients treated with RMC-6236 shortly after or concurrently with pembrolizumab
- Data strongly support continued evaluation of the combination of RMC-6236 with pembrolizumab in 1L NSCLC patients

NSCLC, non-small cell lung cancer; 1L, first line.

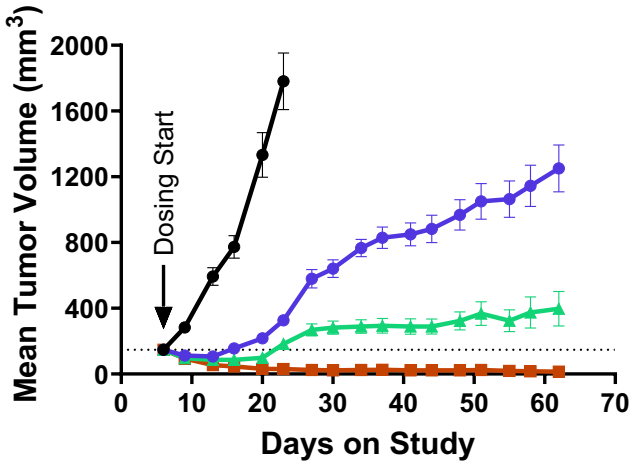
Initial Evaluation of Antitumor Activity of RAS(ON) Inhibitor Doublet: RMC-6291 + RMC-6236

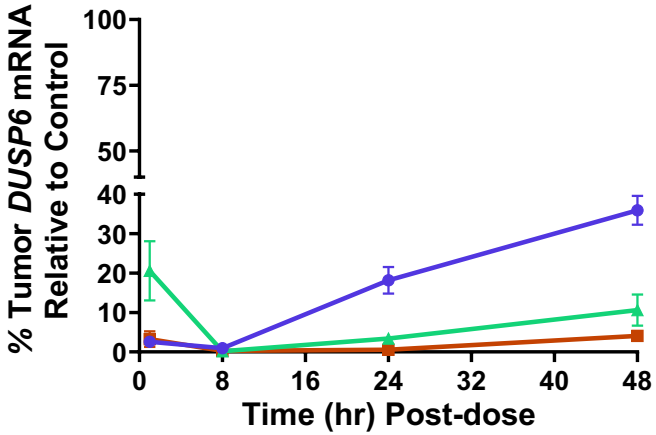
RAS(ON) Inhibitor Doublet Drives Deep RAS Pathway Suppression and Durable Regressions in G12C Tumor Models Resistant to Monotherapy

Tumor Volume

MAPK Pathway Suppression

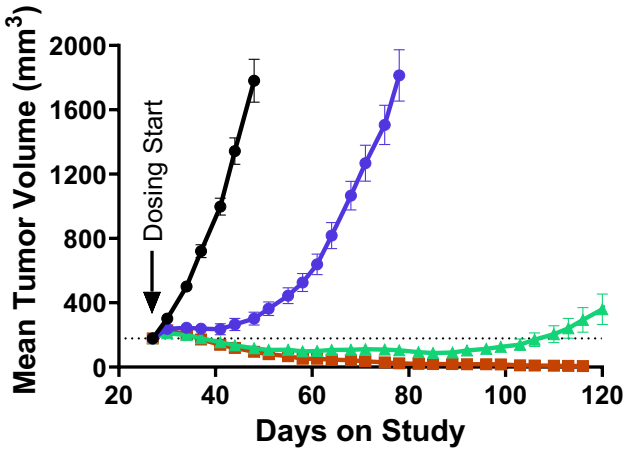
NCI-H2122
(NSCLC, *KRAS*^{G12C}, *STK11*^{mut}, *KEAP1*^{mut})

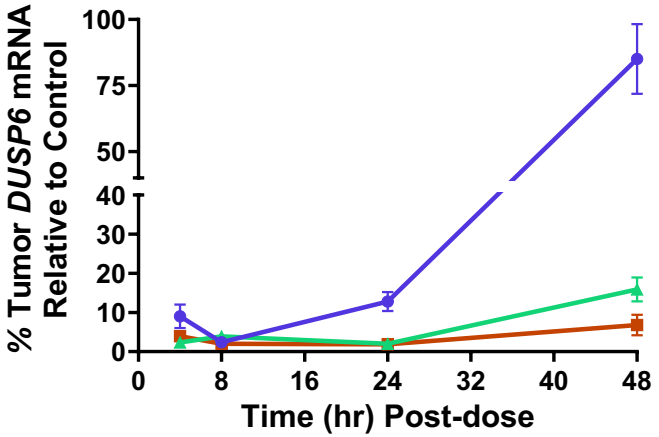




Control
RMC-6291
RMC-6236
Combination

NCI-H2030
(NSCLC, *KRAS*^{G12C}, *STK11*^{mut}, *KEAP1*^{mut})





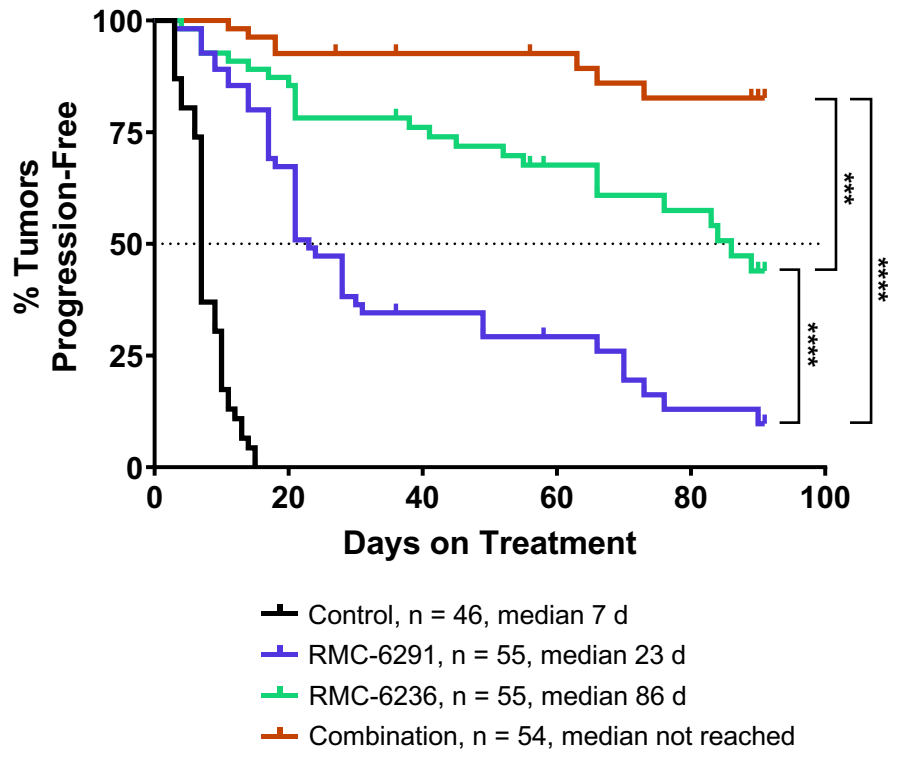
Revolution Medicines

NSCLC, non-small cell lung cancer; QD, once daily.

RMC-6291 dosed at 100 mg/kg PO QD
RMC-6236 dosed at 25 mg/kg PO QD

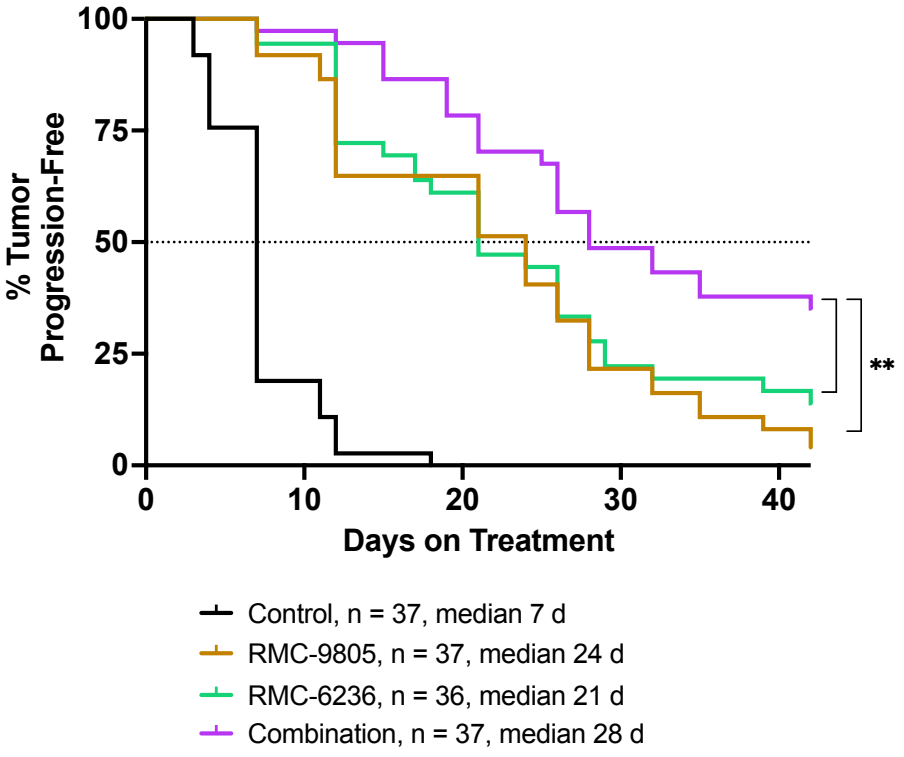
RAS(ON) Inhibitor Doublets Provide Durable Responses in Preclinical Models

KRAS G12C NSCLC Xenograft Models



RMC-6291 dosed at 100 or 200 mg/kg PO QD; RMC-6236 dosed at 25 mg/kg PO QD; Combination: RMC-6291 100 or 200 mg/kg PO QD + RMC-6236 25 mg/kg PO QD.
8 Models: NCI-H2122, CTG-2026, CTG-2536, NCI-H2030, LXFA-1335, LUN055, CTG-2579 and LUN092.

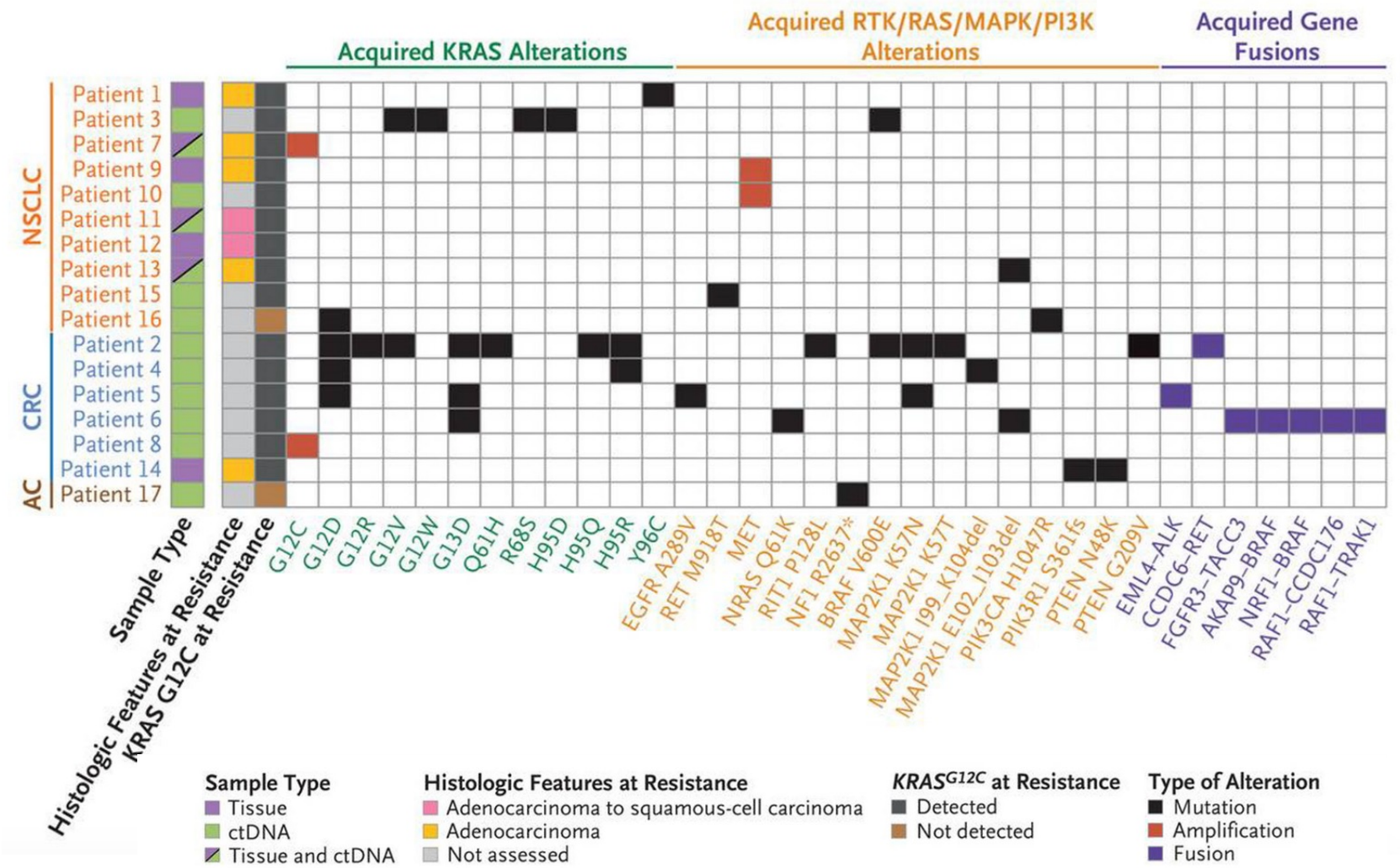
KRAS G12D PDAC Allograft Models



RMC-9805 dosed at 100 mg/kg PO QD; RMC-6236 dosed at 25 mg/kg PO QD; Combination: RMC-9805 100 mg/kg PO QD + RMC-6236 10 mg/kg PO QD.
4 KPCY (*KRAS*$^{G12D/+}$; *Trp53*$^{LSL-R172H/+}$ - PDAC) models: KPCYc2, c3, c4 and c5 derived as described in Li et al. Immunity 2018.

NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; QD, once daily.

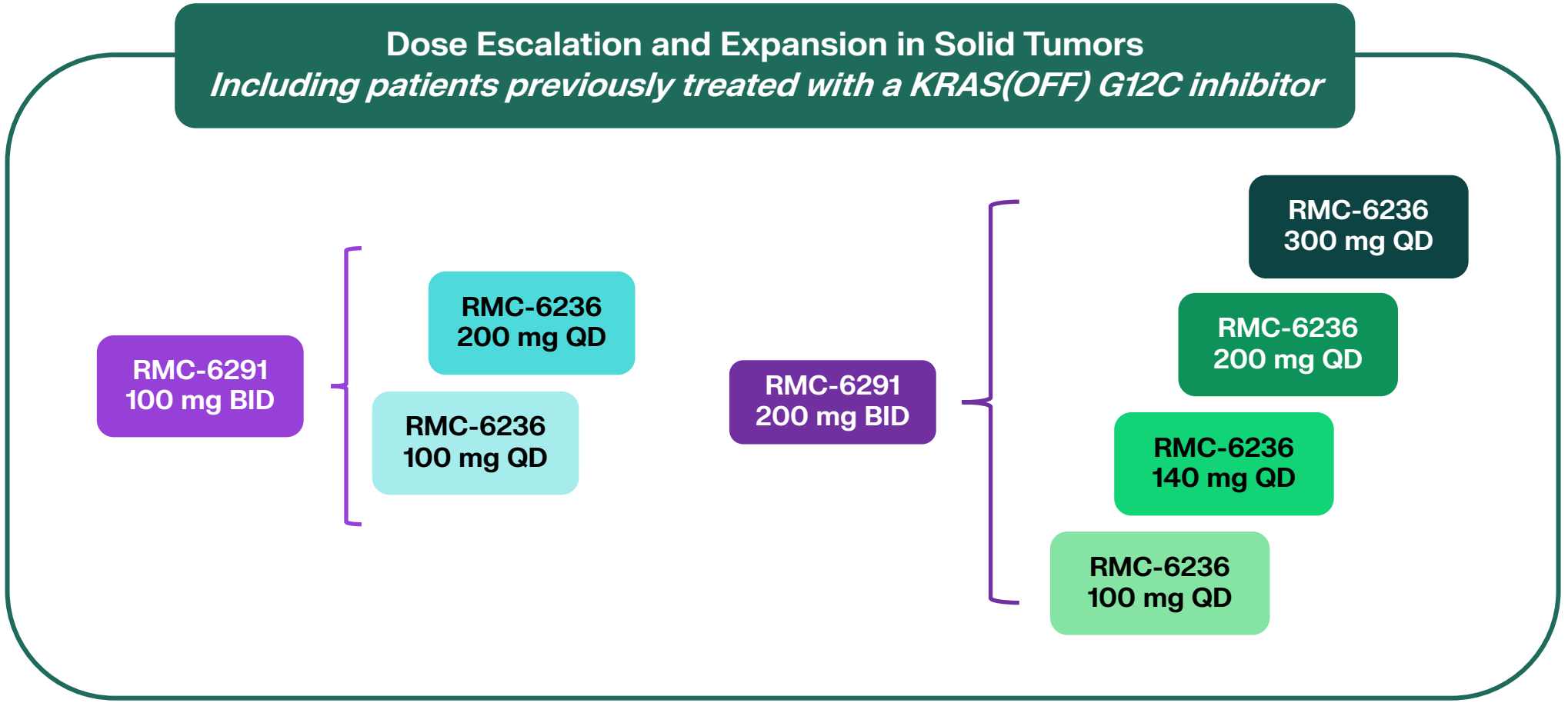
Many Putative Mechanisms of Acquired Resistance to KRAS(OFF) G12C Inhibition Expected to be Sensitive to RAS(ON) Inhibitor Doublet



AC, adenocarcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; ctDNA, circulating tumor DNA.

Awad et al., NEJM 2021.

Dose Exploration of RMC-6291 and RMC-6236 as RAS(ON) Inhibitor Doublet



- Preliminary PK analysis demonstrates steady-state exposures of RMC-6291 and RMC-6236 within the range of variability of their exposures as monotherapy agents at equivalent doses

BID, twice daily; QD, once daily; PK, pharmacokinetics.

PK data extract: Oct 31, 2024.

Safety Exploration for RAS(ON) Inhibitor Doublet of RMC-6291 and RMC-6236 in Patients with Advanced RAS G12C Mutant Solid Tumors

Baseline Characteristics	N=74
Age, median (range), years	61.5 (36, 84)
Male, n (%)	31 (42%)
ECOG PS 1, n (%)	51 (69%)
Tumor type, n (%)	
CRC	33 (45%)
NSCLC	25 (34%)
PDAC	7 (10%)
Other	9 (12%)
Previously treated with a KRAS(OFF) G12C inhibitor, n (%)	41 (55%)
Number of prior anti-cancer therapies, median (range)	3 (1, 9)
Liver metastasis at baseline, n (%)	32 (43%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

Data cutoff: Oct 28, 2024.

Combination of RMC-6291 and RMC-6236 was Well Tolerated Across All Dose Levels Tested

All Dose Levels (N=74)					
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
Any TRAE	14 (19%)	26 (35%)	16 (22%)	1 (1%)	57 (77%)
TRAEs occurring in ≥10% of patients, n (%)					
Rash[1]	21 (28%)	23 (31%)	4 (5%)	0 (0%)	48 (65%)
Diarrhea	23 (31%)	10 (14%)	1 (1%)	0 (0%)	34 (46%)
Nausea	17 (23%)	7 (10%)	0 (0%)	0 (0%)	24 (32%)
Vomiting	18 (24%)	6 (8%)	0 (0%)	0 (0%)	24 (32%)
Mucositis/Stomatitis	8 (11%)	9 (12%)	1 (1%)	0 (0%)	18 (24%)
Fatigue	8 (11%)	2 (3%)	3 (4%)	0 (0%)	13 (18%)
Anemia	4 (5%)	4 (5%)	2 (3%)	0 (0%)	10 (14%)
ALT increased	3 (4%)	6 (8%)	0 (0%)	0 (0%)	9 (12%)
AST increased	4 (5%)	3 (4%)	1 (1%)	0 (0%)	8 (11%)
Other select TRAEs, n (%)					
Electrocardiogram QT prolonged	0 (0%)	0 (0%)	2 (3%)	0 (0%)	2 (3%)
TRAEs leading to dose interruption of any study drug, n (%)	0 (0%)	12 (16%)	9 (12%)	1 (1%)	22 (30%)
TRAEs leading to dose reduction of any study drug, n (%)	1 (1%)	4 (5%)	2 (3%)	0 (0%)	7 (10%)
TRAEs leading to treatment discontinuation of any study drug, n (%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	2 (3%)

- Median duration of treatment was 2.3 months. The mean dose intensities for RMC-6291 and RMC-6236 were 95% and 92%, respectively
- No treatment-related Grade 5 AEs have been reported
- 1 subject with a Grade 4 TRAE of hypokalemia, which led to dose interruption, was associated with Grade 3 diarrhea

Revolution Medicines

(1) Rash bundled term includes dermatitis acneiform, rash maculopapular, rash, rash pustular, erythema.
TRAE, treatment-related adverse event; ALT, alanine transaminase; AST, aspartate transferase.

Data cutoff: Oct 28, 2024.

Significant Need for Improved Efficacy and Tolerability for Late Lines of Treatment of Patients with Metastatic CRC

Study	Regimen	Treatment line	No. of patients	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
RECOURSE [1]	**Trifluridine/tipiracil**	3L+	534	2%	44%	2.0 (1.9–2.1)	7.1 (6.5–7.8)
SUNLIGHT [2]	**Trifluridine/tipiracil + Bevacizumab**	3L	246	6%	77%	5.6 (4.5–5.9)	10.8 (9.4–11.8)
CORRECT [3]	**Regorafenib**	2L+	505	1%	41%	2.0 (1.9–2.3)	6.4 (5.8–7.3)

(1) Mayer R, et al. N Engl J Med 2015;372:1909-19; Lonsurf USPI (2) Prager GW, et al. N Engl J Med 2023;388:1657-67; Lonsurf USPI (3) Grothey A, et al. Lancet 2013; 381: 303–12; STIVARGA USPI.
CRC, colorectal cancer; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; 3L, third line; 2L, second line.

Limited Monotherapy Activity of Either RMC-6236 in RAS Mutant CRC or RMC-6291 in CRC Previously Treated with G12C(OFF) Inhibitor

RAS Inhibitor	Population	ORR n/N (%)
RMC-6236 in RAS Mutant CRC[1,3] 300 mg QD	RAS inhibitor naive	2/22 (9%)
RMC-6291 in KRAS G12C Mutant CRC[2] 200 mg BID	Previously treated with a G12C(OFF) Inhibitor	0/6

Revolution Medicines

(1) KRAS G12X-C; all patients treated at 300 mg QD; (2) RMC-6291 200 mg BID (RP2D); (3) ORR (by RECISTv1.1) includes confirmed CRs/PRs. The analysis is based on patients who received first dose of RMC-6236 at least 14 weeks prior to data cutoff date (to allow 2 potential scans).
CRC, colorectal cancer; ORR, objective response rate; QD, once daily; BID, twice daily.

6291-001 data cutoff: Oct 28, 2024.
6236-001 data cutoff: Sep 30, 2024.

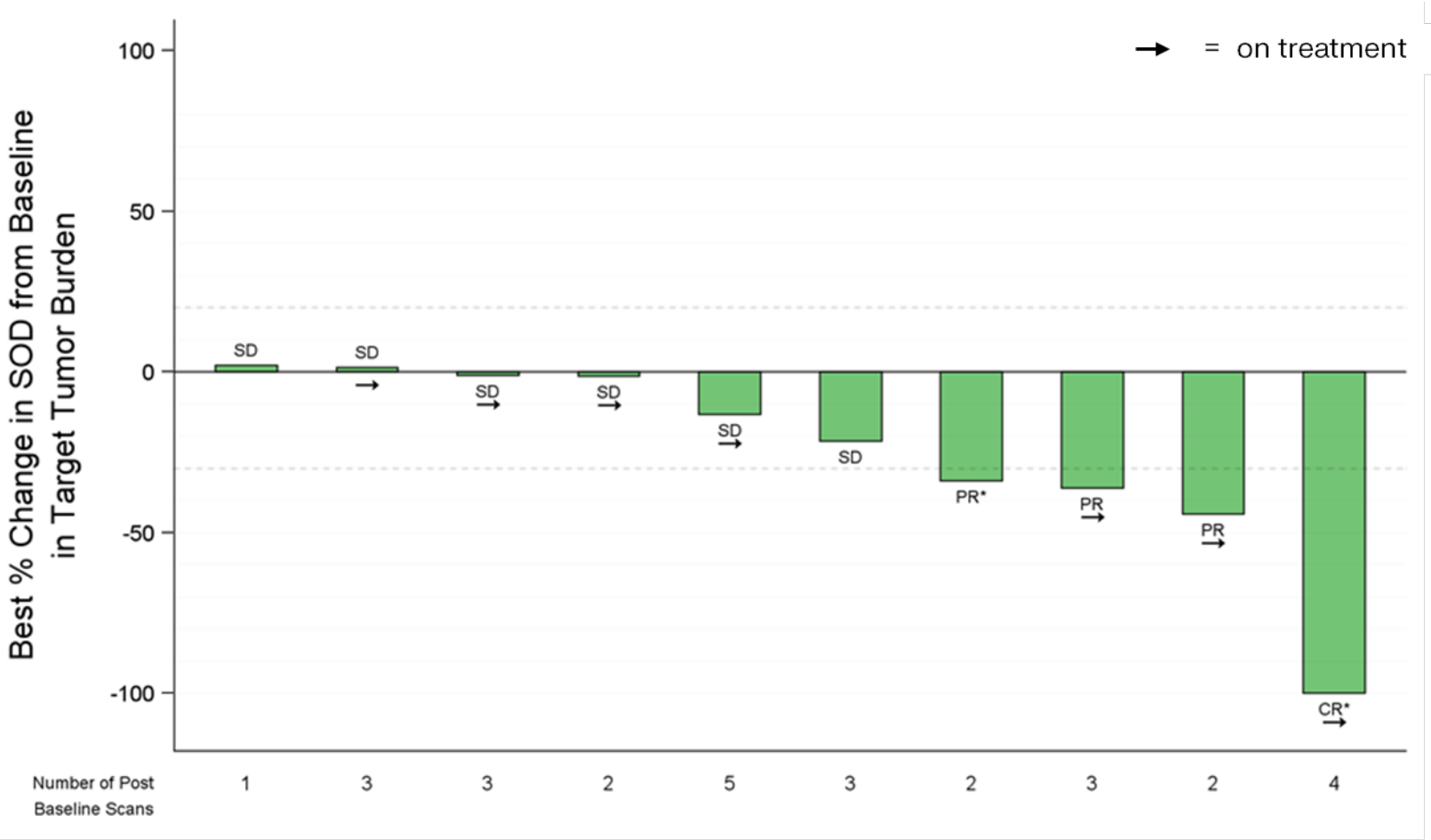
Patient Demographics and Baseline Characteristics for CRC Patients Previously Treated with a G12C(OFF) Inhibitor, All Dose Levels

Baseline Characteristics	N=15
Age, median (range), years	55 (36–72)
Male, n (%)	8 (53%)
ECOG PS 1, n (%)	10 (67%)
Number of prior anti-cancer therapies, median (range)	5 (2–8)
Liver metastasis at baseline, n (%)	12 (80%)

CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Data cutoff: Oct 28, 2024.

RMC-6291 + RMC-6236 Doublet Shows Encouraging Antitumor Activity in Patients with CRC Previously Treated with KRAS(OFF) G12C Inhibitor



	ORR	DCR
% (n/N)	25% (3/12)	92% (11/12)

ORR and DCR (CR+PR+SD) analyses include all patients who received first dose of study drug(s) at least 8 weeks prior to data cutoff date (to allow 1 potential scan). Unconfirmed PRs (PR*) with treatment discontinued (will never confirm) were not considered responders but included 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. Two patients with 8 weeks follow up do not appear in waterfall due to one patient with no tumor assessment entered in database and one patient with missing target lesion measurements (overall response entered as SD). One patient with unconfirmed CR (CR*) has confirmed PR.

CRC, colorectal cancer; SOD, sum of diameters; SD, stable disease; CR, complete response; CR*, unconfirmed complete response; PR, partial response; PR*, unconfirmed PR; ORR, objective response rate; DCR, disease control rate.

Data cutoff: Oct 28, 2024.

RMC-6291 + RMC-6236 Case Report: Patient with KRAS G12C CRC

Baseline Characteristics

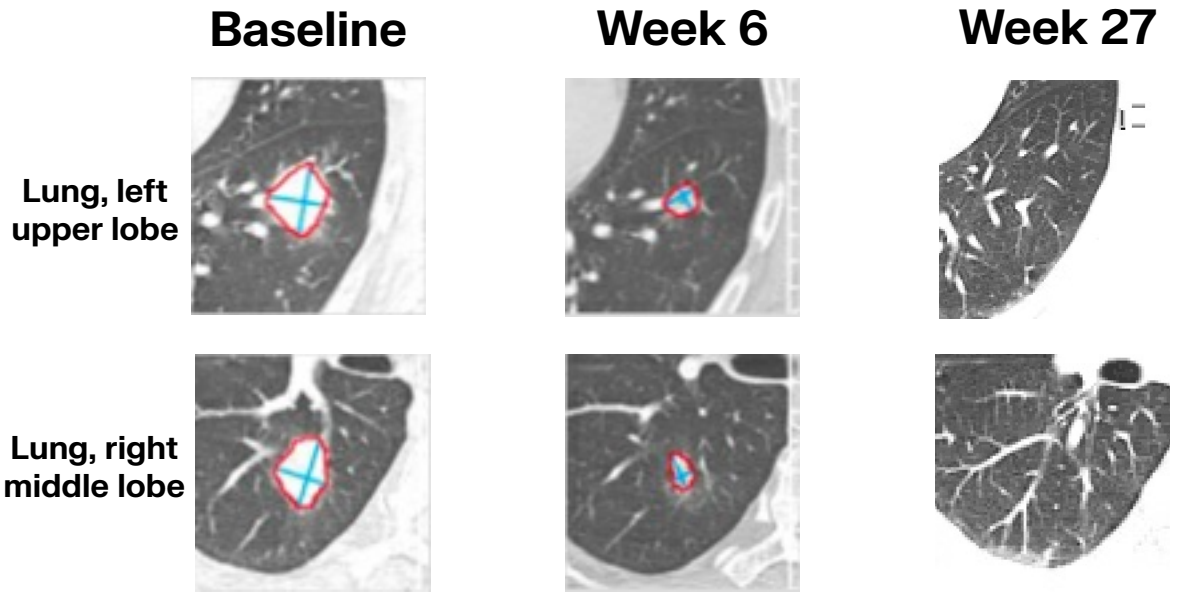
- 55 year-old male initially diagnosed with colorectal adenocarcinoma in 2019
- ECOG 1
- KRAS G12C, KRAS Y96N and RTK rearrangements (ALK and MET fusions) detected in baseline ctDNA

Treatment History

- Laparoscopic low anterior resection in 2019 (Stage I)
- Metastatic recurrence and left hepatectomy in 2021
- FOLFIRINOX + bevacizumab
- Adagrasib + cetuximab
- Investigational agent + pembrolizumab

RAS(ON) Doublet Treatment Course

- Started treatment with RMC-6291 100 mg BID + RMC-6236 200 mg QD on Mar 11, 2024 in Dose Exploration Phase
- C3D1: Partial Response
- C5D1: Partial Response with complete resolution of all non-target lesions
- C10D1: Complete Response
- Continues on treatment with no G3 or higher TRAEs



Target Lesion	Baseline (mm)	Week 6 (mm)	Week 27 (mm)
Lung, left upper lobe	28.8	14.1	0
Lung, right middle lobe	25	13.4	0
Sum of Diameters	53.8	27.5 (-49%)	**0 (-100%)**
Overall Response	-	**PR**	**CR**

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CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; BID, twice daily; QD, once daily; TRAE, treatment-related adverse event.

Data cutoff: Oct 28, 2024.

Encouraging Activity of RAS(ON) Inhibitor Doublet in Patients with CRC Who Progressed on KRAS(OFF) G12C Inhibitor

- Preclinical data demonstrate strong rationale for the potential of a RAS(ON) inhibitor doublet of RMC-6291 + RMC-6236 to provide deep and durable antitumor activity
- Preliminary clinical safety and antitumor activity provide initial proof-of-mechanism for RAS(ON) inhibitor doublet in KRAS(OFF) G12C inhibitor-experienced CRC patients
- Strong rationale for continued development of RAS(ON) doublets in broad range of tumor types and earlier lines of therapy

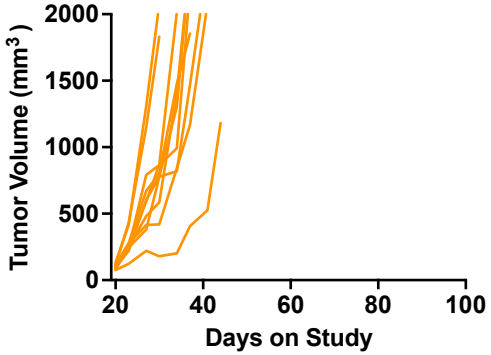
CRC, colorectal cancer.

Safety Evaluation of RMC-6291 + Pembrolizumab Combination

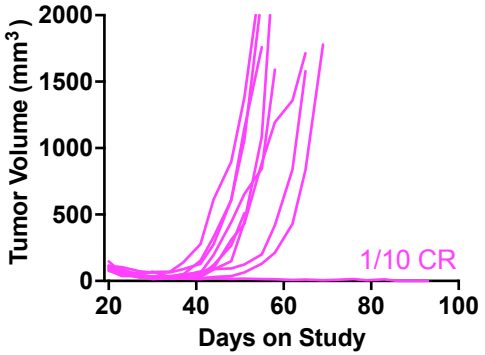
RAS(ON) Inhibitor Doublet Sensitizes Immune-Refractory NSCLC Model to Anti-PD-1

e3LL (NSCLC, *KRAS*$^{G12C/G12C}$, *NRAS*^{KO})

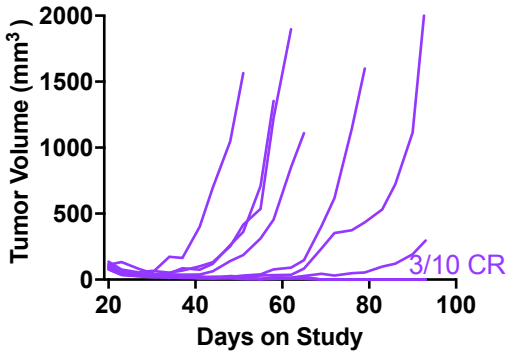
Anti-PD-1



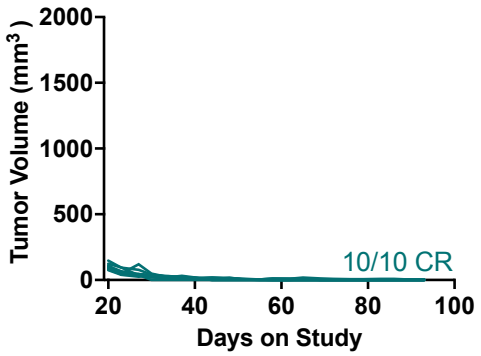
RMC-6291 + Anti-PD-1

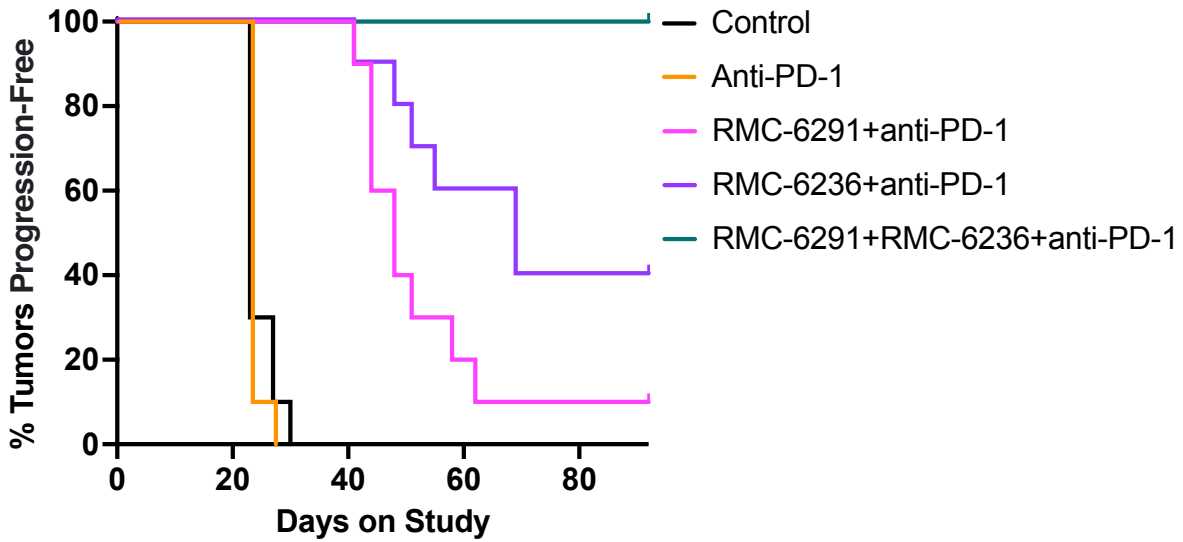


RMC-6236 + Anti-PD-1



RMC-6291 + RMC-6236 + Anti-PD-1





CR-complete regressions defined as at least three consecutive measurements at <30 mm^3; RMC-6236 (25 mg/kg PO QD), RMC-6291 (30 mg/kg, PO QD); anti-PD-1 clone RMP1-14 CP151 (10 mg/kg IP BIW).
NSCLC, non-small cell lung cancer.

Exploration of Safety of RMC-6291 200 mg BID + Pembrolizumab in Previously Treated Patients with RAS G12C Solid Tumors

Baseline Characteristics	N=15
Age, median (range), years	61 (44-80)
Male, n (%)	11 (73%)
ECOG PS 1, n (%)	7 (47%)
Number of prior anti-cancer therapies, median (range)	2 (1, 4)
Previously treated with immune checkpoint inhibitor	11 (73%)
Previously treated with KRAS(OFF) G12C inhibitor	5 (33%)
Brain metastasis at baseline	4 (27%)
Tumor Type	
NSCLC	13 (87%)
CRC	2 (13%)

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; CRC, colorectal cancer.

Data cutoff: Oct 28, 2024.

Initial Data Support Combinability of RMC-6291 200 mg BID and Pembrolizumab 200 mg Q3W

(N=15)					
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4/5**	**Any Grade**
Any TRAEs, n (%)	6 (40%)	1 (7%)	0 (0%)	0 (0%)	7 (47%)
Pruritus	1 (6%)	1 (7%)	0 (0%)	0 (0%)	2 (13%)
Rash	2 (13%)	0 (0%)	0 (0%)	0 (0%)	2 (13%)
ALT increased	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
AST increased	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Diarrhea	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Erythema	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Fatigue	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Hot flush	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Lymphocyte count decreased	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Nausea	1 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Other select TRAEs, n (%)					
Electrocardiogram QT prolonged	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- Median duration on treatment at time of data cutoff was 1.8 months
- 7 (47%) of patients have remained on treatment for ≥60 days
- No TRAEs leading to treatment discontinuation, dose reduction or dose interruption at this dose level
- Mean dose intensity of RMC-6291 was 98%

BID, twice daily; Q3W, once every three weeks; TRAE, treatment-related adverse event; ALT, alanine transaminase; AST, aspartate transferase.

Data cutoff: Oct 28, 2024.

Combination of RMC-6291 + Pembrolizumab in Patients with NSCLC Appears to be Generally Well Tolerated

- Encouraging initial safety data from combination of RMC-6291 + pembrolizumab
- Encouraging pairwise combinations of RMC-6291 + RMC-6236, RMC-6236 + pembrolizumab and RMC-6291 + pembrolizumab strongly justify investigation of the RMC-6291 + RMC-6236 + pembrolizumab triplet as a potential chemotherapy-sparing option for patients with 1L NSCLC

NSCLC, non-small cell lung cancer; 1L, first line.

Conclusion

Expanding Late-Stage Development of RAS(ON) Inhibitors Driven by Continued Clinical Progress Against RAS-Addicted Cancers

3 Investigational RAS(ON) Inhibitors

- RMC-6236 (Multi-Selective)
- RMC-6291 (G12C-Selective)
- RMC-9805 (G12D-Selective)

Differentiated RAS-targeted profiles

3 Common, Challenging Tumors

- PDAC
- NSCLC
- CRC

Promising clinical activity

3 Treatment Paradigms

- Monotherapy
- Pembrolizumab Combination
- RAS(ON) Inhibitor Doublets

Oral, generally well tolerated

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PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer.

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