Preliminary Safety and Anti-Tumor Activity of RMC-6291, a First-in-Class, Tri-Complex KRAS^{G12C}(ON) Inhibitor, in Patients With or Without Prior KRAS^{G12C}(OFF) Inhibitor Treatment

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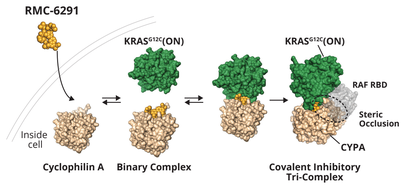
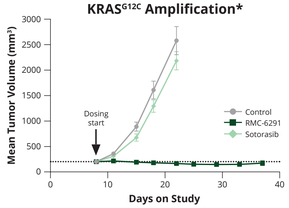
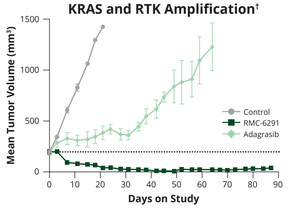
RMC-6291 Background and Mechanism of Action

- KRAS^{G12C} occurs in ~13% of non-small cell lung cancer and ~3–4% of colorectal cancer.
- Currently approved KRAS^{G12C} inhibitors target the inactive, GDP-bound or OFF state of KRAS^{G12C} and are limited by the rate, depth, and duration of response.
- RMC-6291 is a potent, covalent, orally bioavailable KRAS^{G12C}(ON) inhibitor that uses a novel tri-complex mechanism to selectively target the active, GTP-bound, or ON state of the KRAS^{G12C} protein.
- Targeting the (ON) state showed superior response rates, deeper regressions, and longer duration of response preclinically while retaining potency in the presence of RTK overexpression or KRAS amplification.



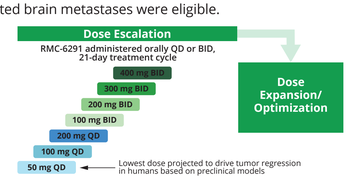




Revolution Medicines preclinical research. *Sotorasib-resistant MIA PaCa-2 CDX (PDAC, KRAS$^{G12C/G12C}$, KRAS^{amp}), RMC-6291 dosed at 100 mg/kg PO QD, sotorasib dosed at 100 mg/kg PO QD. ‡LUN055 PDX (NSCLC, KRAS$^{G12C/WT}$, ERBB3^{amp}, KRAS^{amp}), RMC-6291 dosed at 200 mg/kg PO QD, adagrasib dosed at 100 mg/kg PO QD.

Methods

- RMC-6291 is being investigated in an ongoing Phase I study (NCT05462717). The cutoff date for all clinical data was 05 October 2023.
- Eligible patients were ≥18 years old with ECOG PS 0–1 and advanced solid tumors with KRAS^{G12C} mutations, who received prior standard therapy (prior treatment with KRAS^{G12C}[OFF] inhibitors was permitted).
- Patients with stable/previously treated brain metastases were eligible.
- RMC-6291 (50–400 mg) was administered orally, once or twice daily; additional patients were enrolled at dose levels that cleared DLT evaluation.
- Objectives included assessment of safety/tolerability, pharmacokinetics, and anti-tumor activity.

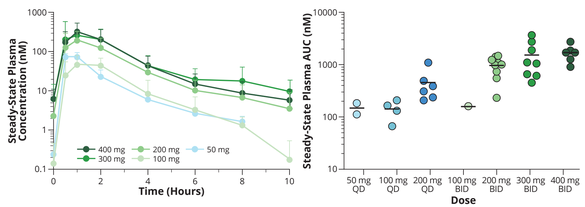


Results

Demographics and Baseline Characteristics

	NSCLC N=23	CRC N=33	Other N=7	All Histologies N=63
Age, median (range), years	65 (45–85)	54 (26–84)	66 (52–78)	64 (26–85)
Male, n (%)	13 (57)	21 (64)	2 (29)	36 (57)
ECOG PS, n (%)				
0	8 (35)	13 (39)	3 (43)	24 (38)
1	15 (65)	20 (61)	4 (57)	39 (62)
Smoking status, n (%)				
Current	5 (22)	2 (6)	0	7 (11)
Past	18 (79)	12 (36)	1 (14)	31 (49)
Never	0	19 (58)	6 (86)	25 (40)
Number of prior therapies, median (range)	3 (1–7)	3 (1–7)	4 (2–6)	3 (1–7)
Prior KRAS^{G12C} inhibitor, n (%)				
Yes	13 (57)	8 (24)	4 (57)	25 (40)
No	10 (44)	25 (76)	3 (43)	38 (60)
Time between prior KRAS^{G12C} inhibitor and RMC-6291 first dose, median (range), weeks	6 (2–86)	10 (3–31)	9 (8–128)	9 (2–128)
Prior checkpoint inhibitor within 12 weeks of RMC-6291 first dose				
Yes	9 (39)	0	1 (14)	10 (16)
No	14 (61)	32 (97)	6 (86)	52 (83)

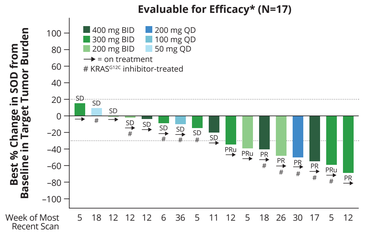
RMC-6291 Shows Dose-Dependent Increase in Exposure



*PK curves for 100 and 200 mg up to 10 hours post-dose represent combined QD and BID cohorts following the first dose on C1D15; no accumulation observed following repeat dose of RMC-6291.

- Exposure/target engagement relationship in preclinical studies predicts ≥ ~90% cross-linking of KRAS^{G12C} in human subjects receiving 100 mg BID or higher.

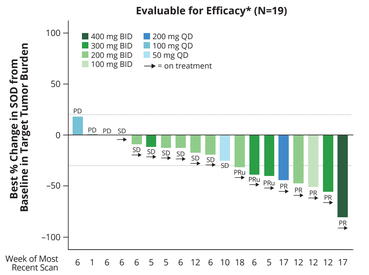
KRAS^{G12C}-Mutant NSCLC Previously Treated With, or Naïve to, a KRAS^{G12C}(OFF) Inhibitor: Best Response



Tumor response (per RECIST v1.1)		
Best overall response, n (%)	**Prior G12Ci (n=10)**	**Naïve to G12Ci (n=7)**
Partial response†	5 (50)	3 (43)
Stable disease	5 (50)	4 (57)
Progressive disease	0	0
ORR, n (%)	5 (50)	3 (43)
DCR (CR+PR+SD), n (%)	10 (100)	7 (100)

*All treated patients who received a first dose of RMC-6291 at least 8 weeks prior to data extract date; †PR includes 5 confirmed and 3 unconfirmed.

KRAS^{G12C}-Mutant CRC Naïve to KRAS^{G12C}(OFF) Inhibitor: Best Response



Tumor response (per RECIST v1.1)	
Best overall response, n (%)	**n=20†**
Partial response‡	8 (40)
Stable disease	8 (40)
Progressive disease†	4 (20)
ORR, n (%)	8 (40)
DCR (CR+PR+SD), n (%)	16 (80)

*All treated patients who received first dose of RMC-6291 at least 8 weeks prior to data extract date.

†One patient had PD due to a new lesion and target lesion measurements were not available.

‡PR includes 5 confirmed and 3 unconfirmed.

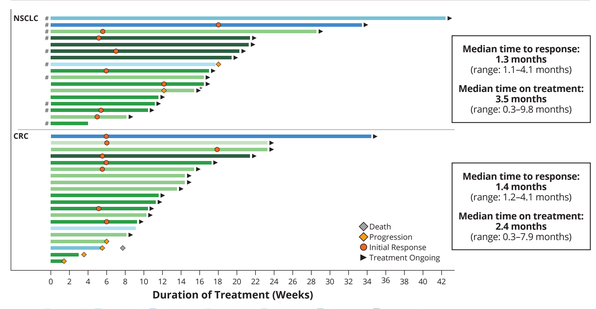
RMC-6291 was Generally Well Tolerated Across Dose Levels

Total (N=63)				
Maximum severity of treatment-related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)				
Diarrhea	10 (16)	7(11)	1 (2)	18 (29)
Nausea	14 (22)	3 (5)	0	17 (27)
ECG QT prolonged	8 (13)	1 (2)	7 (11)	16 (25)
QTcF* ≥ 501 ms	–	–	1 (2)	–
Fatigue	4 (6)	4 (6)	0	8 (13)
Vomiting	6 (10)	2 (3)	0	8 (13)
AST increased	7 (11)	0	0	7 (11)
TRAEs leading to dose reduction, n (%)	0	1 (2)	8 (13)	9 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	1 (2)	1 (2)

*QTcF refers to QT interval corrected for heart rate by Fridericia's formula.

- No treatment-related Grade 4 or 5 AEs or SAEs have been reported.
- No patients had cardiac sequalae (e.g., torsade de pointes) associated with an ECG QT prolonged event.

Duration of Treatment and Responses for KRAS^{G12C} Inhibitor-Treated or Naïve NSCLC and Naïve CRC

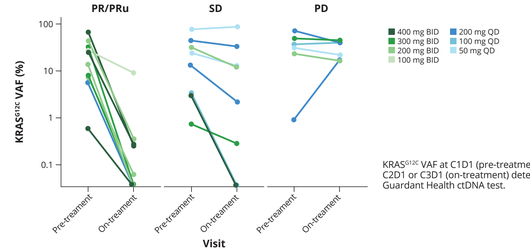


Median time to response: 1.3 months (range: 1.1–4.1 months)
Median time on treatment: 3.5 months (range: 0.3–9.8 months)

Median time to response: 1.4 months (range: 1.2–4.1 months)
Median time on treatment: 2.4 months (range: 0.3–7.9 months)

KRAS^{G12C} inhibitor-treated; *The date of treatment discontinuation due to PD was missing as of data extract date.

Reduction in ctDNA of the KRAS^{G12C} Allele Across Doses Correlates With Clinical Response



KRAS^{G12C} VAF at C1D1 (pre-treatment) to C2D1 or C3D1 (on-treatment) determined by Guardant Health ctDNA test.

Conclusions

- RMC-6291 is a potent, mutant-selective, covalent inhibitor of the active, GTP-bound or ON state of KRAS^{G12C}.
- RMC-6291 is orally bioavailable and demonstrates dose-dependent plasma PK.
- RMC-6291 is well tolerated, with manageable adverse events.
- RMC-6291 has demonstrated encouraging clinical activity in patients with KRAS^{G12C}-mutant NSCLC who were previously treated or naïve to a KRAS^{G12C}(OFF) inhibitor and in patients with KRAS^{G12C}-mutant CRC naïve to treatment with a KRAS^{G12C}(OFF) inhibitor.
- Reduction in ctDNA of the KRAS^{G12C} allele across doses correlates with clinical response.
- Dose optimization is ongoing in KRAS^{G12C}-mutant tumors.
- Preliminary safety and clinical activity data support the ongoing development of RMC-6291 as a single agent and/or in combination with RMC-6236 or immunotherapy.

Abbreviations: AE, adverse event; AST, aspartate transferase; AUC, area under the curve; BID, twice daily; C, cycle; CDX, cell-line derived xenograft; CR, complete response; CRC, colorectal cancer; ctDNA, circulating tumor DNA; CYPA, cyclophilin A; D, day; DCR, disease control rate; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; G12Ci, G12C inhibitor; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; PK, pharmacokinetic; PO, orally; PR, partial response; PRu, unconfirmed partial response; QD, once daily; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain; RECIST, Response Evaluation Criteria in Solid Tumors; RTK, receptor tyrosine kinase; SAE, serious adverse event; SD, stable disease; SOD; sum of diameters; TRAE, treatment-related adverse event; VAF, variant allele frequency; WT, wild type.

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