Preliminary Safety and Pharmacokinetic Profiles of RMC-6236, a First-in-Class, RAS-Selective, Tri-Complex RAS^{MULTI}(ON) Inhibitor in Patients with KRAS-Mutant Solid Tumors on the Phase 1 Trial RMC-6236-001

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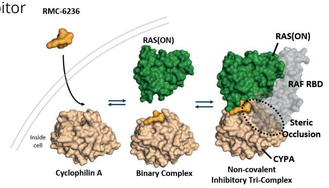
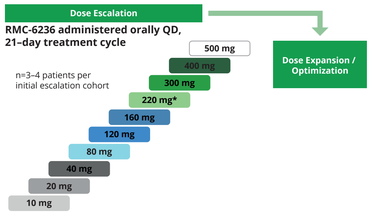
RMC-6236 Mechanism of Action

- RMC-6236 is a novel, oral, non-covalent, RAS^{MULTI}(ON) inhibitor that is selective for the active, GTP-bound or ON state of both mutant and wild-type variants of the canonical RAS isoforms.
- Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly those harboring KRAS^{G12X} mutations.



Methods

- RMC-6236 is being investigated in an ongoing Phase I study (NCT05379985). The data extract date for clinical data was 11 September 2023.
- Eligible patients were ≥18 years old with ECOG PS 0–1 and advanced solid tumors with KRAS^{G12X} mutations (currently excluding KRAS^{G12C}), who had received prior standard therapy appropriate for tumor type and stage, and had no active brain metastases.
- Patients received RMC-6236 orally QD (10–400 mg) on a 21-day treatment cycle.
- Additional patients with PDAC or NSCLC were enrolled at dose levels that cleared DLT evaluation (backfill enrollment/dose optimization).
- Intra-patient dose escalation to a dose level that had cleared DLT evaluation was permitted.
- Objectives included assessment of safety/tolerability, pharmacokinetics, and anti-tumor activity.



Dose Level (mg)	Number of Patients Treated[‡]
10	3
20	13[‡]
40	9
80	10
120	19
160	20
200/220*	27
300	26
400	4
TOTAL	**131**

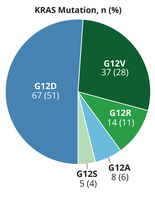
*220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization; [‡]Additional patients enrolled for backfill and/or dose optimization; [§]Includes patients treated in the preliminary food effect cohort (n=8).

Results

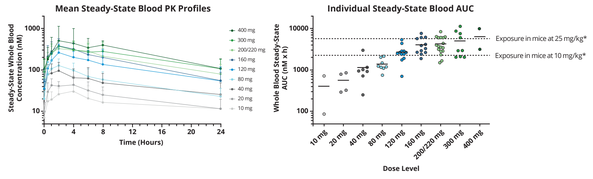
Demographics and Baseline Characteristics

	Total (N=131)
Age, median (range), years	64 (30–86)
Male, n (%)	69 (53)
Tumor type, n (%)	
PDAC	69 (53)
NSCLC	47 (36)
CRC	10 (7)
Other*	5 (4)
ECOG PS, n (%)	
0	40 (31)
1	91 (69)
Number of prior anti-cancer therapies, median (range)	2 (1–7)

*Includes appendiceal cancer, carcinoma of ampulla, cholangiocarcinoma, and ovarian cancer.



Exposure Showed Dose-Dependent Increases and Achieved Levels Predicted to Induce Tumor Regressions



*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 is Cycle 1 Day 15 AUC_{last}. Each circle represents an individual patient AUC. Horizontal bars represent mean AUC for each dose level (10 mg: n=2; 20 mg: n=4; 40 mg: n=7; 80 mg: n=8; 120 mg: n=12; 160 mg: n=12, 200 mg: n=13; 220 mg: n=4; 300 mg: n=9; 400 mg: n=2).

- Dose-dependent increases in exposure with minimal accumulation were observed after repeat daily dosing.
- Dose levels ≥80 mg achieved exposures that induced tumor regressions in human xenograft models with KRAS^{G12X} mutations in mice.[1]
  - 10 mg/kg QD induces tumor regressions in sensitive models.
  - 25 mg/kg QD induces tumor regressions in the majority of models.

RMC-6236 Was Generally Well Tolerated Across Dose Levels

- Median DOT at the time of data extraction was 2.27 months (range: 0.2–14).
- One Grade 4 TRAE occurred in a patient with PDAC treated at 80 mg who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment (TRAE leading to treatment discontinuation).
- No fatal TRAEs were observed. Two patients discontinued study treatment due to death: one patient with PDAC (120 mg) died due to PD; one patient with NSCLC (200 mg) died due to an unknown cause reported as unrelated to RMC-6236.

	Total (N=131)				
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash*	57 (44)	29 (22)	6 (5)	0	92 (70)
Nausea	41 (31)	14 (11)	0	0	55 (42)
Diarrhea	32 (24)	9 (7)	1(1)	0	42 (32)
Vomiting	27 (21)	9 (7)	0	0	36 (28)
Stomatitis	10 (8)	9 (7)	2 (2)	0	21 (16)
Fatigue	12 (9)	4 (3)	0	0	16 (12)
Other select TRAEs, n (%)					
ALT elevation	6 (5)	1 (1)	1 (1)[‡]	0	8 (6)
AST elevation	6 (5)	0	1 (1)[‡]	0	7 (5)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction[†], n (%)	0	9 (7)	2 (2)	0	11 (8)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)	1 (1)

*Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema, rash erythematous; multiple types of rash may have occurred in the same patient; [†]The most common TRAE leading to dose reduction was rash (acneiform or maculopapular); there were no reductions at doses ≤80 mg; [‡]Post-data extraction, the Grade 3 ALT and AST elevations were associated with biliary obstruction and reported as unrelated to RMC-6236.

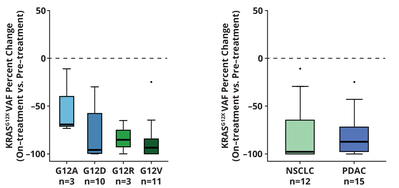
Rashes Observed Were Generally Mild and Manageable with Standard Supportive Care

	20 mg* (n=13)	40 mg* (n=9)	80 mg (n=10)	120 mg (n=19)	160 mg (n=20)	200 / 220 mg (n=27)	300 mg (n=26)	400 mg (n=4)
Rash[†], n (%)	4 (31)	6 (67)	7 (70)	15 (79)	20 (100)	21 (78)	15 (58)	4 (100)
Dermatitis acneiform	3 (23)	4 (44)	5 (50)	11 (58)	19 (95)	16 (59)	10 (39)	4 (100)
Rash maculopapular	1 (8)	1 (11)	3 (30)	4 (21)	1 (5)	5 (19)	5 (19)	0
Rash by maximum Grade, n (%)								
1	3 (23)	4 (44)	5 (50)	12 (63)	11 (55)	11 (41)	10 (39)	1 (25)
2	1 (8)	2 (22)	2 (20)	2 (11)	8 (40)	7 (26)	5 (19)	2 (50)
3	0	0	0	1 (5)	1 (5)	3 (11)	0	1 (25)
Time to first event in days, median (range)	112 (42–225)	54 (17–136)	15 (8–22)	11 (1–57)	13 (3–22)	9 (2–22)	11 (6–16)	7 (5–11)
Required dose reduction, n (%)	0	0	0	2 (11)	1 (5)	3 (11)	0	1 (25)

No adverse events of rash were reported at 10 mg; *Includes onset after intra-patient dose escalation to 80 mg: 20 mg (n=3); onset 13–31 days at 80 mg; 40 mg (n=3); onset 5–31 days at 80 mg; [†]Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema, rash erythematous; multiple types of rash may have occurred in the same patient.

- Rash generally occurred in Cycles 1 or 2, and the presentation of acneiform or maculopapular rash was consistent with on-target activity of RAS pathway inhibitors.

Marked Reduction in KRAS Variant Allele Frequency in ctDNA Across Multiple Tumor Types Indicative of Anti-Tumor Activity

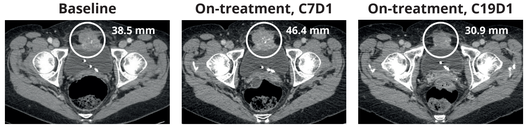


- Patients with NSCLC or PDAC were dosed at 20–300 mg.
- Overall, 27/54 patients (50%) were evaluable for change in mutant KRAS VAF on-treatment.

Lines inside box plots indicate median values; whiskers indicate largest or smallest values (at most ± 1.5x the interquartile range). Dots indicate data points >1.5x the interquartile range; KRAS^{G12X} VAF at Cycle 1 Day 1 (pre-treatment) to Cycle 2 Day 1 or Cycle 3 Day 1 (on-treatment), determined by Guardant Health ctDNA test.

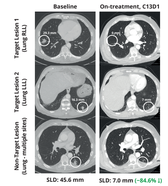
Case Report: Patient with KRAS^{G12V} Ovarian Cancer

- A 59-year-old woman with stage III ovarian cancer diagnosed in 2004, with metastatic disease to the liver and peritoneum at study entry.
- The patient received prior therapy with carboplatin/paclitaxel. Best response was SD with PD in May 2022.
- She was started at 10 mg QD RMD-6236 and experienced a 60% decrease in KRAS^{G12V} VAF at C2D1. There was intra-patient dose escalation at two timepoints: 40 mg QD at C7 and 80 mg QD at C10. CA-125 tumor marker began to normalize after C7. Confirmed PR at C13, ongoing. Treatment ongoing for >14 months.



Case Report: Patient with KRAS^{G12D} PDAC

- A 76-year-old man diagnosed with Stage II PDAC in 2017 and metastatic disease to the lung in January 2022.
- Most recent prior therapy was gemcitabine/nab-paclitaxel/investigational agent, with SD as best response and PD in Aug 2022.
- The patient was started at 80 mg QD RMC-6236 (baseline ctDNA not detectable), with confirmed PR at C5; ongoing. Treatment ongoing for >10 months.



Conclusions

- The RAS^{MULTI}(ON) inhibitor RMC-6236 demonstrated a well-tolerated safety profile across dose levels, and in patients with diverse tumor types.
- RMC-6236 demonstrated dose-dependent pharmacokinetics compatible with once-daily dosing, and achieved exposures predicted to induce tumor regressions.
- Reductions in variant allele frequency by ctDNA were observed for multiple KRAS-mutated alleles in multiple tumor types, indicative of anti-tumor activity by RMC-6236.
- Radiographic partial responses per RECIST v1.1 were also observed across several tumor types and KRAS genotypes at well-tolerated doses, representing preliminary evidence of broad anti-tumor activity.
- The dose escalation and dose optimization portion of the study is ongoing, and includes plans for expansion into additional monotherapy solid tumor cohorts.

Reference: 1. Singh M, et al. Presentation at American Association for Cancer Research Annual Meeting, 8–13 April 2022, New Orleans, USA; abstract #3597.

Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; AUC, area under the curve; CA-125, cancer antigen 125; C, cycle; CMQ, customized MedDRA Query; CRC, colorectal cancer; CYPA, cyclophilin A; D, day; DLT, dose-limiting toxicity; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; LLL, left lower lobe; NSCLC, non-small cell lung cancer; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; QD, once daily; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain; RECIST, Response Evaluation Criteria in Solid Tumors; RLL, right lower lobe; SD, stable disease; SLD, sum of longest diameter of the target lesions; TRAE, treatment-related adverse event; VAF, variant allele frequency.

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