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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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Leadership role with NEXT Oncology-Virginia and holds stock in Eli Lilly.

Honoraria from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol Myers Squibb, and Bayer.

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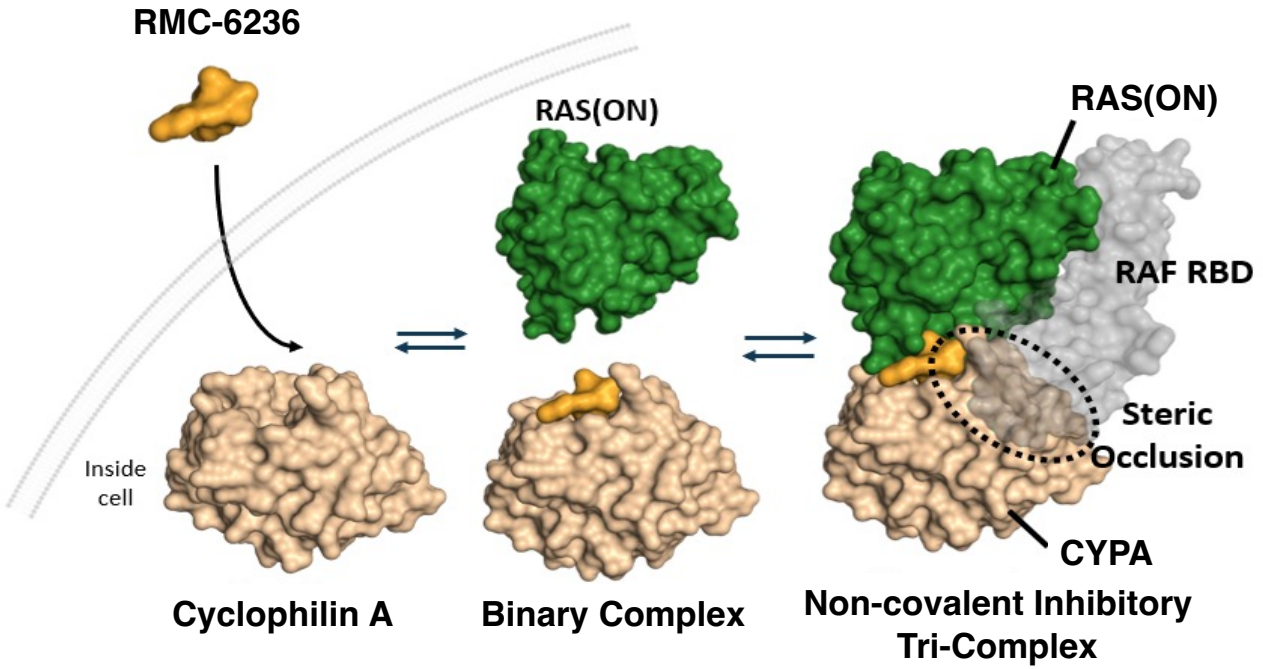
RMC-6236 Is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

- RMC-6236 is a novel, oral, non-covalent, RAS^{MULTI}(ON) inhibitor 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



KRAS^{G12X} defined as mutation at codon 12, which encodes glycine (G), to X where X = A, D, R, S, or V.
CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma virus; Mut, mutated; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

RMC-6236-001 Phase 1 Study Design

Key Eligibility Criteria

- Advanced solid tumors with KRAS^{G12X} mutations (currently excluding KRAS^{G12C})
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

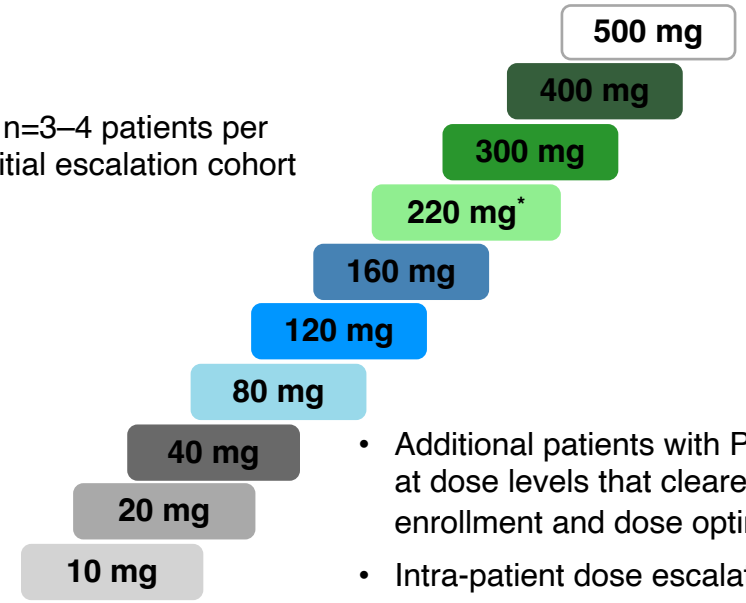
Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD, 21-day treatment cycle

n=3–4 patients per initial escalation cohort



- Additional patients with PDAC or NSCLC were enrolled at dose levels that cleared DLT evaluation (backfill enrollment and dose optimization)
- Intra-patient dose escalation to a dose level that has cleared DLT evaluation permitted

Dose Expansion / Optimization

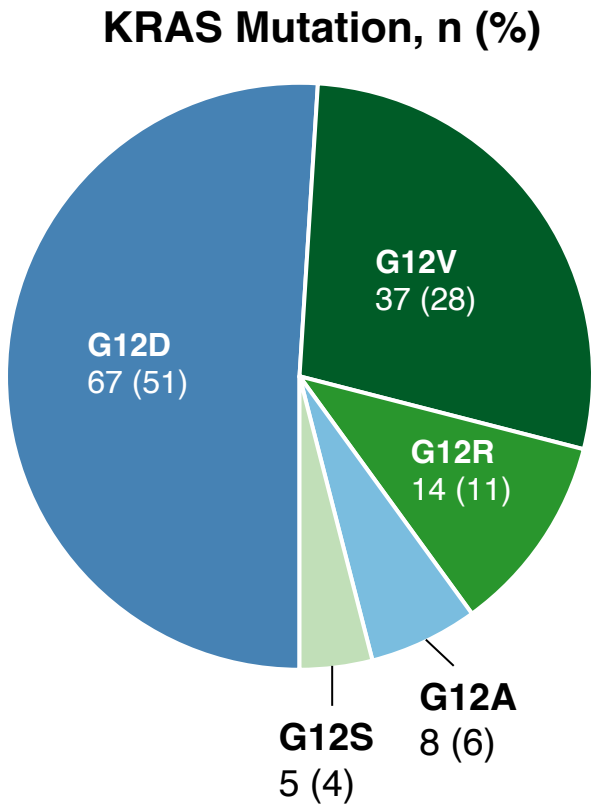
Dose Level (mg)	# Patients Treated†
10	3
20	13‡
40	9
80	10
120	19
160	20
200/220	27
300	26
400	4
TOTAL	131

*220 mg cleared DLT evaluation and dose of 200 mg was selected for further expansion/optimization; †Additional patients enrolled for backfill and/or dose optimization; ‡Includes patients treated in preliminary food effect cohort (n=8). KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X= A, D, R, S, or V; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily.

Data Extracted 11 Sep 2023.

Demographics and Baseline Characteristics

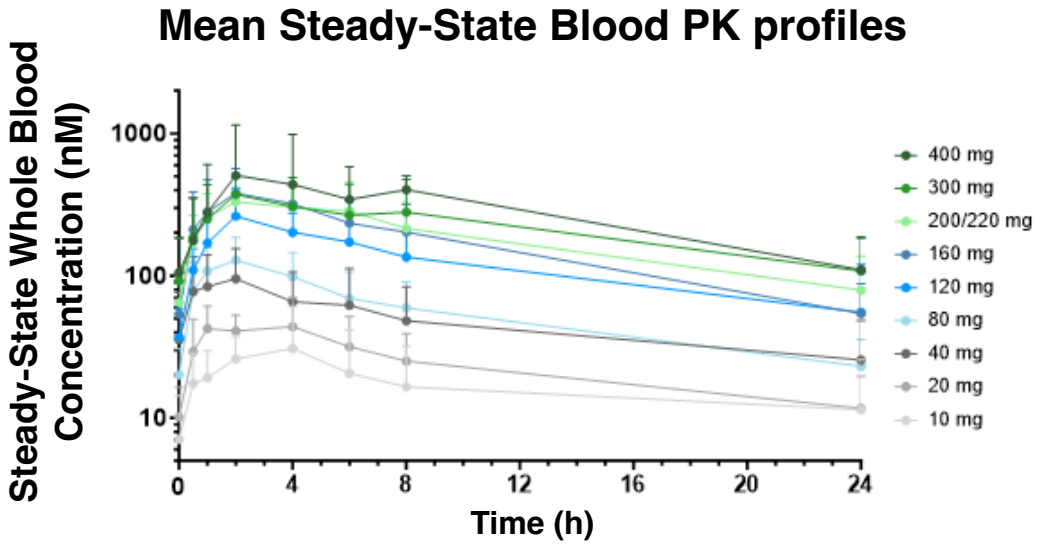
	Total N=131
Age, median (range), years	64 (30–86)
Male, n (%)	69 (53)
Tumor type, n (%)	
PDAC	69 (53)
NSCLC	47 (36)
CRC	10 (7)
Other*	5 (4)
ECOG PS, n (%)	
0	40 (31)
1	91 (69)
Number of prior anti-cancer therapies, median (range)	2 (1–7)

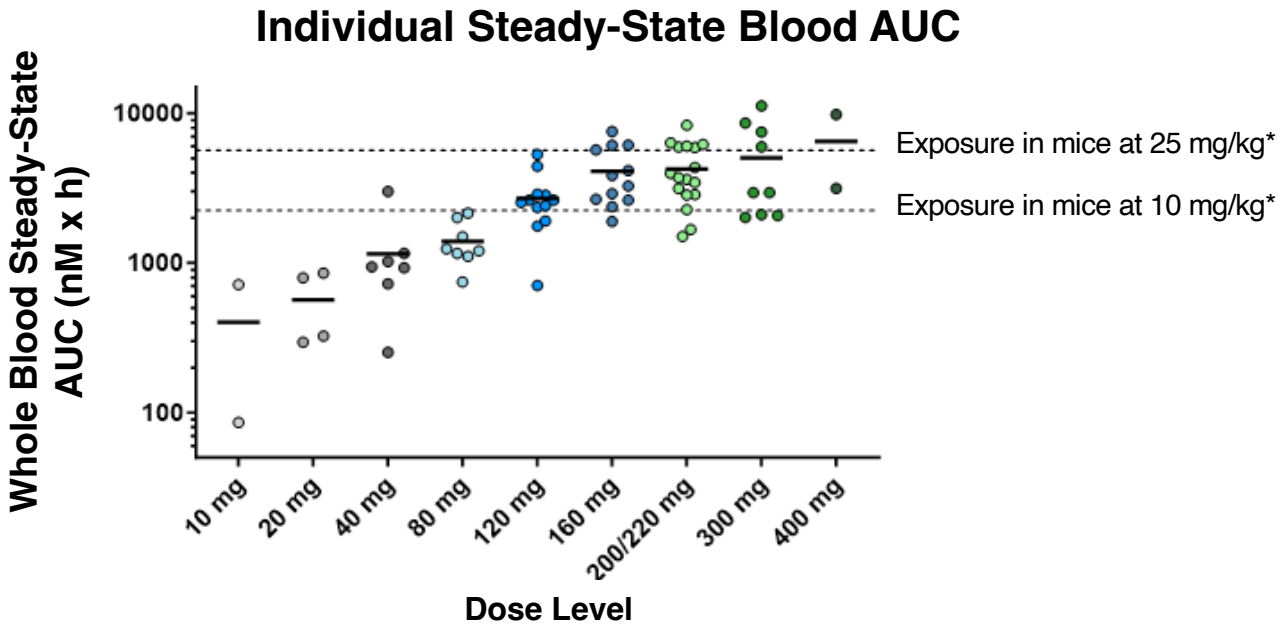


*Includes appendiceal cancer, carcinoma of ampulla, cholangiocarcinoma, and ovarian cancer.
CRC, colorectal cancer.

Data Extracted 11 Sep 2023.

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





- 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

*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).

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

AUC, area under the curve; PK, pharmacokinetics.

RMC-6236 Was Generally Well Tolerated Across Dose Levels

	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)

- Median duration of treatment 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 unknown cause reported as unrelated to RMC-6236.

‡ Post-data extraction, the Grade 3 ALT and AST elevations were associated with biliary obstruction and reported as unrelated to RMC-6236.

*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. AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; PD, progressive disease; TRAEs, treatment-related adverse events.

Rashes Observed Were Generally Mild and Manageable with Standard Supportive Care

Summary of Treatment-Related Rash by Dose Level

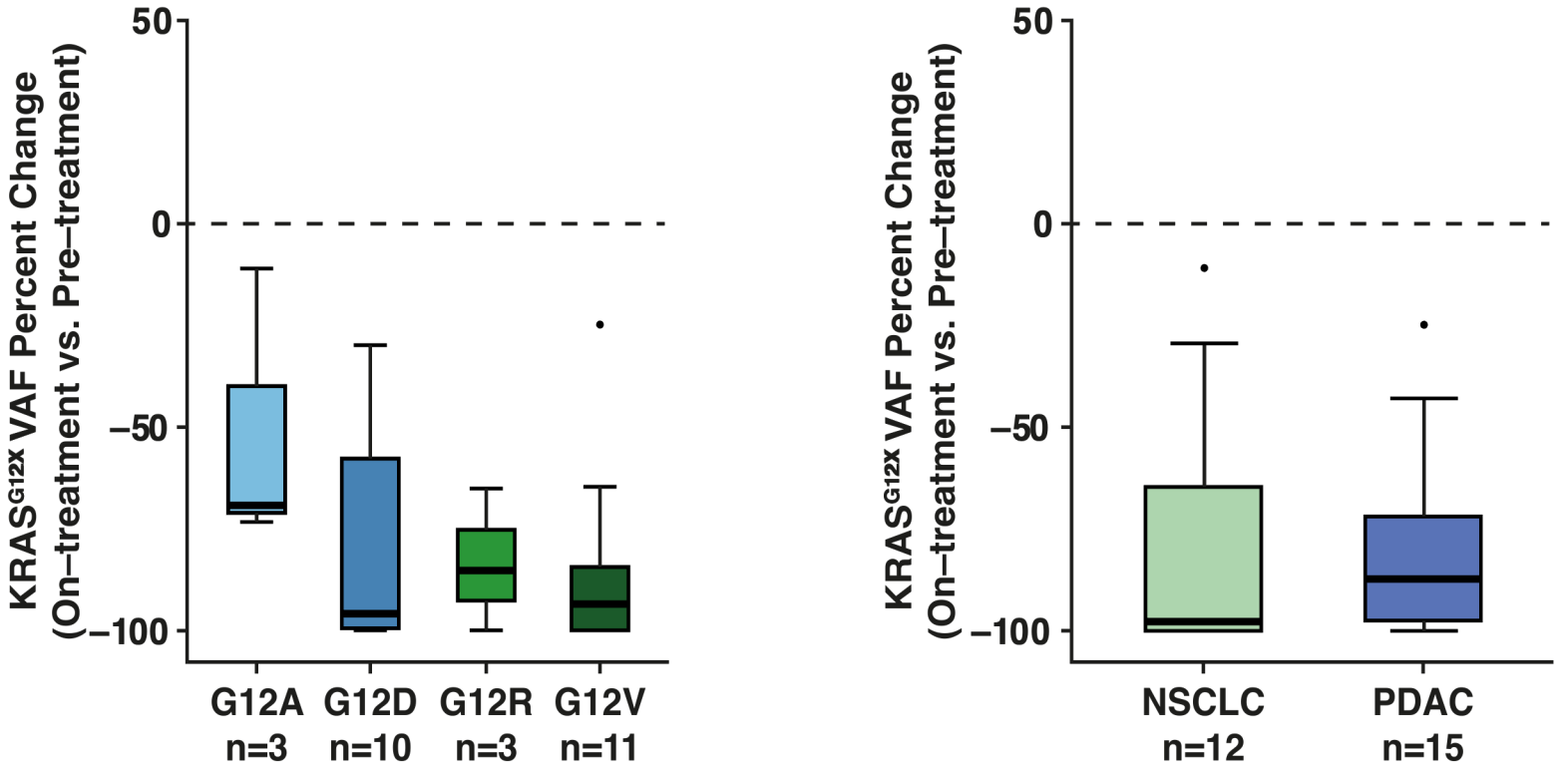
	20 mg* (n=13)	40 mg* (n=9)	80 mg (n=10)	120 mg (n=19)	160 mg (n=20)	200/220 mg (n=27)	300 mg (n=26)	400 mg (n=4)
Rash†, n (%)	4 (31)	6 (67)	7 (70)	15 (79)	20 (100)	21 (78)	15 (58)	4 (100)
Dermatitis acneiform	3 (23)	4 (44)	5 (50)	11 (58)	19 (95)	16 (59)	10 (39)	4 (100)
Rash maculopapular	1 (8)	1 (11)	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)

- The presentation of acneiform or maculopapular rash is consistent with on-target activity of RAS pathway inhibitors.
- Rash generally occurred in Cycle 1 or 2 and was primarily Grade 1 or 2 in severity.
- Supportive care interventions included topical antibiotics, topical steroids, and/or oral antibiotics.

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.

Data Extracted 11 Sep 2023.

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 value (at most ±1.5x the interquartile range). Circles indicate data points >1.5 times 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. ctDNA, circulating tumor DNA; VAF, variant allele frequency.

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

Demographics and Baseline Characteristics

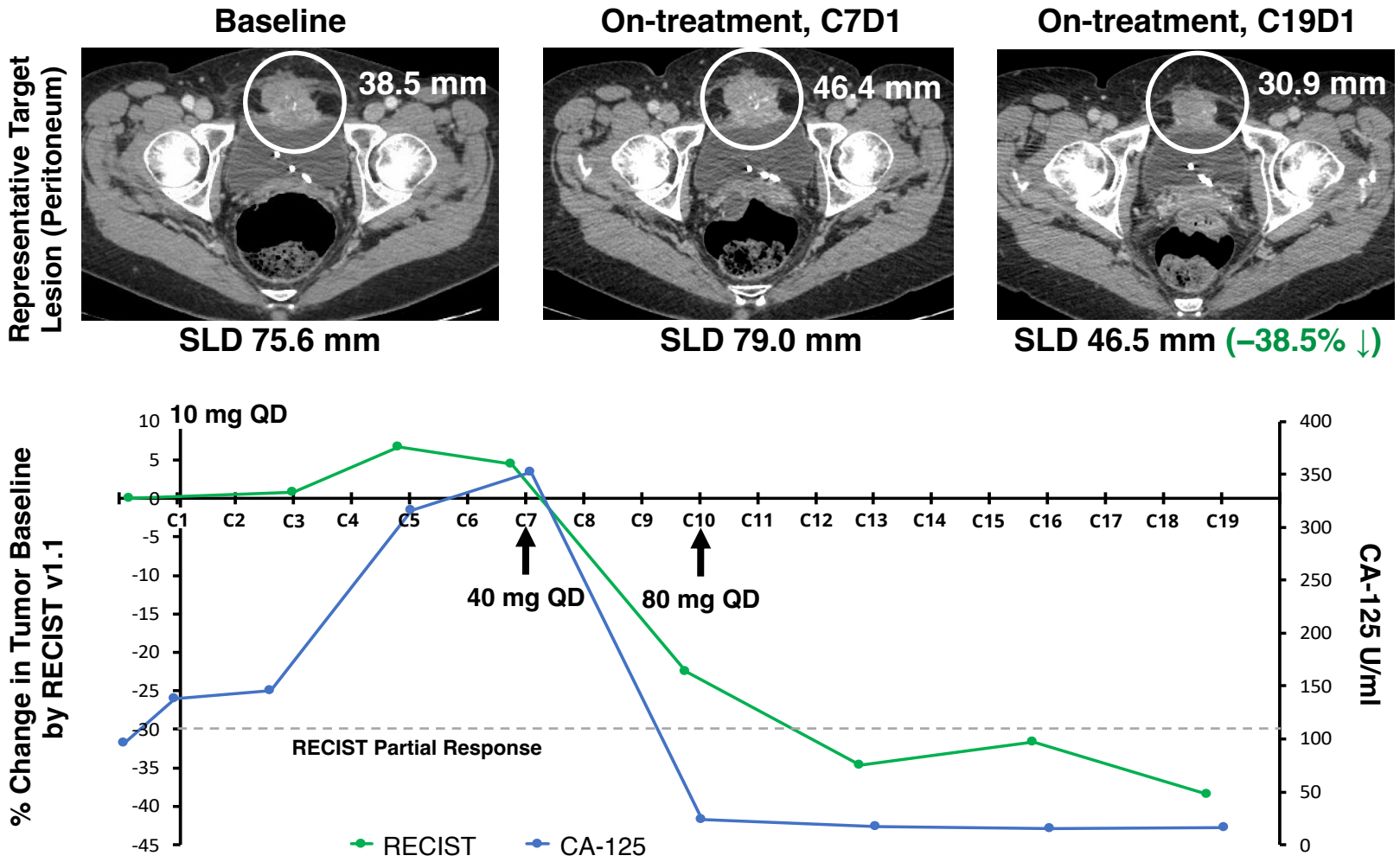
- 59-year-old woman
- Diagnosed with Stage III ovarian cancer in 2004
- Metastatic disease to liver and peritoneum at time of study entry

Treatment History

- **Prior surgery:** ovarian resection (2004)
- **Prior therapy:** carboplatin/paclitaxel
  - Sep 2021–Jan 2022
  - Best response SD with PD in May 2022

RMC-6236 Treatment Course

- Started at 10 mg QD
- 60% ↓ in KRAS^{G12V} VAF (ctDNA) at C2D1
- Intra-patient dose escalation:
  - 40 mg QD at C7
  - 80 mg QD at C10
- Confirmed PR at C13; ongoing
- Treatment ongoing for >14 months



C, cycle; D, day; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SLD, sum of longest diameter of the target lesions.

Case Report: Patient with KRAS^{G12D} PDAC

Demographics and Baseline Characteristics

- 76-year-old man
- Diagnosed with Stage II PDAC in November 2017
- Metastatic disease to lung in January 2022

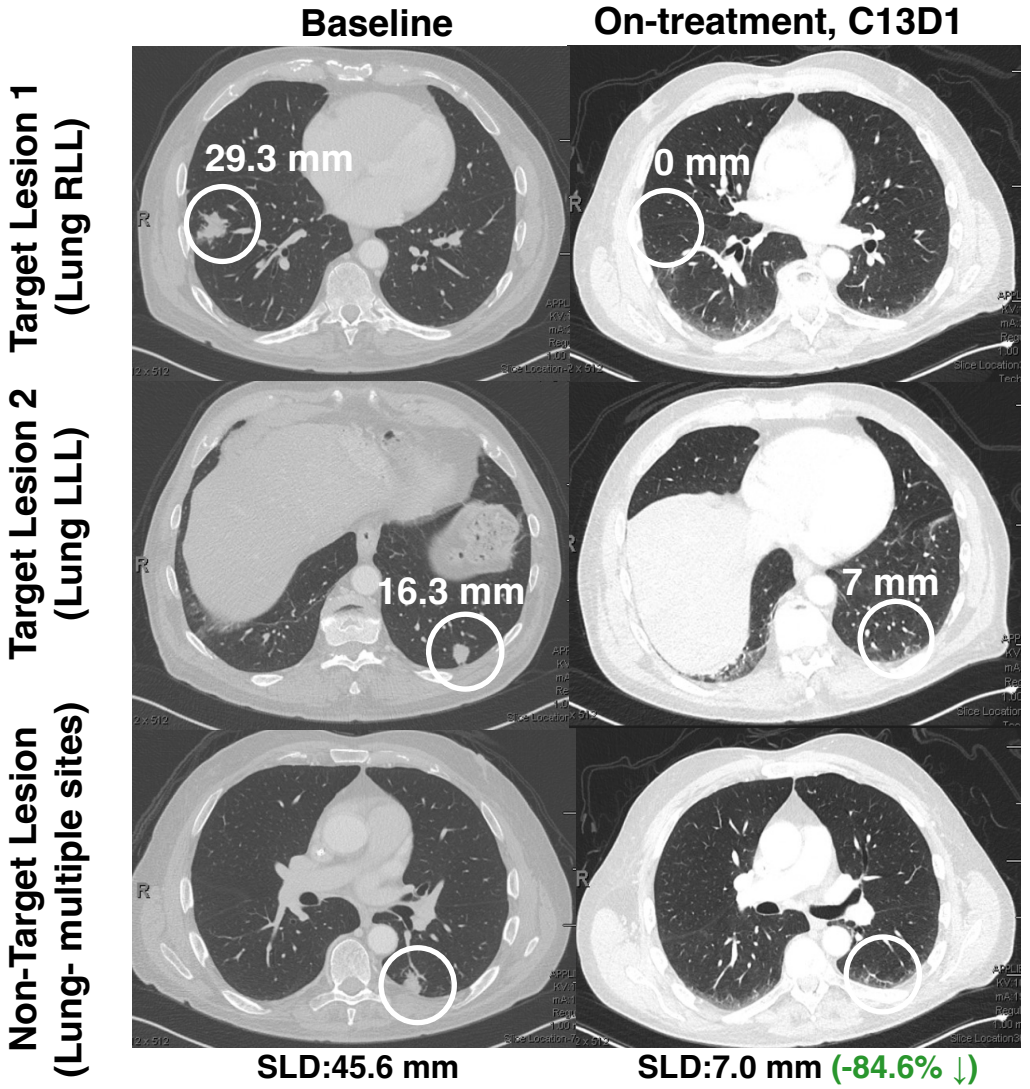
Treatment History

- **Prior surgery:** distal pancreatectomy (March 2018)
- **Prior therapies:**
  - Gemcitabine/nab-paclitaxel (neoadjuvant)
    - Nov 2017–Feb 2018
  - Gemcitabine/capecitabine (adjuvant)
    - Apr 2018–Jun 2018
  - Gemcitabine/nab-paclitaxel/investigational agent
    - Mar 2022–Oct 2022
    - Best response SD with PD Aug 2022

RMC-6236 Treatment Course

- Started at 80 mg QD
- Baseline ctDNA not detectable
- Confirmed PR at C5; ongoing
- Treatment ongoing for >10 months

LLL, left lower lobe; RLL, right lower lobe.



Data Extracted 11 Sep 2023.

Case Report: Patient with KRAS^{G12D} NSCLC

Demographics and Baseline Characteristics

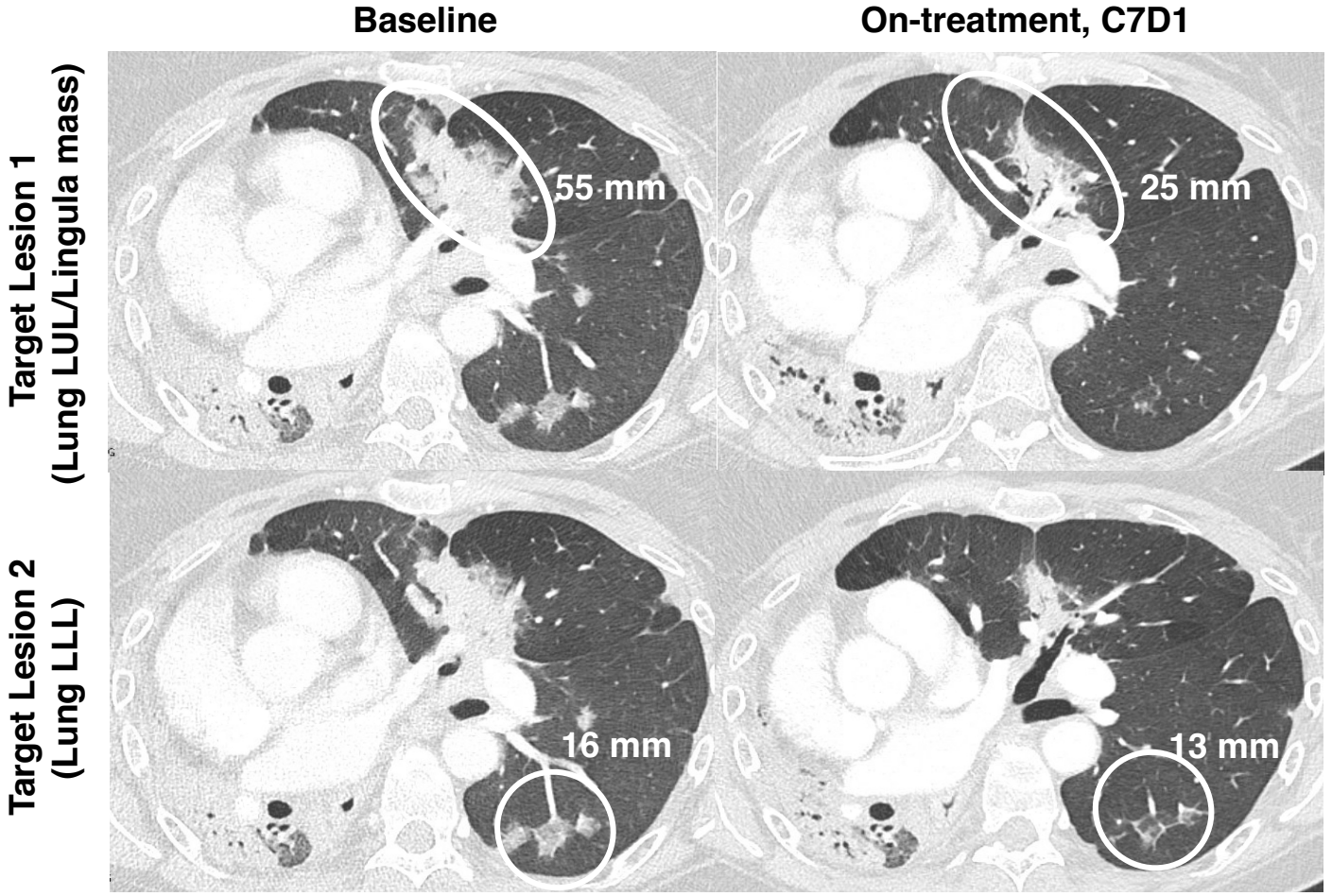
- 54-year-old woman
- Diagnosed with Stage IV NSCLC in Jan 2020
- Never smoked

Treatment History

- **Prior therapies:**
  - Carboplatin/pemetrexed/pembrolizumab
    - Aug 2020–Feb 2021
  - Docetaxel
    - Feb 2021–Oct 2021
  - Pembrolizumab/investigational agent
    - Sep 2022–Oct 2022
    - PD Nov 2022

RMC-6236 Treatment Course

- Started at 80 mg QD
- Baseline ctDNA not detectable
- Confirmed PR at C5; ongoing



LUL, left upper lobe.

Data Extracted 11 Sep 2023.

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.
- Additional clinical activity data in patients with KRAS^{G12X}-mutant PDAC and NSCLC will be presented at ESMO Congress 2023.

Acknowledgments

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