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Preliminary Clinical Activity of RMC-6236, a First-in-Class, RAS-Selective, Tri-Complex RAS^{MULTI}(ON) Inhibitor in Patients with KRAS-Mutant Pancreatic Ductal Adenocarcinoma (PDAC) and Non-Small Cell Lung Cancer (NSCLC)

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Declaration of Interests

Kathryn C. Arbour

Consulting: Amgen, Novartis, G1 Therapeutics, AstraZeneca, and Sanofi-Genzyme

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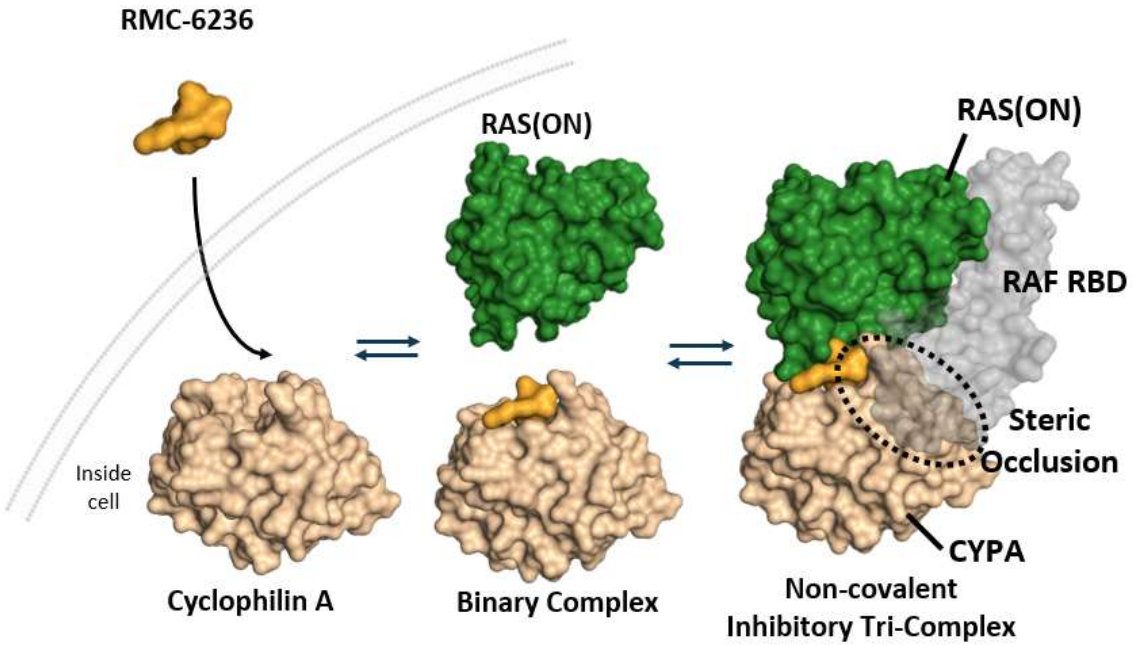
RMC-6236 is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

- RMC-6236 is a novel, oral, non-covalent RAS^{MULTI}(ON) inhibitor 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 PDAC and NSCLC 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 viral oncogene homolog; Mut, mutant; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

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RMC-6236-001 Phase 1 Study Design

Key Eligibility Criteria

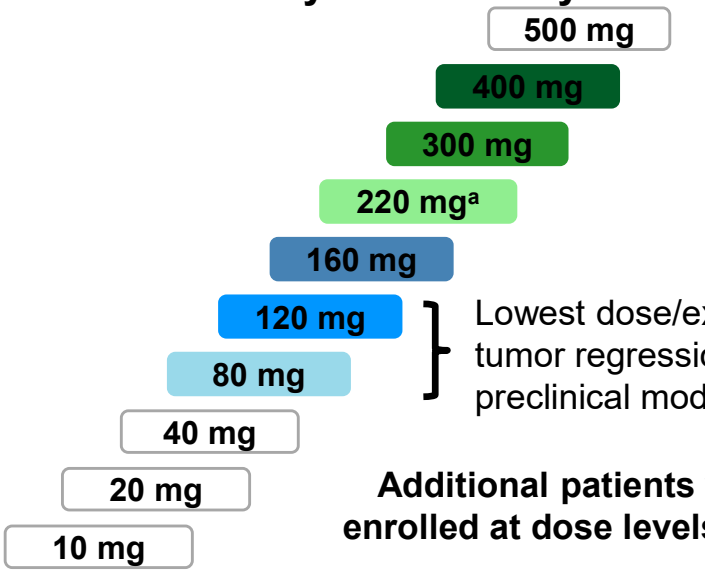
- Advanced solid tumors with KRAS^{G12X} mutations (currently excluding KRAS^{G12C})
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability[1]
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

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



Lowest dose/exposure range projected to drive tumor regressions in humans based on preclinical models

Dose Expansion / Optimization

Additional patients with NSCLC or PDAC were enrolled at dose levels that cleared DLT evaluation

[a]220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization.
KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.
1. Spira A, et al. Presentation at AACR-NCI-EORTC International Conference On Molecular Targets And Cancer Therapeutics; abstract #33378.
DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily.

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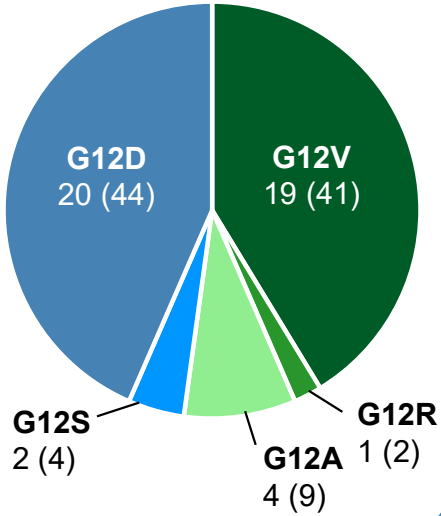
Patient Demographics and Baseline Characteristics

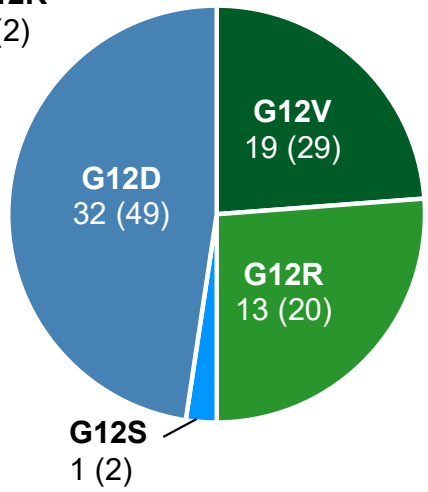
	NSCLC[a] N = 46	PDAC[a] N = 65
Age, median (range), years	65 (31–83)	64 (30–86)
Female, n (%)	25 (54)	31 (48)
ECOG PS, n (%)		
0	11 (24)	20 (31)
1	35 (76)	45 (69)
Smoking status, n (%)		
Current	2 (4)	2 (3)
Past	28 (61)	14 (22)
Never	16 (35)	49 (75)
Number of prior anti-cancer therapies, median (range)	2 (1–6)	3 (1–7)
Select type of prior anti-cancer therapy/regimens, n (%)		
Checkpoint inhibitor[b]	44 (96)	–
Platinum-based chemotherapy	46 (100)	–
FOLFIRINOX	–	45 (69)
Gemcitabine + nab-paclitaxel	–	49 (75)

[a]Includes patients with NSCLC or PDAC treated at 80 mg or above.
[b]Two patients enrolled in the expansion/optimization cohort received platinum-based chemotherapy and targeted therapy (checkpoint inhibitor not required).



NSCLC
KRAS mutation
n, (%)

PDAC
KRAS mutation
n, (%)



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Summary of Treatment-Related Adverse Events

Patients with NSCLC and PDAC Treated at ≥80 mg QD (N = 111)					
Maximum severity of treatment-related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash[a]	58 (52)	25 (23)	7 (6)	0	90 (81)
Nausea	40 (36)	11 (10)	0	0	51 (46)
Diarrhea	28 (25)	14 (13)	1 (1)	0	43 (39)
Vomiting	30 (27)	7 (6)	0	0	37 (33)
Stomatitis	13 (12)	9 (8)	2 (2)	0	24 (22)
Fatigue	11 (10)	6 (5)	0	0	17 (15)
Other select TRAEs, n (%)					
ALT elevation	8 (7)	1 (1)	0	0	9 (8)
AST elevation	8 (7)	0	0	0	8 (7)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction[b], n (%)	0	10 (9)	5 (5)[c]	0	15 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)[d]	1 (1)

- Median time on treatment was 2.1 months (range: 0.2–10.9).
- No fatal TRAEs were observed.

[a]Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, erythema, rash erythematous; multiple types of rash may have occurred in the same patient; [b]The most common reason for dose reduction was rash; [c]Grade 3 TRAEs leading to reduction were rash (n = 4), including one patient with a dose reduction due to rash and decreased appetite, and stomatitis (n = 1); [d]One Grade 4 TRAE occurred in a patient with PDAC at the 80 mg dose level who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment.
ALT, alanine transaminase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

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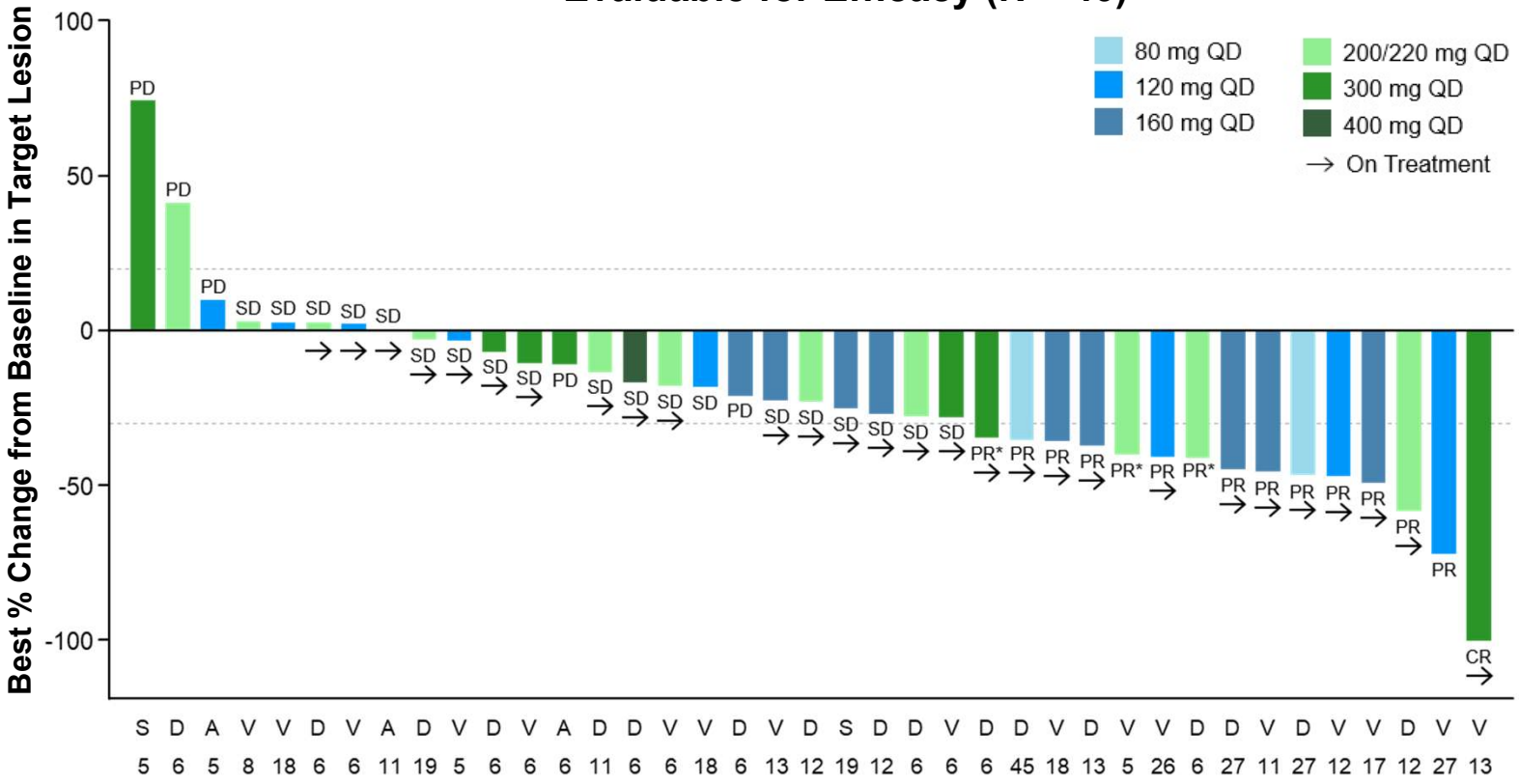
KRAS^{G12X} NSCLC: Best Response

Evaluable for Efficacy (N = 40)[a]



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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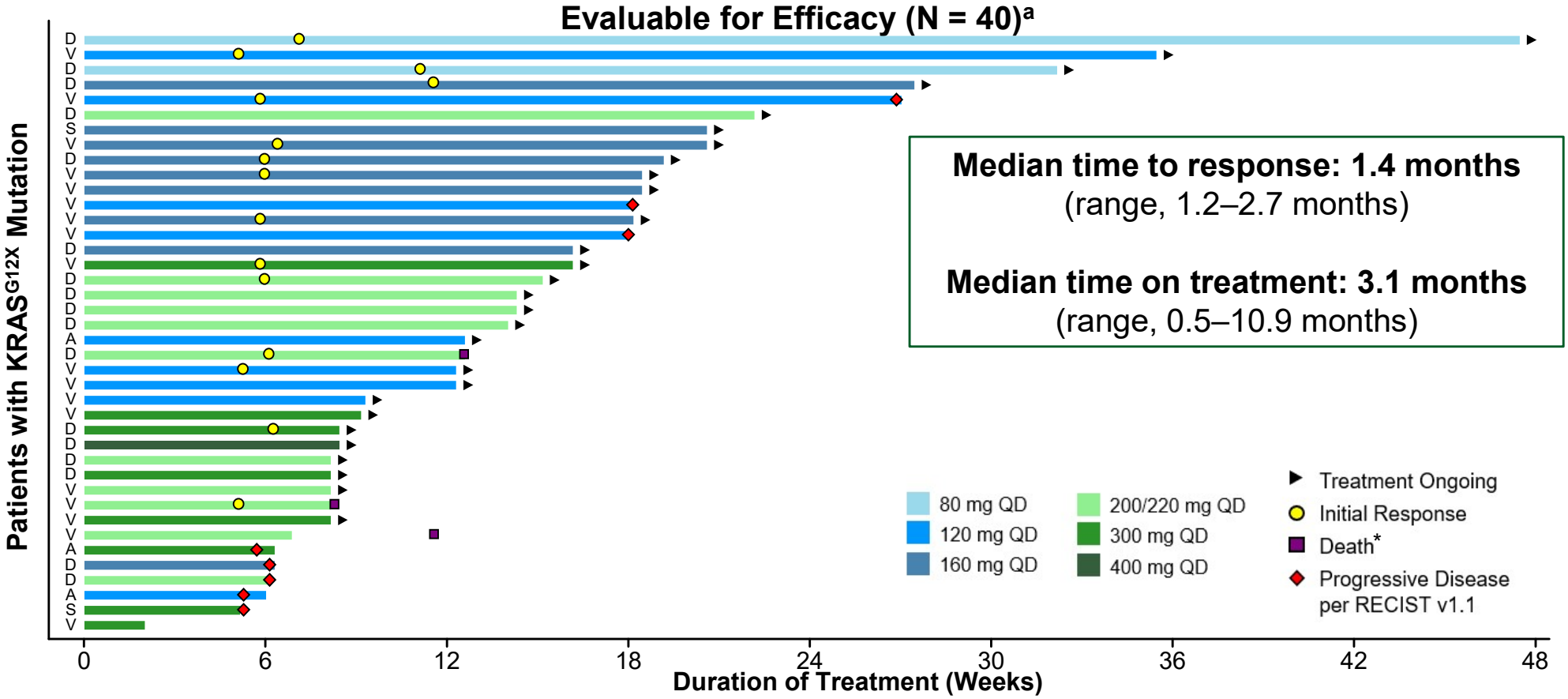
KRAS^{G12X} NSCLC: Duration of Treatment and Responses



[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.
*Death due to PD (n=1), Death due to unrelated AE (n=1), Death due to unknown cause reported as unrelated to RMC-6236 (n=1).

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Case Report: Patient with KRAS^{G12V} NSCLC

Demographics and Baseline Characteristics

- 83-year-old woman
- Former smoker (~60 pack years)
- Diagnosed with NSCLC in 2021

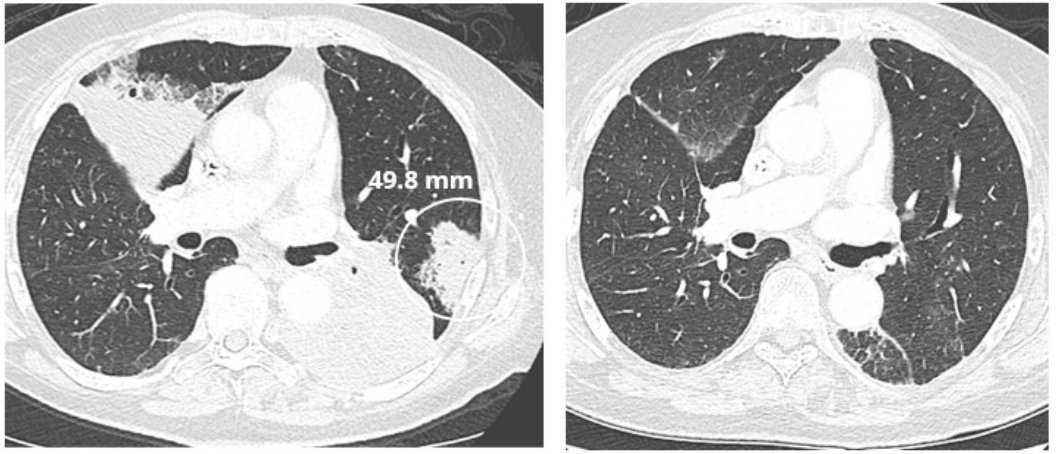
Treatment History

- Prior therapies:
  - Ipilimumab/nivolumab
  - Paclitaxel
  - Carboplatin/pemetrexed

RMC-6236 Treatment Course

- Started at 300 mg QD
- Clinical improvement in cough and dyspnea within one week of start of treatment
- Dose reduced to 200 mg due to Grade 2 fatigue
- Complete response achieved at Week 6 (confirmed); ongoing

Baseline **On-Treatment, Week 6**



Target Lesion: Lung, Left Lower Lobe

Target Lesion	Baseline	On Treatment
1. Lung (left upper lobe)	11.6 mm	0 mm
2. Lung (left lower lobe)	49.8 mm	0 mm
Sum of Diameters	61.4 mm	**0 mm (−100% ↓)**
Overall Response (RECIST 1.1)	--	**CR**

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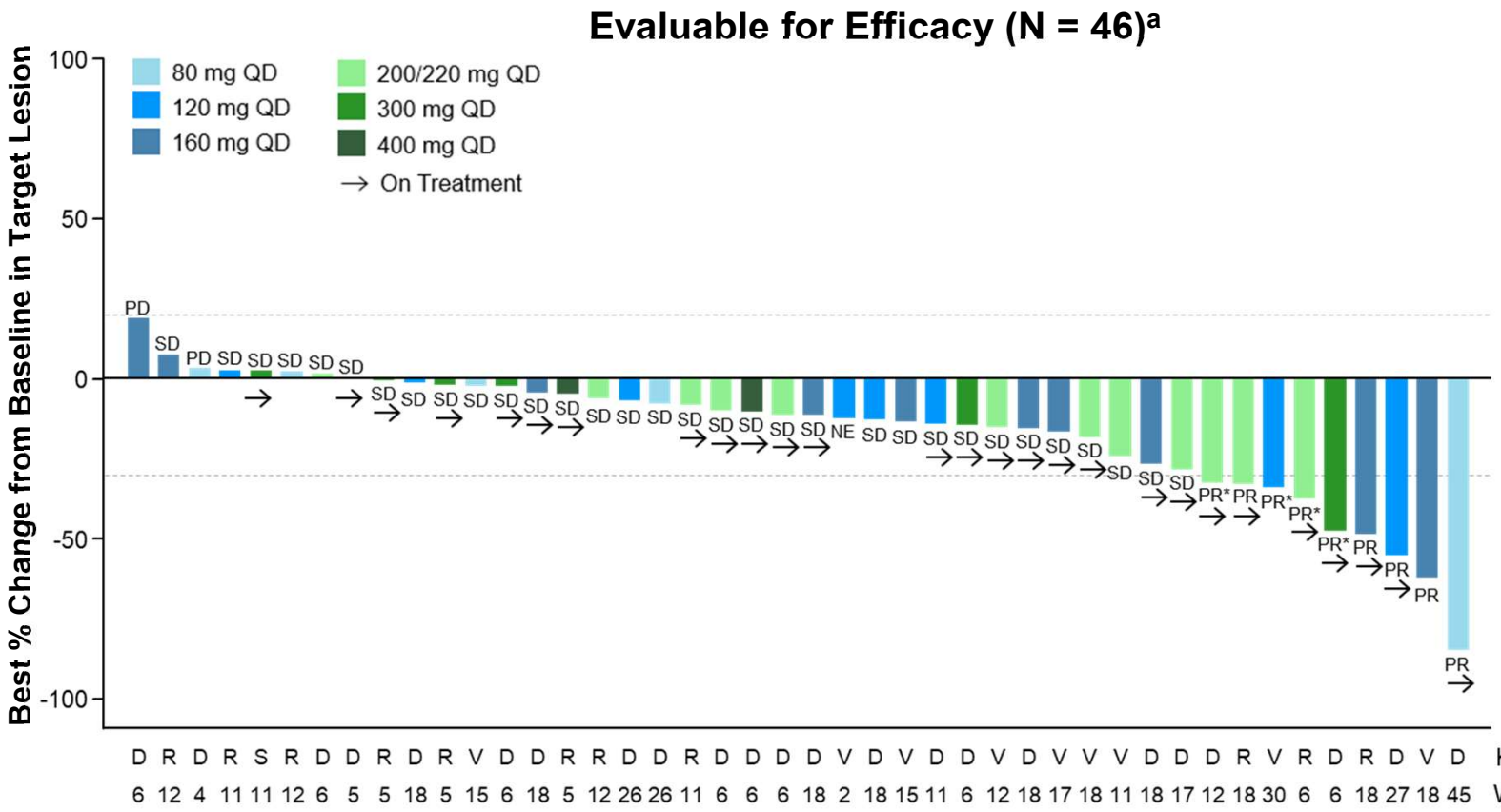
KRAS^{G12X} PDAC: Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

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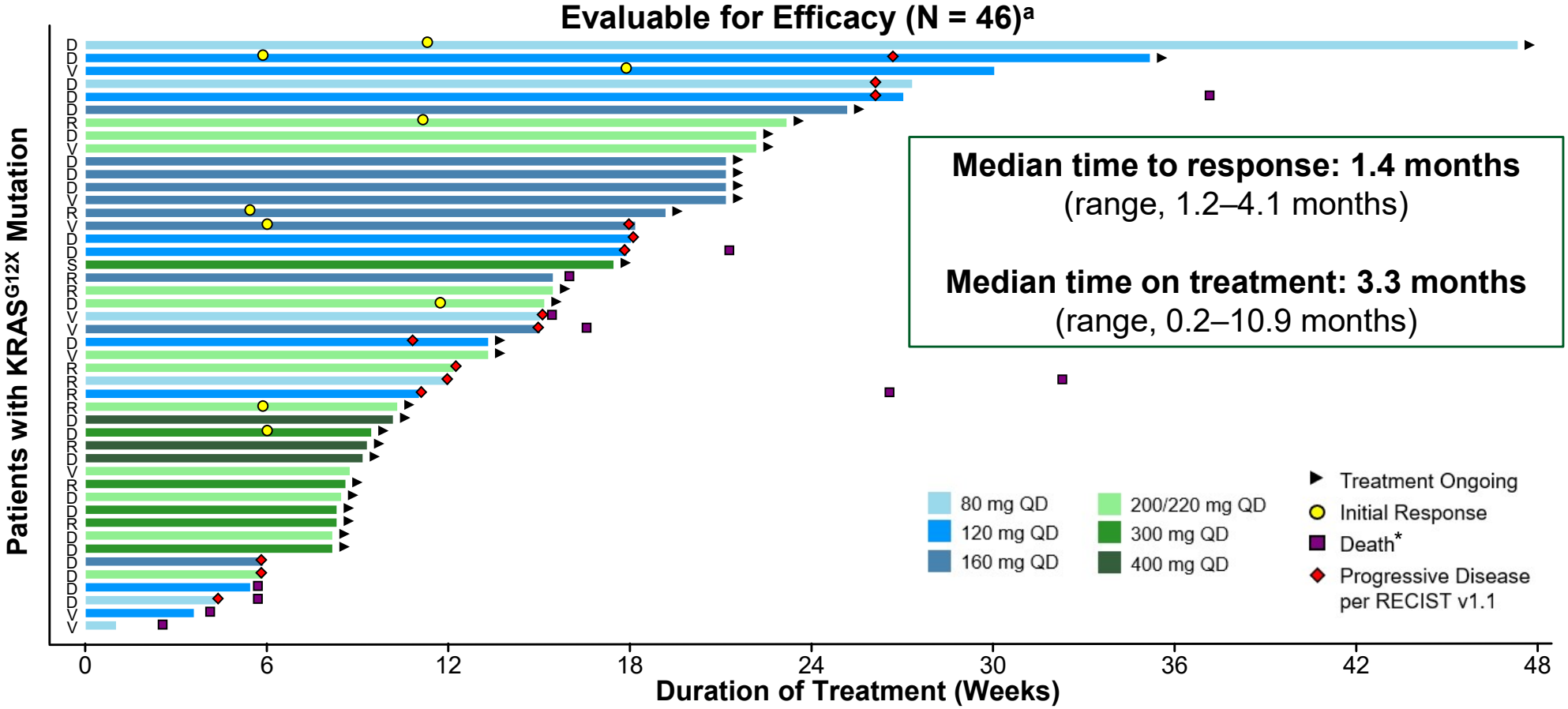
KRAS^{G12X} PDAC: Duration of Treatment and Responses



[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date. *Death due to PD (n = 9), Death due to unrelated AE (n = 2).

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Case Report: Patient with KRAS^{G12R} PDAC

Demographics and Baseline Characteristics

- 57-year-old man
- Diagnosed with PDAC in 2022

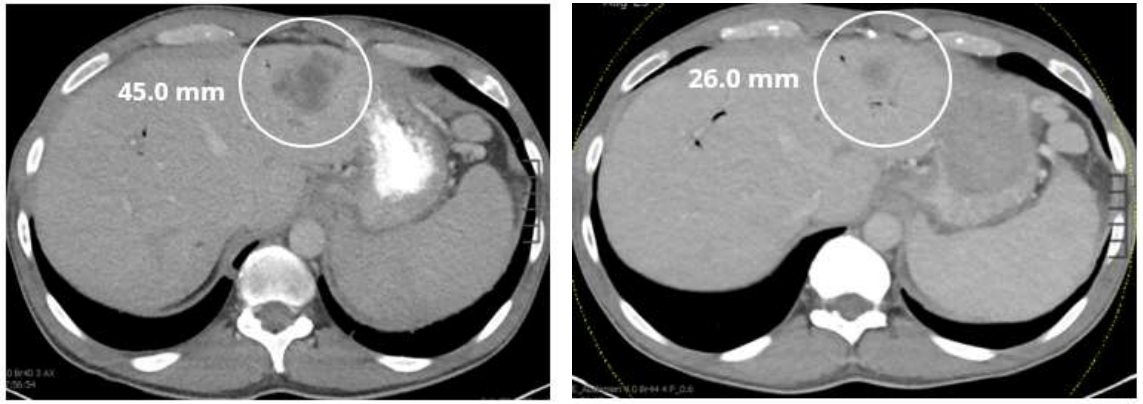
Treatment History

- Prior therapies
  - Gemcitabine/nab-paclitaxel/ canakinumab/spartalizumab
  - FOLFIRINOX

RMC-6236 Treatment Course

- Started at 160 mg QD
- Partial response achieved at Week 6 (confirmed); ongoing

Baseline **On-Treatment, Week 12**



Target Lesion: Segment 2 Liver

Target Lesion	Baseline	On Treatment
1. Segment 2 liver	45 mm	26 mm
2. Lung (medial basilar left lower lobe nodule)	17 mm	6 mm
3. Lung (right lower lobe nodule)	10 mm	6 mm
Sum of Diameters	72 mm	38 mm **(−47% ↓)**
Overall Response (RECIST 1.1)	--	**PR**

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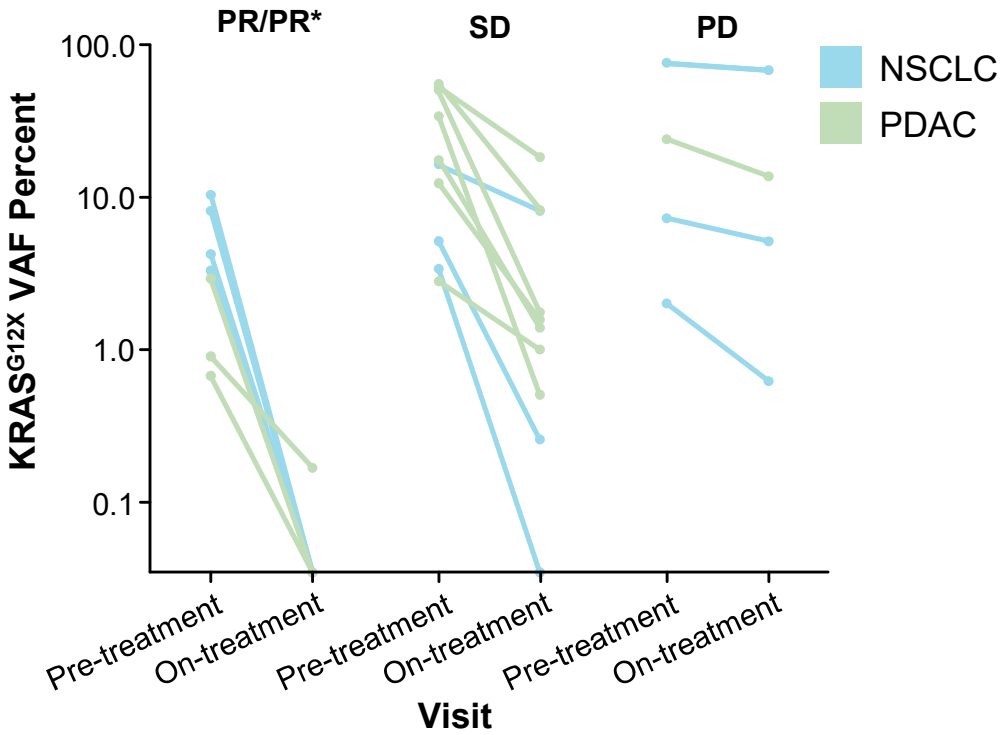
KRAS Variant Allele Frequency in ctDNA Across Tumor Types and Correlation with Clinical Response

- Patients with NSCLC or PDAC were dosed at 80–300 mg
- Overall, 23/50 patients (46%) were evaluable for change in mutant KRAS VAF while on-treatment[a]
- In total, 8/10 (80%) patients with NSCLC and 12/13 (92%) patients with PDAC showed >50% reduction of the mutated KRAS allele



[a]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; KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X= A, D, R, or V; two patients were non-evaluable for best overall response; *Unconfirmed partial response per RECIST 1.1.

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Conclusions

- RMC-6236 is an oral, first-in-class, RAS-selective, RAS^{MULTI}(ON) inhibitor.
- At clinically active doses, RMC-6236 was generally well tolerated.
- RMC-6236 demonstrated encouraging anti-tumor activity in patients with previously treated NSCLC and PDAC across several dose levels and $KRAS^{G12X}$ genotypes, including KRAS mutant genotypes G12D, G12V, and G12R.
- Reduction in KRAS VAF in ctDNA correlated with clinical response across tumor types.
- The dose escalation and dose optimization portion of the study is ongoing and includes plans for monotherapy expansion into additional solid tumor cohorts.
- Preliminary safety and clinical activity data support the ongoing development of RMC-6236 as a single agent and future explorations of RMC-6236 in combination with RMC-6291, immunotherapy, and other anti-cancer therapies.

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Acknowledgements

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