

# MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 11-15, 2023 | Hynes Convention Center | Boston, MA

## Preliminary Safety and Anti-Tumor Activity of RMC-6291, a First-in-Class, Tri-Complex KRAS<sup>G12C</sup>(ON) Inhibitor in Patients With or Without Prior KRAS<sup>G12C</sup>(OFF) Inhibitor Treatment

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# Disclosure Information

Molecular Targets and Cancer Therapeutics  
October 11–15, 2023 | Boston, MA



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**Consultant for:** AstraZeneca, Boehringer Ingelheim, Pfizer, Genentech/Roche, Chugai Pharmaceuticals, ACEA Biosciences, Ignyta, LOXO Oncology, Eli-Lilly, Araxes Pharmaceuticals, Mirati Therapeutics, SFJ Pharmaceuticals, Daiichi-Sankyo, Biocartis, Takeda Oncology, Novartis, Trascenta, Silicon Therapeutics, Nuvalent, Esai, Bayer Pharmaceuticals, Frontier Medicines, Scorpion Therapeutics, Merus, Duality, Hongyun Biotechnology, Monte Rosa, Abbvie, Phanes Therapeutics, Blueprint Medicines

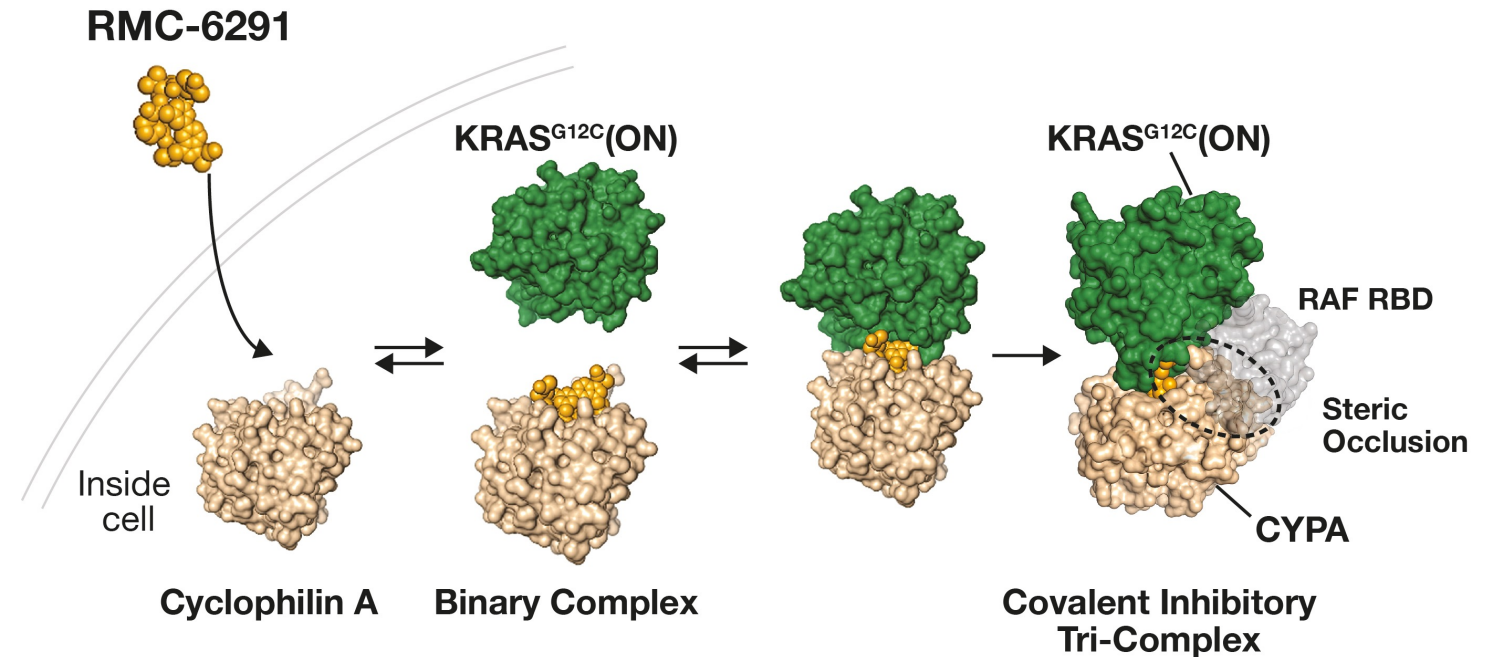
**Research Support:** Astellas, AstraZeneca, Daiichi-Sankyo, PUMA, Eli-Lilly, Boehringer Ingelheim, Takeda Oncology, Revolution Medicines

**Stockholder in:** Gatekeeper Pharmaceuticals

**Other:** LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations

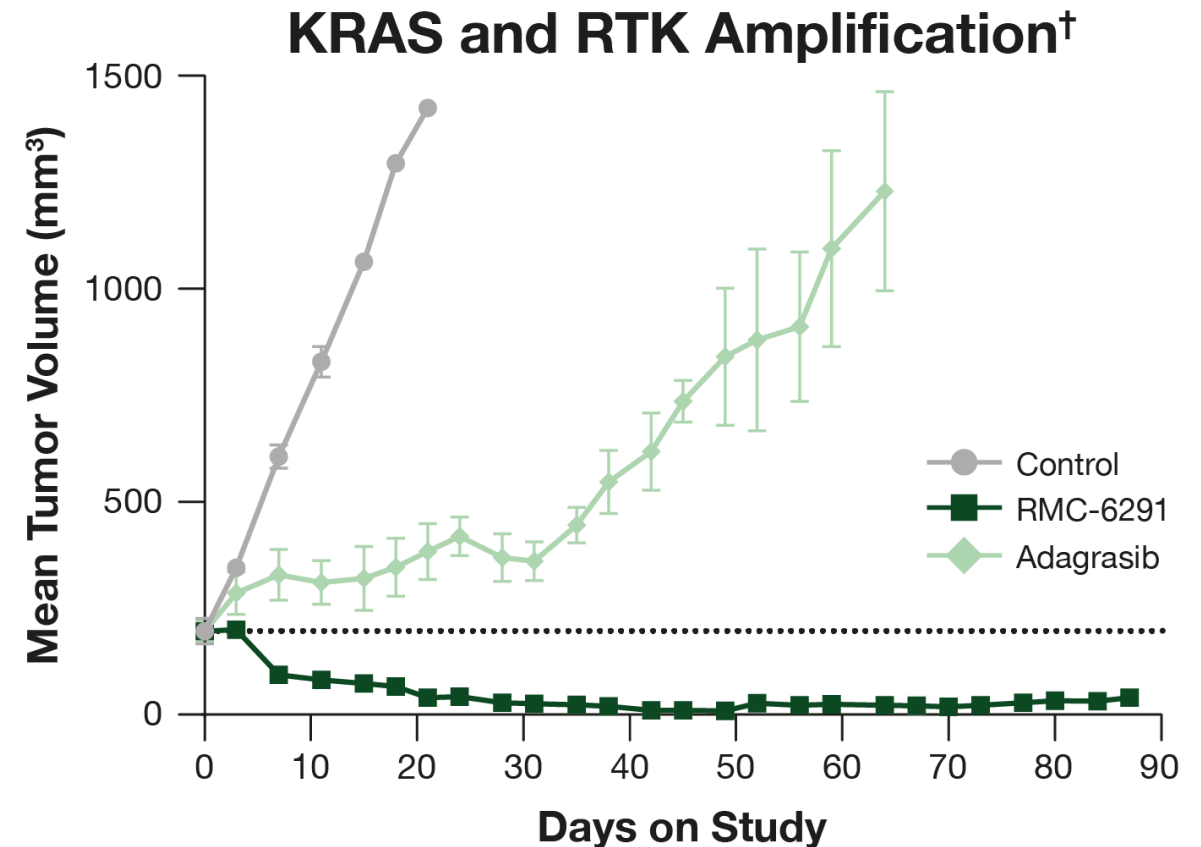
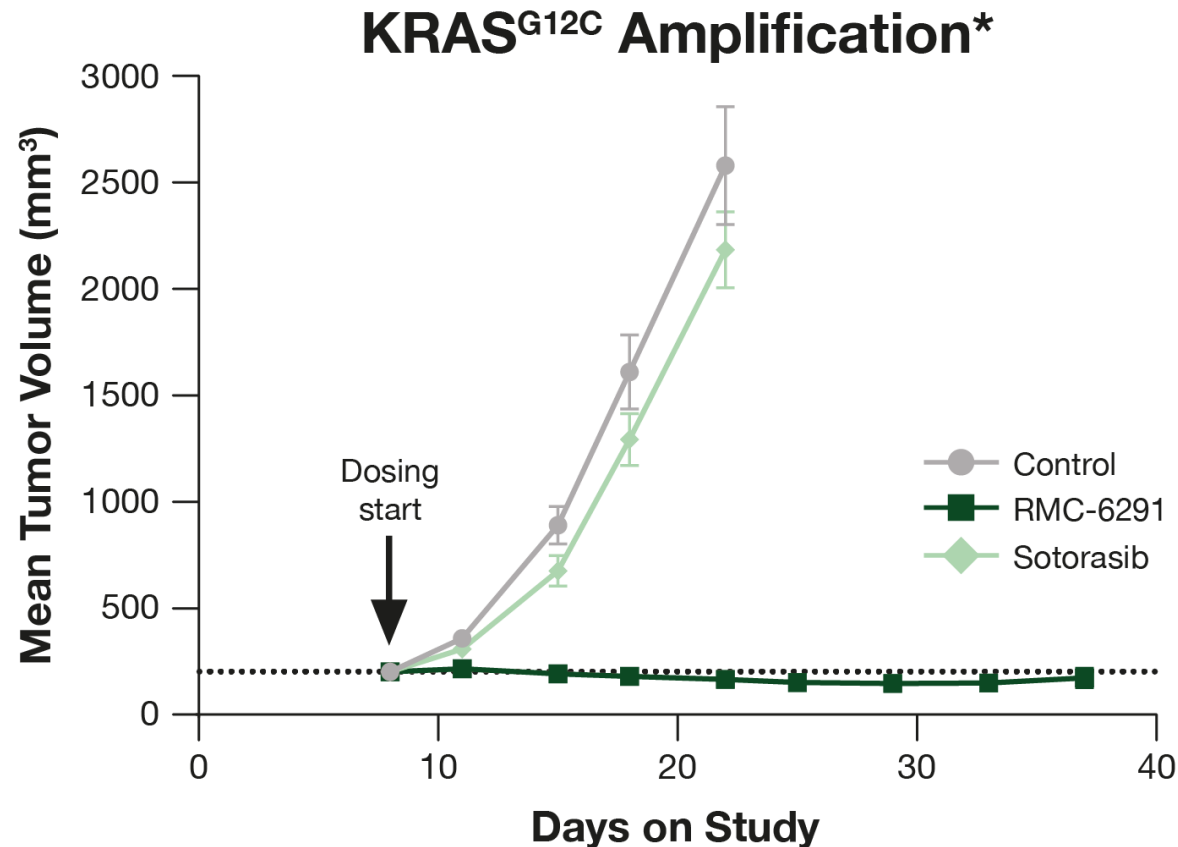
# RMC-6291 is a Potential Best-in-Class KRAS<sup>G12C</sup>(ON) Inhibitor

- KRAS<sup>G12C</sup> occurs in ~13% of non-small cell lung cancer and ~3–4% of colorectal cancer
- Currently approved KRAS<sup>G12C</sup> inhibitors target the inactive, GDP-bound or OFF state of KRAS<sup>G12C</sup> and are limited by the rate, depth, and duration of response
- RMC-6291 is a potent, covalent, orally bioavailable KRAS<sup>G12C</sup>(ON) inhibitor that uses a novel tri-complex mechanism to selectively target the active, GTP-bound, or ON state of the KRAS<sup>G12C</sup> 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



CRC, colorectal cancer; CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; RAF, rapidly accelerated fibrosarcoma; RBD, RAS-binding domain.

# RMC-6291 Drives Tumor Regressions in Preclinical Models of KRAS<sup>G12C</sup>(OFF) Clinical Resistance Mechanisms



Revolution Medicines preclinical research.

\*Sotorasib-resistant MIA PaCa-2 CDX (PDAC, KRAS<sup>G12C/G12C</sup>, KRAS<sup>amp</sup>). RMC-6291 was dosed at 100 mg/kg PO QD; sotorasib was dosed at 100 mg/kg PO QD;

†LUN055 PDX (NSCLC, KRAS<sup>G12C/WT</sup>, ERBB3<sup>amp</sup>, KRAS<sup>amp</sup>). RMC-6291 was dosed at 200 mg/kg PO QD; adagrasib was dosed at 100 mg/kg PO QD.

CDX, cell-line derived xenograft; PDX, patient-derived xenograft; PO, oral dosing; QD, once daily.

# RMC-6291-001 Phase I Study Design

## Key Eligibility Criteria

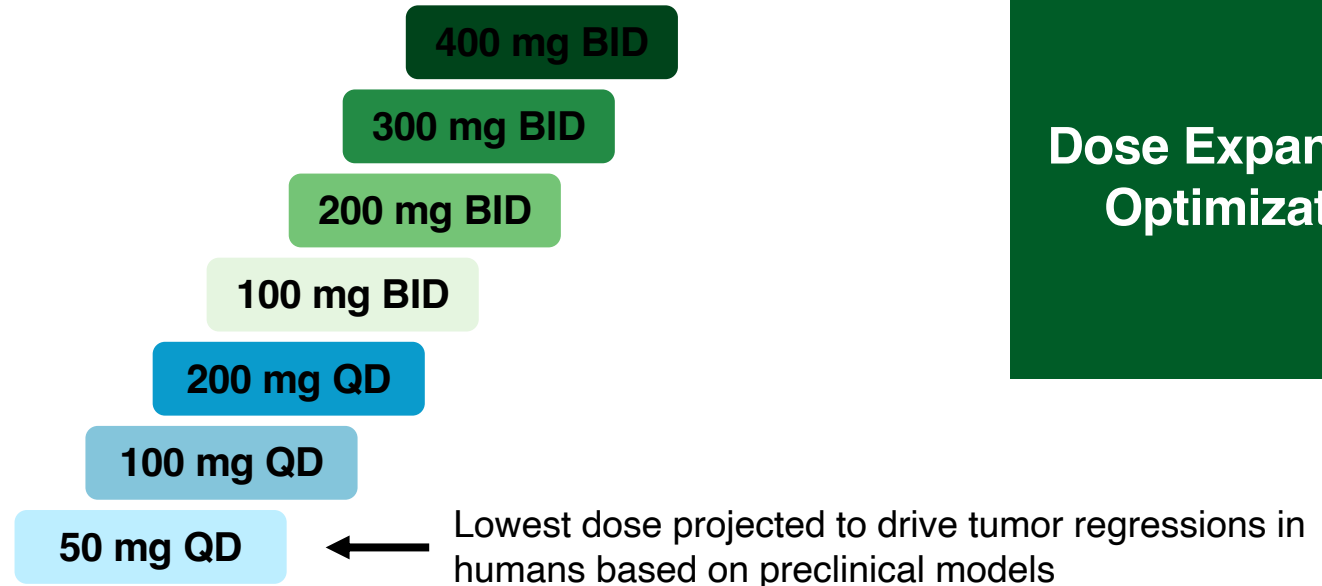
- Advanced solid tumors with KRAS<sup>G12C</sup> mutations
- Received prior standard therapy including treatment with KRAS<sup>G12C</sup>(OFF) inhibitors
- ECOG PS 0–1
- No active brain metastases

## Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

## Dose Escalation

RMC-6291 administered orally QD or BID,  
21-day treatment cycle



Dose Expansion /  
Optimization

Additional patients with NSCLC and CRC were enrolled at dose levels that cleared DLT evaluation (backfill enrollment and dose optimization).

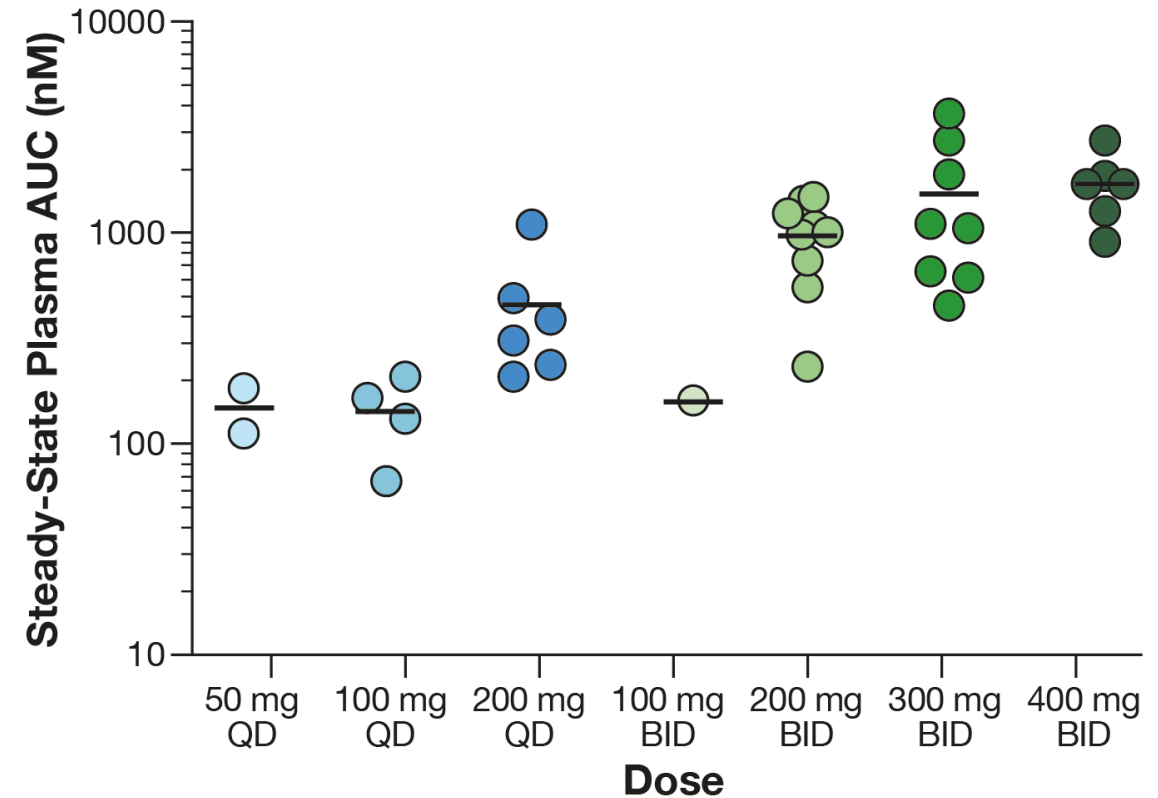
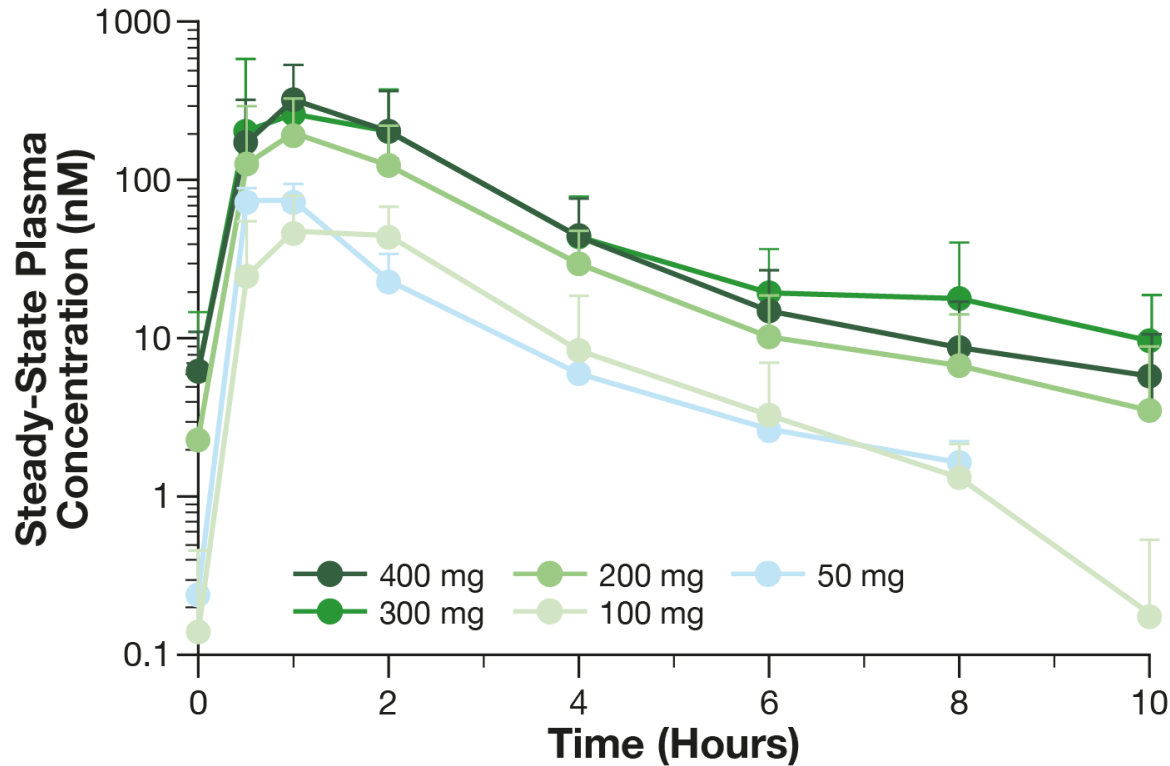
BID, twice daily; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

# Demographics and Baseline Characteristics

	<b>NSCLC N=23</b>	<b>CRC N=33</b>	<b>Other N=7</b>	<b>All Histologies N=63</b>
<b>Age, median (range), years</b>	65 (45–85)	54 (26–84)	66 (52–78)	64 (26–85)
<b>Male, n (%)</b>	13 (57)	21 (64)	2 (29)	36 (57)
<b>ECOG PS, n (%)</b>				
0	8 (35)	13 (39)	3 (43)	24 (38)
1	15 (65)	20 (61)	4 (57)	39 (62)
<b>Smoking status, n (%)</b>				
Current	5 (21.7)	2 (6)	0	7 (11)
Past	18 (78)	12 (36)	1 (14)	31 (49)
Never	0	19 (58)	6 (86)	25 (40)
<b>Number of prior therapies, median (range)</b>	3 (1–7)	3 (1–7)	4 (2–6)	3 (1–7)
<b>Prior KRAS<sup>G12C</sup> inhibitor, n (%)</b>				
Yes	13 (57)	8 (24)	4 (57)	25 (40)
No	10 (44)	25 (76)	3 (43)	38 (60)
<b>Time between prior KRAS<sup>G12C</sup> inhibitor and RMC-6291 first dose, median (range), weeks</b>	6 (2–86)	10 (3–31)	9 (8–128)	9 (2–128)
<b>Prior checkpoint inhibitor within 12 weeks of RMC-6291 first dose</b>				
Yes	9 (39)	0	1 (14)	10 (16)
No	14 (61)	32 (97)	6 (86)	52 (83)

Data Extracted 05 October 2023.

# RMC-6291 Shows Dose-Dependent Increases in Exposure



- Exposure/target engagement relationship in preclinical studies predicts  $\geq \sim 90\%$  cross-linking of KRAS<sup>G12C</sup> in patients receiving 100 mg BID or higher

\*PK curves for 100 and 200 mg up to 10 hours post-dose represent combined QD and BID cohorts following the first dose on Cycle 1 Day 15; no accumulation observed following repeat dose of RMC-6291.

AUC, area under the curve; PK, pharmacokinetics.

Data Extracted 05 October 2023.

# RMC-6291 was Generally Well Tolerated Across Dose Levels

Total (N=63)				
Maximum Severity of TRAEs	Grade 1	Grade 2	Grade 3	Any Grade
<b>TRAEs occurring in ≥10% of patients, n (%)</b>				
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)
<b>TRAEs leading to dose reduction, n (%)</b>	0	1 (2)	8 (13)	9 (14)
<b>TRAEs leading to treatment discontinuation, n (%)</b>	0	0	1 (2)	1 (2)

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

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

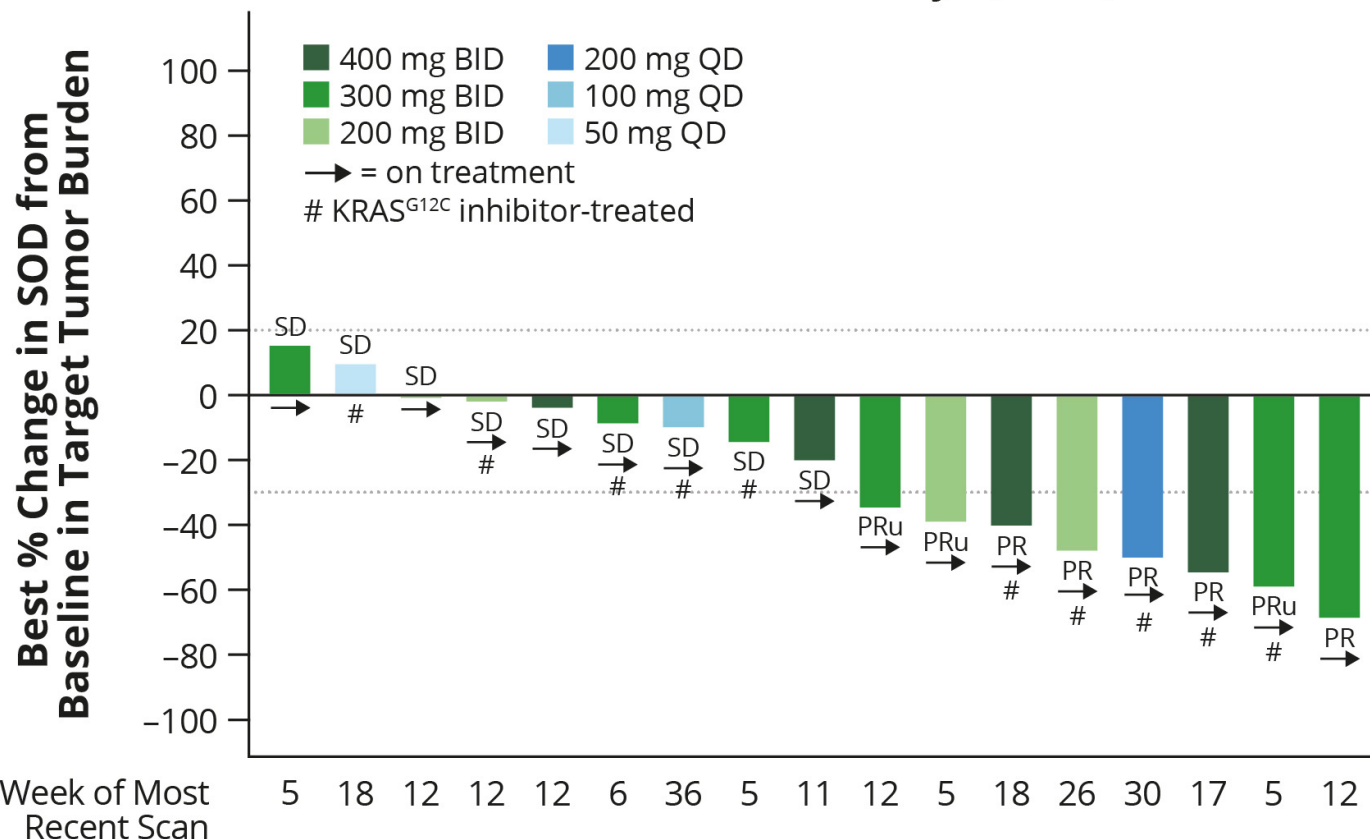
AE, adverse event; AST, aspartate transferase; ECG, electrocardiogram; SAE, serious adverse event, TRAE, treatment-related adverse event.

Data Extracted 05 October 2023.



# KRAS<sup>G12C</sup>-Mutant NSCLC Previously Treated With or Naïve to a KRAS<sup>G12C</sup>(OFF) Inhibitor: Best Response

Evaluable for Efficacy\* (N=17)



## Tumor Response (per RECIST 1.1)

	Prior G12Ci (n=10)	Naïve to G12Ci (n=7)
<b>Best overall response, n (%)</b>		
Partial response <sup>†</sup>	5 (50)	3 (43)
Stable disease	5 (50)	4 (57)
Progressive disease	0	0
<b>ORR, n (%)</b>	5 (50)	3 (43)
<b>DCR (CR+PR+SD), n (%)</b>	10 (100)	7 (100)

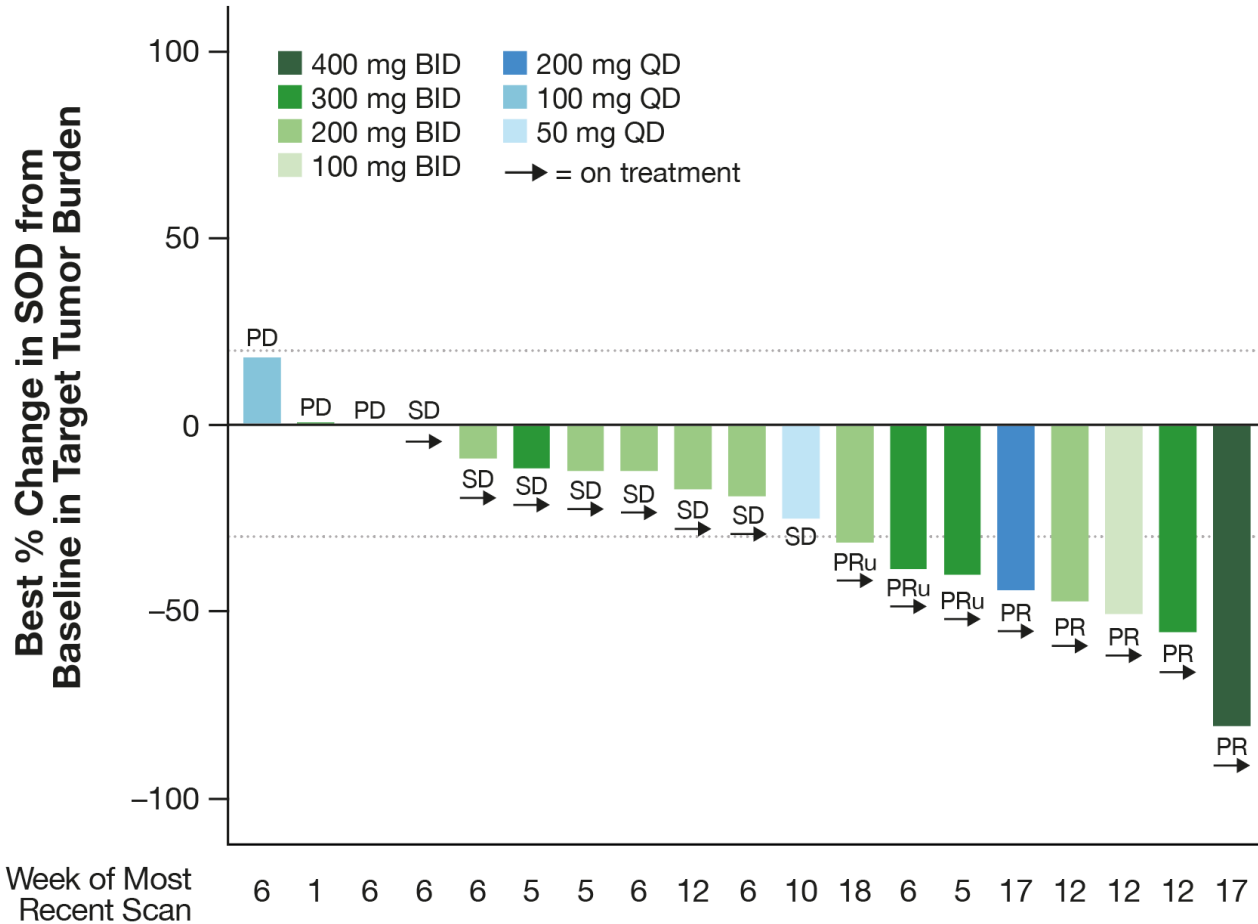
\*All treated patients who received a first dose of RMC-6291 at least 8 weeks prior to data extract date; <sup>†</sup>PR includes 5 confirmed and 3 unconfirmed.

CR, complete response; DCR, disease control rate; G12Ci, G12C inhibitor; PD, progressive disease; PR, partial response; PRu, unconfirmed partial response; SD, stable disease; SOD, sum of diameters; ORR, objective response rate; DCR, disease control rate; RECIST, response evaluation criteria in solid tumors.

Data Extracted 05 October 2023.

# KRAS<sup>G12C</sup>-Mutant CRC Naïve to KRAS<sup>G12C</sup>(OFF) Inhibitor: Best Response

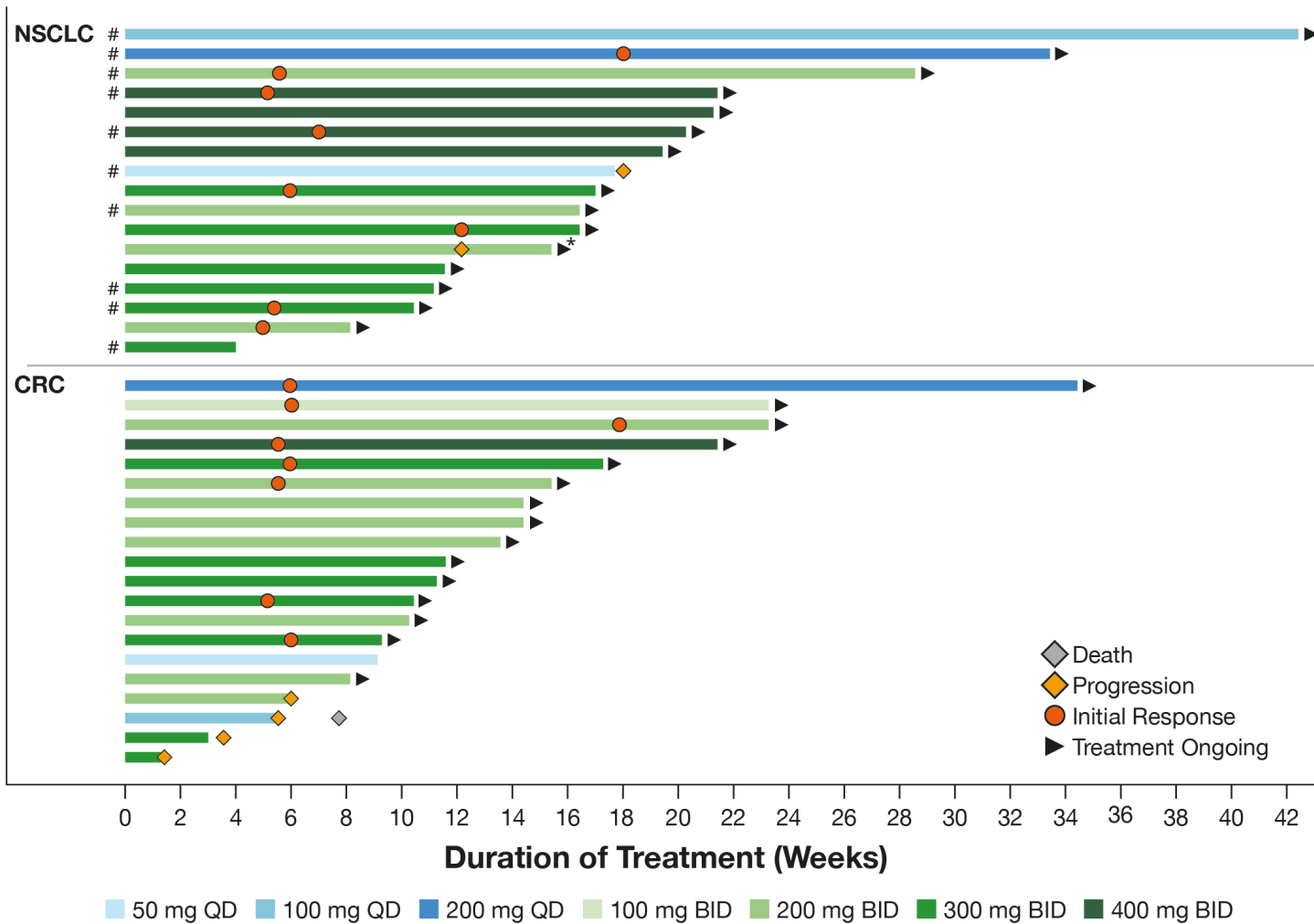
Evaluable for Efficacy\* (N=19)



Tumor Response (per RECIST 1.1)	
<b>Best overall response, n (%)</b>	<b>N=20<sup>†</sup></b>
Partial response <sup>‡</sup>	8 (40)
Stable disease	8 (40)
Progressive disease <sup>†</sup>	4 (20)
<b>ORR, n (%)</b>	<b>8 (40)</b>
<b>DCR (CR+PR+SD), n (%)</b>	<b>16 (80)</b>

\*All treated patients who received first dose of RMC-6291 at least 8 weeks prior to data extract date; <sup>†</sup>One patient had PD due to a new lesion and target lesion measurements were not available; <sup>‡</sup>PR includes 5 confirmed and 3 unconfirmed.

# Duration of Treatment and Responses for KRAS<sup>G12C</sup> 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)

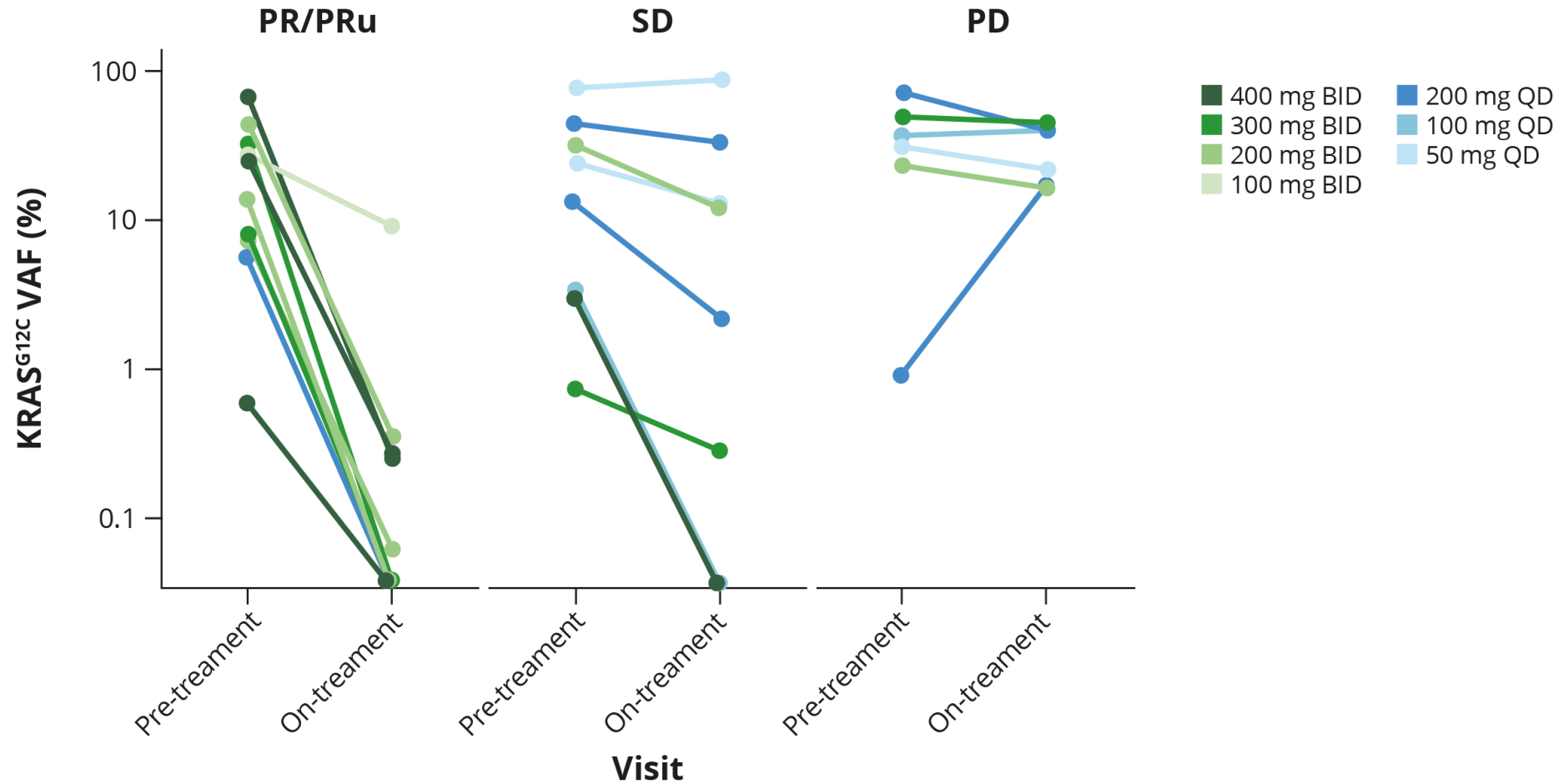
**Median time to response: 1.4 months**  
(range: 1.2–4.1 months)

**Median time on treatment: 2.4 months**  
(range: 0.3–7.9 months)

# = KRAS<sup>G12C</sup> inhibitor-treated. \*The date of treatment discontinuation due to PD was missing as of data extract date.

Data Extracted 05 October 2023.

# Reduction in ctDNA of the KRAS<sup>G12C</sup> Allele Across Doses Correlates With Clinical Response



KRAS<sup>G12C</sup> 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 (circulating tumor DNA) test. ctDNA, circulating tumor DNA; VAF, variant allele frequency.

Data Extracted 05 October 2023.

- RMC-6291 is a potent, mutant-selective, covalent inhibitor of the active, GTP-bound or ON state of KRAS<sup>G12C</sup>.
- 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<sup>G12C</sup>-mutant NSCLC who were previously treated with or naïve to a KRAS<sup>G12C</sup>(OFF) inhibitor and in patients with KRAS<sup>G12C</sup>-mutant CRC naïve to treatment with a KRAS<sup>G12C</sup>(OFF) inhibitor.
- Reduction in ctDNA of the KRAS<sup>G12C</sup> allele across doses correlates with clinical response.
- Dose optimization is ongoing in KRAS<sup>G12C</sup>-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.

# Acknowledgements



- We would like to thank the patients and their families, physicians, and study teams for participating in this study.
- This study is being conducted by Revolution Medicines, Inc. (ClinicalTrials.gov ID: NCT05462717).