AACR American Association for Cancer Research®
ANNUAL MEETING 2025 CHICAGO
APRIL 25–30
AACR.ORG/AACR2025
#AACR25

Preliminary Safety and Antitumor Activity of Zoldonrasib (RMC-9805), an Oral, RAS(ON) G12D-Selective, Tri-Complex Inhibitor in Patients with KRAS G12D Non-Small Cell Lung Cancer (NSCLC) from a Phase 1 Study in Advanced Solid Tumors

Kathryn C Arbour[1], Tanvetyanon Tawee, Rona Yaeger, Aparna R Parikh, Paul Oberstein, Kyriakos P Papadopoulos, John Strickler, Alex Spira, John Powderly, Minal Barve, Judy Wang, Jia Luo, Nilofer Saba Azad, Alexander Starodub, Patricia LoRusso, Avantika Elgin, Michelle Yang, Walter Yu, Mark McCleland, Satwant Lally, Sophia Sohoni, David S Hong

[1]Memorial Sloan Kettering Cancer Center, New York, NY

Disclosure Information

Kathryn C Arbour

I have the following relevant financial relationships to disclose:

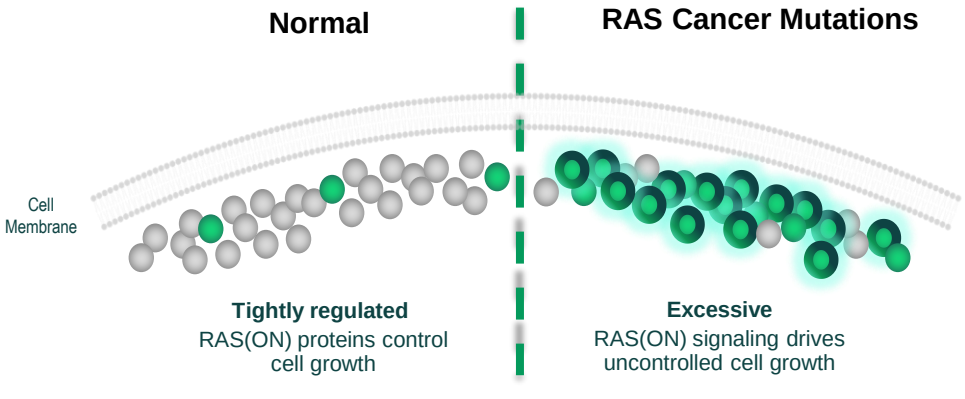
Advisory Board: Bristol Myers Squibb, Revolution Medicines, Merck, Amgen, Regeneron, AstraZeneca, G1 Therapeutics, Novartis

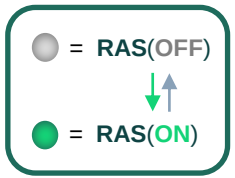
Grant/Research support: Revolution Medicines, Bristol Myers Squibb, Mirati, Genentech, Lilly

Large Unmet Need in RAS G12D Mutant Cancers

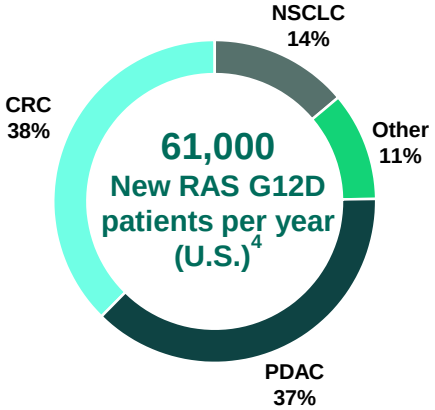
AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

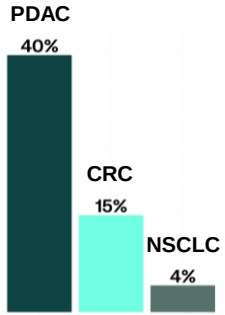
Uncontrolled RAS(ON) Signaling Drives Cells to an Oncogenic State[1-3]





RAS G12D Cancers are Common





KRAS G12D Frequency[5]

- G12D is the most common oncogenic RAS mutation in human tumors and lacks a targeted treatment
- There is a high unmet need in previously treated patients with NSCLC
- KRAS G12D mutation in NSCLC associates with non-smokers and lower TMB and PD-L1 status compared to non-G12D KRAS mutant tumors[6]
- Suboptimal efficacy with immune checkpoint inhibitors has been reported in patients with KRAS G12D NSCLC[6,7]

CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; [1]Holderfield M, et al. *Nature.* 2024;629:919-926. [2]Lokhandwala J, et al. *Front Oncol.* 2024;14:1394702. [3]Jiang J, et al. *Cancer Discov.* 2024;14:994-1017. [4]Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer isalcts and Figures 2023. [5]Lee JK, et al. *NPJ Precis Oncol*. 2022;6:91. [6]Ricciuti et al. Ann Oncol. 2022;33(10):1029–1040. [7]Liu C, et al. *Cancer Commun (Lond)*. 2022; 42(9):828-847

Zoldonrasib is an Oral, Mutant-Selective Covalent Inhibitor Targeting the ON (Active, GTP-bound) State of RAS G12D

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Multiple Approaches to Target RAS G12D in the GTP-bound or ON State

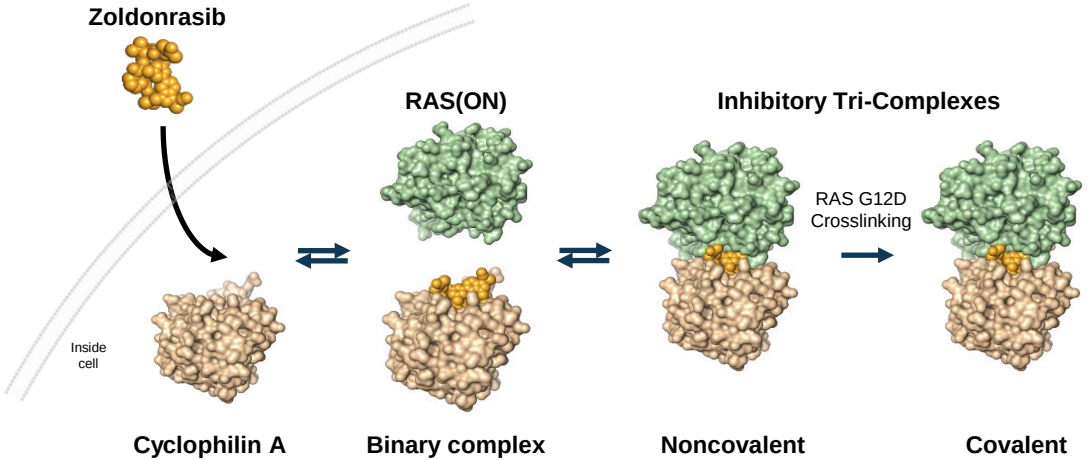
Daraxonrasib (RMC-6236)
RAS(ON) Multi-Selective

- Noncovalent, multi-selective inhibitor of mutant and wild-type RAS(ON) proteins
- Phase 3 studies underway in previously treated PDAC[1] and NSCLC[2]

Zoldonrasib (RMC-9805)
RAS(ON) G12D-Selective

- Mutant-selective covalent inhibitor of RAS(ON) G12D proteins
- Promising preliminary safety and clinical antitumor activity reported in PDAC[3]
  - 30% ORR[4] and 80% DCR at 1200 mg daily dose

Zoldonrasib Mechanism of Action



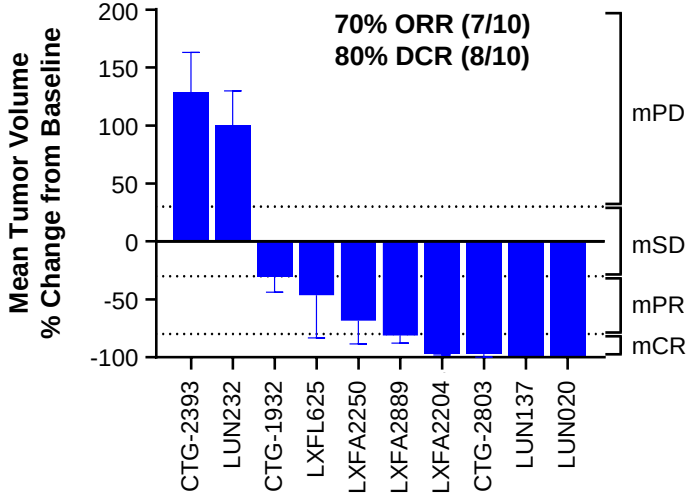
Zoldonrasib tri-complex sterically occludes RAF interaction and inhibits RAS(ON) oncogenic activity and downstream signaling

DCR, disease control rate; ORR, objective response rate; [1]RASolute 302 study (NCT06625320) in patients with previously treated PDAC. [2]RASolve 301 study (NCT06881784) in patients with previously treated RAS mutant NSCLC. [3]David S. Hong et al., Preliminary Safety, Pharmacokinetics, and Antitumor Activity of RMC-9805, an Oral, RAS(ON) G12D-Selective, Tri-Complex Inhibitor in Patients with KRAS G12D Pancreatic Ductal Adenocarcinoma (PDAC) from a Phase 1 Study in Advanced Solid Tumors. [4]Confirmed or pending confirmation (Data cutoff: 02 Sep 2024)

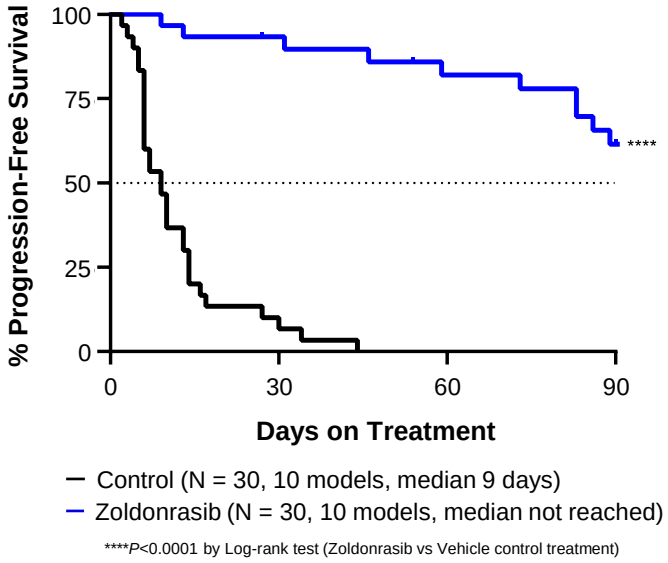
Zoldonrasib Drives Deep and Durable Regressions in KRAS G12D NSCLC Preclinical Models *in Vivo*

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Deep Responses in NSCLC KRAS G12D Preclinical Xenograft Models



Durable Responses in NSCLC KRAS G12D Preclinical Xenograft Models



****P<0.0001 by Log-rank test (Zoldonrasib vs Vehicle control treatment)

CR, complete response; DCR, disease control rate; mCR, modified complete response; mPD, modified progressive disease; mPR, modified partial response; mRECIST, modified response evaluation criteria in solid tumors; mSD, modified stable disease; NSCLC, non-small cell lung cancer; ORR, overall response rate; Zoldonrasib dosed at 100 mg/kg po qd; n = 3/group; Responses after 28 ± 2 days of treatment unless maximal tumor burden reached sooner, or control tumor reached 2 doublings (4* initial tumor volume) later; Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015); Progression defined as tumor doubling from baseline

RMC-9805-001 Phase 1 Study Design
Arm A: Zoldonrasib Monotherapy

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Key Eligibility Criteria

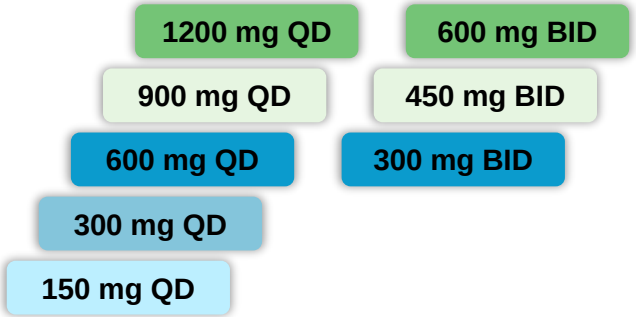
- Advanced solid tumors with KRAS G12D mutations
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Antitumor activity

Part 1: Dose Escalation

Zoldonrasib administered orally QD or BID, 21-day treatment cycle



Part 2: Expansion and Dose Optimization (NSCLC and PDAC)

- Max administered dose was 1200 mg daily
- No dose limiting toxicities observed in Part 1
- Maximum tolerated dose not reached

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer PDAC, pancreatic ductal adenocarcinoma; QD, once daily

Demographics and Baseline Characteristics for Patients Treated with Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

	All Doses (N = 211)	1200 mg QD (N = 90)
Age, median (range), years	62 (25-86)	62 (25-86)
Male, n (%)	116 (55%)	51 (57%)
ECOG PS 1, n (%)	148 (70%)	64 (71%)
Tumor type, n (%)		
NSCLC	30 (14%)	28 (31%)
PDAC	115 (55%)	42 (47%)
Other	66 (31%)	20 (22%)
Number of prior anti-cancer therapies, median (range)	2 (0-10)[1]	2 (0-10)
Liver metastasis at baseline, n (%)	146 (69%)	51 (57%)
Metastatic at diagnosis [stage IV], n (%)	129 (61%)	55 (61%)

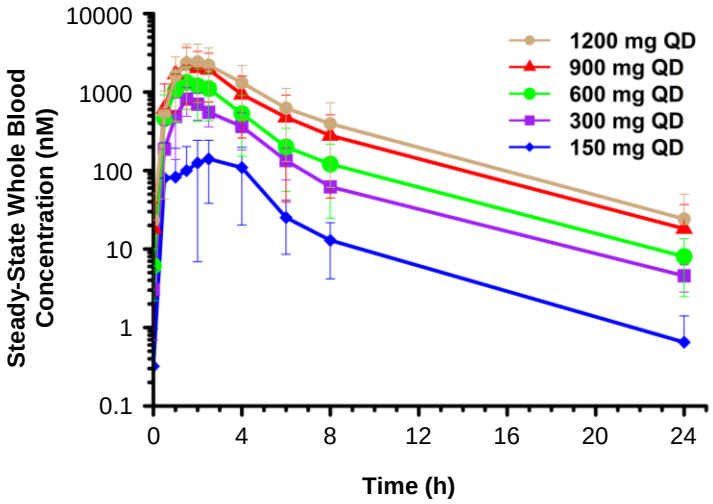
Data cutoff: Dec 2, 2024.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; [1]One patient reported no prior lines of anti-cancer therapy

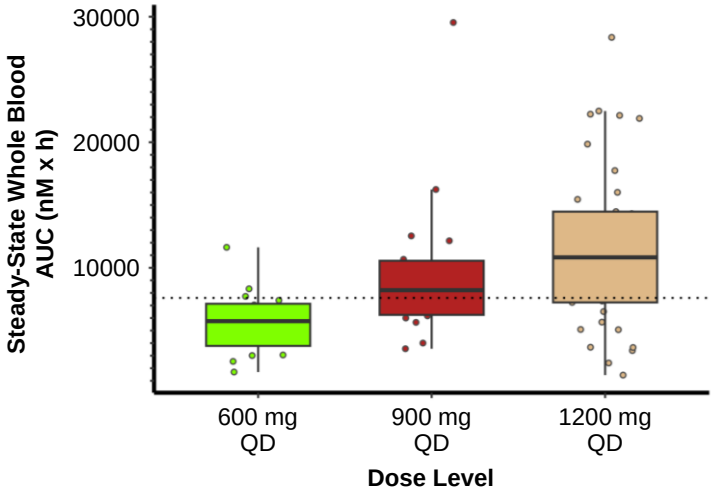
Exposure Showed Dose-Dependent Increases and Achieved Levels Predicted to Induce Tumor Regressions

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Mean Steady-State Blood PK Profiles



Individual Steady-State Blood AUC[1]



Exposure in mice at 100 mg/kg (Dose that induces tumor regressions in majority of preclinical models)

1200 mg QD identified as the candidate RP2DS in NSCLC and PDAC

AUC, area under the curve; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; QD, once daily; RP2DS, recommended phase 2 dose and schedule; PK data as of 02 Dec 2024; Left: steady-state concentrations from Cycle 1 Day 15; Error bars represent standard deviation; Right: steady-state AUC in Cycle 1 Day 15; Each circle represents an individual patient; [1] Comparable AUC observed for QD and BID schedules at same daily dose level

Treatment Related Adverse Events (TRAEs) for Patients Receiving Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

All Patients Treated with Zoldonrasib (N = 211)[1]				
Maximum Severity of Treatment-Related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
Any TRAE	109 (52%)	32 (15%)	2 (1%)	143 (68%)
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	61 (29%)	8 (4%)	0	69 (33%)
Diarrhea	32 (15%)	6 (3%)	1 (1%)	39 (19%)
Vomiting	23 (11%)	8 (4%)	0	31 (15%)
Fatigue	23 (11%)	4 (2%)	0	27 (13%)
Other select TRAEs, n(%)				
Rash[2]	17 (8%)	0	0	17 (8%)
ALT increased	13 (6%)	1 (1%)	1 (1%)	15 (7%)
AST increased	12 (6%)	3 (1%)	0	15 (7%)
Stomatitis/mucositis[3]	1 (1%)	0	0	1 (1%)
TRAEs leading to dose reduction, n (%)	3 (1%)	2 (1%)	0	5 (2%)
TRAEs leading to dose interruption, n (%)	3 (1%)	5 (2%)	2 (1%)	10 (5%)
TRAEs leading to treatment discontinuation, n (%)	1 (1%)	0	0	1 (1%)

No treatment-related Grade 4 or 5 AEs or SAEs have been reported

AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; TRAE, treatment-related adverse event; [1]Includes all dose levels and all tumor types (PDAC, CRC, NSCLC, and other types). [2]Includes preferred terms of Dermatitis acneiform, Rash, Rash maculo-papular. [3]Includes preferred terms of stomatitis and mucosal inflammation; Median time on treatment was 3.22 months (range: 0.03–10.81)

Data cutoff: 02 Dec 2024.

Treatment Related Adverse Events (TRAEs) for Patients Receiving Zoldonrasib 1200 mg QD

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Patients Treated with 1200 mg QD Zoldonrasib (N = 90)[1]				
Maximum Severity of Treatment-Related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
Any TRAE	49 (54%)	16 (18%)	2 (2%)	67 (74%)
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	30 (33%)	5 (6%)	0	35 (39%)
Diarrhea	18 (20%)	3 (3%)	1 (1%)	22 (24%)
Vomiting	12 (13%)	4 (4%)	0	16 (18%)
Rash[2]	11 (12%)	0	0	11 (12%)
Other select TRAEs, n(%)				
AST increased	5 (6%)	2 (2%)	0	7 (8%)
ALT increased	4 (4%)	1 (1%)	1 (1%)	6 (7%)
Stomatitis/mucositis[3]	1 (1%)	0	0	1 (1%)
TRAEs leading to dose reduction, n (%)	2 (2%)	2 (2%)	0	4 (4%)
TRAEs leading to dose interruption, n (%)	3 (3%)	3 (3%)	2 (2%)	8 (9%)
TRAEs leading to treatment discontinuation, n (%)	1 (1%)	0	0	1 (1%)
Mean dose intensity		98%		

No treatment-related Grade 4 or 5 AEs or SAEs have been reported

AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; QD, once daily; TRAE, treatment-related adverse event; [1]Includes all tumor types (PDAC, NSCLC, CRC, and other types). [2]Includes preferred terms of Dermatitis acneiform, Rash, Rash maculo-papular. [3]Includes preferred terms of stomatitis and mucosal inflammation; Median time on treatment was 2.89 months (range: 0.03–9.66)

Data cutoff: 02 Dec 2024.

Demographics and Baseline Characteristics for Patients with NSCLC Treated with 1200 mg QD Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

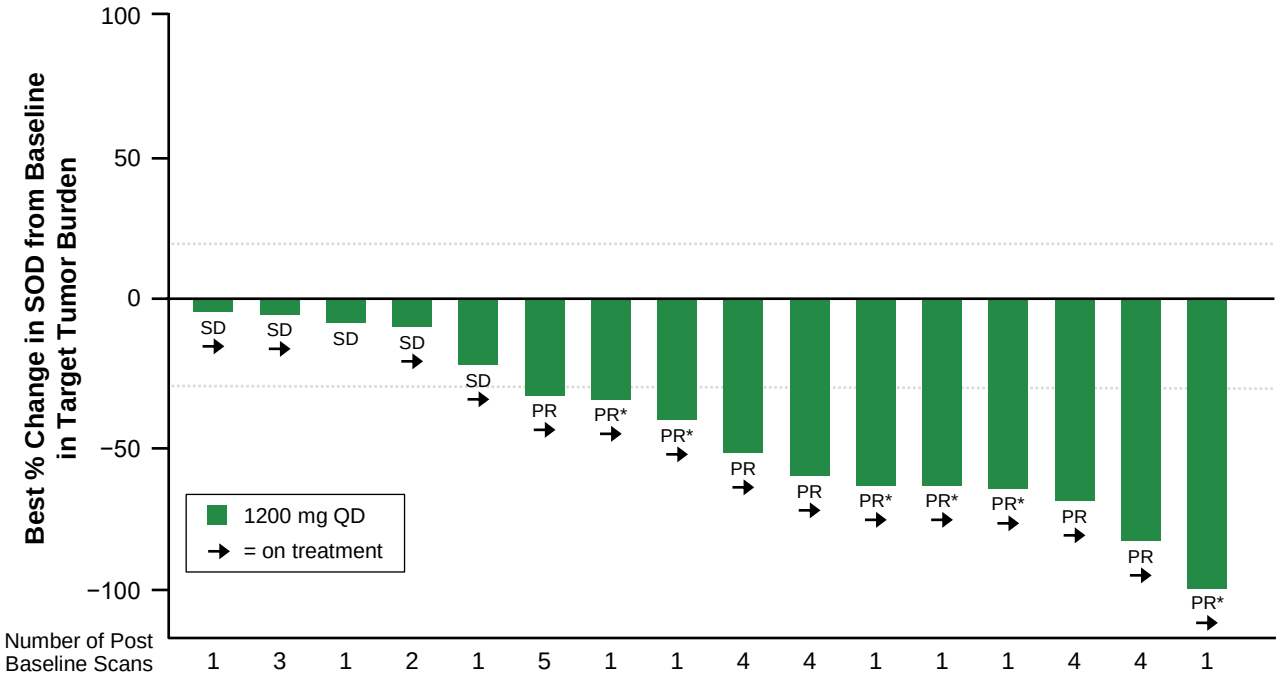
	Patients with NSCLC Treated with 1200 mg QD Zoldonrasib (N = 28)
Age, years, median (range)	64 (36-86)
Male, n (%)	14 (50%)
ECOG PS 1, n (%)	18 (64%)
Smoking Status	
Current	1 (4%)
Past	12 (43%)
Never	15 (54%)
Number of prior anti-cancer therapies, median (range)	2 (0-6)[1]
Prior treatment with platinum chemotherapy	24 (86%)
Prior treatment with immune checkpoint inhibitor	24 (86%)
Brain metastases at baseline, n (%)	6 (21%)
Metastatic at diagnosis [stage IV], n (%)	21 (75%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; QD, once daily; [1]One patient reported no prior lines of anti-cancer therapy

Data cutoff: 02 Dec 2024.

ORR and DCR in Patients with KRAS G12D NSCLC Treated with 1200 mg QD Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



Tumor Response for Patients with NSCLC Treated with 1200 mg QD (N = 18)[1]	
ORR[2], % (n)	61% (11)
DCR (CR+PR+SD), % (n)	89% (16)

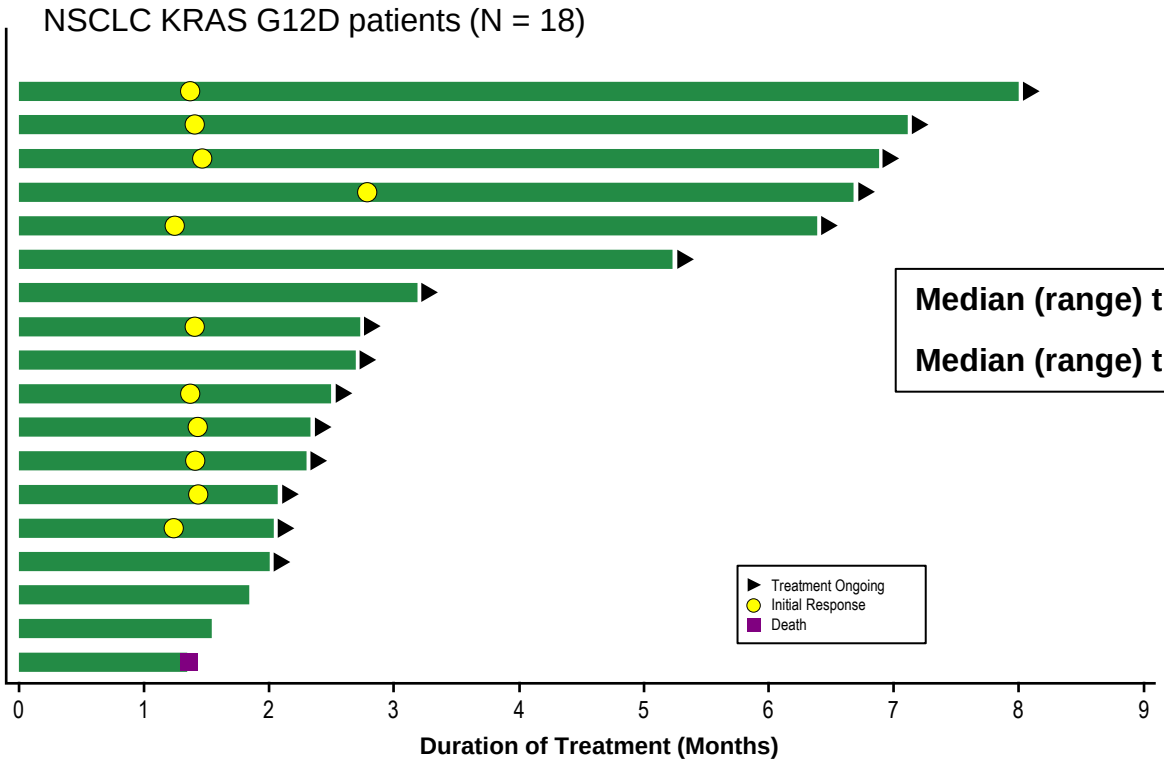
[1] per RECIST v1.1
[2] Includes confirmed PRs and unconfirmed PRs who were still on treatment and may yet be confirmed

CR, complete response; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, objective response rate; PR, partial response; PR*, unconfirmed partial response; QD, once daily; RECIST, response evaluation criteria in solid tumors; SD, stable disease; All patients with NSCLC who received first dose of zoldonrasib at least 8 weeks prior to data cutoff date (applies to waterfall plot and ORR table); Two patients treated with 1200 mg QD are not displayed on the waterfall plot (but are included in the denominator for ORR/DCR) due to death prior to the first scan (1 patient: unrelated adverse event) or due to unevaluable scan (1 patient)

Data cutoff: 02 Dec 2024.

Duration of Treatment and Responses in Patients with KRAS G12D NSCLC Treated with 1200 mg QD Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



Median (range) time to response: 1.4 months (1.2–2.8)

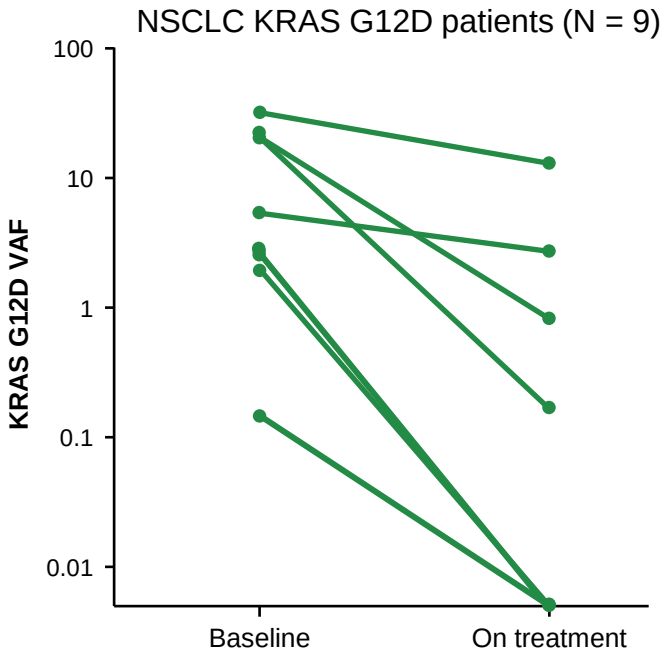
Median (range) time on treatment: 2.6 months (1.3–8.0)

Swimmer plot includes all patients who received first dose of zoldonrasib at least 8 weeks prior to data cutoff date; No patients had progressive disease per RECIST v1.1 at the time of data cutoff; One death was reported due to unrelated adverse event

Data cutoff: 02 Dec 2024.

ctDNA Clearance in Patients with KRAS G12D NSCLC Treated with 1200 mg QD Zoldonrasib

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25



- 9 patients with NSCLC treated at 1200 mg QD zoldonrasib had detectable KRAS G12D at baseline and were evaluable for changes in KRAS G12D VAF on treatment[1]
- Marked reduction in KRAS G12D VAF in ctDNA

KRAS G12D VAF Clearance	1200 mg QD Zoldonrasib (N = 9)
≥50% clearance, % (n)	89% (8)
100% clearance, % (n)	56% (5)

ctDNA, circulating tumor DNA; NSCLC, non-small cell lung cancer; QD, once daily; VAF, variant allele frequency; Plasma samples at baseline and on treatment (C2D1 or C3D1) were analyzed for changes in KRAS G12D VAF (in ctDNA) by Guardant Health; [1]Of the patients with NSCLC who received first dose of zoldonrasib at least 8 weeks prior to data cutoff date (N = 18), 9 were not evaluable due to no detectable KRAS G12D in ctDNA (potential ctDNA non-shedder) at baseline (n = 7) or unsuccessful sequencing (n = 2)

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Case Report: Patient with KRAS G12D NSCLC

Demographics and Baseline Characteristics

- 70-year-old Caucasian woman
- Initially diagnosed with KRAS G12D NSCLC (Stage IIIA) in February 2018; Metastatic progression: May 2022
- Past-smoker
- Concurrent TP53 and MGA mutations; TMB low (7.9 mut/Mb); PD-L1 high (TPS = 95%)

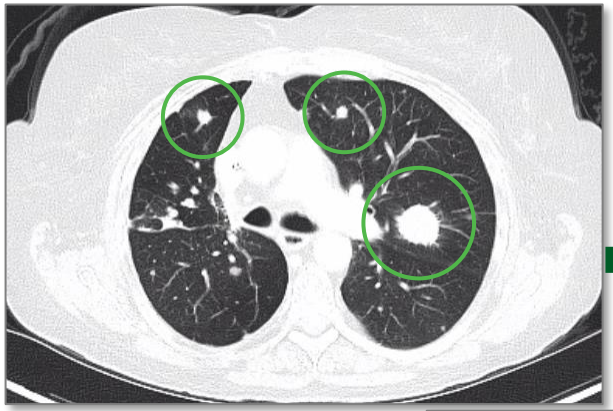
Treatment History

- Pemetrexed, Cisplatin (Adjuvant)
- Right Upper Lobe Lobectomy
- Left Upper Lobe Cryoablation
- Paclitaxel, Carboplatin, Durvalumab (Metastatic)
- Mediastinum Radiotherapy (Metastatic)

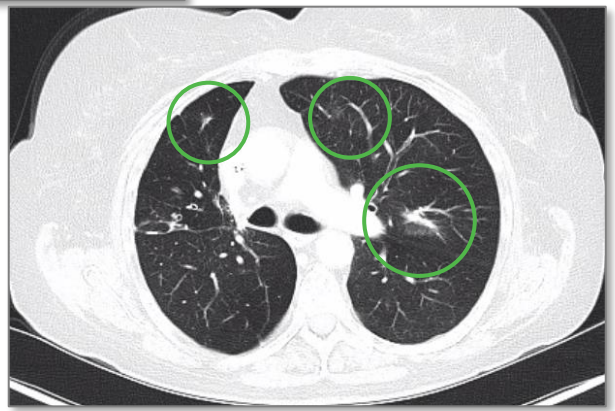
RMC-9805 Treatment Course

- C1D1: Received zoldonrasib at 1200 mg QD
- C3D1: Partial Response (PR) per RECIST 1.1 (-100%)
- C5D1: Confirmed PR (-100%)
- C7D1: Confirmed PR (-100%)
- Complete clearance of KRAS G12D VAF in ctDNA at C2D1
- TRAE included G1 intermittent diarrhea (ongoing), G1 fatigue (resolved within 8 days) – No nausea or rash
- Continues to work full time while on treatment

Baseline CT



C3D1 CT



CT, computed tomography; G1, grade 1; G2, grade 2; NSCLC, non-small cell lung cancer; PR, partial response; QD, once daily

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Case Report: Patient with KRAS G12D NSCLC

Demographics and Baseline Characteristics

- 36-year-old Asian woman, with no PMH
- Initially diagnosed with KRAS G12D NSCLC (Stage IIIA disease, T4N0) in Sept 2022; Metastatic progression: Nov 2023
- Non-smoker
- Concurrent NOTCH1 mutation; TMB low (1.6 mut/Mb); PD-L1 neg (TPS < 1%)

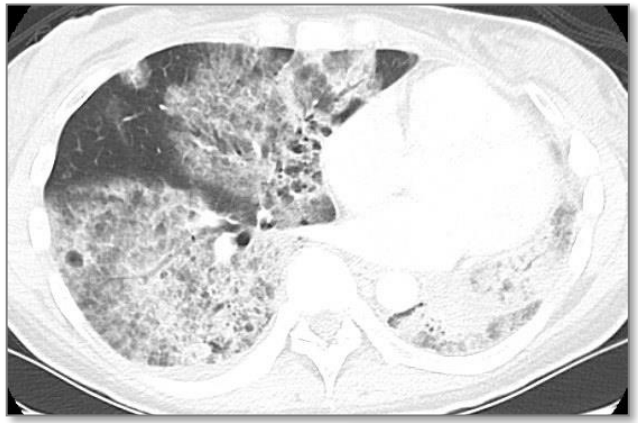
Treatment History

- Carboplatin, Pemetrexed, Nivolumab (Neoadjuvant)
- VATS Lobectomy LLL, LUL wedge resection
- Atezolizumab (Adjuvant)
- Left Lung Radiotherapy
- Carb/Pac/Atezo/Bev

RMC-9805 Treatment Course

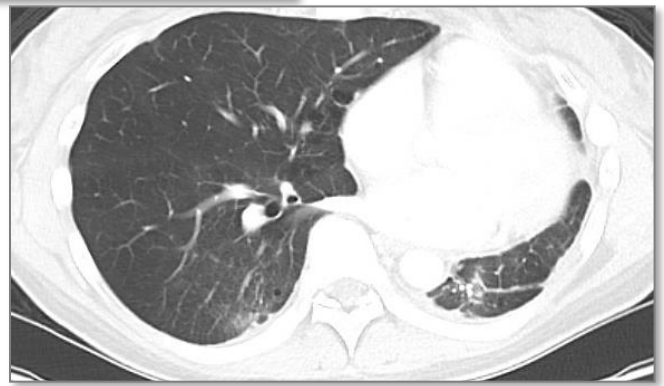
- C1D1: Received zoldonrasib at 1200 mg QD
- C3D1: Partial Response per RECIST 1.1 (-70%)
- C5D1: Confirmed PR (-84%)
- C12D1: Confirmed PR (-87%)
- TRAE included G1 Nausea, resolved (9 days)
- TEAE G3 increase in CPK (suspected due to exercise), dose interrupted and resumed at 900 mg QD
- Within 1 week of C1D1, came off oxygen with resolved cough
- Exercising daily in the gym

Baseline CT



Disappearance of extensive lung and lymphangitic carcinomatosis

C3D1 CT



CPK, creatine phosphokinase; CT, computed tomography; G1, grade 1; G3; grade 3; NSCLC, non-small cell lung cancer; PMH, prior medical history; PR, partial response; QD, once daily

Conclusions

AACR American Association for Cancer Research® ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

- Zoldonrasib is a potent, mutant-selective, covalent inhibitor of RAS(ON) G12D
- Zoldonrasib is orally bioavailable and demonstrates dose-dependent blood PK reaching exposures consistent with those inducing tumor regressions in preclinical KRAS G12D NSCLC models
- Zoldonrasib is well tolerated with manageable and primarily Grade 1 treatment-related adverse events
- Zoldonrasib has demonstrated encouraging preliminary antitumor activity in patients with KRAS G12D NSCLC
  - Encouraging antitumor activity previously reported in PDAC
- Dose optimization and expansion are ongoing in patients with KRAS G12D NSCLC and other solid tumor types
  - 1200 mg QD identified as the candidate RP2DS
- Preliminary safety and antitumor activity support the continuing development of zoldonrasib as a single agent and in combination with other therapies, including:
  - Daraxonrasib (RMC-6236) in solid tumors (NCT06040541)
  - Standard of care regimens for NSCLC (NCT06162221)
  - Standard of care regimens for GI cancers (NCT06445062)

Acknowledgements

- We thank all patients who participated in this study, their families who supported them, and the clinical investigators and research staff who cared for them
- Revolution Medicines Research and Development team
- The RMC-9805-001 study is sponsored by Revolution Medicines, Inc. (ClinicalTrials.gov identifier: NCT06040541)