

Preliminary Safety and Clinical Activity of Zoldonrasib (RMC-9805), an Oral, RAS(ON) G12D-Selective, Tri-Complex Inhibitor in Patients with Previously Treated KRAS G12D Non-Small Cell Lung Cancer (NSCLC)

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Disclosure Information

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Dr. Jonathan Riess

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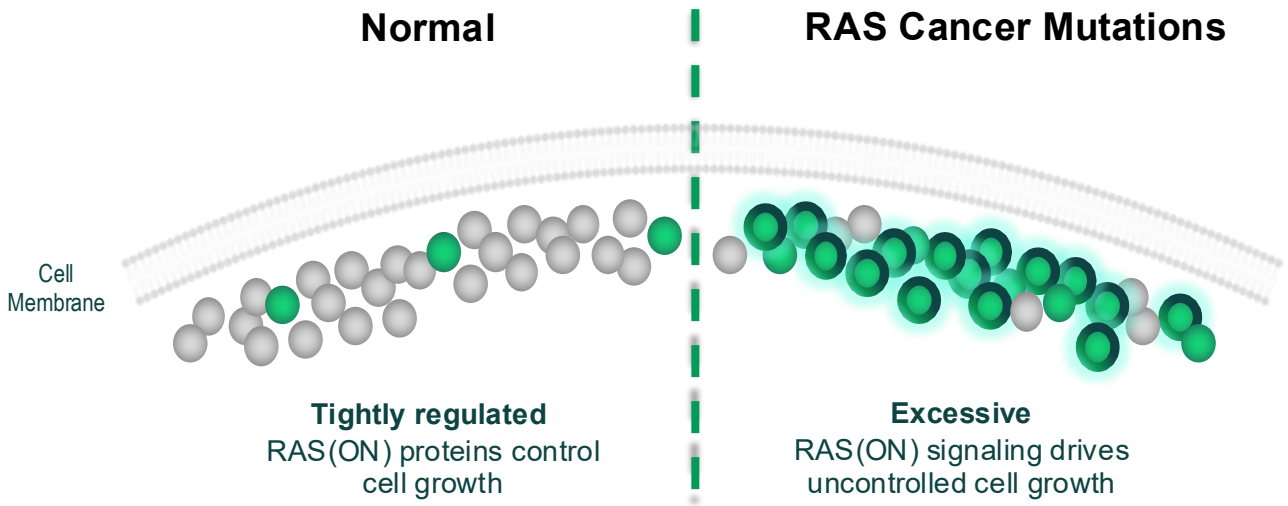
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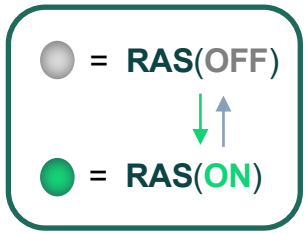
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Large Unmet Need in RAS G12D Cancers

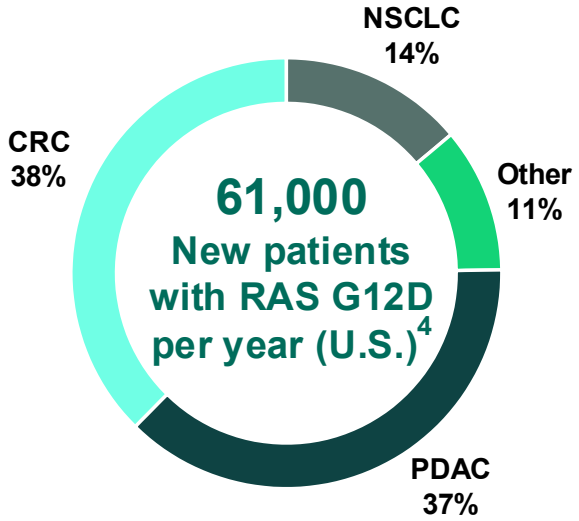
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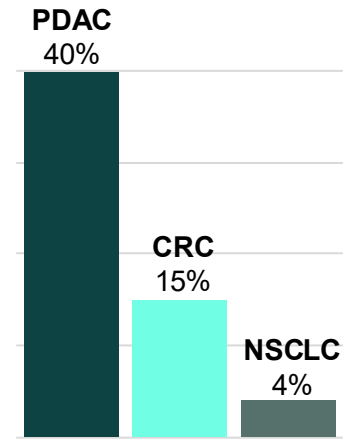
Uncontrolled RAS(ON) Signaling Drives Cells to an Oncogenic State[1-3]





RAS G12D Cancers are Common





KRAS G12D Frequency[5]

- G12D is the most common oncogenic RAS mutation in human tumors and lacks an approved targeted treatment[4]
- KRAS G12D mutation in NSCLC is associated with non-smokers and lower TMB and PD-L1 status compared to non-G12D KRAS mutant tumors[6]
- Treatment options for patients with 2L+ NSCLC are limited
  - Docetaxel: ORR, 9.2%–14.7%; mPFS, 3–4.5 mo; mOS, 9.1–11.8 mo[7-13]

2L, second-line; CRC, colorectal cancer; KRAS, Kirsten rat sarcoma virus; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death-ligand 1; PDAC, pancreatic adenocarcinoma; TMB, tumor mutation burden. [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 Facts and Figures 2023. [5]Lee JK, et al. *NPJ Precis Oncol.* 2022;6:91. [6]Ricciuti et al. *Ann Oncol.* 2022;33:1029-1040. [7]Garon EB, et al. *Lancet.* 2014;384:665-673. [8]Borghaei H, et al. *N Engl J Med.* 2015;373:1627-1639. [9]Rittmeyer A, et al. *Lancet.* 2017;389:255-265. [10]Fehrenbacher L, et al. *Lancet.* 2016;387:1837-1846. [11]de Langen AJ, et al. *Lancet.* 2023;401:733-746. [12]Ahn MJ, et al. *J Clin Oncol.* 2025;43:260-272. [13]Mok TSK, et al. *J Clin Oncol.* 2024;42(17_suppl):LBA8509.

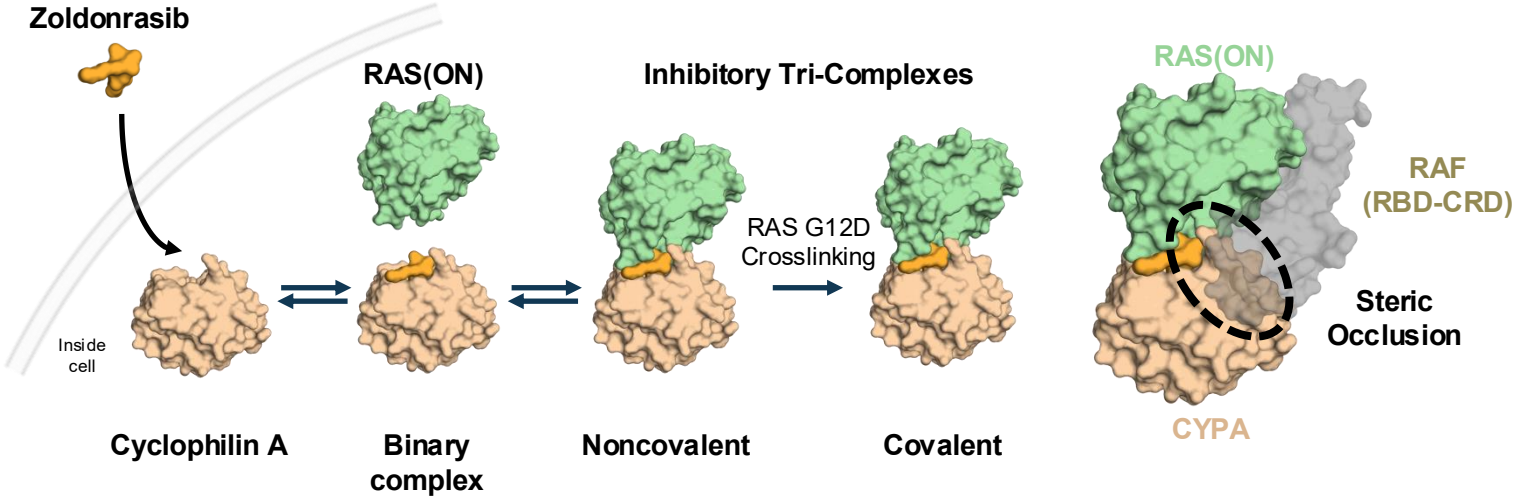
Zoldonrasib is an Oral, Mutant-Selective, Covalent Inhibitor Targeting the ON (Active, GTP-bound) State of RAS G12D

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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[1] and NSCLC[2]

Zoldonrasib Mechanism of Action



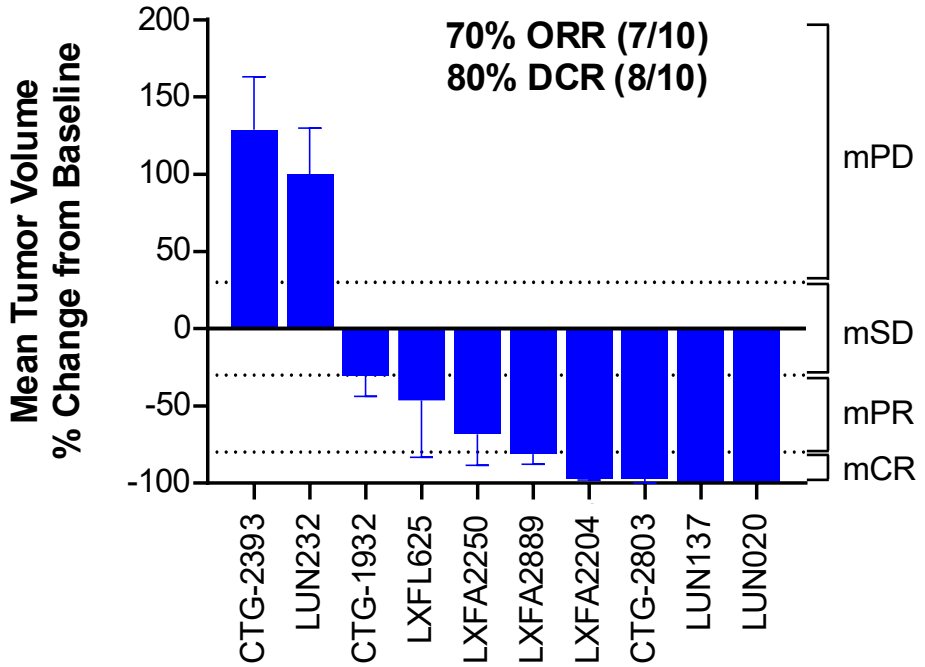
Zoldonrasib tri-complex sterically occludes RAF interaction and inhibits RAS(ON) oncogenic activity and downstream signaling

GTP, guanosine triphosphate; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma; RAF, rapidly accelerated fibrosarcoma. [1]Hong DS, et al. *Eur J Cancer*. 2024;211(Suppl1):114980. [2]Arbour KC, et al. *Cancer Res*. 2025;85(8_Suppl_2).

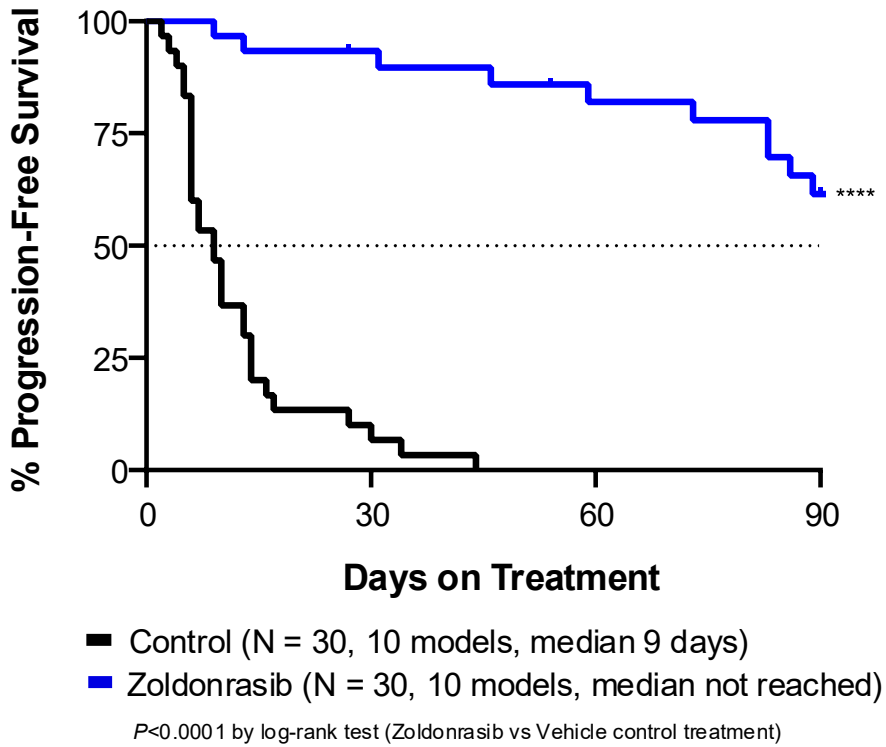
Zoldonrasib Drives Deep and Durable Regressions in KRAS G12D NSCLC Preclinical Models *In Vivo*

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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; KRAS, Kirsten rat sarcoma virus; 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; PO QD, orally once daily. 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 H, et al. *Nat Med*. 2015;21:1318-1325.); Progression defined as tumor doubling from baseline.

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

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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

- 1200 mg QD
- 600 mg BID
- 900 mg QD
- 450 mg BID
- 600 mg QD
- 300 mg BID
- 300 mg QD
- 150 mg QD

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

- Max administered dose was 1200 mg daily
- No dose-limiting toxicities observed
- Maximum tolerated dose not reached
- **1200 mg PO QD selected as the RP2D** in PDAC and NSCLC

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma; PO, orally, QD, once daily; RP2D, recommended phase 2 dose.

Demographics and Baseline Characteristics for Patients with KRAS G12D NSCLC Treated with Zoldonrasib 1200 mg QD

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	All treated (N = 40)	ICI and Platinum Chemo Treated (No Prior Docetaxel) (N = 27)
	Safety Population	**Efficacy Population**
Age, years, median (range)	66 (36, 86)	65 (36, 86)
Male, n (%)	17 (43)	10 (37)
ECOG PS 1, n (%)	27 (68)	18 (67)
Smoking Status		
Current/Past	22 (55)	12 (44)
Never	18 (45)	15 (56)
Number of prior anti-cancer therapies, median (range)	2 (0, 5)	1 (1, 4)
Number of prior anti-cancer therapies in metastatic setting, n (%)[a]		
0	1 (3)	0
1	21 (53)	18 (67)
2	13 (33)	9 (33)
2+	5 (13)	0
Brain metastases at baseline, n (%)	10 (25)	5 (19)
Metastatic at diagnosis [stage IV], n (%)	27 (68)	19 (70)

[a]One prior line of therapy in the metastatic setting included patients who progressed on prior therapy in an earlier setting within 6 months of last dose.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; QD, once daily.

Data cutoff: Dec 1, 2025

Treatment-Related Adverse Events (TRAEs) for Patients with KRAS G12D NSCLC Treated with Zoldonrasib 1200 mg QD

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All Patients with NSCLC Treated with Zoldonrasib 1200 mg PO QD (N = 40)				
Maximum Severity of Treatment-Related AEs	**Grade 1**	**Grade 2**	**Grade 3[a]**	**Any Grade**
Any TRAE, n (%)	23 (58)	8 (20)	5 (13)	36 (90)
TRAEs occurring in ≥10% of all patients, n (%)				
Nausea	16 (40)	1 (3)	0	17 (43)
Vomiting	12 (30)	1 (3)	0	13 (33)
Diarrhea	11 (28)	0	1 (3)	12 (30)
Rash[b]	7 (18)	0	0	7 (18)
Decreased appetite	3 (8)	2 (5)	0	5 (13)
Anemia	2 (5)	1 (3)	1 (3)	4 (10)
Fatigue	4 (10)	0	0	4 (10)
AST increased	4 (10)	0	0	4 (10)

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

Median time on zoldonrasib, months (range): 10.5 (1.3, 19.3).
[a]Grade 3 TRAEs include: 1 G3 diarrhea, 1 G3 anemia, 2 G3 blood creatine phosphokinase increased, 1 G3 facial paresis.
[b]Includes preferred terms of Dermatitis acneiform, Rash, Rash erythematous, Rash maculo-papular.
AE, adverse event; AST, aspartate transferase; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; PO, orally; QD, once daily; SAE, serious adverse event; TRAE, treatment-related adverse event.

Data cutoff: Dec 1, 2025

Dose Modification and Dose Intensity in Patients with KRAS G12D NSCLC Treated with Zoldonrasib 1200 mg QD

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TRAEs Leading to Zoldonrasib Action Taken	All NSCLC Treated 1200 mg PO QD (N = 40)
Dose modification, n (%)	
Dose interruption	6 (15)
Dose reduction	1 (3)
Dose discontinuation, n (%)	2 (5)[a]
Zoldonrasib Relative Dose Intensity	
Mean/Median dose intensity (%)	94/97

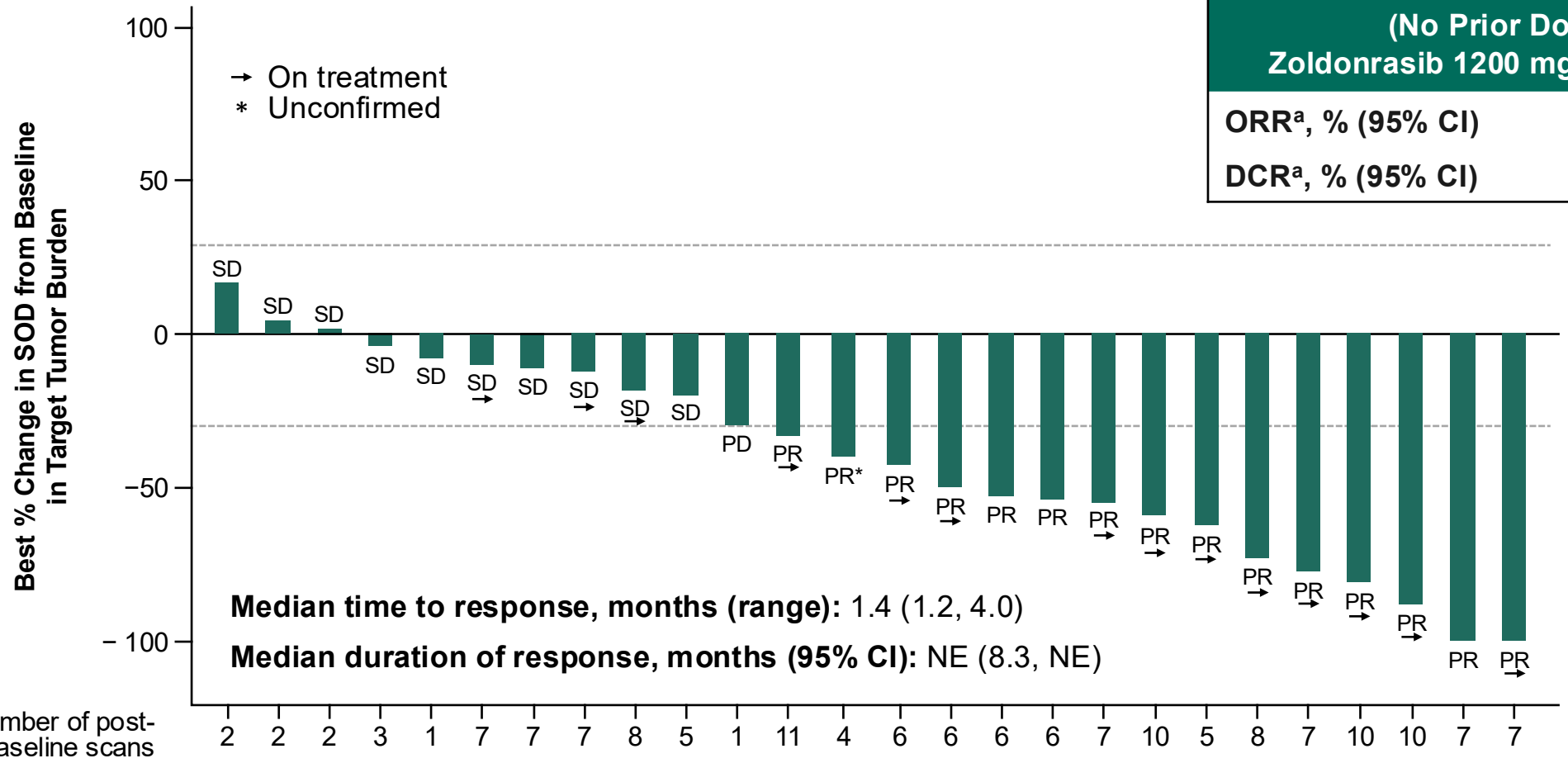
[a]TRAE dose discontinuations include: 1 patient with G1 pneumonitis, 1 patient with G1 vomiting.
G1, Grade 1; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; PO, orally; QD, once daily; TRAE, treatment-related adverse event.

Data cutoff: Dec 1, 2025

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

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ICI and Platinum Chemo Treated (No Prior Docetaxel) Zoldonrasib 1200 mg PO QD (N = 27)	
ORR[a], % (95% CI)	52 (32, 71)
DCR[a], % (95% CI)	93 (76, 99)



Median follow-up, months (range): 13.1 (9.1, 19.9).

[a]ORR (confirmed CR and PR) and DCR (CR+PR+SD) analyses included all NSCLC patients (with prior ICI and platinum chemotherapy treatment, but no docetaxel) who received first dose of zoldonrasib at least 14 weeks prior to data cutoff date. One patient was included in the denominator of ORR but not displayed on the waterfall plot due to lack of adequate baseline/post-baseline assessments.

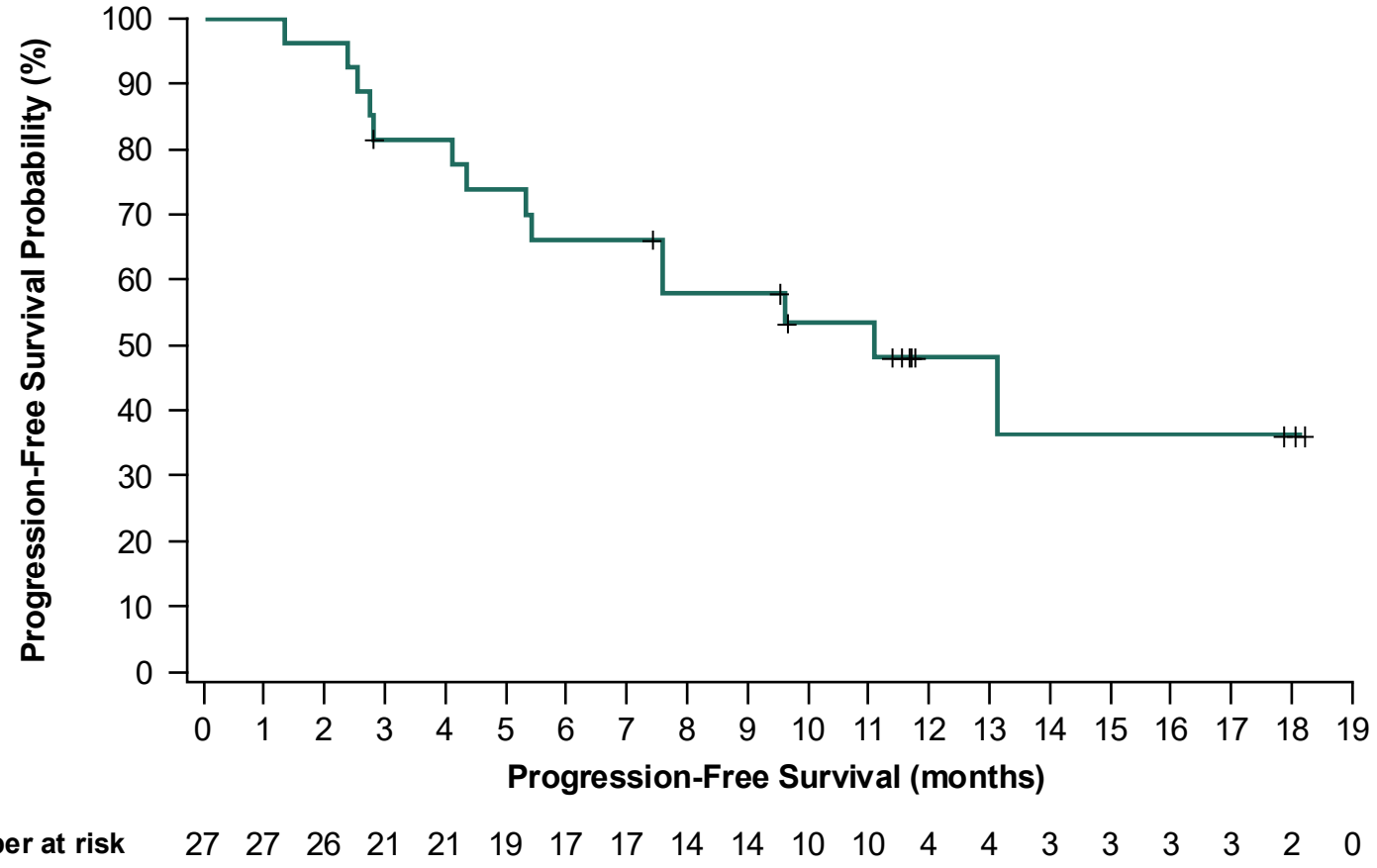
*One unconfirmed PR was excluded from the numerator of ORR because it will not confirm but was included in the denominator.

CI, confidence interval; CR, complete response; DCR, disease control rate; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma virus; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PO, orally; PR, partial response; QD, once daily; SD, stable disease; SOD, sum of diameters.

Data cutoff: Dec 1, 2025

Progression-Free Survival in Patients with KRAS G12D NSCLC Treated with Zoldonrasib 1200 mg QD

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ICI and Platinum Chemo Treated (No Prior Docetaxel) Zoldonrasib 1200 mg PO QD (N = 27)	
mPFS, months (95% CI)	11.1 (5.3, NE)
12-month PFS, % (95% CI)	48 (27, 66)

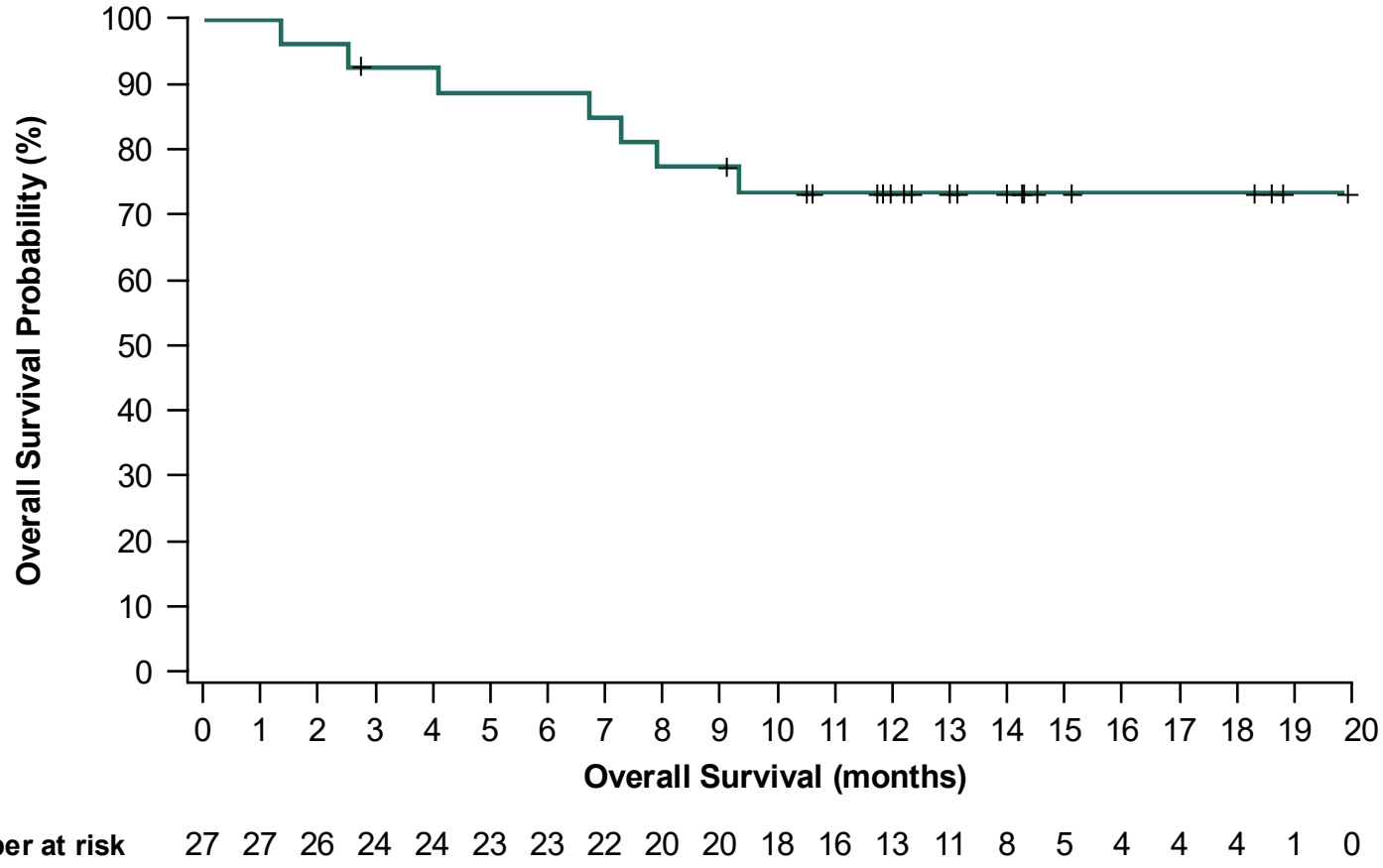
Median follow-up, months (range): 13.1 (9.1, 19.9).

CI, confidence interval; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma virus; m, median; NE, not estimable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PO, orally; QD, once daily.

Data cutoff: Dec 1, 2025

Overall Survival in Patients with KRAS G12D NSCLC Treated with Zoldonrasib 1200 mg QD

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ICI and Platinum Chemo Treated (No Prior Docetaxel) Zoldonrasib 1200 mg PO QD (N = 27)	
mOS, months (95% CI)	NE (NE, NE)
12-month OS, % (95% CI)	73 (52, 86)

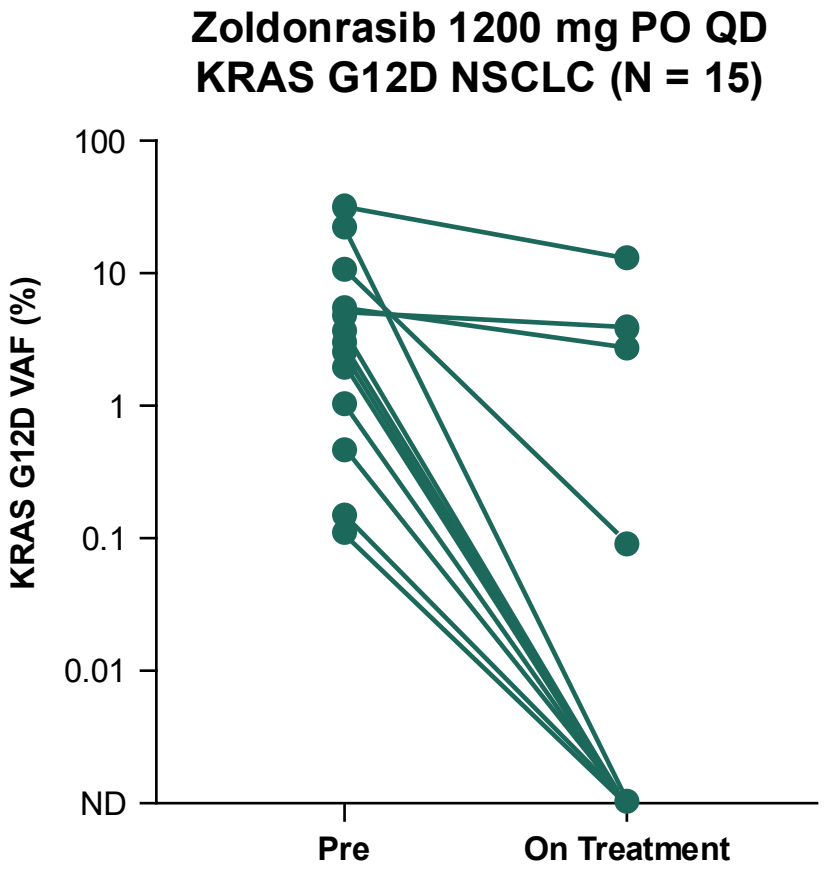
Median follow-up, months (range): 13.1 (9.1, 19.9).

CI, confidence interval; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma virus; m, median; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PO, orally; QD, once daily.

Data cutoff: Dec 1, 2025

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

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KRAS G12D VAF Clearance	Zoldonrasib 1200 mg PO QD
≥50% Clearance, % (n/N)	87 (13/15)
100% Clearance, % (n/N)	73 (11/15)

- 15 out of 27 patients with NSCLC treated with zoldonrasib 1200 mg PO QD (with prior ICI and platinum chemotherapy; no prior docetaxel) had detectable KRAS G12D in ctDNA at baseline (C1D1) and were evaluable for changes in KRAS G12D VAF on treatment (C2D1)
- Marked reduction in KRAS G12D VAF in ctDNA

C, cycle; ctDNA, circulating tumor DNA; D, day; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; PO, orally; QD, once daily; VAF, variant allele frequency.

Data cutoff: Dec 1, 2025

Conclusions

Zoldonrasib (RMC-9805) is an oral, potent, mutant-selective, covalent inhibitor of RAS(ON) G12D

Zoldonrasib is well tolerated and manageable with primarily Grade 1 treatment-related adverse events, no Grade 4 or 5 TRAEs, and high dose intensity

Zoldonrasib has demonstrated encouraging clinical activity at the RP2D of 1200 mg QD as measured by ORR, PFS, and preliminary OS in patients with previously treated KRAS G12D NSCLC

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)

GI, gastrointestinal; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; QD, once daily; RAS, rat sarcoma virus; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse events.

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