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Abstract 637

Safety and Efficacy of Zoldonrasib (RMC-9805) Plus Daraxonrasib (RMC-6236) in Patients With 2L+ KRAS G12D Metastatic Pancreatic Adenocarcinoma (mPDAC)

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Declaration of Interests

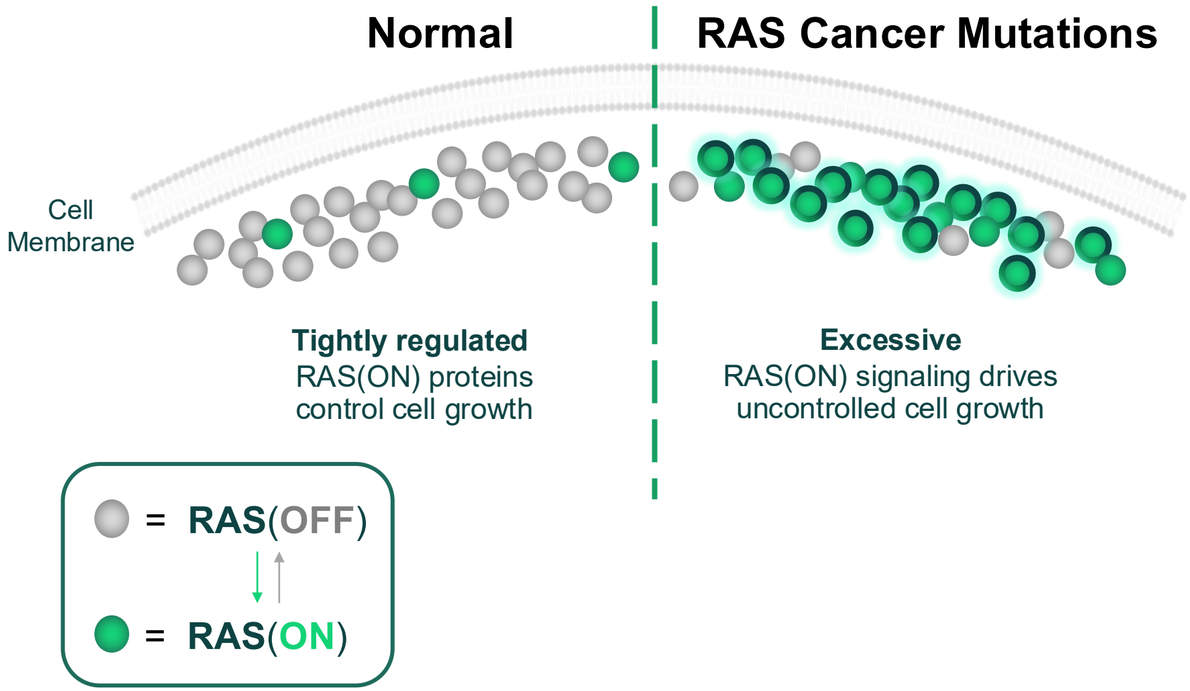
Nilofer S. Azad

- I have the following relevant financial relationships to disclose:
  Honoraria from: Agenus, Astellas, AstraZeneca, Beigene, Eli Lilly, GlaxoSmithKline, Incyte, Revolution Medicines, Tempus
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Large Unmet Need in RAS G12D Mutant Cancers

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



- PDAC is a high unmet need and RAS-driven disease, with 40% of patients harboring a KRAS G12D mutation[4]
- Patients with RAS G12D mutant mPDAC are reported to have an overall poorer prognosis vs those with RAS wild-type and other RAS mutations[5,6]
- Outcomes with chemotherapy include:
  - 2L: ORR, 3–7%; mPFS, 2.0–3.5 mo; mOS, 6.3–6.7 mo[7-10]
  - 3L+: ORR, 3–6%; mPFS, 1.9 mo; mOS, 5.0–5.1 mo[11,12]
- Outcomes with daraxonrasib in RAS G12 population include:
  - 2L (RASolute 302; randomized Phase 3): ORR, 33.2%; mPFS, 7.3 mo; mOS, 13.2 mo[13]
  - 3L+ (NCT05379985; single-arm): ORR, 21%; mPFS, 4.3 mo; mOS, 8.6 mo[14]

2L, second line; 3L+, third line and beyond; m, metastatic; mo, month; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PDAC, pancreatic adenocarcinoma; RAS, rat sarcoma virus.

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. Lee JK, et al. *NPJ Precis Oncol*. 2022;6:91. 5. Yousef A, et al. *NPJ Precis Oncol*. 2024;8:27. 6. Norton B, et al. *JAMA Netw Open*. 2025;8:e2453588. 7. Chung V, et al. *JAMA Oncol*. 2017;3:516-522; 8. Hecht JR, et al. *J Clin Oncol.* 2021;39:1108-1118; 9. Huffman BM, et al. *JAMA Network Open*. 2023;6:e2249720. 10. Hammel P, et al. ASCO GI 2022; 11. Gupta A, et al. *Frontiers Oncol*. 2023:13:1250136; 12. Enzler T, et al. *Eur J Cancer.* 2024:113950; 13. O'Reilly EM, et al. *N Engl J Med* 2026 doi: 10.1056/NEJMoa2605555 [online ahead of print]. 14. Wolpin BM, et al. *N Engl J Med*. 2026;394:1790-1802.

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Multiple Approaches to Targeting RAS G12D in the ON (Active, GTP-Bound) State

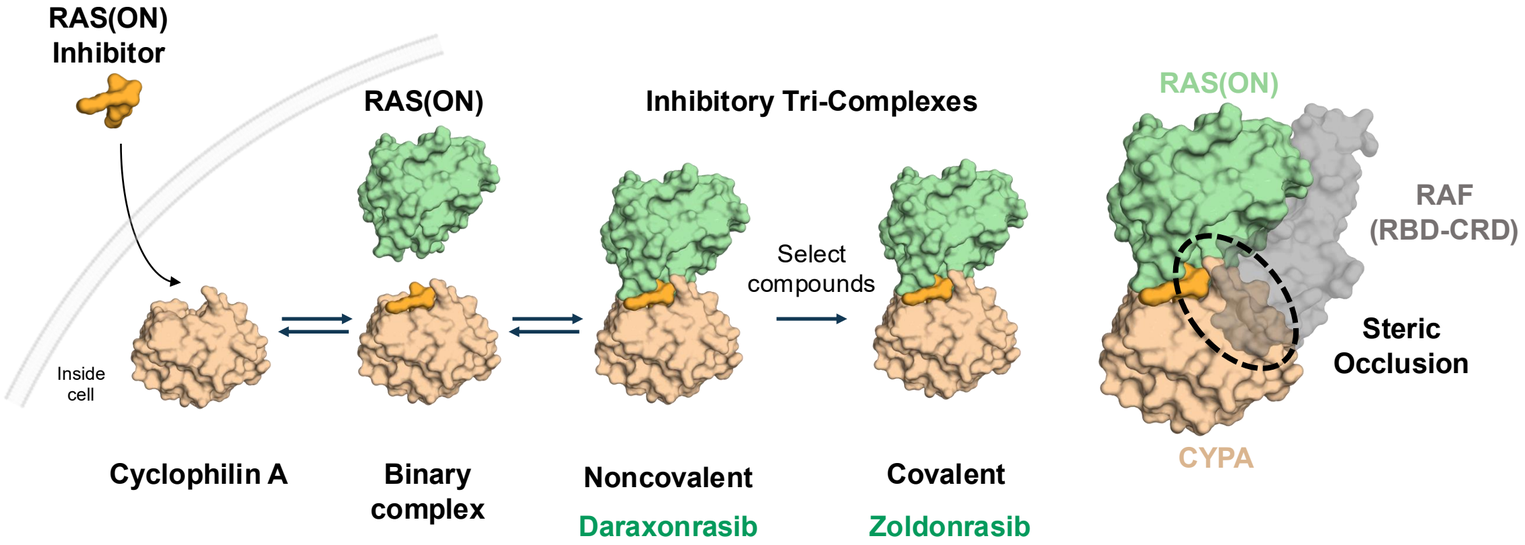
Daraxonrasib (RMC-6236)
RAS(ON) Multi-selective

- Noncovalent, multi-selective inhibitor of mutant and wild-type RAS(ON) proteins
- Overall survival improvement reported in 2L mPDAC vs SOC in RASolute 302[1]

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[2] and NSCLC[3,4]

Tri-Complex Inhibitor Mechanism of Action



Tri-complexes sterically occlude RAF interaction and inhibit RAS(ON) oncogenic activity and downstream signaling

2L, second line; GTP, guanosine triphosphate; m, metastatic; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; SOC, standard of care.

1. O'Reilly EM, et al. *N Engl J Med* 2026 doi: 10.1056/NEJMoa2605555 [online ahead of print]. 2. Hong DS, et al. *Eur J Cancer.* 2024;211(Suppl1):114980. 3. Arbour KC, et al. *Cancer Res*. 2025;85(8_Suppl_2). 4. Riess J, et al. Presented at: American Association of Cancer Research Annual Meeting. 2026 April 17-22; San Diego, CA.

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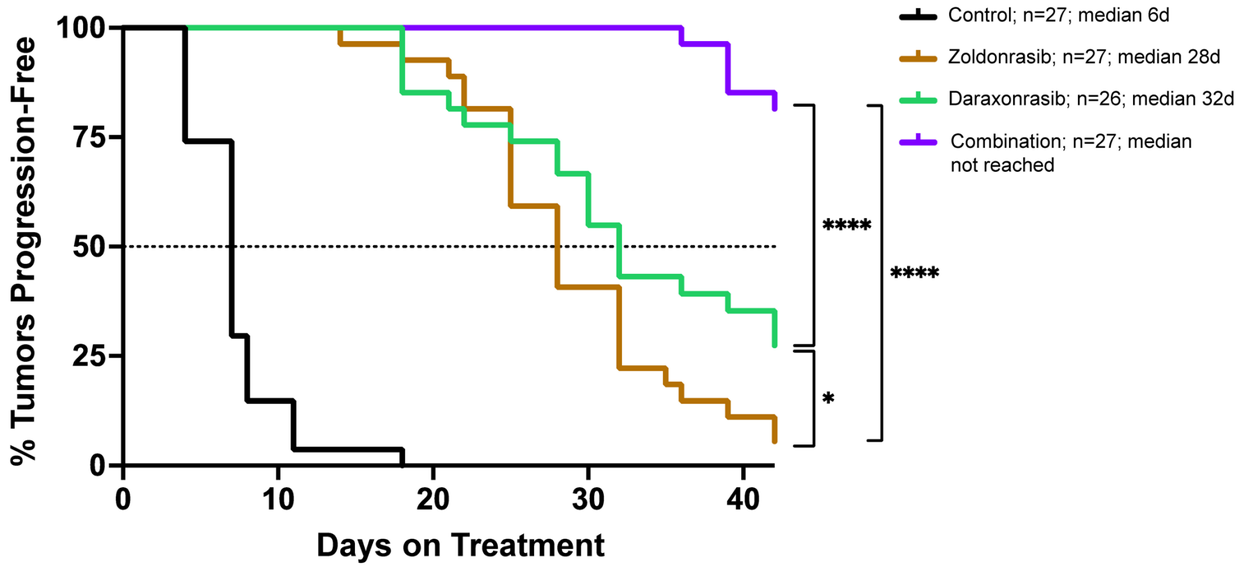
Clinical Development of RAS(ON) Inhibitor Doublet Supported by Durable Responses in Preclinical Models of KRAS G12D PDAC

In patients with PDAC, the RAS(ON) inhibitor doublet (zoldonrasib + daraxonrasib), compared with either agent alone, is hypothesized to:

- Increase RAS wild-type and mutant pathway suppression
- Deepen responses and increase response rate
- Delay acquired resistance

KPCY (*Kras*^{G12D}; *Trp53*^{R172H} - PDAC)[1]

Durable antitumor responses



In preclinical models, the RAS(ON) inhibitor doublet:

- Sustains KRAS G12D covalent target engagement
- Increases tumor RAS pathway suppression
- Deepens tumor responses and delays time to tumor progression

*P<.05 by log-rank test. ****P<.001 by log-rank test. Zoldonrasib dosed at 100 mg/kg PO QD. Daraxonrasib dosed at 25 mg/kg PO QD. Combination: zoldonrasib 100 mg/kg PO QD + daraxonrasib 25 mg/kg PO QD. KPCYc3 (2838c3), c4 (6499c4) and c5 (6419c5) derived as described in Li J, et al. *Immunity.* 2018;12(Suppl 2). d, day; PDAC, pancreatic adenocarcinoma; PO, orally; QD, once daily; RAS, rat sarcoma virus.

1. Singh M. Presented at: AACR Special Conference in Cancer Research: RAS Oncogenesis and Therapeutics. 2026 March 5-8; Los Angeles, CA.

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RMC-9805-001 Phase 1 Study (NCT06040541) Zoldonrasib + Daraxonrasib

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
- No prior treatment with a RAS-targeted therapy

Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Antitumor activity

Part 1: Dose Escalation

Zoldonrasib and daraxonrasib co-administered orally QD, 21-day treatment cycle

- **Zoldonrasib 1200 mg Daraxonrasib 300 mg**
- **Zoldonrasib 1200 mg Daraxonrasib 200 mg**
- **Zoldonrasib 1200 mg Daraxonrasib 100 mg**
- **Zoldonrasib 900 mg Daraxonrasib 100 mg**
- **Zoldonrasib 600 mg Daraxonrasib 100 mg**

Part 2: Dose Expansion and Dose Optimization

- No DLTs observed at any dose level
- No clinically meaningful exposure changes compared with monotherapy
- Zoldonrasib 1200 mg QD + daraxonrasib 300 mg QD was the maximum administered dose and selected as the RP2D in PDAC
- PDAC expansion cohorts enrolled at RP2D

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; KRAS, Kirsten rat sarcoma virus; PDAC, pancreatic adenocarcinoma; QD, once daily; RAS, rat sarcoma virus; RP2D, recommended Phase 2 dose.

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Demographics and Baseline Characteristics

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD	
	2L PDAC (N=30)	3L+ PDAC (N=30)
Age, median (range), years	69 (44–85)	69 (39–83)
Male, n (%)	12 (40)	15 (50)
ECOG PS 1, n (%)	19 (63)	22 (73)
Liver metastases at baseline, n (%)	25 (83)	21 (70)
Metastatic at diagnosis (stage IV), n (%)	18 (60)	13 (43)
Prior anticancer therapies, median (range), n	1 (1–3)	2 (2–8)
Prior anticancer therapies in metastatic setting, n (%)[a]		
1	30 (100)	0
2	0	18 (60)
>2	0	12 (40)

Data cutoff: 9 Feb 2026.

[a]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. 2L, second line; 3L+, third line and beyond; ECOG PS, Eastern Cooperative Oncology Group performance status; PDAC, pancreatic adenocarcinoma; QD, once daily.

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Treatment-Related Adverse Events With Zoldonrasib + Daraxonrasib in 2L+ KRAS G12D PDAC

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD All 2L+ PDAC Treated (N=60)	
	Any Grade	**Grade ≥3**
Any study drug-related AE, n (%)	58 (97)	21 (35)[a]
TRAEs occurring in ≥10% of all patients, n (%)		
Rash[b]	54 (90)	7 (12)
Diarrhea	38 (63)	3 (5)
Nausea	34 (57)	1 (2)
Stomatitis/mucositis[c]	32 (53)	4 (7)
Fatigue	17 (28)	2 (3)
Vomiting	17 (28)	1 (2)
Anemia	12 (20)	6 (10)
Aspartate aminotransferase increased	7 (12)	0
Decreased appetite	7 (12)	0
Thrombocytopenia	7 (12)	0
Alanine aminotransferase increased	6 (10)	0
Edema peripheral	6 (10)	0

- No new or unexpected safety findings; TRAEs broadly consistent with the established profile of daraxonrasib monotherapy[1,2]

Data cutoff: 9 Feb 2026. Median (range) treatment duration of zoldonrasib is 7.9 (0.1–14.9) months. Median (range) treatment duration of daraxonrasib is 7.5 (0.1–14.9) months.

[a]No Grade 4 TRAES were reported. One Grade 5 TRAE of intestinal perforation was reported in a patient treated with zoldonrasib 1200 mg QD + daraxonrasib 300 mg QD. [b]Rash includes preferred terms of dermatitis acneiform, rash, rash maculo-papular, and rash pruritic. [c]Stomatitis/mucositis includes preferred terms of stomatitis, mucosal inflammation, and aphthous ulcer. 2L+, second line and beyond; AE, adverse event; KRAS, Kirsten rat sarcoma virus; PDAC, pancreatic adenocarcinoma; QD, once daily; TRAE, treatment-related adverse event.

1. O'Reilly EM, et al. *N Engl J Med* 2026 doi: 10.1056/NEJMoa2605555 [online ahead of print].
2. Wolpin BM, et al. *N Engl J Med*. 2026;394:1790-1802.

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Dose Modifications of Zoldonrasib + Daraxonrasib in 2L+ KRAS G12D PDAC

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD All 2L+ PDAC Treated (N=60)	
	Zoldonrasib 1200 mg QD	Daraxonrasib 300 mg QD
Dose modification, n (%)[a]		
Dose interruption	24 (40)	34 (57)
Dose reduction	5 (8)	18 (30)
Dose discontinuation, n (%)[a]	1 (2)[b]	3 (5)[c]
Mean dose intensity, %	88	76
Median dose intensity, %	96	82

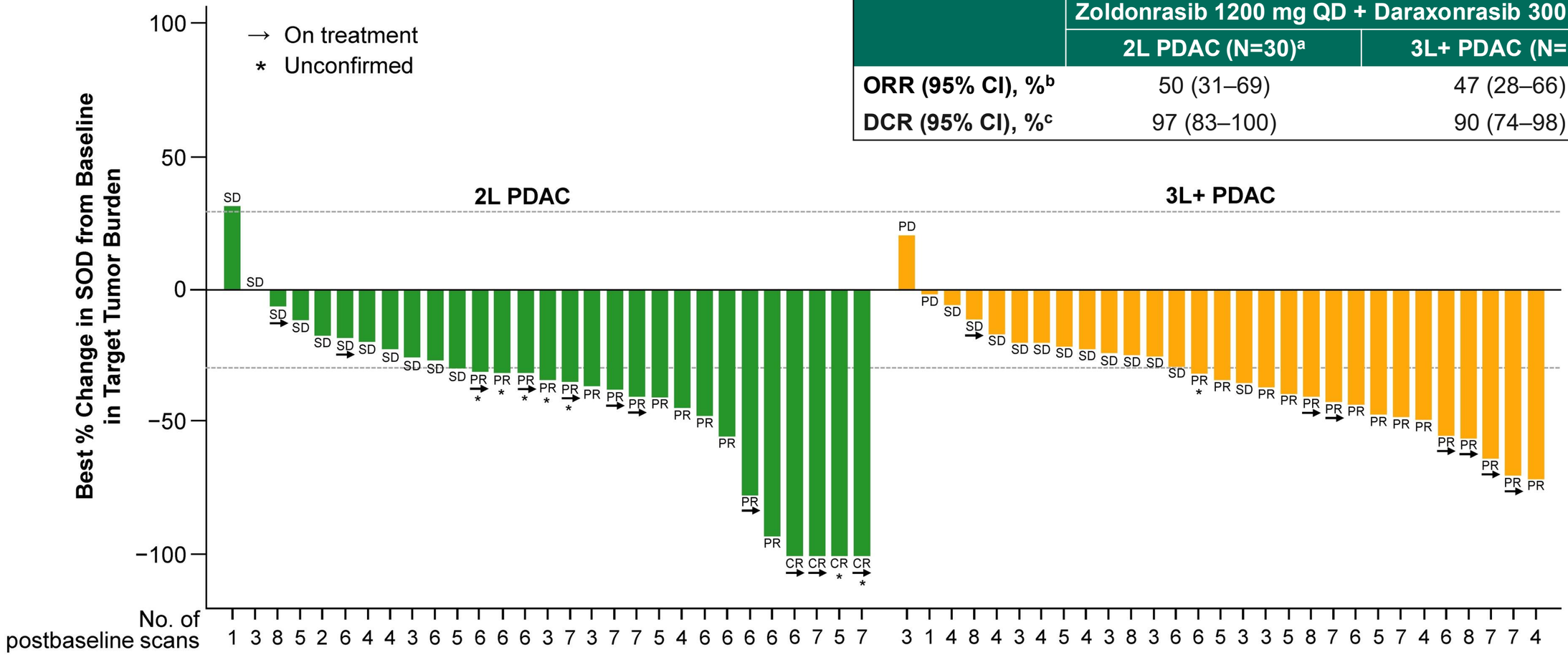
- Dose intensity of zoldonrasib and daraxonrasib remained high in combination
- Few patients discontinued either study drug

Data cutoff: 9 Feb 2026. Median (range) treatment duration of zoldonrasib is 7.9 (0.1–14.9) months. Median (range) treatment duration of daraxonrasib is 7.5 (0.1–14.9) months.
[a]Action taken due to TRAEs related to any study drug. [b]One patient discontinued due to Grade 2 diarrhea and flatulence. [c]Two patients discontinued due to Grade 1 and Grade 2 mucosal inflammation. One patient discontinued due to Grade 3 rash. 2L+, second line and beyond; KRAS, Kirsten rat sarcoma virus; PDAC, pancreatic adenocarcinoma; QD, once daily; TRAE, treatment-related adverse event.

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ORR and DCR of Zoldonrasib + Daraxonrasib in 2L and 3L+ KRAS G12D PDAC

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD	
	2L PDAC (N=30)[a]	3L+ PDAC (N=30)[a]
ORR (95% CI), %[b]	50 (31–69)	47 (28–66)
DCR (95% CI), %[c]	97 (83–100)	90 (74–98)



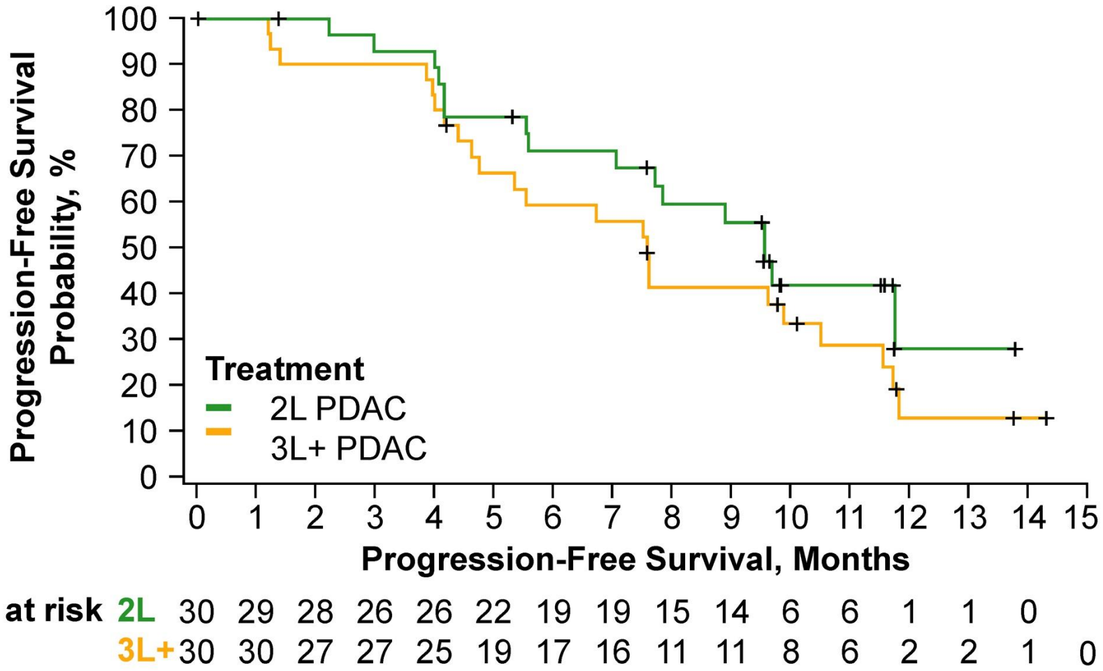
Data cutoff: 9 Feb 2026. Median follow-up (2L PDAC), months (range): 12.0 (9.9–14.1); Median follow-up (3L+ PDAC), months (range): 12.6 (10.7–14.9).

[a]Includes all patients with PDAC who had ≥14 weeks of follow up prior to data cutoff. One patient with unconfirmed (PR*) in 2L will never confirm due to PD but remains on treatment. [b]ORR includes confirmed and pending CR and PR. One patient in 2L and one patient in 3L+ were included in the denominator for ORR and DCR but not the waterfall plot due to lack of adequate post-baseline assessments. [c]DCR includes CR+PR+SD. 2L, second line; 3L+, third line and beyond; CR, complete response; DCR, disease control rate; KRAS, Kirsten rat sarcoma virus; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PR, partial response; QD, once daily; SD, stable disease; SOD, sum of diameters.

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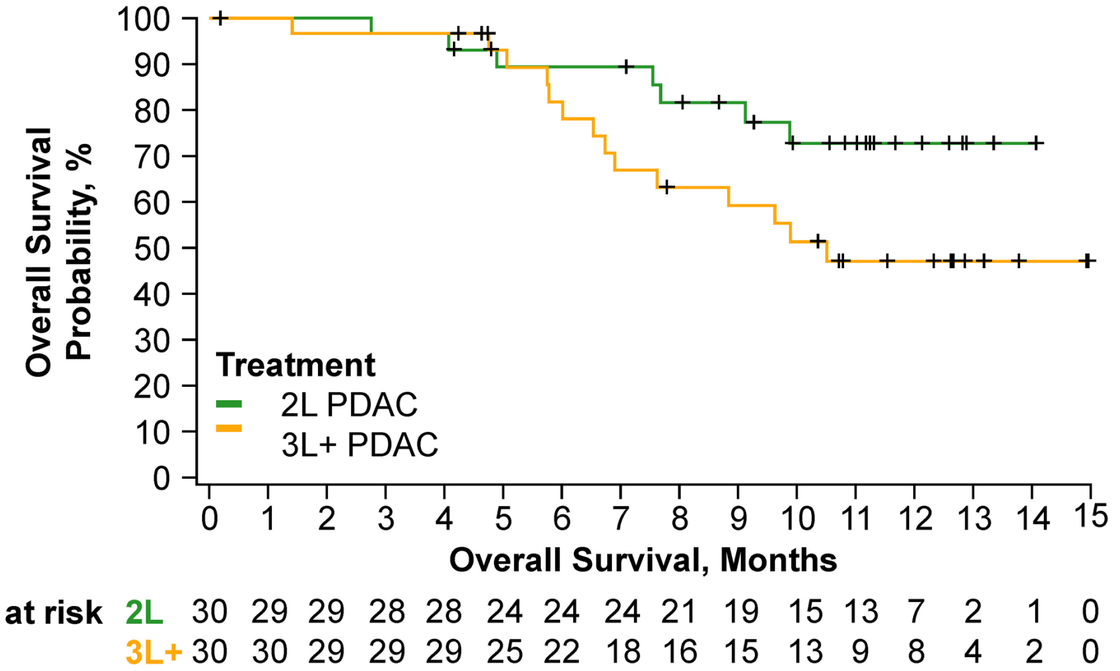
PFS and OS of Zoldonrasib + Daraxonrasib in 2L and 3L+ KRAS G12D PDAC

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD	
	2L PDAC (N=30)	3L+ PDAC (N=30)
mPFS (95% CI), months	9.6 (7.1–NE)	7.6 (4.6–10.5)
6-month PFS (95% CI), %	71 (50–84)	59 (39–74)



No. at risk																
2L	30	29	28	26	26	22	19	19	15	14	6	6	1	1	0	
3L+	30	30	27	27	25	19	17	16	11	11	8	6	2	2	1	0

	Zoldonrasib 1200 mg QD + Daraxonrasib 300 mg QD	
	2L PDAC (N=30)	3L+ PDAC (N=30)
mOS (95% CI), months	NE (NE–NE)	10.5 (6.7–NE)
6-month OS (95% CI), %	89 (71–97)	82 (62–92)



No. at risk																
2L	30	29	29	28	28	24	24	24	21	19	15	13	7	2	1	0
3L+	30	30	29	29	29	25	22	18	16	15	13	9	8	4	2	0

Data cutoff: 9 Feb 2026. Median follow-up (2L PDAC), months (range): 12.0 (9.9–14.1); Median follow-up (3L+ PDAC), months (range): 12.6 (10.7–14.9).

2L, second line; 3L+, third line and beyond; KRAS, Kirsten rat sarcoma virus; m, median; NE, not estimable; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; QD, once daily.

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Conclusions

- Zoldonrasib 1200 mg PO QD plus daraxonrasib 300 mg PO QD (RP2D) showed a manageable safety and tolerability profile in patients with 2L+ KRAS G12D PDAC that was broadly consistent with the established profile of daraxonrasib monotherapy
- The novel RAS(ON) doublet demonstrated compelling preliminary clinical activity in patients with 2L and 3L+ mPDAC, consistent with hypotheses derived from preclinical data
- These safety and clinical activity data support the planned pivotal global, Phase 3 RASolute 309 study of zoldonrasib plus daraxonrasib in patients with 1L KRAS G12D PDAC

1L, first line; 2L, second line; 2L+, second-line and beyond; 3L+, third line and beyond; KRAS, Kirsten rat sarcoma virus; m, metastatic; PDAC, pancreatic adenocarcinoma; PO, orally; QD, once daily; RP2D, recommended Phase 2 dose.

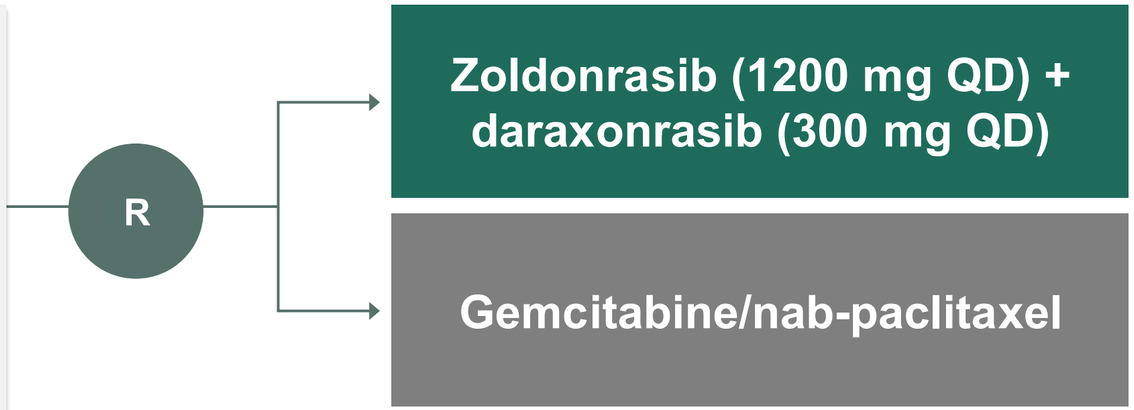
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RASolute 309

Phase 3, Global, Randomized, Open-Label Study of Zoldonrasib + Daraxonrasib vs Gemcitabine/Nab-Paclitaxel in Patients With 1L KRAS G12D mPDAC

Key Eligibility Criteria

- Confirmed metastatic pancreatic adenocarcinoma
- No prior systemic therapy for metastatic disease
- Documented KRAS G12D mutation
- ECOG PS 0–1



Study initiation remains on track for the second half of 2026

1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; KRAS, Kirsten rat sarcoma virus; mPDAC, metastatic pancreatic adenocarcinoma; QD, once daily.

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