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Abstract 635

Safety and Efficacy of Zoldonrasib (RMC-9805) Plus Chemotherapy in Patients (Pts) With 1L RAS G12D Metastatic Pancreatic Adenocarcinoma (mPDAC)

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Declaration of Interests

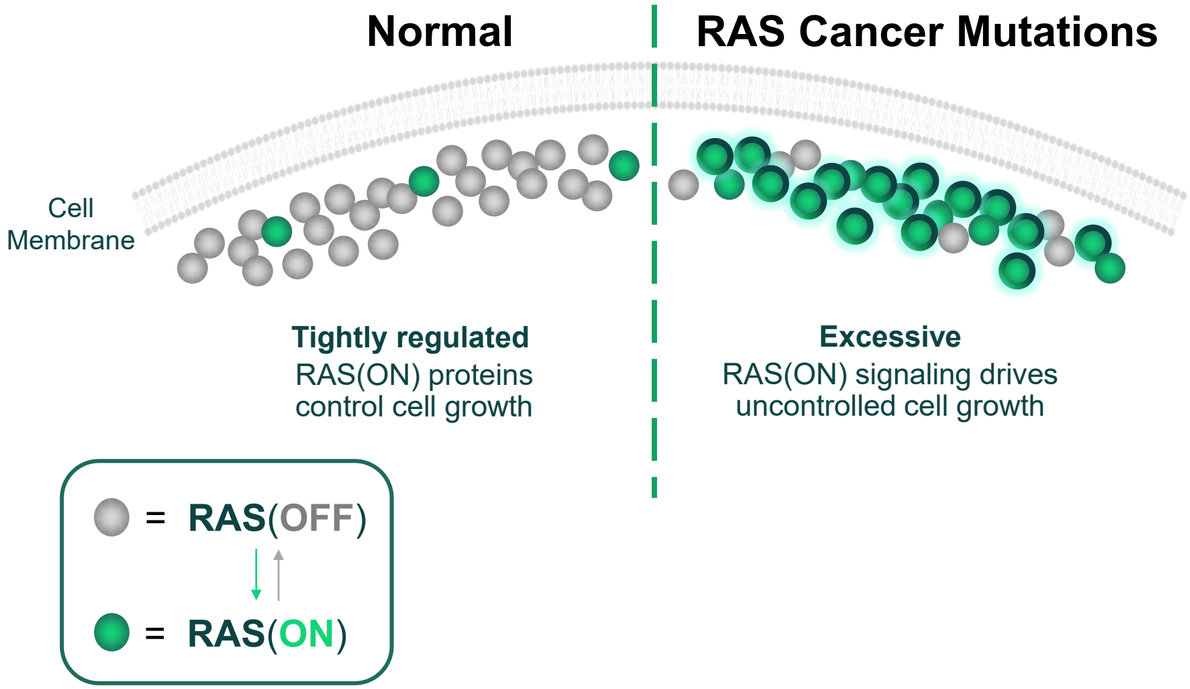
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- I have the following relevant financial relationships to disclose:
  Employee of: Dana-Farber Cancer Institute, Boston, MA, USA
  Consultant for: Agenus, BeiGene, BMS/Mirati, Cancer Panels, EcoR1 Capital, GRAIL, Harbinger Health, Immuneering, Ipsen, Lustgarten Foundation, Revolution Medicines, SystImmune, Takeda, Tango Therapeutics, Third Rock Ventures
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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 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]
- Standard 1L chemotherapy for PDAC provides limited benefit
  - 1L: ORR, 23–43%; mPFS, 5.5–7.1 mo; mOS, 8.5–11.7 mo[7-10]

1L, first line; m, metastatic; mPFS, median progression-free survival; mo, month; mOS, median overall 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. Conroy T, et al. *N Engl J Med.* 2011;364:1817-1825. 8. Von Hoff DD, et al. *N Engl J Med.* 2013;369:1691-1703. 9. Wainberg ZA, et al. *Lancet*. 2023;402:1272-1281. 10. Bekaii-Saab T, et al. *eClinMed*. 2023; 58:101897.

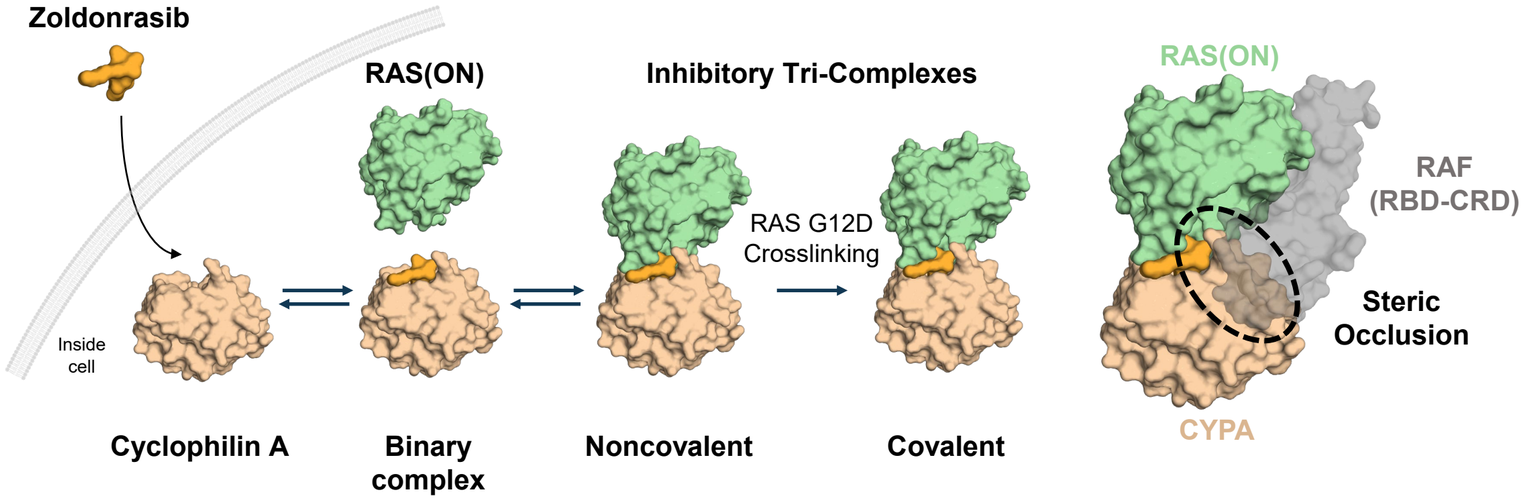
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Zoldonrasib Is an Oral, Mutant-Selective Covalent Inhibitor Targeting the ON (Active, GTP-Bound) State of RAS G12D

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[2,3]
- Breakthrough Therapy Designation granted by the FDA for previously treated NSCLC[4]

Zoldonrasib Mechanism of Action



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

FDA, US Food and Drug Administration; GTP, guanosine triphosphate; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus. 1. Hong DS, et al. *Eur J Cancer.* 2024;211(Suppl1):114980. 2. Arbour KC, et al. *Cancer Res.* 2025;85(8_Suppl_2). 3. Riess J, et al. Presented at: American Association of Cancer Research Annual Meeting. 2026 April 17-22; San Diego, CA. 4. Revolution Medicines. News Release. Accessed 2026 May 22. https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy-1.

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RMC-GI-102 Platform Study (NCT06445062)

Key Eligibility Criteria[a]

- Metastatic PDAC with RAS G12D mutations
- No prior systemic therapy for metastatic disease
- ECOG PS 0–1
- Patients with untreated CNS metastases or impaired gastrointestinal function were not allowed

Key Endpoints

- Safety and tolerability
- Antitumor activity
- Determine zoldonrasib RP2D in combination with mFFX or GnP

Part 1: Dose Escalation

Zoldonrasib 1200 mg QD + **Modified FOLFIRINOX[b]** → **Part 2: Dose Expansion**

Zoldonrasib 1200 mg QD + **Gemcitabine + nab-paclitaxel[c]** → **Part 2: Dose Expansion**

Choice of chemotherapy per Investigator
(Dose-escalation and -expansion cohorts were not randomized)

- Zoldonrasib administered orally QD on a 28-day treatment cycle[d]
- The zoldonrasib starting dose was 1200 mg QD (monotherapy RP2D)
- No DLTs were observed in Part 1 for either regimen
- Zoldonrasib 1200 mg QD was selected as the combination RP2D for both regimens

[a]Refers to zoldonrasib-only sub-protocols. [b]mFFX = oxaliplatin IV at 85 mg/m^2, leucovorin IV at 400 mg/m^2, irinotecan IV at 150 mg/m^2, 5-fluorouracil IV at 2400 mg/m^2 (over 46-hour) given Q2W. [c]GnP = gemcitabine IV at 1000 mg/m^2, nab-paclitaxel IV at 125 mg/m^2 given Days 1, 8, and 15 on a 28-day cycle. [d]One treatment cycle equals 2 days. CNS, central nervous system; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; GnP, gemcitabine and nab-paclitaxel; IV, intravenous; mFFX, modified FOLFIRINOX; PDAC, pancreatic adenocarcinoma; Q2W, every 2 weeks; QD, once daily; RAS, rat sarcoma virus; RP2D, recommended phase 2 dose.

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Demographics and Baseline Characteristics

	Zoldonrasib 1200 mg QD + mFFX (N=41)	Zoldonrasib 1200 mg QD + GnP (N=40)
Age, median (range), years	62 (40–83)	69 (36–83)
Male, n (%)	23 (56)	24 (60)
ECOG PS 1, n (%)	27 (66)	22 (55)
Liver metastases at baseline, n (%)	36 (88)	26 (65)
Metastatic at diagnosis (stage IV), n (%)	36 (88)	17 (43)
Baseline tumor burden, median (range), mm[a]	87 (19–207)	46 (10–263)
Prior anticancer therapies in nonmetastatic setting, n (%)[b]		
Neoadjuvant/adjuvant	3 (7)	19 (48)
Locally advanced	0	2 (5)
History of pancreatic resection, n (%)	5 (12)	21 (53)

Among patients selected by investigators for zoldonrasib + GnP (vs zoldonrasib + mFFX):

- Tumor burden and the presence of liver metastasis were lower at baseline
- Approximately half were diagnosed with early-stage disease and received prior anticancer therapy

Data cutoff: 8 Feb 2026.

[a]Tumor burden is defined as the sum of diameters of target lesions. [b]Patients who received neoadjuvant or adjuvant therapy were eligible if metastatic disease occurred ≥6 months after completing neoadjuvant or adjuvant therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; GnP, gemcitabine and nab-paclitaxel; mFFX, modified FOLFIRINOX; QD, once daily.

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Treatment-Related Adverse Events With Zoldonrasib + mFFX in 1L RAS G12D PDAC

	Zoldonrasib 1200 mg QD + mFFX (N=41)	
	Any Grade	**Grade ≥3**
Any study drug-related AE, n (%)	40 (98)	25 (61)
TRAEs occurring in ≥20% of all patients, n (%)		
Diarrhea	32 (78)	4 (10)
Nausea	25 (61)	1 (2)
Fatigue	21 (51)	2 (5)
Neutrophil count decreased	20 (49)	15 (37)
Vomiting	20 (49)	0
Platelet count decreased	18 (44)	3 (7)
Peripheral sensory neuropathy	15 (37)	1 (2)
Anemia	11 (27)	5 (12)
Paresthesia	11 (27)	0

- TRAEs broadly consistent with the established profile of the mFFX regimen[1]
- No new or unexpected safety findings
- Diarrhea was the most common TRAE, with the majority of cases being Grade 1 or 2
- No Grade 5 TRAEs

Data cutoff: 8 Feb 2026. Median (range) treatment duration for zoldonrasib is 3.9 (0.2–10.3) months.

1L, first-line; AE, adverse event; mFFX, modified FOLFIRINOX; PDAC, pancreatic adenocarcinoma; QD, once daily; RAS, rat sarcoma virus; TRAE, treatment-related adverse event. 1. Conroy T, et al. *N Engl J Med*. 2011;364:1817-1825.

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Treatment-Related Adverse Events With Zoldonrasib + GnP in 1L RAS G12D PDAC

	Zoldonrasib 1200 mg QD + GnP (N=40)	
	Any Grade	**Grade ≥3**
Any study drug-related AE, n (%)	40 (100)	32 (80)
TRAEs occurring in ≥20% of all patients, n (%)		
Fatigue	32 (80)	10 (25)
Nausea	28 (70)	1 (3)
Neutrophil count decrease	22 (55)	14 (35)
Anemia	19 (48)	11 (28)
Rash[a]	17 (43)	0
Diarrhea	17 (43)	0
Peripheral sensory neuropathy	17 (43)	1 (3)
Alopecia	15 (38)	0
Vomiting	15 (38)	1 (3)
Decreased appetite	12 (30)	1 (3)
Platelet count decreased	10 (25)	4 (10)
Aspartate aminotransferase increased	9 (23)	1 (3)
Edema	9 (23)	1 (3)
White blood cell count decreased	8 (20)	4 (10)

- TRAEs broadly consistent with the established profile of the GnP regimen[1]
- No new or unexpected safety findings
- Fatigue was the most common TRAE, with the majority of cases being Grade 1 or 2
- No Grade 5 TRAEs

Data cutoff: 8 Feb 2026. Median (range) treatment duration for zoldonrasib is 4.7 (0.5–11.9) months.

[a]Rash consists of dermatitis acneiform, rash, rash macular, and rash maculopapular. 1L, first line; AE, adverse event; GnP, gemcitabine and nab-paclitaxel; PDAC, pancreatic adenocarcinoma; QD, once daily; RAS, rat sarcoma virus; TRAE, treatment-related adverse event. 1. Wainberg ZA, et al. *Lancet*. 2023;402:1272-1281.

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Dose Modification Due to TRAEs and Dose Intensity of Zoldonrasib + Chemotherapy in 1L RAS G12D PDAC

	Zoldonrasib 1200 mg QD + mFFX (N=41)		Zoldonrasib 1200 mg QD + GnP (N=40)	
	Zoldonrasib	mFFX	Zoldonrasib	GnP
Dose modification, n (%)[a]				
Dose interruption	15 (37)	24 (59)	14 (35)	30 (75)
Dose reduction	7 (17)	21 (51)	2 (5)	27 (68)
Dose discontinuation, n (%)[a]	0	10 (24)	1 (3)[b]	9 (23)
Mean dose intensity, %	86	73[c]	90	60[c]
Median dose intensity, %	99	72[c]	97	59[c]

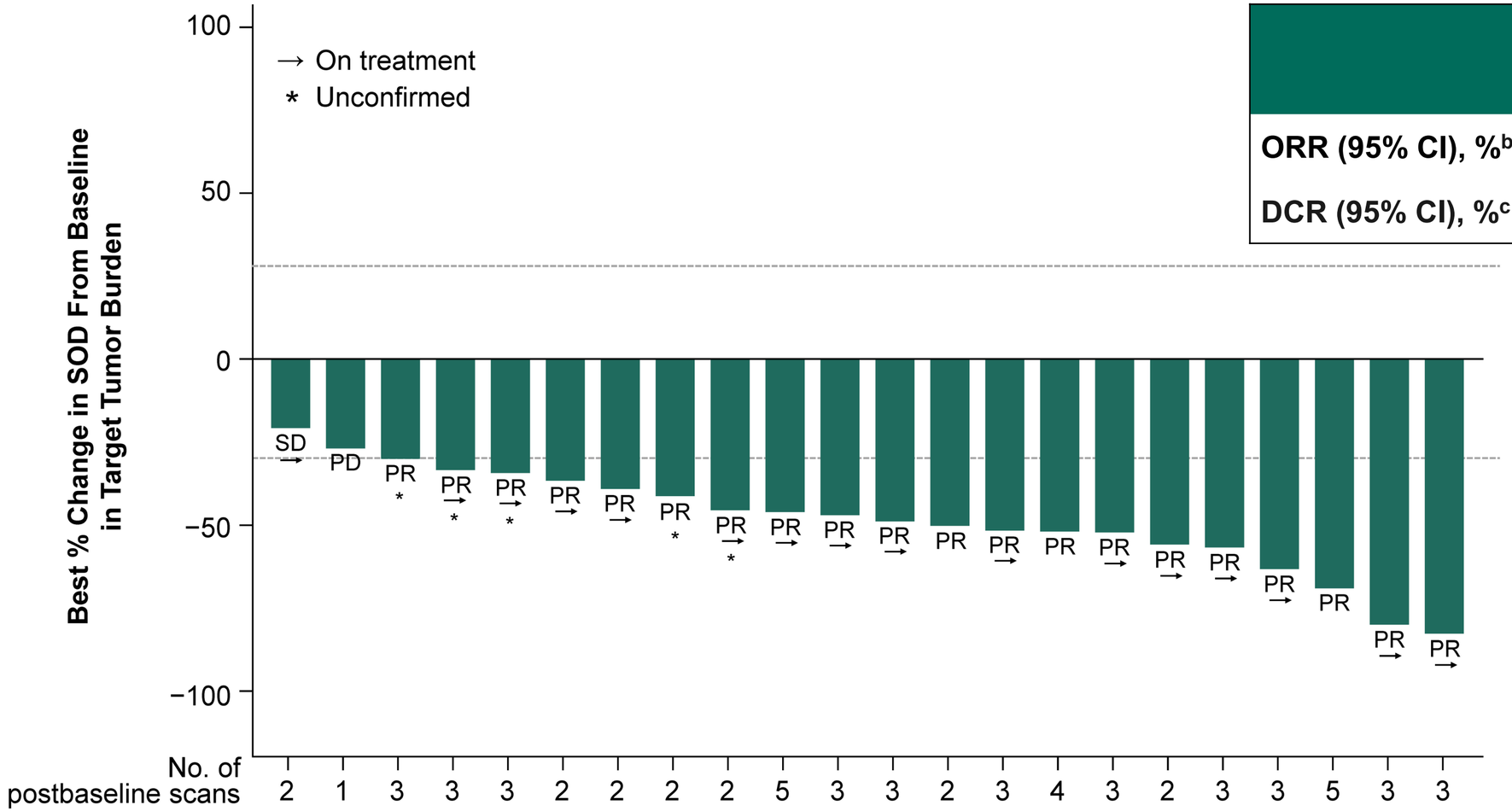
Zoldonrasib dose intensity remained high in combination with mFFX or GnP

Data cutoff: 8 Feb 2026. Median (range) treatment duration for zoldonrasib (given with mFFX) is 3.9 (0.2–10.3) months. Median (range) treatment duration for zoldonrasib (given with GnP) is 4.7 (0.5–11.9) months.

[a]Action taken related to any study drug. [b]Due to Grade 4 retroperitoneal hemorrhage. [c]The dose intensity for chemotherapy was derived as the minimum relative dose intensity among all chemotherapy components. 1L, first line; GnP, gemcitabine and nab-paclitaxel; mFFX, modified FOLFIRINOX; PDAC, pancreatic adenocarcinoma; QD, once daily; RAS, rat sarcoma virus; TRAE, treatment-related adverse event.

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ORR and DCR With Zoldonrasib + mFFX in 1L RAS G12D PDAC



	Zoldonrasib 1200 mg QD + mFFX[a] (N=22)
ORR (95% CI), %[b]	82 (60–95)
DCR (95% CI), %[c]	96 (77–100)

- PFS and OS estimates remain immature due to limited follow-up at time of DCO

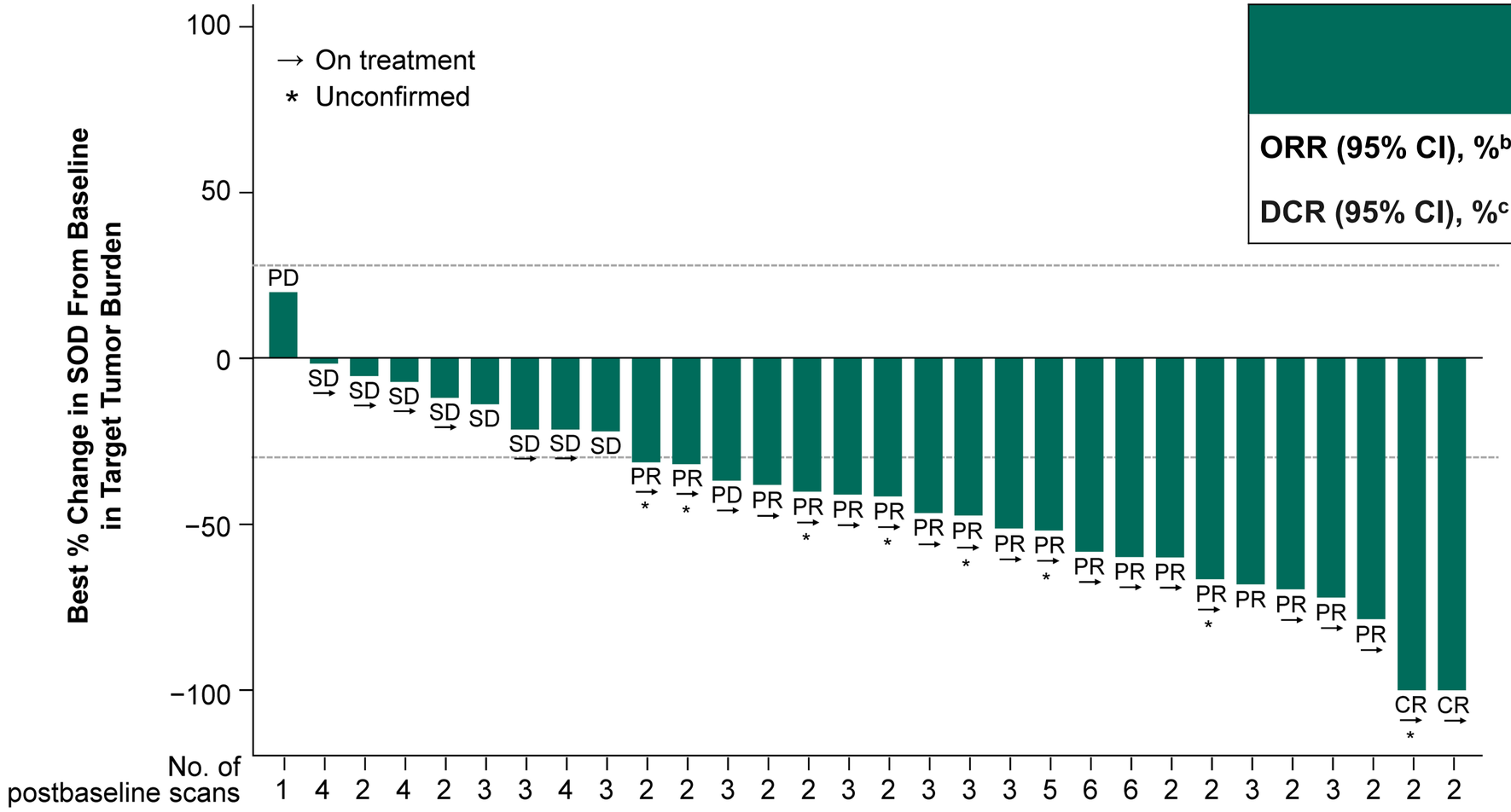
Data cutoff: 8 Feb 2026. Median follow-up (N=22; ≥18 weeks follow up), months (range): 6.1 (4.1–10.3).

[a]Includes all patients with PDAC who had ≥18 weeks of follow up prior to data cutoff. [b]ORR includes confirmed and pending CR and PR with treatment ongoing and without PD reported. [c]DCR includes CR+PR+SD.

1L, first line; CR, complete response; DCO, data cutoff; DCR, disease control rate; mFFX, modified FOLFIRINOX; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PR, partial response; QD, once daily; RAS, rat sarcoma virus; SD, stable disease; SOD, sum of diameters.

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ORR and DCR With Zoldonrasib + GnP in 1L RAS G12D PDAC



	Zoldonrasib 1200 mg QD + GnP[a] (N=31)
ORR (95% CI), %[b]	61 (42–78)
DCR (95% CI), %[c]	90 (74–98)

- PFS and OS estimates remain immature due to limited follow-up at time of DCO

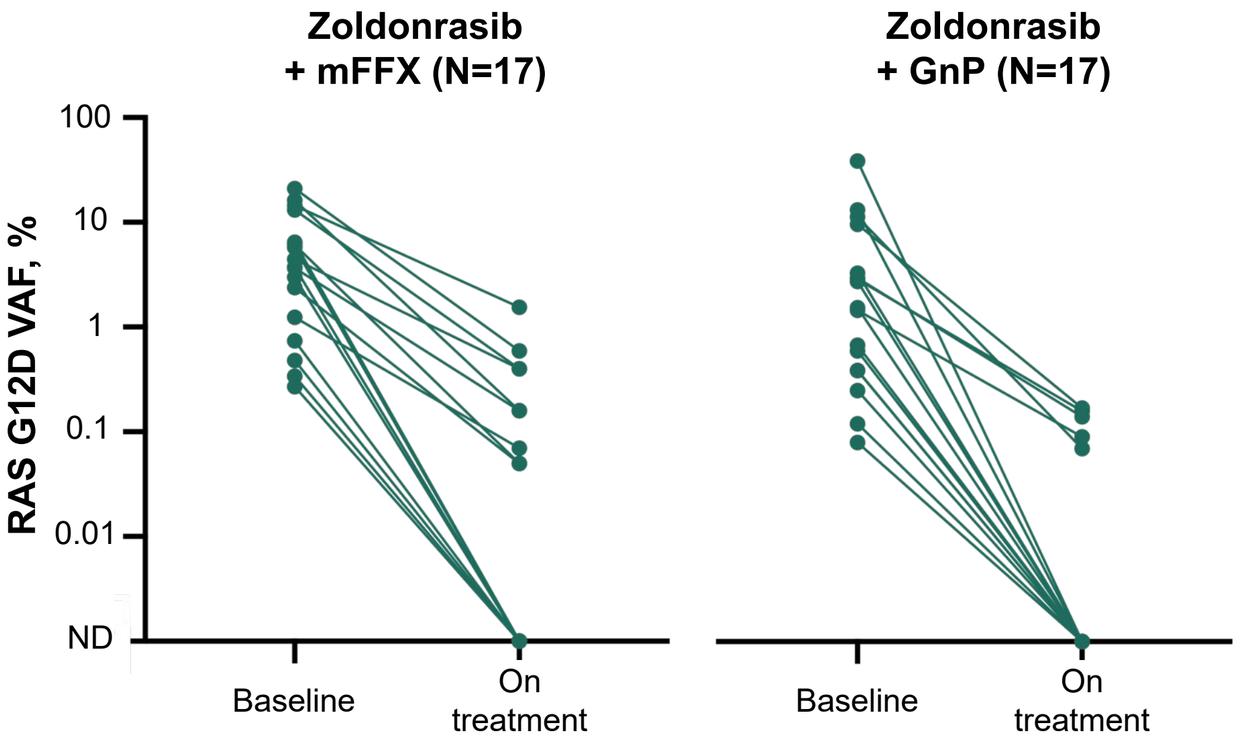
Data cutoff: 8 Feb 2026. Median follow-up (N=31; ≥18 weeks follow up), months (range): 5.7 (4.1–11.9).

[a]Includes all patients with PDAC who had ≥18 weeks of follow up prior to data cutoff. One patient with unconfirmed (PR*) will never confirm due to PD but remains on treatment. [b]ORR includes confirmed and pending CR and PR with treatment ongoing and without PD reported. One patient was included in the denominator of ORR but not displayed on the waterfall plot due to lack of adequate post-baseline assessments. [c]DCR includes CR+PR+SD. 1L, first line; CR, complete response; DCO, data cutoff; DCR, disease control rate; GnP, gemcitabine and nab-paclitaxel; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PR, partial response; QD, once daily; RAS, rat sarcoma virus; SD, stable disease; SOD, sum of diameters.

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ctDNA Molecular Response With Zoldonrasib + Chemotherapy in 1L RAS G12D PDAC

Change in ctDNA RAS G12D VAF on Treatment (C2D1)



On-Treatment ctDNA Molecular Response Rates

	Zoldonrasib 1200 mg QD + mFFX (N=17)	Zoldonrasib 1200 mg QD + GnP (N=17)
>50% RAS VAF decrease from pretreatment, n (%)	17 (100)	17 (100)
Complete ctDNA clearance (100% RAS VAF decrease from pretreatment), n (%)	8 (47)	12 (71)

- 17 patients treated with zoldonrasib + mFFX (of 17 tested) were evaluable for molecular response[a]
- 17 patients treated with zoldonrasib + GnP (of 24 tested) were evaluable for molecular response[a]
- A marked decrease was observed in RAS G12D VAF in ctDNA, with all evaluable patients having >50% clearance with both regimens

ctDNA Data cutoff: 6 Mar 2026.

[a]Molecular response was evaluated only in patients with RAS G12D detectable in baseline (C1D1) plasma samples. 1L, first line; C, cycle; ctDNA, circulating tumor DNA; D, day; GnP, gemcitabine and nab-paclitaxel; mFFX, modified FOLFIRINOX; PDAC, pancreatic adenocarcinoma; QD, once daily; RAS, rat sarcoma virus; VAF; variant allele frequency.

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Conclusions

- The favorable safety and tolerability profile of zoldonrasib enables mean high dose intensities of 86% and 90% in combination with mFFX and GnP, respectively
  - TRAEs were broadly consistent with the established profiles of mFFX and GnP
- Zoldonrasib with chemotherapy showed compelling preliminary antitumor activity in patients with 1L PDAC
  - Zoldonrasib + mFFX: ORR,[a] 82%; DCR, 96%; zoldonrasib + GnP: ORR,[a] 61%; DCR, 90%
  - Additional follow-up is needed for durability (PFS and OS) assessment
  - Observed differences in baseline characteristics limit direct comparison of antitumor activity between chemotherapy regimens
- These preliminary safety and clinical activity data support the pivotal global, Phase 3 RASolute 305 study of zoldonrasib plus mFFX or GnP in patients with 1L RAS G12D PDAC, which is now actively enrolling (NCT07621718)

[a]Includes confirmed and pending CR and PR with treatment ongoing and without PD reported. 1L, first line; CR, confirmed response; DCR, disease control rate; GnP, gemcitabine and nab-paclitaxel; mFFX, modified FOLFIRINOX; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PR, partial response; RAS, rat sarcoma virus; TRAE, treatment-related adverse event.

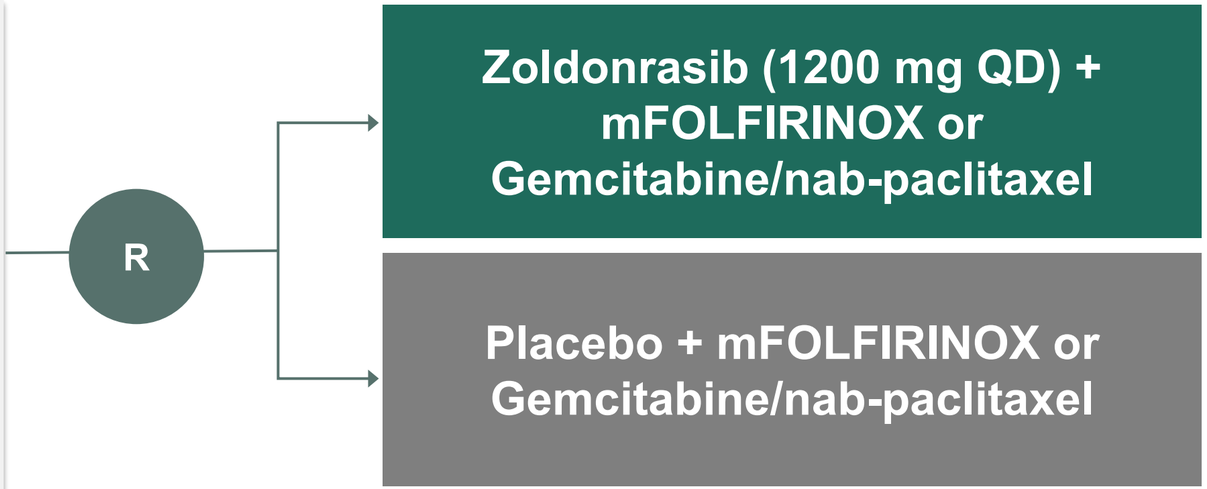
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RASolute 305

Phase 3, Global, Double-Blind, Randomized Study of Zoldonrasib + Chemotherapy vs Placebo + Chemotherapy as 1L Treatment for Patients With KRAS G12D mPDAC (NCT07621718)

Key Eligibility Criteria

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



The study is actively enrolling

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

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