Abstract LB407

Daraxonrasib plus Chemotherapy (CT) as First Line (1L) Treatment for Patients (Pts) with Metastatic Pancreatic Adenocarcinoma (mPDAC)

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Disclosure Information

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Brian M. Wolpin

- I have the following relevant financial relationships to disclose:

  Employee of: Dana-Farber Cancer Institute, Boston, MA, USA

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RAS(ON) Proteins Are Key Therapeutic Targets in RAS-Driven Pancreatic Cancers

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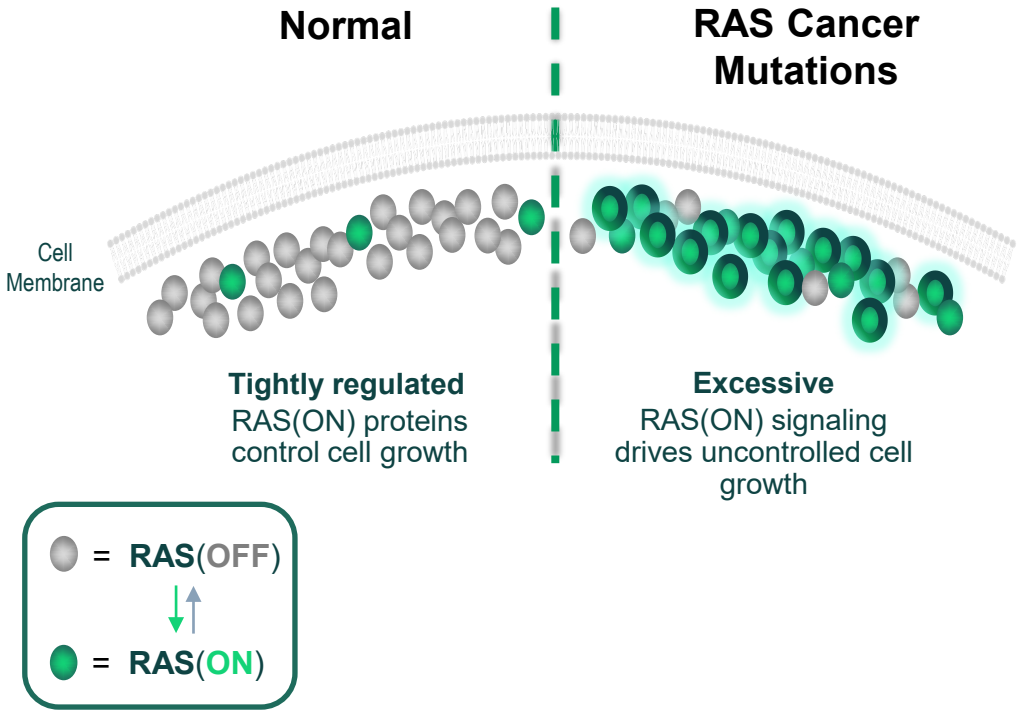
Uncontrolled RAS(ON) Signaling Drives Cells to an Oncogenic State[1-3]



- Outcomes for patients with mPDAC treated with 1L standard of care chemotherapy remain poor, with 5-year survival of ~3%[4]
  - Standard 1L chemotherapy (ie, FOLFIRINOX, NALIRIFOX, Gemcitabine/Nab-Paclitaxel [GnP]) has substantial toxicity and limited benefit, with ORR of 23–43%, 6-month PFS of 44–56%, 6-month OS of 55–76%, and median OS of 8.5–11.7 months[5-7]
- **>90% of PDAC tumors harbor an oncogenic RAS mutation[8]**

1L, first line; ORR, objective response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; 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. Siegel RN, et al. *CA Cancer J Clin* 2026;76:e70043; 5. Conroy T, et al. *N Engl J Med* 2011;364:1817-25; 6. Von Hoff DD, et al. *N Engl J Med* 2013;369:1691-1703; 7. Wainberg ZA, et al. *Lancet* 2023;402:1272-1281; 8. Pant S, et al. *J Clin Oncol* 2025;43:777.

Daraxonrasib is an Oral, Potent, RAS(ON) Multi-Selective, Noncovalent Inhibitor

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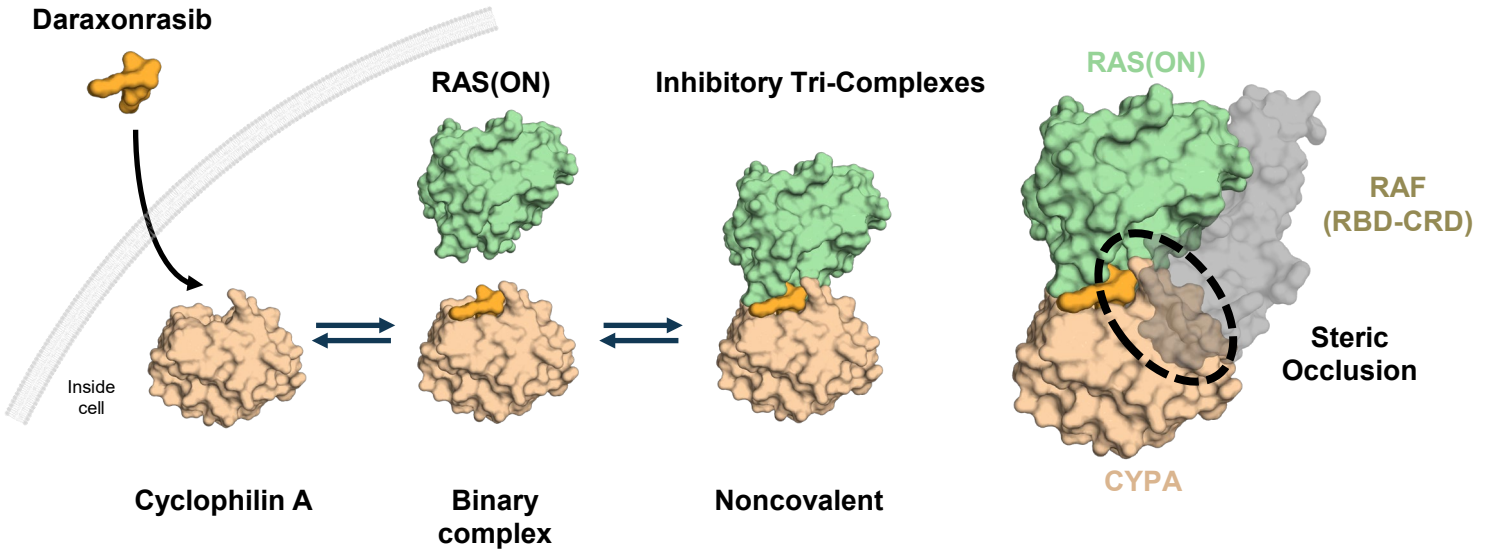
- Daraxonrasib targets GTP-bound mutant RAS (including mutations at G12, G13, and Q61) as well as wild-type RAS. By forming a tri-complex with cyclophilin A and GTP-bound RAS within cells, daraxonrasib sterically blocks RAS effector binding and potently suppresses downstream signaling[1-3]
- A Phase 1/2 study (NCT05379985) in second line PDAC showed daraxonrasib 300 mg QD had manageable safety and encouraging efficacy[4]



GTP, guanosine triphosphate; PDAC, pancreatic adenocarcinoma; QD, once daily; 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. Garrido-Laguna I, et al. *J Clin Oncol* 2025; 43:722.

GI-102 Platform Study

Subprotocol C: Daraxonrasib + GnP in 1L mPDAC

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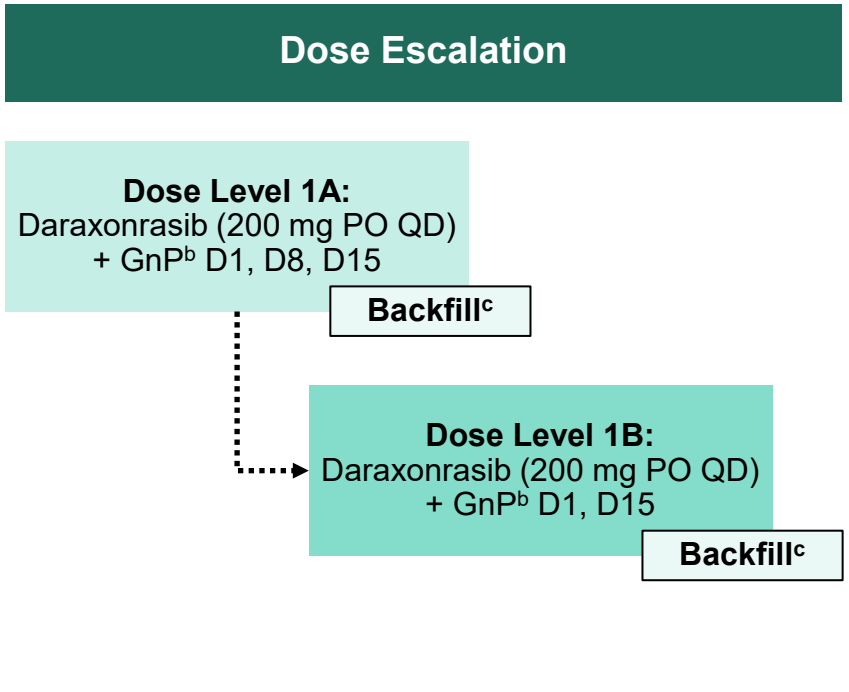
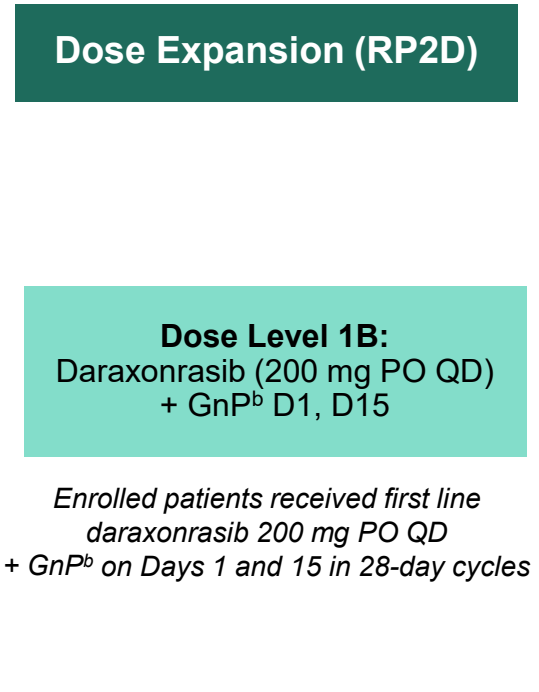
- Daraxonrasib is currently being investigated in clinical trials for multiple advanced solid tumors
- The GI-102 Platform Study (NCT06445062) is a Phase 1/2 open-label, multicenter study of RAS(ON) inhibitors in patients with RAS mutant gastrointestinal tumors[a]
  - Here, we present results for a subset of patients with 1L mPDAC treated with daraxonrasib + GnP (D1, D15)

N=40

- Previously untreated mPDAC
- ≥18 years old
- ECOG PS of 0 or 1
- Measurable disease per RECIST 1.1
- Adequate organ function
- Patients with primary CNS tumors, active brain metastases or impaired gastrointestinal function were excluded





Objectives

- Primary: Safety, tolerability
- Secondary: Antitumor activity
- Exploratory: ctDNA response

1L, first line; CNS, central nervous system; ctDNA, circulating tumor DNA; D, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; GnP, gemcitabine and nab-paclitaxel; mPDAC, metastatic pancreatic adenocarcinoma; PO, orally; QD, once daily; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.
[a]Patients with wild-type RAS tumors were permitted. [b]GnP: G, 1000 mg/m^2; nP, 125 mg/m^2. [c]Backfilling of cohorts will open once a dose level clears DLT assessment and is considered safe and tolerable.

Demographics and Baseline Characteristics

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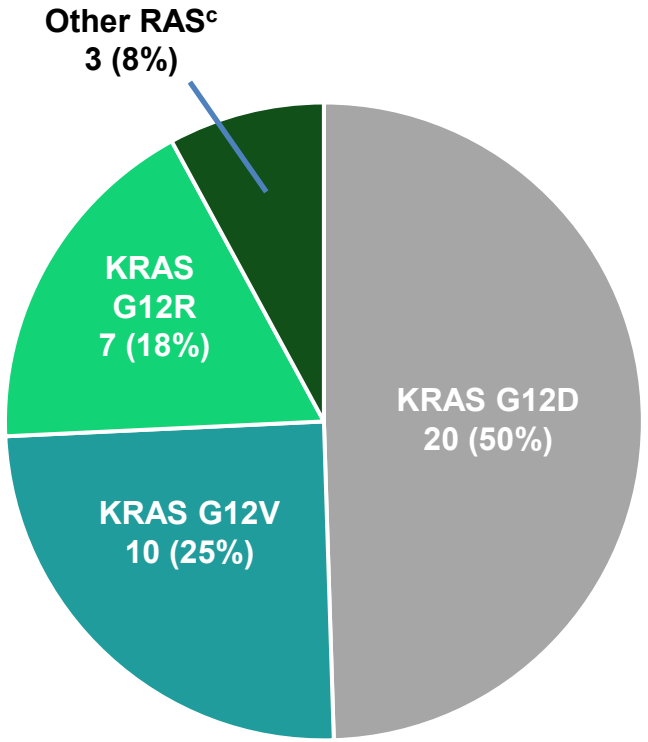
	All treated patients[a] (n=40)
Age, median (range), years	69 (34-83)
Male, n (%)	25 (63)
ECOG PS 1, n (%)	20 (50)
Liver metastases at enrollment, n (%)	28 (70)
Metastatic at diagnosis (Stage IV), n (%)	20 (50)
Prior anti-cancer therapy in the non-metastatic setting, n (%)	
Adjuvant/neoadjuvant	18[b] (45)
Locally advanced	1 (3)
Pancreatic resection, n (%)	17 (43)

RAS Genotypes (n=40)



Data cutoff: 1 Dec 2025.

ECOG PS, Eastern Cooperative Oncology Group performance status; PDAC, pancreatic adenocarcinoma; RAS, rat sarcoma virus.

[a]The population includes all treated patients who have been followed up for at least 18 weeks. [b]One patient had prior systemic therapy for gynecological cancer. [c]Other RAS includes patients with KRAS Q61H (n=1), KRAS G13P (n=1) and RAS mutation status unknown (n=1).

Daraxonrasib + GnP Treatment-Related Adverse Events (TRAEs)

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	All treated patients (n=40)	
	Any grade	**Grade ≥3**
TRAEs (any drug), n (%)	40 (100)	29 (73)
Serious TRAEs, n (%)	11 (28)	10 (25)
TRAEs occurring in ≥30% of patients, n (%)		
Rash[a]	36 (90)	6 (15)
Diarrhea	30 (75)	6 (15)
Fatigue	28 (70)	7 (18)
Nausea	27 (68)	2 (5)
Vomiting	22 (55)	0
Anemia	20 (50)	13 (33)
Stomatitis/mucositis[b]	18 (45)	4 (10)
Edema peripheral	17 (43)	0
Neutrophil count decreased	17 (43)	8 (20)
Peripheral neuropathy	15 (38)	0
Platelet count decreased	15 (38)	3 (8)
Alopecia	13 (33)	0
AST increased	12 (30)	1 (3)

- Rash was the most common TRAE, with the majority being Grade 1 or Grade 2
- No Grade 5 TRAEs occurred

Data cutoff: 1 Dec 2025. Median (range) treatment duration is 8.2 (0.5-13.5) months.
AE, adverse event; AST, aspartate transferase; GnP, gemcitabine and nab-paclitaxel; TRAE, treatment-related adverse event.
[a]Rash comprising multiple MedDRA preferred terms: catheter site rash, dermatitis, dermatitis acneiform, erythema, eyelid rash, rash, rash erythematous, rash macular, rash maculo-papular, and rash pustular. [b]Stomatitis/mucositis comprising multiple MedDRA preferred terms: mucosal inflammation and stomatitis.

TRAEs Leading to Dose Modifications

	All treated patients (n=40)	
	Daraxonrasib	**GnP**
Patients with dose modification due to TRAEs, n (%)	24 (60)	30 (75)
Dose interruption	24 (60)	21 (53)
Dose reduction	14 (35)	23 (58)
Patients with dose discontinuation due to TRAEs, n (%)	2 (5)[a]	6 (15)
Mean dose intensity, %	82	80
Median dose intensity, %	87	81

- Rash was the most common daraxonrasib-related AE leading to dose modification of daraxonrasib

Data cutoff: 1 Dec 2025. Median (range) treatment duration is 8.2 (0.5-13.5) months.
GnP, gemcitabine and nab-paclitaxel; TRAE, treatment-related adverse event.
[a]TRAEs that led to daraxonrasib dose discontinuation included Grade 3 acute pancreatitis in one patient and Grade 3 nausea and Grade 2 vomiting in one patient.

Efficacy of Daraxonrasib + GnP in 1L mPDAC

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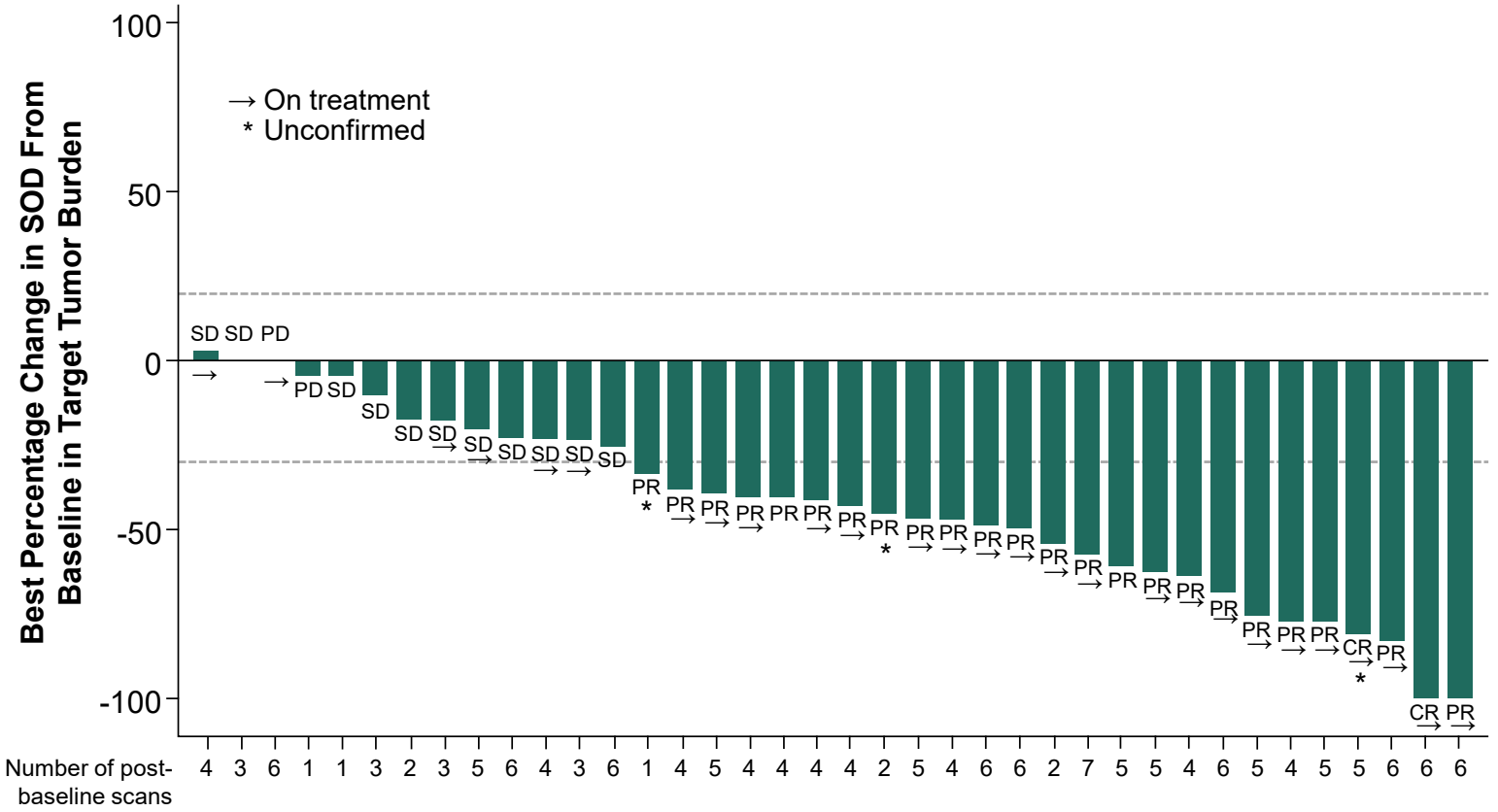

	All treated (n=40)[a]
ORR[b], % (95% CI)	58 (41, 73)
DCR[c], % (95% CI)	90 (76, 97)
6-month PFS[d], % (95% CI)	84 (68, 93)
6-month OS[d], % (95% CI)	90 (76, 96)

Data cutoff: 1 Dec 2025. Median (range) follow-up was 9.7 (5.7−13.8) months.

1L, first line; CI, confidence interval; CR, complete response; DCR, disease control rate; GnP, gemcitabine and nab-paclitaxel; mPDAC, metastatic pancreatic adenocarcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease; SOD, sum of diameters.

*One unconfirmed CR was a confirmed PR.

[a]All treated patients received an initial dose of 200 mg QD of daraxonrasib and GnP every 2 weeks and had at least 18 weeks of follow up prior to data cutoff date. [b]Includes confirmed CR and PR. Two patients were included in the denominator of ORR but not displayed on the waterfall plot due to lack of adequate baseline/post-baseline assessments. [c]DCR includes CR, PR and SD. [d] Estimate based on Kaplan-Meier method. PFS and OS data remain immature.

ctDNA Molecular Response

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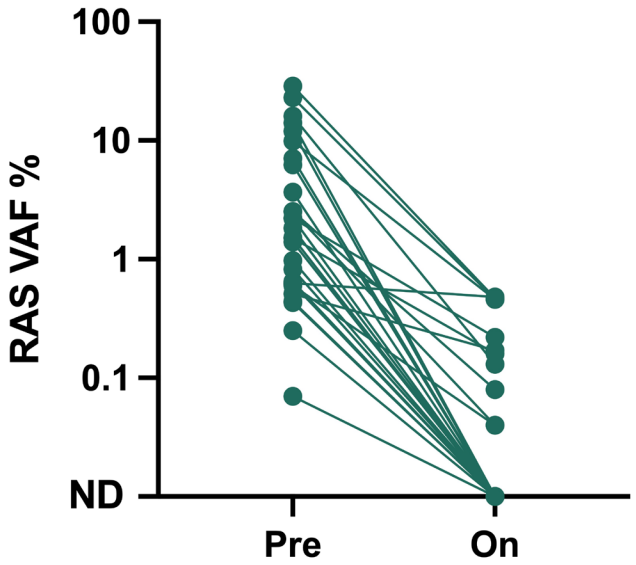
- Of 37 1L mPDAC patients with paired plasma samples, 28 had detectable RAS mutant allele in ctDNA at baseline and were evaluable for ctDNA response
- 96% of patients had >50% decrease in RAS VAF; Complete and early on-treatment clearance of ctDNA was seen in 61% of patients treated with daraxonrasib + GnP

Change in ctDNA RAS VAF On Treatment



On-Treatment ctDNA Molecular Response Rates

	ctDNA-evaluable patients (n=28)[a]
>50% RAS VAF decrease from pre-treatment, n (%)	27 (96)
Complete ctDNA clearance (100% RAS VAF decrease from pre-treatment), n (%)	17 (61)

C, cycle; ctDNA, circulating tumor DNA; D, day; GnP, gemcitabine and nab-paclitaxel; ND, not detected; RAS, Rat sarcoma virus; VAF, variant allele frequency.
[a]Patients who had ctDNA sequenced at baseline (C1D1) and at least once on-treatment (C2D1 or C3D1).

Summary and Conclusions

- Daraxonrasib + GnP as 1L treatment for mPDAC showed a manageable safety profile, consistent with known toxicities of each component, and maintained high mean dose intensity of 82% for daraxonrasib and 80% for GnP
- The combination demonstrated compelling preliminary antitumor activity with a confirmed ORR of 58% and DCR of 90% in patients with 1L mPDAC
- Efficacy data also demonstrated an encouraging early trend in durability, with 6-month landmark PFS of 84% and 6-month landmark OS of 90%
- Early on-treatment clearance of ctDNA was seen in 61% of patients treated with daraxonrasib + GnP
- RASolute 303 study (NCT07491445) is a global 3-arm Phase 3 study of daraxonrasib with or without GnP compared with GnP alone as 1L treatment for patients with mPDAC and is currently enrolling
- A separate study of daraxonrasib monotherapy demonstrated encouraging efficacy in patients with 1L RAS mutant mPDAC (NCT05379985)
  - These results are being presented as a poster at AACR 2026 (O'Reilly et al; Abstract LB337)

1L, first line; ctDNA, circulating tumor DNA; GnP, gemcitabine and nab-paclitaxel; mPDAC, metastatic pancreatic adenocarcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus.

RASolute 303: A Phase 3, Global, Open-label, Randomized, 3-Arm Study of Daraxonrasib +/- GnP vs GnP as a 1L Treatment for Patients with mPDAC (NCT07491445)

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N~900

- Confirmed metastatic PDAC, regardless of RAS status
- No prior systemic therapy for metastatic disease
- ECOG PS 0 or 1
- RAS mutation status (required for stratification)

R 1:1:1

- **Daraxonrasib** (300 mg)
- **Daraxonrasib** (200 mg) **+ GnP[a]** → **Daraxonrasib** (300 mg)
- **GnP[b]**

Endpoints

- Primary: PFS, OS
- Secondary: ORR, DOR, safety, PROs

Treatment until disease progression or intolerance for all three arms.
1L, first line; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized; GnP, gemcitabine and nab-paclitaxel; OS, overall survival; ORR, objective response rate; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PROs, patient reported outcomes; RAS, rat sarcoma virus.
[a]Daraxonrasib (200 mg) + GnP (1000 mg/m^2 and 125 mg/m^2) given on Days 1, 15 in a 28-day cycle for up to 6 months, followed by daraxonrasib monotherapy (300 mg). [b]GnP (1000 mg/m^2 and 125 mg/m^2) on Days 1, 8, and 15 in a 28-day cycle.

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