Daraxonrasib, a RAS(ON) multi-selective inhibitor vs chemotherapy in previously treated metastatic pancreatic adenocarcinoma (mPDAC): Primary and final analysis from the Phase 3 RASolute 302 study

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On behalf of RASolute 302 investigators

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Data presented at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting

Key Takeaways

- **Daraxonrasib met all primary and key secondary endpoints** with statistically significant and clinically meaningful improvements in OS, PFS, and ORR in patients with previously treated metastatic PDAC
- Median OS was 13.2 months with daraxonrasib vs 6.7 months with chemotherapy (HR, 0.40 [95% CI: 0.30–0.53]; $p=4.6\times10^{-11}$) in the overall population (patients with and without an identified tumor RAS mutation)

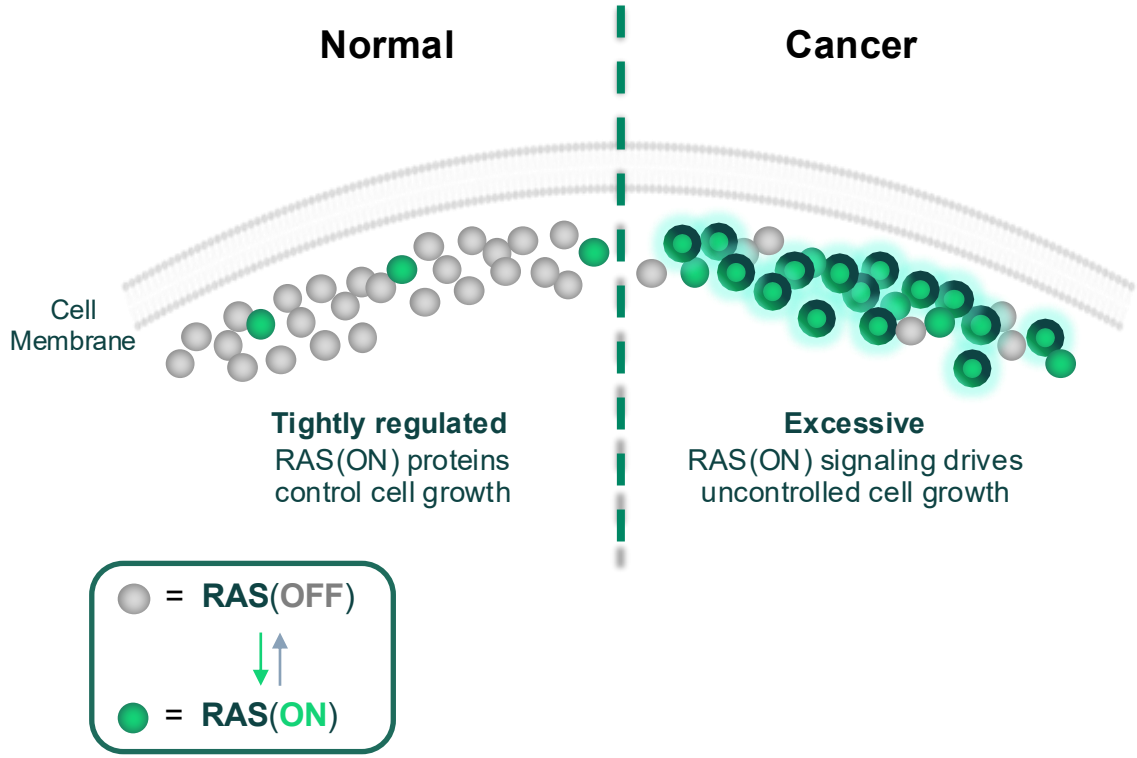
Results support daraxonrasib as the new standard of care for patients with previously treated metastatic PDAC

ORR, objective response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival.

Background

- PDAC is among the most challenging and lethal cancers, with limited therapeutic options
- Standard cytotoxic chemotherapy provides limited benefit in previously treated mPDAC: mPFS 3–4 months; mOS 6–7 months[1-3]
- Excessive RAS(ON) signaling drives tumor growth across RAS-mutant and RAS wild-type PDAC
  - >90% of PDAC tumors harbor an oncogenic RAS mutation[4,5]
- No RAS-targeted therapies are approved for PDAC, highlighting a substantial unmet need

Uncontrolled RAS(ON) Signaling Drives Cells to an Oncogenic State[6-8]



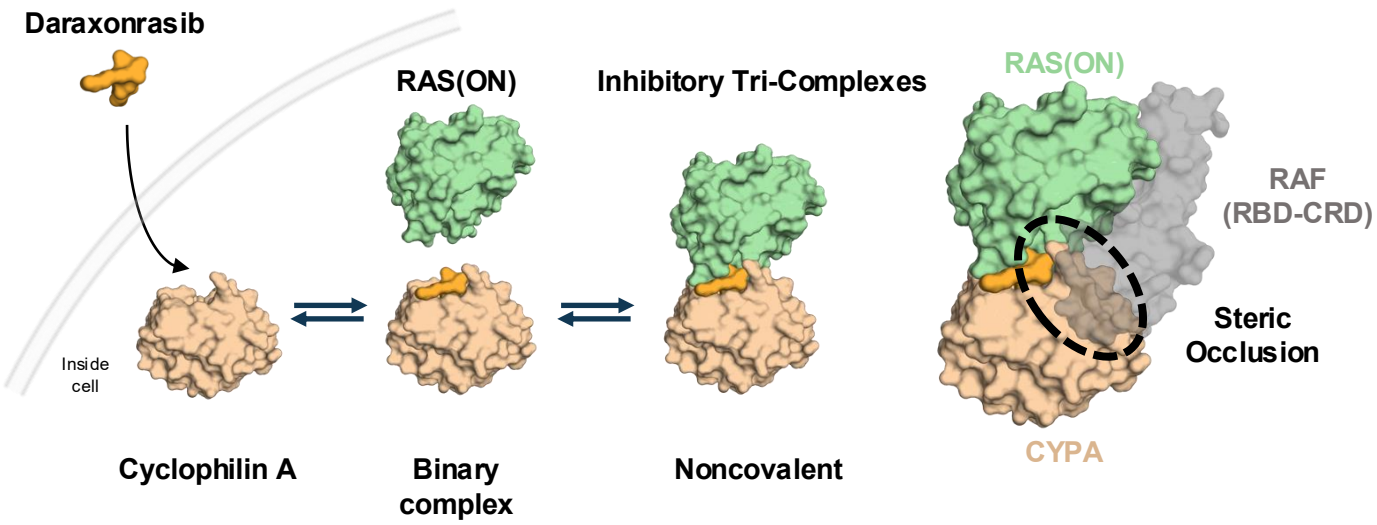
m, median; mPDAC, metastatic pancreatic adenocarcinoma; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival.

1. Park W, et al. JAMA. 2021;326:851-62; 2. Petrelli F, et al. BMC Gastroenterol. 2023;23:212; 3. Dayyani F, et al. Cancer Treat Rev. 2023;113:102502; 4. Pant S, et al. J Clin Oncol. 2025;43:777; 5. Cancer Genome Atlas Research Network. Cancer Cell. 2017;32:185-203.e13; 6. Holderfield M, et al. Nature. 2024;629:919-26; 7. Lokhandwala J, et al. Front Oncol. 2024;14:1394702; 8. Jiang J, et al. Cancer Discov. 2024;14:994-1017.

Daraxonrasib Mechanism of Action

Daraxonrasib is an oral RAS(ON) multi-selective inhibitor

- Daraxonrasib is an oral, potent, RAS(ON), multi-selective, tri-complex inhibitor of GTP-bound mutant RAS (including variants with G12, G13, and Q61 mutations) and wild-type RAS[1-4]
- In a prior Phase 1/2 trial, daraxonrasib showed clinical activity with a manageable safety profile in patients with previously treated advanced PDAC[5]



Daraxonrasib binds to intracellular cyclophilin A to form a binary complex that engages RAS(ON) and suppresses downstream signaling[1-4]

CRD, cysteine rich domain; GTP, guanosine triphosphate; PDAC, pancreatic adenocarcinoma; RBD, RAS-binding domain.

1. Holderfield M, et al. Nature. 2024;629:919-26; 2. Cregg J, et al. J Med Chem. 2025;68:6064-83; 3. Lokhandwala J, et al. Front Oncol. 2024;14:1394702; 4. Jiang J, et al. Cancer Discov. 2024;14:994-1017; 5. Wolpin B, et al. N Engl J Med. 2026;394:1790-1802.

Study Design

Key eligibility criteria:

- Adults with mPDAC
- One prior fluoropyrimidine- or gemcitabine-based regimen in the metastatic setting
- ECOG PS 0-1
- Documented tumor RAS mutational status[a] by local testing

R 1:1

Daraxonrasib
300 mg, PO QD

Investigator's choice chemotherapy (1 of 4)
GnP, mFOLFIRINOX, Nal-IRI + 5-FU/LV, FOLFOX

Dual primary endpoints

- OS and PFS[b] (RAS G12 population)

Key secondary endpoints

- OS and PFS[b] (overall population[c])
- ORR[b] (RAS G12 and overall populations)
- TTD in PROs[d] (RAS G12 and overall populations)

Stratification factors

- ECOG PS (0 vs 1)
- Metastatic disease at diagnosis (yes vs no)
- Liver metastases at baseline (yes vs no)
- Tumor RAS mutational status (RAS G12D/V vs other RAS G12 vs RAS G13 or Q61 mutation or no RAS mutation identified)

Global enrollment: 59 sites across 6 countries

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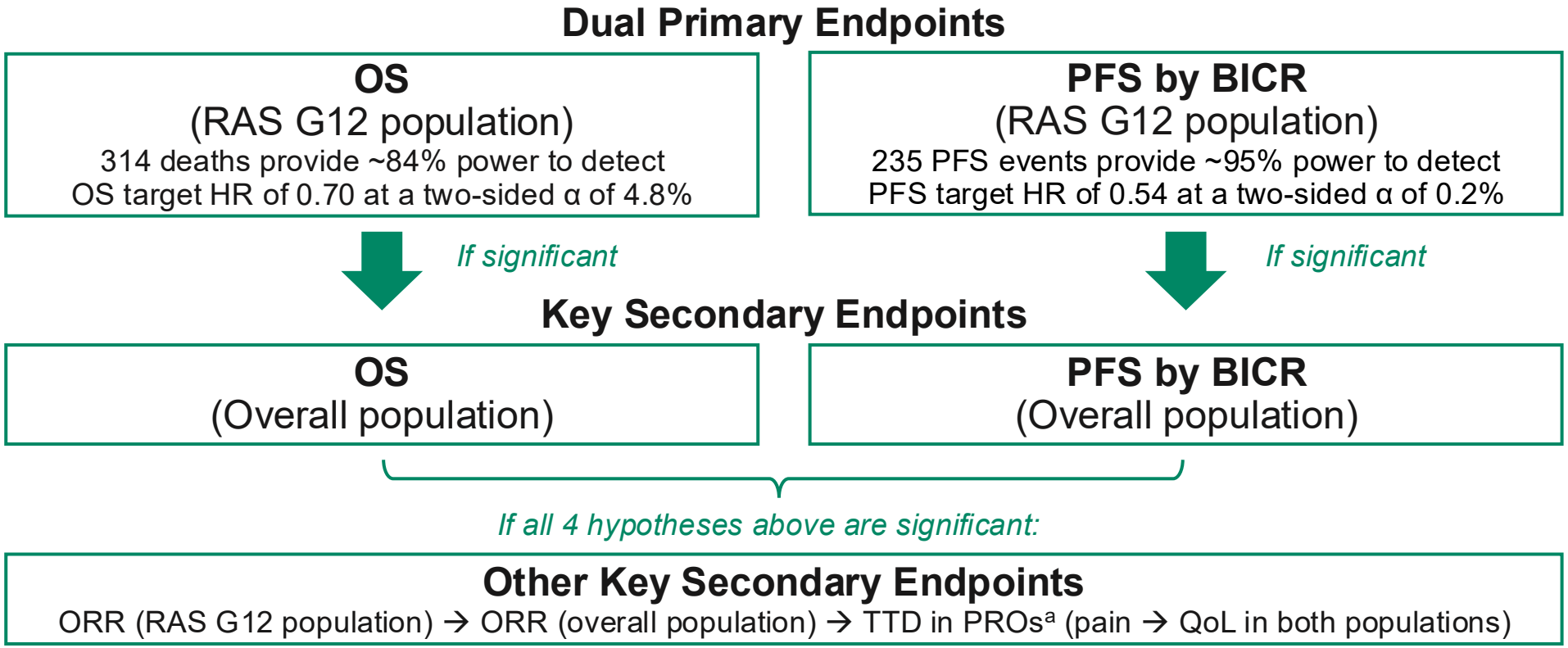
5-FU, 5-fluorouracil; BICR, blinded independent central review; ECOG Eastern Cooperative Oncology Group; FOLFOX, leucovorin, 5-FU, and oxaliplatin; GnP, gemcitabine and nab-paclitaxel; LV, leucovorin; mFOLFIRINOX, modified 5-FU, irinotecan, leucovorin, and oxaliplatin; mPDAC, metastatic pancreatic adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral administration; PRO, patient-reported outcome; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTD, time to deterioration.

[a]Either mutant, defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61), or no RAS mutation identified. [b]By BICR per RECIST 1.1. [c]Including patients whose tumors harbor RAS G12, G13, or Q61 mutations, or had no RAS mutation identified. [d]TTD in symptom of pain and in global health status/quality of life.

Statistical Analysis Overview

Two interim OS analyses were planned before the final analysis in the RAS G12 population

- First OS interim analysis (IA1): planned after enrollment completion and ≥166 deaths; final analysis for PFS
- Results reported are based on IA1



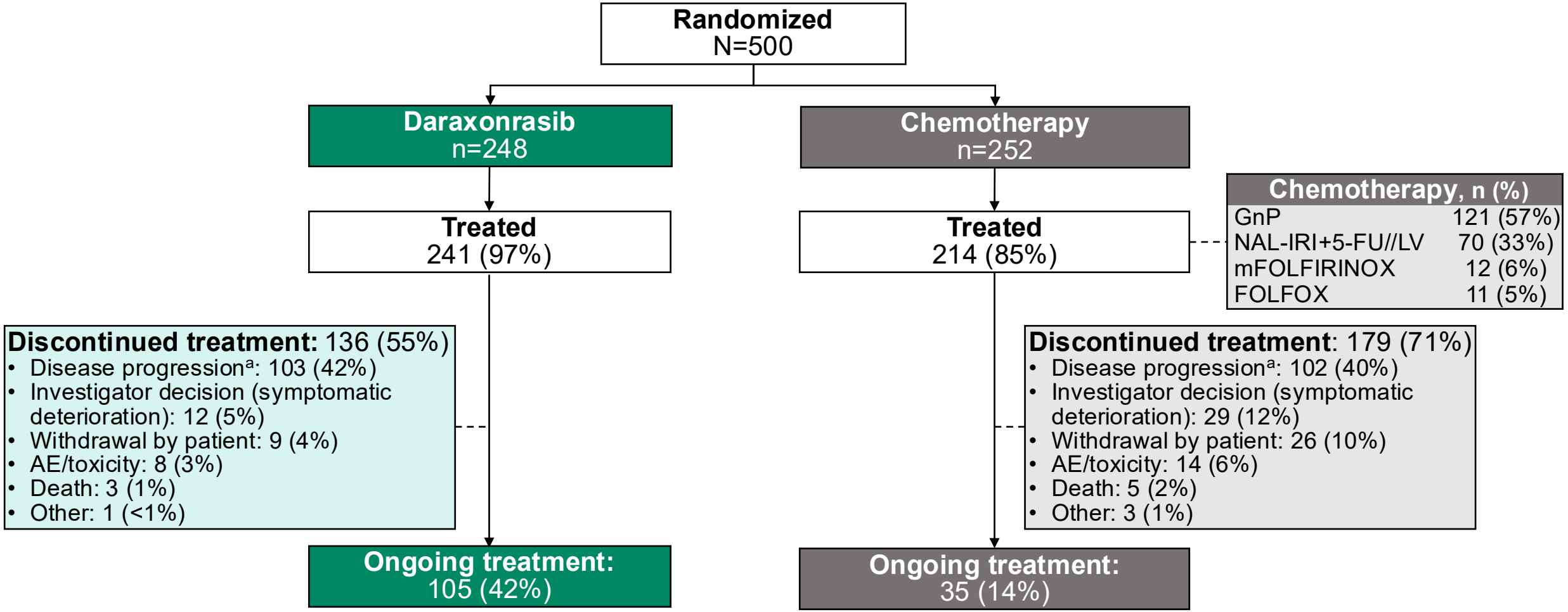
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BICR, blinded independent central review; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PAN26, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Pancreatic Cancer Module; GHS, global health status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; TTD, time to deterioration.

[a]TTD in symptom of pain and in GHS/QoL, defined as a change of at least 10 points from baseline or death (whichever occurs first) in the EORTC QLQ-PAN26 pain scale and in the EORTC QLQ-C30 GHS/QoL scale, respectively.

Patient Disposition

Enrollment period: October 16, 2024 – November 7, 2025



Data cutoff: 10 Feb 2026.

5-FU, 5-fluorouracil; AE, adverse event; FOLFOX, leucovorin, 5-FU, and oxaliplatin; GnP, gemcitabine and nab-paclitaxel; LV, leucovorin; mFOLFIRINOX, modified 5-FU, irinotecan, leucovorin, and oxaliplatin; Nal-IRI, nanoliposomal irinotecan; RECIST, Response Evaluation Criteria for Solid Tumors.

[a]Documented based on RECIST 1.1.

Baseline Demographics and Disease Characteristics

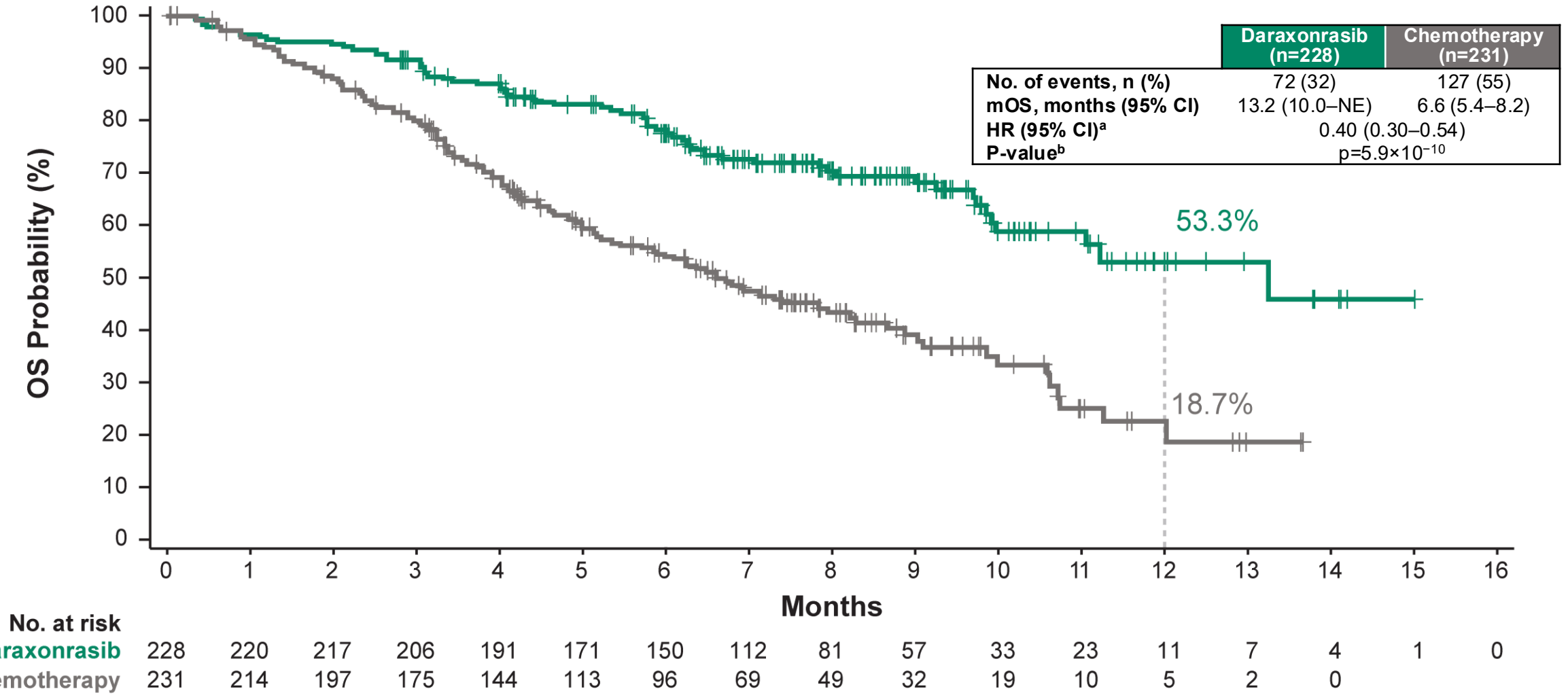
	Daraxonrasib (n=248)	Chemotherapy (n=252)
Age, median (range), years	66 (30-88)	65 (36-86)
Female, n (%)	117 (47)	108 (43)
Region, n (%): North America | Europe | APAC	145 (58) | 87 (35) | 16 (6)	158 (63) | 74 (29) | 20 (8)
ECOG PS, n (%): 0 | 1[a]	129 (52) | 119 (48)	118 (47) | 134 (53)
Metastatic disease at initial diagnosis, n (%)	154 (62)	154 (61)
Prior chemotherapy regimens in metastatic setting, n (%)		
(m)FOLFIRINOX	98 (40)	105 (42)
Gemcitabine + nab-paclitaxel	94 (38)	94 (37)
Other	56 (23)	53 (21)
Prior pancreatectomy, n (%)	83 (33)	92 (37)
Liver metastases at baseline, n (%)	174 (70)	176 (70)
Tumor RAS mutational status, n (%)		
RAS G12 D/V	197 (79)	197 (78)
Other RAS G12	31 (13)	34 (13)
RAS G13 or Q61, or no RAS mutation identified	20 (8)	21 (8)

Data cutoff: 10 Feb 2026.

5-FU, 5-fluorouracil; APAC, Asia-Pacific; ECOG, Eastern Cooperative Oncology Group; mFOLFIRINOX, modified 5-FU, irinotecan, leucovorin, oxaliplatin; PS, performance status.

[a]Three patients (including 2 patients randomized to the daraxonrasib arm and 1 patient randomized to the chemotherapy arm) had ECOG PS >1 at baseline. These patients were not dosed due to no longer meeting trial eligibility criteria.

Primary Endpoint: Overall Survival in the RAS G12 Population



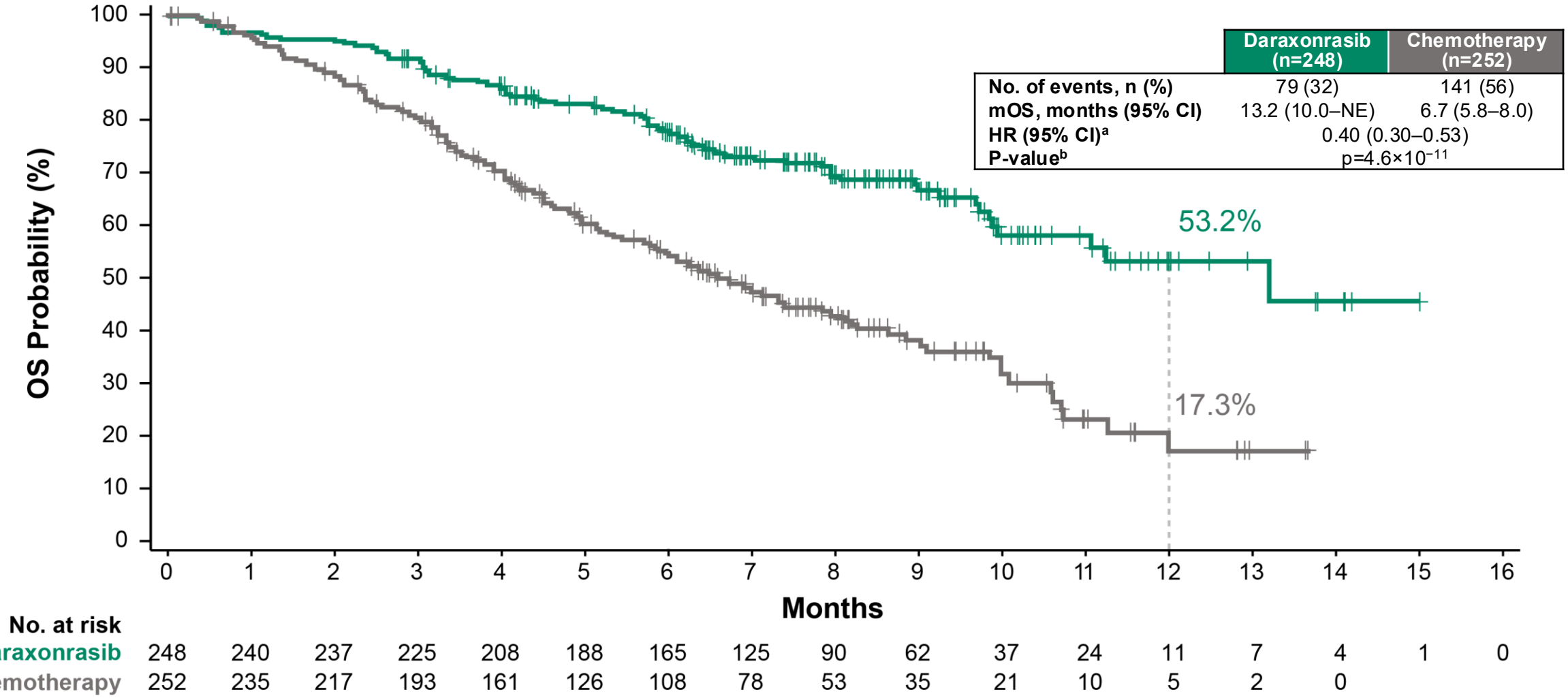
	Daraxonrasib (n=228)	Chemotherapy (n=231)
No. of events, n (%)	72 (32)	127 (55)
mOS, months (95% CI)	13.2 (10.0–NE)	6.6 (5.4–8.2)
HR (95% CI)[a]	0.40 (0.30–0.54)	
P-value[b]	$p=5.9\times10^{-10}$	

Data cutoff: 10 Feb 2026. Median (range) follow-up time was 8.5 (3.2−15.9) months.

m, median; NE, not estimable; OS, overall survival.

[a]HRs and 95% CIs were based on the stratified Cox model with Efron's method of tie handling. [b]P-values were calculated using the stratified log-rank test.

Key Secondary Endpoint: Overall Survival in the Overall Population



	Daraxonrasib (n=248)	Chemotherapy (n=252)
No. of events, n (%)	79 (32)	141 (56)
mOS, months (95% CI)	13.2 (10.0–NE)	6.7 (5.8–8.0)
HR (95% CI)[a]	0.40 (0.30–0.53)	
P-value[b]	$p=4.6\times10^{-11}$	

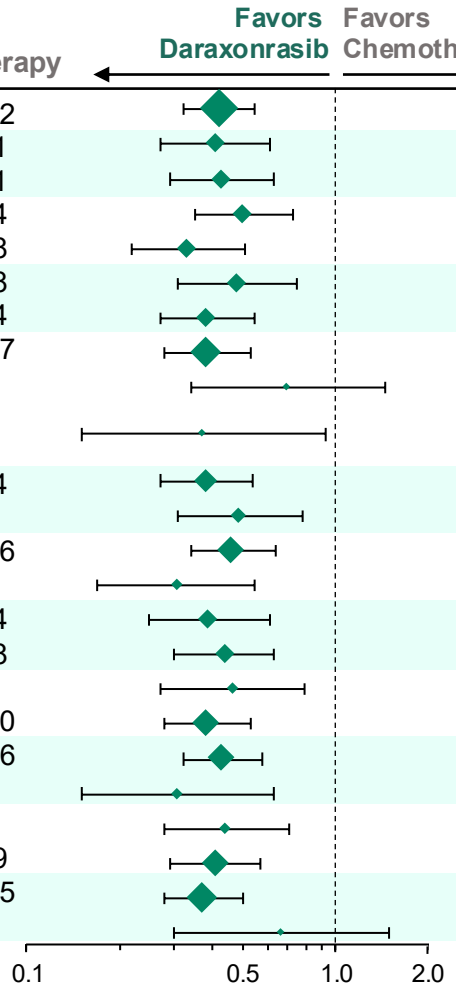
Data cutoff: 10 Feb 2026. Median (range) follow-up time was 8.5 (3.2−15.9) months.

m, median; NE, not estimable; OS, overall survival.

[a]HRs and 95% CIs were based on the stratified Cox model with Efron's method of tie handling. [b]P-values were calculated using the stratified log-rank test.

Overall Survival Subgroup Analysis – Overall Population

Population		Events/N Daraxonrasib	Events/N Chemotherapy	HR (95% CI)[a]
Overall		79/248	141/252	0.42 (0.32–0.55)
Age, years	<65	37/114	68/121	0.41 (0.27–0.61)
	≥65	42/134	73/131	0.43 (0.29–0.63)
Sex	Male	45/131	77/144	0.50 (0.35–0.73)
	Female	34/117	64/108	0.33 (0.22–0.51)
ECOG PS	0	33/129	51/118	0.48 (0.31–0.75)
	1[b]	46/119	90/134	0.38 (0.27–0.55)
Tumor RAS mutational status	RAS G12D/V	59/197	110/197	0.38 (0.28–0.53)
	Other RAS G12	13/31	17/34	0.70 (0.34–1.44)
	RAS G13 or Q61, or no RAS mutation identified	7/20	14/21	0.37 (0.15–0.93)
Metastatic disease at diagnosis	Yes	51/154	94/154	0.38 (0.27–0.54)
	No	28/94	47/98	0.49 (0.31–0.78)
Prior 5-FU-based regimen	Yes	62/181	103/186	0.46 (0.34–0.64)
	No	17/67	38/66	0.31 (0.17–0.55)
Prior gemcitabine-based regimen	Yes	31/110	61/114	0.39 (0.25–0.61)
	No	48/138	80/138	0.44 (0.30–0.63)
Prior pancreatectomy	Yes	21/83	40/92	0.47 (0.27–0.79)
	No	58/165	101/160	0.38 (0.28–0.53)
Liver metastases at baseline	Yes	68/174	113/176	0.43 (0.32–0.58)
	No	11/74	28/76	0.31 (0.15–0.63)
Peritoneal metastases at baseline	Yes	28/76	48/83	0.44 (0.28–0.71)
	No	51/172	93/169	0.41 (0.29–0.57)
CA19-9 level at baseline	≥40 U/mL	70/211	121/195	0.37 (0.28–0.50)
	<40 U/mL	9/36	19/56	0.67 (0.30–1.49)



Data cutoff: 10 Feb 2026.

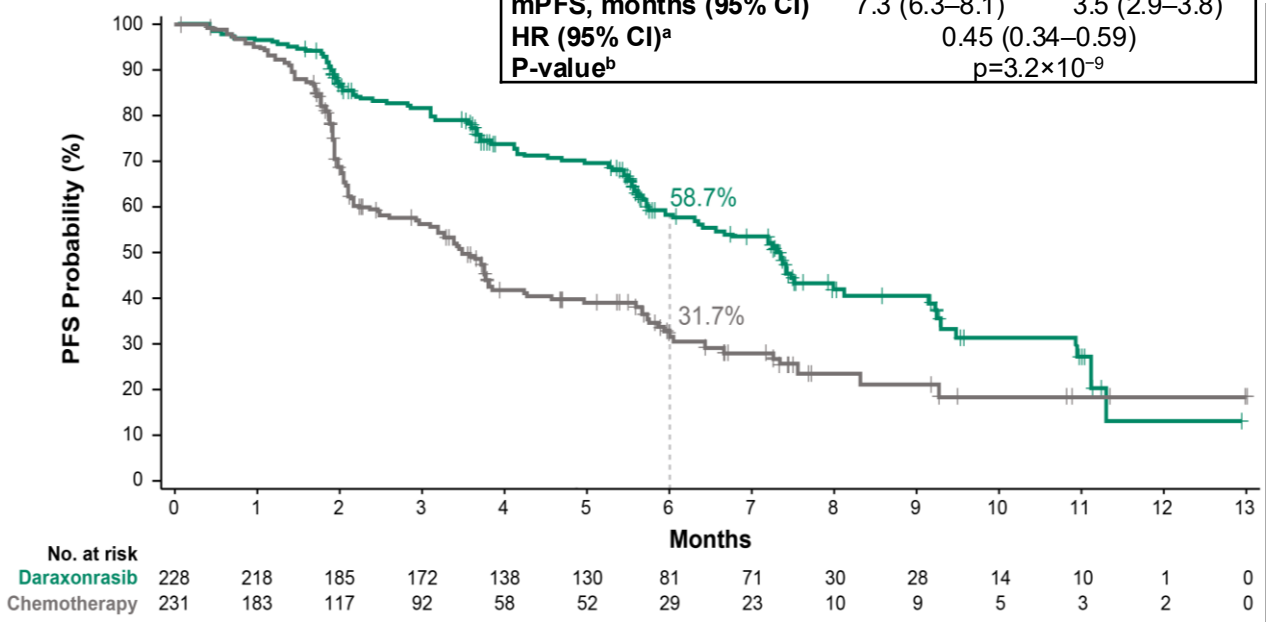
5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

[a]The size of diamonds is relative to the size of the population in each subgroup. HRs and 95% CIs were based on the unstratified Cox model with Efron's method of tie handling. [b]Three patients (including 2 patients randomized to the daraxonrasib arm and 1 patient randomized to the chemotherapy arm) had ECOG PS >1 at baseline. These patients were not dosed due to no longer meeting trial eligibility criteria.

Progression-Free Survival by BICR

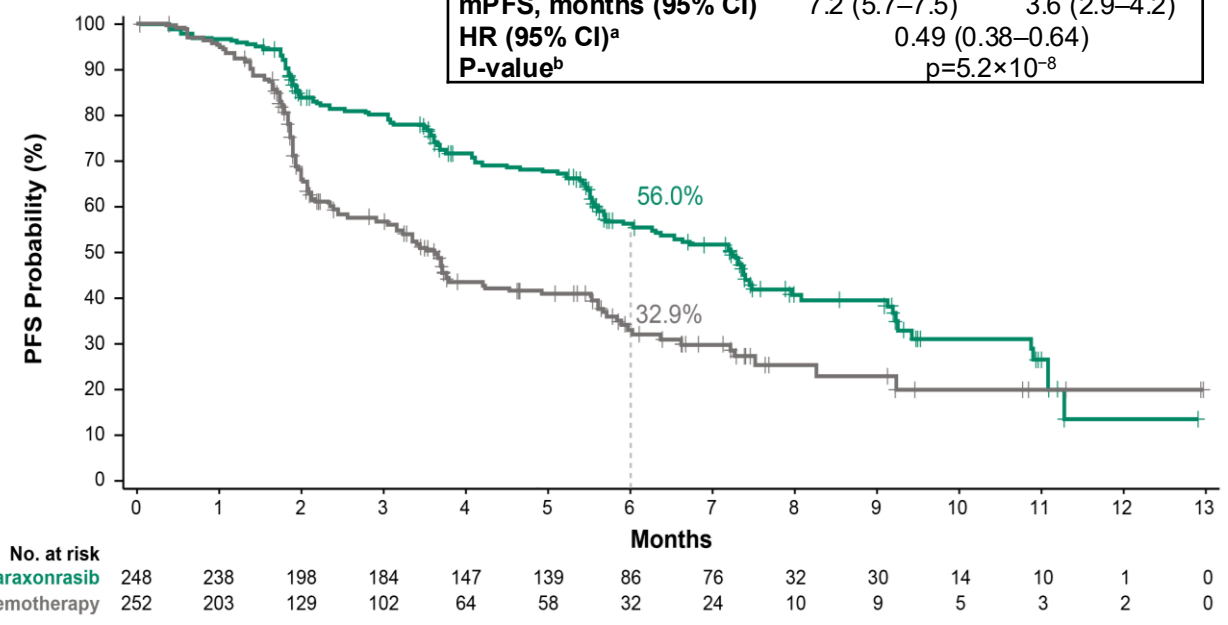
RAS G12 Population

	Daraxonrasib (n=228)	Chemotherapy (n=231)
No. of events, n (%)	112 (49)	121 (52)
mPFS, months (95% CI)	7.3 (6.3–8.1)	3.5 (2.9–3.8)
HR (95% CI)[a]	0.45 (0.34–0.59)	
P-value[b]	$p=3.2\times10^{-9}$	



Overall Population

	Daraxonrasib (n=248)	Chemotherapy (n=252)
No. of events, n (%)	127 (51)	130 (52)
mPFS, months (95% CI)	7.2 (5.7–7.5)	3.6 (2.9–4.2)
HR (95% CI)[a]	0.49 (0.38–0.64)	
P-value[b]	$p=5.2\times10^{-8}$	

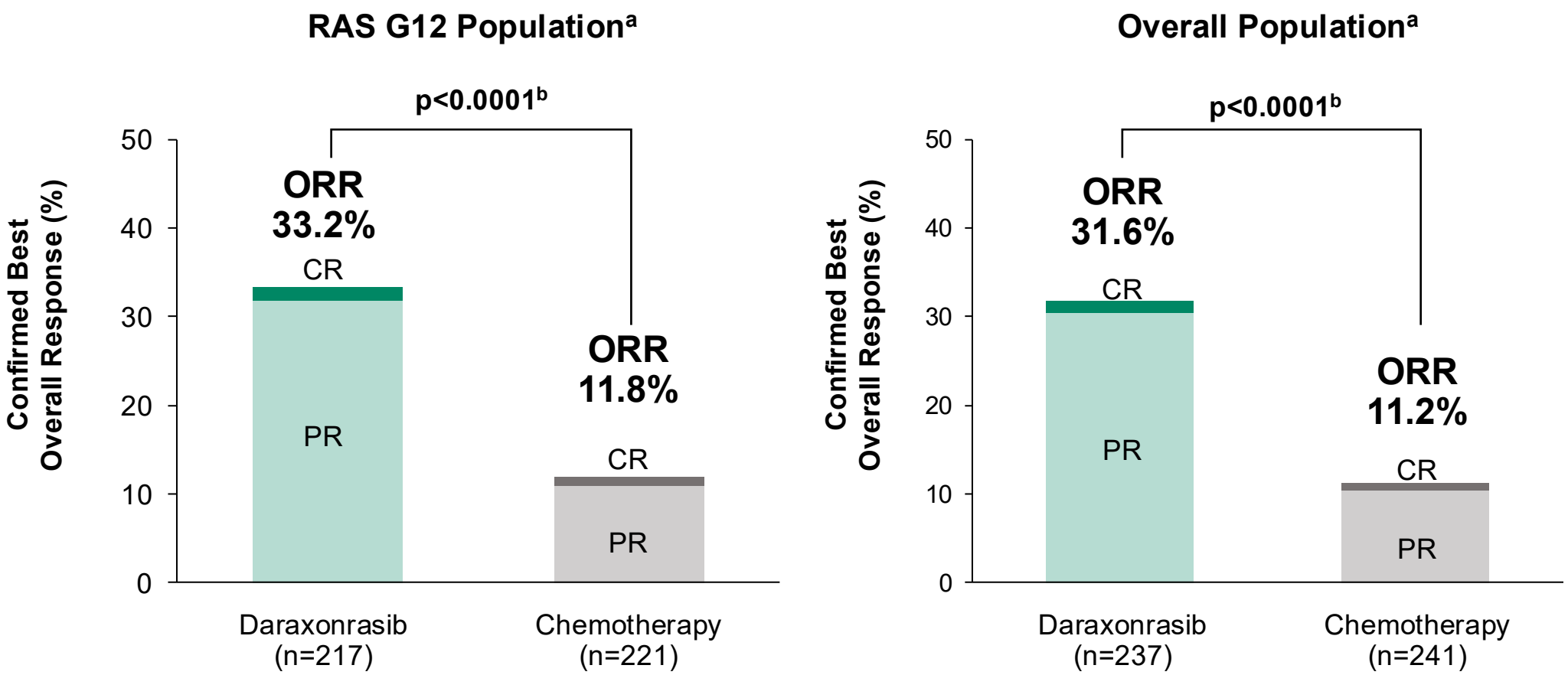


Data cutoff: 10 Feb 2026. Median (range) follow-up time was 8.5 (3.2−15.9) months.

BICR, blinded independent central review; m, median; PFS, progression-free survival.

[a]HRs and 95% CIs were based on the stratified Cox model with Efron's method of tie handling. [b]P-values were calculated using the stratified log-rank test.

Confirmed Objective Response Rate by BICR



Data cutoff: 10 Feb 2026.

BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PR, partial response.

[a]Only patients with measurable disease at baseline per BICR were included in the ORR analysis. [b]P-values were calculated using stratified Cochran-Mantel-Haenszel chi-square test.

Safety Overview

	Daraxonrasib (n=241)	Chemotherapy (n=214)
Median time on treatment, months (range)	6.2 (0.03-14.1)	1.5-3.2[a] (0.03-12.9)
Any TEAEs, n (%)	241 (100)	209 (97.7)
Any TRAEs, n (%)	236 (97.9)	200 (93.5)
TRAEs leading to dose interruption	135 (56.0)	118 (55.1)
TRAEs leading to dose reduction	87 (36.1)	123 (57.5)
TRAEs leading to discontinuation	3 (1.2)[b]	24 (11.2)
Grade ≥3 TRAEs	105 (43.6)	123 (57.5)
Serious TRAEs	26 (10.8)	40 (18.7)
Grade 5 TRAEs	1 (0.4)[c]	0

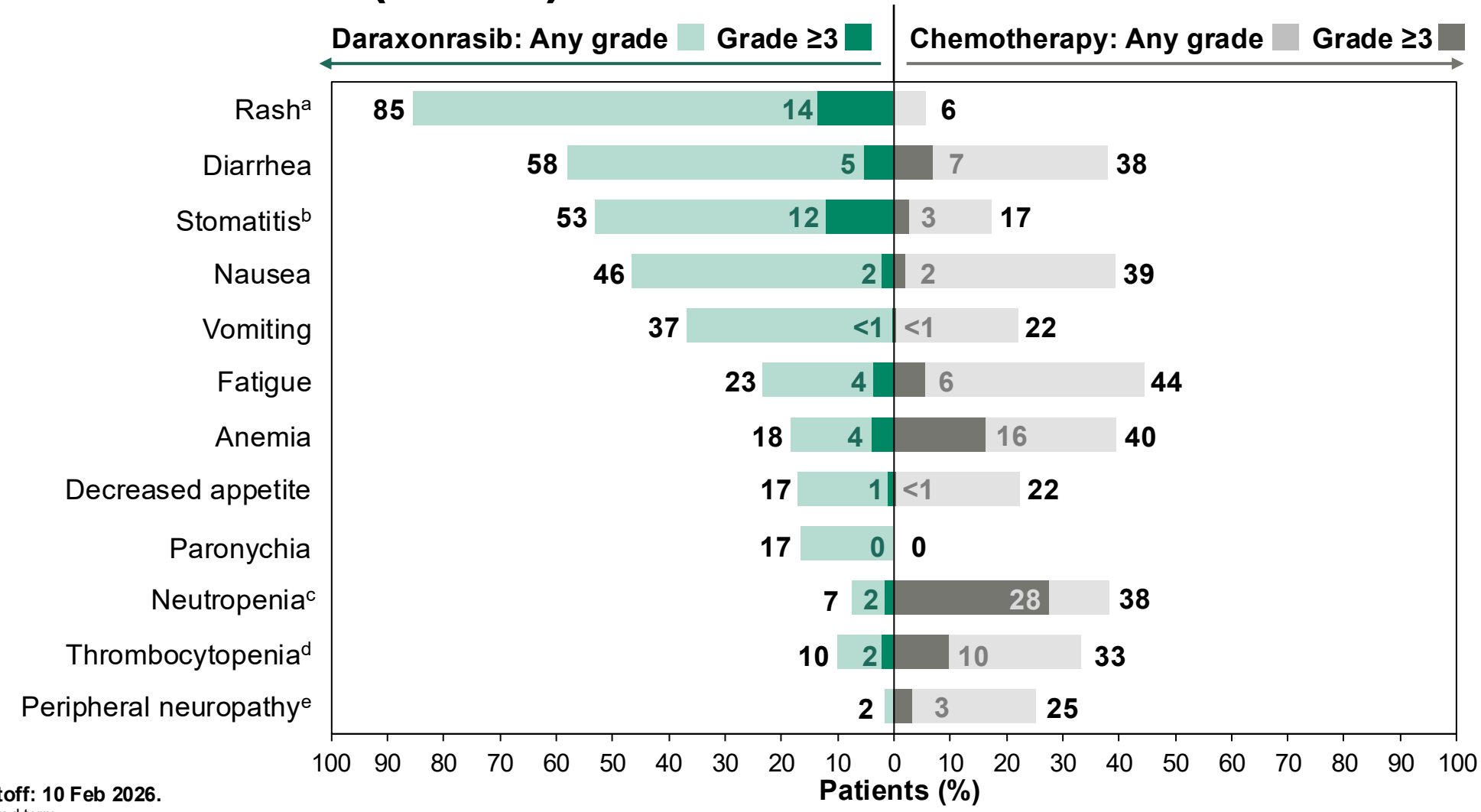
- Median dose intensity was 93.1% with daraxonrasib and 65.3-95.0%[a] across chemotherapy regimens
- Most common (≥5%) TRAEs leading to dose reduction
  - Daraxonrasib: rash (17.4%) and stomatitis (6.6%)
  - Chemotherapy: neutropenia (16.8%), thrombocytopenia (13.6%), fatigue (12.6%), diarrhea (10.3%), and peripheral neuropathy (7.9%)
- TRAEs leading to treatment discontinuation
  - Daraxonrasib (1.2%): 2 patients discontinued due to maculo-papular rash and 1 due to elevated liver function enzymes
  - Chemotherapy (11.2%): the most frequent TRAE leading to discontinuation was peripheral neuropathy (4.7%)

Data cutoff: 10 Feb 2026.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a]Medians across each component of the chemotherapy regimens. [b]Two patients with grade 3 maculo-papular rash, and 1 patient with grade 3 ALT increased and grade 4 AST increased. [c]One patient in the daraxonrasib arm died from treatment-related pneumonitis.

Most Common (>15%) Treatment-Related Adverse Events

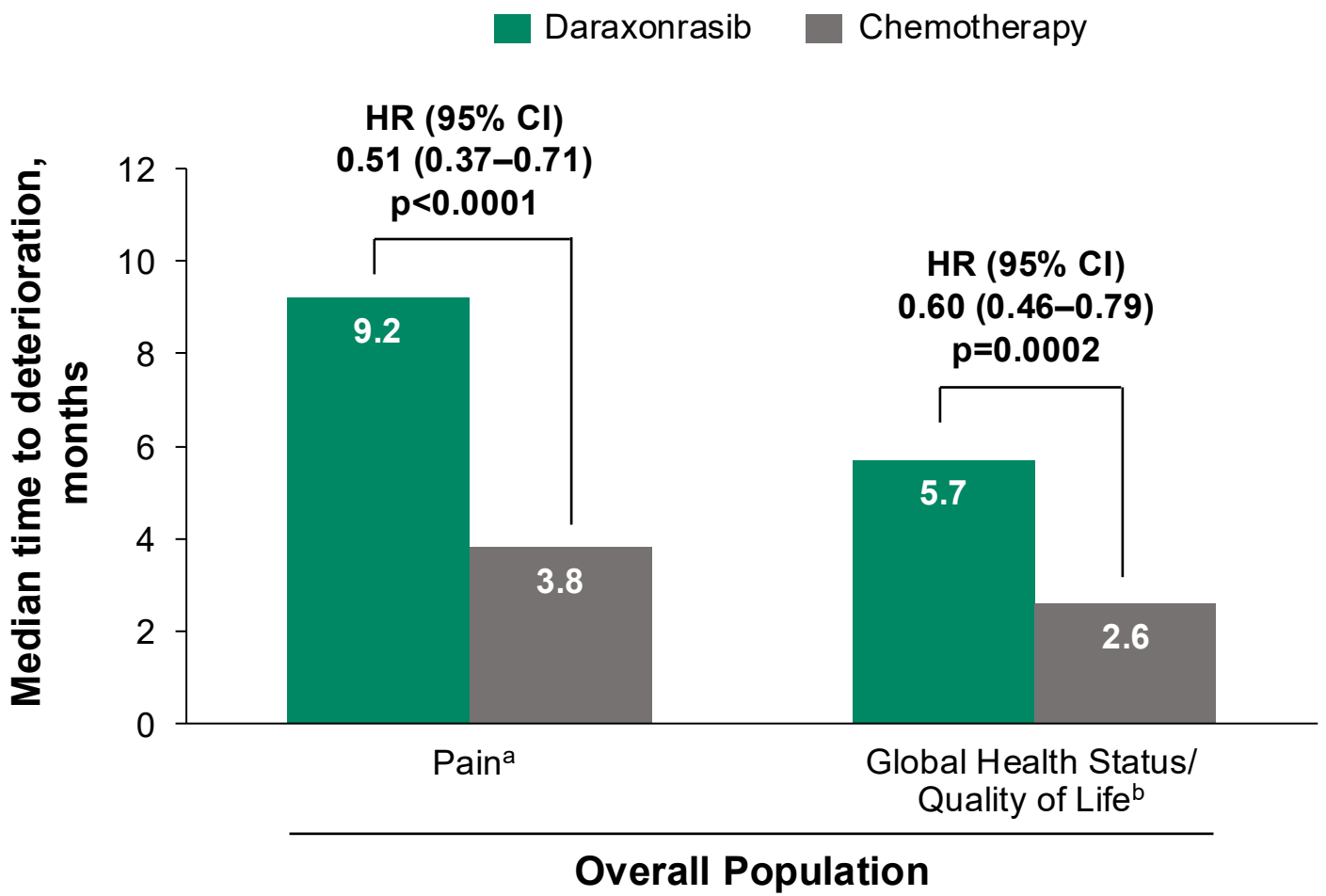


Data cutoff: 10 Feb 2026.

PT, preferred term.

[a]Includes PTs of acne, butterfly rash, dermatitis, dermatitis acneiform, eczema, hand dermatitis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin ulcer. [b]Includes PTs of aphthous ulcer, mucosal inflammation, mucosal ulceration, and stomatitis. [c]Includes PTs of febrile neutropenia, leukopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased. [d]Includes PTs of platelet count decreased and thrombocytopenia. [e]Includes PTs of neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Patient-Reported Outcomes



- EORTC QLQ-PAN26 and EORTC QLQ-C30 questionnaires were administered on day 1 of each cycle and at end of treatment visit
- Daraxonrasib significantly delayed time to deterioration in both symptom of pain and global health status/quality of life compared with chemotherapy

Data cutoff: 10 Feb 2026.

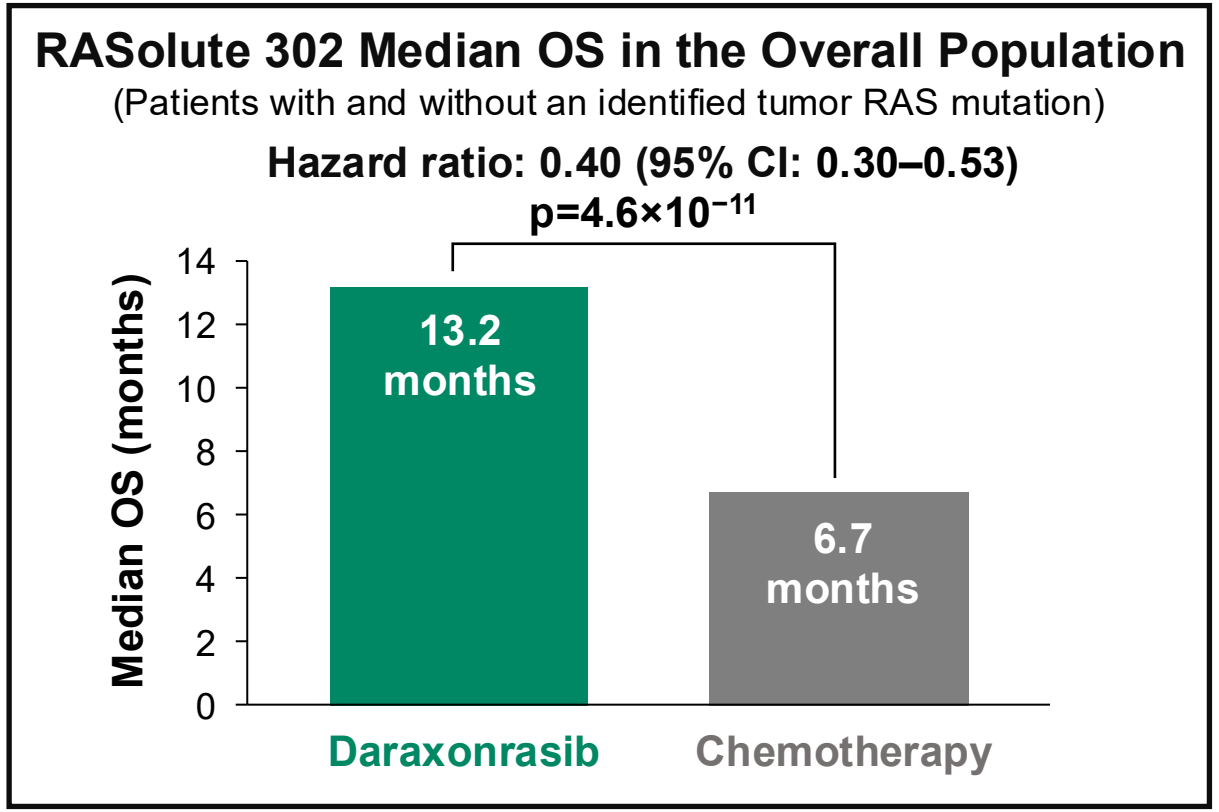
EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PAN26, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Pancreatic Cancer Module.

[a]Time to deterioration in clinically relevant symptom of pain was defined as the time from randomization to an increase of at least 10 points from baseline in pain, or death, whichever occurs first, in the EORTC QLQ-PAN26 pain scale. [b]Time to deterioration in global health status/quality of life was defined as the time from randomization to a decrease of at least 10 points from baseline in global health status/quality of life, or death, whichever occurs first, in EORTC QLQ-C30.

Conclusions

Daraxonrasib (300 mg PO QD):

- Demonstrated statistically significant and clinically meaningful improvements in OS, PFS, and ORR vs standard cytotoxic chemotherapy
- Showed a consistent treatment effect in patients with and without an identified tumor RAS mutation
- Exhibited a manageable safety profile with no unexpected safety findings[1,2]
- Significantly delayed time to deterioration for the symptom of pain and global health status/quality of life



ORR, objective response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PO, oral administration; QD, once daily.

1. Garrido-Laguna I, et al. J Clin Oncol. 2025;43:722; 2. Wolpin B, et al. N Engl J Med. 2026;394:1790-1802.

Key Takeaways

- **Daraxonrasib met all primary and key secondary endpoints** with statistically significant and clinically meaningful improvements in OS, PFS, and ORR in patients with previously treated metastatic PDAC
- Median OS was 13.2 months with daraxonrasib vs 6.7 months with chemotherapy (HR, 0.40 [95% CI: 0.30–0.53]; $p=4.6\times10^{-11}$) in the overall population (patients with and without an identified tumor RAS mutation)

Results support daraxonrasib as the new standard of care for patients with previously treated metastatic PDAC

ORR, objective response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer

E.M. O'Reilly,[1] Z.A. Wainberg,[2] A.E. Hendifar,[3] M.J. Borad,[4] F. Pietrantonio,[5] S. Pant,[6] P. Hammel,[7] C. Cremolini,[8] G.A. Manji,[9] P.E. Oberstein,[10] I. Garrido-Laguna,[11] C. Springfeld,[12] N.S. Azad,[13] M. Ueno,[14] S.Y. Chui,[15] Y. Zhang,[15] H. Patel,[15] Y. Lee,[15] Z. Salman,[15] and B.M. Wolpin,[16] for the RASolute 302 Trial Investigators*

Lay Summary

- **What did this research tell us?**
  - In the RASolute 302 study, participants who received daraxonrasib lived longer overall and were less likely to have their cancer get worse or die during the study than participants who received chemotherapy. This benefit was seen in the overall study population, including in participants whose cancer had a specific change in the RAS gene and in participants whose cancer did not have an identified change.
  - More patients had their cancer shrink or respond to treatment with daraxonrasib than with chemotherapy.
  - Side effects were generally considered manageable with treatment modifications or addition of standard medications used in oncology to manage side effects. Fewer patients on daraxonrasib discontinued treatment due to side effects compared with chemotherapy.
  - Patients receiving daraxonrasib had significantly more time before important quality of life measures worsened, including pain, or death, compared with patients receiving chemotherapy.
- **Who did this research impact?**
  - This research is important for people with metastatic pancreatic adenocarcinoma, a type of cancer that starts in the pancreas and has spread to other parts of the body. Changes, or mutations, in the RAS gene occur in the vast majority of people with pancreatic adenocarcinoma. In this study, benefit was seen in participants whose cancer had a RAS mutation, as well as in participants without an identified RAS mutation.
  - Participants in this study had received one previous treatment for their metastatic pancreatic adenocarcinoma.
- **What does this mean for patients?**
  - These results support daraxonrasib as the new standard of care for patients with previously treated metastatic pancreatic adenocarcinoma.

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- The study was sponsored by Revolution Medicines (ClinicalTrials.gov identifier: NCT06625320)
- Medical writing support was provided by Akshaya Srinivasan, PhD and Asu Erden, PhD of Nucleus Global, an Inizio Company, and was funded by Revolution Medicines

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Acknowledgments

- We thank the patients who participated in this study, as well as all patients who have contributed to pancreatic cancer clinical trials, for helping advance research and improve standards of care
- We are equally grateful to their families and caregivers for their support
- We look forward to the continued evolution of RAS inhibition and its potential to transform the treatment of pancreatic cancer