ORIGINAL ARTICLE

Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer

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ABSTRACT

BACKGROUND

Current therapies offer limited benefit for patients with previously treated metastatic pancreatic ductal adenocarcinoma (mPDAC). Aberrant activation of the RAS pathway is the key driver of PDAC, with oncogenic *RAS* mutations present in more than 90% of cases. Daraxonrasib is an oral RAS(ON) multiselective, tri-complex inhibitor of the active guanosine triphosphate–bound state of mutant and wild-type RAS.

METHODS

In this phase 3, international, open-label, randomized trial, we randomly assigned patients with previously treated mPDAC to receive daraxonrasib or chemotherapy of the investigator's choice. The dual primary end points were overall survival and progression-free survival in the subpopulation of patients with *RAS* G12 mutations (the *RAS* G12 population). Key secondary end points included overall survival and progression-free survival in the overall population (which included patients with *RAS* G12, G13, or Q61 mutations or with no *RAS* mutation identified) and objective response and patient-reported quality of life in the *RAS* G12 and overall populations. Safety was also assessed.

RESULTS

A total of 500 patients, including 91.8% with *RAS* G12 mutations, were randomly assigned to receive daraxonrasib (248 patients) or chemotherapy (252 patients). The median overall survival in the *RAS* G12 population was 13.2 months with daraxonrasib and 6.6 months with chemotherapy, and the median overall survival in the overall population was 13.2 months and 6.7 months, respectively; the hazard ratio was 0.40 in both populations (P<0.001). The median progression-free survival in the *RAS* G12 population was 7.3 months with daraxonrasib and 3.5 months with chemotherapy, and that in the overall population was 7.2 months and 3.6 months, respectively; the hazard ratios were 0.45 and 0.49, respectively (P<0.001 for both comparisons). Adverse events that occurred after the start of treatment were reported in all the patients in the daraxonrasib group and in 97.7% of those in the chemotherapy group; the incidence of adverse events of grade 3 or higher was 61.8% and 69.6%, respectively. Treatment-related adverse events that led to treatment discontinuation occurred in 1.2% of the patients in the daraxonrasib group and in 11.2% of those in the chemotherapy group.

CONCLUSIONS

Among patients with previously treated mPDAC, treatment with daraxonrasib led to significantly longer overall survival and progression-free survival than chemotherapy. (Funded by Revolution Medicines; RASolute 302 ClinicalTrials.gov number, NCT06625320.)

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*A list of the investigators in the RASolute 302 trial is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on May 31, 2026, at NEJM.org.

DOI: 10.1056/NEJMoa2605555

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, with most patients presenting with advanced disease at the time of diagnosis.[1-3] Among patients with metastatic PDAC (mPDAC), the median overall survival is less than 1 year.[2-5] No single standard treatment has been established for the population of patients with previously treated mPDAC.[6] Although a small number of targeted therapies are available, their use is limited to rare molecular subgroups, and most patients receive cytotoxic chemotherapy.[7] These chemotherapy options typically involve fluoropyrimidine- or gemcitabine-based regimens, but patient outcomes are poor, with a low incidence of response, a median progression-free survival of 3 to 4 months, a median overall survival of 6 to 7 months, and substantial toxic effects.[6,8-14]

Oncogenic mutations of the gene family that encodes rat sarcoma virus (*RAS*) are primary drivers of PDAC that are present in more than 90% of tumors, and most of these mutations (>80%) involve substitutions at *KRAS* codon 12.[15-18] These alterations result in constitutive activation of RAS with accumulation of the guanosine triphosphate (GTP)–bound state of RAS, known as RAS(ON), which drives aberrant signaling.[18,19] Tumors lacking *RAS* mutations and other clinically actionable mutations can also be dependent on RAS signaling through genomic amplification or alterations in upstream or downstream components of the RAS–mitogen-activated protein kinase (MAPK) pathway.[20-22]

Daraxonrasib is an oral, potent RAS(ON) multiselective, tri-complex inhibitor that binds to cyclophilin A intracellularly to form a binary complex that engages RAS(ON) and suppresses downstream signaling.[19,23-25] Daraxonrasib is selective for the active state of both mutant and wild-type RAS across KRAS, NRAS, and HRAS, including variants with mutations at glycine 12 (G12), glycine 13 (G13), and glutamine 61 (Q61).[23,24] In a phase 1–2 trial, daraxonrasib showed clinical activity with mainly low-grade adverse events, including rash and gastrointestinal side effects, in patients with advanced PDAC.[26] These findings led to the phase 3 RASolute 302 trial, in which daraxonrasib is being compared with the investigator's choice of standard chemotherapy in patients with previously treated mPDAC. Here, we report the primary results of the RASolute 302 trial.

Methods

Trial Design and Oversight

The RASolute 302 trial is a phase 3, international, open-label, randomized trial. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent. An independent data monitoring committee oversaw safety for the trial.

The trial protocol (available with the full text of this article at NEJM.org) was developed by the sponsor (Revolution Medicines) in collaboration with trial investigators. The statistical analyses were performed and validated by the sponsor according to the prespecified statistical analysis plan. All the authors had access to the data, participated in the interpretation of the data, and contributed to the preparation of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Medical writing assistance with the submitted manuscript was funded by the sponsor.

Patients

Eligible patients were at least 18 years of age, had histologically or cytologically confirmed mPDAC, and had previous disease progression after the receipt of one previous line of a fluoropyrimidine- or gemcitabine-based therapy for metastatic disease or after the receipt of neoadjuvant or adjuvant therapy if metastatic disease was diagnosed less than 6 months after the last dose of such therapy. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating greater disability); and adequate organ function.[27] Additional eligibility criteria included a tumor with a documented *RAS* mutational status, defined as either a nonsynonymous mutation in *KRAS*, *NRAS*, or *HRAS* at codon 12, 13, or 61 (G12, G13, or Q61), or no tumor with a *RAS* mutation identified. Patients who did not have a tumor harboring an identified *RAS* mutation but who had another actionable driver alteration were required to have received approved targeted therapy. Key

exclusion criteria were known central nervous system metastases and previous RAS-targeted therapy. Full eligibility criteria are provided in the protocol.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive daraxonrasib at a dose of 300 mg orally once daily or the investigator's choice of chemotherapy (gemcitabine plus nab-paclitaxel, modified FOLFIRINOX [fluorouracil, irinotecan, leucovorin, and oxaliplatin], FOLFOX [fluorouracil, leucovorin, and oxaliplatin], or liposomal irinotecan plus fluorouracil and leucovorin). Chemotherapy was administered according to the local prescribing practice.

Randomization was performed with the use of an interactive response technology system and was stratified according to ECOG performance-status score (0 or 1), presence or absence of metastatic disease at the time of initial diagnosis, presence or absence of liver metastases at baseline, and *RAS* mutational status (*RAS* G12D or G12V mutation, other *RAS* G12 mutation, or *RAS* G13 or Q61 mutation or no tumor with a *RAS* mutation identified). Treatment continued until disease progression or unacceptable toxic effects had occurred or consent was withdrawn, whichever happened first. Crossover to the other treatment group was not permitted.

END POINTS

The dual primary end points were overall survival and progression-free survival as assessed by blinded independent central review according to RECIST, version 1.1, in the subpopulation of patients with *RAS* G12 mutations (the *RAS* G12 population). Key secondary end points included overall survival and progression-free survival as assessed by blinded independent central review in the overall population (defined as the subpopulation of patients whose tumors harbored *RAS* mutations at G12, G13, or Q61 or patients in whom no *RAS* mutation was identified), objective response in the *RAS* G12 and overall populations, and patient-reported quality-of-life end points in the *RAS* G12 and overall populations. The specific patient-reported end points were the time to deterioration as assessed on the basis of pain (defined as the time to an increase of ≥10 points from baseline in the score on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire pancreatic cancer pain scale [EORTC QLQ-PAN26] or death, whichever occurred first) and the time to deterioration as assessed on the basis of global health status–quality of life (defined as the time to a decrease of ≥10 points from baseline in the score on the EORTC Core Quality of Life Questionnaire–Core 30 [EORTC QLQ-C30] global health status–quality-of-life scale or death, whichever occurred first).

Additional secondary end points included time to response and safety. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[28] The safety population included all the patients who received at least one dose of the trial treatment.

STATISTICAL ANALYSIS

The Kaplan–Meier method was used to estimate overall survival and progression-free survival. Differences between the treatment groups were assessed with the stratified log-rank test. Hazard ratios and corresponding 95% confidence intervals were calculated with the stratified Cox model with Efron's method of handling ties. The same stratification factors that were used for randomization were applied to the stratified log-rank test and Cox model.

The overall type I error rate was controlled at a two-sided alpha level of 5% with the use of a graphical multiple testing procedure.[29] The alpha was initially split between the dual primary end points in the *RAS* G12 population, whereby 0.2% was allocated to progression-free survival (blinded independent central review) and 4.8% to overall survival. Progression-free survival and overall survival were tested sequentially in the *RAS* G12 population and then in the overall population. If significance for the treatment effect was shown for both progression-free survival and overall survival in both populations, key secondary end points including objective response and patient-reported end points were tested sequentially in the *RAS* G12 population and then in the overall population. Additional analyses that were not included in the prespecified multiplicity-controlled testing procedure were descriptive in nature.

For the analysis of overall survival in the *RAS* G12 population, 314 deaths would need to occur to provide the trial with approximately 84% power at a two-sided alpha level of 4.8%, under the assumption of a hazard ratio of 0.70 (darax-

onrasib vs. chemotherapy). For the analysis of progression-free survival in the *RAS* G12 population, 235 events would need to occur to provide the trial with approximately 95% power at a two-sided alpha level of 0.2%, under the assumption of a hazard ratio of 0.54.

Two interim analyses of overall survival were planned to be performed before the final analysis in the *RAS* G12 population. The first interim analysis, which was also the final analysis for progression-free survival, was planned to be performed after the completion of enrollment and after at least 166 deaths had occurred in the *RAS* G12 population. All the data reported here are based on the first interim analysis. The full statistical analysis plan, including the analysis methods for the key secondary end points, is provided with the protocol.

RESULTS

PATIENTS

Between October 16, 2024, and November 7, 2025, a total of 500 patients at 59 sites in six countries were randomly assigned to receive daraxonrasib (248 patients) or chemotherapy (252 patients) (Fig. 1). A total of 459 patients (91.8%) who were enrolled in the trial had *RAS* G12 mutations.

The demographic and baseline disease characteristics of the patients were generally balanced across the treatment groups (Table 1). In the overall population, both treatment groups included patients with no *RAS* mutation identified: 9 patients in the daraxonrasib group and 7 patients in the chemotherapy group. A table showing the representativeness of the trial population as compared with the disease distribution is provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

A total of 241 of the randomly assigned patients in the daraxonrasib group (97.2%) and 214 of those in the chemotherapy group (84.9%) received at least one dose of the trial treatment. In the chemotherapy group, in which patients received the investigator's choice of chemotherapy, the regimens that were administered were gemcitabine plus nab-paclitaxel (in 56.5% of the patients), liposomal irinotecan plus fluorouracil and leucovorin (in 32.7%), modified FOLFIRINOX (in 5.6%), and FOLFOX (in 5.1%).

At the time of data cutoff (February 10, 2026), the median duration of follow-up was 8.5 months (range, 3.2 to 15.9). The median duration of treatment in the daraxonrasib group was 6.2 months (range, <0.1 to 14.1), with a median dose intensity of 93.1% (range, 32.9 to 100.0). In the chemotherapy group, the median duration of treatment was 1.9 months (range, <0.1 to 12.5) with gemcitabine plus nab-paclitaxel, 3.1 months (range, 0.1 to 11.2) with liposomal irinotecan plus fluorouracil and leucovorin, 3.2 months (range, 0.1 to 12.9) with modified FOLFIRINOX, and 1.5 months (range, 0.1 to 7.0) with FOLFOX. The median dose intensity across the chemotherapy regimens ranged from 65 to 95%.

EFFICACY

Overall Survival

In the *RAS* G12 population (459 patients), the median overall survival was 13.2 months (95% confidence interval [CI], 10.0 to not reached) in the daraxonrasib group as compared with 6.6 months (95% CI, 5.4 to 8.2) in the chemotherapy group (hazard ratio for death, 0.40; 95% CI, 0.30 to 0.54; P<0.001) (Fig. 2A). In the overall population (500 patients), the median overall survival was 13.2 months (95% CI, 10.0 to not reached) in the daraxonrasib group as compared with 6.7 months (95% CI, 5.8 to 8.0) in the chemotherapy group (hazard ratio for death, 0.40; 95% CI, 0.30 to 0.53; P<0.001) (Fig. 2B). At 9 months, overall survival among the patients without *RAS* G12 mutations (those with *RAS* G13 or Q61 mutations or no *RAS* mutation) was 55.4% (95% CI, 25.6 to 77.4) in the daraxonrasib group and 31.6% (95% CI, 10.4 to 55.7) in the chemotherapy group. Among the patients without *RAS* G12 mutations (41 patients), 7 of 20 patients have died in the daraxonrasib group as compared with 14 of 21 patients in the chemotherapy group (hazard ratio, 0.37; 95% CI, 0.15 to 0.93). The observed overall survival benefit of daraxonrasib over chemotherapy appeared to be generally consistent across prespecified subgroups, including *RAS* mutational status (Fig. S1).

Progression-free Survival

In the *RAS* G12 population, the median progression-free survival, assessed by blinded independent central review, was 7.3 months (95% CI, 6.3 to 8.1) with daraxonrasib as compared with 3.5 months (95% CI, 2.9 to 3.8) with chemotherapy (hazard

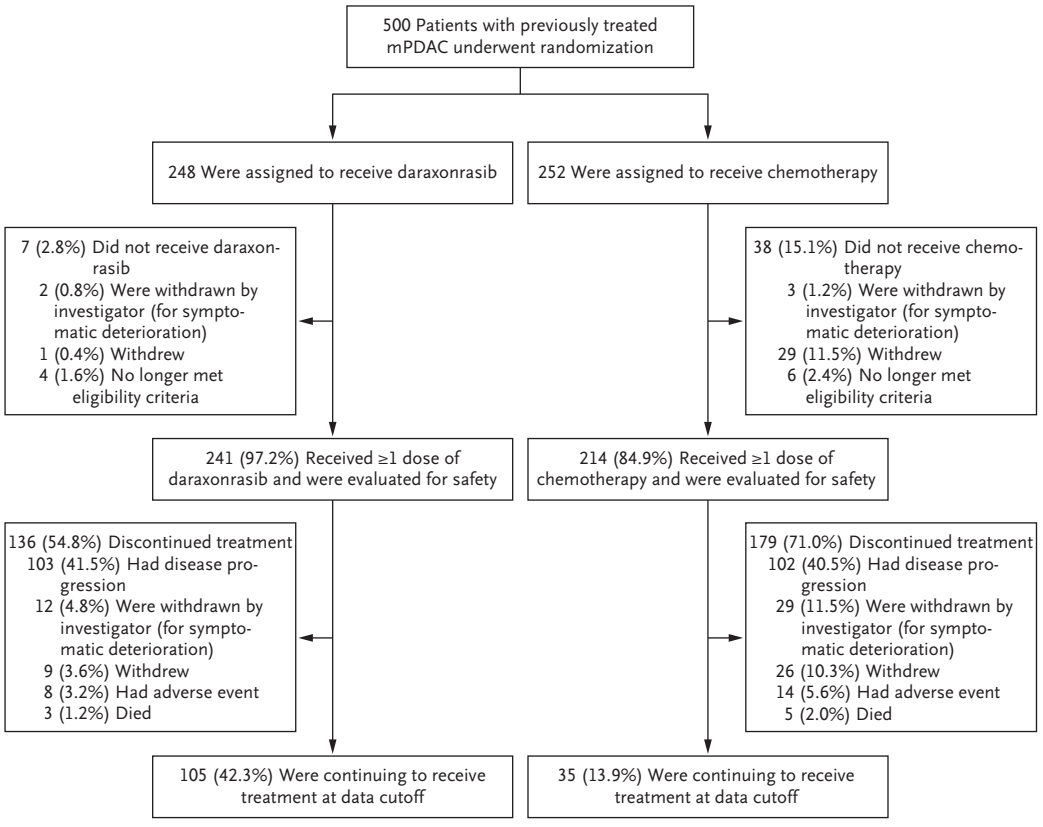


Figure 1. Randomization and Follow-up.

Among the 45 patients who underwent randomization but never received a dose of the trial treatment, data on deaths were obtained for 7 of the 7 patients (100%) in the daraxonrasib group and for 27 of the 38 patients (71.1%) in the chemotherapy group; 5 of 38 patients (13.2%) in the chemotherapy group continued to be followed for survival at the time of data cutoff (February 10, 2026). One patient (0.4%) in the daraxonrasib group and 3 patients (1.2%) in the chemotherapy group, in which patients received chemotherapy of the investigator's choice, discontinued treatment for reasons other than those listed. Discontinuation of treatment owing to disease progression was documented on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Symptomatic deterioration leading to discontinuation of treatment was documented by the investigator as discontinuation because of clinical progression (i.e., the patient did not meet the criteria for progressive disease according to RECIST, version 1.1) and not because of an adverse event. The efficacy analyses were based on data from all the patients who had undergone randomization. The safety analyses were based on data from all the patients who received at least one dose of the trial treatment. mPDAC denotes metastatic pancreatic ductal adenocarcinoma.

ratio for disease progression or death, 0.45; 95% CI, 0.34 to 0.59; P<0.001) (Fig. 3A). In the overall population, the median progression-free survival was 7.2 months (95% CI, 5.7 to 7.5) and 3.6 months (95% CI, 2.9 to 4.2) in the daraxonrasib and chemotherapy groups, respectively (hazard ratio for disease progression or death, 0.49; 95% CI, 0.38 to 0.64; P<0.001) (Fig. 3B). Among the 41 patients without *RAS* G12 mutations, disease progression or death occurred in 15 of 20 patients in the daraxonrasib group as compared with 9 of 21 patients in the chemotherapy group (hazard ratio, 1.38; 95% CI, 0.60 to 3.17). There appeared to be a progression-free survival benefit of daraxonrasib over chemotherapy in most of the prespecified subgroups (Fig. S2).

Objective Response

In the *RAS* G12 population, the objective response was 33.2% (95% CI, 27.0 to 39.9) with daraxonrasib as compared with 11.8% (95% CI, 7.8 to 16.8) with chemotherapy (Table S2). In the overall popu-

Table 1. Demographic and Baseline Disease Characteristics (*RAS* G12 Population and Overall Population).*

Characteristic	*RAS* G12 Population		Overall Population	
	Daraxonrasib (N=228)	Chemotherapy (N=231)	Daraxonrasib (N=248)	Chemotherapy (N=252)
Median age (range) — yr	66 (30–88)	65 (36–86)	66 (30–88)	65 (36–86)
Age ≥65 yr — no. (%)	123 (53.9)	121 (52.4)	134 (54.0)	131 (52.0)
Sex — no. (%)				
Female	111 (48.7)	100 (43.3)	117 (47.2)	108 (42.9)
Male	117 (51.3)	131 (56.7)	131 (52.8)	144 (57.1)
Race or ethnic group — no. (%)†				
American Indian or Alaska Native	0	1 (0.4)	0	1 (0.4)
Asian	29 (12.7)	25 (10.8)	29 (11.7)	28 (11.1)
Black	6 (2.6)	14 (6.1)	7 (2.8)	15 (6.0)
White	155 (68.0)	152 (65.8)‡	172 (69.4)	167 (66.3)‡
Other	5 (2.2)	5 (2.2)	5 (2.0)	6 (2.4)
Race or ethnic group not obtained	30 (13.2)	27 (11.7)	32 (12.9)	28 (11.1)
Unknown	3 (1.3)	7 (3.0)	3 (1.2)	7 (2.8)
Geographic region — no. (%)				
North America	132 (57.9)	143 (61.9)	145 (58.5)	158 (62.7)
Europe	80 (35.1)	70 (30.3)	87 (35.1)	74 (29.4)
Asia Pacific	16 (7.0)	18 (7.8)	16 (6.5)	20 (7.9)
ECOG performance-status score — no. (%)§				
0	120 (52.6)	109 (47.2)	129 (52.0)	118 (46.8)
1¶	108 (47.4)	122 (52.8)	119 (48.0)	134 (53.2)
Metastatic disease at initial diagnosis — no. (%)	139 (61.0)	140 (60.6)	154 (62.1)	154 (61.1)
No. of previous systemic therapies for metastatic disease — no. (%)				
0‖	41 (18.0)	33 (14.3)	42 (16.9)	34 (13.5)
1	187 (82.0)	198 (85.7)	206 (83.1)	218 (86.5)
Select previous chemotherapy regimens for metastatic disease — no. (%)				
Modified FOLFIRINOX or FOLFIRINOX	91 (39.9)	98 (42.4)	98 (39.5)	105 (41.7)
Gemcitabine plus nab-paclitaxel	85 (37.3)	82 (35.5)	94 (37.9)	94 (37.3)
NALIRIFOX	4 (1.8)	7 (3.0)	4 (1.6)	8 (3.2)
Liposomal irinotecan plus fluorouracil and leucovorin	1 (0.4)	3 (1.3)	2 (0.8)	3 (1.2)
FOLFOX	2 (0.9)	3 (1.3)	2 (0.8)	3 (1.2)
Previous pancreatectomy — no. (%)	80 (35.1)	86 (37.2)	83 (33.5)	92 (36.5)
Previous Whipple procedure	54 (23.7)	52 (22.5)	57 (23.0)	56 (22.2)
Sites of metastases — no. (%)				
Liver	161 (70.6)	162 (70.1)	174 (70.2)	176 (69.8)
Lung	89 (39.0)	82 (35.5)	96 (38.7)	88 (34.9)
Peritoneum	72 (31.6)	77 (33.3)	76 (30.6)	83 (32.9)
Blood level of CA 19-9 ≥40 U/ml — no. (%)	194 (85.1)	179 (77.5)	211 (85.1)	195 (77.4)

Table 1. (Continued.)

Characteristic	*RAS* G12 Population		Overall Population	
	Daraxonrasib (N=228)	Chemotherapy (N=231)	Daraxonrasib (N=248)	Chemotherapy (N=252)
RAS mutational status — no. (%)				
RAS G12D or G12V mutation	197 (86.4)	197 (85.3)	197 (79.4)	197 (78.2)
Other *RAS* G12 mutation	31 (13.6)	34 (14.7)	31 (12.5)	34 (13.5)
RAS G13 or Q61 mutation, or no *RAS* mutation identified	0	0	20 (8.1)**	21 (8.3)**

* The *RAS* G12 population comprised patients with *RAS* G12 mutations. The overall population comprised patients whose tumors harbored *RAS* mutations at G12, G13, or Q61 or patients in whom no *RAS* mutation was identified. Percentages may not total 100 because of rounding. FOLFIRINOX denotes fluorouracil, irinotecan, leucovorin, and oxaliplatin; FOLFOX fluorouracil, leucovorin, and oxaliplatin; and NALIRIFOX liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin.
† Race and ethnic group were reported by the patients.
‡ The number of patients includes 1 patient whose race was documented as White and Asian.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ Three patients (2 randomly assigned to the daraxonrasib group and 1 to the chemotherapy group) had an ECOG performance-status score higher than 1 at baseline; therefore, these patients no longer met the trial eligibility criteria and received no doses of the trial treatment.
‖ This category includes 42 patients in the daraxonrasib group and 33 patients in chemotherapy group who received previous treatment in the context of neoadjuvant or adjuvant disease but progressed to metastatic disease less than 6 months after the last dose of such therapy. One patient with a diagnosis of metastatic disease had a line of therapy that was incorrectly categorized as treatment for locally advanced disease.
** Nine patients in the daraxonrasib group and 7 patients in the chemotherapy group had no identified *RAS* mutation.

lation, the response was 31.6% (95% CI, 25.8 to 38.0) with daraxonrasib as compared with 11.2% (95% CI, 7.5 to 15.9) with chemotherapy. The median time to response across the *RAS* G12 and overall populations was 1.9 months (range, 1.3 to 7.4) in the daraxonrasib group and 1.9 months (range, 1.7 to 7.3) in the chemotherapy group.

Patient-Reported End Points

The time to deterioration as assessed on the basis of pain and global health status–quality of life was significantly longer with daraxonrasib than with chemotherapy in both the *RAS* G12 population and the overall population. The median time to deterioration, which included death as an event, for the symptom of pain was 9.0 months with daraxonrasib and 3.7 months with chemotherapy in the *RAS* G12 population and was 9.2 months with daraxonrasib and 3.8 months with chemotherapy in the overall population (hazard ratio, 0.51; 95% CI, 0.37 to 0.71; P<0.001, for both comparisons). For global health status–quality of life, the corresponding medians were 5.6 months and 2.4 months in the *RAS* G12 population (hazard ratio, 0.60; 95% CI, 0.45 to 0.80; P<0.001) and 5.7 months and 2.6 months in the overall population (hazard ratio, 0.60; 95% CI, 0.46 to 0.79; P<0.001) (Fig. S3).

SAFETY

Adverse events of any grade, and regardless of attribution, that occurred after the start of treatment were reported in 100% of the patients in the daraxonrasib group and in 97.7% of those in the chemotherapy group (Table 2). The most common events in the daraxonrasib group were rash (in 86.3% of the patients), diarrhea (in 67.2%), stomatitis (in 54.8%), nausea (in 52.3%), vomiting (in 42.3%), fatigue (in 33.6%), and anemia (in 29.9%). In the chemotherapy group, the most commonly reported events were fatigue (in 45.3% of the patients), anemia (in 44.9%), nausea (in 42.1%), diarrhea (in 41.6%), neutropenia (in 39.3%), thrombocytopenia (in 33.6%), decreased appetite (in 27.1%), and peripheral neuropathy (in 26.6%). Adverse events of grade 3 or higher that occurred after the start of treatment were reported in 61.8% of the patients in the daraxonrasib group and in 69.6% of those in the chemotherapy group.

Adverse events that were considered by the investigators to be related to the trial treatment oc-

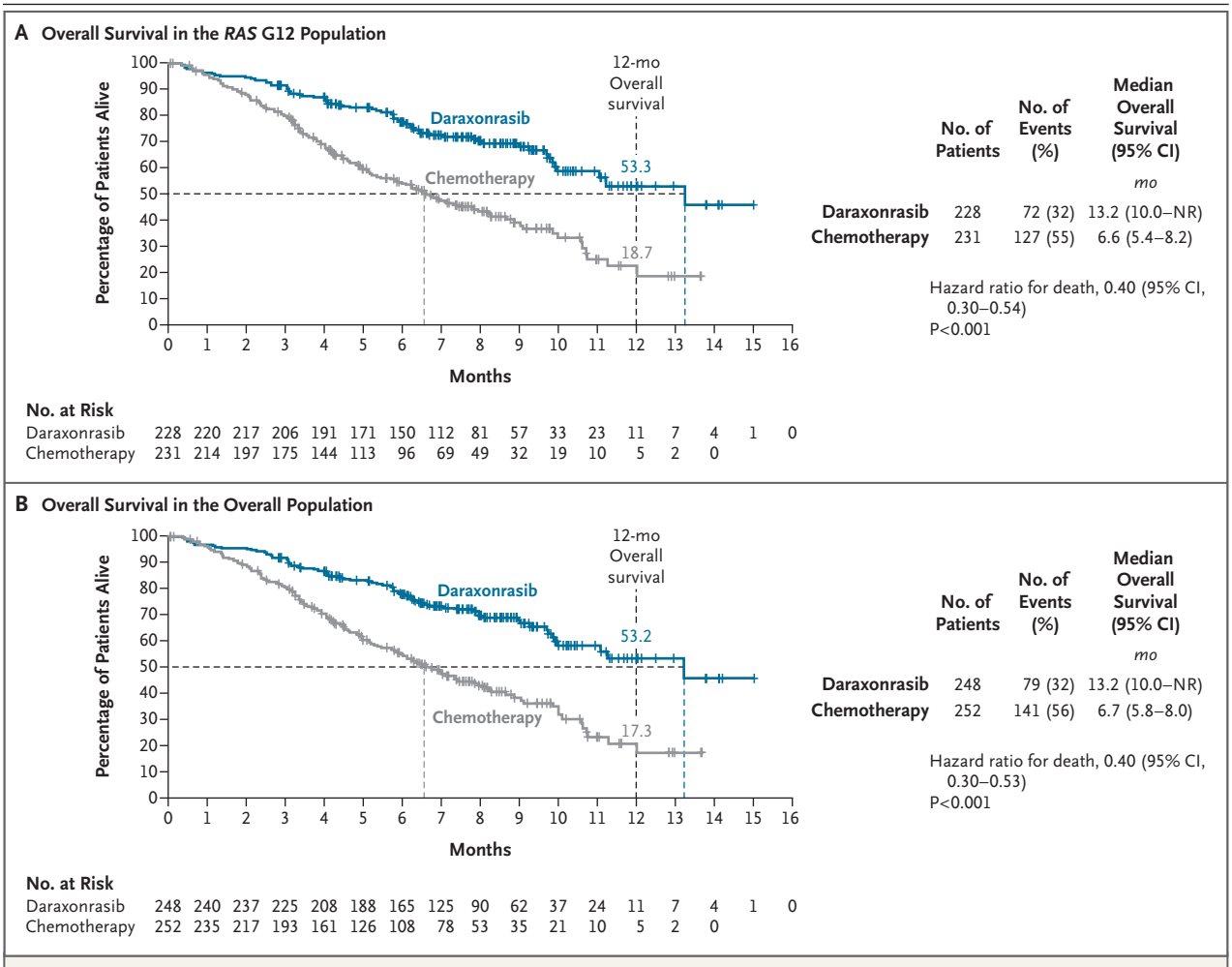


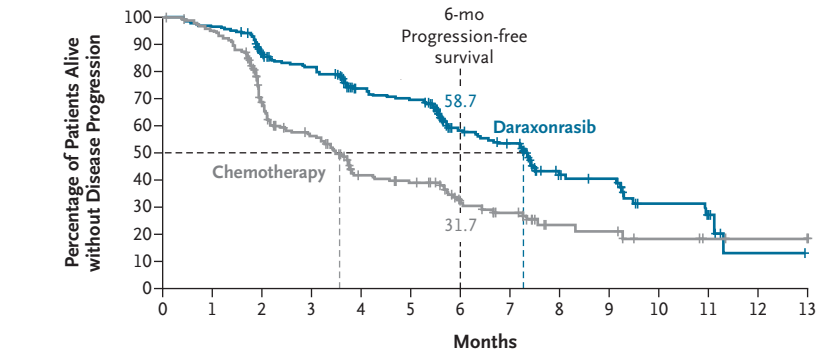
Figure 2. Overall Survival.

The *RAS* G12 population comprised patients with *RAS* G12 mutations. The overall population comprised patients whose tumors harbored *RAS* mutations at G12, G13, or Q61 or patients in whom no *RAS* mutation was identified. Hazard ratios and 95% confidence intervals were based on the stratified Cox model with Efron's method of handling ties. P values were calculated with the stratified log-rank test. NR denotes not reached.

curred in 97.9% of the patients in the daraxonrasib group and in 93.5% of those in the chemotherapy group. Treatment-related adverse events of grade 3 or higher were less common with daraxonrasib than with chemotherapy (in 43.6% of the patients vs. 57.5%), as were serious treatment-related adverse events (in 10.8% vs. 18.7%). The incidence of treatment-related adverse events that led to dose reduction was also lower in the daraxonrasib group than in the chemotherapy group (in 36.1% of the patients vs. 57.5%).

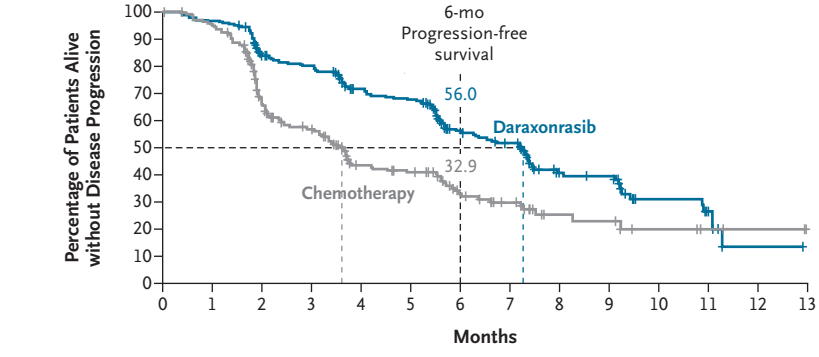
The most commonly reported treatment-related adverse events in the daraxonrasib group were rash (in 85.5% of the patients), diarrhea (in 58.1%), stomatitis (in 53.1%), nausea (in 46.5%), and vomiting (in 36.9%). In the chemotherapy group, the most common such events were fatigue (in 44.4% of the patients), anemia (in 39.7%), nausea (in 39.3%), neutropenia (in 38.3%), diarrhea (in 37.9%), thrombocytopenia (in 33.2%), and peripheral neuropathy (in 25.2%) (Table 2).

Treatment-related adverse events of grade 3 or higher that occurred in at least 10% of the patients in the daraxonrasib group were rash (in 13.7% of the patients) and stomatitis (in 12.0%). In the chemotherapy group, the treatment-related adverse events of grade 3 or higher that occurred in at least 10% of the patients were neutropenia



	No. of Patients	No. of Events (%)	Median Progression-free Survival (95% CI)
			mo
Daraxonrasib	228	112 (49)	7.3 (6.3–8.1)
Chemotherapy	231	121 (52)	3.5 (2.9–3.8)

Hazard ratio for disease progression or death, 0.45 (95% CI, 0.34–0.59)
P<0.001



	No. of Patients	No. of Events (%)	Median Progression-free Survival (95% CI)
			mo
Daraxonrasib	248	127 (51)	7.2 (5.7–7.5)
Chemotherapy	252	130 (52)	3.6 (2.9–4.2)

Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.64)
P<0.001

Figure 3. Progression-free Survival.

Progression-free survival was assessed by blinded independent central review according to RECIST, version 1.1. Hazard ratios and 95% confidence intervals were based on the stratified Cox model with Efron's method of handling ties. P values were calculated with the stratified log-rank test.

(in 27.6% of the patients) and anemia (in 16.4%) (Table 2).

The most common serious treatment-related adverse events that led to hospitalization were gastrointestinal events in both the daraxonrasib group (in 4.1% of the patients) and the chemotherapy group (in 5.6%). The incidence of hematologic toxic effects that led to hospitalization was higher with chemotherapy than with daraxonrasib (0% vs. 4.2% in the daraxonrasib and chemotherapy groups, respectively), as was the incidence of infections that led to hospitalization (0.4% vs. 3.3%). One patient in the daraxonrasib group died from treatment-related pneumonitis.

Treatment-related adverse events that led to dose modifications occurred in 56.8% of the patients in the daraxonrasib group and in 71.5% of those in the chemotherapy group. Treatment-related adverse events that led to a dose reduction in at least 5% of the patients in the daraxonrasib group were rash (in 17.4% of the patients) and stomatitis (in 6.6%); in the chemotherapy group, the treatment-related adverse events that led to a dose reduction in at least 5% of the patients were neutropenia (in 16.8% of the patients), thrombocytopenia (in 13.6%), fatigue (in 12.6%), diarrhea (in 10.3%), and peripheral neuropathy (in 7.9%) (Table S3). Discontinuation of treatment owing to a treatment-related adverse event was uncommon in the daraxonrasib group as compared with the

Table 2. Adverse Events (Safety Population).*

Event	Daraxonrasib (N=241)	Chemotherapy (N=214)
	no. of patients (%)	
Any adverse event	241 (100)	209 (97.7)
Grade ≥3 event	149 (61.8)	149 (69.6)
Treatment-related adverse event	236 (97.9)	200 (93.5)
Grade ≥3 treatment-related adverse event	105 (43.6)†	123 (57.5)
Serious treatment-related adverse event	26 (10.8)	40 (18.7)
Grade 5 treatment-related adverse event	1 (0.4)	0
Treatment-related adverse event leading to dose modification	137 (56.8)	153 (71.5)
Dose interruption	135 (56.0)	118 (55.1)
Dose reduction	87 (36.1)	123 (57.5)
Treatment-related adverse event leading to treatment discontinuation	3 (1.2)‡	24 (11.2)
Treatment-related adverse event of any grade reported in ≥10% of patients; corresponding grade ≥3 treatment-related adverse event		
Rash§	206 (85.5); 33 (13.7)	12 (5.6); 0
Diarrhea	140 (58.1); 13 (5.4)	81 (37.9); 15 (7.0)
Stomatitis¶	128 (53.1); 29 (12.0)	37 (17.3); 6 (2.8)
Nausea	112 (46.5); 5 (2.1)	84 (39.3); 4 (1.9)
Vomiting	89 (36.9); 1 (0.4)	47 (22.0); 1 (0.5)
Fatigue	56 (23.2); 9 (3.7)	95 (44.4); 12 (5.6)
Anemia	44 (18.3); 10 (4.1)	85 (39.7); 35 (16.4)
Decreased appetite	41 (17.0); 3 (1.2)	48 (22.4); 1 (0.5)
Paronychia	40 (16.6); 0	0; 0
Dry skin	32 (13.3); 0	4 (1.9); 0
Aspartate aminotransferase increased	30 (12.4); 6 (2.5)	22 (10.3); 2 (0.9)
Asthenia	26 (10.8); 1 (0.4)	31 (14.5); 4 (1.9)
Neutropenia‖	18 (7.5); 4 (1.7)	82 (38.3); 59 (27.6)
Alanine aminotransferase increased	23 (9.5); 4 (1.7)	22 (10.3); 1 (0.5)
Edema peripheral	21 (8.7); 0	27 (12.6); 0
Thrombocytopenia**	24 (10.0); 5 (2.1)	71 (33.2); 21 (9.8)
Alopecia	8 (3.3); 0	32 (15.0); 0
Pyrexia	7 (2.9); 0	23 (10.7); 2 (0.9)
Peripheral neuropathy††	4 (1.7); 0	54 (25.2); 7 (3.3)

* All adverse events occurred after the start of treatment. The safety population included all the patients who received at least one dose of the trial treatment.

† Three patients (1.2%) had treatment-related adverse events of grade 4: an increased aspartate aminotransferase level in two patients and a decreased platelet count in one patient.

‡ Two patients had a maculopapular rash of grade 3, and one patient had an increased alanine aminotransferase level of grade 3 and an increased aspartate aminotransferase level of grade 4.

§ Preferred terms include dermatitis acneiform, rash, rash maculopapular, skin ulcer, rash erythematous, eczema, dermatitis, rash pruritic, rash macular, acne, rash papular, butterfly rash, and hand dermatitis.

¶ Preferred terms include stomatitis, mucosal inflammation, aphthous ulcer, and mucosal ulceration.

‖ Preferred terms include neutrophil count decreased, neutropenia, white-cell count decreased, leukopenia, and febrile neutropenia.

** Preferred terms include platelet count decreased and thrombocytopenia.

†† Preferred terms include peripheral sensory neuropathy, neuropathy peripheral, neuralgia, polyneuropathy, and peripheral motor neuropathy.

chemotherapy group (in 1.2% vs. 11.2% of the patients); two patients discontinued treatment with daraxonrasib owing to a maculopapular rash and one patient owing to elevated liver enzyme levels. Among the patients who discontinued chemotherapy owing to a treatment-related adverse event, the most common of these events was peripheral neuropathy (in 4.7% of the patients).

DISCUSSION

PDAC is one of the most challenging and lethal cancers. In the context of second-line treatment, cytotoxic chemotherapy is associated with a low incidence of response, short median progression-free survival, and a median overall survival of only 6 to 7 months.[13,14] In this trial, in which 91.8% of the patients had *RAS* G12 mutations, treatment with daraxonrasib led to significantly longer overall survival and progression-free survival than the investigator's choice of chemotherapy in the *RAS* G12 and overall populations of patients with previously treated mPDAC, and the percentage of patients with a response was twice as high with daraxonrasib. The inclusion of multiple commonly used chemotherapy regimens in the control group reflects contemporary clinical practice.[6] It is important to note that the results in the chemotherapy group were as expected, with outcomes consistent with those of previous clinical trials and closely aligned with historical benchmarks — findings that further underscore the magnitude of benefit observed in the daraxonrasib group.[8,9,11]

In both the *RAS* G12 population and the overall population, treatment with daraxonrasib reduced the risk of death by 60%, with a median overall survival of 13.2 months among patients with previously treated mPDAC. Although cross-trial comparisons should be interpreted with caution, previous randomized mPDAC trials of first-line treatment with FOLFIRINOX, gemcitabine plus nab-paclitaxel, and NALIRIFOX (liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin) have shown median overall survival ranging from 8.5 to 11.1 months.[30-32] The median overall survival observed with daraxonrasib is notable in this context, given that our trial enrolled patients who had previously received chemotherapy; however, differences in patient populations and potential selection bias among patients eligible for second-line therapy should be considered.

Treatment with daraxonrasib resulted in a significantly longer time to deterioration with respect to both pain — a clinically relevant symptom in patients with mPDAC — and global health status–quality of life than chemotherapy. These patient-reported benefits complement the improvements in overall survival and progression-free survival observed with daraxonrasib.

The results of subgroup analyses of overall survival and progression-free survival are suggestive but not definitive, given the limited numbers of patients and wide confidence intervals. In prespecified subgroup analyses of overall survival, the magnitude and direction of treatment benefit with daraxonrasib were consistent across most of the clinical and molecular subgroups, including ECOG performance-status score, stage at initial diagnosis, presence of liver metastases, treatment history, and *RAS* mutational status. The hazard ratio estimates of progression-free survival favored daraxonrasib across most of the prespecified subgroups, with variability across smaller molecularly defined *RAS* subgroups. Given that less than 10% of the patients had tumors without a *RAS* G12 mutation, findings in this subgroup should be interpreted descriptively and in the context of the overall efficacy results in the *RAS* G12 and overall populations. Additional studies may be warranted to better characterize outcomes in these smaller molecular subgroups. These findings may provide clinical support for sustained inhibition of the active, GTP-bound state of RAS as a therapeutic strategy for patients with previously treated mPDAC, whereby oncogenic RAS-MAPK pathway signaling is the primary driver of tumor growth and progression.[15-18,33] It is important to note that the pattern of prevalence of different *RAS* mutations was consistent with reported patterns of prevalence in PDAC.[15,33]

The safety profiles of daraxonrasib and chemotherapy showed no unexpected findings. The median duration of treatment was 6.2 months in the daraxonrasib group as compared with 1.5 to 3.2 months across the chemotherapy regimens. Even with a longer duration of treatment, patients in the daraxonrasib group had fewer adverse events after the start of treatment that were grade 3 or higher or that led to a dose reduction or treatment discontinuation than patients in the

chemotherapy group. The safety profile of daraxonrasib was characterized primarily by treatment-related, low-grade dermatologic and gastrointestinal adverse events; among these, events of grade 3 were uncommon, and no events of grade 4 were reported. The safety of the once-daily 300-mg dose of daraxonrasib was supported by a high relative dose intensity and a low incidence of treatment discontinuation, with adverse events managed through routine clinical interventions and dose modifications as needed (see the Supplementary Appendix for management guidelines).

Some limitations should be considered when interpreting these results. The open-label design may have influenced adverse-event reporting and treatment modifications, as well as the decision not to begin treatment after randomization; treatment was not initiated in 15.1% of the patients assigned to the chemotherapy group, in most cases owing to the patient's decision. In addition, subgroup analyses were exploratory and may have been limited by small sample sizes, particularly with respect to uncommon *RAS* subtypes and patients with no *RAS* mutation identified. Given the rarity of these subgroups in patients with PDAC, the results of those subgroup analyses should be interpreted descriptively.

In the RASolute 302 trial, once-daily treatment with oral daraxonrasib resulted in significantly longer overall survival and progression-free survival than standard cytotoxic chemotherapy among patients with previously treated mPDAC, more than 90% of whom had *RAS* G12 mutations. Overall survival results were largely consistent across patient subgroups, and patient-reported end points favored daraxonrasib. The results of this trial support daraxonrasib as a clinically meaningful advance in the treatment of patients with previously treated mPDAC.

Supported by Revolution Medicines.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participating patients, their families, and the clinicians and research staff and Akshaya Srinivasan and Asu Erden (of Nucleus Global, an Inizio Company) for medical writing support (funded by Revolution Medicines).

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