ORIGINAL ARTICLE

Daraxonrasib in Previously Treated Advanced *RAS*-Mutated Pancreatic Cancer

Brian M. Wolpin, M.D., M.P.H.,[1] Wungki Park, M.D.,[2] Ignacio Garrido-Laguna, M.D., Ph.D.,[3] Alexander Spira, M.D., Ph.D.,[4] Alexander Starodub, M.D., Ph.D.,[5]* David Sommerhalder, M.D.,[6] Salman R. Punekar, M.D.,[7] Minal Barve, M.D.,[8] Meredith Pelster, M.D.,[9] Benjamin Herzberg, M.D.,[10] Nilofer S. Azad, M.D.,[11] Joel Randolph Hecht, M.D.,[12] Sai Hong Ignatius Ou, M.D., Ph.D.,[13] Tong Lin, Ph.D.,[14] Sumit Kar, Ph.D.,[14] Lin Tao, M.S.,[14] Rashmi Vora, M.B., B.S.,[14] Aparna Hegde, M.D.,[14] Kyaw Aung, M.B., B.S., Ph.D.,[15] and David S. Hong, M.D.,[16] for the RMC-6236-001 Investigators†

ABSTRACT

BACKGROUND

Current therapies for patients with pancreatic ductal adenocarcinoma (PDAC) provide modest benefit. Activating *RAS* mutations occur in more than 90% of PDAC tumors. Daraxonrasib (RMC-6236) is an oral RAS(ON) multiselective inhibitor that targets guanosine triphosphate–bound mutant and wild-type RAS.

METHODS

In this phase 1–2 study, we evaluated daraxonrasib in patients with advanced solid tumors with activating *RAS* mutations. Patients received 10 to 400 mg of daraxonrasib orally once daily; 300 mg was selected as the phase 3 dose. The primary end point was safety. Pharmacokinetics and antitumor activity were secondary end points. This report focuses on the 168 study patients with previously treated *RAS*-mutated PDAC.

RESULTS

Among the 168 patients with PDAC who received daraxonrasib at a dose of 300 mg or less, treatment-related adverse events of any grade were reported in 96%; such events of grade 3 or higher were reported in 30%. Treatment-related adverse events that occurred in at least 10% of the patients included rash, diarrhea, nausea, stomatitis or mucositis, vomiting, and fatigue. In a subgroup of 26 patients with *RAS* G12 mutations who were treated with second-line daraxonrasib at a dose of 300 mg, an objective response to therapy was reported in 35% (95% confidence interval [CI], 17 to 56). The median duration of response was 8.2 months (95% CI, 3.8 to not evaluable), with median values of 8.5 months for progression-free survival and 13.1 months for overall survival. Among the 38 patients with *RAS* G12, G13, or Q61 mutations, 29% (95% CI, 15 to 46) had an objective response. The median duration of response was 8.2 months (95% CI, 3.8 to 8.8), with median values of 8.1 months for progression-free survival and 15.6 months for overall survival.

CONCLUSIONS

Daraxonrasib was associated with treatment-related adverse events of grade 3 or higher in one third of patients with previously treated *RAS*-mutated PDAC; antitumor activity was also reported. (Funded by Revolution Medicines; RMC-6236-001 ClinicalTrials.gov number, NCT05379985.)

Author affiliations are listed at the end of the article. Brian M. Wolpin can be contacted at brian_wolpin@dfci.harvard.edu or at the Hale Family Center for Pancreatic Cancer Research, Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215. David S. Hong can be contacted at dshong@mdanderson.org or at the Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, Unit 455, P.O. Box 301402, Houston, TX 77230.

*Deceased.

†A complete list of the investigators in the RMC-6236-001 study is provided in the Supplementary Appendix, available at NEJM.org.

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Most patients with pancreatic ductal adenocarcinoma (PDAC), a highly lethal cancer, present with advanced disease at the time of diagnosis.[1] For patients with metastatic disease, the median overall survival is less than a year, and only 3% of the patients are alive after 5 years.[2,3] Apart from a small subgroup of patients who are eligible for targeted therapies,[4] the standard treatment for metastatic PDAC relies on 5-fluorouracil– or gemcitabine-based chemotherapy.[5-7] Second-line chemotherapy options provide limited benefit, with an objective response (i.e., a confirmed complete or partial response) of less than 10% and a median overall survival of 5 to 7 months.[5-12]

Oncogenic mutations in canonical members of the gene family encoding rat sarcoma virus (*RAS*) — namely, *KRAS*, *HRAS*, and *NRAS* — are found in more than 90% of PDAC tumors, with most of these mutations (>80%) being substitutions at *KRAS* codon 12.[13-15] In mouse models, *KRAS* mutations initiate PDAC,[16] and mutant protein ablation induces tumor regression.[17,18] Mutations at glycine 12 (G12), glycine 13 (G13), and glutamine 61 (Q61) impair the activity of guanosine triphosphatases (GTPases), which drives the accumulation of active RAS protein bound by GTP and sustained oncogenic signaling.[19,20]

Therapeutic targeting of RAS with a drug has long been considered to be unachievable,[21] but the development of covalent KRAS G12C(OFF) inhibitors — which lock the KRAS G12C–mutant protein in an "off" state through covalent binding — proved that the direct targeting of RAS is feasible.[22,23] However, *KRAS* G12C mutations are rare in PDAC (with a frequency of 1 to 2%), which limits the clinical utility of these agents in this disease.[24] Moreover, because most *RAS* mutations in PDAC drive constitutive signaling through the GTP-bound(ON) state, the inhibition of activated RAS by RAS(OFF) inhibitors is often incomplete.[25] The efficacy of these inhibitors is further limited by resistance, including the development of secondary *RAS* mutations.[26] Thus, therapies that target active, GTP-bound RAS and address diverse *RAS* variants are needed.

Daraxonrasib (RMC-6236) is an orally bioavailable, RAS(ON) multiselective, noncovalent inhibitor with activity against the active state of mutant and wild-type KRAS, HRAS, and NRAS.[27-30] 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.[29] Preclinical studies have shown deep and durable responses to daraxonrasib across *RAS*-mutated cancers, which have been most pronounced in tumors with mutations at codon 12. These findings have included marked regressions in pancreatic cancer models.[30] In an earlier analysis of this multicenter, open-label, phase 1–2 study[28] involving patients with advanced solid tumors harboring *RAS* mutations, treatment-related adverse events of grade 3 or more occurred in 16 of 111 (14.4%) patients, and preliminary antitumor activity was observed. Here, we report the results of the RMC-6236-001 study, in which we evaluated the safety, dose-optimization level, and antitumor activity of daraxonrasib in patients with previously treated advanced *RAS*-mutated PDAC.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted the phase 1–2 open-label study of daraxonrasib at 16 sites in the United States. The study protocol is available with the full text of this article at NEJM.org.

The study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. The protocol and its amendments were approved by the institutional review board at each participating site and by the regulatory authorities in participating countries. All the patients provided written informed consent.

This current study was designed by the funder, Revolution Medicines, with input provided by the investigators who were serving on committees that were evaluating doses and related activities. The data were collected by the investigators and analyzed by statisticians employed by Revolution Medicines. A medical writer who was employed by the funder provided assistance.

All the authors had access to the data and contributed to the interpretation of the data and to the preparation of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

PATIENTS

Eligible patients were adults (≥18 years of age) who had advanced solid tumors harboring *KRAS*, *NRAS*,

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=168)
Median age (range) — yr	65 (30–86)
Sex — no. (%)	
Female	75 (45)
Male	93 (55)
Race — no. (%)†	
White	129 (77)
Black	3 (2)
Other	22 (13)
Missing data	14 (8)
ECOG performance-status score — no. (%)‡	
0	53 (32)
1	115 (68)
Cancer stage at diagnosis — no. (%)	
I	15 (9)
II	30 (18)
III	32 (19)
IV	88 (52)
Missing data	3 (2)
Previous systemic therapy	
Median number (range)	2 (1–6)
Anticancer treatment for metastatic disease — no. (%)	
1	70 (42)
≥2	98 (58)
Specific chemotherapy regimen for metastatic disease — no. (%)	
Gemcitabine and nab-paclitaxel	101 (60)
FOLFIRINOX§	73 (43)
FOLFIRI¶	19 (11)
FOLFOX‖	13 (8)
Nanoliposomal irinotecan, 5-fluorouracil, and leucovorin	5 (3)
History of pancreatic resection — no. (%)	66 (39)
Whipple procedure	60 (36)
Other	6 (4)
Sites of metastases — no. (%)	
Liver	112 (67)
Lung	78 (46)
RAS mutation — no. (%)	
KRAS G12D	65 (39)
KRAS G12V	52 (31)
KRAS G12R	28 (17)
Other *RAS* G12**	4 (2)
Non-*RAS* G12††	19 (11)

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Table 1. (Continued.)

Characteristic	All Patients (N=168)
Co-occurring genomic alterations — no./total no. (%)	
TP53	120/162 (74)
SMAD4	40/162 (25)
CDKN2A	56/162 (35)
CDKN2B	13/162 (8)
Missing data	6/168 (4)

* Listed are data for patients with pancreatic ductal adenocarcinoma (PDAC) with mutant rat sarcoma virus (RAS) who were treated with daraxonrasib (≤300 mg). All the patients had received second-line therapy (i.e., only one previous line of therapy for metastatic disease or previous neoadjuvant or adjuvant therapy followed by disease progression within 6 months) or third- or later-line therapy.
† Race was reported by the patients.
‡ Study eligibility included having an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (as measured on a 5-point scale, with higher numbers reflecting greater disability).
§ This four-drug regimen includes leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin.
¶ This three-drug regimen includes leucovorin, 5-fluorouracil, and irinotecan.
‖ This three-drug regimen includes leucovorin, 5-fluorouracil, and oxaliplatin.
** Other *RAS* G12 mutations included *KRAS* G12A, *KRAS* G12L, *KRAS* G12S, and *NRAS* G12D (1 patient each).
†† Non–*RAS* G12 mutations included *KRAS* G13D (1 patient), *KRAS* Q61H (14 patients), *KRAS* Q61R (2 patients), and *KRAS* Q61K (2 patients).

or *HRAS* mutations at codons 12, 13, or 61. Patients with PDAC were eligible if they had disease progression or unacceptable side effects after the receipt of fluoropyrimidine- or gemcitabine-based chemotherapy; measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (as measured on a 5-point scale, with higher numbers reflecting greater disability). Key exclusion criteria included untreated central nervous system metastases and previous RAS-targeted therapy. Full eligibility criteria are provided in the protocol.

TREATMENT

In the dose-escalation phase, patients with *RAS*-mutated solid tumors received daraxonrasib once daily in 21-day cycles at doses ranging from 10 mg to 400 mg. Bayesian analysis was used to determine the maximum tolerated dose (MTD) and recommended phase 2 dose. The MTD was not formally reached, although frequent dose modifications at 400 mg limited the ability to sustain the continuous administration of daraxonrasib.

Expansion cohorts of *KRAS* G12–mutated PDAC were enrolled at doses of 120 mg, 200 mg, or 300 mg, and additional patients who had PDAC with mutations other than *RAS* G12 were enrolled in a separate cohort at 300 mg. Data for patients who were enrolled in three exploratory 300-mg cohorts (consisting of those who had undergone mandated biopsy, had *RAS* wild-type tumors, or had not received previous treatment for *RAS*-mutated PDAC) were excluded from this report because of differing end points or eligibility criteria. Treatment continued until the occurrence of unacceptable toxic effects, disease progression, withdrawal of consent, or study discontinuation, whichever occurred first. Patients who met the predefined criteria could continue treatment beyond disease progression.

END POINTS AND ASSESSMENTS

The primary objective was to evaluate safety and side effects. In this report, we summarize the adverse events that were deemed by the investigator to be related to treatment with daraxonrasib, as graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5. Key secondary end points were preliminary antitumor activity and pharmacokinetics. End points for antitumor activity included objective response, duration of response, and pro-

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gression-free survival and were assessed by investigators according to RECIST, version 1.1. Imaging was performed at baseline and every two to three cycles until the end of treatment, as specified in the protocol. Exploratory end points included overall survival and analysis of co-occurring genomic alterations assessed in plasma (Guardant Infinity test) and in tumor tissue (Tempus xE test).

SAFETY AND EFFICACY

Safety and efficacy were assessed in all the patients who had undergone previous therapy for metastatic PDAC and had received at least one dose of daraxonrasib at a level of 300 mg or less, regardless of whether the drug had been administered in a dose-escalation phase or a dose-optimization phase. Patients who had received doses of 120 mg or less were grouped together for this analysis. Patients who had received doses of 160 to 220 mg were grouped together owing to overlapping exposures; 300 mg was the highest dose evaluated in the dose-optimization group.

Because preclinical models indicated that *RAS* G12–mutated tumors were the most sensitive to daraxonrasib,[27,30] prespecified descriptive analyses of efficacy were conducted in subgroups defined according to the presence of this mutation. These patients were also included in a group analysis of *RAS*-mutated tumors with substitutions at G12, G13, and Q61. Additional efficacy analyses were conducted according to the line of therapy, with second line defined as one previous line of therapy for metastatic disease and third or later lines defined as two or more previous lines of therapy for metastatic disease.

STATISTICAL ANALYSIS

We summarized the characteristics of the patients at baseline, safety, and efficacy using descriptive statistics. No formal statistical hypothesis testing was performed. Two-sided 95% confidence intervals were calculated when appropriate. We estimated confidence intervals for proportions using the exact Clopper–Pearson method and used Kaplan–Meier methods to estimate median progression-free survival, response duration, and overall survival. Two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley method.

RESULTS

PATIENTS

From June 22, 2022, to June 30, 2025, a total of 168 patients with *RAS*-mutated PDAC received at least one dose of daraxonrasib as a second-line (or later) therapy: 83 patients received a dose of 300 mg, 51 patients received a dose of 160 to 220 mg, and 34 patients received a dose of 120 mg or less (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

The demographic and clinical characteristics of the patients at baseline are summarized in Table 1. Across all dose levels, the median age was 65 years (range, 30 to 86), and 45% of patients were women. The ECOG performance-status score was 1 in 68% of the patients. All the patients had stage IV disease at study entry, with liver and lung metastases in 67% and 46%, respectively.

Of the 168 patients, 149 (89%) had *RAS* G12 mutations. These mutations included *KRAS* G12D (in 39% of the patients), *KRAS* G12V (in 31%), *KRAS* G12R (in 17%), and other *RAS* G12 (in 2%). Among the 19 patients with non-*RAS* G12 mutations, 14 had *KRAS* Q61H, 2 had *KRAS* Q61R, 2 had *KRAS* Q61K, and 1 had *KRAS* G13D mutations. Frequent co-occurring genomic alterations were identified in *TP53* (in 74% of patients), *SMAD4* (in 25%), *CDKN2A* (in 35%), and *CDKN2B* (in 8%). These mutations were found with an incidence that was consistent with the expected prevalence in PDAC.[31]

The median number of previous systemic therapies among all patients was two (range, one to six). One previous line of therapy had been administered to 70 patients (42%), and 98 patients (58%) had received two or more lines for metastatic disease. Previous regimens for metastatic disease included gemcitabine plus nab-paclitaxel (in 60% of patients) and FOLFIRINOX (consisting of folinic acid, fluorouracil, irinotecan, and oxaliplatin) or modified FOLFIRINOX (in 43%). The baseline characteristics of the patients who received the 300-mg dose of daraxonrasib as second-line or third- or later-line therapy are summarized in Table S1.

The median duration of treatment was 5.7 months (range, 0.03 to 31.5) among the 168 patients in the safety population, 5.8 months (range, 0.03 to 22.3) among those who received a 300-mg dose, 6.0 months (range, 0.4 to 25.5)

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Table 2. Safety Summary in Patients with *RAS*-Mutated PDAC.*

Adverse Event	Dose of Daraxonrasib							
	All Doses (N=168)		≤120 mg (N=34)		160–220 mg (N=51)		300 mg (N=83)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)							
Treatment-related adverse event								
Any	161 (96)	50 (30)	30 (88)	9 (26)	51 (100)	13 (25)	80 (96)	28 (34)
Leading to dose modification	67 (40)	34 (20)	8 (24)	5 (15)	19 (37)	11 (22)	40 (48)	18 (22)
Dose interruption	62 (37)	33 (20)	8 (24)	5 (15)	18 (35)	11 (22)	36 (43)	17 (20)
Dose reduction	36 (21)	19 (11)	4 (12)	3 (9)	7 (14)	5 (10)	25 (30)	11 (13)
Leading to discontinuation	1 (1)	1 (1)	1 (3)	1 (3)	0	0	0	0
Treatment-related serious adverse event	10 (6)	7 (4)	2 (6)	1 (3)	3 (6)	2 (4)	5 (6)	4 (5)
Treatment-related adverse event reported in >10% of patients								
Rash†	147 (88)	11 (7)	26 (76)	0	46 (90)	5 (10)	75 (90)	6 (7)
Diarrhea	77 (46)	5 (3)	13 (38)	2 (6)	21 (41)	0	43 (52)	3 (4)
Nausea	70 (42)	0	11 (32)	0	27 (53)	0	32 (39)	0
Stomatitis or mucositis‡	67 (40)	6 (4)	4 (12)	1 (3)	18 (35)	2 (4)	45 (54)	3 (4)
Vomiting	52 (31)	0	10 (29)	0	12 (24)	0	30 (36)	0
Fatigue	33 (20)	3 (2)	5 (15)	0	14 (27)	2 (4)	14 (17)	1 (1)
Paronychia	25 (15)	0	2 (6)	0	8 (16)	0	15 (18)	0
Decreased appetite	18 (11)	2 (1)	4 (12)	1 (3)	4 (8)	1 (2)	10 (12)	0
Dry skin	17 (10)	0	1 (3)	0	4 (8)	0	12 (14)	0

* The study investigators decided whether an adverse event was related to the receipt of daraxonrasib. A patient with multiple severities of grade for a given adverse event was counted only once at the highest grade of severity.
† The category of rash includes dermatitis, dermatitis acneiform, dermatitis bullous, eczema, erythema, rash, rash erythematous, rash macular, rash maculopapular, and rash pustular.
‡ The category of stomatitis or mucositis includes any mucosal inflammation and stomatitis.

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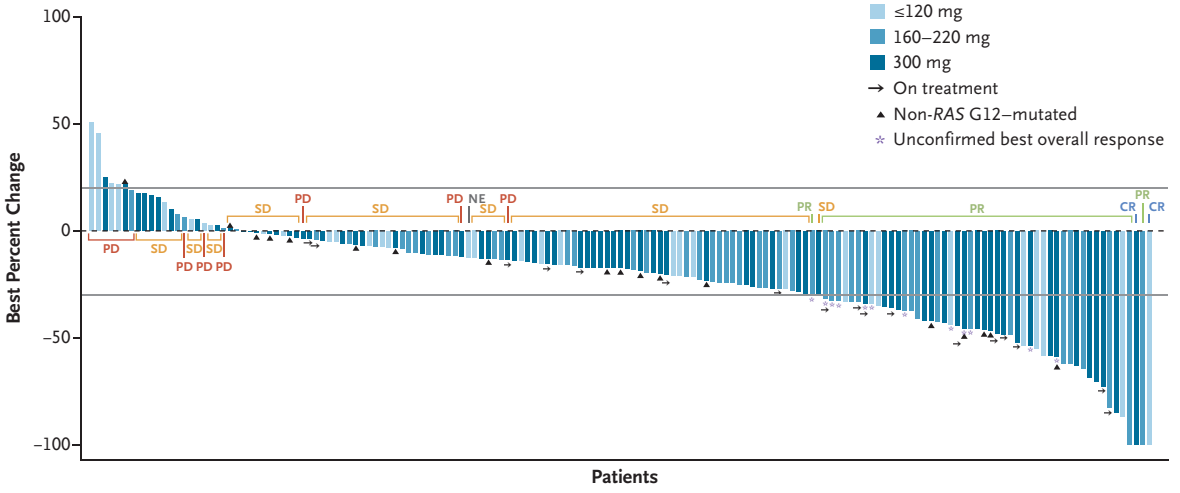
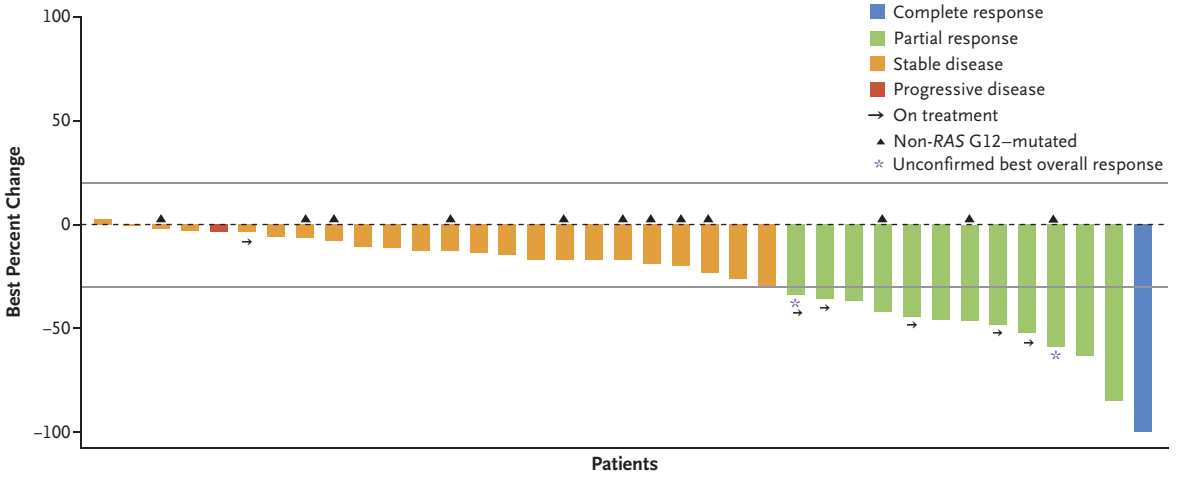
A Best Percent Change in Sum of Diameters in Target Tumor at Daily Doses of ≤300 mg as Second- or Later-Line Therapy



B Best Percent Change in Sum of Diameters in Target Tumor at Daily Dose of 300 mg as Second-Line Therapy



C Best Percent Change in Sum of Diameters in Target Tumor at Daily Dose of 300 mg as Third- or Later-Line Therapy

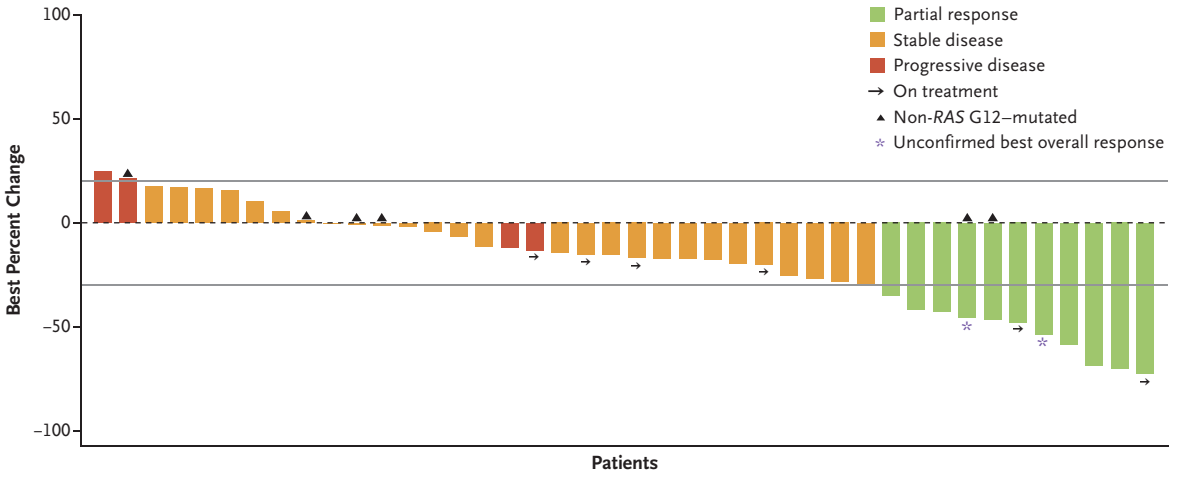


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Figure 1 (facing page). Antitumor Activity of Daraxonrasib in *RAS*-Mutated PDAC.

Shown is the best percent change from baseline in tumor burden among patients with pancreatic ductal adenocarcinoma (PDAC) who received daraxonrasib at daily doses of 300 mg or less as second- or later-line therapy (Panel A), among those who received 300 mg as second-line therapy (Panel B), and among those who received 300 mg as third- or later-line therapy (Panel C). In each panel, the asterisk indicates that the value was the unconfirmed best overall response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR denotes complete response, G12 glycine 12, NE not evaluable, PD progressive disease, PR partial response, and SD stable disease.

among those who received a dose of 160 to 220 mg, and 5.1 months (range, 0.2 to 31.5) among those who received a dose of 120 mg or less. Treatment was discontinued in 150 of 168 patients, most commonly because of disease progression (in 93 patients [55%]), clinical progression (in 21 patients [12%]), or adverse events (in 8 patients [5%]).

SAFETY

In the safety population of 168 patients, adverse events of any grade that occurred during treatment, regardless of attribution, were observed in 166 patients (99%). The most common adverse events (occurring in ≥30% of patients) were rash (89%), diarrhea (50%), and nausea (47%). Adverse events of grade 3 or higher were reported in 110 patients (65%).

Adverse events that were deemed by the investigator to be related to treatment with daraxonrasib were reported in 96% of the patients; a majority of these events were grade 1 or 2 (Table 2). The most common treatment-related adverse events of any grade were rash (88%), diarrhea (46%), and nausea (42%). Treatment-related adverse events of grade 3 or higher occurred in 30% of the patients, and no grade 5 events were observed. Serious treatment-related adverse events occurred in 6%, with diarrhea (2%) as the most frequent. The MTD was not reached, and 400 mg was the maximum administered dose. Dose-related increases in treatment-related adverse events and modifications supported the selection of 300 mg for further evaluation.

Among the 83 patients who received the 300-mg dose, treatment-related adverse events of any grade occurred in 96% of the patients, with the most common being rash (in 90%), stomatitis or mucositis (in 54%), diarrhea (in 52%), and nausea (in 39%). Such events of grade 3 or higher occurred in 34% of the patients, with rash and anemia in 7% each. These events led to dose modifications in 48% of the patients receiving the 300-mg dose, including dose interruption in 43% and dose reduction in 30%. Such events of any grade that led to dose modifications in more than 10% of the patients were rash and stomatitis or mucositis (Table S2). Rash and gastrointestinal events were manageable with routine clinical interventions, such as topical glucocorticoids and antibiotics (e.g., clindamycin), systemic antibiotics (doxycycline or minocycline), sun protection measures, antidiarrheal therapy, and dose modifications (Table S3). In the 300-mg group, 13% of the patients had a treatment-related adverse event of grade 3 or higher that led to a dose reduction, and a subgroup of dose reductions occurred because of grade 1 or 2 events, such as rash and stomatitis or mucositis. The median duration of cumulative dose interruptions caused by treatment-related adverse events was 16 days. The mean relative dose intensity at 300 mg was 86%, and no patients discontinued treatment because of such events. When dose interruption was necessary, most patients were able to resume treatment at the same or reduced dose, thereby maintaining overall dose intensity.

PHARMACOKINETICS

Daraxonrasib is orally bioavailable and showed dose-dependent increases in exposure (Fig. S2). The area under the curve for the steady-state whole-blood concentration of daraxonrasib was approximately dose-proportional from 80 mg to 300 mg, with minimal accumulation after repeated administration. The median time until the maximum observed concentration was 1.6 to 3.9 hours, and the mean terminal half-life was 11.8 hours (coefficient of variation, 28%), according to a preliminary population pharmacokinetic model. Doses of 160 mg and 200 mg to 220 mg were pooled for meaningful assessment of safety and efficacy owing to substantial overlap in exposures.

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Table 3. Confirmed Best Overall Response, According to Line of Therapy.*

Response	Second-Line Therapy†		Third- or Later-Line Therapy	
	RAS G12–Mutated (N=26)	All *RAS*-Mutated (N=38)	*RAS* G12–Mutated (N=38)	All *RAS*-Mutated (N=45)
Any objective response‡				
No. of patients	9	11	8	9
% (95% CI)	35 (17–56)	29 (15–46)	21 (10–37)	20 (10–35)
Type of response — no. (%)				
Complete	1 (4)	1 (3)	0	0
Partial	8 (31)	10 (26)	8 (21)	9 (20)
Stable disease	15 (58)	25 (66)	25 (66)	29 (64)
Progressive disease	1 (4)	1 (3)	4 (11)	5 (11)
Not evaluable§	1 (4)	1 (3)	1 (3)	2 (4)
Disease control¶				
No. of patients	24	36	33	38
% (95% CI)	92 (75–99)	95 (82–99)	87 (72–96)	84 (71–94)
Median duration of response (95% CI) — months	8.2 (3.8–NE)	8.2 (3.8–8.8)	3.5 (2.9–NE)	3.3 (2.8–NE)

* NE denotes not evaluable.
† Second-line therapy was defined as treatment in patients who had received only one previous line of therapy for metastatic disease or previous neoadjuvant or adjuvant therapy followed by disease progression within 6 months.
‡ An objective response was defined as a confirmed complete or partial response.
§ The response was not evaluable for 1 patient who withdrew consent from the study before the postbaseline scan and 2 patients who discontinued the study treatment before a baseline scan.
¶ Disease control was defined as a complete or partial response or stable disease.

EFFICACY

Daraxonrasib showed antitumor activity across doses of 300 mg or less and across diverse *RAS* mutations (Fig. 1A). The response rates were generally higher at 300 mg than at lower doses and in earlier rather than later lines of therapy (Table S4). The frequency of landmark progression-free and overall survival at 6 and 9 months was higher with the 300-mg dose than with lower doses as second-line treatment (Tables S5 and S6). These efficacy data also supported the 300-mg dose for further evaluation.

In the subgroup of patients with a *RAS* G12 mutation who were receiving 300 mg of daraxonrasib as second-line therapy, 35% (95% confidence interval [CI], 17 to 56) had an objective response to treatment. Among these patients, the disease control rate (calculated as a complete or partial response and stable disease) was 92% (95% CI, 75 to 99) (Fig. 1B and Table 3). The median time until response was 2.6 months (range, 1.2 to 8.5), and the median duration of response was 8.2 months (95% CI, 3.8 to not evaluable).

After a median follow-up of 17 months (range, 10.3 to 24.6) in the *RAS* G12 subgroup, the median progression-free survival was 8.5 months (95% CI, 6.7 to 10.5) (Fig. 2A), and the median overall survival was 13.1 months (95% CI, 10.9 to not evaluable) (Fig. 2B). The Kaplan–Meier estimate of progression-free survival was 78% (95% CI, 54 to 90) at 6 months and 46% (95% CI, 24 to 66) at 9 months (Table S5); the estimate of overall survival was 100% (95% CI, 100 to 100) at 6 months and 89% (95% CI, 62 to 97) at 9 months (Table S5).

Among the patients with any *RAS* mutation who were receiving 300 mg of daraxonrasib as second-line therapy, 11 of 38 patients (29%; 95% CI, 15 to 46) had an objective response, including patients with *KRAS* G12D, *KRAS* G12V, *KRAS* G12R, and *KRAS* Q61H mutations (Table 3). The median time until an objective response was 2.6 months (range, 1.2 to 8.5). The median dura-

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tion of response was 8.2 months (95% CI, 3.8 to 8.8). At a median follow-up of 17 months (range, 10.3 to 24.6), the median progression-free survival was 8.1 months (95% CI, 5.9 to 10.1) (Fig. 2A), and the median overall survival was 15.6 months (95% CI, 10.9 to not evaluable) (Fig. 2B). The Kaplan–Meier estimate of progression-free survival was 66% (95% CI, 47 to 80) at 6 months and 38% (95% CI, 21 to 55) at 9 months (Table S5); the estimate of overall survival was 97% (95% CI, 80 to 100) at 6 months and 79% (95% CI, 59 to 90) at 9 months (Table S5). The efficacy in patients who received daraxonrasib as third- or later-line therapy is shown in Figures 1C, 2C, and 2D and Table S6.

DISCUSSION

Current chemotherapy options for patients with previously treated metastatic PDAC provide limited benefit, with response rates of less than 10%, median progression-free survival of 2 to 3 months, and median overall survival of 5 to 7 months.[6,8-12,32] These options are associated with frequent grade 3 or 4 toxic effects, including neutropenia, diarrhea, and fatigue — side effects that often lead to dose reductions or discontinuations.[10,11] The high prevalence of *RAS* mutations (>90%) in PDAC highlights an opportunity for RAS-targeted therapies to expand treatment options for patients with PDAC and to improve patient outcomes.

In the phase 1–2 study, daraxonrasib was associated with treatment-related adverse events of grade 3 or higher in one third of the patients. Most treatment-related adverse events were grade 1 or 2 and were on-target toxic effects such as rash and diarrhea, which were responsive to routine clinical interventions. Such events led to dose modifications in nearly half the patients who received 300 mg of daraxonrasib, but most patients were able to resume treatment at the same or reduced dose, thereby maintaining overall dose intensity. No patients discontinued therapy because of such events. Prophylaxis is recommended in future trials to limit grade 3 adverse events such as rash.

At 300 mg, daraxonrasib produced objective responses and disease control in patients with *RAS*-mutated PDAC. Although preclinical data suggested greatest activity against *RAS* G12 mutations, the current clinical dataset is too small to establish variant-specific differences. Although direct comparisons cannot be made, the results of this study suggest that across PDAC with varied *RAS* mutations, progression-free and overall survival estimates exceeded those that have been historically reported with second-line chemotherapy. By inhibiting all three *RAS* isoforms, as well as all key *RAS* mutations and wild-type *RAS* in the active, GTP-bound state, daraxonrasib offers comprehensive RAS inhibition as compared with the allele-specific activity of KRAS G12C inhibitors that target only the inactive, GDP-bound state. Daraxonrasib appeared to show a higher response rate and longer survival relative to published results for KRAS G12C inhibitors in PDAC,[33] although cross-trial comparisons are not reliable.

Preclinical studies and translational pharmacokinetic or pharmacodynamic modeling established that tumor regression in PDAC requires sustained RAS pathway inhibition (≥90%).[30] In preclinical models, daraxonrasib reached this goal through preferential intratumoral accumulation and durable mitogen-activated protein kinase (MAPK) suppression. These findings indicate that efficacy depends both on sufficient exposure and on maintenance of pathway inhibition.[30] Translational pharmacokinetic or pharmacodynamic modeling predicted that approximately 100 mg of daraxonrasib once daily would produce tumor stasis to modest regressions, whereas approximately 300 mg daily was most likely to sustain pathway suppression and maximize antitumor activity.[30] Population pharmacokinetic simulations (unpublished data) supported an expectation that the 300-mg once-daily dose would have a higher probability of achieving target exposures than the dose that was efficacious in murine models.[30] Clinical safety and efficacy data supported a dose of 300 mg once daily as the recommended monotherapy dose.

The antitumor activity of daraxonrasib reflects direct inhibition of GTP-bound RAS, the predominant signaling form in PDAC, in which nearly all tumors harbor *RAS* mutations, and the most common variants (e.g., *KRAS* G12D, G12V, and G12R) lack approved targeted therapies.[14,15,30] Objective responses align with preclinical observations that the activity of daraxonrasib is driven by potent, sustained MAPK suppression through intratumoral accumulation and exposure-dependent pathway inhibition.[30] Although mechanisms

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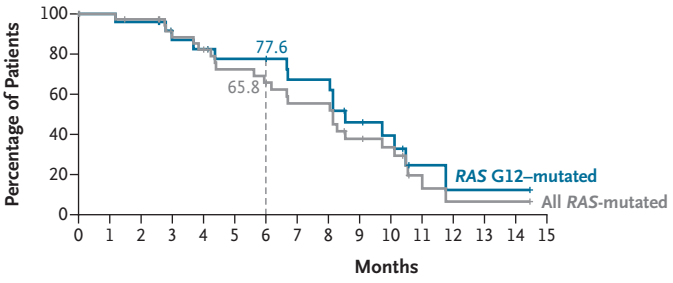
A Progression-free Survival with Second-Line Therapy

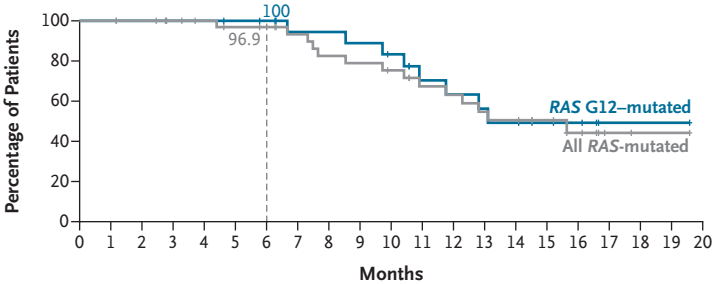


	Median Progression-free Survival (95% CI)
	mo
***RAS* G12–mutated**	8.5 (6.7–10.5)
All *RAS*-mutated	8.1 (5.9–10.1)

No. at Risk

RAS G12–mutated	26	25	24	19	18	16	16	13	13	8	6	2	1	1	1	0
All *RAS*-mutated	38	37	35	29	27	22	20	16	16	10	8	3	1	1	1	0

B Overall Survival with Second-Line Therapy

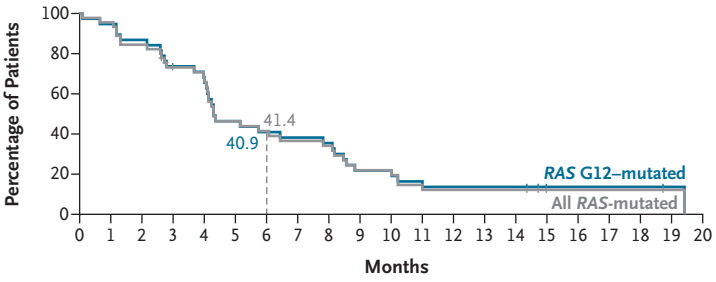


	Median Overall Survival (95% CI)
	mo
***RAS* G12–mutated**	13.1 (10.9–NE)
All *RAS*-mutated	15.6 (10.9–NE)

No. at Risk

RAS G12–mutated	26	26	25	24	22	21	20	17	17	16	14	10	9	8	7	5	4	1	1	1	0
All *RAS*-mutated	38	38	37	34	32	30	29	26	23	22	20	16	15	13	12	9	6	2	1	1	0

C Progression-free Survival with Third- or Later-Line Therapy

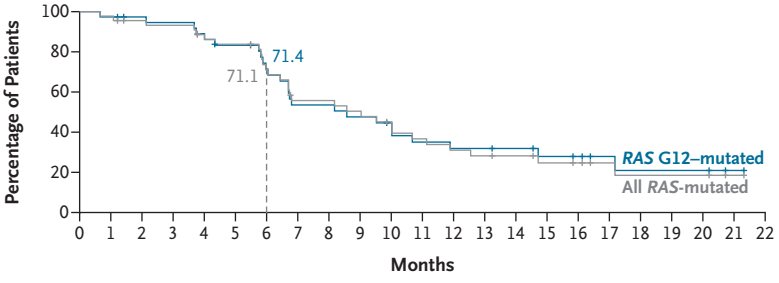


	Median Progression-free Survival (95% CI)
	mo
***RAS* G12–mutated**	4.3 (4.1–8.1)
All *RAS*-mutated	4.3 (4.1–7.8)

No. at Risk

RAS G12–mutated	38	36	33	27	25	17	15	14	13	8	8	6	5	5	5	2	2	2	2	1	0
All *RAS*-mutated	45	43	38	30	28	19	17	15	14	9	9	6	5	5	5	2	2	2	2	1	0

D Overall Survival with Third- or Later-Line Therapy



	Median Overall Survival (95% CI)
	mo
***RAS* G12–mutated**	8.6 (6.4–11.9)
All *RAS*-mutated	9.0 (6.7–11.1)

No. at Risk

RAS G12–mutated	38	37	35	34	31	29	24	18	18	16	14	11	10	10	9	7	6	4	3	3	3	1	0
All *RAS*-mutated	45	44	41	40	37	34	28	21	21	19	16	13	11	10	9	7	6	4	3	3	3	1	0

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Figure 2 (facing page). Survival in Patients with *RAS* G12–Mutated and All-*RAS*-Mutated PDAC.

Shown are data for the study patients who received 300 mg of daraxonrasib daily, as reported according to whether they received the drug as second-line therapy (Panels A and B) or third- or later-line therapy (Panels C and D). In these two categories, data are shown regarding the median progression-free survival (Panels A and C) and overall survival (Panels B and D). The two curves indicate whether the patients had tumors with *RAS* G12 mutations or any *RAS* mutations.

of resistance to daraxonrasib are still being characterized, the response durability may reflect multiselective activity across RAS variants, including wild-type RAS, which potentially mitigates resistance from secondary mutations or compensatory signaling through other oncogenic alterations that have been reported with allele-selective inhibitors.[26,30,34,35] The therapeutic index appears to be supported by selectivity for active GTP-bound RAS, dependence of PDAC on sustained pathway signaling,[36] and preferential intratumoral accumulation relative to normal tissues[30] — all of which enable clinically active exposures.

Because this is a phase 1–2 study, the results should be interpreted with caution. Small subgroup sample sizes restrict the precision of estimates of antitumor activity and their interpretation on the basis of allele or co-mutation status. The single-group design precludes definitive comparisons with standard treatment regimens. Nonetheless, the consistent evidence of clinical activity, rapid and durable responses, and a profile of mainly low-grade adverse events support the further evaluation of daraxonrasib in randomized trials involving patients with advanced PDAC. These results support the ongoing RASolute 302 study, a global randomized phase 3 trial of daraxonrasib as compared with chemotherapy as second-line treatment in patients with metastatic PDAC (ClinicalTrials.gov number, NCT06625320).

Among patients with previously treated *RAS*-mutated PDAC, daraxonrasib showed antitumor activity and was associated with treatment-related adverse events of grade 3 or higher in one third of patients.

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

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AUTHOR INFORMATION

[1] Dana–Farber Cancer Institute, Boston; [2] Memorial Sloan Kettering Cancer Center, New York; [3] Huntsman Cancer Institute, University of Utah, Salt Lake City; [4] NEXT Oncology Virgina, Virginia Cancer Specialists Research Institute, Fairfax; [5] Christ Hospital, Cincinnati; [6] NEXT Oncology, San Antonio, TX; [7] NYU Langone Health, New York; [8] Mary Crowley Cancer Research, Dallas; [9] Sarah Cannon Research Institute, Nashville; [10] Columbia University, New York; [11] Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore; [12] David Geffen School of Medicine at UCLA, Los Angeles; [13] University of California, Irvine, Irvine; [14] Revolution Medicines, Redwood City, CA; [15] Miami Cancer Institute, Miami; [16] M.D. Anderson Cancer Center, Houston.

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