ORIGINAL ARTICLE

Divarasib as Compared with Sotorasib or Adagrasib in *KRAS* G12C–Mutated NSCLC

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ABSTRACT

BACKGROUND

Divarasib, a next-generation, oral KRAS G12C inhibitor, is more potent and selective in vitro than the first-generation KRAS G12C inhibitors sotorasib and adagrasib.

METHODS

In this phase 3, international, open-label trial, patients with previously treated *KRAS* G12C–mutated advanced or metastatic non–small-cell lung cancer (NSCLC) were randomly assigned to receive divarasib orally at a dose of 400 mg once daily or control treatment (sotorasib orally at a dose of 960 mg once daily or adagrasib orally at a dose of 600 mg twice daily) until the occurrence of disease progression, unacceptable adverse events, loss of clinical benefit, withdrawal of consent, death, or trial termination. The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included overall survival, confirmed overall response, duration of response, patient-reported outcomes, and safety.

RESULTS

A total of 338 patients received divarasib (167 patients) or control treatment (171 patients; 156 received sotorasib and 15 received adagrasib). The median follow-up was 14.3 months. The median progression-free survival was 9.8 months with divarasib and 5.7 months with control treatment (hazard ratio for disease progression or death, 0.58; 95% confidence interval [CI], 0.44 to 0.76; P<0.001). The median overall survival was 17.7 months with divarasib and 12.0 months with control treatment (hazard ratio for death, 0.56; 95% CI, 0.41 to 0.78; P<0.001). Of the 328 patients who could be evaluated for response, a confirmed response occurred in 58.4% in the divarasib group and in 32.3% in the control group. The median duration of response was 11.9 months with divarasib and 6.9 months with control treatment. Fewer grade 3 or 4 treatment-related adverse events were noted with divarasib (24.6%) than with control treatment (34.5%).

CONCLUSIONS

Among patients with previously treated *KRAS* G12C–mutated advanced or metastatic NSCLC, divarasib led to significantly longer progression-free and overall survival than control treatment. (Supported by F. Hoffmann–La Roche; Krascendo 1 ClinicalTrials.gov number, NCT06497556.)

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This article was published on October 25, 2026, at NEJM.org.

DOI: 10.1056/NEJMoa2605703

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Activating mutations in the Kirsten rat sarcoma viral oncogene homologue (*KRAS*) represent the most frequent oncogenic driver event (in 25 to 30% of cases) in nonsquamous non–small-cell lung cancer (NSCLC)[1] and are associated with a poor prognosis.[2-4] *KRAS* G12C is the most frequent *KRAS* mutation in NSCLC and occurs in approximately 14% of cases.[2,5,6] *KRAS*-mutated NSCLCs are clinically heterogeneous and are characterized by distinct patterns of co-occurring genomic alterations (including in *TP53*, *STK11*, *KEAP1*, *CDKN2A*, and *CDKN2B*) that affect response to systemic therapies, including KRAS G12C inhibitors.[4,7-13]

Sotorasib and adagrasib are first-generation KRAS G12C inhibitors that have been granted accelerated Food and Drug Administration approval and conditional European Medicines Agency approval for patients with previously treated *KRAS* G12C–mutated advanced or metastatic NSCLC; however, more effective therapies are needed.[14-19] In the phase 3 CodeBreaK 200 trial of sotorasib as compared with docetaxel, the median progression-free survival was 5.6 months with sotorasib and 4.5 months with docetaxel (hazard ratio for disease progression or death, 0.66), and the percentage of patients with an overall response was 28.1% and 13.2%, respectively.[15] Overall survival did not differ substantially between the treatment groups (median, 10.6 months with sotorasib and 11.3 months with docetaxel). Similarly, in the phase 3 KRYSTAL-12 trial of adagrasib as compared with docetaxel, the median progression-free survival was 5.5 months with adagrasib and 3.8 months with docetaxel (hazard ratio, 0.58), and the percentage of patients with a response was 32% and 9%, respectively.[14] Overall survival has not yet been reported from this trial.

Divarasib is a next-generation, oral KRAS G12C inhibitor that selectively binds to the oncoprotein and irreversibly locks it in an inactive state to inhibit oncogenic signaling.[20,21] In preclinical studies, divarasib showed greater potency than sotorasib (by a factor of 12 to >100) and adagrasib (by a factor of 6 to 20) and was more selective for KRAS G12C than either inhibitor, findings consistent with observed differences in covalent switch II pocket engagement.[20,22] In the phase 1 GO42144 study, single-agent divarasib (400 mg once daily) showed robust antitumor activity and durable clinical benefit in patients with previously treated *KRAS* G12C–mutated advanced or metastatic NSCLC: a confirmed response occurred in 59% of the patients (95% confidence interval [CI], 43 to 74), the median progression-free survival was 15.3 months (95% CI, 12.3 to 26.1), and the median duration of response was 14.0 months (95% CI, 11.1 to 24.9).[23] Divarasib was associated with mostly low-grade and reversible adverse events across all dose levels up to 400 mg once daily.[23,24]

Krascendo 1 is a phase 3, international, open-label, randomized trial evaluating the efficacy and safety of divarasib as compared with an approved KRAS G12C inhibitor (sotorasib or adagrasib) in patients with previously treated *KRAS* G12C–mutated advanced or metastatic NSCLC. Here we report the primary analysis of this trial.

METHODS

PATIENTS

Eligible patients were 18 years of age or older with histologically or cytologically confirmed locally advanced or metastatic NSCLC with a *KRAS* G12C mutation. Patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1; had had disease progression during or after treatment with at least one previous systemic therapy (including platinum-based doublet chemotherapy and a programmed cell death protein 1 or programmed death ligand 1 [PD-L1] inhibitor) but had received no more than three lines of previous systemic therapy for advanced or metastatic disease; and had a baseline Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores reflecting greater disability).

Patients were excluded if they had known concomitant actionable oncogenic driver mutations; had received previous treatment with any KRAS G12C, pan-KRAS, or pan–rat sarcoma virus (RAS) inhibitor or had received anticancer treatment within 3 weeks before initiation of the trial treatment; had undergone previous radiotherapy of more than 30 Gy to the lung within 6 months before randomization; or had known untreated or active central nervous system (CNS) metastases. Full inclusion and exclusion criteria are provided in the trial protocol, available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT

The trial protocol and subsequent amendments were approved by the institutional review board or ethics committee at the participating centers and complied with the Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. An independent data monitoring committee evaluated safety. All the patients provided written informed consent. F. Hoffmann–La Roche sponsored the trial and collaborated with the academic authors on the collection, analysis, and interpretation of the data. Medical-writing assistance, under the direction of the authors, was funded by F. Hoffmann–La Roche. All the authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

TRIAL DESIGN AND TREATMENT

The trial design is shown in Figure S1 in the Supplementary Appendix, available at NEJM.org. Eligible patients were randomly assigned in a 1:1 ratio to receive either divarasib or a locally approved KRAS G12C inhibitor (sotorasib or adagrasib; the control group). If both sotorasib and adagrasib were locally approved and available, investigators chose between the two drugs before randomization, with patients receiving the same drug throughout the trial. Randomization was stratified according to *KEAP1* mutation status (detected vs. not detected or unknown), history of CNS metastases (yes vs. no), and intended KRAS G12C inhibitor in the control group (sotorasib vs. adagrasib). Crossover between trial groups was not permitted.

Patients received either divarasib orally at a dose of 400 mg once daily or control treatment (sotorasib orally at a dose of 960 mg once daily or adagrasib orally at a dose of 600 mg twice daily). Treatment continued until disease progression, unacceptable adverse events, loss of clinical benefit, withdrawal of consent, death, or trial termination, whichever occurred first. Treatment after disease progression and dose modifications for the management of treatment-related toxic effects were permitted (see the Supplementary Methods section in the Supplementary Appendix for more information).

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival as assessed by blinded independent central review. Investigator-assessed progression-free survival was assessed as a sensitivity analysis. Key secondary end points were overall survival, overall confirmed response as assessed by blinded independent central review, and patient-reported outcomes (including time to confirmed deterioration). Other secondary end points were response duration as assessed by blinded independent central review and safety. Safety and side-effect profile were evaluated through the incidence and severity of adverse events, with severity determined according to the grading scale of the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute. Exploratory end points included correlation of antitumor efficacy with genomic, transcriptomic, and proteomic biomarkers.

Tumor assessments (including magnetic resonance imaging or computed tomography of the chest, abdomen and pelvis, and head) were performed at screening, every 6 weeks for the initial 48 weeks, and every 9 weeks thereafter until disease progression, loss of clinical benefit, withdrawal of consent, death, or trial termination, whichever occurred first. Further information about tumor assessments can be found in the Supplementary Methods.

STATISTICAL ANALYSIS

Efficacy was assessed in all the patients who underwent randomization (the full analysis population). Safety was assessed in all the patients who received trial treatment. A stratified log-rank test was used to compare progression-free and overall survival between the treatment groups. The difference in response was estimated with G-Computation, in which a logistic regression was fitted with adjustment for the stratification factors, with 95% confidence intervals estimated with the use of bootstrap resampling.

We calculated that approximately 216 events (disease progression or death) would provide the trial with 90% power to detect a hazard ratio of 0.64, which would require a planned sample size of approximately 320 patients. We planned to perform one interim analysis of overall survival, with the use of a Lan–DeMets alpha-spending function with O'Brien–Fleming boundaries, at the time of the primary analysis of progression-free survival. To control the overall level of significance at a two-sided error rate of 0.05, a hierarchical testing plan was used in the following

order: progression-free survival, overall survival, confirmed overall response, and time to confirmed deterioration (further information is provided in the Supplementary Methods). The full statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS

Patients were recruited between September 23, 2024, and November 30, 2025, at 151 centers in 26 countries. A full list of the trial investigators and trial sites can be found in the Supplementary Appendix. A total of 338 patients were enrolled and randomly assigned to either the divarasib group (167 patients) or the control group (171 patients, with 156 assigned to receive sotorasib and 15 assigned to receive adagrasib); these patients comprised the full analysis population (Fig. S2). At the data-cutoff date (May 19, 2026), more patients in the divarasib group (79 patients [47.3%]) than in the control group (47 patients [27.5%]) were still receiving treatment; 20 patients (12%) and 24 patients (14%), respectively, remained alive and in follow-up.

Demographic and clinical characteristics of the patients at baseline were well balanced in the treatment groups (Table 1). The trial population was broadly representative of patients with KRAS G12C–mutated advanced or metastatic NSCLC except that Black patients were underrepresented (Table S1). The median age of the patients was 66 years (range, 39 to 89), most of the patients were White (77.5%), and most had an ECOG performance-status score of 1 at baseline (60.7%); 29.3% of the patients had a history of CNS metastases at baseline.

EFFICACY

At the data-cutoff date, the median duration of follow-up was 14.3 months. The median progression-free survival as assessed by blinded independent central review was significantly longer in the divarasib group (9.8 months; 95% CI, 8.1 to 12.9) than in the control group (5.7 months; 95% CI, 4.2 to 6.8), with a hazard ratio for disease progression or death of 0.58 (95% CI, 0.44 to 0.76; P<0.001) (Fig. 1 and Table 2). The 12-month progression-free survival was 43.9% in the divarasib group and 24.0% in the control group. The progression-free survival benefit with divarasib across subgroups is shown in Figure S3A. The median investigator-assessed progression-free survival (11.1 months in the divarasib group vs. 5.6 months in the control group) was similar to the median progression-free survival as assessed by blinded independent central review (Table 2 and Fig. S4).

The median overall survival was significantly longer in the divarasib group (17.7 months; 95% CI, 16.3 to could not be estimated) than in the control group (12.0 months; 95% CI, 10.0 to 15.2), with a between-group difference of 5.7 months and a hazard ratio for death of 0.56 (95% CI, 0.41 to 0.78; P<0.001) (Fig. 2 and Table 2). The 12-month overall survival was 67.1% in the divarasib group and 49.2% in the control group. The overall survival benefit across subgroups is shown in Figure S3B.

The incidence of a confirmed response as assessed by blinded independent central review was significantly higher (by 25.8 percentage points) with divarasib than with control treatment. A response occurred in 58.4% of the patients receiving divarasib (95% CI, 50.4 to 66.1; complete response, 4.3%; partial response, 54.0%) and in 32.3% of those receiving control treatment (95% CI, 25.3 to 40.0; complete response, 3.6%; partial response, 28.7%) (Table 2 and Fig. S5). Among the patients who had a response to treatment, the median duration of response was 11.9 months (95% CI, 9.7 to could not be estimated) in the divarasib group and 6.9 months (95% CI, 5.3 to 8.3) in the control group. Similar treatment effects were observed for investigator-assessed confirmed overall response (Table 2).

PATIENT-REPORTED OUTCOMES

The results for time to confirmed deterioration with respect to cough did not meet the criteria for significance; the median time to confirmed deterioration could not be estimated in either treatment group. In accordance with the hierarchical testing strategy, no further patient-reported outcomes with respect to time to confirmed deterioration were tested. Results of the full analyses of patient-reported outcomes are being analyzed separately.

SAFETY

The median duration of treatment was longer with divarasib (11.3 months) than with control treatment (5.0 months). The median dose intensity

with respect to the total dose received was 98.7% in the divarasib group and 97.7% in the control group.

A total of 166 patients (99.4%) in the divarasib group and 167 (97.7%) in the control group had at least one adverse event of any grade; 72 (43.1%) and 88 (51.5%), respectively, had an adverse event of grade 3 or 4 (Table 3). Adverse events that led to death were reported in 10 patients (6.0%) in the divarasib group and in 7 (4.1%) in the control group (Table S2); none of these adverse events were considered to be related to treatment according to investigator assessment, although this assessment can be subjective. Adverse events related to gastrointestinal toxic effects and hepatotoxic effects were the most common overall and were also the most common adverse events leading to treatment discontinuation (Table S3); of note, 3 patients in the control group had pneumonitis leading to treatment discontinuation, as compared with no patients in the divarasib group.

Grade 3 or 4 treatment-related adverse events occurred in 41 patients (24.6%) in the divarasib group and in 59 (34.5%) in the control group (Table S4). The most common treatment-related adverse events were related to gastrointestinal toxic effects and hepatotoxic effects. Treatment-related QT prolongation and pneumonitis occurred in 2 and 3 patients, respectively, in the control group. Serious treatment-related adverse events occurred in 13 patients (7.8%) in the divarasib group and in 26 (15.2%) in the control group. Treatment-related adverse events leading to dose reductions or interruptions occurred in 44 patients (26.3%) and 33 patients (19.8%), respectively, in the divarasib group and in 51 (29.8%) and 40 (23.4%), respectively, in the control group. Treatment-related adverse events leading to treatment discontinuation occurred in fewer patients in the divarasib group (8 patients [4.8%]) than in the control group (20 patients [11.7%]).

Adverse events of special interest (comprising adverse-event terms associated with gastrointestinal toxic effects and hepatotoxic effects) were reported in 156 patients (93.4%) in the divarasib group and 130 (76.0%) in the control group (Table S5). However, the percentage of patients with grade 3 or 4 treatment-related adverse events of special interest was lower in the divarasib group (18.6% [31 patients]) than in the control group (27.5% [47 patients]). Although the percentage of patients with gastrointestinal toxic effects was higher with divarasib than with control treatment (91.0% vs. 68.4%), diarrhea, nausea, and vomiting were mainly grade 1 (in 40.7%, 33.5%, and 32.3% of patients, respectively, in the divarasib group and in 25.7%, 17.0%, and 11.1%, respectively, in the control group). The percentage of patients with hepatotoxic effects was lower with divarasib than with control treatment (26.9% vs. 39.2%).

BIOMARKER ANALYSES

Among patients harboring *KEAP1*-mutated tumors, a benefit with respect to progression-free and overall survival was observed with divarasib as compared with control treatment. Progression-free and overall survival favored divarasib over control treatment regardless of PD-L1 status.

DISCUSSION

In this phase 3, randomized trial, divarasib led to significantly longer progression-free survival than the first-generation KRAS G12C inhibitor sotorasib or adagrasib (P<0.001). Critically, divarasib also led to significantly longer overall survival; the median overall survival was 17.7 months in the divarasib group and 12.0 months in the control group (5.7 months longer with divarasib; P<0.001). Furthermore, efficacy benefits were seen with divarasib in patients with *KEAP1*-mutated tumors; however, these patients generally have poor outcomes.[7,8,11-13,25] In addition, divarasib showed a significant benefit over control treatment with respect to confirmed overall response.

Outcomes in the Krascendo 1 control group were similar to those observed with sotorasib and adagrasib in the phase 3 CodeBreaK 200 and KRYSTAL-12 trials involving patients with previously treated *KRAS* G12C–mutated NSCLC.[14,15] However, cross-trial comparisons should be interpreted with caution given the differences in trial designs, patient populations, and data maturity. Our trial was designed to evaluate divarasib as compared with sotorasib or adagrasib; however, only a small number of patients received adagrasib owing to limited drug availability worldwide (156 patients received sotorasib and 15 received adagrasib).

The safety profile of divarasib in our trial was consistent with that in previous trials, with no new safety signals.[23,24] A lower percentage of pa-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Divarasib (N=167)	Control (N=171)	All Patients (N=338)
Age			
Median (range) — yr	66 (42–87)	66 (39–89)	66 (39–89)
≥65 yr — no. (%)	97 (58.1)	99 (57.9)	196 (58.0)
Female sex — no. (%)	72 (43.1)	75 (43.9)	147 (43.5)
Race or ethnic group — no. (%)†			
Asian	17 (10.2)	23 (13.5)	40 (11.8)
Black	5 (3.0)	1 (0.6)	6 (1.8)
White	127 (76.0)	135 (78.9)	262 (77.5)
Other	18 (10.8)	12 (7.0)	30 (8.9)
ECOG performance-status score — no. (%)‡			
0	65 (38.9)	68 (39.8)	133 (39.3)
1	102 (61.1)	103 (60.2)	205 (60.7)
Smoking status — no. (%)			
Never smoked	4 (2.4)	6 (3.5)	10 (3.0)
Previous smoker	137 (82.0)	130 (76.0)	267 (79.0)
Current smoker	26 (15.6)	35 (20.5)	61 (18.0)
Histologic type			
Adenocarcinoma	158 (94.6)	164 (95.9)	322 (95.3)
Squamous	2 (1.2)	4 (2.3)	6 (1.8)
Other	7 (4.2)	3 (1.8)	10 (3.0)
KEAP1 mutation status — no. (%)§			
Detected	35 (21.0)	37 (21.6)	72 (21.3)
Not detected or unknown	132 (79.0)	134 (78.4)¶	266 (78.7)¶
PD-L1 status according to local testing — no. (%)‖			
Negative	57 (34.1)	70 (40.9)	127 (37.6)
Low	62 (37.1)	65 (38.0)	127 (37.6)
High	43 (25.7)	32 (18.7)	75 (22.2)
Missing	5 (3.0)	4 (2.3)	9 (2.7)
Previous lines of therapy — no. (%)			
One line	121 (72.5)	118 (69.0)	239 (70.7)
Two lines	41 (24.6)	51 (29.8)	92 (27.2)
Three lines	5 (3.0)	2 (1.2)	7 (2.1)
Geographic region — no. (%)			
Europe	106 (63.5)	103 (60.2)	209 (61.8)
North America	28 (16.8)	27 (15.8)	55 (16.3)
Rest of the world	33 (19.8)	41 (24.0)	74 (21.9)
History of CNS metastases — no. (%)§			
Yes	48 (28.7)	51 (29.8)	99 (29.3)
No	119 (71.3)	120 (70.2)	239 (70.7)
Intended *KRAS* G12C inhibitor if assigned to control group — no. (%)§**			
Sotorasib	153 (91.6)	156 (91.2)	309 (91.4)
Adagrasib	14 (8.4)	15 (8.8)	29 (8.6)

Table 1. (Continued.)

Characteristic	Divarasib (N=167)	Control (N=171)	All Patients (N=338)
Previous checkpoint inhibitor — no. (%)			
None	2 (1.2)	0	2 (0.6)
<30 days before trial-treatment initiation	5 (3.0)	12 (7.0)	17 (5.0)
30 to <60 days before trial-treatment initiation	58 (34.7)	60 (35.1)	118 (34.9)
60 to <90 days before trial-treatment initiation	33 (19.8)	16 (9.4)	49 (14.5)
≥90 days before trial-treatment initiation	69 (41.3)	82 (48.0)	151 (44.7)
Unknown	0	1 (0.6)	1 (0.3)

* The control group included patients who received treatment with sotorasib or adagrasib. Percentages may not total 100 because of rounding. CNS denotes central nervous system.
† Race and ethnic group were reported by the patients. The "Other" category includes American Indian or Alaska Native (1 patient in the divarasib group), multiracial (3 patients in the divarasib group), unknown (3 patients in the divarasib group and 4 in the control group), and not reported (11 patients in the divarasib group and 8 in the control group).
‡ Eastern Cooperative Oncology Group (ECOG) scores range from 0 to 5, with higher scores reflecting greater disability.
§ Data were recorded with an interactive voice- and Web-based response system.
¶ Three patients (all in the control group) had an unknown *KEAP1* mutation status.
‖ Programmed death ligand 1 (PD-L1) status was assessed with the tumor proportion score, which is the percentage of tumor cells expressing PD-L1. A score of less than 1% indicates negative PD-L1 status, 1 to less than 50% indicates low PD-L1 expression, and 50% or higher indicates high PD-L1 expression.
** Whether patients would receive sotorasib or adagrasib was determined by the investigator before randomization.

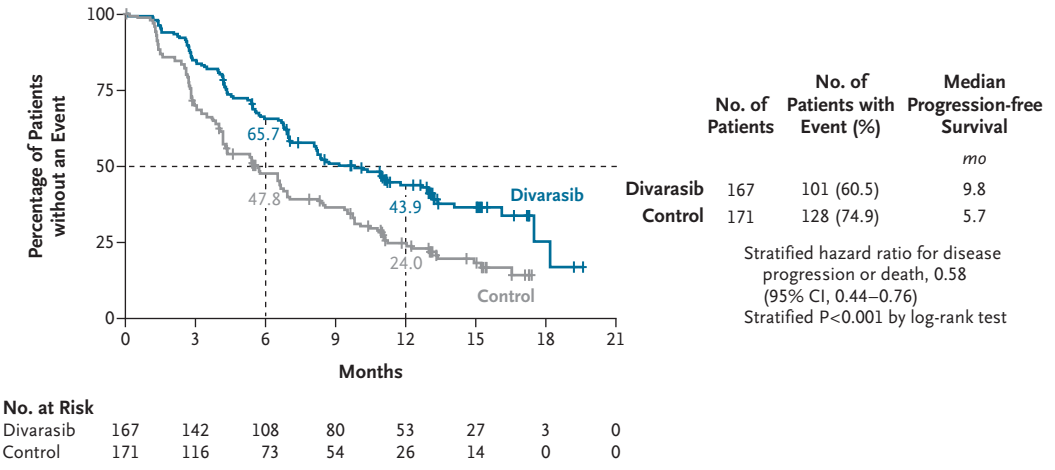


Figure 1. Progression-free Survival in the Full Analysis Population.

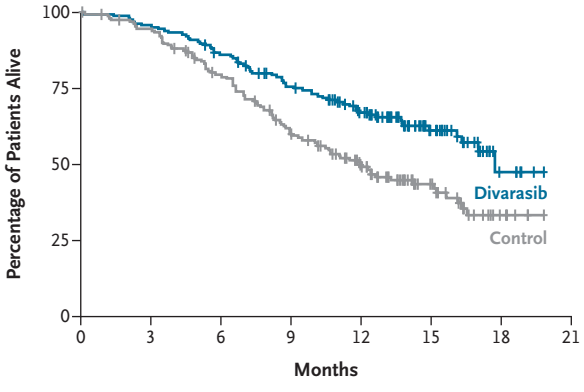
Shown is the progression-free survival, as assessed by blinded independent central review, among the patients who received divarasib and those who received control treatment (sotorasib or adagrasib). The full analysis population included all the patients who underwent randomization.

tients in the divarasib group than in the control group had grade 3 or 4 adverse events (43.1% vs. 51.5%), grade 3 or 4 treatment-related adverse events (24.6% vs. 34.5%), serious adverse events of any grade (30.5% vs. 40.9%), and serious treatment-related adverse events of any grade (7.8% vs. 15.2%). Adverse events leading to death occurred infrequently in both treatment groups (in 10 patients in the divarasib group and in 7 in the control group), and none of these events were considered to be related to trial treatment. The most common treatment-related adverse events

Table 2. Overall Efficacy Summary.*

Efficacy Variable	Divarasib (N=167)	Control (N=171)	Hazard Ratio or Difference (95% CI)†
Median progression-free survival as assessed by BICR (95% CI) — mo	9.8 (8.1–12.9)	5.7 (4.2–6.8)	0.58 (0.44–0.76)‡
Median overall survival (95% CI) — mo	17.7 (16.3–NE)	12.0 (10.0–15.2)	0.56 (0.41–0.78)‡
Confirmed overall response as assessed by BICR§			
No./total no.	94/161	54/167	
% (95% CI)	58.4 (50.4–66.1)	32.3 (25.3–40.0)	25.8 (15.6–36.0)
Complete response — no./total no. (%)	7/161 (4.3)	6/167 (3.6)	
Partial response — no./total no. (%)	87/161 (54.0)	48/167 (28.7)	
Duration of response as assessed by BICR§			
No. of patients	94	54	
Median (95% CI) — mo	11.9 (9.7–NE)	6.9 (5.3–8.3)	
Median progression-free survival as assessed by the investigator (95% CI) — mo	11.1 (8.8–14.1)	5.6 (4.4–7.0)	
Confirmed overall response as assessed by the investigator¶			
No.	97	50	
% (95% CI)	58.1 (50.2–65.7)	29.2 (22.5–36.7)	
Complete response — no. (%)	6 (3.6)	1 (0.6)	
Partial response — no. (%)	91 (54.5)	49 (28.7)	

* The control group included patients treated with sotorasib or adagrasib. BICR denotes blinded independent central review, and NE could not be estimated.
† Values are the hazard ratio for disease progression or death for progression-free survival, the hazard ratio for death for overall survival, and the difference (in percentage points) for confirmed overall response.
‡ P<0.001.
§ Ten patients (6 in the divarasib group and 4 in the control group) did not have measurable disease at baseline as assessed by BICR and were excluded from these analyses.
¶ All 338 patients who could be evaluated for response as assessed by the investigator were included.



	No. of Patients	No. of Patients Who Died (%)	Median Overall Survival (mo)
Divarasib	167	63 (37.7)	17.7
Control	171	93 (54.4)	12.0

Stratified hazard ratio for death, 0.56 (95% CI, 0.41–0.78)
Stratified P<0.001 by log-rank test

No. at Risk

Divarasib	167	160	142	120	95	41	6	0
Control	171	159	128	94	65	31	6	0

Figure 2. Overall Survival in the Full Analysis Population.
Shown is the overall survival among the patients who received divarasib and those who received control treatment (sotorasib or adagrasib).

Table 3. Safety Summary.*

Event	Divarasib (N = 167)		Control (N = 171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	166 (99.4)	72 (43.1)	167 (97.7)	88 (51.5)
Serious adverse event	51 (30.5)	NA	70 (40.9)	NA
Adverse event of special interest†	156 (93.4)	38 (22.8)	130 (76.0)	52 (30.4)
Adverse event leading to any dose reduction or interruption or treatment discontinuation	82 (49.1)	NA	93 (54.4)	NA
Adverse event leading to treatment discontinuation	12 (7.2)	NA	25 (14.6)	NA
Adverse event leading to dose reduction	44 (26.3)	NA	52 (30.4)	NA
Adverse event leading to dose interruption	57 (34.1)	NA	62 (36.3)	NA
Adverse events that occurred in ≥10% of patients in either treatment group				
Diarrhea	124 (74.3)	16 (9.6)	80 (46.8)	7 (4.1)
Nausea	98 (58.7)	3 (1.8)	47 (27.5)	4 (2.3)
Vomiting	76 (45.5)	1 (0.6)	26 (15.2)	3 (1.8)
Increased alanine aminotransferase level	30 (18.0)	9 (5.4)	40 (23.4)	16 (9.4)
Constipation	44 (26.3)	1 (0.6)	23 (13.5)	1 (0.6)
Increased aspartate aminotransferase level	29 (17.4)	4 (2.4)	37 (21.6)	15 (8.8)
Decreased appetite	31 (18.6)	1 (0.6)	29 (17.0)	5 (2.9)
Fatigue	27 (16.2)	0	30 (17.5)	2 (1.2)
Anemia	26 (15.6)	9 (5.4)	28 (16.4)	4 (2.3)
Increased lipase level	21 (12.6)	6 (3.6)	29 (17.0)	10 (5.8)
Back pain	25 (15.0)	2 (1.2)	21 (12.3)	2 (1.2)
Increased blood alkaline phosphatase level	14 (8.4)	2 (1.2)	31 (18.1)	8 (4.7)
Cough	23 (13.8)	0	20 (11.7)	0
Arthralgia	19 (11.4)	0	22 (12.9)	2 (1.2)
Peripheral edema	24 (14.4)	1 (0.6)	15 (8.8)	0
Pruritus	20 (12.0)	0	18 (10.5)	0
Headache	26 (15.6)	0	11 (6.4)	0
Pneumonia	19 (11.4)	5 (3.0)	14 (8.2)	6 (3.5)
Dyspnea	13 (7.8)	2 (1.2)	19 (11.1)	4 (2.3)
Insomnia	17 (10.2)	1 (0.6)	9 (5.3)	0
Increased γ-glutamyltransferase level	4 (2.4)	2 (1.2)	19 (11.1)	13 (7.6)

* The control group included patients treated with sotorasib or adagrasib. NA (not applicable) indicates that the events in the category are not shown according to severity.

† Adverse events of special interest comprised adverse-event terms associated with gastrointestinal toxic effects and hepatotoxic effects. Adverse-event terms according to a standard *Medical Dictionary for Regulatory Activities* (MedDRA) query for gastrointestinal toxic effects include gastrointestinal nonspecific symptoms and therapeutic procedure (narrow), noninfectious diarrhea (narrow), and colitis (excluding infective). Adverse-event terms according to a standard MedDRA query for hepatotoxic effects include hepatic failure, fibrosis and cirrhosis and other liver damage–related conditions (narrow), liver-related investigation, signs and symptoms (narrow), and hepatitis, noninfectious (narrow).

were gastrointestinal toxic effects and hepatotoxic effects, but these events were mostly low grade. Although prophylactic antiemetic agents were not mandatory in the trial, anecdotal experience with prophylactic 5-hydroxytryptamine type 3 receptor antagonists or dexamethasone showed a better side-effect profile. The divarasib group had a higher incidence of gastrointestinal

toxic effects and a lower incidence of hepatotoxic effects than the control group, which indicates relative differences in safety profiles of KRAS G12C inhibitors. Half as many patients in the divarasib group as in the control group had treatment-related adverse events leading to treatment discontinuation (4.8% vs. 11.7%).

Our trial has several notable strengths. First, it is a randomized trial that compares divarasib with the first-generation KRAS G12C inhibitors sotorasib and adagrasib. Second, established clinical and state-of-the art molecular stratification factors (e.g., *KEAP1* status) were incorporated. Third, overall survival was a key secondary end point; the trial was powered for overall survival as well as progression-free survival as assessed by blinded independent central review. Fourth, benefits of divarasib were noted in most subgroups, and the performance of the active control treatment was in accordance with previous expectations.

The trial also had limitations. First, the majority of the patients in the control group received sotorasib because adagrasib was available in only one country, which resulted in a small number of patients receiving adagrasib (15 patients). Second, the open-label trial design was required given the different dose regimens for the drugs in the control group, although this limitation was mitigated by the inclusion of end points assessed by blinded independent central review. Third, Black patients were underrepresented. Fourth, in accordance with the trial design, patients with untreated CNS metastases were not eligible, although patients with a history of treated CNS metastases were included. However, regular imaging of the head was performed in all the patients, and intracranial outcomes will be further analyzed.

The benefits with respect to progression-free and overall survival among the patients who received divarasib in the Krascendo 1 trial, alongside the promising results from the phase 1b–2 Krascendo 170 trial evaluating divarasib plus pembrolizumab in patients with *KRAS* G12C–mutated advanced or metastatic NSCLC who have not previously received treatment,[26] support further investigation of divarasib as a targeted treatment in combination with pembrolizumab in patients with *KRAS* G12C–mutated advanced or metastatic NSCLC who have not previously received treatment (Krascendo 2 ClinicalTrials.gov number, NCT06793215).[27] In addition, the results of Krascendo 1, coupled with the results from the phase 2 NAUTIKA1 study evaluating divarasib as neoadjuvant therapy for resectable early-stage *KRAS* G12C–mutated NSCLC,[28] support further investigation of divarasib as monotherapy in patients with surgically resected early-stage NSCLC who have not had a pathological complete response (Krascendo 3, NCT07541170).

In our trial, divarasib showed superiority over the first-generation KRAS G12C inhibitor sotorasib or adagrasib with respect to antitumor efficacy. The safety profile of divarasib was consistent with the known safety profile for KRAS G12C inhibitors, with gastrointestinal toxic effects and hepatotoxic effects being the most common treatment-related adverse events in both treatment groups. These results establish divarasib as a new, efficacious treatment for patients with previously treated *KRAS* G12C–mutated advanced or metastatic NSCLC.

Supported by F. Hoffmann–La Roche.

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 patients who participated in this trial, their family and caregivers, the personnel at the trial sites, and Rebecca Benatan, B.Sc., and Claire White, Ph.D., of Ashfield MedComms, an Inizio company, for providing third-party medical-writing assistance under the direction of the authors, which was funded by F. Hoffmann–La Roche.

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