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BACKGROUND
Divarasib (GDC-6036) is a covalent KRAS G12C inhibitor that was designed to have high potency and selectivity.

METHODS
In a phase 1 study, we evaluated divarasib administered orally once daily (at doses ranging from 50 to 400 mg) in patients who had advanced or metastatic solid tumors that harbor a KRAS G12C mutation. The primary objective was an assessment of safety; pharmacokinetics, investigator-evaluated antitumor activity, and biomarkers of response and resistance were also assessed.

RESULTS
A total of 137 patients (60 with non–small-cell lung cancer [NSCLC], 55 with colorectal cancer, and 22 with other solid tumors) received divarasib. No dose-limiting toxic effects or treatment-related deaths were reported. Treatment-related adverse events occurred in 127 patients (93%); grade 3 events occurred in 15 patients (11%) and a grade 4 event in 1 patient (1%). Treatment-related adverse events resulted in a dose reduction in 19 patients (14%) and discontinuation of treatment in 4 patients (3%). Among patients with NSCLC, a confirmed response was observed in 53.4% of patients (95% confidence interval [CI], 39.9 to 66.7), and the median progression-free survival was 13.1 months (95% CI, 8.8 to could not be estimated). Among patients with colorectal cancer, a confirmed response was observed in 29.1% of patients (95% CI, 17.6 to 42.9), and the median progression-free survival was 5.6 months (95% CI, 4.1 to 8.2). Responses were also observed in patients with other solid tumors. Serial assessment of circulating tumor DNA showed declines in KRAS G12C variant allele frequency associated with response and identified genomic alterations that may confer resistance to divarasib.

CONCLUSIONS
Treatment with divarasib resulted in durable clinical responses across KRAS G12C–positive tumors, with mostly low-grade adverse events. (Funded by Genentech; ClinicalTrials.gov number, NCT04449874.)
Mutations in the Kirsten rat sarcoma viral oncogene homologue (KRAS) gene are the most common oncogenic driver mutations found in human cancer. The glycine-to-cysteine mutation at position 12 (G12C) of the KRAS protein interferes with guanosine triphosphate (GTP) hydrolysis, thus keeping KRAS primarily in the active, GTP-bound state. The increased activity of the KRAS G12C protein drives oncogenic signaling through multiple downstream pathways that directly promote tumor-cell survival, proliferation, and metastasis. The KRAS G12C mutation is present in approximately 12 to 14% of patients with non–small-cell lung cancer (NSCLC), 4% of patients with colorectal cancer, and up to 4% of patients with other solid tumor types (excluding NSCLC and colorectal cancer), with the frequency varying according to race and sex. Standard therapeutic approaches for KRAS G12C–mutant solid tumors vary but generally consist of nonselective chemotherapy, immunotherapy, or both, with therapy resulting in modest benefits in previously treated patients. Although recently developed KRAS G12C inhibitors, including sotorasib and adagrasib, have shown antitumor activity in patients with previously treated KRAS G12C–mutated cancer, the extent of the clinical benefit remains limited, and better therapies to target KRAS G12C remain a high priority.

Divarasib (GDC-6036) is a covalent KRAS G12C inhibitor designed to exhibit high potency and selectivity. It binds to the cysteine residue and irreversibly locks the protein into its inactive state, turning off its oncogenic signaling. Divarasib has been shown to be 5 to 20 times as potent and up to 50 times as selective in vitro as sotorasib and adagrasib. This ongoing phase 1 study is evaluating divarasib as a single agent and in combination with other anticancer therapies in patients with advanced or metastatic solid tumors with a KRAS G12C mutation.

Methods

Study Design

The data we report here are from an ongoing phase 1, open-label, multicenter, dose-escalation, and dose-expansion study of divarasib as a single agent in patients with advanced or metastatic solid tumors that harbor a KRAS G12C mutation. The primary objective of this study is to evaluate the safety of divarasib; other objectives include characterization of the pharmacokinetic profile, preliminary antitumor activity, and biomarkers of response and resistance.

Patients

Patients 18 years of age or older with locally advanced or metastatic solid tumors harboring a KRAS G12C mutation were enrolled at 35 sites in 12 countries. Key inclusion criteria were the following: disease that had progressed after at least one available standard therapy, disease for which standard therapy proved to be ineffective or caused unacceptable side effects, or disease for which a clinical trial of an investigational agent is a recognized standard of care; evaluable or measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 6-point scale, on which higher numbers reflect greater disability); and documentation of the KRAS G12C mutation by either central testing of blood samples (with the use of FoundationOne Liquid CDx [F1LCDx]) or local testing of tumor tissue or blood samples (with the use of a validated molecular testing method).

Key exclusion criteria were previous treatment with a KRAS G12C inhibitor; active, untreated central nervous system metastases (although previously treated central nervous system metastases were not an exclusion criterion); treatment with another anticancer therapy within 3 weeks or five half-lives before the initiation of the study treatment, whichever was shorter; and radiation as cancer therapy within 4 weeks before the initiation of divarasib. The full inclusion and exclusion criteria are listed in the protocol, available with the full text of this article at NEJM.org.

Procedures and Study Assessments

Divarasib was administered orally once daily, at doses ranging from 50 to 400 mg, in 21-day cycles, until unacceptable toxic effects developed, disease progression occurred, or the patient withdrew from the study. Patients were enrolled sequentially into single-patient dose-escalation cohorts of divarasib at the 50-mg and 100-mg dose levels. Subsequently, additional patients were enrolled in the 200-mg and 400-mg dose cohorts with the use of a 3+3 dose-escalation design; in this design, cohorts consisting of 3 patients each
were evaluated for toxic effects that resulted in dose reductions, as defined in the protocol; the dose was escalated until an expansion dose was identified. (Fig. S1 in the Supplementary Appendix.) Subsequently, patients were enrolled in dose-expansion cohorts of divarasib at 400 mg; the dose-expansion cohorts included a biopsy cohort (at 100 to 400 mg), which consisted of patients who underwent a biopsy before treatment and approximately 1 to 2 weeks after the initiation of treatment.

Safety was evaluated in patients who received at least one dose of the study treatment through assessment of adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0), changes in laboratory test results, and changes in vital signs and electrocardiograms. Attribution of adverse events to study treatment was determined by the investigator. For each adverse event that resulted in a dose modification, only one action taken with regard to the study drug was selected for data analysis, according to the following hierarchy: discontinuation, reduction, or interruption. Preliminary antitumor activity was determined by the investigator according to RECIST, version 1.1, and included the confirmed response and progression-free survival (further defined in the Supplementary Appendix). Confirmed response in patients with measurable disease was defined as complete response or partial response on two consecutive tumor assessments at least 4 weeks apart, whereas best response did not require a confirmatory assessment.

Mutational status of TP53, STK11, KEAP1, and APC was assessed with the use of the F1LCDx assay in the blood samples that were collected before divarasib treatment. The programmed death ligand 1 (PD-L1) tumor proportion score (i.e., the fraction of tumor cells expressing PD-L1), was assessed with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) or other assays at a local laboratory. Exploratory profiling of circulating tumor DNA (ctDNA) was performed with the use of PredicineWES+ (for baseline and end-of-treatment plasma samples) and Predicine-BEACON (for on-treatment plasma samples). Pharmacokinetic variables were estimated with the use of a noncompartmental analysis of time-concentration data (methods are further described in the Supplementary Appendix).

STUDY OVERSIGHT
The study was sponsored and designed by Genentech. A medical writer (an employee of Genentech) wrote the initial draft of the manuscript and provided editorial assistance with earlier versions of the manuscript. The sponsor collected and analyzed the data. All the authors contributed to data interpretation and manuscript preparation and vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. This study was conducted in full conformance with the International Council for Harmonisation E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki or the applicable laws and regulations of the country in which the research was conducted, whichever afforded greater protection of the patient. All patients provided written informed consent before enrollment.

STATISTICAL ANALYSIS
We planned to enroll approximately 48 patients in the single-agent dose-escalation stage (stage I), 20 patients in each of the dose-expansion cohorts (stage II) (NSCLC, colorectal cancer, and other solid tumors), and 10 patients in the biopsy cohort. On the basis of available safety, pharmacokinetic, and activity data, additional patients could be enrolled in the dose-expansion cohorts.

The enrollment cutoff date was October 7, 2022, and the data cutoff date was November 21, 2022. This analysis included all patients who received at least one dose of divarasib. Patients were grouped by tumor type (NSCLC, colorectal cancer, or other solid tumors) when applicable. Confirmed response was reported for patients with measurable disease at baseline and summarized with 95% confidence intervals calculated with the use of the Clopper–Pearson method. The time-to-event end points, including the duration of the response and progression-free survival, were reported descriptively and were summarized with the use of the Kaplan–Meier method; the median estimates were reported with 95% confidence intervals.

RESULTS

PATIENTS
A total of 137 patients (60 with NSCLC, 55 with colorectal cancer, and 22 with other solid tumors)
were assigned to receive divarasib as a single agent and received at least one dose between July 29, 2020, and October 7, 2022 (Fig. S1). The 400-mg dose of divarasib was the maximum administered dose and was subsequently the dose selected for the dose-expansion cohorts. The median duration of treatment was 6.9 months (range, 0 to 24.1) for all patients, 8.3 months (range, 0 to 24.1) for patients with NSCLC, and 5.5 months (range, 0.2 to 15.6) for patients with colorectal cancer. The study treatment was discontinued in 94 patients (69%), with the most common reasons being progressive disease according to RECIST (69 patients, 50%), clinical progression (9 patients, 7%), and adverse events regardless of attribution (7 patients, 5%).

Baseline demographics and disease characteristics are summarized according to tumor type in Table 1. Across all tumor types, the median age of the patients was 65 (range, 30 to 85), and patients had previously received a median of 2 (range, 0 to 8) systemic therapies. Black patients were underrepresented in the study. Of the patients with NSCLC, 56 patients (93%) were current or former smokers, 60% (27 of 45 patients for whom information on PD-L1 status was available) had a PD-L1 tumor proportion score of at least 1%, 53 patients (88%) had received previous platinum therapy, and 52 patients (87%) had received previous anti-PD-1 or anti-PD-L1 therapy (22 of whom had received the therapy within 90 days before study enrollment). Of the patients with colorectal cancer, 55 patients (100%) had been previously treated with fluorouracil or capecitabine, 54 patients (98%) with oxaliplatin, 46 patients (84%) with irinotecan, and 34 patients (62%) with bevacizumab.

Table 1. Patient Demographics and Disease Characteristics.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NSCLC (N=60)</th>
<th>Colorectal Cancer (N=55)</th>
<th>Other Solid Tumors† (N=22)</th>
<th>All Patients (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) — yr</td>
<td>67 (43–82)</td>
<td>62 (34–81)</td>
<td>64 (30–85)</td>
<td>65 (30–85)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>34 (57)</td>
<td>33 (60)</td>
<td>10 (45.5)</td>
<td>77 (56)</td>
</tr>
<tr>
<td>Race — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52 (87)</td>
<td>40 (73)</td>
<td>17 (77)</td>
<td>109 (80)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (7)</td>
<td>10 (18)</td>
<td>5 (23)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (5)</td>
<td>5 (9)</td>
<td>0</td>
<td>8 (6)</td>
</tr>
<tr>
<td>ECOG performance-status score — no. (%)§§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (35)</td>
<td>23 (43)</td>
<td>13 (59)</td>
<td>57 (42)</td>
</tr>
<tr>
<td>1</td>
<td>39 (65)</td>
<td>30 (57)</td>
<td>9 (41)</td>
<td>78 (58)</td>
</tr>
<tr>
<td>Previous systemic therapies — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>1</td>
<td>23 (38)</td>
<td>6 (11)</td>
<td>4 (18)</td>
<td>33 (24)</td>
</tr>
<tr>
<td>2</td>
<td>17 (28)</td>
<td>14 (25)</td>
<td>7 (32)</td>
<td>38 (28)</td>
</tr>
<tr>
<td>3</td>
<td>11 (18)</td>
<td>15 (27)</td>
<td>2 (9)</td>
<td>28 (20)</td>
</tr>
<tr>
<td>≥4</td>
<td>8 (13)</td>
<td>20 (36)</td>
<td>9 (41)</td>
<td>37 (27)</td>
</tr>
</tbody>
</table>

* NSCLC denotes non–small-cell lung cancer.
† Other solid tumor types include pancreatic adenocarcinoma (7 patients), cholangiocarcinoma (7 patients), duodenal adenocarcinoma (2 patients), and anal adenocarcinoma, appendiceal adenocarcinoma, breast carcinoma, endometrial squamous-cell carcinoma, large-cell neuroendocrine carcinoma of the lung, and stomach adenocarcinoma (1 patient each).
‡ Race was reported by the patients.
§§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability. Two patients with colorectal cancer had missing ECOG performance-status scores at baseline.
SAFETY

No dose-limiting toxic effects were reported at any investigated dose (50 mg, 100 mg, 200 mg, or 400 mg once daily). Across all tumor types, 136 patients (99%) had an adverse event that occurred during the treatment period (Table S1), and 127 patients (93%) had a treatment-related adverse event (Table 2). The most common treatment-related adverse events were nausea (74%), diarrhea (61%), and vomiting (58%). The majority of treatment-related adverse events (94%) were grade 1 or 2. Grade 3 treatment-related adverse events occurred in 15 patients (11%) and included diarrhea (5 patients), an increase in the alanine aminotransferase (ALT) level (4 patients), an increase in the aspartate aminotransferase (AST) level (4 patients), and nausea, vomiting, fatigue, an increase in the lipase level, hypokalemia, an increase in the blood alkaline phosphatase level, hypophosphatemia, and neutropenia (1 patient each). One grade 4 treatment-related event (anaphylactic reaction) was reported in 1 patient (1%).

All grade 3 treatment-related increases in AST and ALT levels occurred in patients with NSCLC, and the levels normalized after the interruption of divarasisib with or without glucocorticoid therapy.

Table 2. Treatment-Related Adverse Events in 10% or More of Patients.

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event</th>
<th>NSCLC (N = 60)</th>
<th>Colorectal Cancer (N = 55)</th>
<th>All Patients (N = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–5*</td>
<td>Any Grade</td>
</tr>
<tr>
<td></td>
<td>number of patients</td>
<td>percent</td>
<td>number of patients</td>
</tr>
<tr>
<td>At least one event</td>
<td>56 (93)</td>
<td>11 (18)</td>
<td>53 (96)</td>
</tr>
<tr>
<td>Nausea</td>
<td>47 (78)</td>
<td>1 (2)</td>
<td>43 (78)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (60)</td>
<td>2 (3)</td>
<td>38 (69)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38 (63)</td>
<td>0</td>
<td>32 (58)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (27)</td>
<td>1 (2)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (18)</td>
<td>0</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Aspartate aminotransferase level increased</td>
<td>9 (15)</td>
<td>4 (7)</td>
<td>3 (5.5)</td>
</tr>
</tbody>
</table>

* No grade 5 treatment-related adverse events (death) were reported.

diabetes, and increases in the ALT or AST level. A total of 4 patients (3%) withdrew from the study treatment because of divarasisib-related adverse events, which included vomiting, diarrhea, upper abdominal pain, and anaphylactic reaction (1 patient each). Serious adverse events occurred in 42 patients (31%), resulting in dose modifications in 23 patients (17%) and discontinuation of the study treatment in 4 patients (3%); only 2 patients had treatment-related serious adverse events. Seven grade 5 events (death) occurred that were attributed to the disease under study (NSCLC, colorectal cancer, or other solid-tumor cancer), and no deaths were considered to be related to treatment with divarasisib.

EFFICACY

NSCLC

Across all dose levels, of the 58 patients with NSCLC who had measurable disease at baseline, 1 patient (2%) had a complete response, 34 (59%) had a partial response, 17 (29%) had stable disease, and 4 (7%) had progressive disease as their best response; 2 patients (3%) discontinued treatment before the first tumor assessment during the study. A confirmed response was observed in 53.4% of patients (95% confidence interval [CI], 39.9 to 66.7) (Fig. 1 and Fig. S2). The median time to response was 1.3 months (range, 1.2 to 8.3), and the median duration of response was 14.0 months (95% CI, 8.3 to could not be estimated). The median progression-free survival was 13.1
months (95% CI, 8.8 to could not be estimated). Of the 39 patients receiving divarasib at a dose of 400 mg, 56.4% had a confirmed response (95% CI, 39.6 to 72.2), and the median duration of response was 11.9 months (95% CI, 6.9 to could not be estimated). In these patients, the median progression-free survival was 13.7 months (95% CI, 8.1 to could not be estimated). Responses to divarasib were observed across subgroups defined according to PD-L1 status or according to the presence of co-occurring mutations (TP53, STK11, and KEAP1), although the number of patients in each subgroup was small (Table S2).

**Colorectal Cancer**

Across all dose levels, of the 55 patients with colorectal cancer and measurable disease at baseline, 1 patient (2%) had a complete response, 19 (35%) had partial responses, 27 (49%) had stable disease, and 6 (11%) had progressive disease as their best response; 2 patients (4%) discontinued treatment before the first tumor assessment during the study. A confirmed response was observed in 29.1% of patients (95% CI, 17.6 to 42.9) (Fig. 2 and Fig. S3). The median time to response was 2.2 months (range, 1.2 to 6.8), and the median duration of response was 7.1 months (95% CI,
5.5 to 7.8). The median progression-free survival was 5.6 months (95% CI, 4.1 to 8.2). Of the 39 patients who received divarab in at a dose of 400 mg, 35.9% had a confirmed response (95% CI, 21.2 to 52.8), and the median duration of response was 7.7 months (95% CI, 5.7 to could not be estimated). In these patients, the median progression-free survival was 6.9 months (95% CI, 5.3 to 9.1). Responses were observed in subgroups defined according to the presence of co-occurring mutations (APC and TP53), though the numbers of patients in each of these subgroups was small (Table S2).

**Other Solid Tumors**

A total of 22 patients who had solid tumors other than NSCLC and colorectal cancer and measurable disease at baseline were enrolled, all of whom received divarab in at a dose of 400 mg. Partial responses were observed in 8 patients (36%; 3 patients with pancreatic adenocarcinoma and 1 patient each with anal adenocarcinoma, cholangiocarcinoma, endometrial squamous-cell carcinoma, large-cell neuroendocrine carcinoma of the lung, and stomach adenocarcinoma), stable disease in 11 patients (50%; 4 patients each with pancreatic adenocarcinoma and cholangiocar-
cinoma and 1 each with appendiceal adenocarcinoma, breast cancer, and duodenal adenocarcinoma), and progressive disease in 1 patient (5%; cholangiocarcinoma) as the best response; 2 patients (9%) discontinued treatment before the first tumor assessment during the study (Fig. S4).

**PHARMACOKINETICS**
Among 4 patients across tumor types with pharmacokinetic data evaluable for determination of half-life, the mean (±SD) half-life after a single dose of 400 mg of divarasib was 17.6±2.7 hours. At steady state (day 8 of cycle 1 or day 1 of cycle 2) after once-daily receipt of divarasib at a dose of 400 mg, the median time to maximum concentration among 76 patients across tumor types with evaluable pharmacokinetic data was 2.0 hours (range, 0.5 to 8.0), the mean maximum concentration was 657±185 ng per milliliter, the mean area under the curve (0 to 24 hours) was 9130±3160 ng times hours per milliliter, and the mean accumulation ratio relative to day 1 of cycle 1 was 1.4±0.4 (Fig. S5 and Table S3).

**BIOMARKERS OF RESPONSE AND RESISTANCE**
Levels of ctDNA on day 1 of cycle 1, day 15 of cycle 1, and day 1 of cycle 3 were evaluable in 70 patients (26 with NSCLC, 35 with colorectal cancer, and 9 with other solid tumors) in whom the KRAS G12C mutation was detectable in ctDNA on day 1 of cycle 1. In the majority of these patients, a reduction in KRAS G12C variant allele frequency was observed as early as day 15 of cycle 1. All patients with a partial response, across all tumor types, had a KRAS G12C variant allele frequency of less than 1% on day 1 of cycle 3 (Fig. 3D).

Paired baseline and end-of-treatment ctDNA profiling was performed in a subgroup of patients with progression-free survival of more than 3 months (29 patients; 8 with NSCLC, 16 with colorectal cancer, and 5 with other solid tumors) to evaluate possible mechanisms of acquired resistance to divarasib (further described in Table S4). A total of 16 patients (3 with NSCLC, 9 with colorectal cancer, and 4 with other solid tumors) had at least one possible genomic mechanism of resistance identified, such as KRAS copy number gain or amplification; KRAS non-G12C mutations; alterations in receptor tyrosine kinase (RTK), mitogen-activated protein kinase (MAPK), or phosphoinositide 3-kinase (PI3K) pathway components; or RBP copy number loss (Fig. 3B).

Preexisting mutations in RAS genes as possible primary resistance mechanisms were evaluated in 25 patients who had disease progression or died within 3 months after the initiation of treatment. Oncogenic driver mutations in RAS genes other than KRAS G12C were identified in baseline plasma samples in 6 patients (Fig. 3C). In 3 of these 6 patients with longitudinal ctDNA profiling, dynamic clonal evolution was observed during treatment, with an increase in the variant allele frequency of non–KRAS G12C mutations and a decrease in the KRAS G12C variant allele frequency (Fig. 3D).

**DISCUSSION**
The discovery of the switch II pocket within the KRAS protein has led to the rapid development of multiple KRAS G12C inhibitors that have different safety, antitumor activity, and clinical benefit profiles. In this study, single-agent divarasib was shown to have a manageable safety profile and highly promising antitumor activity in patients with previously treated NSCLC, colorectal cancer, or other cancers.

Divarasib was associated with mainly low-grade gastrointestinal adverse effects that were reversible and manageable with supportive medications including antidiarrheal and antiemetic agents. Among patients receiving divarasib, dose reductions and discontinuation of treatment resulting from divarasib-related adverse events were infrequent (dose reduction in 14% and discontinuation in 3%), findings that were similar to or better than those reported in patients with NSCLC who received sotorasib (dose reduction in 15% and discontinuation in 7 to 10%)

17,18 or adagrasib (dose reduction in 52% and discontinuation in 7%).

A mean half-life of 17.6 hours was observed with divarasib, which supports a convenient once-daily dosing regimen.

In this phase 1 study, treatment with divarasib resulted in clinical responses across tumor types with the KRAS G12C mutation. It is encouraging that, among patients with NSCLC, a confirmed response was observed in 56.4% of patients, and a median progression-free survival of 13.7 months was observed at the selected expansion dose of divarasib 400 mg once daily. Cross-trial compar-
sons are often difficult because of differences in demographic features; however, the results with divarasib appear to be numerically higher than those observed with sotorasib as a single agent and in combination with other anticancer therapies. There is a need to identify new effective strategies to delay and prevent resistance to KRAS G12C inhibitors. To this end, divarasib is being investigated in combination with other anticancer therapies, including atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971 (an inhibitor of Src homology region 2–containing PI3K pathway components at the end of treatment that may confer acquired resistance in patients receiving single-agent divarasib treatment; these results are similar to those previously reported for sotorasib and adagrasib. In addition, we hypothesize that preexisting mutations in RAS genes (other than KRAS G12C) in a subgroup of patients with limited clinical benefit represent driver mutation heterogeneity in which non–KRAS G12C–mutant tumor cells are unlikely to respond to divarasib.

The safety profile and encouraging single-agent antitumor activity of divarasib make it a promising clinical candidate both as a single agent and in combination with other anticancer therapies. There is a need to identify new effective strategies to delay and prevent resistance to KRAS G12C inhibitors. To this end, divarasib is being investigated in combination with other anticancer therapies, including atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971 (an inhibitor of Src homology region 2–containing PI3K pathway components at the end of treatment).
protein tyrosine phosphatase-2), and inolisib (a PI3Kα inhibitor), in this current, ongoing study.

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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.

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APPENDIX

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