KRASG12C inhibition with sotorasib in advanced solid tumors

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KRAS<sup>G12C</sup> Inhibition with Sotorasib in Advanced Solid Tumors


ABSTRACT

BACKGROUND
No therapies for targeting KRAS mutations in cancer have been approved. The KRAS p.G12C mutation occurs in 13% of non–small-cell lung cancers (NSCLCs) and in 1 to 3% of colorectal cancers and other cancers. Sotorasib is a small molecule that selectively and irreversibly targets KRAS<sup>G12C</sup>.

METHODS
We conducted a phase 1 trial of sotorasib in patients with advanced solid tumors harboring the KRAS p.G12C mutation. Patients received sotorasib orally once daily. The primary end point was safety. Key secondary end points were pharmacokinetics and objective response, as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

RESULTS
A total of 129 patients (59 with NSCLC, 42 with colorectal cancer, and 28 with other tumors) were included in dose escalation and expansion cohorts. Patients had received a median of 3 (range, 0 to 11) previous lines of anticancer therapies for metastatic disease. No dose-limiting toxic effects or treatment-related deaths were observed. A total of 73 patients (56.6%) had treatment-related adverse events; 15 patients (11.6%) had grade 3 or 4 events. In the subgroup with NSCLC, 32.2% (19 patients) had a confirmed objective response (complete or partial response) and 88.1% (52 patients) had disease control (objective response or stable disease); the median progression-free survival was 6.3 months (range, 0.0+ to 14.9 [with + indicating that the value includes patient data that were censored at data cutoff]). In the subgroup with colorectal cancer, 7.1% (3 patients) had a confirmed response, and 73.8% (31 patients) had disease control; the median progression-free survival was 4.0 months (range, 0.0+ to 11.1+). Responses were also observed in patients with pancreatic, endometrial, and appendiceal cancers and melanoma.

CONCLUSIONS
Sotorasib showed encouraging anticancer activity in patients with heavily pretreated advanced solid tumors harboring the KRAS p.G12C mutation. Grade 3 or 4 treatment-related toxic effects occurred in 11.6% of the patients. (Funded by Amgen and others; CodeBreaK100 ClinicalTrials.gov number, NCT03600883.)
KRAS is the most frequently mutated oncogene in human cancers and encodes a guanosine triphosphatase (GTPase) that cycles between active guanosine triphosphate (GTP)–bound and inactive guanosine diphosphate (GDP)–bound states to regulate signal transduction. KRAS mutations are often associated with resistance to targeted therapies and poor outcomes in patients with cancer, yet no selective KRAS inhibitor has been approved despite more than three decades of scientific effort.

The KRAS p.G12C mutation occurs in approximately 13% of non–small-cell lung cancers (NSCLCs) and in 1 to 3% of colorectal cancers and other solid cancers. The glycine-to-cysteine mutation at position 12 favors the active form of the KRAS protein, resulting in a predominantly GTP-bound KRAS oncoprotein and enhanced proliferation and survival in tumor cells. The mutated cysteine resides next to a pocket (P2) of the switch II region. The P2 pocket is present only in the inactive GDP-bound form of the KRAS and has been exploited to establish covalent inhibitors of KRAS.

Sotorasib (AMG 510) is a small molecule that specifically and irreversibly inhibits KRAS p.G12C through a unique interaction with the P2 pocket (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The inhibitor traps KRAS p.G12C in the inactive GDP-bound state by a mechanism similar to that described for other KRAS p.G12C inhibitors. Preclinical studies showed that sotorasib inhibited nearly all detectable phosphorylation of extracellular signal-regulated kinase (ERK), a key downstream effector of KRAS, leading to durable complete tumor regression in mice bearing KRAS p.G12C tumors.

In this phase 1 trial, we evaluated the safety, pharmacokinetics, and efficacy of sotorasib in patients with advanced solid tumors harboring the KRAS p.G12C mutation.
informed consent. The study was designed by employees of Amgen (the main sponsor) in collaboration with the investigators. The data were collected by investigators and were analyzed by statisticians employed by Amgen. A medical writer employed by Amgen provided the first draft of the manuscript and editorial assistance. All authors contributed to interpretation of the data and preparation of the manuscript and vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

**END POINTS**

The primary end point was safety, including the incidence of dose-limiting toxic effects (defined as sotorasib-related toxic effects within the first 21 days after the first dose), adverse events during the treatment period, and treatment-related adverse events. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Secondary end points included the following pharmacokinetic variables: the maximum plasma concentration, the time to achieve maximum plasma concentration, and the area under the plasma concentration-time curve. Additional secondary end points, measured by computed tomography (CT) or magnetic resonance imaging and assessed by independent radiologic review according to RECIST 1.1, were objective response (complete or partial response), duration of response, disease control (objective response or stable disease at the week 6 assessment, with imaging performed within 1 week before or 1 week after the assessment), progression-free survival, and duration of stable disease. Response data included in this article were evaluated by local investigators.

**STATISTICAL ANALYSIS**

This analysis included all patients enrolled in the cohorts that received monotherapy once daily (dose escalation and expansion cohorts). The date of data cutoff was June 1, 2020.

A maximum enrollment of 92 patients was planned for the dose escalation cohorts, and the outcomes in approximately 30 patients were analyzed to estimate the recommended phase 2 dose. Once the phase 2 dose was determined, the dose expansion cohort was opened to enroll approximately 20 to 60 patients. We calculated that with 60 patients in the expansion cohort, there would be a 45 to 95% probability of observing at least one adverse event if the true event rate was 1 to 5%. After a minimum of 20 patients were treated at the recommended phase 2 dose and at least 10 of these patients had at least one assessment of tumor response, the dose-level review team reviewed all available safety, laboratory, pharmacokinetic, and efficacy data to make a recommendation to proceed to phase 2.

**RESULTS**

**TRIAL POPULATION**

A total of 129 patients, including 59 with NSCLC, 42 with colorectal cancer, and 28 with other tumor types, were enrolled in dose escalation and expansion cohorts (Fig. S2). This analysis was conducted in the full phase 1 population that received daily monotherapy with sotorasib. The median follow-up was 11.7 months (range, 4.6 to 21.2). Treatment was discontinued in 107 patients (82.9%); the most common reason for discontinuation was disease progression. As of the data cutoff date of June 1, 2020, 54 patients (41.9%) had died. The median duration of treatment was 3.9 months (range, 0 to 16.6). A total of 74 patients (57.4%) received treatment for 3 months or more, and 38 (29.5%) for 6 months or more.

Baseline characteristics are summarized in Table 1 (with additional details in Table S1). The median age was 62 years (range, 33 to 83). Most of the enrolled patients were heavily pretreated, with a median of 3 (range, 0 to 11) previous lines of anticancer therapy for metastatic disease; 78 patients (60.5%) had received 3 or more previous lines, and 75% of patients with NSCLC and 98% with colorectal cancer had received 2 or more previous lines of therapy. Of the 59 patients with NSCLC, 53 (89.8%) were current or former smokers, 53 (89.8%) had received anti–programmed cell death protein 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) therapies, and all (100%) had received platinum-based chemotherapy.

**SAFETY**

No dose-limiting toxic effects were observed. No treatment-related adverse events resulted in death. Adverse events of any cause that occurred during treatment were reported in 125 patients (96.9%) (Table 2). The most common events were diarrhea (in 38 patients [29.5%]), fatigue (in 30 [23.3%]), and nausea (in 27 [20.9%]). Adverse events of grade 3 or higher that occurred during treatment were reported in 68 patients (52.7%).
A total of 73 patients (56.6%) had treatment-related adverse events of any grade; 2 patients (1.6%) had serious adverse events. A total of 15 patients (11.6%) reported grade 3 or 4 treatment-related adverse events. Grade 3 treatment-related adverse events included an increase in the alanine aminotransferase (ALT) level (in 4.7% of the patients), diarrhea (in 3.9%), anemia (in 3.1%), an increase in the aspartate aminotransferase (AST) level (in 2.3%), an increase in the blood alkaline phosphatase level (in 1.6%), hepatitis (in 0.8%), a decrease in lymphocyte count (in 0.8%), an increase in the gamma-glutamyltransferase level (in 0.8%), and hyponatremia (in 0.8%). One patient (0.8%) reported a grade 4 treatment-related elevation of ALT, which returned to the baseline level after reduction in the dose of sotorasib and tapering of glucocorticoids, and 1 patient

### Table 1. Patient Characteristics at Baseline.†

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort 1 180 mg (N = 6)</th>
<th>Cohort 2 360 mg (N = 27)</th>
<th>Cohort 3 720 mg (N = 11)</th>
<th>Cohort 4 960 mg (N = 85)</th>
<th>All Patients (N = 129)</th>
</tr>
</thead>
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<tr>
<td>Median age (range) — yr</td>
<td>60 (54–75)</td>
<td>60 (33–78)</td>
<td>67 (40–76)</td>
<td>64 (37–83)</td>
<td>62 (33–83)</td>
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<tr>
<td>Female sex — no. (%)</td>
<td>3 (50.0)</td>
<td>20 (74.1)</td>
<td>6 (54.5)</td>
<td>37 (43.5)</td>
<td>66 (51.2)</td>
</tr>
<tr>
<td>Race — no. (%) †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (100.0)</td>
<td>22 (81.5)</td>
<td>9 (81.8)</td>
<td>61 (71.8)</td>
<td>98 (76.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (3.7)</td>
<td>0</td>
<td>15 (17.6)</td>
<td>16 (12.4)</td>
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<tr>
<td>Black</td>
<td>0</td>
<td>1 (3.7)</td>
<td>1 (9.1)</td>
<td>4 (4.7)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (11.1)</td>
<td>1 (9.1)</td>
<td>5 (5.9)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td>Primary tumor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC — no. (%)</td>
<td>3 (50.0)</td>
<td>16 (59.3)</td>
<td>6 (54.5)</td>
<td>34 (40.0)</td>
<td>59 (45.7)</td>
</tr>
<tr>
<td>Current or former smoker — no./total no. (%)</td>
<td>3/3 (100.0)</td>
<td>15/16 (93.8)</td>
<td>5/6 (83.3)</td>
<td>30/34 (88.2)</td>
<td>53/59 (89.8)</td>
</tr>
<tr>
<td>Female sex — no./total no. (%)</td>
<td>2/3 (66.7)</td>
<td>11/16 (68.8)</td>
<td>4/6 (66.7)</td>
<td>18/34 (52.9)</td>
<td>35/59 (59.3)</td>
</tr>
<tr>
<td>Previous anti–PD-1 or anti–PD-L1 therapies — no./total no. (%)</td>
<td>3/3 (100.0)</td>
<td>16/16 (100.0)</td>
<td>6/6 (100.0)</td>
<td>28/34 (82.4)</td>
<td>53/59 (89.8)</td>
</tr>
<tr>
<td>Previous platinum-based chemotherapy — no./total no. (%)</td>
<td>3/3 (100.0)</td>
<td>16/16 (100.0)</td>
<td>6/6 (100.0)</td>
<td>34/34 (100.0)</td>
<td>59/59 (100.0)</td>
</tr>
<tr>
<td>Colorectal cancer — no. (%)</td>
<td>3 (50.0)</td>
<td>10 (37.0)</td>
<td>4 (36.4)</td>
<td>25 (29.4)</td>
<td>42 (32.6)</td>
</tr>
<tr>
<td>Other — no. (%)</td>
<td>0</td>
<td>1 (3.7)</td>
<td>1 (9.1)</td>
<td>26 (30.6)</td>
<td>28 (21.7)</td>
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<td>ECOG performance status — no. (%)‡</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (33.3)</td>
<td>6 (22.2)</td>
<td>1 (9.1)</td>
<td>26 (30.6)</td>
<td>35 (27.1)</td>
</tr>
<tr>
<td>1</td>
<td>3 (50.0)</td>
<td>21 (77.8)</td>
<td>9 (81.8)</td>
<td>54 (63.5)</td>
<td>87 (67.4)</td>
</tr>
<tr>
<td>2</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (9.1)</td>
<td>5 (5.9)</td>
<td>7 (5.4)</td>
</tr>
<tr>
<td>Previous anticancer systemic therapy for metastatic disease — no. (%)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1 (3.7)</td>
<td>1 (9.1)</td>
<td>15 (17.6)</td>
<td>17 (13.2)</td>
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<tr>
<td>2</td>
<td>2 (33.3)</td>
<td>5 (18.5)</td>
<td>1 (9.1)</td>
<td>24 (28.2)</td>
<td>32 (24.8)</td>
</tr>
<tr>
<td>3</td>
<td>2 (33.3)</td>
<td>4 (14.8)</td>
<td>4 (36.4)</td>
<td>15 (17.6)</td>
<td>25 (19.4)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2 (33.3)</td>
<td>17 (63.0)</td>
<td>5 (45.5)</td>
<td>29 (34.1)</td>
<td>53 (41.1)</td>
</tr>
<tr>
<td>No. of previous anticancer systemic therapies for metastatic diseases — median (range)</td>
<td>3.0 (2.0–5.0)</td>
<td>4.0 (1.0–6.0)</td>
<td>3.0 (1.0–11.0)</td>
<td>3.0 (0–10.0)</td>
<td>3.0 (0–11.0)</td>
</tr>
</tbody>
</table>

† Percentages may not total 100 because of rounding. NSCLC denotes non–small-cell lung cancer, PD-1 programmed cell death protein 1, and PD-L1 programmed death ligand 1.
‡ Race was determined by trial investigators.
§ Eastern Cooperative Oncology Group (ECOG) performance status is measured on a 5-point scale, with higher numbers indicating greater disability.
¶ Adjuvant therapy could be counted if relapse occurred less than 6 months after completion of the therapy.
Adverse events of any cause that occurred during treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
<th>Grade ≥4</th>
<th>Grade 5: Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>125 (96.9)</td>
<td>68 (52.7)</td>
<td>26 (20.2)</td>
<td>22 (17.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>58 (45.0)</td>
<td>51 (39.5)</td>
<td>25 (19.4)</td>
<td>22 (17.1)</td>
</tr>
<tr>
<td>Resulting in discontinuation of treatment*</td>
<td>9 (7.0)</td>
<td>9 (7.0)</td>
<td>4 (3.1)</td>
<td>4 (3.1)</td>
</tr>
</tbody>
</table>

Adverse events of any cause that occurred during treatment in ≥10% of patients

- **Diarrhea**: 38 (29.5) Any Grade, 5 (3.9) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Fatigue**: 30 (23.3) Any Grade, 3 (2.3) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Nausea**: 27 (20.9) Any Grade, 2 (1.6) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Vomiting**: 23 (17.8) Any Grade, 5 (3.9) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Abdominal pain**: 23 (17.8) Any Grade, 4 (3.1) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Dyspnea**: 21 (16.3) Any Grade, 3 (2.3) Grade ≥3, 1 (0.8) Grade ≥4, 1 (0.8) Grade 5: Fatal
- **Cough**: 20 (15.5) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Back pain**: 19 (14.7) Any Grade, 2 (1.6) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Decreased appetite**: 19 (14.7) Any Grade, 1 (0.8) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Headache**: 18 (14.0) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Aspartate aminotransferase increase**: 17 (13.2) Any Grade, 3 (2.3) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Anemia**: 17 (13.2) Any Grade, 6 (4.7) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Dizziness**: 17 (13.2) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Alanine aminotransferase increase**: 15 (11.6) Any Grade, 6 (4.7) Grade ≥3, 1 (0.8) Grade ≥4, 0 Grade 5: Fatal
- **Constipation**: 15 (11.6) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Pyrexia**: 14 (10.9) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Insomnia**: 14 (10.9) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Myalgia**: 13 (10.1) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Peripheral edema**: 13 (10.1) Any Grade, 0 Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal
- **Arthralgia**: 13 (10.1) Any Grade, 2 (1.6) Grade ≥3, 0 Grade ≥4, 0 Grade 5: Fatal

* Among the 22 patients who had fatal adverse events of any cause during treatment, 4 patients discontinued treatment directly because of those adverse events. The remaining patients discontinued treatment before the fatal adverse event occurred, and therefore the fatal adverse event was not recorded as the reason for treatment discontinuation for those patients.

Inhibition in Advanced Solid Tumors

(0.8%) discontinued treatment because of grade 3 treatment-related increases in ALT and AST levels. (Full lists of adverse events are provided in Tables S2 and S3.)

**Pharmacokinetics**

The pharmacokinetic profile of sotorasib administered at a dose of 960 mg daily is shown in Figure S3. The maximum plasma concentration was 7.50 µg per milliliter (coefficient of variation, 98.3%), with a median time to maximum plasma concentration of 2.0 hours (range, 0.3 to 6.0). The 24-hour area under the curve was 65.3 hours × micrograms per milliliter (coefficient of variation, 81.7%). The mean (±SD) elimination half-life was 5.5±1.8 hours. The dose of 960 mg administered daily was identified as the dose for the expansion cohort.

**Efficacy**

**NSCLC**

The median follow-up time in the subgroup with NSCLC was 11.7 months (range, 4.8 to 21.2). Of 59 patients with NSCLC, 19 had a confirmed partial response, and 33 had stable disease; thus, 32.2% of the patients (95% confidence interval [CI], 20.62 to 45.64) had a confirmed response, and 88.1% (95% CI, 77.07 to 95.09) had disease.
A Change from Baseline in Tumor Burden

Planned Dose: 180 mg 360 mg 720 mg 960 mg

B Effect of Sotorasib in a Patient with NSCLC

Baseline

Week 10

Week 16

Lymph Node Cervical
Deep Lower Right

Long axis: 19.1 mm
Short axis: 16.1 mm
Too small

Long axis: 5.0 mm
Short axis: 5.0 mm
Too small

Long axis: 39.3 mm
Short axis: 30.2 mm

Mediastinum

Long axis: 30.8 mm
Short axis: 17.9 mm

Long axis: 28.0 mm
Short axis: 12.8 mm
Among the 34 patients in the 960-mg cohort, 35.3% (12 patients) had a confirmed response and 91.2% (31 patients) had disease control. Responses were seen across all dose levels. One patient with a partial response had a near-complete response, with 100% reduction in the target lesions but persistent nontarget lesions (Fig. 1A). CT images of patients with NSCLC are shown in Figure 1B and Figure S4.

Tumor shrinkage of any magnitude was observed in 42 patients (71.2%) at the first assessment, performed at week 6. The median time to response was 1.4 months (range, 1.1 to 9.5). The median duration of response was 10.9 months (range, 1.1+ to 13.6, with + indicating that the value includes patient data that were censored at data cutoff); in 10 of the 19 patients with a response, the response was ongoing as of the data cutoff date (Fig. 2A and 2B). Among patients who had a response, the duration of response was at least 3 months in 11 patients (57.9%), at least 6 months in 6 patients (31.6%), and at least 9 months in 5 patients (26.3%). The median duration of stable disease was 4.0 months (range, 1.4 to 10.9+). As of the data cutoff date, 14 patients (23.7%) were continuing treatment (Fig. 2A). The median progression-free survival for all patients with NSCLC was 6.3 months (range, 0.0+ to 14.9) (Fig. 2C).

**Colorectal Cancer**

The median follow-up time in the subgroup with colorectal cancer was 12.8 months (range, 9.0 to 20.9). A confirmed partial response was observed in 3 of 42 patients (7.1%) with colorectal cancer, with one response ongoing as of the date of data cutoff (Table 3 and Fig. S5). The three responses lasted for 4.9, 6.9, and 9.9+ months, respectively. A total of 28 patients (66.7%) had stable disease; thus, 73.8% of the 42 patients had disease control. The median duration of stable disease was 5.4 months (range, 2.5+ to 11.1+). Among the 25 patients in the cohort that received 960 mg daily, 12.0% (3 patients) had a confirmed objective response and 80.0% (20 patients) had disease control. Three patients, including 1 patient with an objective response, were continuing treatment as of the data cutoff date. The median progression-free survival for all patients with colorectal cancer was 4.0 months (range, 0.0+ to 11.1+).
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A Time to Response, Disease Progression, and Treatment Duration

B Change in Tumor Burden over Time

C Progression-free Survival

Median progression-free survival, 6.3 mo (95% CI, 3.9–7.8)
Despite the fact that the cancers in our patient population had been refractory to previous treatments, 32.2% of the patients with NSCLC had a confirmed response, and the majority (88.1%) had disease control for a few months or more with sotorasib, leading to a median progression-free survival of 6.3 months. Similarly, most patients in the colorectal cancer subgroup had disease control, with a median duration of stable disease of 5.4 months and median progression-free survival of 4.0 months. With current therapies, approximately 9 to 18% of patients with NSCLC have a response to second- or third-line therapies, with median progression-free survival of 2.5 to 4.0 months, and approximately 1.0 to 1.6% of patients with previously treated colorectal cancer have a response to standard therapies, with median progression-free survival of 1.9 to 2.1 months. Thus, the treatment outcome in patients with NSCLC or colorectal cancer similar to patients in our study is generally poor. Responses and disease stability associated with sotorasib in these patients are encouraging.

In the NSCLC subgroup, the fact that 32.2% of the patients across all dose levels and 35.3% at the target dose of 960 mg had a response was particularly promising. Rapid responses to sotorasib were seen at the first assessment, performed at week 6, and responses were durable and ongoing at a median follow-up of nearly a year. Nine of the 19 patients who had a partial response, as well as 5 patients who had stable disease, were still receiving treatment as of the data cutoff date. The median duration of response among all patients who had a response was 10.9 months. Nevertheless, some patients had disease progression shortly after an initial response. Twenty-four patients (40.7%) had at least one assessment of partial response according to RECIST 1.1 criteria, and 19 (32.2%) had a confirmed partial response. Of the 5 patients who had a partial response that was never confirmed, 1 had long-term stable disease, whereas 4 had rapid disease progression (2 in target lesions and 2 in nontarget lesions). Rapid progression might suggest a high degree of tumor heterogeneity in these patients with late-stage disease or an early adaptation to treatment, as reported in a preclinical study with a precursor inhibitor. The molecular signature of the tumors from patient subgroups with distinct response patterns awaits further investigation.

Other Tumor Types

Among patients with other tumor types, 4 had a confirmed partial response (1 with pancreatic cancer, 1 with endometrial cancer, 1 with appendiceal cancer, and 1 with melanoma), 17 had stable disease, and 4 had progressive disease. The four responses lasted for 4.4, 6.9+, 2.7, and 5.6 months, respectively. Five patients were continuing treatment as of the data cutoff date (Table 3 and Fig. S6).

**DISCUSSION**

Since its discovery in 1982, the mutated KRAS protein has been deemed “undruggable” owing to its high affinity for GTP and lack of accessible binding pockets, as well as toxic effects associated with other KRAS-targeting approaches. However, the discovery by Ostrem et al. of compounds that covalently bind to the switch II pocket of KRASG12C established the foundation for the development of inhibitors suitable for clinical testing. Subsequently, Lito et al. and Patricelli et al. established the mechanism of KRASG12C inhibition (i.e., trapping the oncoprotein in its inactive state by blocking reactivation through nucleotide exchange). Sotorasib inhibits KRASG12C by a similar mechanism, but its potency and selectivity were enhanced through the optimization of novel interactions with a previously unexploited surface groove. The KRASG12C inhibitor sotorasib has the potential to address the unmet need for treatment of tumors harboring the KRAS p.G12C mutation. Here, we evaluated the safety and clinical activity associated with sotorasib in this full phase 1 cohort receiving daily monotherapy. Results showed that a KRASG12C inhibitor produced durable clinical benefit with mainly low-grade gastrointestinal and hepatic toxic effects in a heavily pretreated population.

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**Figure 2 (facing page). Efficacy of Sotorasib in Patients with NSCLC.**

Panel A shows the time to response, the duration of treatment, and patient status by the data cutoff date for all 59 patients with NSCLC, according to the dose of sotorasib. Panel B shows the change in tumor burden over time in 57 of 59 patients with NSCLC for whom postbaseline tumor data were available. Panel C shows a Kaplan–Meier curve of progression-free survival for all 59 patients with NSCLC.
The inconsistency in tumor response between NSCLC and colorectal cancer suggests either that KRAS p.G12C is not the dominant oncogenic driver for colorectal cancer or that other pathways, such as Wnt or EGFR pathways, mediate oncogenic signaling beyond KRAS, a hypothesis supported by recently published preclinical evidence.28-30 Therefore, combining sotorasib with therapies that block additional pathways may be a viable option, as shown by studies in BRAF V600E–mutant colorectal cancer.31-33 Patients who have colorectal cancer with RAS mutations do not benefit from standard anti-EGFR combination therapies.34 These patients have poorer progression-free survival and overall survival than those with wild-type KRAS.35,36 Considering the poor prognosis in patients with metastatic disease and the lack of effective treatments in this population, controlling the tumor burden with an oral therapy for a few months may be meaningful.

Sotorasib is a covalent inhibitor that rapidly occupies KRASG12C and extinguishes its activity. The turnover rate of KRASG12C is relatively slow (with a half-life of approximately 22 hours).20 Therefore, a relatively brief exposure to sotorasib at concentrations sufficient to completely occupy the existing pool of KRASG12C would be predicted to completely inhibit the protein for approximately 24 hours. In a finding consistent with this hypothesis, in multiple KRAS p.G12C in vivo tumor models, plasma exposures to sotorasib above the 90% maximal inhibitory concentration (IC90) of the cellular ERK phosphorylation assay for 4 hours resulted in maximum suppression of ERK phosphorylation for at least 24 hours and maximum tumor regression.20 The observed mean exposure to sotorasib at a dose of 960 mg markedly exceeds this same threshold for approximately 24 hours and is therefore predicted to achieve near total occupancy and inhibition of KRASG12C over the entire dosing interval. The response with a daily dose of 960 mg appeared to be higher than that across all doses combined. The 960-mg daily dose was advanced to later confirmatory trials.

To date, no dose-limiting toxic effects have been observed with sotorasib, even with extended treatment. The majority of patients had some toxic effects, although they were mainly of low-grade. Diarrhea, nausea, vomiting, fatigue, and elevations of aminotransferase levels were the most common adverse events, but few patients stopped treatment because of toxic effects.

We found that sotorasib showed promising anticancer activity in patients with heavily pre-treated KRAS p.G12C mutant solid tumors. Trials evaluating sotorasib as monotherapy or in combination with various agents in patients with NSCLC or other solid tumors are under way (ClinicalTrials.gov numbers, NCT04303780 and NCT04185883).

APPENDIX

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