Title
KRASG12C Inhibition with Sotorasib in Advanced Solid Tumors

Journal
New England Journal of Medicine, 383(13)

ISSN
0028-4793

Authors
Hong, David S
Fakih, Marwan G
Strickler, John H
et al.

Publication Date
2020-09-24

DOI
10.1056/nejmoa1917239

Peer reviewed

HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2021 March 24.

Published in final edited form as:

N Engl J Med. 2020 September 24; 383(13): 1207–1217. doi:10.1056/NEJMoa1917239.

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong[#],
Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, University of Texas M.D. Anderson Cancer Center, Houston

M.G. Fakih[#],
Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California

J.H. Strickler,
Duke University Medical Center, Durham, NC

J. Desai,
Royal Melbourne Hospital/Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

G.A. Durm,
Department of Medicine, Division of Hematology/Oncology, Indiana University School of Medicine, Indianapolis

G.I. Shapiro,
Dana-Farber Cancer Institute, Harvard Medical School, Boston

G.S. Falchook,
Sarah Cannon Research Institute at HealthONE, Denver

T.J. Price,
Queen Elizabeth Hospital and University of Adelaide, Woodville South, SA, Australia

A. Sacher,
Princess Margaret Cancer Centre, University Health Network, Toronto

C.S. Denlinger,
Fox Chase Cancer Center, Philadelphia

Y.-J. Bang,
Seoul National University College of Medicine, Seoul, South Korea

G.K. Dy,
Roswell Park Cancer Institute, Buffalo, New York

J.C. Krauss,
University of Michigan, Ann Arbor

Y. Kuboki,

Address reprint requests to Dr. Hong at the Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, or at dshong@mdanderson.org; or to Dr. Li at the Thoracic Oncology and Early Drug Development Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY 10065, or at lib1@mskcc.org.

Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan

J.C. Kuo,
Scientia Clinical Research, Randwick, NSW, Australia

A.L. Coveler,
Department of Medicine, Division of Oncology, University of Washington, Seattle

K. Park,
Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

T.W. Kim,
Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

F. Barlesi,
Aix Marseille University, Centre National de la Recherche Scientifique, INSERM, Centre de Recherche en Cancérologie de Marseille, Assistance Publique-Hôpitaux de Marseille, Marseille, France

P.N. Munster,
University of California, San Francisco, San Francisco, California

S.S. Ramalingam,
Winship Cancer Institute of Emory University, Atlanta

T.F. Burns,
University of Pittsburgh Medical Center Hillman Cancer Center, University of Pittsburgh, Pittsburgh

F. Meric-Bernstam,
Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, University of Texas M.D. Anderson Cancer Center, Houston

H. Henary,
Amgen, Thousand Oaks, California

J. Ngang,
Amgen, Thousand Oaks, California

G. Ngarmchamnanrith,
Amgen, Thousand Oaks, California

J. Kim,
Amgen, Thousand Oaks, California

B.E. Houk,
Amgen, Thousand Oaks, California

J. Canon,
Amgen, Thousand Oaks, California

J.R. Lipford,

Amgen, Thousand Oaks, California

G. Friberg,
Amgen, Thousand Oaks, California

P. Lito[#],
Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, New York

R. Govindan[#],
Alvin J. Siteman Cancer Center at Washington University School of Medicine, St. Louis

B.T. Li[#]
Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, New York

[#] These authors contributed equally to this work.

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 $KRAS^{G12C}$.

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.)

KIRSTEN RAT SARCOMA VIRAL ONCOGENE homologue (*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.[1] *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.[2–12]

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.[8,13–15] 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.[16,17] 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 conformation of KRAS and has been exploited to establish covalent inhibitors of $KRAS^{G12C}$.[16,18,19]

Sotorasib (AMG 510) is a small molecule that specifically and irreversibly inhibits $KRAS^{G12C}$ 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).[20] The inhibitor traps $KRAS^{G12C}$ in the inactive GDP-bound state by a mechanism similar to that described for other $KRAS^{G12C}$ inhibitors.[18] 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.[20]

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.

METHODS

PATIENTS

Eligibility criteria included an age of 18 years or older; histologically confirmed, locally advanced or metastatic cancer with the *KRAS* p.G12C mutation identified by local molecular testing on tumor tissues; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability); measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; for patients with NSCLC, previous platinum-based combination therapy, targeted therapies, or both; for patients with colorectal cancer, at least two previous lines of systemic therapy for metastatic disease (patients who have colorectal cancer characterized by high microsatellite instability must have received at least nivolumab or pembrolizumab if clinically applicable); and for patients with solid tumors other than NSCLC or colorectal cancer, at least one previous line of systemic therapy.

Key exclusion criteria were untreated active brain metastases, systemic antitumor therapy within 28 days before initiation of sotorasib therapy, and radiation therapy within 2 weeks before initiation of sotorasib therapy. Full eligibility and exclusion criteria are provided in the protocol, available at NEJM.org.

TRIAL DESIGN

We conducted a phase 1, multicenter, open-label trial of sotorasib in patients with advanced solid tumors harboring the *KRAS* p.G12C mutation. The trial consisted of dose escalation and expansion cohorts. Sotorasib was administered orally once daily. The planned dose levels for the escalation cohorts (1 through 4) were 180, 360, 720, and 960 mg, with two to four patients receiving treatment in each cohort. Each treatment cycle was 21 days. Administration of sotorasib continued until occurrence of progressive disease, development of unacceptable side effects, withdrawal of consent, or end of study. A two-parameter Bayesian logistics-regression model was used to guide dose escalation. Intrapatient dose escalations were permitted for cohorts 1 through 3, and additional patients could be enrolled to a particular cohort once a dose for that cohort was deemed safe. The expansion cohort opened once the recommended phase 2 dose had been determined.

STUDY OVERSIGHT

The protocol and amendments were approved by the institutional review board or ethics committee at each participating site. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written 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 (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 control (Table 3 and Fig. 1A). 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+).

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.[21,22] However, the discovery by Ostrem et al. of compounds that covalently bind to the switch II pocket of $KRAS^{G12C}$ established the foundation for the development of inhibitors suitable for clinical testing.[16] Subsequently, Lito et al. and Patricelli et al. established the mechanism of $KRAS^{G12C}$ inhibition (i.e., trapping the oncoprotein in its inactive state by blocking reactivation through nucleotide exchange).[18,19] Sotorasib inhibits $KRAS^{G12C}$ by a similar mechanism, but its potency and selectivity were enhanced through the optimization of novel interactions with a previously unexploited surface groove.[20] The $KRAS^{G12C}$ inhibitor sotorasib has the potential to address the unmet need for treatment of tumors harboring the *KRAS* p.G12C mutation.[16,18] Here, we evaluated the safety and clinical activity associated with sotorasib in this full phase 1 cohort receiving daily monotherapy. Results showed that a $KRAS^{G12C}$ inhibitor produced durable clinical benefit with mainly low-grade gastrointestinal and hepatic toxic effects in a heavily pretreated population.

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,[23,24] 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.[25–27] 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.[28] The molecular signature of the tumors from patient subgroups with distinct response patterns awaits further investigation.

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 $KRAS^{G12C}$ and extinguishes its activity. The turnover rate of $KRAS^{G12C}$ 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 $KRAS^{G12C}$ 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 (IC_{90}) 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 $KRAS^{G12C}$ 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 pretreated *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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by Amgen; also supported in part by a Cancer Prevention Research Institute of Texas Precision Oncology Decision Support Core grant (RP150535)and Comprehensive Cancer Center Core Grants (P30 CA016672 and P30 CA008748) at Memorial Sloan Kettering Cancer Center from the National Institutes of Health (NIH). Dr. Denlinger is supported in part by a Comprehensive Cancer Center Core Grant (P30 CA006927) at Fox Chase Cancer Center from the NIH, and Dr. Lito is supported in part by grants (1R01CA23074501 and 1R01CA23026701A1) from the NIH National Cancer Institute, by the Pew Charitable Trusts, and by the Damon Runyon Cancer Research Foundation.

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 for participating in the trial and their families, as well as Melissa Farley and Peter Alexander for study management, Bob Dawson and Brian Lanman for graphics assistance, Jonathan Aspe and Noella Vang for operational planning assistance, and Yang Li for medical writing assistance (all of Amgen).

REFERENCES

1. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell 2017; 170: 17–33. [PubMed: 28666118]
2. Nadal E, Chen G, Prensner JR, et al. KRAS-G12C mutation is associated with poor outcome in surgically resected lung adenocarcinoma. J Thorac Oncol 2014; 9: 1513–22. [PubMed: 25170638]
3. Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res 2007; 13: 2890–6. [PubMed: 17504988]
4. Fiala O, Buchler T, Mohelnikova-Duchonova B, et al. G12V and G12A KRAS mutations are associated with poor outcome in patients with metastatic colorectal cancer treated with bevacizumab. Tumour Biol 2016; 37: 6823–30. [PubMed: 26662311]
5. Lièvre A, Bachet J-B, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006; 66: 3992–5. [PubMed: 16618717]
6. McCormick F K-Ras protein as a drug target. J Mol Med (Berl) 2016; 94: 253–8. [PubMed: 26960760]
7. Jones RP, Sutton PA, Evans JP, et al. Specific mutations in KRAS codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer. Br J Cancer 2017; 116: 923–9. [PubMed: 28208157]
8. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: mission possible? Nat Rev Drug Discov 2014;13:828–51. [PubMed: 25323927]
9. Ostrem JML, Shokat KM. Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. Nat Rev Drug Discov 2016; 15: 771–85. [PubMed: 27469033]
10. Suzawa K, Offin M, Lu D, et al. Activation of KRAS mediates resistance to targeted therapy in MET exon 14-mutant non-small cell lung cancer. Clin Cancer Res 2019;25:1248–60. [PubMed: 30352902]

11. Clarke PA, Roe T, Swabey K, et al. Dissecting mechanisms of resistance to targeted drug combination therapy in human colorectal cancer. Oncogene 2019; 38: 5076–90. [PubMed: 30905967]
12. Del Re M, Rofi E, Restante G, et al. Implications of KRAS mutations in acquired resistance to treatment in NSCLC. Oncotarget 2017;9:6630–43. [PubMed: 29464099]
13. Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. Cancer Genet 2016;209:195–8. [PubMed: 27068338]
14. Neumann J, Zeindl-Eberhart E, Kirchner T, Jung A. Frequency and type of KRAS mutations in routine diagnostic analysis of metastatic colorectal cancer. Pathol Res Pract 2009; 205: 858–62. [PubMed: 19679400]
15. Ouerhani S, Elgaaied ABA. The mutational spectrum of HRAS, KRAS, NRAS and FGFR3 genes in bladder cancer. Cancer Biomark 2011–2012;10:259–66.
16. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature 2013; 503: 548–51. [PubMed: 24256730]
17. Kargbo RB. Inhibitors of G12C mutant Ras proteins for the treatment of cancers. ACS Med Chem Lett 2018; 10: 10–1. [PubMed: 30655937]
18. Lito P, Solomon M, Li L-S, Hansen R, Rosen N. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science 2016;351:604–8. [PubMed: 26841430]
19. Patricelli MP, Janes MR, Li L-S, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. Cancer Discov 2016; 6: 316–29. [PubMed: 26739882]
20. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 2019; 575:217–23. [PubMed: 31666701]
21. Forbes SA, Bindal N, Bamford S, et al. COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. Nucleic Acids Res 2011; 39(Database issue):D945–D950. [PubMed: 20952405]
22. John J, Sohmen R, Feuerstein J, Linke R, Wittinghofer A, Goody RS. Kinetics of interaction of nucleotides with nucleotidefree H-ras p21. Biochemistry 1990; 29: 6058–65. [PubMed: 2200519]
23. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387:1540–50. [PubMed: 26712084]
24. Hayashi H, Okamoto I, Taguri M, Morita S, Nakagawa K. Postprogression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. Clin Lung Cancer 2013;14:261–6. [PubMed: 23107465]
25. Van Cutsem E, Mayer RJ, Laurent S, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. Eur J Cancer 2018; 90: 63–72. [PubMed: 29274618]
26. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909–19. [PubMed: 25970050]
27. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303–12. [PubMed: 23177514]
28. Xue JY, Zhao Y, Aronowitz J, et al. Rapid non-uniform adaptation to conformation-specific KRAS(G12C) inhibition. Nature 2020;577:421–5. [PubMed: 31915379]
29. Lee S-K, Jeong W-J, Cho Y-H, et al. β-Catenin-RAS interaction serves as a molecular switch for RAS degradation via GSK3β. EMBO Rep 2018; 19(12): e46060. [PubMed: 30413483]
30. Amodio V, Yaeger R, Arcella P, et al. EGFR blockade reverts resistance to $KRAS^{G12C}$ inhibition in colorectal cancer. Cancer Discov 2020;10:1129–39. [PubMed: 32430388]
31. Hong DS, Morris VK, El Osta B, et al. Phase IB study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with BRAFV600E mutation. Cancer Discov 2016;6:1352–65. [PubMed: 27729313]
32. Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with *BRAF* V600E-mutant metastatic colorectal cancer: safety lead-in results

from the phase III BEACON colorectal cancer study. J Clin Oncol 2019;37:1460–9. [PubMed: 30892987]

33. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. N Engl J Med 2019; 381: 1632–43. [PubMed: 31566309]
34. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26: 1626–34. [PubMed: 18316791]
35. Modest DP, Ricard I, Heinemann V, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol 2016; 27: 1746–53. [PubMed: 27358379]
36. Peeters M, Douillard J-Y, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. J Clin Oncol 2013; 31: 759–65. [PubMed: 23182985]

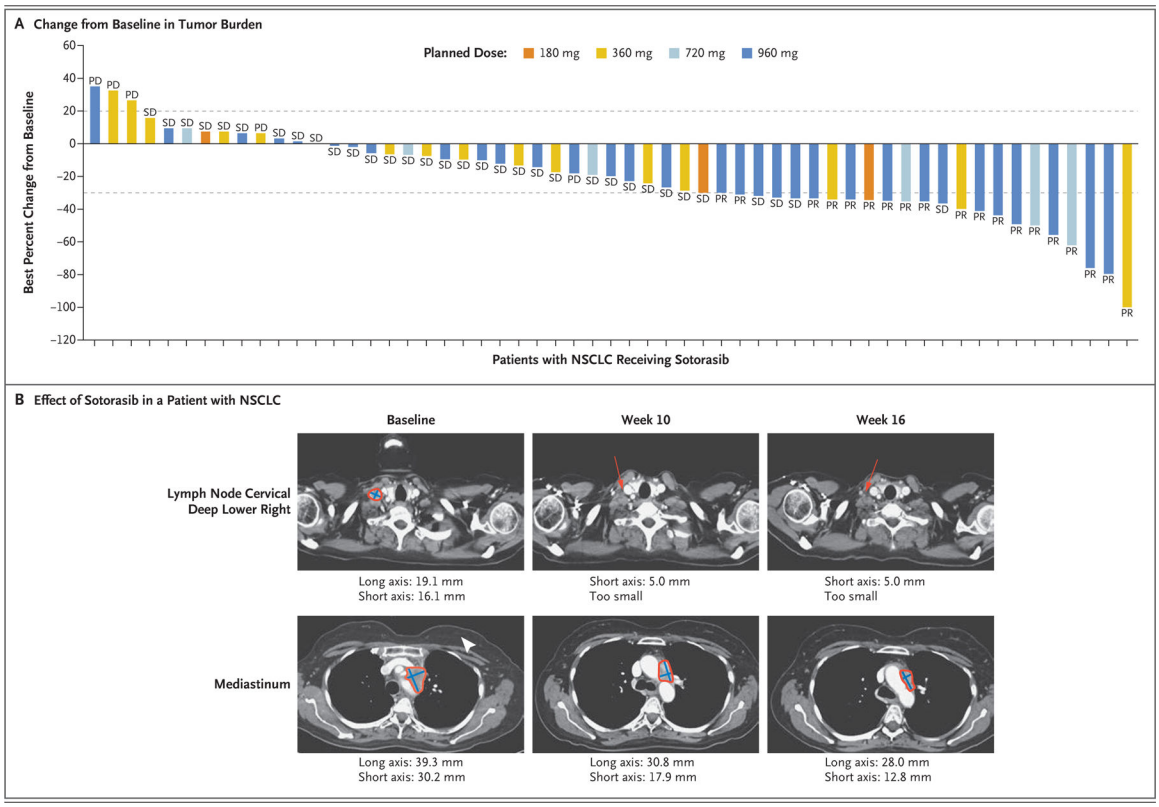

Figure 1. Change from Baseline in Tumor Burden in Patients with NSCLC Receiving Sotorasib.

Panel A shows the best percent change from baseline in tumor burden (defined by the sum of the longest diameters- of all target lesions) in 57 of 59 patients with NSCLC for whom postbaseline tumor data were available. PD denotes progressive disease, PR partial response, and SD stable disease. Panel B shows computed tomographic scans of two target lesions from a 55-year-old female patient with NSCLC, at baseline and after 10 and 16 weeks of treatment with sotorasib. The patient had a partial response. Scans and the tumor measurements are from independent central radiologic review.

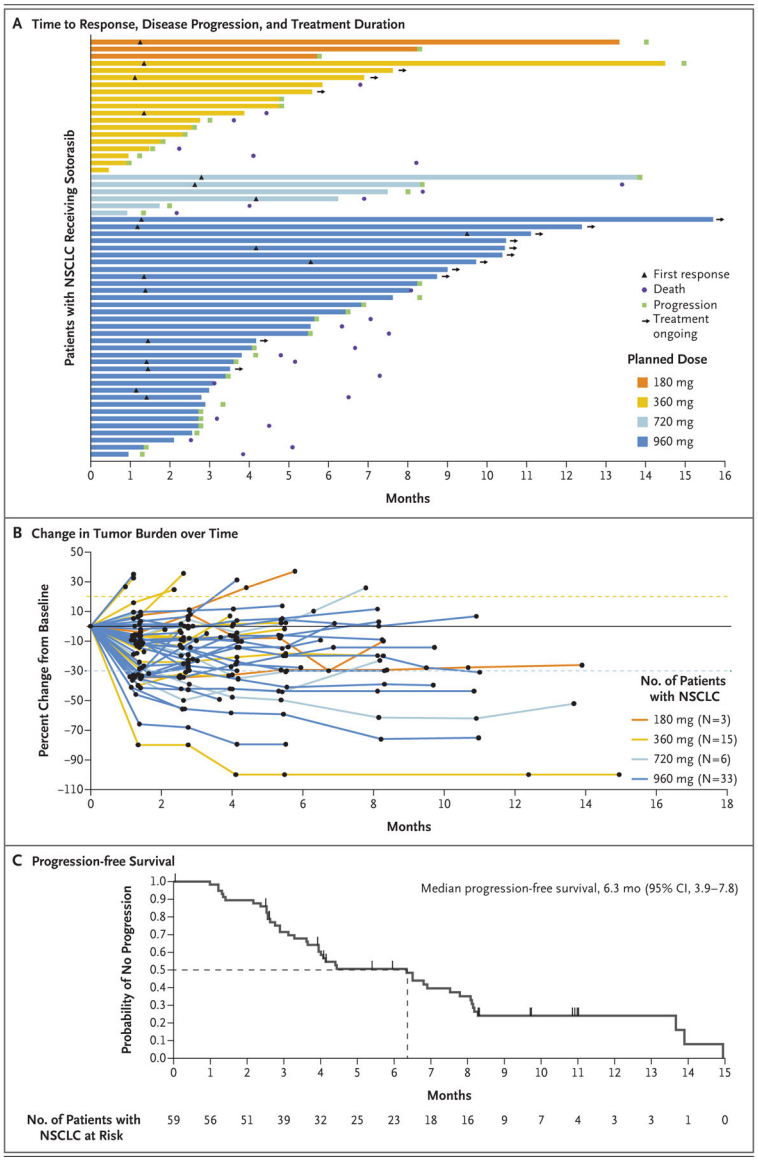

Figure 2. Efficacy of Sotorasib in Patients with NSCLC.

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 Kaplan–Meier curve of progression-free survival for all 59 patients with NSCLC.

Table 1.

Patient Characteristics at Baseline.*

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

*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.

Table 2.

Adverse Events in All 129 Patients.

Events	Any Grade	Grade ≥3	Grade ≥4	Grade 5: Fatal
	number (percent)			
Adverse events of any cause that occurred during treatment				
Any	125 (96.9)	68 (52.7)	26 (20.2)	22 (17.1)
Serious	58 (45.0)	51 (39.5)	25 (19.4)	22 (17.1)
Resulting in discontinuation of treatment*	9 (7.0)	9 (7.0)	4 (3.1)	4 (3.1)
Adverse events of any cause that occurred during treatment in ≥10% of patients				
Diarrhea	38 (29.5)	5 (3.9)	0	0
Fatigue	30 (23.3)	3 (2.3)	0	0
Nausea	27 (20.9)	2 (1.6)	0	0
Vomiting	23 (17.8)	5 (3.9)	0	0
Abdominal pain	23 (17.8)	4 (3.1)	0	0
Dyspnea	21 (16.3)	3 (2.3)	1 (0.8)	1 (0.8)
Cough	20 (15.5)	0	0	0
Back pain	19 (14.7)	2 (1.6)	0	0
Decreased appetite	19 (14.7)	1 (0.8)	0	0
Headache	18 (14.0)	0	0	0
Aspartate aminotransferase increase	17 (13.2)	3 (2.3)	0	0
Anemia	17 (13.2)	6 (4.7)	0	0
Dizziness	17 (13.2)	0	0	0
Alanine aminotransferase increase	15 (11.6)	6 (4.7)	1 (0.8)	0
Constipation	15 (11.6)	0	0	0
Pyrexia	14 (10.9)	0	0	0
Insomnia	14 (10.9)	0	0	0
Myalgia	13 (10.1)	0	0	0
Peripheral edema	13 (10.1)	0	0	0
Arthralgia	13 (10.1)	2 (1.6)	0	0

*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.

Table 3.

Efficacy of Sotorasib in All Tumor Types.

	NSCLC (N = 59)	Colorectal Cancer (N = 42)	Other (N = 28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment *	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI) †	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI) ‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

* One patient with NSCLC withdrew consent before tumor assessment. One patient with colorectal cancer and 2 patients with other tumor types had clinical progression.

† Objective response was defined as a complete or partial response.

‡ Disease control was defined as a complete response, a partial response, or stable disease.