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Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

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Abstract

BACKGROUND—*KRAS* p.G12C mutation occurs in approximately 1 to 2% of pancreatic cancers. The safety and efficacy of sotorasib, a *KRAS* G12C inhibitor, in previously treated patients with *KRAS* p.G12C–mutated pancreatic cancer are unknown.

METHODS—We conducted a single-group, phase 1–2 trial to assess the safety and efficacy of sotorasib treatment in patients with *KRAS* p.G12C–mutated pancreatic cancer who had received at least one previous systemic therapy. The primary objective of phase 1 was to assess safety and to identify the recommended dose for phase 2. In phase 2, patients received sotorasib at a dose of 960 mg orally once daily. The primary end point for phase 2 was a centrally confirmed objective response (defined as a complete or partial response). Efficacy end points were assessed in the pooled population from both phases and included objective response, duration of response, time to objective response, disease control (defined as an objective response or stable disease), progression-free survival, and overall survival. Safety was also assessed.

RESULTS—The pooled population from phases 1 and 2 consisted of 38 patients, all of whom had metastatic disease at enrollment and had previously received chemotherapy. At baseline, patients had received a median of 2 lines (range, 1 to 8) of therapy previously. All 38 patients received sotorasib in the trial. A total of 8 patients had a centrally confirmed objective response (21%; 95% confidence interval [CI], 10 to 37). The median progression-free survival was 4.0 months (95% CI, 2.8 to 5.6), and the median overall survival was 6.9 months (95% CI, 5.0 to 9.1). Treatment-related adverse events of any grade were reported in 16 patients (42%); 6 patients (16%) had grade 3 adverse events. No treatment-related adverse events were fatal or led to treatment discontinuation.

CONCLUSIONS—Sotorasib showed anticancer activity and had an acceptable safety profile in patients with *KRAS* p.G12C–mutated advanced pancreatic cancer who had received previous treatment. (Funded by Amgen and others; CodeBreaK 100 [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03600883) number, NCT03600883.)

IN 2020, PANCREATIC CANCER ACCOUNTED FOR 495,773 new cases of cancer and 466,003 cancer-related deaths worldwide.¹ Aside from surgery, the treatment of pancreatic cancer includes chemotherapy with FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin), albumin-conjugated paclitaxel plus gemcitabine, and nanoliposomal irinotecan plus leucovorin and fluorouracil.^{2–5} Although these chemotherapy regimens offer modest survival and quality-of-life benefits, they cause toxic effects and are unsuitable for many patients because of age, performance status, or disease-related frailty. Several other therapies have been approved for the treatment of pancreatic cancer. Olaparib, a poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor, has been approved as maintenance treatment for pretreated metastatic pancreatic ductal adenocarcinoma harboring

a germline *BRCA* mutation, which occurs in 4 to 7% of patients. Pembrolizumab has been approved to treat unresectable or metastatic, microsatellite-instability–high or defective DNA mismatch-repair–deficient solid tumors (in 1 to 2% of pancreatic ductal adenocarcinomas). Larotrectinib and entrectinib are tropomyosin receptor kinase inhibitors approved to treat solid tumors with an *NTRK* gene fusion.^{6–11} Additional therapies targeting various genetic mutations in pancreatic cancer are currently being explored.¹²

Mutations in the Kirsten rat sarcoma viral oncogene homologue (*KRAS*) gene are found in approximately 90% of pancreatic ductal adenocarcinomas, which is the most prevalent histologic type of pancreatic cancer,^{13–15} with *KRAS* p.G12C (glycine-to-cysteine substitution at codon 12) mutation occurring in approximately 1 to 2% of patients.¹⁶ Sotorasib is a small molecule that specifically and irreversibly inhibits *KRAS* G12C. The Food and Drug Administration recently granted accelerated approval to sotorasib for the treatment of patients with *KRAS* p.G12C–mutated non–small-cell lung cancer who had received at least one previous systemic therapy.¹⁷ Here, we report the results in heavily pretreated patients with *KRAS* p.G12C–mutated pancreatic cancer from the phase 1 and phase 2 portions of the CodeBreaK 100 trial.

METHODS

TRIAL DESIGN AND END POINTS

We conducted an international, multicenter, open-label, phase 1–2 trial to evaluate the efficacy and safety of sotorasib as monotherapy in patients with *KRAS* p.G12C–mutated pancreatic cancer. The primary objectives of phase 1 were to evaluate the safety and side-effect profile of sotorasib monotherapy and to identify the recommended dose for phase 2. In phase 2, we assessed the efficacy of sotorasib at the dose recommended from phase 1 (960 mg daily). The primary end point was a centrally confirmed objective response (defined as a complete or partial response). In both phases, patients received sotorasib treatment until the occurrence of disease progression, development of unacceptable side effects, or withdrawal of consent.

Here, we report the results of the safety and efficacy analyses of sotorasib therapy in the combined populations from phase 1 and phase 2. Efficacy end points included objective response, duration of response, time to objective response, disease control (defined as an objective response or stable disease), progression-free survival, and overall survival. Tumor response was assessed in both phases by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

PATIENTS

Key inclusion criteria were an age of 18 years or older; pathologically documented, locally advanced or metastatic pancreatic cancer with *KRAS* p.G12C mutation identified by means of locally performed molecular testing; treatment with at least one previous systemic therapy (unless the patient was ineligible for available therapies known to provide clinical benefit or these therapies would have caused unacceptable adverse events); and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 2 or less (with scores ranging from 0

to 5 and higher scores indicating greater disability) for patients enrolled in phase 1 or a score of 0 or 1 for patients enrolled in phase 2. Complete eligibility criteria are provided in the protocol, available with the full text of this article at [NEJM.org](https://www.nejm.org).

ASSESSMENTS

Imaging and tumor assessments were performed with the use of magnetic resonance imaging or contrast-enhanced computed tomography or both at screening and every 6 weeks (within a window of ± 1 week) for the first eight assessments and every 12 weeks (within a window of ± 1 week) until the occurrence of disease progression or until sotorasib treatment was stopped, whichever occurred later. Response outcomes were determined on the basis of blinded independent central review according to RECIST, version 1.1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Plasma specimens that were obtained at baseline were analyzed for genomic alterations in cell-free DNA with the use of the Guardant360 assay (Guardant Health), with mutations reported according to the specifications of the test manufacturer. Additional details regarding adverse events and analysis of genomic alterations are provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

TRIAL OVERSIGHT

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. The protocol and amendments were approved by regulatory authorities of participating countries and the institutional review board at each participating site. All the patients provided written informed consent. The trial was designed by employees of the sponsor (Amgen) in collaboration with the investigators. The data were collected by the investigators and analyzed by statisticians employed by the sponsor. A medical writer employed by the sponsor assisted the authors with the first draft of the manuscript and provided editorial assistance with subsequent drafts. All the authors contributed to the interpretation of the data, reviewed the first draft of the manuscript, and provided input for revisions. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

In phase 1, we planned to enroll approximately 20 patients with advanced solid tumors of varying types for dose exploration and 60 patients for dose expansion. In phase 2, a sample of 60 patients with tumor types that were not lung or colorectal cancer was selected on the basis of enrollment feasibility. Patients with pancreatic cancer were included in both phases. We did not establish a prespecified benchmark for response, and we did not plan hypothesis testing in the cohort of patients with tumor types other than lung or colorectal cancer. The protocol specified that the analysis would be performed when sufficient follow-up time had accrued among the patients with tumor types other than lung or colorectal cancer (approximately 8.5 months after the last patient was enrolled).

The percentage of patients with an objective response was summarized with exact 95% confidence intervals, calculated with the use of the Clopper–Pearson method. Time-to-

event end points were summarized with the use of Kaplan–Meier estimates and 95% confidence intervals with log–log transformation. The time to objective response was summarized as a continuous variable with the use of mean, standard deviation, minimum, and maximum values. The confidence intervals for the efficacy end points were not adjusted for multiplicity. Censoring rules for time-to-event end points are outlined in the statistical analysis plan (available with the protocol). Additional details are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

From July 3, 2019, to January 25, 2021, investigators at 25 centers in seven countries enrolled a total of 38 patients with *KRAS* p.G12C–mutated pancreatic cancer; 12 patients were enrolled in phase 1, and 26 patients were enrolled in phase 2 (Fig. S1 in the Supplementary Appendix). All 38 patients received oral sotorasib at a dose of 960 mg daily and were included in the analysis. The median duration of treatment was 18 weeks (range, 1 to 48); 25 patients (66%) received treatment for 3 months or longer, and 8 (21%) received treatment for 6 months or longer. Two patients (5%) continued to receive treatment after disease progression according to the investigator’s assessment that there would be a continued clinical benefit. As of the data-cutoff date (November 1, 2021), 36 patients (95%) had discontinued treatment, with disease progression as the most common reason (in 32 patients [84%]). Of the 36 patients who discontinued treatment, 26 (72%) died or withdrew from the trial and did not receive subsequent anticancer therapy. A majority of the remaining 10 patients were treated with chemotherapy (Table S1).

Overall, the baseline characteristics of the patients enrolled in phase 1 and phase 2 were similar (Table 1). A majority of the patients were men (29 patients [76%]), and the median age was 65.5 years (range, 45 to 81). A total of 21 patients (55%) had stage IV disease at initial diagnosis, and all the patients had metastatic disease at enrollment. Liver metastasis was observed in 31 patients (82%). A total of 14 patients (37%) had a history of pancreatic resection, including 1 patient who had had stage IV disease at initial diagnosis. The patients had received a median of 2 lines (range, 1 to 8) of therapy previously, with 30 patients (79%) having received 2 or more previous lines. Additional details regarding previous regimens are provided in the Supplementary Results section in the Supplementary Appendix. Analysis of the plasma next-generation sequencing data from 28 patients revealed multiple common co-mutations at baseline such as *TP53* (in 75% of patients), *CDKN2A* (in 18%), *BRCA2* (in 18%), and *SMAD4* (in 11%) (Fig. S2). Because of the small sample size, interpretation of the data was difficult and precluded our ability to perform subgroup analyses.

EFFICACY

Among the 38 patients in the two phases, 8 patients (21%; 95% confidence interval [CI], 10 to 37) had a confirmed partial response as assessed by blinded independent central review (Table 2). No patients had a complete response. Responses according to investigator assessment are provided in Table S2. Among these 8 patients, the median time to a response was 1.5 months (range, 1.3 to 5.6), and the duration of response was 5.7 months (95%

CI, 1.6 to could not be evaluated) (Table 2). In 5 of these patients (62%), a response was observed at the time of the first tumor assessment at approximately week 6. As of the data-cutoff date, 2 of the 8 patients (25%) were continuing to receive treatment, with an ongoing treatment duration of approximately 10 months (Fig. 1A).

Tumor shrinkage of target lesions of any magnitude was observed in 30 patients (79%) (Fig. 1B). Tumor shrinkage of target lesions according to investigator assessment is provided in Figure S3.

The median progression-free survival was 4.0 months (95% CI, 2.8 to 5.6) (Fig. 1C). The median progression-free survival as assessed by blinded independent central review and according to investigator assessment is provided in Table S3. The Kaplan–Meier estimate of progression-free survival was 31.6% (95% CI, 16.7 to 47.7) at 6 months and 9.9% (95% CI, 2.0 to 25.6) at 9 months. At a median follow-up of 16.8 months (95% CI, 9.5 to could not be evaluated), the median overall survival was 6.9 months (95% CI, 5.0 to 9.1) (Fig. 1D). The Kaplan–Meier estimate of overall survival at 12 months was 19.6% (95% CI, 7.2 to 36.3).

SAFETY

Overall, the safety profile of sotorasib in the combined population of patients in the two phases (38 patients) was similar to that observed in the cohorts in phase 1 (12 patients) and phase 2 (26 patients). Adverse events of any grade that occurred during treatment, regardless of attribution, were observed in all the patients (100%); the most common adverse events were abdominal pain (in 14 patients [37%]), diarrhea and nausea (in 9 patients [24%] each), and vomiting and pyrexia (in 8 patients [21%] each). Overall, 24 patients (63%) had adverse events of grade 3 or higher.

Adverse events of any grade that were considered by the investigators to be related to treatment were reported in 16 patients (42%); 6 of these events (16%) were grade 3 in severity (Table 3). The most common grade 3 treatment-related adverse events were diarrhea and fatigue (in 2 patients [5%] each). No treatment-related adverse events of grade 4 or 5 were reported. Treatment-related serious adverse events were reported in 3 patients (8%). A total of 14 patients (37%) had fatal events; none were considered by the investigators to be related to treatment. Treatment-related adverse events leading to dose reduction or interruption of sotorasib therapy occurred in 5 patients (13%). Among these events, grade 3 diarrhea that resolved in 4 days and grade 2 or 3 diarrhea that resolved in 16 days were observed in 2 patients (5%). No treatment-related adverse events resulted in the discontinuation of sotorasib therapy. The full list of adverse events that occurred during each phase and that occurred in the combined phase 1 and 2 population is provided in Table S4.

DISCUSSION

In the *RAS* family of genes, *KRAS* is the most commonly mutated isoform in pancreatic cancer, with oncogenic driver mutations occurring most frequently in codons 12, 13, and 61.^{2,18} The mutated *KRAS* protein was considered to be “undruggable” for many years, owing mainly to its complex biochemical characteristics, high affinity for guanosine

triphosphate, and limited number of binding sites.^{19,20} Analysis of the crystal structure of the KRAS G12C bound to guanosine diphosphate (GDP) revealed a previously unknown pocket beneath the switch II region that allowed for direct targeting of the mutated protein.²¹ Sotorasib irreversibly and selectively binds to this pocket, which is present in the mutant KRAS G12C, and locks it in the inactive GDP-bound state, thereby inhibiting oncogenic signaling. On the basis of the potential of sotorasib to treat pancreatic cancer harboring *KRAS* p.G12C mutation, we evaluated the safety and efficacy of sotorasib in this phase 1–2 clinical trial. In this trial, sotorasib therapy had clinically meaningful efficacy and an acceptable safety profile in patients with *KRAS* p.G12C–mutated metastatic pancreatic cancer. A total of 21% of the patients had a centrally confirmed response, and the median time to response was 1.5 months; disease control was observed in 84% of the patients. The median progression-free survival was 4.0 months, and the overall survival was 6.9 months.

The results of this trial are promising in the context of the outcomes observed with approved regimens of second-line treatment of advanced pancreatic cancer.^{5,22–24} In the final analysis of the phase 3 NAPOLI-1 trial, second-line treatment with a combination of liposomal irinotecan, fluorouracil, and leucovorin in patients with metastatic pancreatic ductal adenocarcinoma who had received previous gemcitabine-based treatment resulted in a median overall survival of 6.2 months and a progression-free survival of 3.1 months.⁵ In an open-label, randomized, phase 3 trial involving patients with gemcitabine-resistant advanced pancreatic cancer (the Charité Onkologie 003 [CONKO-003] trial), second-line treatment with oxaliplatin, leucovorin, and fluorouracil in patients with gemcitabine-refractory, advanced pancreatic cancer resulted in a median overall survival of 5.9 months and a progression-free survival of 2.9 months.²² Although the results for the median progression-free survival and overall survival in the current trial are encouraging, additional data from larger trials are needed to confirm these findings.

On the basis of the results of the Pancreas Cancer Olaparib Ongoing (POLO) trial, olaparib was approved as maintenance therapy in patients with germline *BRCA*-mutated metastatic pancreatic cancer.⁶ Although the percentage of patients with a response reported in the POLO trial (23%) was similar to that reported in this trial, it must be acknowledged that the POLO trial was a randomized, placebo-controlled, phase 3 trial, whereas the current study is a nonrandomized, single-group, phase 1–2 trial. In the POLO trial, patient eligibility was limited to those who did not have disease progression after 4 months of first-line platinum-based therapies, which enriched the trial with patients who would most likely benefit from PARP inhibitors. In contrast, approximately 79% of the patients enrolled in the current trial were heavily pretreated with two or more lines of anticancer therapies. Furthermore, clinical studies evaluating various chemotherapeutic regimens as second-line therapy for patients with advanced pancreatic cancer have reported a response in less than 10% of patients.^{24–27}

The response that was observed with sotorasib therapy in this analysis (21%) was numerically lower than that among patients with *KRAS* p.G12C–mutated non–small-cell lung cancer (37.1%; 95% CI, 28.6 to 46.2) and greater than that among patients with *KRAS* p.G12C–mutated colorectal cancer (9.7%; 95% CI, 3.6 to 19.9).^{28–30} At baseline, a majority of patients in those lung and colon cancer cohorts were heavily pretreated with a

median of two or three previous lines of anticancer therapy, which predominantly included chemotherapy, checkpoint inhibitors, or bevacizumab. In addition, the patients with *KRAS* p.G12C–mutated lung and colorectal cancer who were enrolled in phase 2 of this trial had an ECOG performance-status score of 0 or 1. (The results in these patients are not reported here.) In the combined phase 1–2 patient population in the current trial, 11% of the patients with an ECOG performance-status score of 2 were enrolled. (The other 89% of patients had an ECOG performance-status score of 0 or 1.) Although the response observed in this trial is promising, the mechanisms in various tumor types with a sensitivity to *KRAS* pathway inhibition are unknown, and further cancer-cell biology studies are warranted.

An analysis of the data from patients with colorectal cancer who were treated with *KRAS* G12C inhibitors suggests that higher receptor tyrosine kinase signaling in these tumors and reactivation of receptors (particularly epidermal growth factor receptor [EGFR]) with *RAS* inhibition attenuates response to *KRAS* G12C inhibitors, and combination treatment with *KRAS* G12C and EGFR inhibitors improves efficacy.³¹ It is unclear whether a similar receptor reactivation limits sotorasib monotherapy activity in pancreatic cancer. Studies examining new sotorasib combinations, such as CodeBreaK 101 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04185883) number, NCT04185883), are actively under way. Preliminary results from studies evaluating the combinations of *KRAS* G12C inhibitors with EGFR inhibitors for the treatment of patients with *KRAS* p.G12C–mutated colorectal cancer have shown a response in 30 to 43% of patients.^{32–34} Although these data are encouraging, additional analyses in patients with *KRAS* p.G12C–mutated pancreatic cancer are needed to assess the efficacy of these combinations.

Overall, sotorasib was associated with mainly low-grade toxic effects in the heavily pretreated population in this trial, and the safety findings were consistent with those previously reported in other CodeBreaK 100 trials.^{28–30} Diarrhea and fatigue were the most frequently occurring treatment-related adverse events (in 5% of patients). None of these events were fatal, and none resulted in the discontinuation of sotorasib therapy. This safety profile compares favorably with current standard regimens used for the treatment of pancreatic cancer.^{3–5} However, a higher number of patients were enrolled in the pivotal trials evaluating the safety and efficacy of these regimens than were enrolled in the current trial. Therefore, studies with larger cohorts are needed to clarify the prognostic effect of *KRAS* p.G12C mutation in patients with pancreatic cancer.

Pancreatic cancer is one of the most difficult cancers to diagnose and treat. In this phase 1–2 trial, sotorasib monotherapy showed promising anticancer activity in patients with heavily pretreated *KRAS* p.G12C–mutated advanced pancreatic cancer. The clinical activity of sotorasib shown in this trial provides evidence that targeting *KRAS* is a viable strategy for the treatment of advanced pancreatic cancer. In addition, the clinical activity of sotorasib against the *KRAS* p.G12C mutation should invigorate efforts aimed at the design and development of inhibitors relevant to the forms of *KRAS* mutations that are more common in pancreatic ductal adenocarcinomas. Studies assessing the safety and efficacy of sotorasib in combination with other anticancer therapies are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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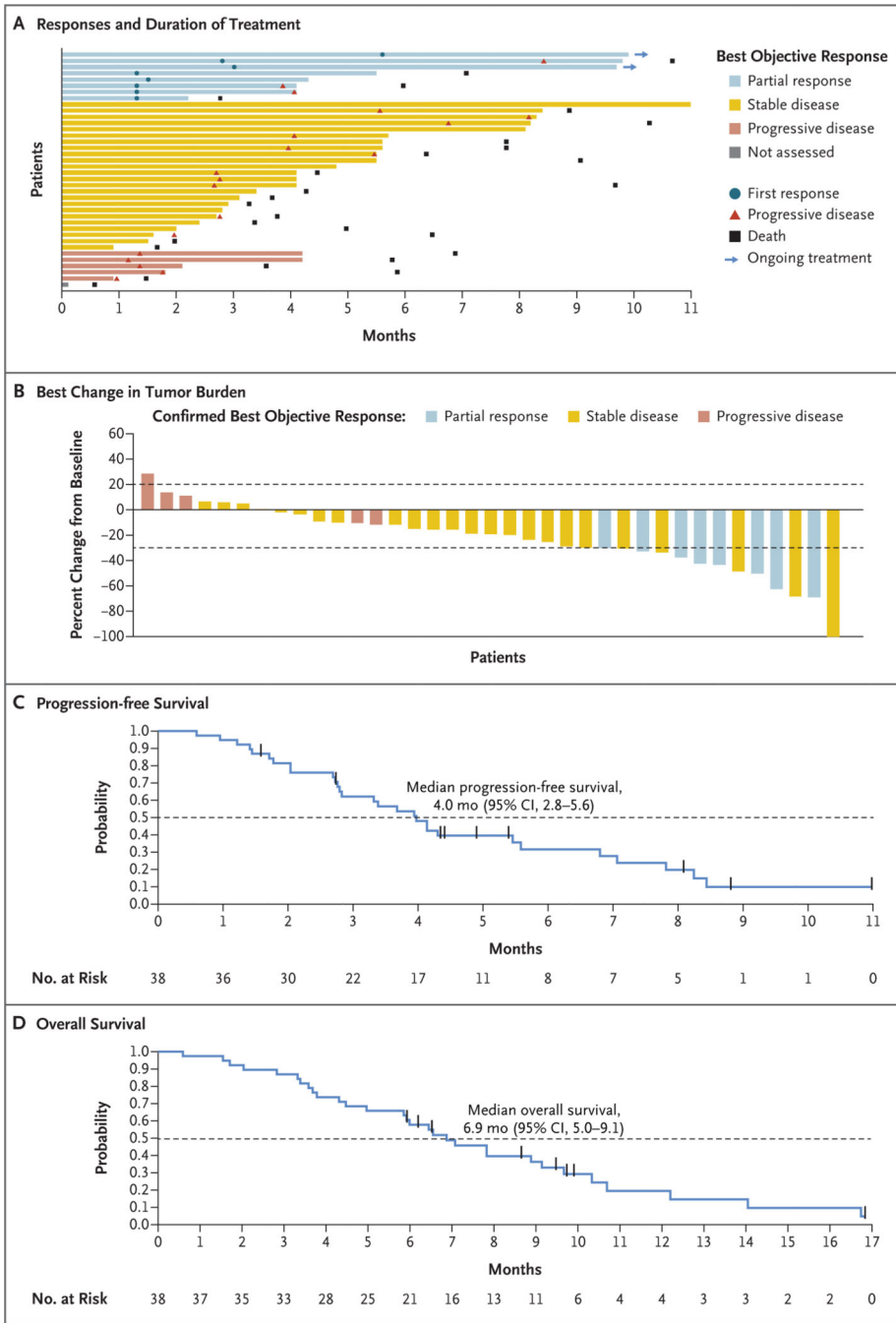


Figure 1. Efficacy Analyses of Sotorasib Therapy.

Panel A shows the responses and the duration of treatment in all patients as assessed by blinded independent central review (which could be different from investigator-assessed timing of progressive disease). Five patients with a best objective response of progressive disease as assessed by blinded independent central review ended treatment within one cycle after the occurrence of progressive disease according to the decision of the investigator. Panel B shows the best percentage change from baseline in tumor burden (defined as the sum of the diameters of all target lesions). The upper dashed line indicates a 20% increase

in tumor burden (progressive disease), and the lower dashed line indicates a 30% decrease in tumor burden (partial response). Progressive disease with less than a 20% increase (from nadir) in the sum diameter of target lesions was due to unequivocal progressive disease in the nontarget lesion or the presence of a new lesion. Panel C shows the Kaplan–Meier curve of progression-free survival; the dashed line indicates 50% progression-free survival probability. Panel D shows the Kaplan–Meier curve of overall survival; the dashed line indicates 50% overall survival probability. The vertical bars in Panels C and D indicate censored data.

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Table 1.

Characteristics of the Patients at Baseline.*

Characteristic	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1–2 (N = 38)
Sex — no. (%)			
Male	9 (75)	20 (77)	29 (76)
Female	3 (25)	6 (23)	9 (24)
Median age (range) — yr	62.5 (45–75)	67 (53–81)	65.5 (45–81)
ECOG performance-status score — no. (%) [†]			
0	1 (8)	11 (42)	12 (32)
1	7 (58)	15 (58)	22 (58)
2	4 (33)	0	4 (11)
Disease stage at initial diagnosis — no. (%)			
I	2 (17)	1 (4)	3 (8)
II	4 (33)	7 (27)	11 (29)
III	1 (8)	2 (8)	3 (8)
IV	5 (42)	16 (62)	21 (55)
Stage IV disease at screening — no. (%)	12 (100)	26 (100)	38 (100)
Histopathological subtype — no. (%)			
Adenocarcinoma	11 (92)	26 (100)	37 (97)
Other or unknown	1 (8)	0	1 (3)
No. of sites of metastatic disease — no. (%)			
1	4 (33)	13 (50)	17 (45)
2	5 (42)	10 (38)	15 (39)
3	3 (25)	3 (12)	6 (16)
Site of metastases — no. (%)			
Liver	9 (75)	22 (85)	31 (82)
Lung	5 (42)	11 (42)	16 (42)
Brain	0	1 (4)	1 (3)
Bone	3 (25)	1 (4)	4 (11)
Previous lines of anticancer therapy — no. (%)			
1	2 (17)	6 (23)	8 (21)

Characteristic	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1–2 (N = 38)
2	3 (25)	10 (38)	13 (34)
3	2 (17)	7 (27)	9 (24)
4	5 (42)	3 (12)	8 (21)
Median lines of previous anticancer therapy (range) — no.	3 (1–5)	2 (1–8)	2 (1–8)
Type of previous anticancer therapy — no. (%)			
Chemotherapy	12 (100)	26 (100)	38 (100)
Fluoropyrimidine	11 (92)	23 (88)	34 (89)
Irinotecan	11 (92)	22 (85)	33 (87)
Oxaliplatin or cisplatin	11 (92)	21 (81)	32 (84)
Gemcitabine	7 (58)	21 (81)	28 (74)
Nab-paclitaxel	7 (58)	18 (69)	25 (66)
Liposomal irinotecan	2 (17)	3 (12)	5 (13)
Erlotinib	1 (8)	0	1 (3)
Select regimens			
FOLFIRINOX	11 (92)	18 (69)	29 (76)
Gemcitabine + nab-paclitaxel	7 (58)	18 (69)	25 (66)
Fluorouracil + liposomal irinotecan	2 (17)	3 (12)	5 (13)

* Percentages may not total 100 because of rounding. FOLFIRINOX denotes fluorouracil, leucovorin, irinotecan, and oxaliplatin, and nab-paclitaxel nanoparticle albumin-bound paclitaxel.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

Table 2.

Efficacy of Sotorasib Therapy.*

Variable	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1-2 (N = 38)
Best overall response — no. (%) [‡]			
Confirmed complete response	0	0	0
Confirmed partial response	3 (25)	5 (19)	8 (21)
Stable disease	6 (50)	18 (69)	24 (63)
Progressive disease	2 (17)	3 (12)	5 (13)
Could not be evaluated	0	0	0
Not assessed	1 (8)	0	1 (3)
Percentage of patients with objective response (95% CI) — %	25 (6–57)	19 (7–39)	21 (10–37)
Percentage of patients with disease control (95% CI) — % [‡]	75 (43–95)	89 (70–98)	84 (69–94)
Median time to objective response (range) — mo [§]	1.4 (1.3–1.5)	2.8 (1.3–5.6)	1.5 (1.3–5.6)
Median duration of response (95% CI) — mo ^{§¶}	—	—	5.7 (1.6–NE)

* An objective response was defined as a complete or partial response. NE denotes could not be evaluated.

[‡]The best overall response was determined by blinded independent central review.

[§]Disease control was defined as an objective response or stable disease.

[§]The median time to objective response and the median duration of response were calculated for the patients who had a confirmed objective response.

[¶]The median duration of response (Kaplan–Meier estimates) is not provided for individual phases because of the small number of patients.

Table 3.

Adverse Events.*

Adverse Event	Adverse Events Reported during Treatment			Treatment-Related Adverse Events		
	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1-2 (N = 38)	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1-2 (N = 38)
Any adverse event	12 (100)	26 (100)	38 (100)	5 (42)	11 (42)	16 (42)
Grade 2	12 (100)	23 (89)	35 (92)	3 (25)	9 (35)	12 (32)
Grade 3	9 (75)	15 (58)	24 (63)	0	6 (23)	6 (16)
Grade 4	7 (58)	7 (27)	14 (37)	0	0	0
Serious adverse event	9 (75)	15 (58)	24 (63)	0	3 (12)	3 (8)
Adverse event leading to dose reduction or interruption of therapy	5 (42)	9 (35)	14 (37)	0	5 (19)	5 (13)
Adverse event leading to discontinuation of therapy	1 (8)	1 (4)	2 (5)	0	0	0
Fatal adverse event	7 (58)	7 (27)	14 (37)	0	0	0

* Shown are adverse events that occurred during treatment and those that occurred within 30 days after the last dose of sotorasib or the end of the trial, whichever occurred earlier. Relatedness to treatment was determined by the investigators. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.