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Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C

M.G. Fakih, L. Salvatore, T. Esaki, D.P. Modest, D.P. Lopez-Bravo, J. Taieb, M.V. Karamouzis, E. Ruiz-Garcia, T.-W. Kim, Y. Kuboki, F. Meriggi, D. Cunningham, K.-H. Yeh, E. Chan, J. Chao, Y. Saportas, Q. Tran, C. Cremolini, and F. Pietrantonio

ABSTRACT

BACKGROUND

KRAS G12C is a mutation that occurs in approximately 3 to 4% of patients with metastatic colorectal cancer. Monotherapy with KRAS G12C inhibitors has yielded only modest efficacy. Combining the KRAS G12C inhibitor sotorasib with panitumumab, an epidermal growth factor receptor (EGFR) inhibitor, may be an effective strategy.

METHODS

In this phase 3, multicenter, open-label, randomized trial, we assigned patients with chemorefractory metastatic colorectal cancer with mutated *KRAS* G12C who had not received previous treatment with a KRAS G12C inhibitor to receive sotorasib at a dose of 960 mg once daily plus panitumumab (53 patients), sotorasib at a dose of 240 mg once daily plus panitumumab (53 patients), or the investigator's choice of trifluridine–tipiracil or regorafenib (standard care; 54 patients). The primary end point was progression-free survival as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Key secondary end points were overall survival and objective response.

RESULTS

After a median follow-up of 7.8 months (range, 0.1 to 13.9), the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 6.3) and 3.9 months (95% CI, 3.6 to 5.7) in the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups, respectively, as compared with 2.0 months (95% CI, 1.9 to 3.9) in the standard-care group. The hazard ratio for disease progression or death in the 960-mg sotorasib–panitumumab group as compared with the standard-care group was 0.48 (95% CI, 0.30 to 0.78; P=0.005), and the hazard ratio in the 240-mg sotorasib–panitumumab group was 0.59 (95% CI, 0.37 to 0.95; P=0.036). Overall survival data are maturing. The objective response was 26.4% (95% CI, 15.3 to 40.3), 5.7% (95% CI, 1.2 to 15.7), and 0% (95% CI, 0.0 to 6.6) in the 960-mg sotorasib–panitumumab, 240-mg sotorasib–panitumumab, and standard-care groups, respectively. Treatment-related adverse events of grade 3 or higher occurred in 35.8%, 30.2%, and 43.1% of patients, respectively. Skin-related toxic effects and hypomagnesemia were the most common adverse events observed with sotorasib–panitumumab.

CONCLUSIONS

In this phase 3 trial of a KRAS G12C inhibitor plus an EGFR inhibitor in patients with chemorefractory metastatic colorectal cancer, 960-mg sotorasib in combination with panitumumab resulted in longer progression-free survival than standard treatment. Toxic effects were as expected for either agent alone and resulted in few discontinuations of treatment. (Funded by Amgen; CodeBreaK 300 ClinicalTrials.gov number, NCT05198934.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fakih can be contacted at mfakih@coh.org or at City of Hope Comprehensive Cancer Center, 1500 E. Duarte Rd., Duarte, CA 91010.

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The KIRSTEN RAT SARCOMA VIRAL ONCOgene homologue (*KRAS*) glycine-to-cysteine mutation at codon 12 (*KRAS* G12C) is a driver mutation that occurs in approximately 3 to 4% of patients with metastatic colorectal cancer and may be associated with poor prognosis.[1-7] In patients with disease that is refractory to initial therapies (fluoropyrimidine-based chemotherapy with or without bevacizumab), the standard late-line treatments — trifluridine–tipiracil or regorafenib — have shown limited efficacy (objective response, 1 to 2%; median progression-free survival, ≤2.0 months) but at the cost of toxic effects.[8,9] Currently, no targeted therapies driven by a positive-selection biomarker are approved specifically for the treatment of patients with *KRAS*-mutated colorectal cancer.

Sotorasib selectively and irreversibly inhibits the KRAS G12C protein to block downstream proliferation and survival signaling.[10] Although single-agent KRAS G12C inhibitors (sotorasib and adagrasib) have shown improved outcomes in patients with non–small-cell lung cancer with *KRAS* G12C mutation, KRAS G12C inhibition alone has shown limited activity in patients with colorectal cancer.[11-13] Treatment-induced resistance selective to KRAS G12C inhibition develops primarily through upstream reactivation of the epidermal growth factor receptor (EGFR) pathway and is supported by the synergistic activity of concomitant KRAS G12C and EGFR inhibition in preclinical models.[14-16] Dual KRAS G12C and EGFR blockade was designed to overcome treatment resistance in patients with colorectal cancer with *KRAS* G12C mutation, a population in which EGFR inhibitors, such as cetuximab and panitumumab, do not elicit a response.[17,18] In CodeBreaK 101, a recent single-group phase 1b trial involving patients with chemorefractory colorectal cancer with mutated *KRAS* G12C, the confirmed response rate was 30% with sotorasib–panitumumab as compared with 9.7% with sotorasib monotherapy.[19,20]

In the past several years, an emphasis has been placed on strategies to better characterize the associations between doses of targeted therapies and the efficacy and safety of such doses in order to inform dose selection and maximize efficacy while minimizing toxic effects.[21-24] Comparisons between the recommended phase 2 dose and lower dose levels are an important part of the dose-selection process.[21,22] The recommended phase 2 dose of sotorasib is 960 mg once daily. A lower dose, 240 mg once daily, is being tested because of the nonlinear pharmacokinetic properties of sotorasib.[24-26]

We conducted the international phase 3 CodeBreaK 300 trial to evaluate the efficacy and safety of two different doses of sotorasib (960 mg and 240 mg) in combination with panitumumab as compared with the investigator's choice of standard-care therapy (trifluridine–tipiracil or regorafenib) in patients with chemorefractory metastatic colorectal cancer with *KRAS* G12C mutation.

METHODS

TRIAL DESIGN AND PATIENTS

In this phase 3, multicenter, open-label, randomized, active-controlled trial, we enrolled adult patients with metastatic colorectal cancer with mutated *KRAS* G12C who had not received previous treatment with a KRAS G12C inhibitor. Key inclusion criteria were disease progression or recurrence after receiving at least one previous line of therapy for metastatic disease, as described below; a *KRAS* G12C mutation as confirmed by prospective central molecular testing; measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0, 1, or 2 (on a 5-point scale, with higher scores indicating greater disability); and adequate organ function. The previous line of therapy for metastatic disease must have included fluoropyrimidine, oxaliplatin, and irinotecan unless the patient had unacceptable side effects, in which case the patient was eligible to receive trifluridine–tipiracil or regorafenib as the next line of therapy, if deemed appropriate by the investigator and if approved by the medical monitor. Complete eligibility criteria and trial procedures are described in the protocol, available with the full text of this article at NEJM.org.

TREATMENT AND RANDOMIZATION

Patients were randomly assigned in a 1:1:1 ratio to receive sotorasib at a dose of 960 mg once daily plus panitumumab (the 960-mg sotorasib–pani-

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tumumab group), sotorasib at a dose of 240 mg once daily plus panitumumab (the 240-mg sotorasib–panitumumab group), or the investigator's choice of standard-care therapy (trifluridine–tipiracil or regorafenib [the standard-care group]). Randomization was stratified according to previous use of antiangiogenic therapy (yes or no), the time from initial diagnosis of metastatic disease to randomization (≥18 months or <18 months), and ECOG performance-status score (0 or 1 vs. 2).

Sotorasib was administered orally once daily. Panitumumab was administered as an intravenous infusion at a dose of 6 mg per kilogram of body weight every 2 weeks. Each treatment cycle was 28 days. Trifluridine–tipiracil was administered orally twice daily at a starting dose of 35 mg per square meter of body-surface area (up to a maximum of 80 mg per dose, or a maximum of 75 mg per dose for patients in Japan, on the basis of the trifluridine component), on days 1 through 5 and days 8 through 12 every 28 days. Regorafenib was administered orally at a dose of 160 mg once daily for the first 21 days of each 28-day cycle.

Treatment continued until the occurrence of disease progression (as assessed by blinded independent central review), unacceptable toxic effects, initiation of another anticancer therapy, withdrawal of consent, or death, whichever

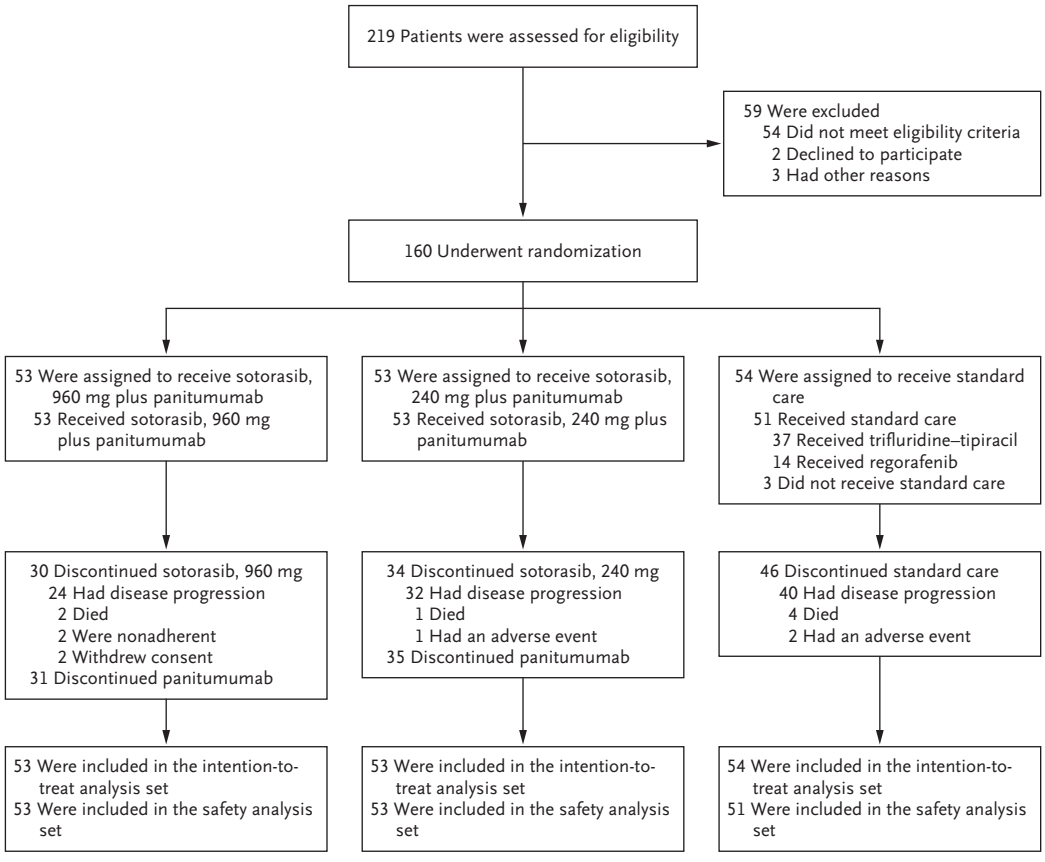

Figure 1. Randomization and Follow-up.

Adult patients with chemorefractory metastatic colorectal cancer with Kirsten rat sarcoma viral oncogene homologue glycine-to-cysteine mutation at codon 12 (*KRAS* G12C) were randomly assigned in a 1:1:1 ratio to receive sotorasib at a dose of 960 mg plus panitumumab, sotorasib at a dose of 240 mg plus panitumumab, or the investigator's choice of trifluridine–tipiracil or regorafenib (standard care).

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Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=54)
Median age (range) — yr	63.0 (37–79)	58.0 (35–82)	64.5 (34–81)
Age category — no. (%)			
<65 yr	32 (60.4)	39 (73.6)	27 (50.0)
≥65 yr	21 (39.6)	14 (26.4)	27 (50.0)
Male sex — no. (%)	29 (54.7)	26 (49.1)	24 (44.4)
Geographic region of enrollment — no. (%)			
North America	5 (9.4)	5 (9.4)	7 (13.0)
Europe	41 (77.4)	28 (52.8)	36 (66.7)
Asia	6 (11.3)	19 (35.8)	11 (20.4)
Rest of the world	1 (1.9)	1 (1.9)	0
Race — no. (%)†			
Asian	6 (11.3)	22 (41.5)	12 (22.2)
Black	0	1 (1.9)	0
White	43 (81.1)	30 (56.6)	37 (68.5)
Other	4 (7.5)	0	5 (9.3)
Previous antiangiogenic therapy — no. (%)	45 (84.9)	47 (88.7)	48 (88.9)
Time from initial diagnosis of metastatic disease to randomization — no. (%)			
≥18 mo	29 (54.7)	29 (54.7)	31 (57.4)
<18 mo	24 (45.3)	22 (41.5)	23 (42.6)
Unknown	0	2 (3.8)	0
ECOG performance-status score — no. (%)‡			
0	32 (60.4)	29 (54.7)	35 (64.8)
1	19 (35.8)	22 (41.5)	18 (33.3)
2	2 (3.8)	2 (3.8)	1 (1.9)
Body site at initial diagnosis — no. (%)			
Colon	37 (69.8)	32 (60.4)	37 (68.5)
Rectum	16 (30.2)	21 (39.6)	17 (31.5)
Location of tumor — no. (%)			
Left side	28 (52.8)	36 (67.9)	37 (68.5)
Right side	24 (45.3)	17 (32.1)	16 (29.6)
Unknown	1 (1.9)	0	1 (1.9)
No. of lines of previous anticancer therapy			
1 — no. (%)	7 (13.2)	8 (15.1)	9 (16.7)
≥2 — no. (%)	46 (86.8)	45 (84.9)	45 (83.3)
Median	2	2	2
Previous treatment with oxaliplatin, irinotecan, and fluoropyrimidine — no. (%)	49 (92.5)	50 (94.3)	51 (94.4)
Previous treatment with trifluridine and tipiracil — no. (%)	7 (13.2)	7 (13.2)	6 (11.1)
Previous treatment with regorafenib — no. (%)	4 (7.5)	1 (1.9)	2 (3.7)

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Table 1. (Continued.)

Characteristic	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=54)
Microsatellite instability status — no. (%)			
High	1 (1.9)	0	0
Stable	42 (79.2)	42 (79.2)	43 (79.6)
Low	3 (5.7)	2 (3.8)	3 (5.6)
Unknown or not tested	7 (13.2)	9 (17.0)	8 (14.8)

* Percentages may not sum to 100 because of rounding.
† Race was either reported by the patient or determined by the investigator.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

occurred first. Patients who discontinued treatment before disease progression as assessed by blinded independent central review had occurred (e.g., because of unacceptable toxic effects) were followed until the occurrence of disease progression (as assessed by imaging), withdrawal of consent, or initiation of another anticancer therapy. Patients who did not withdraw consent underwent additional follow-up, including assessment of survival and documentation of the use of anticancer therapy. Patients were to be followed for up to 2 years after enrollment of the last patient or until consent was withdrawn, the patient was lost to follow-up, or death, whichever occurred first.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to the occurrence of disease progression (as assessed by blinded independent central review according to RECIST, version 1.1) or death from any cause, whichever occurred first. The secondary end points were overall survival; objective response according to RECIST, version 1.1; the duration of response; the time to response; disease control (which was defined as complete response plus partial response plus stable disease for ≥7 weeks) according to blinded independent central review; safety; quality of life (results not reported here); and pharmacokinetics. Investigator-assessed progression-free survival and investigator-assessed objective response according to RECIST, version 1.1, were also evaluated.

Tumors were assessed with the use of computed tomography, magnetic resonance imaging, or both according to RECIST, version 1.1, at baseline and at 8-week intervals (±7 days) until the occurrence of blinded independent central review–assessed disease progression, initiation of another anticancer therapy, withdrawal of consent, loss to follow-up, or death, whichever occurred first.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Blood samples were obtained during the trial for the measurement of plasma and serum concentrations of sotorasib and panitumumab; details are provided in the protocol.

TRIAL OVERSIGHT

The trial was designed by the sponsor (Amgen). An independent data and safety monitoring committee oversaw the trial and assessed safety at the time of prespecified interim analyses. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol and amendments were approved by the institutional review board or the independent ethics committee at each participating site (or both) (Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients provided written informed consent. All the authors had access to the data and participated in the writing or review and editing of

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Table 2. Efficacy According to Blinded Independent Central Review in the Intention-to-Treat Population.*

Variable	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=54)
Primary end point: progression-free survival			
Median (95% CI) — mo†	5.6 (4.2 to 6.3)	3.9 (3.6 to 5.7)	2.0 (1.9 to 3.9)
Hazard ratio (95% CI)‡	0.48 (0.30 to 0.78)	0.59 (0.37 to 0.95)	—
P value§	0.005	0.036	—
Secondary end points			
Best overall response — no. (%)			
Complete response	1 (1.9)	0	0
Partial response	13 (24.5)	3 (5.7)	0
Stable disease	24 (45.3)	33 (62.3)	25 (46.3)
Progressive disease	12 (22.6)	13 (24.5)	17 (31.5)
Noncomplete response or nonprogressive disease	0	2 (3.8)	1 (1.9)
Not assessed	2 (3.8)	1 (1.9)	11 (20.4)
No assessable disease at baseline¶	1 (1.9)	1 (1.9)	0
Percentage of patients with objective response (95% CI)‖	26.4 (15.3 to 40.3)	5.7 (1.2 to 15.7)	0.0 (0.0 to 6.6)
Difference in proportions**	27.0 (14.9 to 39.0)	5.5 (–0.7 to 11.8)	—
Percentage of patients with disease control (95% CI)‖††	71.7 (57.7 to 83.2)	67.9 (53.7 to 80.1)	46.3 (32.6 to 60.4)
Median duration of response (95% CI) — mo‡‡	4.4 (3.6 to not reached)	—	—
Median time to response (range) — mo‡‡	2.1 (1.9 to 3.9)	1.8 (1.7 to 1.9)	—

* The intention-to-treat analysis set included all the patients who had undergone randomization.
† The 95% confidence intervals were estimated with the use of the method by Klein and Moeschberger with log–log transformation.
‡ Hazard ratios in the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups as compared with the standard-care group and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model.
§ Two-sided P values were calculated with the use of a stratified log-rank test. P-value boundaries indicating statistical significance were 0.025 for the comparison of 960-mg sotorasib–panitumumab with standard care and 0.03125 for the comparison of 240-mg sotorasib–panitumumab with standard care in accordance with the prespecified testing procedure.
¶ This variable was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1.
‖ The 95% confidence intervals were estimated with the use of the Clopper–Pearson method.
** The differences in proportions between the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups as compared with the standard-care group and 95% confidence intervals were estimated with the use of the stratified Cochran–Mantel–Haenszel method.
†† Disease control was defined as complete response plus partial response plus stable disease for at least 7 weeks.
‡‡ The duration of response and time to response were estimated only for patients who had a confirmed best overall response of partial response or complete response.

earlier versions of the manuscript. The first draft of the manuscript was written by a medical writer funded by the sponsor with input from all the authors. Data were collected by the investigators with oversight by the sponsor and were analyzed by statisticians employed by the sponsor. The sponsor was also involved in the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

Efficacy was assessed in all the patients who had undergone randomization according to the intention-to-treat principle. Safety was assessed

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in all the patients who had undergone randomization and who received at least one dose of the assigned treatment.

The trial was powered for progression-free survival, the primary end point; approximately 153 patients were planned for enrollment. We anticipated that approximately 90 events would occur, which would provide the trial with 90% power to detect superiority of each of the two sotorasib–panitumumab groups over standard care, assuming a hazard ratio for disease progression or death of 0.4.

The overall type I error was preserved at a two-sided alpha level of 5% with the use of the graphical method of Maurer–Bretz (Fig. S1); hierarchical testing was to be performed for progression-free survival, followed by overall survival, and then objective response. Progression-free survival in the 960-mg sotorasib–panitumumab group as compared with the standard-care group was to be tested first at one half of the alpha (two-sided alpha level of 2.5%). If statistical significance was shown, one fourth of that alpha portion would be propagated to test progression-free survival in the 240-mg sotorasib–panitumumab group as compared with the standard-care group, along with the other half of the alpha (i.e., 3.125%).

On the basis of the outcome of this testing, the remaining alpha will be propagated to test overall survival at the time of the final analysis of overall survival, which is planned to be performed after 50% of the patients have died (i.e., after approximately 80 deaths have been reported). If the final analysis of overall survival shows statistical significance, objective response will be tested. The expected number of deaths at the time of the final analysis does not provide sufficient power to detect the hypothesized difference in survival. This timing was selected to enable more mature overall survival data, given that awaiting the occurrence of more deaths would not substantially increase the power to detect between-group differences in overall survival under the constraint of the total sample size. At the time of the interim analysis of overall survival, reported here, the alpha level was 0.0001.

Progression-free survival was tested with the use of the stratified log-rank test. Overall survival was estimated with the use of the Kaplan–Meier method. The hazard ratios and 95% confidence intervals were estimated with the use of a Cox proportional-hazards model, stratified according to the same stratification factors as those used for randomization. The proportional-hazards assumption was supported by graphical assessment of the Schoenfeld residuals. Objective response and Clopper–Pearson 95% confidence intervals were calculated. Prespecified subgroup analyses were performed with the use of the Cox proportional-hazards model, without adjustment for multiplicity. Details of the pharmacokinetic analyses are provided in the protocol.

RESULTS

PATIENTS

Between April 19, 2022, and March 14, 2023, a total of 219 patients were screened at 76 sites across 12 countries. Of these patients, 160 from Europe (65.6%), Asia (22.5%), North America (10.6%), and other regions (1.2%) were eligible for participation and were randomly assigned to receive sotorasib at a dose of 960 mg once daily plus panitumumab (53 patients), sotorasib at a dose of 240 mg once daily plus panitumumab (53 patients), or standard care (54 patients, of whom 37 received trifluridine–tipiracil and 14 received regorafenib) (Fig. 1). Three patients in the standard-care group did not receive the assigned treatment and therefore were not included in the safety analysis. As of June 15, 2023, disease progression or death had occurred in 91 patients, thus triggering the data-cutoff date of the primary analysis on June 19, 2023.

The demographic and clinical characteristics of the patients at baseline were generally balanced across the three groups (Table 1). Overall, the median age was 62.0 years (range, 34 to 82), and 49.4% of the patients were men. The ECOG performance-status score was 0 in 60.0% of the patients, 1 in 36.9% of the patients, and 2 in 3.1% of the patients. A total of 15.0% of the patients had received one previous line of therapy, and 85.0% had received two or more previous lines of therapy. A higher percentage of patients in the 960-mg sotorasib–panitumumab group (45.3%) than in the 240-mg sotorasib–panitumumab and standard-care groups (32.1% and 29.6%, respectively) had a tumor on the right side.

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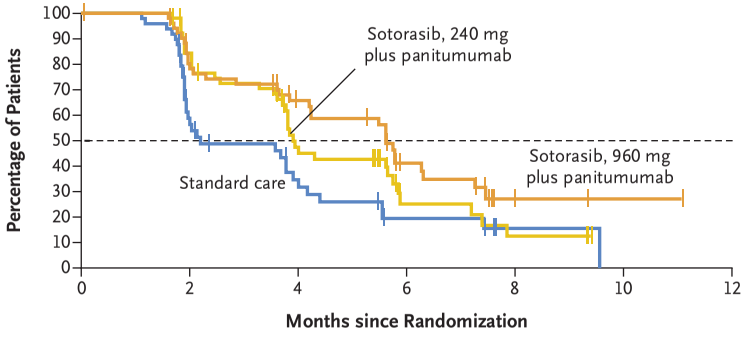
A Progression-free Survival (Intention-to-Treat Population)



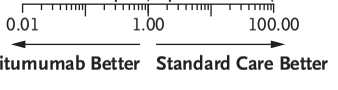
	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.48 (0.30–0.78)	0.005
Sotorasib, 240 mg plus Panitumumab	3.91	0.59 (0.37–0.95)	0.036
Standard Care	2.04		

No. at Risk

Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

B Subgroup Analysis for Progression-free Survival — Sotorasib, 960 mg plus Panitumumab

Subgroup	Sotorasib, 960 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.48 (0.30–0.78)
Age			
<65 yr	32	27	0.52 (0.26–1.04)
≥65 yr	21	27	0.43 (0.20–0.92)
Sex			
Male	29	24	0.59 (0.30–1.15)
Female	24	30	0.35 (0.17–0.73)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.42 (0.20–0.84)
<18 mo	24	23	0.51 (0.24–1.07)
Location of tumor			
Right side	24	16	0.41 (0.19–0.90)
Left side	28	37	0.62 (0.32–1.20)
Body site at initial diagnosis			
Colon	37	37	0.45 (0.25–0.80)
Rectum	16	17	0.57 (0.24–1.31)
No. of lines of previous therapy for metastatic disease			
1 or 2	37	28	0.39 (0.21–0.72)
≥3	16	26	0.58 (0.22–1.47)
Liver metastasis			
Yes	38	38	0.35 (0.20–0.61)
No	15	16	0.82 (0.30–2.21)



C Subgroup Analysis for Progression-free Survival — Sotorasib, 240 mg plus Panitumumab

Subgroup	Sotorasib, 240 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.59 (0.37–0.95)
Age			
<65 yr	39	27	0.63 (0.32–1.23)
≥65 yr	14	27	0.36 (0.14–0.91)
Sex			
Male	26	24	0.71 (0.37–1.37)
Female	27	30	0.63 (0.31–1.27)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.49 (0.25–0.97)
<18 mo	22	23	0.78 (0.40–1.52)
Location of tumor			
Right side	17	16	0.59 (0.27–1.32)
Left side	36	37	0.58 (0.33–1.03)
Body site at initial diagnosis			
Colon	32	37	0.53 (0.30–0.95)
Rectum	21	17	0.47 (0.21–1.02)
No. of lines of previous therapy for metastatic disease			
1 or 2	29	28	0.56 (0.31–1.02)
≥3	24	26	0.58 (0.27–1.26)
Liver metastasis			
Yes	36	38	0.47 (0.28–0.80)
No	17	16	0.56 (0.20–1.51)

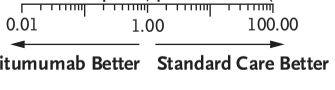


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Figure 2 (facing page). Progression-free Survival as Assessed by Blinded Independent Central Review (Intention-to-Treat Population).

Panel A shows Kaplan–Meier curves of progression-free survival with stratified Cox proportional-hazards ratios and stratified log-rank P values for 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab as compared with standard care. The dashed horizontal gray line indicates the median percentage of patients who were alive without disease progression. The vertical bars indicate censoring. Panel B shows the treatment effect of 960-mg sotorasib–panitumumab on progression-free survival in prespecified subgroups. Some subgroups were not included in this analysis because hazard ratios were not estimated when there were fewer than 10 patients in either treatment group in a subgroup. Panel C shows the treatment effect of 240-mg sotorasib–panitumumab on progression-free survival in prespecified subgroups. In both Panel B and Panel C, prespecified subgroups defined according to race, geographic region, previous therapies, and baseline Eastern Cooperative Oncology Group performance-status score are not shown because large percentages of patients were in a single category within these subgroups. The observed hazard ratios in the subgroups evaluated were consistent with those of the main intention-to-treat analysis (which included all the patients who had undergone randomization). The confidence intervals are not corrected for multiplicity and should not be used in place of a hypothesis test.

At the time of data cutoff, the median duration of follow-up was 7.8 months (range, 0.1 to 13.9). The median duration of treatment was 5.8 months (range, 1.0 to 13.2), 4.1 months (range, 0.9 to 10.1), and 2.2 months (range, 0.8 to 10.3) in the 960-mg sotorasib–panitumumab, 240-mg sotorasib–panitumumab, and standard-care groups, respectively; 23 patients (43.4%), 19 patients (35.8%), and 5 patients (9.3%), respectively, continued to receive treatment after data cutoff.

PRIMARY END POINT

Treatment with sotorasib at a dose of 960 mg, in combination with panitumumab, resulted in significantly longer progression-free survival than standard-care treatment. The median progression-free survival as assessed by blinded independent central review was 5.6 months (95% confidence interval [CI], 4.2 to 6.3) and 3.9 months (95% CI, 3.6 to 5.7) in the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups, respectively, as compared with 2.0 months (95% CI, 1.9 to 3.9) in the standard-care group. The hazard ratio for disease progression or death in the 960-mg sotorasib–panitumumab group as compared with the standard-care group was 0.48 (95% CI, 0.30 to 0.78; P=0.005). The hazard ratio in the 240-mg sotorasib–panitumumab group as compared with the standard-care group was 0.59 (95% CI, 0.37 to 0.95; P=0.036) (Table 2 and Fig. 2A). The treatment effects of 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab on progression-free survival across key prespecified subgroups are shown in Figures 2B and 2C, respectively. The results of the analysis of investigator-assessed progression-free survival in the sotorasib–panitumumab groups as compared with the standard-care group were consistent with those of the main analysis (Table S2).

TUMOR RESPONSE

The objective response as assessed by blinded independent central review was 26.4% (95% CI, 15.3 to 40.3) and 5.7% (95% CI, 1.2 to 15.7) in the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups, respectively, as compared with 0% (95% CI, 0.0 to 6.6) in the standard-care group; 1 patient (1.9%) in the 960-mg sotorasib–panitumumab group had a complete response (Table 2). The analysis of objective response as assessed by the investigators showed similar results (Table S2). The results of the analysis of tumor shrinkage from baseline as assessed by blinded independent central review are shown in Figure S2.

Best overall responses as assessed by blinded independent central review according to RECIST, version 1.1, are shown in Table 2. The median duration of response was 4.4 months (95% CI, 3.6 to not reached) in the 960-mg sotorasib–panitumumab group and was not estimated in the other groups owing to insufficient responses.

OVERALL SURVIVAL

At the time of data cutoff, the data on overall survival were not mature; 55 patients (34.4%) had died. The hazard ratio in the 960-mg sotorasib–panitumumab group as compared with the standard-care group was 0.77 (95% CI, 0.40 to 1.45). The hazard ratio in the 240-mg sotorasib–panitumumab group as compared with the standard-care group was 0.91 (95% CI, 0.48 to 1.71) (Fig. S3).

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Table 3. Treatment-Related Adverse Events in the Safety Population.*

Adverse Event	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=51)
	number of patients (percent)		
Any adverse event	50 (94.3)	51 (96.2)	42 (82.4)
Grade ≥3 event	19 (35.8)	16 (30.2)	22 (43.1)
Grade ≥4 event	2 (3.8)	0	2 (3.9)
Serious adverse event	3 (5.7)	0	4 (7.8)
Adverse event that resulted in death	0	0	0
Sotorasib-related adverse event	32 (60.4)	34 (64.2)	—
Panitumumab-related adverse event	49 (92.5)	50 (94.3)	—
Leading to treatment discontinuation			
Any treatment	2 (3.8)	1 (1.9)	1 (2.0)
Sotorasib	1 (1.9)	1 (1.9)	—
Panitumumab	2 (3.8)	1 (1.9)	—
Sotorasib and panitumumab	1 (1.9)	1 (1.9)	—
Leading to dose reduction†			
Any treatment	10 (18.9)	9 (17.0)	9 (17.6)
Sotorasib	3 (5.7)	0	—
Panitumumab	7 (13.2)	9 (17.0)	—
Sotorasib and panitumumab	0	0	—
Leading to dose interruption			
Any treatment	19 (35.8)	16 (30.2)	20 (39.2)
Sotorasib	11 (20.8)	10 (18.9)	—
Panitumumab	14 (26.4)	13 (24.5)	—
Sotorasib and panitumumab	5 (9.4)	7 (13.2)	—
Skin and subcutaneous tissue disorders‡	44 (83.0)	45 (84.9)	11 (21.6)
Any event; grade ≥3 event§			
Anemia	1 (1.9); 1 (1.9)	4 (7.5); 1 (1.9)	10 (19.6); 3 (5.9)
Thrombocytopenia	0; 0	2 (3.8); 0	4 (7.8); 1 (2.0)
Leukopenia	0; 0	0; 0	4 (7.8); 1 (2.0)
Neutropenia	0; 0	0; 0	16 (31.4); 12 (23.5)
Diarrhea	11 (20.8); 2 (3.8)	10 (18.9); 3 (5.7)	10 (19.6); 0
Nausea	6 (11.3); 1 (1.9)	9 (17.0); 2 (3.8)	15 (29.4); 1 (2.0)
Vomiting	3 (5.7); 0	6 (11.3); 0	4 (7.8); 0
Stomatitis	3 (5.7); 0	4 (7.5); 0	5 (9.8); 0
Fatigue	4 (7.5); 0	3 (5.7); 0	6 (11.8); 0
Mucosal inflammation	4 (7.5); 0	0; 0	2 (3.9); 0
Asthenia	3 (5.7); 0	3 (5.7); 0	7 (13.7); 1 (2.0)
Xerosis	3 (5.7); 0	0; 0	0; 0
Malaise	0; 0	2 (3.8); 1 (1.9)	3 (5.9); 0
Pyrexia	0; 0	0; 0	3 (5.9); 0
Folliculitis	8 (15.1); 0	2 (3.8); 1 (1.9)	0; 0

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Table 3. (Continued.)

Adverse Event	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=51)
	number of patients (percent)		
Paronychia	3 (5.7); 0	6 (11.3); 1 (1.9)	0; 0
Weight decreased	1 (1.9); 0	1 (1.9); 0	3 (5.9); 0
Neutrophil count decreased	0; 0	2 (3.8); 0	4 (7.8); 2 (3.9)
Hypomagnesemia	15 (28.3); 3 (5.7)	16 (30.2); 4 (7.5)	1 (2.0); 0
Decreased appetite	3 (5.7); 0	3 (5.7); 1 (1.9)	6 (11.8); 1 (2.0)
Hypocalcemia	3 (5.7); 1 (1.9)	2 (3.8); 0	0; 0
Rash	15 (28.3); 3 (5.7)	13 (24.5); 1 (1.9)	1 (2.0); 0
Dermatitis acneiform	12 (22.6); 6 (11.3)	20 (37.7); 2 (3.8)	1 (2.0); 0
Dry skin	10 (18.9); 0	12 (22.6); 0	0; 0
Pruritus	8 (15.1); 0	7 (13.2); 0	2 (3.9); 0
Skin fissures	7 (13.2); 0	4 (7.5); 0	0; 0
Skin-related toxic effect	5 (9.4); 2 (3.8)	4 (7.5); 1 (1.9)	1 (2.0); 1 (2.0)
Palmar–plantar erythrodysesthesia syndrome	4 (7.5); 0	3 (5.7); 0	5 (9.8); 2 (3.9)
Nail cuticle fissure	3 (5.7); 0	0; 0	0; 0
Rash maculopapular	2 (3.8); 0	3 (5.7); 1 (1.9)	1 (2.0); 0
Alopecia	0; 0	1 (1.9); 0	3 (5.9); 0
Hypertension	0; 0	1 (1.9); 0	7 (13.7); 3 (5.9)

* The safety analysis set included all the patients who had undergone randomization and who received at least one dose of the assigned treatment. Treatment-related adverse events were adverse events that occurred after the start of treatment and were determined by the investigator to be related to the trial treatment, as reported on the electronic case-report form. An adverse event was considered to be a treatment-related adverse event if there was a reasonable possibility that the event may have been caused by the trial treatment. In the unlikely event that the relationship to treatment was missing, the adverse event was considered to be treatment-related. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 26.0. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

† Sotorasib dose reduction was not allowed for the 240-mg sotorasib–panitumumab group. Patients could resume the same dose after interruption or could permanently discontinue sotorasib treatment.

‡ "Skin and subcutaneous tissue disorders" refers to the system organ class.

§ Adverse events that are listed as any grade are those that occurred in at least 5% of the patients in any group. Adverse events that are listed as grade 3 or higher are those that occurred in at least 3% of the patients in any group.

SAFETY

Treatment-related adverse events occurred in 50 of 53 patients (94.3%) in the 960-mg sotorasib–panitumumab group, in 51 of 53 patients (96.2%) in the 240-mg sotorasib–panitumumab group, and in 42 of 51 patients (82.4%) in the standard-care group (Table 3). The most common such events in both sotorasib–panitumumab groups were hypomagnesemia (in 28.3% of the patients in the 960-mg sotorasib–panitumumab group and in 30.2% of the patients in the 240-mg sotorasib–panitumumab group), rash (in 28.3% and 24.5%, respectively), and dermatitis acneiform (in 22.6% and 37.7%, respectively). In the standard-care group, the most common treatment-related adverse events were neutropenia (in 31.4% of the patients) and nausea (in 29.4%). Treatment-related adverse events of grade 3 or higher occurred in 35.8%, 30.2%, and 43.1% of the patients in the 960-mg sotorasib–panitumumab, 240-mg sotorasib–panitumumab, and standard-care groups, respectively. The most common (incidence of ≥5%) treatment-related adverse events of grade 3 or higher were dermatitis acneiform (11.3%), hypomagnesemia (5.7%), and rash (5.7%) in the 960-mg sotorasib–panitumumab group; hypomagnesemia (7.5%) and diarrhea (5.7%) in the 240-mg sotorasib–panitumumab

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group; and neutropenia (23.5%), anemia (5.9%), and hypertension (5.9%) in the standard-care group. Treatment-related serious adverse events were reported in 5.7%, 0%, and 7.8% of the patients, respectively. Treatment-related adverse events led to treatment discontinuation in 3.8%, 1.9%, and 2.0% of the patients, respectively.

Adverse events of interest in this trial included hepatotoxic events. Hepatotoxic adverse events of any grade (which consisted primarily of laboratory abnormalities) were reported in 11.3%, 5.7%, and 7.8% of the patients, respectively (Table S3).

PHARMACOKINETICS

The pharmacokinetic properties of sotorasib and panitumumab were consistent with those seen in previous studies, and similar exposures were observed with the two dose levels of sotorasib (Fig. S4). No pharmacokinetic drug–drug interactions were observed between sotorasib and panitumumab.

DISCUSSION

The primary end point in this trial was progression-free survival, and the trial was not powered to detect a difference in overall survival owing to the low prevalence of *KRAS* G12C mutation in patients with metastatic colorectal cancer. In this phase 3 trial, treatment with sotorasib (at a dose of 960 mg) plus panitumumab resulted in significantly longer progression-free survival, as assessed by blinded independent central review, than standard-care therapy with trifluridine–tipiracil or regorafenib in patients with chemorefractory colorectal cancer with *KRAS* G12C mutation. The objective response was higher with both sotorasib combinations than with standard-care therapy, although this end point was not formally assessed. Efficacy outcomes in the standard-care group were as expected.[8,10] These findings are important in the context of the poor survival outcomes associated with *KRAS* G12C mutation in patients with colorectal cancer.[2-4,6,7]

In the 960-mg sotorasib–panitumumab group, the percentage of patients with a response (26.4%) and the median progression-free survival (5.6 months) appear to be well aligned with the efficacy outcomes observed in the phase 1b trial with 960-mg sotorasib–panitumumab.[19] In that trial, which also involved patients with chemorefractory colorectal cancer with *KRAS* G12C mutation, the investigator-assessed confirmed response according to RECIST, version 1.1, was 30.0%, and the median progression-free survival was 5.7 months. Progression-free survival with 960-mg sotorasib–panitumumab was not influenced by the side of the colon or rectum in which the primary tumor was located; these findings are similar to those that were previously observed for dual BRAF–EGFR blockade in patients with metastatic colorectal cancer with *BRAF* V600E mutation.[27]

Despite similar exposure for the two dose levels of sotorasib, differences at the tissue and cellular level may affect targeted therapies; therefore, Project Optimus (an initiative of the Food and Drug Administration Oncology Center of Excellence that was designed to ascertain the dose levels of molecularly targeted agents that may be appropriate to maximize efficacy and safety) emphasized the importance of evaluating at least two doses for a clear understanding of the effect of different doses on efficacy and safety.[28] Although this trial was not powered to compare the two sotorasib–panitumumab groups with each other, the 960-mg sotorasib dose appeared to yield more clinically significant benefits than the 240-mg dose with respect to all the efficacy end points, without additional toxic effects. The percentage of patients in the 960-mg sotorasib–panitumumab group who had a response is particularly notable, considering the greater potential to relieve tumor-related symptoms associated with a high burden of metastatic disease in the context of late-line treatment. These observations support the 960-mg dose as the more favorable regimen of the two groups. Whether a lower sotorasib dose may be associated with different mechanisms of primary and secondary resistance remains to be investigated by translational analyses of the trial. Potential resistance mechanisms are the focus of future research. However, *KRAS* G12C amplification and secondary *KRAS* mutations have been identified.[29,30]

The observed safety profile of sotorasib–panitumumab was generally similar in the two dose combinations, and no new safety concerns were identified. No treatment-related fatal events occurred. The percentage of patients with treatment-related adverse events of grade 3 or higher was similar in the sotorasib–panitumumab

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groups (35.8% and 30.2%) and was higher in the standard-care group (43.1%) than in either sotorasib–panitumumab group. The most common adverse events observed with sotorasib–panitumumab (hypomagnesemia, rash, and dermatitis acneiform) are as expected with this combination and with EGFR-based therapies in general.[31,32] Skin-related toxic effects are well-documented adverse events seen with EGFR inhibitors, and management strategies such as the use of prophylactic antibiotic agents have been studied.[33,34] The trial protocol strongly recommended the use of prophylactic treatment for skin-related toxic effects, and treatment with sotorasib–panitumumab did not appear to exacerbate the incidence of these effects beyond that expected for panitumumab alone.

One limitation of this trial is that it was neither designed nor powered to detect a significant difference among the groups in overall survival. Overall survival data are maturing, and longer follow-up is needed to determine the effects of treatment on this end point. In addition, the trial population was composed primarily of White and Asian patients, with limited representation of Black patients (1 patient).

This trial has several strengths. This is an international, phase 3, randomized, active-controlled trial involving dual KRAS G12C and EGFR blockade in patients with colorectal cancer with *KRAS* G12C mutation. Two doses of sotorasib were evaluated as part of the combination regimen, and the trial was adequately powered to compare each treatment group directly with the standard-care group. Although the treatment used in the standard-care group in this trial was the approved standard treatment for chemorefractory colorectal cancer at the time of the trial, the results of two recent trials (SUNLIGHT and FRESCO-2) have shown an overall survival benefit with trifluridine–tipiracil plus bevacizumab and with fruquintinib (an inhibitor of vascular endothelial growth factor receptors), respectively, as later-line therapies.[35,36] However, these trials are distinct from our trial in that they did not enroll a biomarker-selected population of patients with colorectal cancer, and they had other differences in eligibility.[35,36] The results of the current phase 3 trial confirm those of previously reported single-group studies that have shown greater efficacy with combined KRAS G12C and EGFR inhibition (sotorasib–panitumumab, adagrasib–cetuximab, or divarasib–cetuximab) than with KRAS G12C inhibitor monotherapy and support this combination as a therapeutic regimen for metastatic colorectal cancer with mutated *KRAS* G12C.[19,32,37] Dual KRAS G12C and EGFR blockade is also currently being studied in an earlier line of treatment in a randomized trial (KRYSTAL-10).[38]

In this phase 3 trial of a KRAS G12C inhibitor plus an anti-EGFR antibody in patients with chemorefractory metastatic colorectal cancer, 960-mg sotorasib plus panitumumab resulted in significantly longer progression-free survival and a higher incidence of response than standard care. Adverse events associated with sotorasib–panitumumab at both doses were as expected, with no new safety concerns and the occurrence of few discontinuations related to adverse events.

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APPENDIX

The authors' full names and academic degrees are as follows: Marwan G. Fakih, M.D., Lisa Salvatore, M.D., Taito Esaki, M.D., Dominik P. Modest, M.D., David P. Lopez-Bravo, M.D., Julien Taieb, M.D., Michalis V. Karamouzis, M.D., Erika Ruiz-Garcia, M.D., Tae-Won Kim, M.D., Yasutoshi Kuboki, M.D., Fausto Meriggi, M.D., David Cunningham, M.D., Kun-Huei Yeh, M.D., Emily Chan, M.D., Ph.D., Joseph Chao, M.D., Yaneth Saportas, Ph.D., Qui Tran, Ph.D., Chiara Cremolini, M.D., and Filippo Pietrantonio, M.D.

The authors' affiliations are as follows: Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte (M.G.F.), and Amgen, Thousand Oaks (E.C., J.C., Y.S., Q.T.) — both in California; Oncologia Medica, Università Cattolica del Sacro Cuore, and Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome (L.S.), the Oncology Department, Fondazione Poliambulanza Istituto Ospedaliero, Brescia (F.M.), the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa (C.C.), and the Medical Oncology Department, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan (F.P.) — all in Italy; the Department

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of Gastrointestinal and Medical Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka (T.E.), and the Experimental Therapeutics and GI Oncology Department, National Cancer Center Hospital East, Kashiwa (Y.K.) — both in Japan; the Medicine Department of Hematology, Oncology, and Tumor Immunology, Charité–Universitätsmedizin Berlin, Berlin (D.P.M.); the Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona (D.P.L.-B.); Université Paris Cité, Site de Recherche Intégrée sur le Cancer, Cancer Research for Personalized Medicine Comprehensive Cancer Center, Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges–Pompidou, Paris (J.T.); the Department of Biological Chemistry, National and Kapodistrian University of Athens–School of Medicine, Athens (M.V.K.); Gastrointestinal Oncology Department and Translational Medicine Laboratory, Instituto Nacional de Cancerologia, Mexico City (E.R.-G.); the Oncology Department, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (T.W.K.); the Medicine Department, Royal Marsden Hospital, London (D.C.); and the Department of Oncology, National Taiwan University Hospital, and the Graduate Institute of Oncology, National Taiwan University College of Medicine — both in Taipei (K.H.Y.).

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