Overall Survival Analysis of the Phase III CodeBreaK 300 Study of Sotorasib Plus Panitumumab Versus Investigator's Choice in Chemorefractory *KRAS* G12C Colorectal Cancer

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ABSTRACT

In the phase III CodeBreaK 300 study, sotorasib 960 mg-panitumumab significantly prolonged progression-free survival (PFS) versus investigator's choice (trifluridine/tipiracil or regorafenib) in patients with *KRAS* G12C-mutated chemorefractory metastatic colorectal cancer (mCRC). One hundred sixty patients were randomly assigned 1:1:1 to receive sotorasib 960 mg-panitumumab (n = 53), sotorasib 240 mg-panitumumab (n = 53), or investigator's choice (n = 54; crossover permitted after primary analysis). Overall survival (OS) analysis, a key secondary end point, although not adequately powered, was prespecified at 50% maturity (after approximately 80 deaths). In this study, we report the OS, updated overall response rates (ORRs), and data for safety. After a median follow-up of 13.6 months, 24, 28, and 30 deaths occurred in the sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice arms, respectively; updated objective response rates (ORRs; 95% CI) were 30.2% (95% CI, 18.3 to 44.3), 7.5% (95% CI, 2.1 to 18.2), and 1.9% (95% CI, 0.0 to 9.9), respectively. Compared with investigator's choice, the hazard ratios (HRs [95% CI]) for OS were 0.70 (95% CI, 0.41 to 1.18; two-sided $P = .20$) with sotorasib 960 mg-panitumumab and 0.83 (95% CI, 0.49 to 1.39; two-sided $P = .50$) with sotorasib 240 mg-panitumumab. No new safety signals were observed. Although not statistically significant, the observed OS HR and ORR along with prior PFS and safety findings support sotorasib 960 mg-panitumumab as a standard of care in patients with chemorefractory *KRAS* G12C mCRC.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

The randomized, phase III CodeBreaK 300 study (ClinicalTrials.gov identifier: NCT05198934) evaluated sotorasib, a specific and irreversible $KRAS^{G12C}$ inhibitor, at two doses (960 and 240 mg) in combination with panitumumab, an epidermal growth factor receptor (EGFR) inhibitor, for the treatment of patients with *KRAS* G12C-mutated chemorefractory metastatic colorectal cancer (mCRC).[1] The primary analysis showed significantly prolonged progression-free survival (PFS) with sotorasib 960 mg-panitumumab versus investigator's choice of trifluridine/tipiracil or regorafenib (median PFS, 5.6 *v* 2.0 months; hazard ratio [HR], 0.48; 95% CI, 0.30-0.78; $P = .005$).[1] In this study, we report findings from the protocol-specified final analysis of overall survival (OS), a key secondary end point.

METHODS

Trial Design and Patients

Details of the CodeBreaK 300 trial have been published previously.[1] Adult patients with *KRAS* G12C-mutated chemorefractory mCRC who were $KRAS^{G12C}$ inhibitor naïve were randomly assigned 1:1:1 to receive sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, or investigator's choice (trifluridine/tipiracil or regorafenib). The protocol was approved by the institutional review boards or independent ethics committees at each site. All patients

provided written informed consent as per the Declaration of Helsinki principles.

End Points and Assessments

OS (time from random assignment to death from any cause) and objective response rate (ORR) by blinded independent central review (BICR) per RECIST v1.1 were the key secondary end points. Other secondary end points included time to response, duration of response (DOR), and disease control (complete response, partial response, and stable disease) per BICR and safety. Criteria for tumor response assessment and adverse event (AE) severity grading have been described previously.[1] Testing strategy (Appendix Fig A1) and statistical analysis methodology are reported in Appendix 1.

RESULTS

Patients and Treatment

Between April 19, 2022, and March 14, 2023, 160 patients (intention-to-treat [ITT] population) were randomly assigned to receive sotorasib 960 mg-panitumumab (n = 53), sotorasib 240 mg-panitumumab (n = 53), or investigator's choice (n = 54 [trifluridine/tipiracil, n = 37; regorafenib, n = 14]; Fig 1). Baseline demographic and clinical characteristics of the treatment arms were generally balanced (Table 1).

The median duration of follow-up was 13.6 months. At data cutoff, 11 patients (20.8%), 8 patients (15.1%), and 1 patient (1.9%) remained on treatment in the sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice arms, respectively; the median (range) treatment duration was 6.0 months (1.0-16.3), 4.6 months (0.9-15.8), and 2.2 months (0.8-13.3), and after the randomly assigned treatment, 1 patient (1.9%), 0 patients, and 17 patients (31.5%) received subsequent $KRAS^{G12C}$ inhibitor off-protocol.

Final OS Analysis

At data cutoff, 82 deaths occurred (Table 2). The estimated HR for OS was 0.70 (95% CI, 0.41 to 1.18; two-sided $P = .20$ *v* statistically significance threshold 0.01875) with sotorasib 960 mg-panitumumab and 0.83 (95% CI, 0.49 to 1.39; descriptive two-sided $P = .50$) with sotorasib 240 mg-panitumumab (Fig 2 and Table 2). Median OS was not reached (not estimable [NE], 95% CI, 8.61 to NE) with sotorasib 960 mg-panitumumab, and it was 11.9 months (95% CI, 7.52 to NE) with sotorasib 240 mg-panitumumab and 10.3 months (95% CI, 7.00 to NE) with investigator's choice (Fig 2 and Table 2). The OS trend with sotorasib 960 mg-panitumumab in prespecified key subgroups was consistent with that in the ITT population; however, the small sample size of some subgroups caused wide CIs (Fig 2).

Subsequent Anticancer Therapy and OS Adjustment

While crossover was permitted after the primary analysis, no official on-protocol crossover had occurred at the time of the

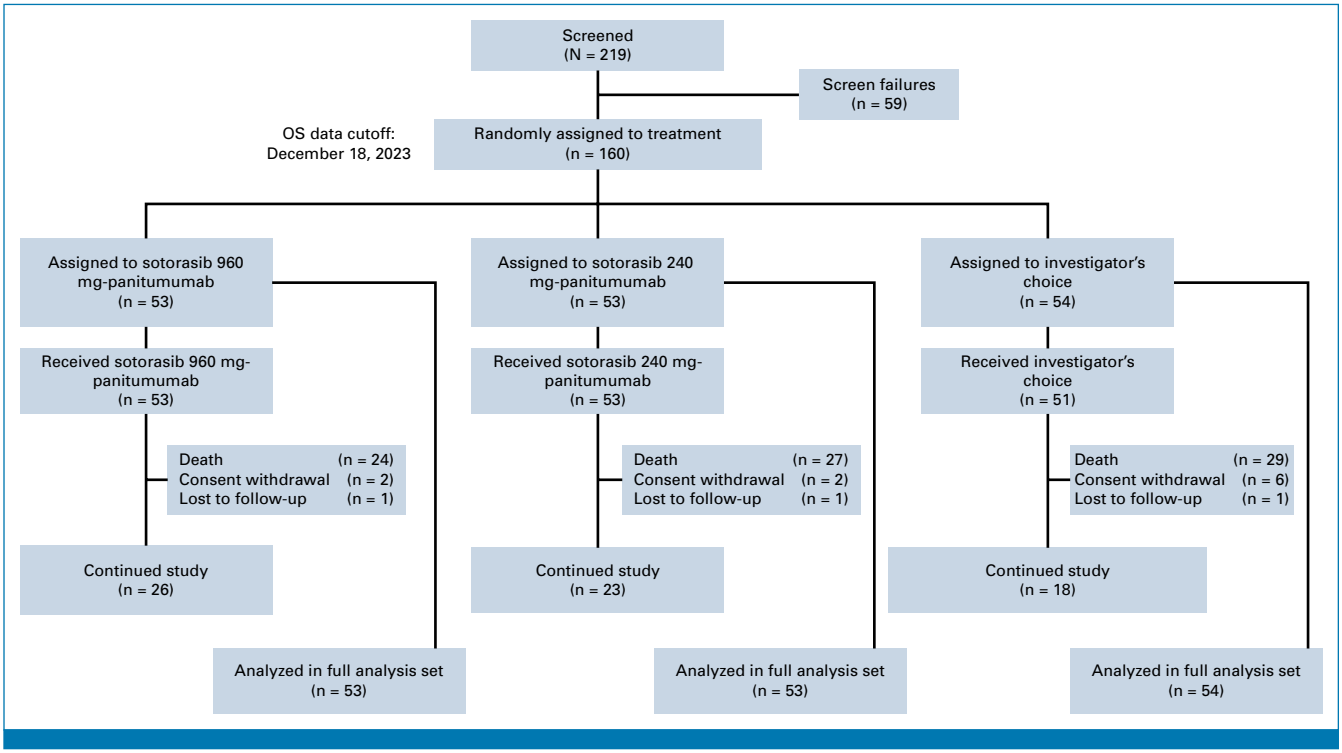

FIG 1. CONSORT diagram of patient disposition. For the sotorasib-panitumumab arms, data on patient numbers continuing treatment (treatment ongoing) represents continuing any component of the doublet for a patient. OS, overall survival.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Sotorasib 960 mg-Panitumumab (n = 53)	Sotorasib 240 mg-Panitumumab (n = 53)	Investigator's Choice (n = 54)
Age, years, median (range)	63.0 (37-79)	58.0 (35-82)	65 (34-81)
Age category, years, No. (%)			
<65	32 (60.4)	39 (73.6)	27 (50.0)
≥65	21 (39.6)	14 (26.4)	28 (51.9)
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. (%)[a]			
Asian	6 (11.3)	22 (41.5)	12 (22.2)
Black	0	1 (1.9)	0
White	42 (79.2)	30 (56.6)	37 (68.5)
Other	5 (9.4)	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 random assignment, months, No. (%)			
≥18	29 (54.7)	29 (54.7)	31 (57.4)
<18	24 (45.3)	22 (41.5)	23 (42.6)
Unknown	0	2 (3.8)	0
ECOG performance status score, No. (%)[b]			
0	32 (60.4)	29 (54.7)	36 (66.7)
1	19 (35.8)	22 (41.5)	17 (31.5)
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)
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)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a]Race was either reported by the patient or determined by the investigator.

[b]The ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.

TABLE 2. Overall Survival, Kaplan-Meier Estimates, Efficacy Summary According to Blinded Independent Central Review, and Details of Subsequent Anticancer Therapies After Progression on Study

Variable	Sotorasib 960 mg-Panitumumab (n = 53)	Sotorasib 240 mg-Panitumumab (n = 53)	Investigator's Choice (n = 54)
Key secondary end point			
Death	24 (45.3)	28 (52.8)	30 (55.6)
Data censored	29 (54.7)	25 (47.2)	24 (44.4)
HR (95% CI)[a]	0.70 (0.41 to 1.18)	0.83 (0.49 to 1.39)	
P value (two-sided)[b]	.20	.50	
Median OS, months (95% CI)[c]	NE (8.61 to NE)	11.9 (7.5 to NE)	10.3 (7.0 to NE)
KM estimated OS, % (95% CI)[d]			
At 12 months	52.2 (37.4 to 65.1)	50.0 (35.6 to 62.7)	45.6 (31.1 to 59.1)
At 18 months	52.2 (37.4 to 65.1)	38.7 (20.9 to 56.2)	35.5 (20.8 to 50.5)
Primary end point			
PFS			
Median, months (95% CI)[c]	5.7 (4.2 to 7.5)	4.01 (3.7 to 5.9)	2.04 (1.9 to 3.9)
HR (95% CI)[a]	0.45 (0.29 to 0.72)	0.57 (0.37 to 0.88)	
Secondary end points			
Best overall response			
Complete response	1 (1.9)	1 (1.9)	0 (0.0)
Partial response	15 (28.3)	3 (5.7)	1 (1.9)
Stable disease	22 (41.5)	33 (62.3)	24 (44.4)
Progressive disease	12 (22.6)	13 (24.5)	19 (35.2)
Noncomplete response/nonprogressive disease	0 (0.0)	2 (3.8)	1 (1.9)
Not done	2 (3.8)	0 (0.0)	9 (16.7)
No assessable disease at baseline	1 (1.9)	1 (1.9)	0 (0.0)
ORR, % (95% CI)[e]	30.2 (18.3 to 44.3)	7.5 (2.1 to 18.2)	1.9 (0.0 to 9.9)
Difference of ORR (95% CI)[f]	28.9 (15.5 to 42.3)	5.3 (-2.8 to 13.3)	
Disease control rate, % (95% CI)[e]	71.7 (57.7 to 83.2)	69.8 (55.7 to 81.7)	46.3 (32.6 to 60.4)
DOR[g]			
Median, months (95% CI)	10.1 (3.9 to NE)	—	—
Time to response[g]			
Median, months (range)	3.0 (1.9-5.7)	1.8 (1.7-5.5)	7.6 (7.6-7.6)
Patients with subsequent anticancer therapy	23 (43.4)	27 (50.9)	33 (61.1)
$KRAS^{G12C}$ inhibitor			
Any $KRAS^{G12C}$ inhibitor	1 (1.9)	0	17 (31.5)
Sotorasib monotherapy	1 (1.9)	0	0
$KRAS^{G12C}$ inhibitor plus EGFR antibody[h]	0	0	15 (27.8)
Sotorasib plus panitumumab	0	0	5 (9.3)
$KRAS^{G12C}$ inhibitor plus other combination	0	0	2 (3.7)
$KRAS^{G12C}$ inhibitor monotherapy	1 (1.9)	0	0
Control arm agents			
Regorafenib	8 (15.1)	6 (11.3)	8 (14.8)
Trifluridine/tipiracil	12 (22.6)	19 (35.8)	6 (11.1)
Regorafenib or trifluridine/tipiracil	15 (28.3)	22 (41.5)	14 (25.9)
Antiangiogenics			
Bevacizumab	9 (17.0)	12 (22.6)	7 (13.0)
Aflibercept	0	0	0
Ramucirumab	1 (1.9)	0	0
Chemotherapy agents			
Oxaliplatin	5 (9.4)	3 (5.7)	2 (3.7)
Irinotecan	1 (1.9)	3 (5.7)	4 (7.4)

(continued on following page)

TABLE 2. Overall Survival, Kaplan-Meier Estimates, Efficacy Summary According to Blinded Independent Central Review, and Details of Subsequent Anticancer Therapies After Progression on Study (continued)

Variable	Sotorasib 960 mg-Panitumumab (n = 53)	Sotorasib 240 mg-Panitumumab (n = 53)	Investigator's Choice (n = 54)
Fluoropyrimidine	15 (28.3)	23 (43.4)	13 (24.1)
Oxaliplatin and irinotecan and fluoropyrimidine	1 (1.9)	1 (1.9)	1 (1.9)
Other	6 (11.3)	6 (11.3)	3 (5.6)
Time from random assignment to start of first subsequent anticancer therapy, months			
N	23	27	33
Median (range)	6.2 (2.3-15.0)	4.5 (2.0-13.7)	4.3 (0.2-14.1)

NOTE. Data are No. (%) unless indicated otherwise. The intention-to-treat analysis set included all patients who underwent random assignment. Abbreviations: DOR, duration of response; EGFR, epidermal growth factor receptor; HR, hazard ratio; KM, Kaplan-Meier; KRAS, Kirsten rat sarcoma viral oncogene homolog; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]HRs versus investigator's choice and 95% CIs were estimated using a stratified Cox proportional hazards model.
[b]*P* value was calculated using a stratified log-rank test.
[c]95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.
[d]OS rates and 95% CIs were estimated using the method by Kalbfleisch and Prentice with log-log transformation.
[e]95% CIs were estimated using the Clopper-Pearson method.
[f]Difference of proportions versus investigator's choice and 95% CI were estimated using the stratified Cochran-Mantel-Haenszel method.
[g]DOR and time to response were estimated only for patients who achieved a confirmed best overall response of partial response or complete response.
[h]For patients who crossed over from investigator's choice to sotorasib 960 mg-panitumumab, the data reported are from the date of the first dose of investigator's choice to the date of the first dose of sotorasib 960 mg-panitumumab.

OS final analysis. Details of receiving subsequent anticancer therapy (including $KRAS^{G12C}$ inhibitors) are provided in Table 2. $KRAS^{G12C}$ inhibitor plus anti-EGFR antibody was received by 15 (27.8%) patients in the investigator's choice arm. An ad hoc sensitivity analysis to adjust for confounding effects of initiating subsequent therapies of interest ($KRAS^{G12C}$ inhibitor plus EGFR inhibitor) showed a stratified HR of 0.65 (95% CI, 0.28 to 1.37) for the sotorasib 960 mg-panitumumab versus investigator's choice arm and 0.84 (95% CI, 0.44 to 1.58) for the sotorasib 240 mg-panitumumab arm (Appendix Fig A2, Appendix Table A1).

Updated Efficacy Results

ORR (95% CI) was 30.2% (95% CI, 18.3 to 44.3), 7.5% (95% CI, 2.1 to 18.2), and 1.9% (95% CI, 0.0 to 9.9) with sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice, respectively. As statistical significance for OS was not achieved, ORR per BICR was not formally tested (Appendix Fig A3). Median DOR was 10.1 months (95% CI, 3.9 to NE) in the sotorasib 960 mg-panitumumab arm. Further efficacy updates are provided in Table 2.

Safety

AE profiles across arms were consistent with those previously reported (Appendix Table A2).[1] Grade ≥3 treatment-related AEs (TRAEs) occurred in 45.3%, 34.0%, and 45.1% of patients receiving sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice, respectively; the most common (≥5% patient incidence) were dermatitis acneiform, hypomagnesemia, and rash with sotorasib 960 mg-panitumumab; hypomagnesemia and diarrhea with sotorasib 240 mg-panitumumab; and neutropenia, anemia, and hypertension with investigator's choice. As events of interest, treatment-related grade ≥3 hepatoxicity events occurred in 1.9%, 0%, and 2.0% of patients receiving sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice, respectively.

DISCUSSION

At this protocol-specified analysis of OS, sotorasib 960 mg-panitumumab, although not statistically significant, could suggest a potential 30.0% relative reduction in the risk of death versus investigator's choice (HR, 0.70 [95% CI, 0.41 to 1.18], $P = .2$) in patients with chemorefractory *KRAS* G12C-mutated mCRC. This is promising for an incurable disease with a critical unmet need for molecularly selected therapies providing survival benefit. Updated ORRs across treatment arms were numerically slightly higher than those reported previously and remained higher with sotorasib 960 mg-panitumumab versus investigator's choice. Despite higher use of subsequent therapies in the investigator's choice arm (61.1%) versus both sotorasib-panitumumab arms (43.4% and 50.9%), OS trends were similar after adjusting for subsequent medications such as a $KRAS^{G12C}$ inhibitor plus EGFR inhibitor.

These findings support that the benefit provided by sotorasib 960 mg-panitumumab in PFS and RECIST responses translated toward potential improvement in OS, even with >30% of patients in the control arm receiving $KRAS^{G12C}$ inhibitor

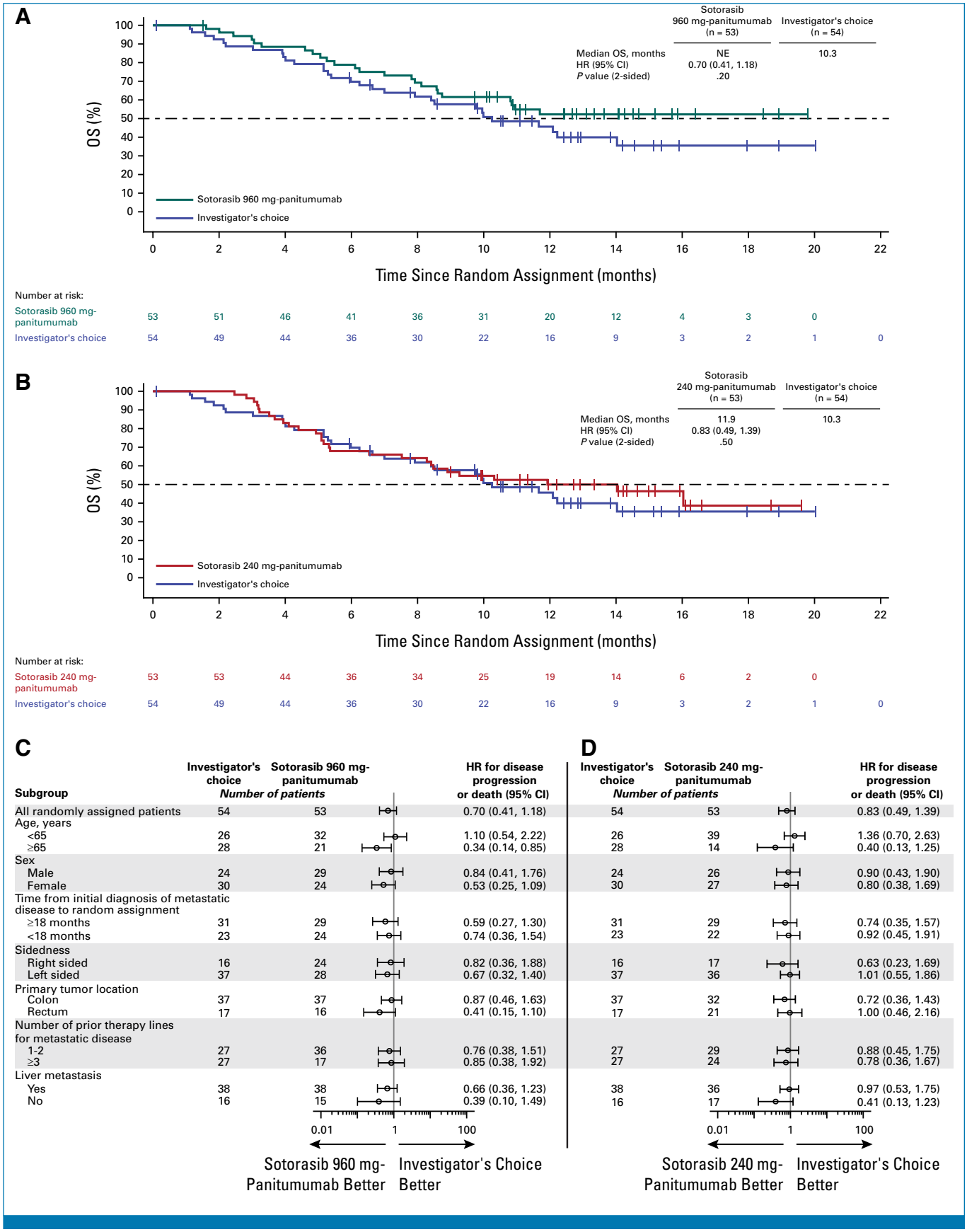

FIG 2. OS of sotorasib-panitumumab versus investigator's choice. (A) Kaplan-Meier curves of OS for sotorasib 960 mg-panitumumab (full analysis set). (B) Kaplan-Meier curves of OS for sotorasib 240 mg-panitumumab (full analysis set). (C) Forest plot of sotorasib 960 mg-panitumumab treatment effect on OS in subgroup analyses. (D) Forest plot of sotorasib 240 mg-panitumumab treatment effect (continued on following page)

FIG 2. (Continued). on OS in subgroup analyses. The dashed horizontal gray line indicates the median value. Vertical bars indicate censoring. Stratified Cox hazard ratio and stratified log-rank *P* value for sotorasib-panitumumab versus investigator's choice are provided. The intention-to-treat population included all patients who underwent random assignment. Hazard ratio was not estimated when there were fewer than 10 patients in either treatment arm in a subgroup. HR, hazard ratio; NE, not estimable; OS, overall survival.

combination as post-trial therapy. As the study was not powered for OS, the observed HR of 0.70 and the median not being reached after 13.6 months of follow-up versus a median of 10.3 months in the control arm indicate that even if not statistically different, OS improvement could be particularly meaningful, especially given that PFS is significantly longer.

The median OS with investigator's choice in this study was higher (10.3 months) than that reported in similar phase III trials of trifluridine/tipiracil (7.1 months)[2] or regorafenib (6.4 months),[3] which could be due to differences in patient populations and study designs (molecularly unselected patients and no crossover between treatment arms) and the availability of additional salvage therapies. Concurrent advances in late-line treatment of refractory mCRC showed significant OS improvements with regimens such as trifluridine/tipiracil plus bevacizumab (SUNLIGHT) and single-agent fruquintinib (FRESCO-2), establishing both regimens as the new standard of care.[4,5]

Real-world data and the phase III RECOURSE trial showed that *KRAS* G12C mutations were predictive biomarkers for reduced OS benefit of trifluridine/tipiracil in late-stage mCRC, affecting patients eligible for treatment with these agents.[6] A recent post hoc analysis of the SUNLIGHT trial showed that trifluridine/tipiracil plus bevacizumab improved OS versus trifluridine/tipiracil alone in patients with *KRAS* G12-mutated mCRC; OS trends were similar across all codon 12 *KRAS* mutations.[7] Owing to differences in patient population and specific mutation, our study cannot be directly compared. While the benefit of adding bevacizumab to trifluridine/tipiracil in this molecular subgroup is unknown, targeting an identified molecular driver alteration is strongly preferred as a therapeutic strategy. As RAS testing, including *KRAS* G12C status, is routinely performed for patients with CRC to guide treatment with EGFR inhibitors, the sotorasib-panitumumab combination strategy can be readily integrated into the current treatment continuum for chemorefractory mCRC owing to its clinical benefits of a high response rate and long DORs.[6] The KRYSTAL-1 trial used a combination of adagrasib and cetuximab for the treatment of mCRC and reported a median PFS of 6.9 months and ORR of 34.0%, which were comparable with our study despite the lack of a control arm and caveats of cross-trial comparison.[8]

The trial allowed crossover considering the unmet need in this chemorefractory patient population only after the primary analysis. However, patients in the control arm who subsequently received $KRAS^{G12C}$ inhibitors had access to these options out of the trial, either in another clinical trial or as off-label usage, which might bias the interpretation of the OS results. As in the unadjusted ITT analysis (HR, 0.70 [95% CI, 0.41 to 1.18], $P = .2$), the benefit with sotorasib 960 mg-panitumumab treatment was generally comparable (HR, 0.65 [95% CI, 0.28 to 1.37]) accounting for 15 of 54 patients in the investigator's choice arm who received a $KRAS^{G12C}$ inhibitor plus EGFR inhibitor as post-trial therapy. In addition, AE profiles across treatment arms remained consistent with the previous report with approximately 6 additional months of follow-up.

In conclusion, while to our knowledge this was the first phase III study of a $KRAS^{G12C}$ inhibitor plus an EGFR inhibitor to show a significant prolongation in PFS over standard therapies in chemorefractory mCRC, it was not powered to detect a statistically significant difference in OS. This was due to the small sample size in the study owing to the rarity of this patient population. Moreover, the post-trial use of $KRAS^{G12C}$ plus EGFR inhibitors in 27.8% of the patients in the investigator's choice arm outside of the trial could have further confounded the OS results. However, the analyses suggest a potential improvement in OS with sotorasib 960 mg-panitumumab versus investigator's choice.

Considering all the reported improved outcomes, this study supports a consistent treatment benefit of sotorasib 960 mg-panitumumab as a new standard-of-care treatment for patients with *KRAS* G12C-mutated chemorefractory mCRC.

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DISCLAIMER

The sponsor was involved in the design and conduct of the study, the analysis and interpretation of the data, and the decision to submit this manuscript. Amgen managed patient data collected at the study sites and provided medical writing support.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Overall Survival Analysis of the Phase III CodeBreaK 300 Study of Sotorasib Plus Panitumumab Versus Investigator's Choice in Chemorefractory *KRAS* G12C Colorectal Cancer

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APPENDIX 1. STATISTICAL ANALYSIS

Statistical analysis methods for this trial have been previously reported.[1] All randomly assigned patients were included in efficacy analyses (intention-to-treat). Safety was assessed in all randomly assigned patients who received at least 1 dose of assigned treatment. The sample size was estimated on the basis of the primary end point of blinded independent central review–assessed progression-free survival (PFS) and has been reported previously.[1] Overall survival (OS) was tested only if PFS results for the sotorasib combination arm (960 or 240 mg) versus control arm reached statistical significance according to the prespecified conditions in the protocol.

A hierarchical testing strategy between PFS, OS, and overall response rate (ORR) was used to control the overall type I error rate at two-sided 5% alpha using the Maurer-Bretz testing procedure (Appendix Fig A1). Because statistical significance was achieved for sotorasib 960 mg-panitumumab at the PFS primary analysis, 2.5%*(3/4) alpha was propagated to test OS for sotorasib 960 mg-panitumumab versus investigator's choice at its final analysis using the stratified log-rank test, which was specified to occur after 50% of patients had observed events (approximately 80 deaths). OS for sotorasib 240 mg-panitumumab is included descriptively. The study sample size was not powered to demonstrate a statistically significant difference in OS. This OS analysis timing aimed to provide more mature OS data subsequent to the previous analysis triggered by PFS. A later timing for additional OS events would not substantially increase the OS power because of sample size constraint. If OS achieved statistical significance at its final analysis, ORR would be tested.

The Kaplan-Meier method was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the hazard ratio and 95% CI for death in the OS analysis. Random assignment stratification factors were applied to the stratified Cox model. The median follow-up time for OS was estimated using the reversed Kaplan-Meier method.

TABLE A1. OS Sensitivity Analyses for Initiation of Subsequent Anticancer Therapies of Interest (full analysis set)

Variable	Sotorasib 960 mg-Panitumumab (n = 53)	Sotorasib 240 mg-Panitumumab (n = 53)	Investigator's Choice (n = 54)
Number of patients received subsequent $KRAS^{G12C}$ inhibitor plus EGFR antibody			15 (27.8)
RPSFTM adjusted			
Number of events after adjustment (%)	24 (45.3)	28 (52.8)	26 (48.1)
Acceleration factor (95% CI)[a]	1.41 (0.68 to 2.28)	1.295 (0.66 to 2.07)	
HR (95% CI)[b]	0.65 (0.28 to 1.37)	0.842 (0.44 to 1.58)	

Data are No. (%) unless indicated otherwise.

Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio; KRAS, Kirsten rat sarcoma viral oncogene homolog; OS, overall survival; RPSFTM, rank preserving structural failure time model.

[a]A g-estimation procedure was used to find the value of the acceleration factor and its 95% CI such that the counterfactual OS times were balanced across the treatment groups. Recensoring was applied to the counterfactual OS times.

[b]HRs were estimated using a stratified Cox proportional hazards model. 95% CIs were estimated using bootstrapping (1,000 samples) for RPSFTM.

TABLE A2. TRAEs in the Safety Population[a]

TRAE[b]	Sotorasib 960 mg-Panitumumab (n = 53)	Sotorasib 240 mg-Panitumumab (n = 53)	Investigator's Choice (n = 51)
Any grade	51 (96.2)	53 (100.0)	42 (82.4)
Grade ≥3	24 (45.3)	18 (34.0)	23 (45.1)
Grade ≥4	2 (3.8)	0	2 (3.9)
Serious	4 (7.5)	0	4 (7.8)
Fatal	0	0	0
Sotorasib-related	34 (64.2)	38 (71.7)	0
Panitumumab-related	49 (92.5)	50 (94.3)	0
Leading to discontinuation of:			
Any treatment	2 (3.8)	2 (3.8)	1 (2.0)
Sotorasib	1 (1.9)	2 (3.8)	0
Panitumumab	2 (3.8)	2 (3.8)	0
Sotorasib and panitumumab	1 (1.9)	2 (3.8)	0
Leading to dose reduction[c] of:			
Any treatment	13 (24.5)	10 (18.9)	10 (19.6)
Sotorasib	3 (5.7)	0	0
Panitumumab	10 (18.9)	10 (18.9)	0
Sotorasib and panitumumab	0	0	0
Leading to dose interruption of:			
Any treatment	24 (45.3)	21 (39.6)	21 (41.2)
Sotorasib	13 (24.5)	14 (26.4)	0
Panitumumab	19 (35.8)	19 (35.8)	0
Sotorasib and panitumumab	7 (13.2)	12 (22.6)	0
Skin and subcutaneous tissue disorders[d]	45 (84.9)	46 (86.8)	11 (21.6)

Event[e]	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Anemia	4 (7.5)	2 (3.8)	5 (9.4)	1 (1.9)	10 (19.6)	4 (7.8)
Thrombocytopenia	1 (1.9)	0	2 (3.8)	0	3 (5.9)	0
Leukopenia	0	0	0	0	4 (7.8)	2 (3.9)
Neutropenia	0	0	0	0	16 (31.4)	12 (23.5)
Diarrhea	12 (22.6)	2 (3.8)	10 (18.9)	3 (5.7)	11 (21.6)	0
Nausea	6 (11.3)	1 (1.9)	12 (22.6)	2 (3.8)	16 (31.4)	1 (2.0)
Vomiting	3 (5.7)	0	7 (13.2)	0	5 (9.8)	0
Constipation	2 (3.8)	0	4 (7.5)	0	2 (3.9)	0
Stomatitis	4 (7.5)	0	5 (9.4)	0	6 (11.8)	0
Fatigue	4 (7.5)	0	4 (7.5)	0	9 (17.6)	2 (3.9)
Mucosal inflammation	7 (13.2)	0	1 (1.9)	0	2 (3.9)	0
Asthenia	4 (7.5)	0	3 (5.7)	0	7 (13.7)	0
Xerosis	6 (11.3)	0	1 (1.9)	0	0	0
Malaise	0	0	2 (3.8)	0	3 (5.9)	0
Pyrexia	0	0	0	0	3 (5.9)	0
Folliculitis	9 (17.0)	0	2 (3.8)	0	0	0
Paronychia	6 (11.3)	0	10 (18.9)	0	0	0
Conjunctivitis	3 (5.7)	0	2 (3.8)	0	0	0
Weight decreased	1 (1.9)	0	1 (1.9)	0	3 (5.9)	0
Neutrophil count decreased	1 (1.9)	0	2 (3.8)	0	4 (7.8)	2 (3.9)
Hypomagnesemia	16 (30.2)	4 (7.5)	16 (30.2)	6 (11.3)	1 (2.0)	0
Decreased appetite	4 (7.5)	0	3 (5.7)	0	6 (11.8)	0
Hypocalcemia	3 (5.7)	0	2 (3.8)	0	0	0

(continued on following page)

TABLE A2. TRAEs in the Safety Population[a] (continued)

Event[e]	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Rash	15 (28.3)	3 (5.7)	13 (24.5)	3 (5.7)	1 (2.0)	0
Dermatitis acneiform	14 (26.4)	9 (17.0)	23 (43.4)	3 (5.7)	1 (2.0)	0
Dry skin	10 (18.9)	0	13 (24.5)	0	0	0
Pruritus	10 (18.9)	0	7 (13.2)	0	2 (3.9)	0
Skin fissures	7 (13.2)		6 (11.3)		0	
Skin toxicity	6 (11.3)	2 (3.8)	4 (7.5)	1 (1.9)	1 (2.0)	1 (2.0)
Palmar-plantar erythrodysesthesia syndrome	6 (11.3)	0	5 (9.4)	0	5 (9.8)	2 (3.9)
Rash maculopapular	3 (5.7)	0	3 (5.7)	0	1 (2.0)	0
Hypertrichosis	1 (1.9)	0	3 (5.7)	0	0	0
Alopecia	0	0	2 (3.8)	0	3 (5.9)	0
Hypertension	0	0	1 (1.9)	0	7 (13.7)	3 (5.9)

NOTE. Data are No. (%). AEs were coded using MedDRA version 26.1. The CTCAE version 5.0 was used to grade severity of AEs.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic case report form; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]The safety analysis set included all randomly assigned patients who received at least 1 dose of their assigned treatment.
[b]TRAEs are those TEAEs deemed related to study treatment as per the investigator as reported on the eCRF. A TEAE was considered a TRAE if there was a reasonable possibility that the event may have been caused by the study treatment. In the unlikely event that the relationship was missing, the TEAE was considered treatment related.
[c]Sotorasib dose reduction was not allowed for the 240-mg group. Patients could resume the same dose after interruption or permanently discontinue.
[d]Data denote the "Skin and subcutaneous tissue disorders" system organ class.
[e]Any-grade events listed are those that occurred in at least 5% of patients in any arm. Grade ≥3 events listed are those that occurred in at least 3% of patients in any arm.

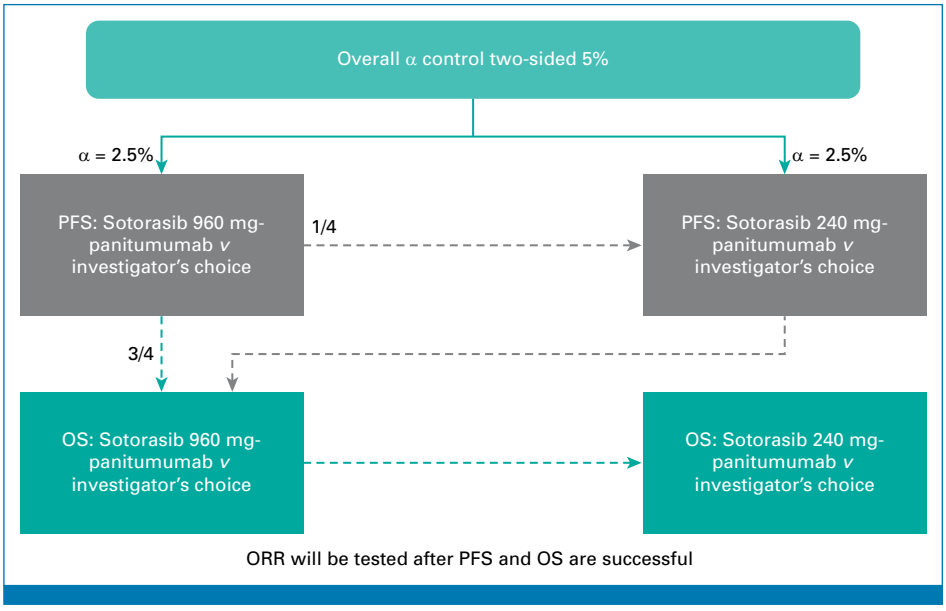

FIG A1. Multiple testing procedure for PFS and OS. OS, overall survival; PFS, progression-free survival.

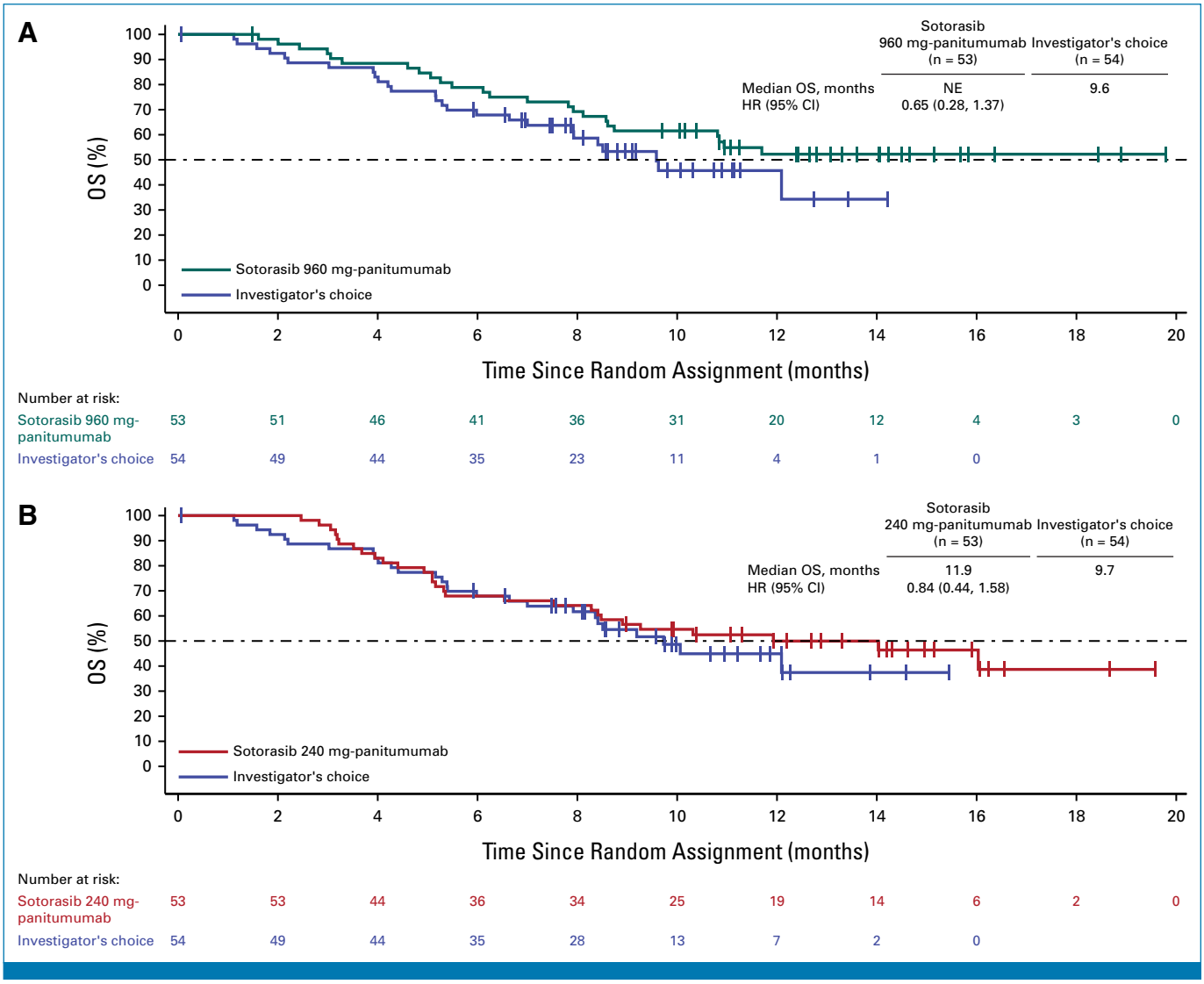

FIG A2. OS of sotorasib-panitumumab versus investigator's choice adjusting for control patients receiving subsequent KRAS^{G12C} inhibitor plus EGFR antibody (full analysis set). EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; NE, not estimable.

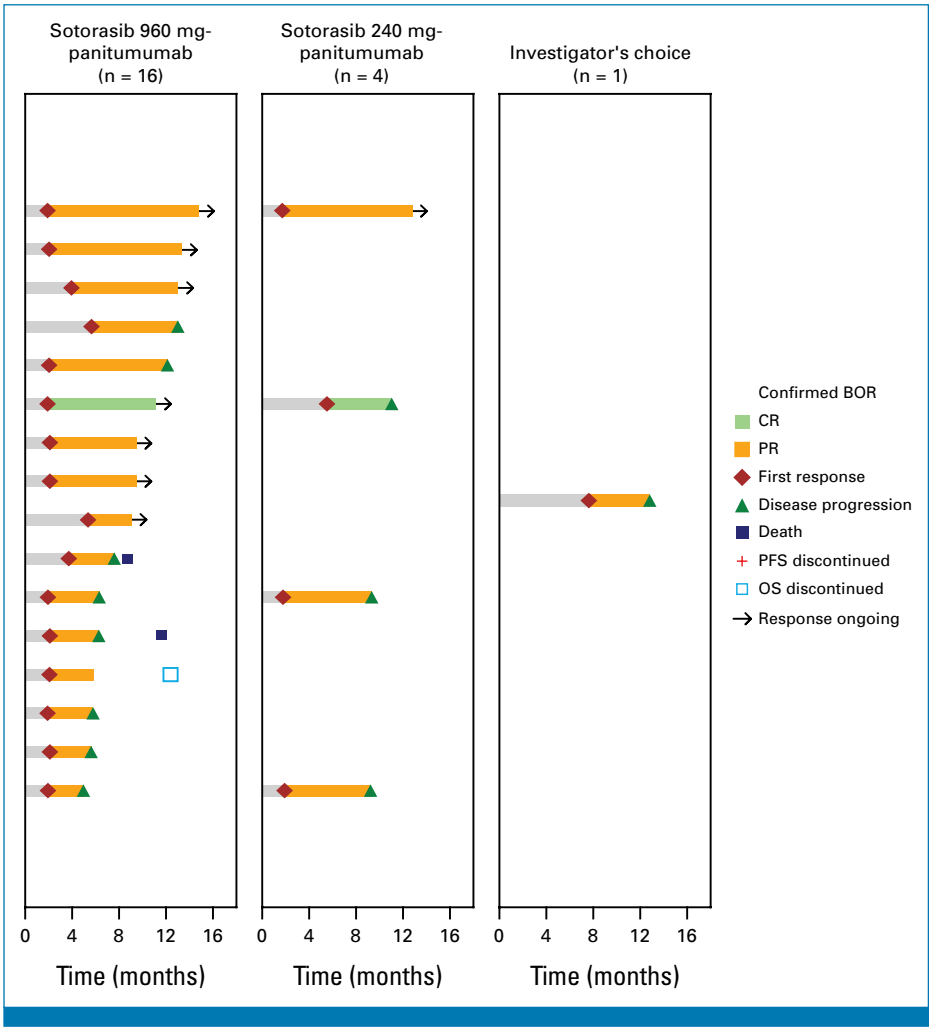

FIG A3. Swimmer plot of duration of response by BICR (responders in the full analysis set). BICR, blinded independent central review; BOR, best overall response; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response.