



Health-related quality of life in patients with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer treated with sotorasib plus panitumumab or standard of care (CodeBreak 300): results from a phase 3, randomised clinical trial



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Summary

Lancet Oncol 2025; 26: 1240–51

Published Online

August 11, 2025

[https://doi.org/10.1016/S1470-2045\(25\)00352-3](https://doi.org/10.1016/S1470-2045(25)00352-3)

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Background In the phase 3 CodeBreak 300 study, sotorasib (*KRAS*^{G12C} inhibitor) plus panitumumab (EGFR inhibitor) significantly prolonged progression-free survival versus investigator's choice of trifluridine–tipiracil or regorafenib (standard of care) in patients with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer. This analysis evaluated patient-reported outcomes (PROs) as secondary and exploratory endpoints.

Methods In this open-label, randomised clinical trial, adult (aged ≥18 years) patients from 67 centres in 13 countries in Asia, Australia, Europe, and North America with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer (as assessed by central molecular testing of tumour biopsy specimens) who were *KRAS*^{G12C} inhibitor-naïve, had progressed to recurrence after previous therapy with fluoropyrimidine, oxaliplatin, and irinotecan, with measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1, and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, were enrolled. Patients were randomly assigned 1:1:1 using interactive response technology to receive sotorasib 960 mg (daily, orally)–panitumumab (6 mg/kg every 2 weeks, intravenous infusion), sotorasib 240 mg (daily, orally)–panitumumab (6 mg/kg every 2 weeks, intravenous infusion), or investigator's choice of trifluridine–tipiracil (35 mg/m² [up to 80 mg per dose] on days 1–5 and 8–12 twice a day, orally) or regorafenib (160 mg daily for the first 21 days, orally). Randomisation was stratified by previous anti-angiogenic therapy, time from initial diagnosis of metastatic disease to randomisation, and ECOG performance status. The primary endpoint was progression-free survival (reported previously). PROs included fatigue at its worst according to the Brief Fatigue Inventory, pain at its worst according to the Brief Pain Inventory (where lower score is better), and Global Health Status–Quality of Life (GHS–QoL) and physical function subscales of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (where higher score is better) assessed via validated PRO questionnaires, administered at baseline, day 1 of each 4-week cycle until disease progression, and safety follow-up. Analyses were conducted in a modified intention-to-treat population. Least squares mean changes from baseline to week 9 were estimated using a mixed effects model for repeated measures. Time to deterioration (TTD), change in overall status, and patient-reported tolerability were also evaluated as prespecified exploratory outcomes. TTD was summarised using a stratified Cox proportional hazards model and Kaplan–Meier curve. Change in overall status and patient-reported tolerability were also summarised descriptively over time. The study is registered with ClinicalTrials.gov, NCT05198934, and prespecified analyses are completed.

Findings Between April 19, 2022, and March 14, 2023, 160 patients were enrolled and randomly assigned to receive sotorasib 960 mg–panitumumab (n=53), sotorasib 240 mg–panitumumab (n=53), and investigator's choice (n=54). Median duration of treatment was 6.0 months (IQR 3.7–7.0), 4.6 months (3.3–6.2), and 2.2 months (1.8–4.2) in these groups, respectively. 81 (51%) patients in the study were female; 109 (68%) patients were White, 40 (25%) were Asian, one (1%) was Black, and ten (6%) were of another race or not reported; 12 (8%) were Hispanic or Latino and three (2%) were of unknown ethnicity. Compliance rates for PRO assessments at week 9 were high (approximately 80%) and similar across treatment groups. Least squares mean changes in PROs at week 9 favoured the two sotorasib groups. Differences in changes from baseline for sotorasib 960 mg–panitumumab and sotorasib 240 mg–panitumumab (both vs investigator's choice), respectively were: –0.89 (95% CI –1.80 to 0.01) and –0.58 (–1.47 to 0.30) for fatigue at its worst, –1.45 (–2.32 to –0.58) and –1.14 (–2.00 to –0.28) for pain at its worst, 9.43 (2.31 to 16.56) and 6.49 (–0.43 to 13.41) for GHS–QoL, and 5.38 (–0.01 to 10.78) and 6.34 (1.07 to 11.62) for physical function.

Interpretation Along with improved clinical outcomes, these analyses suggest that sotorasib plus panitumumab could represent a valuable new treatment in patients with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer.

Funding Amgen.

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Introduction

Colorectal cancer is one of the leading causes of death from cancer worldwide, with metastases being the major cause of colorectal cancer-related mortality; the 5-year survival rate for metastatic colorectal cancer is approximately 15%.^{1,2} In addition to poor survival, the disease burden and toxicity associated with treatment can have a substantial effect on patients' health-related quality of life (HRQoL) with impairments reported for various HRQoL aspects such as fatigue, pain, and diminished physical functioning.^{3,4}

KRAS mutations are one of the most common activating mutations, present in about 40–50% of patients with colorectal cancer, with the KRAS^{G12C} mutation occurring in approximately 3% of cases.⁵ Although the prognostic relevance of KRAS^{G12C} is not fully established, studies suggest that KRAS^{G12C} mutation might be associated with worse clinical outcomes compared with non-G12C or KRAS wild-type colorectal cancer.^{5,6}

Historically, trifluridine–tipiracil or regorafenib has been the standard late-line therapy for chemorefractory metastatic colorectal cancer, demonstrating statistically superior yet clinically modest overall survival benefits versus placebo.^{7,8} Sotorasib is a specific and irreversible KRAS^{G12C} inhibitor that blocks downstream cell

proliferation and signalling, and has shown improved outcomes in patients with non-small-cell lung cancer with KRAS^{G12C} mutation.⁹ However, similar to other KRAS^{G12C} inhibitors, sotorasib monotherapy has shown limited activity in patients with colorectal cancer. This difference could be due to the sensitivity of KRAS^{G12C} to upstream signalling, primarily EGFR, in colorectal cancer.¹⁰ The phase 3 CodeBreak 300 study (NCT05198934) showed that treatment with the combination of sotorasib 960 mg and panitumumab (an EGFR inhibitor) resulted in a significant and clinically meaningful improvement in progression-free survival compared with investigator's choice of trifluridine–tipiracil or regorafenib (standard of care); median progression-free survival with sotorasib 960 mg–panitumumab was 5.6 months (95% CI 4.2–6.3) and with investigator's choice was 2.0 months (1.9–3.9; hazard ratio [HR] 0.48 [95% CI 0.30–0.78], $p=0.0047$) in patients with chemorefractory KRAS^{G12C}-mutated metastatic colorectal cancer.¹¹ This was accompanied by a non-significant risk reduction in death (overall survival HR 0.70 [95% CI 0.41–1.18]; $p=0.20$) with sotorasib 960 mg–panitumumab versus investigator's choice. Adverse events in the study were consistent with the well defined safety profiles of each agent, occurring in

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Research in context

Evidence before this study

We conducted a thorough search of PubMed from March 21, 2015, to March 21, 2025, with the search terms ("patient reported outcomes" OR "PRO") AND ("KRAS^{G12C}") for any data linking patient-reported outcomes (PROs) to KRAS^{G12C}-mutated cancers. No language restrictions were applied. The search identified two clinical studies, and both were related to non-small-cell lung cancer (NSCLC). The CodeBreak 200 study reported PROs in previously treated KRAS^{G12C}-mutated NSCLC where sotorasib was compared with docetaxel. The other article described an ongoing phase 2 study of neoadjuvant opnurasib (a KRAS^{G12C} inhibitor) in patients with surgically resectable NSCLC (CCTG IND.242A) which plans to report PROs. We found no phase 3 clinical trials assessing the effect of a combination of similar inhibitors on PROs in patients with KRAS^{G12C}-mutated chemorefractory metastatic colorectal cancer.

Added value of this study

To our knowledge, this is the first multicentre, randomised, phase 3 trial evaluating PROs in patients receiving a molecularly targeted treatment in KRAS^{G12C}-mutated chemorefractory metastatic colorectal cancer. Using validated PRO questionnaires, this study measured fatigue, pain, physical functioning, and several other symptoms that affect the

quality of life of patients receiving sotorasib plus panitumumab compared with those receiving investigator's choice of trifluridine–tipiracil or regorafenib (standard of care). The results of this study showed an overall improvement in several PRO measures from baseline to week 9 with sotorasib plus panitumumab compared with investigator's choice, which was also accompanied by delayed deterioration of PRO measures. A higher proportion of patients receiving sotorasib plus panitumumab also reported feeling improvement in their overall status compared with standard of care.

Implications of all the available evidence

Treatment with both doses of sotorasib combined with panitumumab improved several aspects of PROs directly relevant to patients. Parameters such as pain at its worst, Global Health Status–Quality of Life, and physical function, along with time to deterioration of physical function were considered to be meaningfully better with the combination of sotorasib and panitumumab. Combined with previous reports of improved clinical outcomes with this combination, the current analyses support the use of combination of sotorasib and panitumumab as a new standard-of-care treatment in patients with KRAS^{G12C}-mutated chemorefractory metastatic colorectal cancer.

51 (96%) of 53 patients receiving sotorasib 960 mg–panitumumab, 53 (100%) of 53 patients receiving sotorasib 240 mg–panitumumab, and 42 (82%) of 51 patients receiving investigator's choice of treatment.¹² The most common treatment-related adverse events were hypomagnesemia and skin toxicities with sotorasib and panitumumab combinations and neutropenia and nausea with investigator's choice. Treatment-related adverse events led to treatment discontinuation in two or fewer (2–4% of 53) patients in each of the sotorasib–panitumumab groups versus one (2% of 51) patient in the investigator's choice group.¹¹

In addition to evaluating the survival and safety outcomes, it is important to understand the impact of treatment on patients' HRQoL and symptom experiences. Therefore, the objective of this study was to assess patients' quality of life, symptom burden, and patient-reported tolerability of sotorasib plus panitumumab versus investigator's choice in patients with chemorefractory *KRAS*^{G12C}-mutated metastatic colorectal cancer, based on patient-reported outcome (PRO) measures included in CodeBreak 300.

Methods

Study design and participants

Details of the study design and patient eligibility for the CodeBreak 300 study are in the protocol (appendix 1) and have also been published previously.¹¹ Briefly, the trial enrolled adult (aged ≥18 years) patients from 67 centres in Australia, France, Germany, Greece, Italy, Japan, Mexico, South Korea, Spain, Taiwan, the UK, and the USA (appendix 2 pp 3–4) with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer as assessed by central molecular testing of tumour biopsy specimens who were *KRAS*^{G12C} inhibitor-naïve with measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, and had progressed to recurrence after receiving prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan (unless there was a medical contraindication to one of these chemotherapies). Sex and race or ethnicity were self-reported by study participants. The protocol and amendments were approved by site-specific ethics review boards,¹¹ and the study was conducted according to the principles of Good Clinical Practice and Declaration of Helsinki. This study is registered with ClinicalTrials.gov, NCT05198934.

Randomisation and masking

In this open-label study, patients were randomly assigned 1:1:1 to receive sotorasib 960 mg once daily plus panitumumab, sotorasib 240 mg once daily plus panitumumab, or investigator's choice of standard-care therapy (trifluridine–tipiracil or regorafenib), as described previously.¹¹ Randomisation was performed by an interactive response technology system, which

provided randomisation numbers. Eligible patients were stratified by previous anti-angiogenic therapy (yes vs no), time from initial diagnosis of metastatic disease to randomisation (≥18 months vs <18 months), and ECOG performance status (0 or 1 vs 2).

Procedures

Details related to treatment are provided in the protocol (appendix 1). Briefly, patients received sotorasib at a dose of 960 mg once daily orally along with panitumumab at a dose of 6 mg/kg every 2 weeks by intravenous infusion, sotorasib at a dose of 240 mg once daily orally along with panitumumab at a dose of 6 mg/kg every 2 weeks by intravenous infusion, or investigator's choice of trifluridine–tipiracil at a dose of 35 mg/m² (up to 80 mg per dose) on days 1–5 and 8–12 twice a day orally or regorafenib at a dose of 160 mg daily for the first 21 days orally. Treatment continued until independent central assessment of disease progression, unacceptable toxicity, initiation of another systemic anticancer therapy, patient request, or death, whichever occurred first.

PRO questionnaires administered in CodeBreak 300 included the Brief Fatigue Inventory (BFI); Brief Pain Inventory (BPI); European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), including the Global Health Status–Quality of Life (GHS–QoL) and physical function subscales; Patient Global Impression of Change (PGIC) questionnaire; and GP5 single item of the Functional Assessment of Cancer Therapy—General questionnaire (FACT-G GP5; a detailed description of the instruments is provided in appendix 2 p 2).^{13–17} These questionnaires, translated to the local language as applicable, were administered using an electronic device at baseline, before dosing on day 1 of each 4-week cycle thereafter until disease progression, and at the safety follow-up. Since PGIC captures changes from baseline, it was administered on day 1 of the second cycle before dosing. Questionnaires were also administered for economic modelling (see protocol).

Outcomes

The primary endpoint of CodeBreak 300 was progression-free survival, defined as the time from randomisation to the occurrence of disease progression or death from any cause (whichever occurred first), where disease progression was defined as per RECIST version 1.1 as assessed by blinded independent central review, and has been published previously.¹¹ Key secondary endpoints were overall survival (defined as time from randomisation until death from any cause) and objective response rate (defined as the proportion of participants in each treatment group who had complete or partial response) as per RECIST 1.1 as assessed by blinded independent central review, and

See Online for appendix 1

See Online for appendix 2

both have been published elsewhere.¹² The secondary and exploratory endpoints reported here are PROs at week 9 day 1, including BFI, BPI, EORTC QLQ-C30 (GHS-QoL and physical functioning), PGIC, and FACT-G GP5.

Statistical analysis

The analyses used data from the CodeBreak 300 primary analysis (data cutoff June 19, 2023; data snapshot March 7, 2024). The study was powered for the primary endpoint of progression-free survival, and statistical methods for the efficacy and safety analyses have been reported previously.¹¹ For PRO endpoints, sample size and power calculation were not considered, and hypothesis testing was not specified. PRO analyses were conducted as prespecified in the study statistical analysis plan. The analysis set for each questionnaire consisted of all randomly assigned participants with a non-missing baseline and at least one non-missing post-baseline results. Questionnaire compliance rates at each study visit were defined as the percentage of patients completing PRO assessments relative to all patients who were expected to have a visit. PRO

assessment at baseline was defined as the assessment before the first treatment administration. To account for delayed or missed treatment administration and varying end-of-treatment timepoints, PRO visit dates were classified into the analytical windows labelled by the week of the target assessment date (appendix 2 p 5).

The protocol emphasised four PRO measures: fatigue at its worst for BFI, pain at its worst for BPI, and the GHS-QoL and physical function subscales of EORTC QLQ-C30, as these were considered most important and directly relevant to patients with chemorefractory metastatic colorectal cancer.^{18,19} Nonetheless, changes in PRO scale scores from baseline to week 9 day 1 for all domains of the BPI, BFI, and EORTC QLQ-C30 were summarised descriptively. The week 9 day 1 timepoint was prespecified (protocol secondary endpoint “change from baseline over time to week 8” corresponds to the same assessment at week 9 day 1, since PRO visits were scheduled at the beginning of each 4-week treatment cycle). This timepoint was selected based on assumptions from the pivotal studies of the control group (trifluridine–tipiracil or regorafenib) and aligned with the first radiological assessment after baseline.

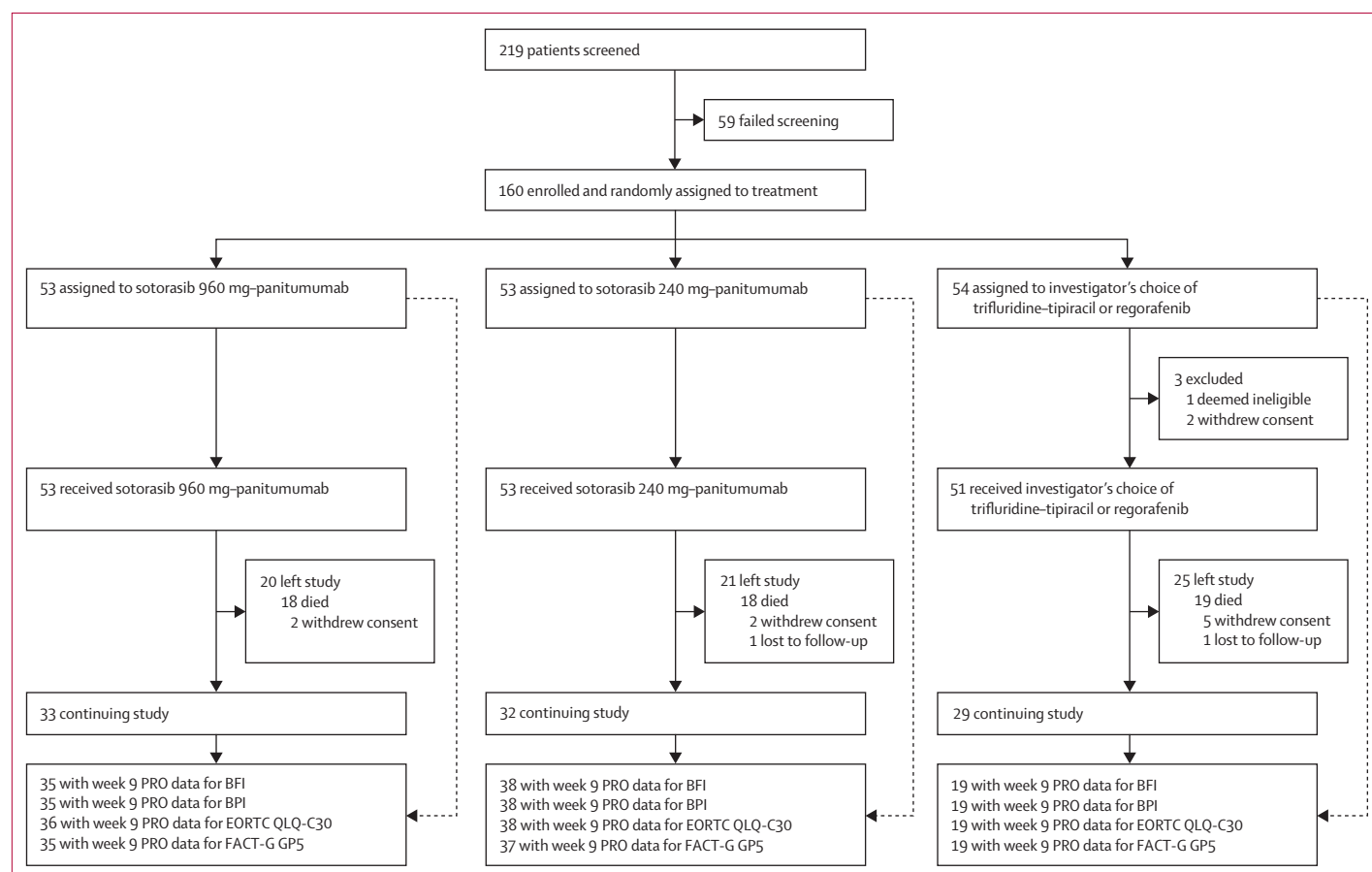


Figure 1: CONSORT diagram for PROs endpoints

BFI=Brief Fatigue Inventory. BPI=Brief Pain Inventory. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. FACT-G=Functional Assessment of Cancer Therapy-general. GP5=the single item “I am bothered by side effects of treatment,” rated on a 5-point Likert scale and part of the FACT-G. PRO=patient-reported outcome.

Additionally, given that the median progression-free survival in the control group, and therefore the expected treatment duration and PRO collection period for that group, was anticipated to be approximately 2 months, less than half of the control patients were expected to remain after this timepoint. Choosing week 9 thus allows for meaningful comparison of treatment-related effects with minimal dropout-related bias. For each questionnaire, the differences in least squares mean change from baseline to week 9 between the

sotorasib–panitumumab groups and investigator's choice group were estimated using a mixed effects model for repeated measures under the assumption of data missing at random. The models considered change in PRO score from baseline, measured on day 1 of each treatment cycle, as the dependent variable; covariates included intercept, time (defined as days since randomisation), baseline PRO score, treatment, treatment-by-time interactions, and randomisation stratification factors as fixed effects, and patient intercept and slope of time for change from baseline as random effects. The analysis set comprised all randomly assigned patients with baseline and at least one post-baseline PRO score; missing data were not imputed. Patients were analysed according to the treatment to which they were assigned.

Time to deterioration (TTD) in PRO scale scores was defined as the time from randomisation to the date of first clinically meaningful deterioration, or death by any cause if no clinically meaningful deterioration was observed. Death was counted as an event only if it occurred before or on the last scheduled PRO assessment. Patients without a clinically meaningful deterioration and who were alive before or on the last scheduled PRO assessment were censored at the time of last available PRO assessment. Deterioration thresholds were predefined as an increase of at least 2 points for BFI and BPI,²⁰ a decrease of at least 10 points for QLQ-C30 GHS–QoL and function subscales, and an increase of at least 10 points for QLQ-C30 symptom subscales.²¹ Patients with a baseline score that could never meet the clinically important deterioration threshold were censored at the date of randomisation. TTD was assessed for BFI (worst fatigue), BPI (worst pain), and all subscales of EORTC QLQ-C30. Median TTD, while on treatment, was analysed by treatment group using the Kaplan–Meier method. To summarise TTD, HRs along with 95% CIs were calculated using a Cox proportional hazards model stratified by randomisation stratification factors. The proportional hazards assumption was not assessed.

FACT-G GP5 and PGIC were summarised descriptively by visit and treatment group using the number and percentage of patients with non-missing data within each ordinal level. The number of missing observations was also recorded.

As all analyses were exploratory in nature, neither was hypothesis testing implemented nor were adjustments made for multiple testing. An increase in least squares mean score from baseline indicated a deterioration in BFI, BPI, and QLQ-C30 symptom scales but an improvement in QLQ-C30 GHS–QoL and function subscales. An estimate of the difference in change from baseline between the treatment groups with the 95% CI not including 0 was considered as meaningfully different. Similarly, an HR estimated to compare TTD across the treatment groups with the 95% CI not

	Sotorasib 960 mg–panitumumab (n=53)	Sotorasib 240 mg–panitumumab (n=53)	Investigator's choice of trifluridine–tipiracil or regorafenib (n=54)
Age, years	63 (37–79)	58 (34–82)	65 (34–81)
Sex			
Male	29 (55%)	26 (49%)	24 (44%)
Female	24 (45%)	27 (51%)	30 (56%)
Race			
Asian	6 (11%)	22 (42%)	12 (2%)
Black	0	1 (2%)	0
White	42 (79%)	30 (57%)	37 (69%)
Other or unknown	5 (9%)	0	5 (9%)
Ethnicity			
Hispanic or Latino	4 (8%)	0	8 (15%)
Not Hispanic or Latino	47 (89%)	53 (100%)	45 (83%)
Unknown	2 (4%)	0	1 (2%)
Prior anti-angiogenic therapy	45 (85%)	47 (89%)	48 (89%)
Time from initial diagnosis of metastatic disease to randomisation			
≥18 months	29 (55%)	29 (55%)	31 (57%)
<18 months	24 (45%)	22 (42%)	23 (43%)
Unknown	0	2 (4%)	0
Liver metastasis			
Yes	38 (72%)	36 (68%)	38 (70%)
No	15 (28%)	17 (32%)	16 (30%)
ECOG performance status			
0	32 (60%)	29 (55%)	36 (67%)
1	19 (36%)	22 (42%)	17 (31%)
2	2 (4%)	2 (4%)	1 (2%)
Body site at initial diagnosis			
Colon	37 (70%)	32 (60%)	37 (69%)
Rectum	16 (30%)	21 (40%)	17 (31%)
Tumour sidedness			
Left	28 (53%)	36 (68%)	37 (69%)
Right	24 (45%)	17 (32%)	16 (30%)
Unknown	1 (2%)	0	1 (2%)
Patient-reported outcomes			
Brief Fatigue Inventory*			
Fatigue at its worst	3.34 (2.74)	3.53 (3.07)	3.21 (3.24)
Global Score	2.34 (2.28)	3.03 (2.79)	2.50 (2.57)
Brief Pain Inventory†			
Pain at its worst	2.78 (2.71)	3.27 (2.90)	2.65 (2.88)
Pain severity index	2.02 (2.03)	2.53 (2.32)	1.95 (2.09)
Pain interference index	1.92 (2.41)	2.38 (2.84)	1.97 (2.49)

(Table continues on next page)

including 1 was considered indicative of treatment difference. Given the exploratory nature of the study, this approach was used to indicate the direction and precision of the observed change and might not necessarily imply clinical significance.

Statistical analyses were performed using SAS (version 9.4).

Role of the funding source

The sponsor was involved in the design and conduct of the study, the analysis and interpretation of the data, writing of the manuscript, and the decision to submit the manuscript for publication. Data were collected by the respective sites and managed by Amgen.

Results

Between April 19, 2022, and March 14, 2023, 160 eligible patients were enrolled and 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 [trifluridine–tipiracil, n=37; regorafenib, n=14]). Three patients in the investigator's choice group did not receive their assigned treatment (figure 1). Median duration of treatment was 6·0 months (IQR 3·7–7·0), 4·6 months (3·3–6·2), and 2·2 months (1·8–4·2) in the sotorasib 960 mg–panitumumab, sotorasib 240 mg–panitumumab, and investigator's choice groups, respectively.¹² Baseline characteristics were generally well balanced across treatment groups (table). Patient disposition for PRO analyses is provided in figure 1.

Baseline scores for all PRO scales were generally similar across treatment groups (table). Mean scores were 3·34 (SD 2·74), 3·53 (3·07), and 3·21 (3·24) for fatigue at its worst; 2·78 (2·71), 3·27 (2·90), and 2·65 (2·88) for pain at its worst; 68·09 (21·72), 63·65 (24·78), and 65·89 (21·35) for GHS–QoL; and 85·37 (15·93), 78·16 (20·98), and 82·17 (20·09) for physical function in the sotorasib 960 mg–panitumumab, sotorasib 240 mg–panitumumab, and investigator's choice groups, respectively. The percentage of patients reporting different levels of side-effects bother at baseline were broadly similar across treatment groups.

The completion and compliance rates are summarised for the EORTC QLQ-C30 GHS–QoL scale (appendix 2 p 6). The completion rate was higher for the sotorasib–panitumumab groups compared with the investigator's choice group. The compliance rate was high and similar across treatment groups, and remained high throughout treatment. Lower rates were recorded only at later cycles where patient numbers were small (<20% of the intention-to-treat population; appendix 2 p 6). At baseline, the rates were 77% (41 of 53), 93% (49 of 53), and 89% (48 of 54) in the sotorasib 960 mg–panitumumab, sotorasib 240 mg–panitumumab, and investigator's choice groups, respectively; the corresponding rates at week 9 were 82% (32 of 39), 76% (32 of 42), and

	Sotorasib 960 mg–panitumumab (n=53)	Sotorasib 240 mg–panitumumab (n=53)	Investigator's choice of trifluridine–tipiracil or regorafenib (n=54)
(Continued from previous page)			
EORTC QLQ-C30†			
Global Health Status QoL	68·09 (21·72)	63·65 (24·78)	65·89 (21·35)
Physical functioning	85·37 (15·93)	78·16 (20·98)	82·17 (20·09)
Role functioning	82·52 (24·42)	76·60 (26·84)	75·97 (24·21)
Emotional functioning	78·86 (18·08)	76·95 (20·43)	79·46 (23·38)
Cognitive functioning	87·80 (20·42)	83·33 (22·52)	86·82 (19·77)
Social functioning	81·71 (24·67)	75·89 (25·73)	82·17 (22·83)
Fatigue	29·00 (22·89)	37·35 (24·46)	28·68 (25·69)
Nausea or vomiting	8·13 (18·68)	10·28 (20·43)	7·36 (18·65)
Pain	21·14 (24·73)	28·72 (31·79)	23·64 (26·78)
Dyspnoea	13·01 (18·07)	19·86 (22·69)	17·83 (25·56)
Insomnia	24·39 (28·89)	30·50 (29·35)	21·71 (28·99)
Appetite loss	15·45 (24·83)	19·86 (30·82)	18·60 (26·53)
Constipation	12·20 (24·45)	19·15 (24·81)	17·05 (26·60)
Diarrhoea	13·82 (25·79)	16·31 (27·69)	9·30 (19·69)
Financial difficulties	14·63 (26·92)	17·73 (24·92)	12·40 (21·85)
FACT-G GP5‡			
Not at all	28 (68%)	30 (67%)	27 (63%)
A little bit	7 (17%)	10 (22%)	12 (28%)
Somewhat	4 (10%)	1 (2%)	3 (7%)
Quite a bit	2 (5%)	3 (7%)	0
Very much	0	1 (2%)	1 (2%)

Data are median (range), n (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group. EORTC=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. FACT-G=Functional Assessment of Cancer Therapy–General. GP5=The single item "I am bothered by side effects of treatment," rated on a 5-point Likert scale and part of the FACT-G. HRQoL=health-related quality of life. QoL=quality of life. *The BFI is a 9-item questionnaire to assess fatigue severity and interference due to fatigue (numeric rating scale from 0 to 10) categorised based on a score of mild (1–3), moderate (4–6), and severe (7–10);¹³ there were 41 participants with available baseline data in the sotorasib 960 mg–panitumumab group, 45 in the sotorasib 240 mg–panitumumab group, and 43 in the investigator's choice group. †The BPI is a 9-item questionnaire wherein the level of pain and pain interference assessed can be categorised based on the score of mild (1–4), moderate (5–6), and severe (7–10);¹⁴ there were 41 participants with available baseline data in the sotorasib 960 mg–panitumumab group, 45 in the sotorasib 240 mg–panitumumab group, and 43 in the investigator's choice group. ‡EORTC QLQ-C30 scale scores range from 0 to 100, with higher scores indicating better HRQoL on the global and functional scales and greater symptom burden on the symptom scales;¹⁵ there were 41 participants with available baseline data in the sotorasib 960 mg–panitumumab group, 47 in the sotorasib 240 mg–panitumumab group, and 43 in the investigator's choice group. §The side-effect burden to the individual patient was assessed using item 5 on the physical wellbeing subscale of the FACT-G GP5 (5-point Likert scale);²¹ there were 41 participants with available baseline data in the sotorasib 960 mg–panitumumab group, 45 in the sotorasib 240 mg–panitumumab group, and 43 in the investigator's choice group.

Table: Patient characteristics and PRO scale scores at baseline

88% (15 of 17; appendix 2 p 6). Compliance rates were similar for other domains of the EORTC QLQ-C30 and other questionnaires (data not shown).

The estimated least squares mean change from baseline in PRO scores to week 9 indicated different patterns between treatment groups over time, generally suggestive of improvement in HRQoL with sotorasib–panitumumab combinations and deterioration with investigator's choice. Change from baseline to week 9 in participants with observed data at week 9 for the PRO scales of interest in the sotorasib 960 mg–panitumumab, sotorasib 240 mg–panitumumab, and investigator's choice groups, respectively were –0·48 (95% CI

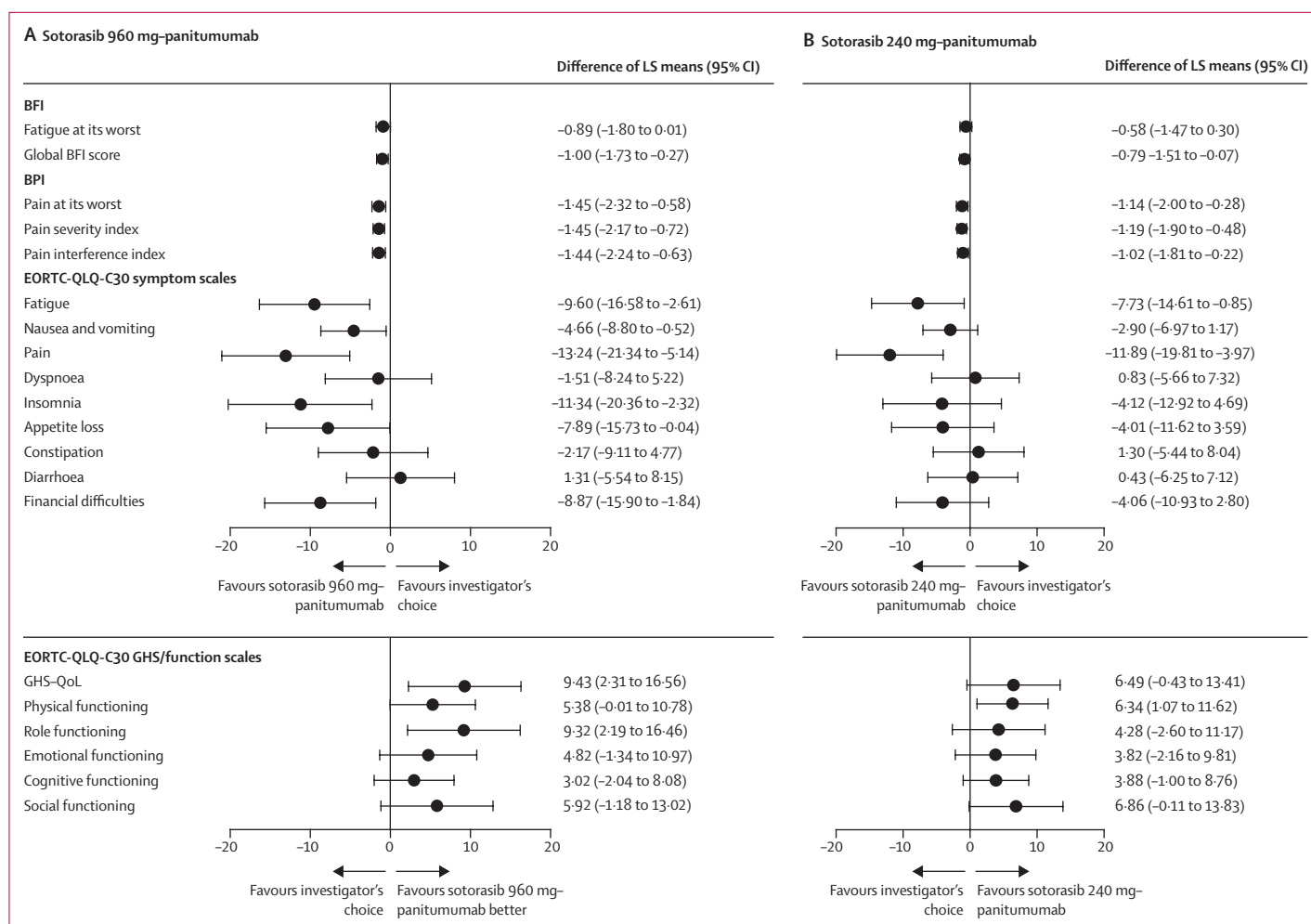


Figure 2: Change in PRO scale scores from baseline to week 9 by treatment for (A) sotorasib 960 mg-panitumumab and (B) sotorasib 240 mg-panitumumab

Data are least squares mean (95% CI) change from baseline estimated by a mixed model for repeated measures. BFI=Brief Fatigue Inventory. BPI=Brief Pain Inventory. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. GHS=Global Health Status. LS=least squares. PRO=patient-reported outcome. QoL=Quality of Life.

-1.18 to 0.23; $n=31$), -0.17 (-0.86 to 0.52; $n=34$), and 0.42 (-0.35 to 1.19; $n=17$) for fatigue at its worst (lower is better); -0.83 (-1.50 to -0.15; $n=31$), -0.52 (-1.18 to 0.15; $n=34$), and 0.63 (-0.11 to 1.36; $n=17$) for pain at its worst (lower is better); 4.23 (-1.39 to 9.85; $n=31$), 1.29 (-4.13 to 6.70; $n=36$), and -5.21 (-11.27 to 0.86; $n=17$) for GHS-QoL (higher is better); and -0.27 (-4.54 to 4.00; $n=31$), 0.69 (-3.44 to 4.81; $n=36$), and -5.66 (-10.24 to -1.07; $n=17$) for physical function (higher is better; appendix 2 pp 7-8). Although the sotorasib and panitumumab combinations showed an overall potential improvement in the measured scales compared with investigator's choice, only the change from baseline in pain at its worst was considered to be meaningfully different (the 95% CI of the change from baseline to week 9 did not overlap with 0) in the sotorasib 960 mg-panitumumab group.

The difference in least squares mean change from baseline to week 9 between sotorasib

960 mg-panitumumab versus investigator's choice and between sotorasib 240 mg-panitumumab versus investigator's choice was -0.89 (95% CI -1.80 to 0.01) and -0.58 (-1.47 to 0.30) for fatigue at its worst (lower favours sotorasib-panitumumab); -1.45 (-2.32 to -0.58) and -1.14 (-2.00 to -0.28) for pain at its worst (lower favours sotorasib-panitumumab); 9.43 (2.31 to 16.56) and 6.49 (-0.43 to 13.41) for GHS-QoL (higher favours sotorasib-panitumumab); and 5.38 (-0.01 to 10.78) and 6.34 (1.07 to 11.62) for physical function (higher favours sotorasib-panitumumab; figure 2, appendix 2 p 7). These results suggested a meaningful improvement in pain at its worst for both the sotorasib dose groups, in GHS-QoL for the sotorasib 960 mg-panitumumab group, and in physical function for the sotorasib 240 mg-panitumumab group (appendix 2 p 7).

The estimated HRs for TTD indicated a potential delay in deterioration in most PRO measures in both the sotorasib-panitumumab groups versus investigator's

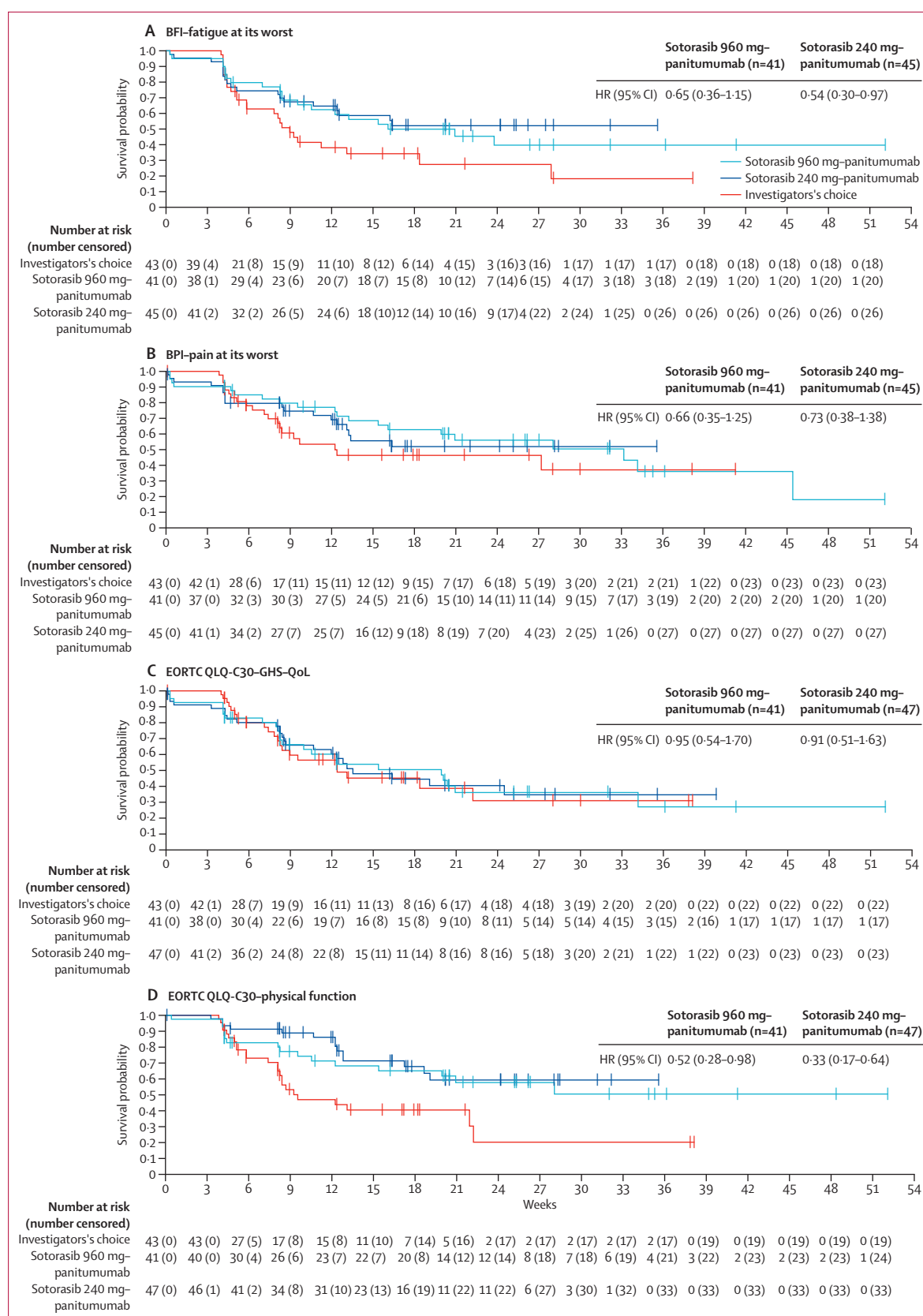


Figure 3: Kaplan-Meier curves of TTD for (A) BFI, (B) BPI, (C) EORTC QLQ-C30 GHS-QoL, and (D) EORTC QLQ-C30 physical function scales
 BFI=Brief Fatigue Inventory.
 BPI=Brief Pain Inventory.
 EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
 GHS=Global Health Status.
 PRO=patient-reported outcome. QoL=quality of life.
 TTD=time to deterioration.

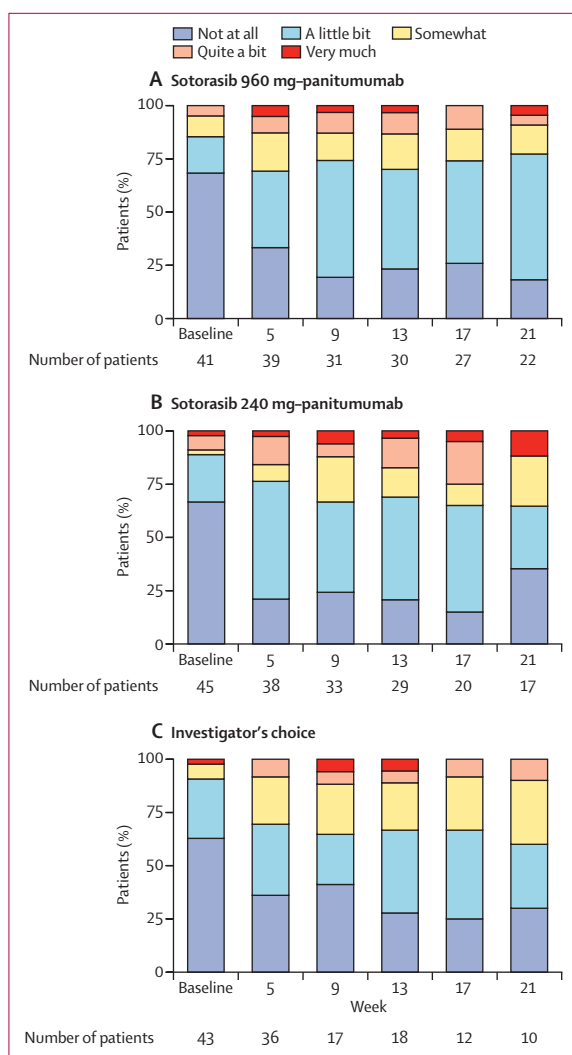


Figure 4: Patient-reported side-effect tolerability as assessed by the FACT-G GP5 questionnaire for (A) sotorasib 960 mg-panitumumab, (B) sotorasib 240 mg-panitumumab, and (C) investigator's choice. Investigator's choice was trifluridine-tipiracil or regorafenib (standard of care). FACT-G=Functional Assessment of Cancer Therapy-general. GP5=the single item "I am bothered by side effects of treatment," rated on a 5-point Likert scale and part of the FACT-G.

choice group. In the sotorasib 960 mg-panitumumab, sotorasib 240 mg-panitumumab, and investigator's choice groups, respectively, median TTD was 16.09 weeks (95% CI 9.54-not estimable [NE]), NE (10.68-NE), and 8.97 weeks (5.84-18.37) for fatigue at its worst; 33.17 weeks (15.38-45.42), NE (12.39-NE), and 12.24 weeks (8.11-NE) for pain at its worst; and 19.93 weeks (8.40-34.17), 13.52 weeks (8.68-NE), and 12.39 weeks (8.26-NE) for GHS-QoL (appendix 2 p 7). For all these scales, the estimated HRs ranged from 0.54 to 0.95 (figure 3, appendix 2 p 10). In physical function, deterioration was reported only in a small proportion of patients in the sotorasib-panitumumab groups as median TTD was NE (95% CI 15.38-NE)

for the the sotorasib 960 mg-panitumumab and NE (17.23-NE) for sotorasib 240 mg-panitumumab versus 9.54 weeks (8.11-22.21) for the investigator's choice (appendix 2 p 9). The estimated HR of 0.52 (95% CI 0.28-0.98) for sotorasib 960 mg-panitumumab and 0.33 (0.17-0.64) for sotorasib 240 mg-panitumumab versus investigator's choice was considered to be meaningfully different (the 95% CIs excluded 1; figure 3).

Figure 4 shows patient-reported side-effect bother as a measure of treatment tolerability estimated through FACT-G GP5. The scores at baseline were similar across treatment groups: six (15%) of 41 patients in the sotorasib 960 mg-panitumumab, five (11%) of 45 patients in the sotorasib 240 mg-panitumumab, and four (9%) of 43 patients in the investigator's choice groups, reported being somewhat, quite a bit, or very much bothered by treatment side-effects. Across multiple assessment timepoints after baseline until week 21, the percentage of patients who reported being somewhat, quite a bit, or very much bothered by treatment side-effects were similar across treatments groups 23% (five of 22) to 31% (12 of 39) in the sotorasib 960 mg-panitumumab, 24% (nine of 38) to 35% (seven of 20) in the sotorasib 240 mg-panitumumab, and 31% (11 of 36) to 40% (four of ten) in the investigator's choice groups. Similarly, 69% (27 of 39) to 77% (17 of 22) of patients in the sotorasib 960 mg-panitumumab, 65% (13 of 20) to 76% (29 of 38) of patients in the sotorasib 240 mg-panitumumab, and 60% (six of ten) to 69% (25 of 36) of patients in the investigator's choice groups reported being not at all bothered or a little bit bothered by treatment side-effects. In terms of patient perception of their condition during the course of the treatment, 10 (53%) of 19 patients receiving investigator's choice perceived no change in their overall status, whereas 22 (63%) of 35 receiving sotorasib 960 mg-panitumumab and 31 (84%) of 37 patients receiving sotorasib 240 mg-panitumumab perceived an improvement from baseline at week 9 (appendix 2 p 11).

Discussion

In the phase 3 CodeBreaK 300 study, the combination of sotorasib 960 mg and panitumumab has previously shown a clinically meaningful and statistically significant improvement in progression-free survival versus investigator's choice of trifluridine-tipiracil or regorafenib in *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer.¹¹ As part of the prespecified secondary and exploratory endpoints of CodeBreaK 300, the current analyses showed improvements across some PRO measures over time with either dose of sotorasib plus panitumumab, compared with investigator's choice of trifluridine-tipiracil or regorafenib. While studies have assessed HRQoL among patients receiving first-line and second-line treatment for metastatic colorectal cancer, data for late-line treatment options are scarce.^{22,23} To the best of our knowledge, this is the first study that reports comparative PRO data for molecularly

targeted treatment in *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer.

For the selection and evaluation of optimal therapies, it is important to assess the efficacy benefit relative to the impact of disease symptoms and treatment on different domains of HRQoL.²⁴ As published previously, grade 3 or worse treatment-related adverse events occurred in 19 (36%) of 53 patients in the sotorasib 960 mg–panitumumab group, 16 (30%) of 53 patients in the sotorasib 240 mg–panitumumab group, and 22 (43%) of 51 patients in the investigator's choice group.¹¹ One of the most common treatment-related adverse events in the sotorasib–panitumumab groups was skin toxicity.¹¹ Skin toxicities, as a result of EGFR treatments such as panitumumab, are common and associated with a detrimental impact on patients' QoL and treatment adherence.²⁵ However, despite the increased skin toxicity, PROs were improved in patients receiving the sotorasib–panitumumab combinations than in those receiving the investigator's choice standard-of-care therapy; there was no difference in reported side-effect bother across treatment groups.

The combination of either dose of sotorasib with panitumumab suggest directional improvement in many PRO domains compared with investigator's choice, even though the study was not designed to formally test these endpoints. TTD HR suggested a potential benefit with sotorasib–panitumumab, and TTD in EORTC QLQ-C30 physical function indicated a meaningful delay with both sotorasib 960 mg–panitumumab (HR 0.52 [95% CI 0.28–0.98]) and sotorasib 240 mg–panitumumab (0.33 [0.17–0.64]).

As patient perception is an important component of cancer-related care, in this study, a much higher proportion of patients receiving either combination of sotorasib and panitumumab perceived an improvement from baseline compared with investigator's choice. Additionally, the proportion of patients bothered by the side effects of their respective treatments was similar across all treatment groups. These findings, along with improvements in clinical outcomes,¹¹ suggest that the combination of sotorasib and panitumumab is a suitable treatment option for patients with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer.

While treatment efficacy in advanced cancers is largely assessed through conventional endpoints such as overall survival, progression-free survival, and response rates, these endpoints are often insufficient to measure the functional aspects of patients' lives.²⁶ Reports suggest a high prevalence of fatigue, pain, and poor wellbeing in patients with colorectal cancer during and after treatment.²⁷ Thus, in patients with advanced incurable disease, it is especially important that the benefit of treatment is also assessed through validated PRO measures that capture patients' perspectives on key aspects of HRQoL. Similar to the findings in the current analyses, the addition of bevacizumab to

trifluridine–tipiracil in patients with refractory metastatic colorectal cancer has been reported to prolong TTD (HR 0.49, 95% CI 0.40–0.60) as assessed by EORTC QLQ-C30 (GHS–QoL domain), compared with trifluridine–tipiracil monotherapy.²⁸

The current study has several strengths, including the use of extensively validated PRO instruments and questionnaires to assess disease-related and treatment-related outcomes in an international, phase 3, randomised, multicentre setting. The BFI, BPI, and EORTC QLQ-C30 questionnaires used in this study have been widely validated and extensively used to assess PROs in various cancer settings, including metastatic colorectal cancer.^{29–31} In this study, the compliance rates for PRO assessments were high across treatment groups, especially in earlier timepoints up to week 9, which was the protocol-specified timepoint of interest for the mixed effects model for repeated measures analyses. Additionally, the frequent administration of these questionnaires ensured a thorough evaluation of patients' perceptions throughout their treatment duration. Given the high compliance rate across treatment groups, the data missing at random assumption appears reasonable, although it cannot be definitively verified. Lower compliance rates were observed at later timepoints when fewer patients remained eligible for assessments and beyond the estimated median time to deterioration, and therefore we believe that any effect on the results would be limited. Owing to the similarity in patient characteristics between the treatment groups, including demographics, treatment history, and baseline values for all parameters assessed through PRO questionnaires, changes from baseline observed at subsequent timepoints allowed for meaningful and interpretable comparisons across groups. A potential limitation of this analysis could be the open-label design of the trial; however, a systematic review of clinical trials of immunotherapy in patients with advanced or metastatic cancer showed that neither PRO compliance nor baseline PRO scores are affected by the trial design.³² The study was not designed to detect statistically significant differences in the PRO measures. Assessments included multiple analyses of validated PRO measures without formal statistical testing or adjustments for multiple comparisons. These findings should, therefore, be considered as exploratory. Additionally, in CodeBreaK 300, PRO assessments were carried out only during the treatment period and not for a longer follow-up period where subsequent events after treatment could also have been captured. However, since the aim of this analysis was to report the PROs during the treatment, an extended follow-up was not preferred. Owing to the relatively rare patient population, the small sample size in the study was also a limitation. However, the direction of results across the different PRO outcomes was largely similar, suggesting consistent patterns. Another limitation is the risk of selection bias,

which is common in PRO analyses of oncology trials due to the underrepresentation of patients who discontinue the study after disease progression. In our study, higher completion rates at week 9 in the sotorasib groups (sotorasib 960 mg–panitumumab: 68% [36 of 53] and sotorasib 240 mg–panitumumab: 72% [38 of 53]) indicated a greater proportion of patients continuing the treatment compared with the investigator's choice (35% [19 of 54]). This aligned with the improved clinical outcomes observed in previous analyses. These differences in discontinuation can potentially affect PRO assessments. However, the compliance rates at week 9, when mixed effects model for repeated measures analyses were conducted, remained high and similar for all treatment groups (sotorasib 960 mg–panitumumab: 88·2% [32 of 39], sotorasib 240 mg–panitumumab: 76·2% [32 of 42], and investigator's choice: 88·2% [15 of 17]; appendix 2 p 6), suggesting robustness of our findings. Finally, although trifluridine–tipiracil plus bevacizumab or fruquintinib were not available when the CodeBreaK 300 study was designed, patients in the control group had access to all approved standard-of-care therapies available at the time of their enrolment. The absence of these newer therapies in the study could limit the generalisability of the results to current clinical practices. Despite these limitations, the PRO analyses presented in this study provide valuable data beyond the traditional clinical outcomes, that are difficult to measure outside a clinical trial setting.

In conclusion, the combination of sotorasib 960 mg and panitumumab not only significantly improved clinical outcomes but also resulted in better PROs that covered domains related to fatigue, pain, and disease-related and treatment-related symptoms and functions. Although not statistically tested, the combination also showed decreased risk of deterioration compared with investigator's choice of trifluridine–tipiracil or regorafenib. Furthermore, the combination of two active agents in the study showed a promising trend towards improved patients' quality of life compared with the choice of using a single therapeutic option. A possible explanation could be that since the combination of sotorasib and panitumumab had greatly increased efficacy (overall response rate 30%), it could have alleviated tumour-related symptoms. This could potentially offset the additional adverse events experienced with doublet therapy. In the context of the exploratory nature of the PRO analyses, these findings suggest that sotorasib 960 mg combined with panitumumab could represent a valuable new treatment for patients with *KRAS*^{G12C}-mutated chemorefractory metastatic colorectal cancer with a favourable profile concerning its effects on quality of life.

Contributors

DPM, MF, LS, TE, DPL-B, JT, MK, ER-G, TWK, YK, FM, DC, K-HY, CC, and FP were responsible for the collection of patient data. QT and EC were responsible for conceptualisation and design of the study. All authors,

including JC and IMM, had access to the data included in the manuscript, and were responsible for reviewing, editing, and approving the final paper. All authors were involved in data analysis and manuscript preparation and vouch for the completeness and accuracy of data and adherence to the study protocol. All authors approved the final version of the manuscript and had final responsibility to submit for publication.

Declaration of interests

DPM reports honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cor2Ed, GlaxoSmithKline, Lilly, Merck, Merck Serono, Onkowsissen, Pierre Fabre, Sanofi, Seagen, Servier, Taiho Pharmaceutical, and Takeda; fees for consulting or advisory services from Amgen, Cor2Ed, GlaxoSmithKline, Lilly, Merck Serono, Onkowsissen, Pierre Fabre, Regeneron, Servier, and Takeda; research funding (to the institution) from Amgen and Servier; and fees for travel, accommodations and expenses from Amgen, Merck Serono, and Servier. MF reports grants (to the institution) from AgenusBio, BMS, Genentech/Roche, Verastem; consulting fees from AbbVie, Adagene, Bayer, BMS, Delcath, Eisai, Merck, Microbial Machines, Mirati, Pfizer, Summit, Taiho, and Totus; advisory roles for Eisai, Entos, Janssen, Mirati, Nouscom, Roche/Genentech, Tempus, Xenthera, and Xilio; and study-related drugs provision (to the institution) from BMS. LS reports current support by the Associazione Italiana per la Ricerca sul Cancro under My First Grant (number MFAG27367); and consulting or advisory roles for Amgen, AstraZeneca, Bayer, GSK, Incyte, Leo Pharma, Merck, MSD, Pierre-Fabre, Servier, and Takeda. TE reports grants (to the institution) from ALX Oncology, Amgen, Asahikasei Pharma, Astellas, Astellas Amgen Biopharma, Bristol, Chugai, Daiichi Sankyo, Ignyta, IQVIA, Jazz Pharmaceuticals, MSD, Nihon Kayaku, Ono, Pfizer, Quintiles, Seagen, Syneos Health Clinical, and Taiho; honoraria from Chugai, Daiichi Sankyo, Hisamitsu, Lilly, MSD, Ono, Roche Diagnostics, Taiho, and Zeria. DPL-B reports research funding from Merck; consulting or advisory roles for AAA, Amgen, Takeda, and Terumo; speakers' honoraria from Amgen and MSD; and travel or accommodation expenses from Advanz Pharma, Amgen, and Merck. JT reports personal fees for speakers' bureau or advisory services from Amgen, Astellas, AstraZeneca, BMS, Boehringer, Lilly, Merck KGaA, MSD, Pierre Fabre, Servier, and Takeda. ER-G reports honoraria for lectures from Amgen, Astellas, AstraZeneca, Merck, MSD, Pfizer, Servier, and Takeda; travel grants from Bayer and Gilead Sciences; and being ASCO President-elect for educational programmes. TWK reports research funding (to the institution) from Genentech and Inocras. YK reports research funding from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Chugai Pharma, Genmab, GlaxoSmithKline, Incyte, Janssen Oncology, Lilly, Merck Serono, Ono Pharmaceutical, Taiho Pharmaceutical, and Takeda; and fees for consulting or advisory services from Amgen, Boehringer Ingelheim, and Takeda. DC reports grants from 4SC, Bayer, Clegene, Clovis, and Eli Lilly; and a scientific board member role for OVIBIO (unpaid). K-HY reports honoraria from Astellas, Amgen, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Merck, MSD, Novartis, ONO, Pierre Fabre, Pfizer, and Roche. CC reports honoraria from Amgen, Bayer, Merck, MSD, Pierre Fabre, Roche, and Servier; fees for consulting or advisory services from Amgen, Bayer, MSD, Nordic Bioscience, Pierre Fabre, and Roche; fees for speakers' bureau services from Merck, Pierre Fabre, and Servier; and research funding from Bayer, Merck, Roche, and Servier. QT, EC, JC, and IMM report Amgen employment and stock. FP reports research funding (to the institution) from Agenus, Amgen, AstraZeneca, BMS, Incyte, Lilly, and Rottapharm; personal honoraria as an invited speaker from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Daiichi Sankyo, Ipsen, Johnson & Johnson, Merck Serono, MSD, Pierre Fabre, Seagen, Servier, and Takeda; and advisory or consultancy roles for Agenus, Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Daiichi Sankyo, Gilead, GSK, Incyte, Italfarmaco, Jazz Pharmaceuticals, Johnson & Johnson, Merck-Serono, MSD, Pfizer, Pierre Fabre, Rottapharm, Servier, and Takeda. MK and FM declare no competing interests.

Data sharing

Qualified researchers with appropriate proposals can request deidentified data from Amgen clinical studies. Complete details are available at <http://www.amgen.com/datasharing>.

Acknowledgments

The study was sponsored and funded by Amgen. We thank the patients, investigators, study staff, and the data monitoring committee who contributed to this study. Medical writing support was provided by Saimah Raza (Cactus Life Sciences, part of Cactus Communications) and Christopher Nosala (Amgen), and was funded by Amgen.

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