Published in final edited form as:

Nat Med. 2024 January ; 30(1): 265–270. doi:10.1038/s41591-023-02717-6.

---

*Corresponding author David S Hong, MD, Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Postal address: Unit 455, PO Box 301402, Houston, TX 77230-1402, USA, dshong@mdanderson.org;.

Author contributions statement

Emily Chan contributed to the design and conception of the study. Yasutoshi Kuboki, Marwan Fakih, John Strickler, Rona Yaeger, Toshiki Masuishi, Edward J Kim, Christine M Bestvina, Scott Kopetz, Gerald S Falchook, Corey Langer, John Krauss, Sonam Puri, and David S Hong contributed to patient data collection. All authors contributed to the data analysis and interpretation. All authors contributed to the writing and editing of the manuscript, and approval of the final version for submission to the journal. All authors are accountable for all aspects of the work.

Author information

These authors contributed equally: Yasutoshi Kuboki, MD, PhD, Marwan Fakih, MD, John Strickler, MD, Rona Yaeger, MD.

Competing interests statement

Yasutoshi Kuboki:

Honoraria - Bristol-Myers Squibb Japan; Lilly Japan; Taiho Pharmaceutical

Consulting or Advisory Role - Amgen; Boehringer Ingelheim; Takeda

Research Funding - Abbvie (Inst); Amgen (Inst); Astellas Pharma (Inst); AstraZeneca (Inst); Boehringer Ingelheim (Inst); Chugai Pharma (Inst); Genmab (Inst); GlaxoSmithKline (Inst); Incyte (Inst); Janssen Oncology (Inst); Lilly (Inst); Merck Serono (Inst); Ono Pharmaceutical (Inst); Taiho Pharmaceutical (Inst); Takeda (Inst); Hengrui (Inst); Novartis Pharma (Inst)

Travel, Accommodations, Expenses - Amgen

Marwan Fakih:

Grants or contracts: Amgen (Inst), (AgenusBio (Inst), Verastem (Inst), Genentech / imCORE (Inst)

Consulting fees (payments made to self): AstraZeneca, Bristol Myers Squibb, Bayer, Incyte, Pfizer, Taiho Oncology

Participation on a data safety monitoring board or advisory board (payments made to self): Bayer, Eisai Oncology, Entos, Merck, Mirati Therapeutics, Nouscom, Roche/Genentech, Seattle Genetics, Xenthera, Inc.

Receipt of equipment, materials, drugs, medical writing, gifts or other services: Bristol Myers Squibb (study-related drugs provided to institution)

John Strickler:

Consultant or advisory role: Abbvie, Amgen, AstraZeneca, Bayer, Beigene, Daiichi-Sankyo, Eli Lilly, GSK, Janssen, Natera, Pfizer, Pionyr Immunotherapeutics, Roche/Genentech, Seagen, Silverback Therapeutics, Taiho Pharmaceutical, Takeda, Viatris, Zentalis.

Research funding or contracted research: Abbvie (inst), Amgen (inst), AStar D3 (inst), Bayer (inst), Beigene (inst), Curegenix (inst), Daiichi-Sankyo (inst), Eli Lilly (inst), Erasca (inst), Leap Therapeutics (inst), Roche/ Genentech (inst), Seagen (inst), Silverback Therapeutics (inst)

Rona Yaeger:

Honoraria - Zai Lab

Consulting or Advisory Role - Mirati Therapeutics, Amgen Inc.

Research Funding - Array BioPharma (Inst); Boehringer Ingelheim (Inst); Mirati Therapeutics (Inst); Pfizer (Inst), Daiichi Sankyo (Inst).

Toshiki Masuishi:

Honoraria - Bayer Yakuhin; Bristol-Myers Squibb; Chugai Pharma; Daiichi Sankyo; Lilly; Merck Serono; Ono Pharmaceutical; Sanofi; Taiho Pharmaceutical; Takeda; Yakult Honsha; MSD; Nippon Kayaku

Research Funding - Amgen (Inst); Boehringer Ingelheim (Inst); CMIC (Inst); Daiichi Sankyo (Inst); Lilly Japan (Inst); MSD (Inst); Novartis (Inst); Ono Pharmaceutical (Inst); Pfizer (Inst); Syneos Health (Inst)

Edward J Kim:

Grants or contracts: NGM (Inst), Erytech (Inst), Fibrogen (Inst), Eureka (Inst), Merck (Inst), BMS (Inst), Astellas (Inst), Boston Biomedical (Inst), AZ (Inst), Celgene (Inst), Halozyme (Inst), Samumed (Inst), Epicentrx (Inst), Medimmune (Inst), Beigene (Inst), Theriva Biologics (Inst).

Consulting fees: Eisai (self), Taiho (self), Lilly (self), Relay (self).

Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Eisai (speaker), Seagen (speaker).

Monitoring board or advisory board: Lilly (self), Relay (self).

Stock or stock options: ROMTech.

Christine M Bestvina:

Consulting or Advisory Role - Abbvie (I); AstraZeneca; Bristol-Myers Squibb/Celgene; Clinical Care Options; Creative Educational Concepts; Curio Science; CVS; Daiichi Sankyo; EMD Serono; Genentech; Janssen; Jazz Pharmaceuticals; Medical Learning Institute; MJH Holdings; Novartis; Novocure; OncLive Clinical Congress Consultants; Sanofi/Regeneron; Seagen; Takeda; Targeted Oncology; Tempus

Speakers' Bureau - Merck

Research Funding – Amgen; AstraZeneca/MedImmune; Bristol-Myers Squibb

Scott Kopetz:

Stock and Other Ownership Interests - Frontier Medicines; Iylon; Lutris; Navire; Xilis

Consulting or Advisory Role - Abbvie; Accademia Nazionale Di Medicina (ACCMED); Amal Therapeutics; Amgen; AstraZeneca/MedImmune; Bayer Health; Bicara Therapeutics; Black Diamond Therapeutics; Boehringer Ingelheim; Bristol-Myers Squibb/Medarex; Cardiff Oncology; Carina Biotech; CureTeq; EMD Serono; Endeavor BioMedicines; Flame Biosciences; Foundation

Medicine; Frontier Medicines; Genentech; Genomic Health; Gilead Sciences; GlaxoSmithKline; HalioDx; Harbinger Oncology, Inc; Hengrui Therapeutics; Incyte; Ipsen; Jazz Pharmaceuticals; Johnson & Johnson/Janssen; Lilly; Merck; Mirati Therapeutics; NeoGenomics Laboratories; Novartis; Numab; Ono Pharmaceutical; Pfizer; Redx Pharma; Repare Therapeutics; Replimune; Servier; Taiho Pharmaceutical; Takeda; Tempus; Xilis; Zentalis

Research Funding - Amgen; Array BioPharma; Biocartis; Daiichi Sankyo; EMD Serono; Genentech/Roche; Guardant Health; Lilly; MedImmune; Novartis; Sanofi

Gerald S Falchook:

Royalties (self): Wolters Kluwer (2014-present)

Advisory role (to institution): AbbVie (2022), Fujifilm (2018), Silicon (2020, 2021), Navire (2021), Turning Point (2021), Predicine (2021), Inspirna (2021), Regeneron (2021), Jubilant (2022), BostonGene (2022), Teon (2022), Merck (2022), Sanofi (2023), BridgeBio (2023)

Advisory role (self): EMD Serono (2010, 2011)

Speakers honorarium for CME: Total Health Conferencing (2019), Rocky Mountain Oncology Society (2020)

Travel (self, for work and/or research related to institution): Amgen (2022), Bristol-Myers Squibb (2015), EMD Serono (2011, 2012, 2013), Fujifilm (2018), Millennium (2013), Sarah Cannon Research Institute (employer, at least once yearly), Synthorx/Sanofi (2022)

Research funding [to institution, for any trial for which I have been the PI (ever) or sub investigator (minimum last 4 years)]: 3-V Biosciences, Abbisko, Abbvie, ABL Bio, ADC Therapeutics, Accutar, Agenus, Aileron, American Society of Clinical Oncology, Amgen, ARMO/Eli Lilly, Artios, AstraZeneca, Bayer, BeiGene, Bioatla, Bioinvent, Biothera, Bicycle, Black Diamond, Boehringer Ingelheim, Celgene, Celldex, Ciclomed, Curegenix, Curis, Cyteir, Daiichi, DelMar, eFFECTOR, Eli Lilly, EMD Serono, Epizyme, Erasca, Exelixis, Freenome, Fujifilm, Genmab, GlaxoSmithKline, Hutchison MediPharma, IGM Biosciences, Ignyta, Immunitas, ImmunoGen/MacroGenics, Incyte, Jacobio, Jazz, Jounce, Jubilant, Kineta, Kolltan, Loxo/Bayer, MedImmune, Merck, Metabomed, Millennium, Mirati, miRNA Therapeutics, Molecular Templates, National Institutes of Health, Navire/BridgeBio, NGM Bio, NiKang, Novartis, OncoMed, Oncorus, Oncothyreon, Poseida, Precision Oncology, Prelude, PureTech, Pyramid, Pyxis, RasCal, Regeneron, Relay, Rgenix, Ribon, Roche, Samumed, Sapience, Seagen, Silicon, Simcha, Sirnaomics, Strategia, Syndax, Synthorx/Sanofi, Taiho, Takeda, Tallac, Tarus, Tarveda, Teneobio, Tesaro, Tocagen, Turning Point, U.T. MD Anderson Cancer Center, Vegenics, Xencor, Zhuhai Yufan

Corey Langer:

Honoraria - AstraZeneca; Genentech/Roche; Lilly/ImClone; Merck; Takeda Science Foundation

Consulting or Advisory Role - Abbott Biotherapeutics; ARIAD; AstraZeneca; Bayer/Onyx; Bristol-Myers Squibb; Cancer Support Community; Celgene; Clarient; Clovis Oncology; Genentech/Roche; Gilead Sciences; Lilly/ImClone; Merck; Novocure; Pfizer; Regeneron; Takeda

Research Funding - Advantagene (Inst); Amgen; Ariad (Inst); AstraZeneca; Celgene (Inst); Clovis Oncology (Inst); Genentech/Roche (Inst); GlaxoSmithKline (Inst); Incyte; Inovio Pharmaceuticals (Inst); Johnson & Johnson/Janssen; Lilly; Merck (Inst); Stem CentRx (Inst); Trizell (Inst)

John Krauss:

Bristol-Myers Squibb, Hutchison Medipharma/Syneos Health, Sumitomo Dainippon/Paraexel, Tempest Therapeutics, Merck/Nsabp Foundation, Ignyta/Qintiles, Tempest Therapeutics/ICON, AstraZeneca/Nsabp Foundation, AbbVie, Bristol-Myers Squibb/Mayo Clinic, MedImmune, Pfizer, Daiichi Sankyo/Syneos Health, Xencor, Amgen, Inc, Merck, Gilead Sciences, Janssen.

Sonam Puri:

Honoraria - Aptitude Health (Inst); IntegrityCE

Consulting or Advisory Role - AstraZeneca (Inst); G1 Therapeutics; Jazz Pharmaceuticals (Inst), Pfizer

Travel, Accommodations, Expenses - Dava Oncology

Panli Cardona:

Employee and stockholder of Amgen Inc.

Patents, Royalties, Other Intellectual Property: Amgen

Emily Chan: Employee and stockholder: Amgen Inc.

Tracy Varrieur: Employee and stockholder: Amgen Inc.

Lata Mukundan: Employee and stockholder: Amgen Inc.

Abraham Anderson: Employee and stockholder: Amgen Inc.

Qui Tran: Employee and stockholder: Amgen Inc.

David S Hong:

Stock and Other Ownership Interests - MolecularMatch; OncoResponse; Telperian

Consulting or Advisory Role - Acuta; Adaptimmune; Alkermes; Alphasights; Amgen; AUM Biosciences; Axiom Biotechnologies; Baxter; Bayer; Boxer Capital; Bridgebio; COG; Cor2Ed; Cowen; EcoR1 Capital; Genentech; Gennao Bio; Gerson Lehrman Group; Gilead Sciences; GroupH; Guidepoint Global; HCW Precision; Immunogen; Infinity Pharmaceuticals; Janssen; Liberum; MedaCorp; Medscape; Numab; Oncologia Brasil; Pfizer; Pharma Intelligence; Precision Oncology Experimental Therapeutics; Prime Oncology; RAIN; ST Cube; Takeda; Tavistock Life Sciences; Trieza Therapeutics; Turning Point Therapeutics; WebMD; YingLing Pharma; ZIOPHARM Oncology

Research Funding - Abbvie (Inst); Adaptimmune (Inst); Adlai Nortye (Inst); Amgen (Inst); AstraZeneca (Inst); Bayer (Inst); Bristol Myers Squibb (Inst); Daiichi Sankyo (Inst); Deciphera (Inst); Eisai (Inst); Endeavor BioMedicines (Inst); Erasca, Inc (Inst); F. Hoffmann LaRoche (Inst); Fate Therapeutics (Inst); Genentech (Inst); Genmab (Inst); Ignyta (Inst); Infinity Pharmaceuticals (Inst); Kite, a Gilead company (Inst); Kyowa (Inst); Lilly (Inst); Loxo (Inst); MedImmune (Inst); Merck (Inst); Mirati Therapeutics (Inst); Mologen (Inst); National Cancer Institute (Inst); Navire (Inst); Novartis (Inst); Numab (Inst); Pfizer (Inst); Pyramid Biosciences (Inst); Seagen (Inst); Takeda (Inst); TCR2 Therapeutics (Inst); Teckro (Inst); Turning Point Therapeutics (Inst); VM Pharma (Inst)

G12C-mutated colorectal cancer: a phase 1b trial

Yasutoshi Kuboki, MD, PhD[1], **Marwan Fakih, MD**[2], **John Strickler, MD**[3], **Rona Yaeger, MD**[4], **Toshiki Masuishi, MD**[5], **Edward J Kim, MD, PhD**[6], **Christine M Bestvina, MD**[7], **Scott Kopetz, MD, PhD**[8], **Gerald S Falchook, MD**[9], **Corey Langer, MD**[10], **John Krauss, MD**[11], **Sonam Puri, MD**[12], **Panli Cardona, PharmD**[13], **Emily Chan, MD, PhD**[13], **Tracy Varrieur, BSN**[13], **Lata Mukundan, PhD**[13], **Abraham Anderson, PhD**[13], **Qui Tran, PhD**[13], **David S Hong, MD**[8,*]

[1]National Cancer Center Hospital East, Kashiwa, Chiba, Japan

[2]City of Hope Comprehensive Cancer Center, Duarte, CA, USA

[3]Duke University Medical Center, Durham, NC, USA

[4]Memorial Sloan Kettering Cancer Center, New York, NY, USA

[5]Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

[6]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA

[7]University of Chicago, Chicago, IL, USA

[8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[9]Sarah Cannon Research Institute, Nashville, TN

[10]University of Pennsylvania, Philadelphia, PA, USA

[11]University of Michigan, Ann Arbor, MI, USA

[12]Huntsman Cancer Institute, Salt Lake City, UT, USA

[13]Amgen Inc., Thousand Oaks, CA, USA

Abstract

The current third-line and beyond treatment options for *RAS* mutant metastatic colorectal cancer (mCRC) have yielded limited efficacy. At the time of study start, the combination of sotorasib, a KRAS G12C inhibitor, and panitumumab, an epidermal growth factor receptor inhibitor, was hypothesized to overcome treatment-induced resistance. This phase 1b substudy of the CodeBreaK 101 master protocol evaluated sotorasib plus panitumumab in patients with chemotherapy−refractory *KRAS* G12C-mutated mCRC. Here, we report the results of the dose-exploration cohort and a dose expansion cohort. Patients received sotorasib (960 mg, QD) plus panitumumab (6 mg/kg, Q2W). The primary endpoints were safety and tolerability. Secondary endpoints included efficacy and pharmacokinetics. Exploratory biomarkers at baseline were assessed. Forty-eight patients (dose exploration, n=8; dose expansion, n=40) were treated. Treatment-related adverse events of any grade and grade ≥3 occurred in 45 (94%) and 13 (27%) patients, respectively. In the dose-expansion cohort, the confirmed objective response rate was

---

Travel, Accommodations, Expenses - AACR; ASCO; Bayer Schering Pharma; Genmab; Society for Immunotherapy of Cancer; Telperian

ClinicalTrials.gov identifier: NCT04185883

30.0% (95% CI: 16.6, 46.5). Median progression-free survival (PFS) was 5.7 months (95% CI: 4.2, 7.7). Median overall survival was 15.2 months (95% CI: 12.5, not estimable). Prevalent genomic co-alterations included *APC* (84%), *TP53* (74%), *SMAD4* (33%), *PIK3CA* (28%), and *EGFR* (26%). Sotorasib-panitumumab demonstrated acceptable safety with promising efficacy in chemotherapy-refractory *KRAS* G12C-mutated metastatic CRC.

Colorectal cancer is the third most common type of cancer, with 153,020 new cases and 52,550 deaths in the United States annually.[1,2] First- and second-line treatment of metastatic colorectal cancer with *RAS* mutation includes combinations of chemotherapy, immunotherapy in the case of microsatellite instability–high disease, and antiangiogenic agents.[3] The standard of care for third-line treatment for these patients is either regorafenib or trifluridine-tipiracil, with objective response rates <2%, median progression-free survival ≤2 months, and overall survival of 6.4 and 7.1 months, respectively.[4,5] In a recent study of trifluridine-tipiracil combined with bevacizumab, the median progression-free survival was 5.6 months, and the median overall survival was 10.8 months.[6] These outcomes emphasize the need for novel treatment options and combinations.

The *KRAS* G12C mutation is found in about 3%–4% of colorectal cancers.[7] Real-world studies of treatment outcomes in *KRAS* G12C-mutated metastatic colorectal cancer have reported mixed results; some describe a negative association with prognosis, while others report no difference.[8–13] Sotorasib, a first-in-class small molecule, selectively and irreversibly inhibits KRAS G12C.[14] Sotorasib monotherapy in patients with *KRAS* G12C-mutated metastatic colorectal cancer resulted in a modest objective response rate (9.7%).[15] We hypothesized that treatment-induced resistance may be occurring via feedback reactivation of the RAS-MAPK pathway and epidermal growth factor receptor (EGFR) reactivation.[16,17]

The combination of adagrasib, a KRAS G12C inhibitor, and cetuximab, an anti-EGFR monoclonal antibody, demonstrated clinical activity and acceptable safety in *KRAS* G12C-mutated metastatic colorectal cancer.[18] In this phase 1b substudy of the CodeBreaK 101 master protocol (subprotocol H, Part 1 Cohort A and Part 2 Cohort A), we evaluated the safety, pharmacokinetics, and efficacy of sotorasib plus panitumumab in patients with chemotherapy--refractory *KRAS* G12C-mutated metastatic colorectal cancer. We also report co-occurring genomic alterations at baseline and their association with the outcomes.

Results

Study population

Forty-eight patients enrolled in the United States and Japan with previously treated *KRAS* G12C-mutated metastatic colorectal cancer who had received at least 1 dose of sotorasib and panitumumab were included (Figure 1 and Supplementary Table S1). Of these, 8 patients were enrolled in the dose-exploration cohort and 40 in the dose-expansion cohort between June 24, 2020, and December 21, 2021 (Figure 2). The data cutoff for both cohorts was January 4, 2023.

Table 1 summarizes the baseline characteristics of the 48 patients enrolled in the dose-exploration and dose-expansion cohorts. Of the 8 patients in the dose-exploration cohort, the median age was 61 years (range: 31–79) and 63% were female. Patients received a median of 4 prior lines of systemic therapy for metastatic disease (including adjuvant therapy if there was progression within 6 months following treatment). All 5 patients who received a prior KRAS G12C inhibitor had been treated with sotorasib as either monotherapy or in combination with trametinib.

Of the 40 patients in the dose-expansion cohort, the median age was 58 years (range: 30–78) and 75% were female. Primary tumor location was left-sided in 27 (68%) patients and right-sided in 13 (33%) patients. Patients received a median of 2 prior lines of systemic therapy for metastatic disease. Prior lines of treatment included oxaliplatin, irinotecan, fluoropyrimidine, and antiangiogenic therapy in 40 (100%) patients. Regorafenib and trifluridine-tipiracil were a prior line of therapy in 7 (18%) patients each; 13 (33%) had received prior regorafenib and/or trifluridine-tipiracil.

Safety

Seven patients in the dose-exploration cohort were evaluable for DLTs; no DLTs were observed (one unevaluable due to panitumumab dose interruption for non-DLT grade 3 rash acneiform). Therefore, dose level 1 was determined to be the recommended phase 2 dose.

Among 48 patients, treatment-related adverse events of any grade and grade ≥3 were observed in 45 (94%) and 13 (27%) patients, respectively; 30 (63%) and 45 (94%) experienced treatment-related adverse events related to sotorasib and panitumumab, respectively (Table 2). Additional details are provided in Supplementary Tables S2–S6. Grade 3 treatment-related adverse events occurred in 13 (27%) patients; the most common were rash (6%) and acneiform dermatitis and hypomagnesemia (4% each). No patients experienced grade 4 or 5 treatment-related adverse events. Sotorasib-related and panitumumab-related adverse events led to dose interruption or reduction in 7 (15%) and 14 (29%) patients, respectively. No treatment-related adverse events led to discontinuation of either drug.

Pharmacokinetics

For the overall population, the geometric mean maximum plasma concentration was 8,760 ng/mL and 7,470 ng/mL on days 1 and 8, respectively, with a median time to maximum plasma concentration of 1.0 hour (range: 1.0–6.0) for both days (Supplementary Table S7). The geometric mean area under the concentration-time curve from time 0 to 24-hour postdose was 80,000 h*ng/mL and 53,500 h*ng/mL on days 1 and 8, respectively. Sotorasib exposure was similar with overlapping distributions in patients enrolled at sites in Japan and the United States (Extended Data Figures 1 and 2).

Efficacy

Among the 8 patients in the dose-exploration cohort, 1 KRAS G12C inhibitor–naïve patient (12.5%; 95% CI: 0.3, 52.7) had a confirmed partial response (Table 3). The disease control rate was 75.0% (95% CI: 34.9, 96.8), with a median duration of treatment of 4.4 months

(range: 1.4–21.8); no patients remained on treatment at data cutoff. Among the 5 patients with prior sotorasib treatment, 80.0% achieved stable disease during treatment. Target lesion shrinkage of any magnitude was observed in 6 of 7 patients (Figure 3B). Due to clinical progression, the eighth patient ended treatment before tumor assessment. Maximal tumor shrinkage in target lesions ranged from 15% to 30% in 4 of the 5 patients who received prior sotorasib and was 19% and 100% in the 2 patients, respectively, who were KRAS G12C inhibitor–-naïve.

Among the 40 patients in the dose-expansion cohort, 12 (30.0%; 95% CI: 16.6, 46.5) had a confirmed partial response (Table 3, Figure 3A). The disease control rate was 92.5% (95% CI: 79.6, 98.4), the median duration of response was 5.3 months (95% CI: 2.8, 7.4), and target lesion shrinkage of any magnitude was observed in 35 of 40 patients (Figure 3B). The median time to response was 1.5 months (range: 1.3–4.1; Table 3). The median duration of treatment was 6.0 months (range: 0.5–18.9). Three patients remained on treatment at data cutoff and had received the combination for 15.6–19.2 months. At a median follow-up of 16.7 months, the median progression-free survival was 5.7 months (95% CI: 4.2, 7.7; Figure 3C). At a median follow-up of 10.6 months, the median overall survival was 15.2 months (95% CI: 12.5, not evaluable; Figure 3D).

In a subgroup analyses, confirmed response rates were observed among four of nine patients enrolled in Japan (RR% =44.4%) and among eight of 31 (25.8%) enrolled in the United States; response rates in patients with left-sided (n=27) vs right-sided (n=13) primary tumors were 29.6% and 30.8% respectively. The median progression-free survival in patients with left-sided and right-sided primary tumors were 5.8 vs 5.7 months (Extended Data Figure 3A). The median overall survival in patients with left-sided and right-sided primary tumors was not estimable and 12.5 months, respectively (Extended Data Figure 3B).

Exploratory biomarkers at baseline

Centrally measured baseline cfDNA genomic data were available for 3 (37.5%) and 40 (100%) patients in the dose-exploration and dose-expansion cohorts, respectively. Patients treated with prior KRAS G12C inhibitor in the dose-exploration cohort (n=5) were excluded from this analysis. All patients had cfDNA detected at baseline; 41 patients had *KRAS* G12C detected, with *KRAS* G12C variant allelic frequency ranging from 0.0009 to 0.5810. The most prevalent (≥20%) gene alterations included *APC* (84%), *TP53* (74%), *SMAD4* (33%), *PIK3CA* (28%), and *EGFR* (26%; Table S8). Among patients with concurrent *BRAF* alterations (19%), 6 of 8 (75%) had copy number amplifications and 3 of 8 (38%) had missense mutations (one patient had both). None had a *BRAF* V600E mutation. *ARID1A* mutations were observed in 14% of patients with single-nucleotide variants. Concurrent *EGFR* alteration in 11 patients included amplifications (82%) and missense variants (18%). The median progression-free survival (95% CI) was reported in patients with and without baseline *BRAF* alterations (2.9 months [2.4, not evaluable] vs 7.4 months [5.5, 8.3]) and in patients with and without *ARID1A* mutations (4.4 months [2.8, not evaluable] vs 7.4 months [4.4, 8.2]; Extended Data Figure 4).

Discussion

In this phase 1b clinical trial, we evaluated the safety and efficacy of sotorasib plus panitumumab in heavily pretreated patients with *KRAS* G12C-mutated metastatic colorectal cancer. The combination was well-tolerated and mainly associated with low-grade adverse events. Overall, grade 3 treatment-related adverse events, mostly dermatologic, occurred in 27% of patients and were related to sotorasib in 7 (15%) and panitumumab in 11 (23%) of patients. No treatment-related adverse events were grade 4 or 5 or led to treatment discontinuation of either agent. No patients experienced DLTs. There were no discernible differences in sotorasib pharmacokinetics for monotherapy vs the combination, suggesting that there are no clinically meaningful pharmacokinetic drug-drug interactions between sotorasib and panitumumab.[15] These efficacy and safety findings with sotorasib plus panitumumab are further strengthened and confirmed by recent phase 3 data from the CodeBreaK 300 trial that demonstrated significant improvements in progression-free survival with sotorasib plus panitumumab compared with the current standard of care during the study's conduct in patients with chemotherapy-refractory *KRAS* G12C-mutated metastatic colorectal cancer.[19] Further, the objective response rate of 26.4% and median progression-free survival of 5.6 months reported for the sotorasib 960 mg daily plus panitumumab 6 mg/kg Q2W arm of CodeBreaK 300 is similar to the response rate of 30% and median progression-free survival of 5.7 months demonstrated in this phase 1b trial.[19]

The confirmed objective response rate in the dose-expansion cohort was more than twice that in the dose-exploration cohort, likely reflecting that 63% of patients in the dose-exploration cohort had received prior treatment with a KRAS G12C inhibitor. In the dose-expansion cohort, disease control was observed in 93% of patients, tumor shrinkage in 88% of patients, and a median progression-free survival of 5.7 months and a median overall survival of 15.2 months. These findings are analogous to the outcomes observed when a BRAF inhibitor was combined with an anti-EGFR antibody to treat *BRAF* V600E-mutated metastatic colorectal cancer, implying that inhibition of an overactive RAS-BRAF-MAPK pathway requires concurrent EGFR inhibition.[20] These data reflect a marked improvement over those observed for either panitumumab or sotorasib monotherapy in *KRAS* G12C-mutated metastatic colorectal cancer. These findings that a combination approach is more effective than either agent alone is generally consistent with that of the recent phase 2 nonrandomized KRYSTAL-1 trial that tested the combination of the KRAS G12C inhibitor adagrasib with cetuximab in *KRAS* G12C mutated colorectal cancer.[18] The most common treatment-related adverse events with sotorasib plus panitumumab (rash, acneiform dermatitis, hypomagnesemia) are also in accordance with that shown with adagrasib-cetuximab and anti–EGFR therapies for the treatment of metastatic colorectal cancer in general.[18,21] Direct comparisons of the current data with KRYSTAL-1 are challenging to perform because of the inherent differences in study design, prior lines of therapy, patient populations, sample size (KRYSTAL-1 had relatively fewer patients than this study) and regions of enrollment (KRYSTAL-1 enrolled at sites in the US alone while the current study included sites in Japan as well; in the dose expansion portion of the current study, 22.5% of the patients were enrolled in Japan). In this *KRAS* G12C-mutated population where patients were not expected to respond to panitumumab, these results

provide a proof of principle that sotorasib and an anti-EGFR antibody work synergistically as observed in preclinical studies.[16,17]

Our observation that the combination of sotorasib plus panitumumab showed similar efficacy regardless of primary tumor location is consistent with data for BRAF and EGFR inhibitor combination in BRAFV600E metastatic colorectal cancer[22], although owing to the small sample sizes and overlapping CIs in this subgroup analysis, these results must be interpreted with caution. Future research with larger patient populations may yield more definitive results.

Our observation that *BRAF* or *ARID1A* co-alterations are associated with shorter progression-free survival is mechanistically plausible and consistent with studies implicating these genes in EGFR inhibitor resistance.[23–27] While *BRAF* amplification has been observed following treatment with EGFR inhibitors, its association with outcome is unclear.[28] Of note, none of the patients with baseline BRAF alterations have had prior BRAF-targeted therapy and only 1 had prior anti-EGFR (cetuximab) therapy. Thus, this alteration does not seem to be a direct reflection of acquired resistance to prior BRAF/EGFR targeted treatments. The high rate of *BRAF* copy number variants we detected may be related to our methodology for sequencing blood samples vs tumor tissue, as the former may better capture the intertumoral and intratumoral clonal heterogeneity. Higher rates of *BRAF* copy number variants have been observed in other colorectal cancer studies employing blood-based sequencing.[29,30] Loss of *ARID1A* function is thought to destabilize the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex and facilitate tumor growth, in part by modulating EGFR downstream effectors.[31] This role was highlighted in a recent phase 3 study linking dysfunctional *ARID1A* to poor outcome following cetuximab (vs bevacizumab) treatment.[26]

This study has a few limitations. First, this was a single-arm study. Second, the efficacy endpoints were based on investigator assessment rather than blinded independent central review. Finally, the exploratory analysis of genomic co-alterations was not statistically powered.

Concurrent to this study, the phase 3 CodeBreaK 300 trial comparing sotorasib at two doses (960 mg or 240 mg) plus panitumumab with investigator's choice of trifluridine/tipiracil or regorafenib in patients with chemotherapy-refractory *KRAS* G12C-mutated metastatic colorectal cancer was ongoing, and has shown improved progression-free survival with this combination strategy at both the doses tested.[19] Additionally, as part of the master protocol, other studies of solid tumors are ongoing to evaluate the safety and efficacy of sotorasib in combination with other targeted or nontargeted therapies, including inhibition of vertical and horizontal signaling pathways and combination with chemotherapies.

In conclusion, this phase 1b substudy of the CodeBreaK 101 master protocol showed acceptable safety and promising efficacy for sotorasib plus panitumumab in patients with chemotherapy-refractory (on or after treatment with fluoropyrimidine, oxaliplatin, irinotecan, and an antiangiogenic agent) *KRAS*- G12C mutated metastatic colorectal cancer. This substudy is the first report of clinical benefit shown with the combination of a KRAS

G12C inhibitor and an anti-EGFR antibody in a Japanese patient subset. The potential association between baseline non-V600E *BRAF* or *ARID1A* co-alterations with shorter progression-free survival is of interest and clinical importance. Future studies may evaluate the clinical significance of these exploratory biomarker trends. Collectively, our data add to a growing body of evidence demonstrating continued EGFR-MAPK pathway activation in colorectal tumors and may have broader implications for the treatment of colorectal cancers with other *RAS* mutations.

Methods

Study design

This phase 1b, multicenter, open-label study of sotorasib plus panitumumab in adult patients with *KRAS* G12C-mutated advanced colorectal cancer included a dose-exploration cohort and a dose -expansion cohort, with a maximum of 15 and 40 patients planned for each, respectively (Figure 1). The dose-exploration phase was designed to assess the safety of sotorasib in combination with panitumumab. From previously reported monotherapy studies of sotorasib and panitumumab, the recommended phase 2 dose (RP2D) were sotorasib 960mg (oral, once daily) and panitumumab 6mg/kg (intravenous, every 2 week). Because no drug-drug interactions or significant synergistic adverse events were anticipated, we elected a dose de-escalation scheme starting at full RP2D for each drug with plans to de-escalate if needed for toxicity. Patients in the dose-exploration cohort started with sotorasib 960 mg daily and panitumumab 6 mg/kg every 2 weeks, with lower doses (sotorasib 720mg or 480mg daily, panitumumab 6mg/kg or 3mg/kg every 2 weeks) to be explored if needed (Figure 1).

The recommended phase 2 dose of the combination, identified as sotorasib 960 mg (oral, once daily) and panitumumab 6 mg/kg (intravenous, every 2 weeks), was administered in the dose-expansion cohort. Treatment continued until disease progression, intolerance to study medication, withdrawal of consent, or end of study. Details regarding toxicity-related dose modification guidelines are included in the protocol.

Data on sex (male, female) were collected and summarized as part of baseline characteristics. This summary was based on investigator-reported data collected in the case report form (to question “Sex” and available response options “Male”, “Female”). Subgroup analysis based on sex was not conducted given the overall small sample size.

Patients

Key eligibility criteria for patients in both cohorts included age ≥18 years; metastatic colorectal cancer with the *KRAS* G12C mutation confirmed by local molecular testing; and an Eastern Cooperative Oncology Group performance status of 0–2. Prior treatment with a KRAS G12C inhibitor was permitted only in the dose-exploration cohort. Patients in the dose-expansion cohort were required to have disease progression on or after treatment with fluoropyrimidine, oxaliplatin, irinotecan, and an antiangiogenic agent. For patients with locally advanced and unresectable disease, only the following counted as a line of therapy: adjuvant therapy (if progression on or within 6 months of administration) and

chemoradiation or chemoradiation followed by planned systemic therapy or vice versa without documented intervening progression (if progression within 6 months of end of treatment). For patients with metastatic disease, any line of therapy administered before documented metastatic disease was not counted as a line of therapy except for adjuvant therapy for patients who experienced disease progression on or within 6 months of end of adjuvant therapy. For all patients, maintenance therapy or chemotherapy adjustments were not considered a new line of therapy.

Patients whose tumors were microsatellite instability–high must have received a checkpoint inhibitor if approved in their geographic region. Complete eligibility criteria are available in the protocol.

Study endpoints and assessments

Primary endpoints for both cohorts were safety and tolerability as assessed by the incidence of dose-limiting toxicities (DLTs) within the first 28 days and adverse events. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 and coded using the Medical Dictionary for Regulatory Activities version 25.1.

Secondary endpoints included objective response rate, disease control rate, duration of response, time to response, progression-free survival, and overall survival per RECIST version 1.1 and per investigator assessment. Imaging by computed tomography or magnetic resonance imaging occurred at screening and then every 6 weeks (±1 week) for the first four follow-up assessments and every 12 weeks (±1 week) thereafter. Pharmacokinetic parameters were additional secondary endpoints. Exploratory endpoints included assessment of genomic alterations at baseline based on analysis of cell-free DNA (cfDNA) in plasma using the 74-gene Guardant360 circulating tumor DNA test (Guardant Health, Palo Alto, CA). Additional details are provided in the protocol and Supplementary Information. Qualified researchers may request data from Amgen clinical studies. Complete details are available here: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

Trial oversight and ethical approval

This study was conducted in accordance with principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The protocol was approved by an Institutional Review Board/Independent Ethics Committee at each participating site. (Supplementary Table S1). All patients provided written informed consent. The trial was designed by the sponsor (Amgen). A sponsor-funded medical writer assisted with the first draft of the manuscript and provided editorial assistance with subsequent drafts. All authors contributed toward the interpretation of data and reviewed the manuscript drafts. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.1.1 software. During dose exploration, a modified Toxicity

Probability Interval-2 model with a target toxicity level of 30% (equivalence toxicity interval: 25%, 33%) was used to guide dose exploration.[32] The sample size of up to 15 patients in the dose exploration part is consistent with conventional phase 1 oncology studies with the objective to estimate the RP2D from exploring potentially 3 dose levels. The sample size of 40 patients in dose expansion part was also based on practical consideration to evaluate the safety and efficacy of the selected dose. No statistical hypothesis was powered to be tested. Statistical summaries were tabulated for the dose-escalation and dose-expansion cohorts separately. Additional pooled analyses were provided for safety summaries. All patients were included in the safety and efficacy summaries. Statistical analysis of pharmacokinetics included all patients who received at least 1 dose of sotorasib and panitumumab and had at least 1 pharmacokinetic sample collected.

Descriptive statistics were used for select demographic, safety, efficacy, pharmacokinetics, and biomarker data by dose, dose schedule, and time, as appropriate. For the efficacy analysis, objective response and disease control rate were summarized as proportions with 95% Clopper-Pearson exact confidence intervals (CIs).[33] For time-to-event endpoints (duration of response, progression-free survival, and overall survival), Kaplan-Meier methods were used. Time to response and duration of response were summarized among confirmed responders. Additional details are provided in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the patients and their families for participating in this trial. We thank Timothy Harrison, PharmD, of Amgen Inc. and Jennifer Martucci, BFA, of Amgen Inc. for operational planning assistance; Keren Price, Ph.D. (all while employed by Amgen Inc.) and Advait Joshi, PhD, of Cactus Life Sciences (part of Cactus Communications) for medical writing support; Shubha Dastidar, PhD, CMPP, of Cactus Life Sciences (part of Cactus Communications) for editorial assistance; and Robert Dawson of Cactus Life Sciences (part of Cactus Communications) for graphics assistance. This study was sponsored and funded by Amgen Inc. This study received support from the following grants to DSH: MD Anderson Cancer Center Support grant (NIH/NCI P30 CA016672), Clinical Translational Science Award 1UL1 TR003167, Cancer Prevention Research Institute of Texas (CPRIT) Precision Oncology Decision Support Core (RP150535), and Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy.

Funding

This study was funded by Amgen Inc.

Data availability

Qualified researchers may request data from Amgen clinical studies. Complete details are available here: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request

References

1. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71, 209–249 (2021). [PubMed: 33538338]

2. Siegel RL, Miller KD, Wagle NS & Jemal A Cancer statistics, 2023. 73, 17–48 (2023).
3. Benson AB, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 19, 329–359 (2021). [PubMed: 33724754]
4. Grothey A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381, 303–312 (2013). [PubMed: 23177514]
5. Mayer RJ, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 372, 1909–1919 (2015). [PubMed: 25970050]
6. Prager GW, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 388, 1657–1667 (2023). [PubMed: 37133585]
7. Ji J, Wang C & Fakih M Targeting KRAS (G12C)-Mutated Advanced Colorectal Cancer: Research and Clinical Developments. OncoTargets and therapy 15, 747–756 (2022). [PubMed: 35837349]
8. Schirripa M, et al. KRAS G12C Metastatic Colorectal Cancer: Specific Features of a New Emerging Target Population. Clin Colorectal Cancer 19, 219–225 (2020). [PubMed: 32605718]
9. Lee JK, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. NPJ Precis Oncol 6, 91 (2022). [PubMed: 36494601]
10. Henry J, et al. Comprehensive clinical and molecular characterization of KRASG12C-mutant colorectal cancer. JCO Precis Oncol 5, 613–621 (2021).
11. Fakih M, et al. Real-World Study of Characteristics and Treatment Outcomes Among Patients with KRAS p.G12C-Mutated or Other KRAS Mutated Metastatic Colorectal Cancer. Oncologist 27, 663–674 (2022). [PubMed: 35472176]
12. Alawawdeh A, et al. Prognostic Differences of RAS Mutations: Results from the South Australian Metastatic Colorectal Registry. Target Oncol 17, 35–41 (2022). [PubMed: 34822070]
13. Osterlund E, et al. KRAS-G12C Mutation in One Real-Life and Three Population-Based Nordic Cohorts of Metastatic Colorectal Cancer. Front Oncol 12, 826073 (2022). [PubMed: 35251991]
14. Canon J, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 575, 217–223 (2019). [PubMed: 31666701]
15. Fakih MG, et al. Sotorasib for previously treated colorectal cancers with KRAS(G12C) mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol 23, 115–124 (2022). [PubMed: 34919824]
16. Ryan MB, et al. KRAS(G12C)-independent feedback activation of wild-type RAS constrains KRAS(G12C) inhibitor efficacy. Cell Rep 39, 110993 (2022). [PubMed: 35732135]
17. Amodio V, et al. EGFR Blockade Reverts Resistance to KRAS(G12C) Inhibition in Colorectal Cancer. Cancer Discov 10, 1129–1139 (2020). [PubMed: 32430388]
18. Yaeger R, et al. Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C. N Engl J Med 388, 44–54 (2023). [PubMed: 36546659]
19. Fakih MG, et al. Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C. New England Journal of Medicine (2023).
20. Tabernero J, et al. Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study. 39, 273–284 (2021).
21. Fakih M & Vincent M Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol 17 Suppl 1, S18–30 (2010).
22. Tabernero J, et al. Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer: The phase 3 randomized SUNLIGHT study. 41, 4–4 (2023).
23. Ahronian LG, et al. Clinical Acquired Resistance to RAF Inhibitor Combinations in BRAF-Mutant Colorectal Cancer through MAPK Pathway Alterations. Cancer Discov 5, 358–367 (2015). [PubMed: 25673644]
24. Corcoran RB, et al. BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. Sci Signal 3, ra84 (2010). [PubMed: 21098728]

25. De Roock W, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 11, 753–762 (2010). [PubMed: 20619739]

26. Johnson RM, et al. ARID1A mutations confer intrinsic and acquired resistance to cetuximab treatment in colorectal cancer. Nat Commun 13, 5478 (2022). [PubMed: 36117191]

27. Oddo D, et al. Molecular Landscape of Acquired Resistance to Targeted Therapy Combinations in BRAF-Mutant Colorectal Cancer. Cancer Res 76, 4504–4515 (2016). [PubMed: 27312529]

28. Topham JT, et al. Circulating Tumor DNA Identifies Diverse Landscape of Acquired Resistance to Anti–Epidermal Growth Factor Receptor Therapy in Metastatic Colorectal Cancer. 41, 485–496 (2023).

29. Kato S, et al. Genomic Assessment of Blood-Derived Circulating Tumor DNA in Patients With Colorectal Cancers: Correlation With Tissue Sequencing, Therapeutic Response, and Survival. JCO Precis Oncol 3(2019).

30. Gupta R, et al. Guardant360 Circulating Tumor DNA Assay Is Concordant with FoundationOne Next-Generation Sequencing in Detecting Actionable Driver Mutations in Anti-EGFR Naive Metastatic Colorectal Cancer. Oncologist 25, 235–243 (2020). [PubMed: 32162812]

31. Liao S, et al. A genetic interaction analysis identifies cancer drivers that modify EGFR dependency. Genes Dev 31, 184–196 (2017). [PubMed: 28167502]

32. Guo W, Wang SJ, Yang S, Lynn H & Ji Y A Bayesian interval dose-finding design addressingOckham's razor: mTPI-2. Contemp Clin Trials 58, 23–33 (2017). [PubMed: 28458054]

33. <Clopper 1934 The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial.pdf>.

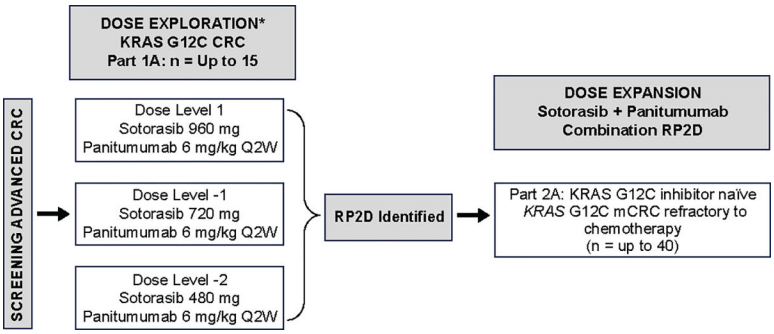

Figure 1. Study schema

Additional cohorts that are not the subject of this manuscript are not shown.

* If dose level 1 was deemed not tolerable from toxicity primarily from panitumumab, a dose level using panitumumab at 3 mg/kg Q2W could be explored with or without dose reduction of sotorasib.

CRC, colorectal cancer; RP2D, recommended phase 2 dose; Q2W, once every 2 weeks.

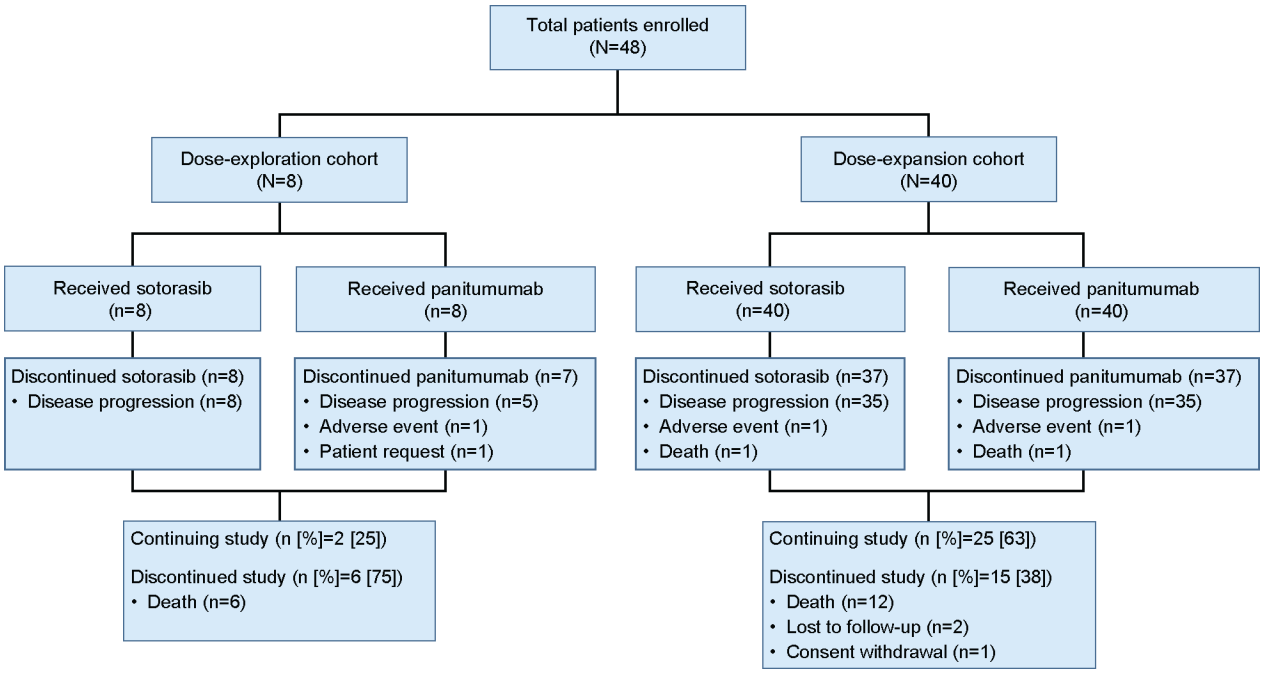

Figure 2. Patient disposition

N, number of patients in the analysis set; n, number of patients with observed data.

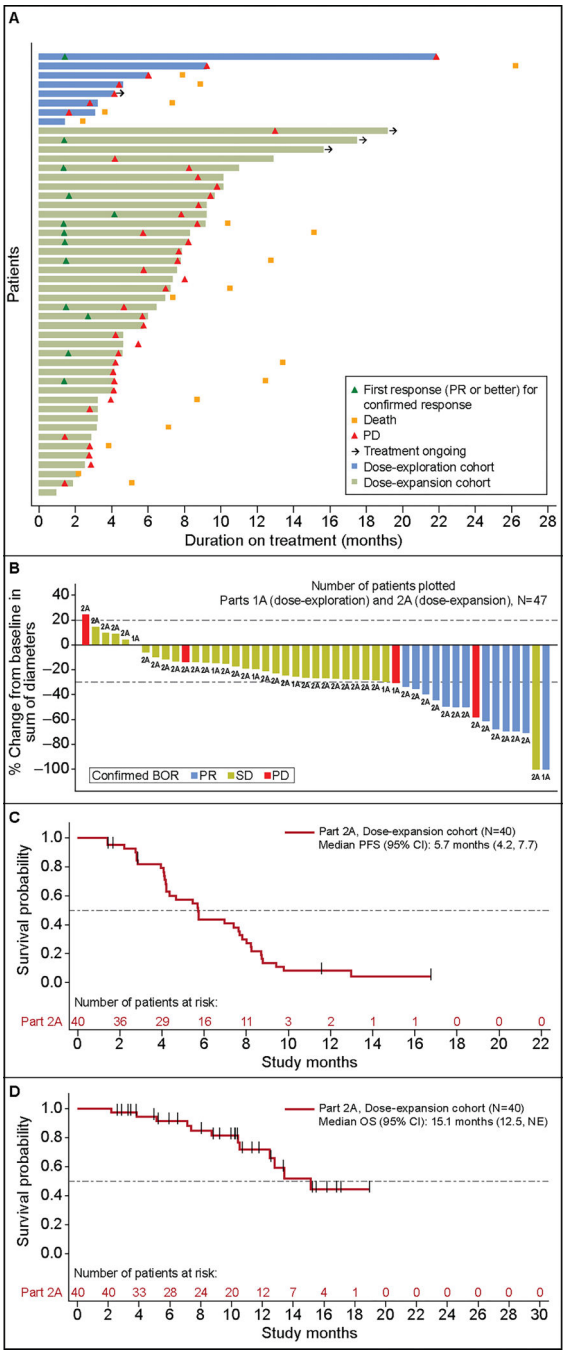

Figure 3. Activity of sotorasib therapy in the dose-expansion cohort

(A) Swimmer plot of duration of treatment and response as of data cutoff. (B) Best percentage change from baseline in sum of diameters (C) Kaplan-Meier curve of progression-free survival; Vertical lines indicate censoring. (D) Kaplan-Meier curve of overall survival; Vertical lines indicate censoring.

Part 1A denotes the dose-exploration cohort and Part 2A denotes the dose-expansion cohort. BOR, best objective response; CRC, colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Table 1.

Characteristics of the patients at baseline

	Dose-exploration cohort (n=8)	Dose-expansion cohort (n=40)	Total (n=48)
Median age, years (range)	61 (31–79)	58 (30–78)	58 (30–79)
Sex			
Male	3 (38)	10 (25)	13 (27)
Female	5 (63)	30 (75)	35 (73)
Race			
American Indian or Alaska Native	0 (0)	1 (3)	1 (2)
Asian	0 (0)	13 (33)	13 (27)
Black or African American	1 (13)	2 (5)	3 (6)
White	7 (88)	22 (55)	29 (60)
Other	0 (0)	2 (5)	2 (4)
ECOG performance status score *			
0	3 (38)	13 (33)	16 (33)
1	4 (50)	26 (65)	30 (63)
2	1 (13)	1 (3)	2 (4)
Primary tumor location †			
Left-sided	6 (75)	27 (68)	33 (69)
Right-sided	2 (25)	13 (33)	15 (31)
Number of prior lines of anticancer systemic therapy			
1	1 (13)	2 (5)	3 (6)
2	1 (13)	20 (50)	21 (44)
3	1 (13)	8 (20)	9 (19)
≥4	5 (63)	10 (25)	15 (31)
Median (range)	4 (1–10)	2 (1–7)	3 (1–10)
Type of prior systemic anticancer therapy ‡			
Oxaliplatin	8 (100)	40 (100)	48 (100)
Irinotecan	7 (88)	40 (100)	46 (96)
Fluoropyrimidine	8 (100)	40 (100)	48 (100)
Trifluridine-tipiracil	4 (50)	7 (18)	11 (23)
Regorafenib	3 (38)	7 (18)	10 (21)
Trifluridine-tipiracil and/or regorafenib	4 (50)	13 (33)	17 (35)
EGFR antibody	1 (13)	0 (0)	1 (2)
Antiangiogenic biologic	8 (100)	40 (100)	48 (100)
Bevacizumab	8 (100)	39 (98)	45 (94)
Aflibercept	0 (0)	1 (3)	1 (2)
Ramucirumab	0 (0)	3 (8)	3 (6)
Anti–PD-1 or anti–PD-L1 §	2 (25)	3 (8)	5 (10)

	Dose-exploration cohort (n=8)	Dose-expansion cohort (n=40)	Total (n=48)
KRAS G12C inhibitor	5 (63)	0 (0)	5 (10)
Type of cancer			
Colon cancer	5 (63)	29 (73)	34 (71)
Rectal cancer	3 (38)	11 (28)	14 (29)

Data are presented as n (%) unless indicated otherwise.

[*] Baseline ECOG is measured at predose on cycle 1, day 1.

[†] Left-sided tumors include those in the rectum, sigmoid colon, descending colon, or transverse colon (with sidedness specified as “left” on the case-report form). Right-sided tumors include those in the cecum, ascending colon, and transverse colon (with sidedness specified as “right” or “unknown” on the case-report form).

[‡] Each patient might have received several prior therapies; types of prior anticancer therapies were adjudicated and included therapies given in any treatment setting.

[§] No patients were known to be microsatellite instability–high.

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Table 2.

Treatment-related adverse events

	Dose-exploration cohort (n=8)	Dose-expansion cohort (n=40)	Total (n=48)
Any grade	8 (100)	37 (93)	45 (94)
Attributed to sotorasib	4 (50)	26 (65)	30 (63)
Attributed to panitumumab	8 (100)	37 (93)	45 (94)
Grade 3	3 (38)	10 (25)	13 (27)
Grade 4	0 (0)	0 (0)	0 (0)
Fatal	0 (0)	0 (0)	0 (0)
Grade ≥3	3 (37.5)	10 (25.0)	13 (27.1)
Leading to dose reduction			
Attributed to sotorasib	1 (13)	1 (3)	2 (4)
Attributed to panitumumab	1 (13)	6 (15)	7 (15)
Leading to dose interruption			
Attributed to sotorasib	1 (13)	5 (13)	6 (13)
Attributed to panitumumab	3 (38)	8 (20)	11 (23)
Leading to treatment discontinuation	0 (0)	0 (0)	0 (0)

Data are presented as n (%).

Table 3.

Tumor response to treatment with sotorasib plus panitumumab

	Dose-exploration cohort (n=8)	Dose-expansion cohort (n=40)
Objective response, n (%) (95% CI)*	1 (12.5) (0.3, 52.7)	12 (30.0) (16.6, 46.5)
Disease control rate, n (%) (95% CI)†	6 (75.0) (34.9, 96.8)	37 (92.5) (79.6, 98.4)
Best response, n (%)		
Confirmed complete response	0 (0)	0 (0)
Confirmed partial response	1 (12.5)	12 (30.0)
Stable disease	5 (62.5)	25 (62.5)
Progressive disease	1 (12.5)	3 (7.5)
Not evaluable	0	0
No assessment‡	1 (12.5)	0
Median time to response, months (range)§	1.4 (1.4–1.4)	1.5 (1.3–4.1)
Median duration of response (KM), months (95% CI)§	--	5.3 (2.8, 7.4)
Median progression-free survival (KM), months (95% CI)	--	5.7 (4.2, 7.7)
Median overall survival (KM), months (95% CI)	--	15.2 (12.5, NE)

*Objective response was defined as complete or partial response.

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

‡One patient ended treatment before tumor assessment.

§Time to response and duration of response were calculated among confirmed responders.

KM estimates were not provided if the analysis set had <10 patients.

CI, confidence interval; KM, Kaplan-Meier; NE, not estimable.