Adagrasib in Advanced Solid Tumors Harboring a *KRAS*^{G12C} Mutation

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ABSTRACT

PURPOSE Adagrasib, a KRAS^{G12C} inhibitor, has demonstrated clinical activity in patients with *KRAS*^{G12C}-mutated non–small-cell lung cancer (NSCLC) and colorectal cancer (CRC). *KRAS*^{G12C} mutations occur rarely in other solid tumor types. We report evaluation of the clinical activity and safety of adagrasib in patients with other solid tumors harboring a *KRAS*^{G12C} mutation.

METHODS In this phase II cohort of the KRYSTAL-1 study (ClinicalTrials.gov identifier: NCT03785249; phase Ib cohort), we evaluated adagrasib (600 mg orally twice daily) in patients with *KRAS*^{G12C}-mutated advanced solid tumors (excluding NSCLC and CRC). The primary end point was objective response rate. Secondary end points included duration of response, progression-free survival (PFS), overall survival, and safety.

RESULTS As of October 1, 2022, 64 patients with *KRAS*^{G12C}-mutated solid tumors were enrolled and 63 patients treated (median follow-up, 16.8 months). The median number of prior lines of systemic therapy was 2. Among 57 patients with measurable disease at baseline, objective responses were observed in 20 (35.1%) patients (all partial responses), including 7/21 (33.3%) responses in pancreatic and 5/12 (41.7%) in biliary tract cancers. The median duration of response was 5.3 months (95% CI, 2.8 to 7.3) and median PFS was 7.4 months (95% CI, 5.3 to 8.6). Treatment-related adverse events (TRAEs) of any grade were observed in 96.8% of patients and grade 3-4 in 27.0%; there were no grade 5 TRAEs. TRAEs did not lead to treatment discontinuation in any patients.

CONCLUSION Adagrasib demonstrates encouraging clinical activity and is well tolerated in this rare cohort of pretreated patients with *KRAS*^{G12C}-mutated solid tumors.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

KRAS represents the most prevalent oncogenic driver in human cancer,[1] with over 80% of mutations occurring at codon 12, normally occupied by a glycine residue.[2,3] KRAS^{G12C}, which favors the active guanosine triphosphate (GTP)–bound form of KRAS and results in enhanced cell proliferation and survival,[1,4] occurs in approximately 14% of patients with non–small-cell lung cancer (NSCLC) and 3%-4% of those with colorectal cancer (CRC).[5-7] *KRAS*^{G12C} mutations have also been identified, although less frequently, in other solid tumors, including appendiceal (3%-4%), pancreatic (1%-3%), small bowel (1%-3%), biliary tract (1%), endometrial (1%-2%), and ovarian cancer (1%-2%).[5,6,8] No approved targeted treatment options are currently available for patients with *KRAS*^{G12C}-driven solid tumors other than NSCLC.[8,9]

After the identification of the KRAS switch II binding pocket, small molecules have been developed that can occupy this region and covalently bind to the mutant cysteine to prevent GTP binding.[10-12] Adagrasib is an oral, small-molecule, covalent inhibitor that irreversibly and selectively binds KRAS^{G12C}, trapping it in its inactive guanosine diphosphate–bound state.[10,11] Adagrasib was selected for favorable properties, including a long half-life of 23 hours, dose-dependent pharmacokinetics, and CNS penetration.[10,13,14]

Adagrasib is currently being evaluated in KRYSTAL-1, a phase I/II multiple expansion cohort trial of patients with

CONTEXT

Key Objective

This KRYSTAL-1 phase II cohort evaluated the clinical activity and safety of adagrasib, a potent covalent KRAS^{G12C} inhibitor, in patients with advanced solid tumors, excluding non–small-cell lung cancer (NSCLC) and colorectal cancer (CRC), harboring a *KRAS^{G12C}* mutation.

Knowledge Generated

To date, to our knowledge, this study is the largest phase II tumor-agnostic data set to evaluate *KRAS^{G12C}*-mutated solid tumors, excluding NSCLC and CRC. Adagrasib demonstrated an encouraging objective response rate of 35.1% in a biomarker-selected population who have declined or have no available standard-of-care treatment option. Responses were observed across a broad range of tumor types, including pancreatic ductal adenocarcinoma and biliary tract cancer; safety and tolerability profiles were manageable across tumor types. The range of responses observed suggest the potential for use of adagrasib as a tumor-agnostic agent, underscoring the importance of wider and more consistent genomic testing when assessing therapeutic approaches.

Relevance *(R.G. Maki)*

Adagrasib is a KRAS^{G12C} inhibitor that demonstrates activity in a number of cancer histologies in which the *KRAS* mutation is observed. This study broadens the diagnoses for which this class of agents may be useful.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

advanced solid tumors harboring a *KRAS^{G12C}* mutation. Data reported previously from other cohorts of this trial demonstrated clinical activity and tolerability of adagrasib in previously treated patients with *KRAS^{G12C}*-mutated NSCLC and CRC.[15,16] On the basis of these data, the US Food and Drug Administration (FDA) granted accelerated approval for adagrasib in previously treated *KRAS^{G12C}*-mutated NSCLC in December 2022.[17] The FDA has also granted breakthrough therapy designation for adagrasib in combination with cetuximab, for the treatment of patients with *KRAS^{G12C}*-mutated CRC.[18] Preliminary results have also been presented for other GI tumors, including pancreatic, biliary tract, and appendiceal cancers, as well as non-GI tumors, such as ovarian and endometrial cancers, demonstrating promising clinical activity in these tumor types.[13,19,20] Herein, we report data from a phase II cohort of KRYSTAL-1 evaluating adagrasib monotherapy in patients with advanced solid tumors, excluding NSCLC and CRC, harboring a *KRAS^{G12C}* mutation.

METHODS

Study Oversight

This open-label, single-arm, nonrandomized study was designed by employees of Mirati Therapeutics, Inc (the sponsor) and the investigators. The data were collected by the investigators and analyzed by sponsor-employed statisticians. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines.[21,22] The Protocol (online only) was approved by the relevant institutional review boards or ethics committees. All the patients provided written informed consent. Trial oversight was provided by the sponsor, the investigators, local institutional review boards, a specifically commissioned central institutional review board, and an independent data monitoring committee.

Patients

Eligible patients were age 18 years and older, with a histologically confirmed diagnosis of an unresectable or metastatic solid tumor (excluding NSCLC and CRC) with a *KRAS^{G12C}* mutation detected in tumor tissue and/or blood. Patients were required to have a life expectancy of ≥3 months, measurable disease per RECIST version 1.1 (v1.1), and an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients must have had no other available treatment with curative intent and have been ineligible for, declined, or had no available standard-of-care treatment option. Key exclusion criteria included previous treatment with another KRAS^{G12C} inhibitor and active CNS metastases; patients were eligible if CNS metastases were adequately treated and/or stable (no corticosteroids for ≥2 weeks before enrollment or stable/decreasing dose of ≤10 mg daily corticosteroids). Full eligibility criteria are provided in the Protocol.

Study Design and End Points

In this phase II cohort, the clinical activity of adagrasib was evaluated in patients with *KRAS^{G12C}*-mutated unresectable or metastatic solid tumors other than NSCLC and CRC. Patients received adagrasib 600 mg (capsule formulation) orally twice daily as monotherapy until disease progression, unacceptable adverse events, withdrawal of consent, or death. Patients experiencing clinical benefit, as judged by the investigator, could

continue therapy beyond RECIST-defined disease progression. The primary end point was objective response rate (ORR) according to RECIST v1.1. Secondary end points included duration of response, progression-free survival (PFS), overall survival (OS), 1-year survival rate, safety, and tolerability.

Study Assessments

Clinical Assessments

Patients were tested for mutations in tumor tissue or circulating tumor DNA using preapproved methods for analysis (see Appendix 1 [online only] for details).

All patients underwent chest (computed tomography [CT] with contrast), abdomen, and pelvis imaging (CT with contrast or magnetic resonance imaging) at baseline, with subsequent assessment every 6 weeks throughout the first year of treatment and every 12 weeks thereafter. Disease evaluation scans continued until documentation of objective disease progression by the investigator; response assessments were evaluated by investigators and a blinded independent central review (BICR) according to RECIST v1.1. Patients with a tumor response (partial or complete response) had a confirmatory assessment at least 4 weeks after initial observation of response.

Safety

Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Patients were followed for adverse events for ≥28 days after the last study dose of study treatment.

Statistical Analysis

Confirmed objective responses were summarized as the frequency and percentage of complete and partial responses, with 95% CIs, on the basis of the full analysis set comprising all patients with measurable disease at baseline who received ≥1 dose of adagrasib. The ORR using currently available therapies to treat patients with advanced solid tumors harboring a $KRAS^{G12C}$ mutation, who have previously received standard-of-care treatments, was assumed to be 10%; therefore, this rate was considered not clinically meaningful. The target ORR using adagrasib in this patient population was 30%. Median duration of response, PFS, and OS, as well as 1-year survival rate, were estimated using the Kaplan-Meier method. Median PFS was summarized on the basis of the full analysis set. OS was summarized on the basis of the enrolled population.

RESULTS

Patients

As of October 1, 2022, with an enrollment period of March 2020 to September 2022 (30 months), 64 patients with $KRAS^{G12C}$-mutated unresectable or metastatic solid tumors (excluding NSCLC and CRC) were enrolled. Presence of $KRAS^{G12C}$ mutation was established using tumor tissue for 54 patients and blood circulating tumor DNA sampling for 10 patients. In

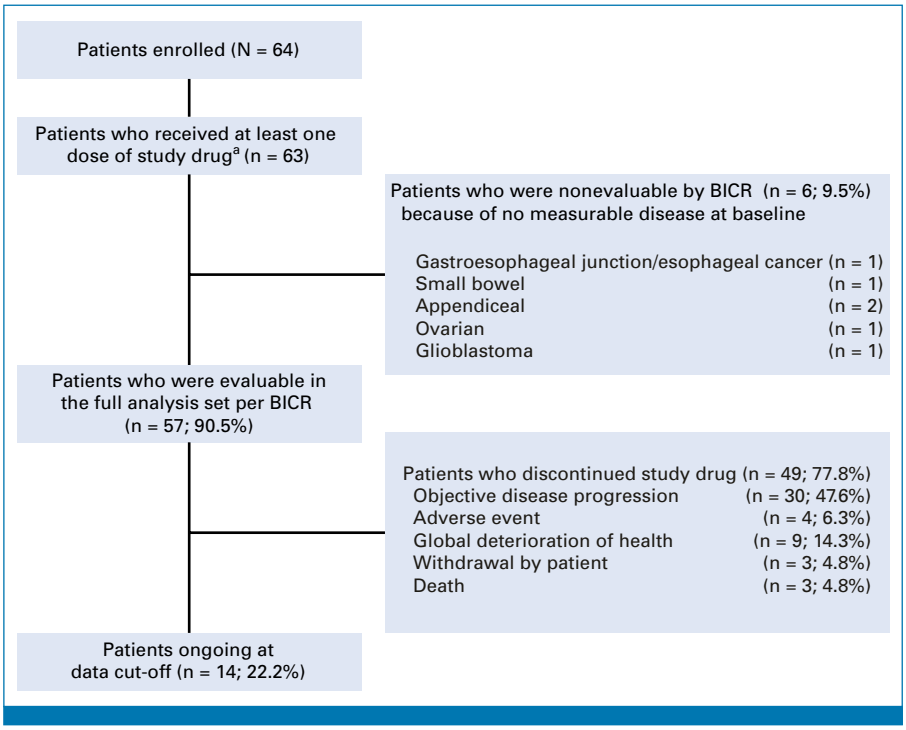

FIG 1. Patient disposition. [a]One patient with appendiceal cancer was enrolled at the point of data cutoff (October 1, 2022) but had not been treated at this time. BICR, blinded independent central review.

TABLE 1. Demographics and Baseline Characteristics of Patients With *KRAS*^{G12C}-Mutated Solid Tumors

Characteristic	Overall Solid Tumors (N = 64)
Age, years, median (range)	65 (21-89)
Female, No. (%)	33 (51.6)
Ethnicity, No. (%)	
White	48 (75.0)
Black or African American	6 (9.4)
Asian/other	3 (4.7)/7 (11.0)
ECOG PS, No. (%)[a]	
0/1	24 (37.5)/39 (60.9)
Tumor type, No.	
Pancreatic[b]	21
Biliary tract[c]	12
Appendiceal[d]	10
Ovarian	5
Unknown primary	4
Gastroesophageal junction/esophageal	4
Endometrial	3
Small bowel	3
Breast	1
Glioblastoma	1
Brain metastases at baseline, No. (%)	2 (3.1)
Prior lines of systemic anticancer therapy, median (range)	2.0 (0-7)
Pancreatic	2.0 (1-4)
Biliary tract[e]	1.5 (0-5)
Appendiceal	2.0 (1-4)
Ovarian	2.0 (0-4)
Unknown primary	1.0 (0-5)
Gastroesophageal junction/esophageal	3.5 (0-4)
Endometrial	2.0 (2-5)
Small bowel	2.0 (2-2)
Breast	7.0 (7-7)
Glioblastoma	3.0 (3-3)
0/1/2/3/≥4 prior treatment lines, %	7.8/21.9/35.9/18.8/15.6
Previous treatment regimen, No. (%)	
Chemotherapy	59 (92.2)
Platinum-based	51 (79.7)
Taxane	30 (46.9)
Gemcitabine	30 (46.9)
Fluoropyrimidine	45 (70.3)
Anti-VEGF	12 (18.8)
Targeted therapy[f]	7 (10.9)
Anti–PD-(L)1 checkpoint inhibitor	7 (10.9)
Previous radiotherapy	18 (28.1)
Previous surgery	44 (68.8)

NOTE. Percentages may not add up to 100 because of rounding. Excluding non–small-cell lung cancer and colorectal cancer.
Abbreviations: BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor.
[a]ECOG PS was unavailable for one patient (1.6%).
[b]For patients with pancreatic cancer, 81.0% previously received gemcitabine-based regimen(s) and 85.7% received prior fluoropyrimidine-based regimen(s).
[c]For patients with biliary tract cancer, 83.3% received gemcitabine-based regimen(s) and 66.7% received prior fluoropyrimidine-based regimen(s).
[d]Seven patients with appendiceal cancer were evaluable per BICR, of which six were mucinous and one was colonic.
[e]Biliary tract cancer includes patients with ampullary (n = 3), cholangiocarcinoma (n = 8), and gallbladder (n = 1) tumors.
[f]Prior targeted therapy includes inhibitors targeting HER2, BRAF, MEK, PARP, CDK4/6, PI3K, and/or multitargeted tyrosine kinase inhibitor.

total, 63 patients had received at least one dose of adagrasib at data cutoff; six patients had measurable disease at baseline according to investigator assessment, but no measurable disease according to the independent committee (Fig 1). The median follow-up was 16.8 months, and the median duration of treatment was 6.6 months. Patient demographics and baseline characteristics are shown in Table 1, with prior treatment regimens detailed in Appendix Table A1 (online only; pancreatic ductal adenocarcinoma and biliary tract cancer), Appendix Table A2 (online only; other GI tumors), and Appendix Table A3 (online only; other tumors). The median age was 65 years and the median number of prior lines of systemic therapy was 2. The cohort included patients with the following tumor types: pancreatic cancer (n = 21), biliary tract cancer (n = 12), appendiceal cancer (n = 10), ovarian cancer (n = 5), unknown primary cancer (n = 4), gastroesophageal junction/esophageal cancer (n = 4), endometrial cancer (n = 3), small bowel cancer (n = 3), breast cancer (n = 1), and glioblastoma (n = 1). As of the data cutoff, 49 patients had discontinued treatment, primarily because of disease progression (n = 30), health deterioration (n = 9), unrelated treatment emergent adverse events (n = 4), withdrawal (n = 3), and death (unrelated to treatment; n = 3), as shown in Figure 1.

Clinical Activity

Among 57 patients with measurable disease, ORR was 35.1% (20/57), all of which were partial responses as determined by BICR. Tumor responses, as determined by BICR and investigator assessment, are summarized in Table 2.

Responses by BICR were observed in nine different tumor histologies; clinical activity results according to tumor type are provided in Table 3, Figure 2A, and Appendix Figure A1 (online only). In the full analysis set, ORRs by tumor type were pancreatic (n = 7/21; 33.3%), biliary tract (n = 5/12; 41.7%), ovarian (n = 2/4; 50.0%), unknown primary (n = 1/4; 25.0%), gastroesophageal junction/esophageal (n = 1/3; 33.3%), endometrial (n = 2/3; 66.7%), small bowel (n = 1/2; 50.0%), and breast (n = 1/1; 100%). No objective responses were observed among seven patients with appendiceal cancer (including six with mucinous appendiceal

TABLE 2. ORRs in Patients With *KRAS*^{G12C}-Mutated Solid Tumors (full analysis set)

Clinical Activity Outcome[a]	Overall Solid Tumors	
	BICR-Assessed (n = 57)[b]	Investigator-Assessed (n = 63)[b]
ORR		
No. (%)	20 (35.1)	19 (30.2)
95% CI	22.9 to 48.9	19.2 to 43.0
Best overall response, No. (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	20 (35.1)	19 (30.2)
Stable disease	29 (50.9)	36 (57.1)
Progressive disease	5 (8.8)	5 (7.9)
Not evaluable	3 (5.3)	3 (4.8)

NOTE. Data as of October 1, 2022 (median follow-up, 16.8 months). Excluding non–small-cell lung cancer and colorectal cancer.
Abbreviations: BICR, blinded independent central review; ORR, objective response rate.
[a]On the basis of BICR and investigator assessment of the full analysis set (measurable disease with ≥1 dose of adagrasib).
[b]Six patients had measurable disease at baseline per investigator assessment but not according to BICR (Fig 1).

TABLE 3. ORR (full analysis set), PFS (full analysis set) by Independent Central Review, and OS (enrolled population) in Patients With *KRAS*^{G12C}-Mutated Solid Tumors According to Tumor Type

Tumor Type	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)
All patients	n = 57 35.1 (22.9 to 48.9)	n = 57 7.4 (5.3 to 8.6)	N = 64 14.0 (8.5 to 18.6)
Pancreatic cancer	n = 21 33.3 (14.6 to 57.0)	n = 21 5.4 (3.9 to 8.2)	n = 21 8.0 (5.2 to 11.8)
Biliary tract cancer	n = 12 41.7 (15.2 to 72.3)	n = 12 8.6 (2.7 to 11.3)	n = 12 15.1 (8.6 to NE)
Cholangiocarcinoma[a]	n = 8 50.0 (15.7 to 84.3)	n = 8 11.3 (1.6 to NE)	n = 8 15.1 (12.5 to NE)
Ampullary	n = 3 33.3 (0.8 to 90.6)	n = 3 5.3 (2.7 to NE)	n = 3 15.5 (8.6 to NE)
Gallbladder	n = 1 0 (0.0 to 97.5)	n = 1 9.2 (NE to NE)	n = 1 14.2 (NE to NE)
Other GI tumors	n = 12 16.7 (2.1 to 48.4)	n = 12 8.5 (2.5 to 17.7)	n = 17 14.0 (6.2 to NE)
Appendiceal	n = 7 0 (0.0 to 41.0)	n = 7 12.4 (1.4 to NE)	n = 10 NR (4.1 to NE)
Small bowel	n = 2 50.0 (1.3 to 98.7)	n = 2 5.6 (2.6 to NE)	n = 3 7.9 (6.2 to NE)
GEJ/esophageal	n = 3 33.3 (0.8 to 90.6)	n = 3 7.6 (4.1 to NE)	n = 4 12.5 (10.9 to NE)
Gynecologic tumors	n = 7 57.1 (18.4 to 90.1)	n = 7 8.1 (1.4 to NE)	n = 8 19.6 (15.1 to NE)
Ovarian	n = 4 50.0 (6.8 to 93.2)	n = 4 9.7 (1.4 to NE)	n = 5 19.6 (15.1 to NE)
Endometrial	n = 3 66.7 (9.4 to 99.2)	n = 3 5.6 (4.4 to NE)	n = 3 20.6 (19.5 to NE)
Other tumors[b]	n = 5 40.0 (5.3 to 85.3)	n = 5 8.2 (7.0 to NE)	n = 6 7.6 (5.6 to NE)
Unknown primary	n = 4 25.0 (0.6 to 80.6)	n = 4 8.2 (7.0 to NE)	n = 4 7.6 (5.6 to NE)
Breast	n = 1 100.0 (2.5 to 100.0)	n = 1 NR (NE to NE)	n = 1 NR (NE to NE)

NOTE. Data as of October 1, 2022 (median follow-up, 16.8 months). Excluding non–small-cell lung cancer and colorectal cancer.
Abbreviations: BICR, blinded independent central review; GEJ, gastroesophageal junction; NE, not evaluable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]Intrahepatic, n = 5; extrahepatic, n = 2; hilar, n = 1.
[b]One patient with glioblastoma had no measurable disease at baseline per BICR; therefore, this patient was not included in response and PFS analyses but was included in the OS analyses. OS data were based on the enrolled population (n = 64). PFS and ORR data were based on the full analysis data set per BICR (n = 57).

adenocarcinoma); six patients (85.7%) had stable disease. Clinical activity results by tumor type according to investigator assessment are presented in Appendix Table A4 (online only); disease control rates as assessed by BICR and investigator assessment are shown in Appendix Table A5 (online only).

Timing and duration of responses in individual patients is shown in Figure 2B; the median time to response was 1.4 months and the median duration of response was 5.3 months (95% CI, 2.8 to 7.3) as per BICR (Fig 2C) and 7.0 months (95% CI, 3.1 to 9.9) as per investigator assessment; at the time of data cutoff, treatment was ongoing in 14 patients. Among patients with measurable disease, the median PFS was 7.4 months (95% CI, 5.3 to 8.6) as per BICR (n = 57; Fig 2D) and 6.9 months (95% CI, 5.3 to 8.3) as per investigator assessment (n = 63). Median OS was 14.0 months (95% CI, 8.5 to 18.6) and the estimated OS rate at 1 year was 53.5% (95% CI, 37.9 to 66.9; n = 64 [Appendix Fig A2, online only]). Median PFS and median OS according to tumor type are presented in Table 3. In total, 22.2% (14/63) patients from the treated population received subsequent anticancer therapy.

Safety

Among the 63 patients within the safety population, treatment-related adverse events (TRAEs) with adagrasib (capsule formulation) of any grade were experienced by 96.8% (Table 4), with grade 3 TRAEs reported in 25.4% of patients and grade 4 TRAEs observed in one patient (1.6%; febrile neutropenia). There were no grade 5 TRAEs. The most common any-grade TRAEs (in ≥20% of patients) were nausea (49.2%), diarrhea (47.6%), fatigue (41.3%), and vomiting (39.7%). The most common grade 3 TRAEs (in ≥5% of patients) were fatigue (6.3%) and electrocardiogram QT prolongation (6.3%). TRAEs of any grade led to adagrasib dose reduction in 25 patients (39.7%) and dose interruption in 28 patients (44.4%). Overall, no patients discontinued adagrasib because of TRAEs. Treatment-emergent adverse events are summarized in Appendix Table A6 (online only).

DISCUSSION

Recently, KRAS^{G12C} inhibitors have demonstrated promising clinical activity in patients with *KRAS*^{G12C}-mutated advanced NSCLC and CRC.[15,16,23,24] In December 2022, the FDA granted accelerated approval for adagrasib in previously treated *KRAS*^{G12C}-mutated NSCLC[17] and breakthrough therapy designation for adagrasib, in combination with cetuximab, in *KRAS*^{G12C}-mutated CRC.[18] Although biomarker-directed treatment strategies have been successful in the treatment

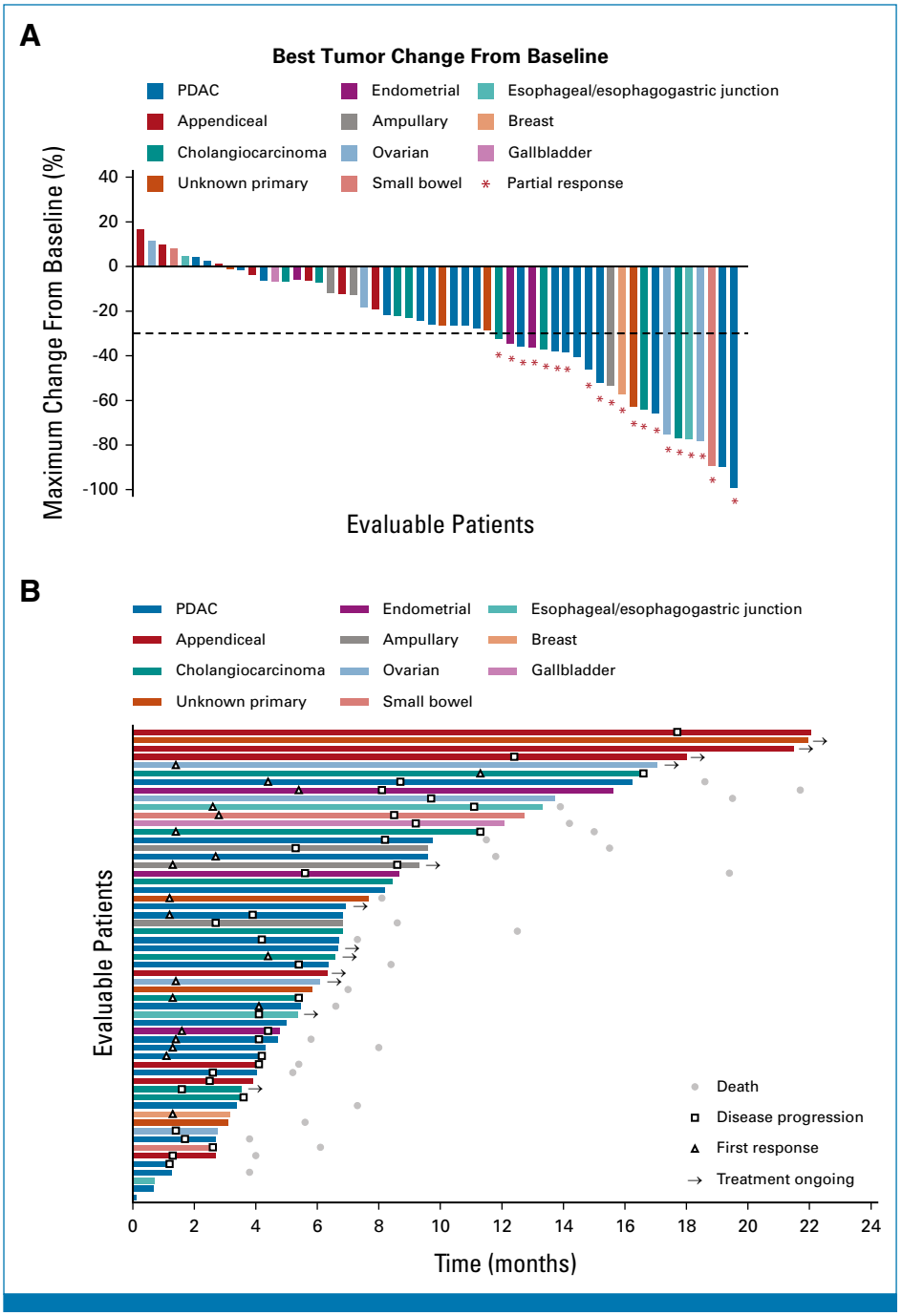

FIG 2. Efficacy outcomes for patients with evaluable disease by BICR. (A) Waterfall plot of best percentage tumor change from baseline (n = 54). (B) Swimmer plot showing individual duration of treatment, response, and clinical outcome at data cutoff (n = 54). (C) Kaplan-Meier graphical representation of duration of response. (D) Kaplan-Meier graphical representation of PFS. Data as of October 1, 2022 (median follow-up, 16.8 months). BICR, blinded independent central review; DOR, duration of response; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival. (continued on following page)

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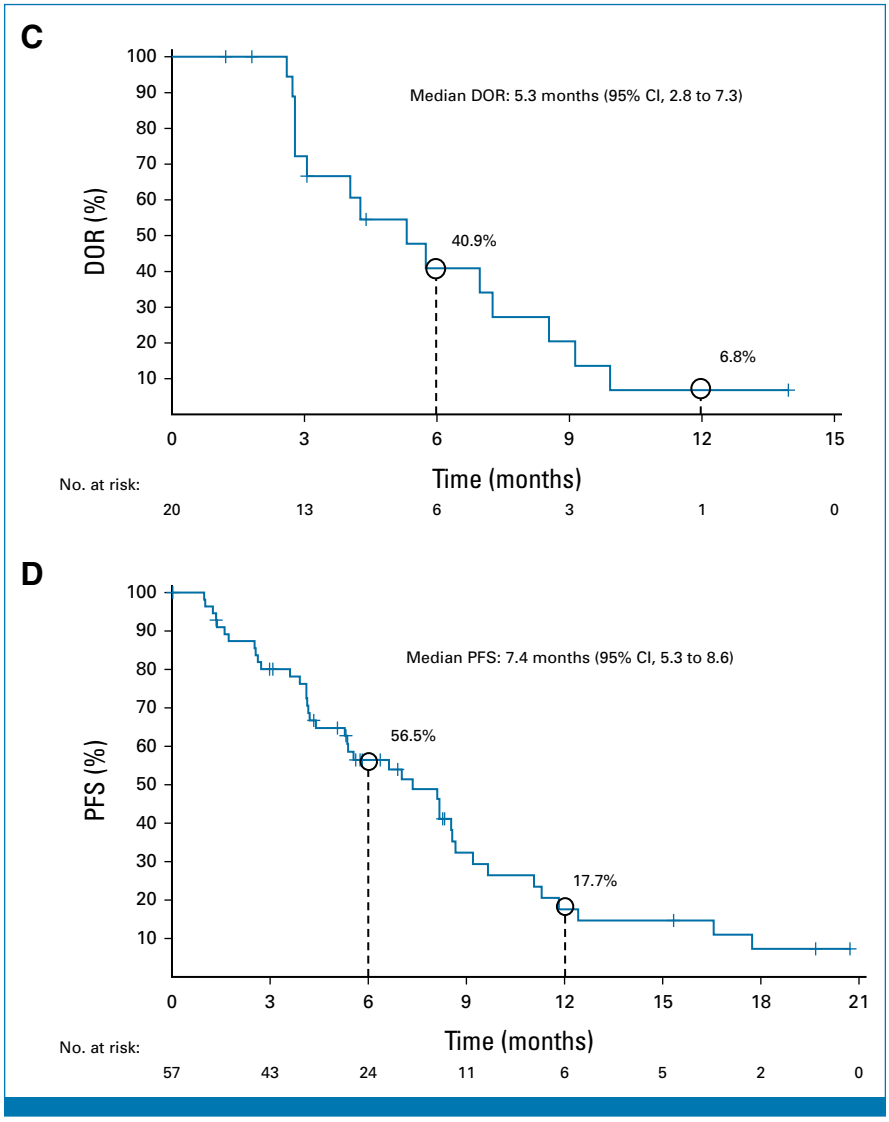

FIG 2. (Continued).

of NSCLC, and preliminary progress has been made in CRC, targeted treatment options for other solid tumors, including pancreatic, biliary tract, and gynecologic cancers, remain extremely limited. The occurrence of the same oncogenic drivers across multiple tumor types has resulted in the treatment landscape evolving toward a tumor-agnostic approach, including recent approvals for larotrectinib and entrectinib (*NTRK* gene fusion–positive solid tumors), selpercatinib (*RET* proto oncogene-gene fusion–positive solid tumors), pembrolizumab (high microsatellite instability [MSI-H]/mismatch repair deficiency [dMMR], and tumor mutational burden-high), dostarlimab (MSI-H/dMMR), and dabrafenib plus trametinib (v-raf murine sarcoma viral oncogene homolog B1 V600E mutation–positive solid tumors).[25] *KRAS*^{G12C} mutations occur uncommonly in solid tumors other than NSCLC and CRC, and adagrasib may represent a matched treatment option for this rare cohort of pretreated patients with *KRAS*^{G12C}-mutated solid tumors.

Early clinical data demonstrated encouraging clinical activity of KRAS^{G12C} inhibitors in *KRAS*^{G12C}-mutated solid tumors.[26,27] In recent phase I trials in patients with advanced solid tumors, other than NSCLC and CRC, responses were documented in 19% of patients receiving GDC-6036 (n = 4/21) and 14% of patients receiving sotorasib (n = 4/28).[26,27] Additionally, recently published data for sotorasib demonstrated an ORR of 21% in patients with *KRAS*^{G12C}-mutated advanced pancreatic cancer.[28] In this study, adagrasib monotherapy demonstrated clinically meaningful activity and a manageable safety and tolerability profile in a variety of tumor types in a heavily pretreated patient population with tumors harboring *KRAS*^{G12C} mutations. Adagrasib resulted in an ORR of 35.1%, median PFS of 7.4 months, and a median OS of 14.0 months in a patient population for whom there were no available standard-of-care treatment options, and 70.3% of whom had received at least two prior therapies and 34.4% had received at least three prior therapies. Prior

TABLE 4. Summary of TRAEs (all grades) in ≥10% of Patients With *KRAS*^{G12C}-Mutated Solid Tumors (safety population)

	Overall Solid Tumors (n = 63), No. (%)					
TRAE[a]	Any Grade	Grade 1	Grade 2	Grade 3[b]	Grade 4[c]	Grade 5
Any TRAE	61 (96.8)	16 (25.4)	28 (44.4)	16 (25.4)	1 (1.6)	0 (0.0)
Most frequent TRAEs[d]						
Nausea	31 (49.2)	23 (36.5)	7 (11.1)	1 (1.6)	0 (0.0)	0 (0.0)
Diarrhea	30 (47.6)	21 (33.3)	8 (12.7)	1 (1.6)	0 (0.0)	0 (0.0)
Fatigue	26 (41.3)	12 (19.0)	10 (15.9)	4 (6.3)	0 (0.0)	0 (0.0)
Vomiting	25 (39.7)	20 (31.7)	4 (6.3)	1 (1.6)	0 (0.0)	0 (0.0)
Blood creatinine increase	10 (15.9)	7 (11.1)	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	9 (14.3)	3 (4.8)	5 (7.9)	1 (1.6)	0 (0.0)	0 (0.0)
AST increase	9 (14.3)	7 (11.1)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)
Decreased appetite	9 (14.3)	5 (7.9)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral edema	9 (14.3)	7 (11.1)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolongation	8 (12.7)	3 (4.8)	1 (1.6)	4 (6.3)	0 (0.0)	0 (0.0)
Dysgeusia	7 (11.1)	6 (9.5)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
TRAEs leading to treatment discontinuation	0 (0.0)	—	—	—	—	—
TRAEs leading to dose reduction	25 (39.7)	—	—	—	—	—
TRAEs leading to dose interruption	28 (44.4)	—	—	—	—	—

NOTE. Data as of October 1, 2022 (median follow-up, 16.8 months). Excluding non–small-cell lung cancer and colorectal cancer.
Abbreviation: TRAE, treatment-related adverse event.
[a]Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).
[b]Grade 3 TRAEs also comprise ALT increase (3.2%), lipase increase (1.6%), abdominal pain (1.6%), amylase increase (1.6%), lymphocyte count decrease (1.6%), rash maculopapular (1.6%), ejection fraction decrease (1.6%), hyperkalemia (1.6%), peripheral neuropathy (1.6%), acute kidney injury (1.6%), cellulitis (1.6%), and hypoxia (1.6%).
[c]One patient exhibited grade 4 febrile neutropenia.
[d]Occurring in ≥10% of patients.

therapies included chemotherapy, targeted therapy, and/or checkpoint inhibitors. In addition, 78.1% (50/64) of patients within the enrolled population had GI malignancies, for whom treatment efficacy has been limited in the second-line setting and beyond.

Second-line standard chemotherapy treatment of unselected patients with metastatic pancreatic cancer has been associated with poor outcomes. Historically, a median PFS of approximately 3 months or less, a median OS of approximately 6.6 months or less, and a lack of meaningful clinical responses have been reported in phase III second-line chemotherapy studies.[29,30] In this study, we observed notable clinical activity with adagrasib in pretreated patients with pancreatic cancer harboring *KRAS*^{G12C} mutations (>80% progressed after prior gemcitabine- and/or fluoropyrimidine-based therapy) including an ORR of 33.3% per BICR, median PFS of 5.4 months per BICR, and median OS of 8.0 months.

Initial reports of treating *KRAS*^{G12C}-mutated biliary tract cancers suggest limited clinical activity with sotorasib and GDC-6036, with 0/2 and 1/6 responses reported, respectively.[26,27] In this study, we observed notable activity for adagrasib in the rare subgroup of 12 refractory patients with biliary tract cancers harboring *KRAS*^{G12C} mutations, with an ORR of 41.7%, median PFS of 8.6 months, and median OS of 15.1 months. As a point of reference, and in a biomarker-unselected patient population, the ABC-06 phase III trial investigating the efficacy of folinic acid, fluorouracil, and oxaliplatin in patients with previously treated advanced or metastatic biliary tract cancer reported an ORR of 5%, with a median PFS of 4.0 months and an OS of 6.2 months.[31]

Moreover, a relatively small number of patients with gynecologic cancers (n = 7) were included with a particularly encouraging observed response rate of 57%. No responses were seen in seven patients with appendiceal cancers, of which one was colonic and six were of the mucinous subtype. This lack of response is consistent with a recent report that distinct mutational subtypes of appendiceal cancers exhibit conserved clinical behavior, and *RAS*-mutated mucinous appendiceal cancers are relatively indolent tumors that may not be clinically aggressive.[17] Colonic-type (nonmucinous) appendiceal cancers are associated with worse outcomes than mucinous appendiceal cancer and may benefit from combination therapy.[32,33]

Overall, the present results consistently demonstrate encouraging activity and a manageable safety and tolerability profile in patients with pretreated *KRAS*^{G12C}-mutated solid

tumors. The most frequently occurring TRAEs are aligned with those reported previously in patients with pretreated NSCLC or heavily pretreated CRC.[15,16]

This study is limited by its nonrandomized, single-arm design. Additionally, $KRAS^{G12C}$ mutations in solid tumors other than NSCLC and CRC are rare, resulting in heterogeneous populations and small patient numbers for each of the tumor types in this study.

Ongoing biomarker analyses may provide additional information on the mechanisms of primary and secondary resistance to $KRAS^{G12C}$ inhibitors, and may be used to identify other drug targets, or combinations thereof, for specific patient populations. For example, there is a rationale for combining adagrasib with other inhibitors targeting different points of the RAS/MAPK signaling pathway, such as the combination of adagrasib and cetuximab (EGFR inhibitor) in $KRAS^{G12C}$–mutated CRC.[16,34] On the basis of this rationale, adagrasib is being evaluated in exploratory combinations in other solid tumors, including pancreatic cancer.

Adagrasib demonstrated clinical activity across a broad range of tumor types and was well tolerated in patients with unresectable or metastatic solid tumors harboring a $KRAS^{G12C}$ mutation. These results provide clinical evidence that $KRAS^{G12C}$ can be therapeutically targeted across diverse tumor types, with activity observed for adagrasib in this tumor-agnostic patient population. The responses observed in tumor types such as pancreatic, where mutation analysis is not routinely conducted, underscore the importance of more consistent genomic testing. Next-generation sequencing for all tumor types is necessary to identify potential treatment targets, and testing for $KRAS^{G12C}$ mutations across solid tumors remains critical to identify patients who may benefit from treatment with adagrasib.

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DATA SHARING STATEMENT

At Mirati Therapeutics, we are committed to patient care, advancing scientific understanding, and enabling the scientific community to learn from and build upon the research we have undertaken. To that end, we will honor legitimate requests for our clinical trial data from qualified researchers and investigators for conducting methodologically sound research. We will share clinical trial data, clinical study reports, study protocols, and statistical analysis plans from clinical trials for which results have been posted on clinicaltrials.gov for products and indications approved by regulators in the United States and/or European Union. Sharing is subject to protection of patient privacy and respect for the patient's informed consent. In general, data will be made available for specific requests approximately 24 months after clinical trial completion from our in-scope interventional trials. For additional information on proposals with regards to data sharing collaborations with Mirati, please e-mail us at medinfo@mirati.com.

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Adagrasib in Advanced Solid Tumors Harboring a *KRAS*^{G12C} Mutation

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APPENDIX 1. APPENDIX METHODS

Statistical Analyses

The full analysis set included all patients with measurable disease at baseline and who received ≥1 dose of adagrasib. A further six patients were included within the analysis set per investigator assessment but excluded per blinded independent central review (BICR) because of no measurable disease at baseline by BICR.

The observed responses were monitored during the trial at prespecified intervals. The futility analysis was based on the Predictive Probability Design with a maximum of approximately 60 patients. The stopping rules (rejection regions), expressed as number of responses per patients treated, were 2/26, 5/40, and 10/60. If the true objective response rate (ORR) was 10% (null hypothesis), the probability of early termination during the study would be 0.807 (under H0) and the expected sample size before termination would be 37 patients. The type 1 error would be 0.0309 and the power would be equal to 0.978. The methodology used to estimate the CI for ORRs was based on the Clopper-Pearson method; estimation of the confidence interval for median duration of response, median progression-free survival, and median overall survival was based on the Brookmeyer-Crowley method.

Tumor Mutation Screening

To establish potential eligibility for enrollment into the study, patients underwent prescreening for *KRAS*^{G12C} mutation in tumor tissue or circulating tumor DNA (ctDNA). Prescreening was performed historically or at the time a patient was considering study entry. The presence of *KRAS*^{G12C} mutation was established using sponsor preapproved methods and laboratories. Platforms used for prescreening tumor mutational analyses included polymerase chain reaction (PCR) and next-generation sequencing (NGS). The sponsor-approved laboratories were

1. Neogenomics Laboratories for tumor tissue, using PCR for eligibility testing and follow-up with NGS for exploratory end points
2. Resolution Bioscience for ctDNA in the blood, using NGS for eligibility testing

In addition, commercial and locally available tests that were preapproved by the sponsor for eligibility determination included, but were not limited to,

1. Neogenomics Laboratories, using PCR for tumor tissue
2. FoundationOne, using NGS on tumor tissue samples
3. PROFILE (Dana Farber Cancer Institute), using NGS on tumor tissue samples
4. IMPACT (Memorial Sloan Kettering Cancer Center), using NGS on tumor tissue samples
5. Archer VariantPlex (University of Colorado), using NGS on tumor tissue samples
6. Caris Life Sciences, using NGS on tumor tissue samples
7. StrataNGS, using NGS on tumor tissue samples
8. Tempus xT, using NGS on tumor tissue samples
9. Resolution ctDx Lung, using NGS on ctDNA
10. FoundationOne Liquid, using NGS on ctDNA
11. Guardant360CDx, using NGS on ctDNA

TABLE A1. Prior Treatment Regimens of Patients With *KRAS*^{G12C}-Mutated Solid Tumors, PDAC and BTC

	Pancreatic, No. (%)	BTC (n = 12), No. (%)		
Characteristic	PDAC (n = 21)	Ampullary (n = 3)	Cholangiocarcinoma[a] (n = 8)	Gallbladder (n = 1)
Previous lines of systemic therapy				
0	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
1	5 (23.8)	1 (33.3)	4 (50.0)	0 (0.0)
2	7 (33.3)	0 (0.0)	2 (25.0)	1 (100.0)
3	7 (33.3)	1 (33.3)	1 (12.5)	0 (0.0)
≥4	2 (9.5)	1 (33.3)	0 (0.0)	0 (0.0)
Previous treatment regimen				
Chemotherapy	21 (100.0)	3 (100.0)	7 (87.5)	1 (100.0)
Platinum-based	17 (81.0)	3 (100.0)	5 (62.5)	1 (100.0)
Taxane	15 (71.4)	2 (66.7)	1 (12.5)	0 (0.0)
Gemcitabine	17 (81.0)	2 (66.7)	7 (87.5)	1 (100.0)
Fluoropyrimidine	18 (85.7)	3 (100.0)	4 (50.0)	1 (100.0)
Anti-VEGF	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Targeted therapy[b]	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Anti–PD-(L)1 checkpoint inhibitor	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Previous radiotherapy	6 (28.6)	0 (0.0)	4 (50.0)	0 (0.0)
Previous surgery	14 (66.7)	3 (100.0)	2 (25.0)	1 (100.0)

NOTE. Excluding NSCLC and CRC.

Abbreviations: BTC, biliary tract cancer; CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; NSCLC, non–small-cell lung cancer; PARP, poly (ADP-ribose) polymerase; PDAC, pancreatic ductal adenocarcinoma; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor.

[a]Intrahepatic, n = 5; extrahepatic, n = 2; hilar, n = 1.

[b]Prior targeted therapy includes inhibitors targeting HER2, BRAF, MEK, PARP, CDK4/6, PI3K, and/or multitargeted tyrosine kinase inhibitor.

TABLE A2. Prior Treatment Regimens of Patients With *KRAS*^{G12C}-Mutated Solid Tumors, Other GI Tumors

Characteristic	Other GI (n = 17), No. (%)		
	GEJ/ Esophageal (n = 4)	Small Bowel (n = 3)	Appendiceal (n = 10)
Previous lines of systemic therapy			
0	1 (25.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	3 (30.0)
2	0 (0.0)	3 (100.0)	5 (50.0)
3	1 (25.0)	0 (0.0)	1 (10.0)
≥4	2 (50.0)	0 (0.0)	1 (10.0)
Previous treatment regimen			
Chemotherapy	3 (75.0)	3 (100.0)	10 (100.0)
Platinum-based	3 (75.0)	3 (100.0)	8 (80.0)
Taxane	3 (75.0)	0 (0.0)	0 (0.0)
Gemcitabine	0 (0.0)	0 (0.0)	0 (0.0)
Fluoropyrimidine	3 (75.0)	3 (100.0)	10 (100.0)
Anti-VEGF	2 (50.0)	0 (0.0)	6 (60.0)
Targeted therapy[a]	1 (25.0)	0 (0.0)	0 (0.0)
Anti–PD-(L)1 checkpoint inhibitor	2 (50.0)	0 (0.0)	0 (0.0)
Previous radiotherapy	2 (50.0)	0 (0.0)	0 (0.0)
Previous surgery	1 (25.0)	3 (100.0)	10 (100.0)

NOTE. Excluding NSCLC and CRC.

Abbreviations: CRC, colorectal cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; NSCLC, non–small-cell lung cancer; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor.

[a]Prior targeted therapy includes inhibitors targeting HER2, BRAF, MEK, PARP, CDK4/6, PI3K, and/or multitargeted tyrosine kinase inhibitor.

TABLE A3. Prior Treatment Regimens of Patients With *KRAS*^{G12C}-Mutated Solid Tumors, Other Tumors

	Gynecologic (n = 8), No. (%)		Other (n = 6), No. (%)		
Characteristic	Endometrial (n = 3)	Ovarian (n = 5)	Unknown Primary (n = 4)	Breast (n = 1)	GBM (n = 1)
Previous lines of systemic therapy					
0	0 (0.0)	1 (20.0)	2 (50.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (66.7)	2 (40.0)	1 (25.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
≥4	1 (33.3)	1 (20.0)	1 (25.0)	1 (100.0)	0 (0.0)
Previous treatment regimen					
Chemotherapy	3 (100.0)	4 (80.0)	2 (50.0)	1 (100.0)	1 (100.0)
Platinum-based	3 (100.0)	4 (80.0)	2 (50.0)	1 (100.0)	1 (100.0)
Taxane	3 (100.0)	4 (80.0)	1 (25.0)	1 (100.0)	0 (0.0)
Gemcitabine	1 (33.3)	1 (20.0)	0 (0.0)	1 (100.0)	0 (0.0)
Fluoropyrimidine	0 (0.0)	0 (0.0)	2 (50.0)	1 (100.0)	0 (0.0)
Anti-VEGF	1 (33.3)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)
Targeted therapy[a]	2 (66.7)	1 (20.0)	0 (0.0)	1 (100.0)	1 (100.0)
Anti–PD-(L)1 checkpoint inhibitor	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Previous radiotherapy	2 (66.7)	2 (40.0)	0 (0.0)	1 (100.0)	1 (100.0)
Previous surgery	3 (100.0)	4 (80.0)	1 (25.0)	1 (100.0)	1 (100.0)

NOTE. Excluding NSCLC and CRC.

Abbreviations: CRC, colorectal cancer; GBM, glioblastoma; HER2, human epidermal growth factor receptor 2; NSCLC, non–small-cell lung cancer; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor.

[a]Prior targeted therapy includes inhibitors targeting HER2, BRAF, MEK, PARP, CDK4/6, PI3K, and/or multitargeted tyrosine kinase inhibitor.

TABLE A4. ORR (full analysis set), PFS (full analysis set), by Investigator Assessment, and OS (enrolled population) in Patients With *KRAS*^{G12C}-Mutated Solid Tumors According to Tumor Type

Tumor Type	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS (95% CI)
All patients	n = 63 30.2 (19.2 to 43.0)	n = 63 6.9 (5.3 to 8.3)	N = 64 14.0 (8.5 to 18.6)
Pancreatic cancer	n = 21 38.1 (18.1 to 61.6)	n = 21 5.6 (3.0 to 6.8)	n = 21 8.0 (5.2 to 11.8)
Biliary tract cancer	n = 12 33.3 (9.9 to 65.1)	n = 12 6.9 (3.6 to 11.3)	n = 12 15.1 (8.6 to NE)
Cholangiocarcinoma[a]	n = 8 25.0 (3.2 to 65.1)	n = 8 6.9 (1.6 to 11.3)	n = 8 15.1 (12.5 to NE)
Ampullary	n = 3 33.3 (0.8 to 90.6)	n = 3 5.3 (4.1 to NE)	n = 3 15.5 (8.6 to NE)
Gallbladder	n = 1 100.0 (2.5 to 100.0)	n = 1 10.6 (NE to NE)	n = 1 14.2 (NE to NE)
Other GI tumors	n = 16 18.8 (4.0 to 45.6)	n = 16 8.3 (4.1 to 13.6)	n = 17 14.0 (6.2 to NE)
Appendiceal	n = 9 11.1 (0.3 to 48.2)	n = 9 10.9 (3.9 to NE)	n = 10 NR (4.1 to NE)
Small bowel	n = 3 33.3 (0.8 to 90.6)	n = 3 7.9 (2.6 to NE)	n = 3 7.9 (6.2 to NE)
GEJ/esophageal	n = 4 25.0 (0.6 to 80.6)	n = 4 9.6 (8.3 to NE)	n = 4 12.5 (10.9 to NE)
Gynecologic tumors	n = 8 50.0 (15.7 to 84.3)	n = 8 NR (1.9 to NE)	n = 8 19.6 (15.1 to NE)
Ovarian	n = 5 40.0 (5.3 to 85.3)	n = 5 NR (1.9 to NE)	n = 5 19.6 (15.1 to NE)
Endometrial	n = 3 66.7 (9.4 to 99.2)	n = 3 5.6 (4.4 to NE)	n = 3 20.6 (19.5 to NE)
Other tumors	n = 6 0.0 (0.0 to 45.9)	n = 6 5.1 (1.3 to NE)	n = 6 7.6 (5.6 to NE)
Unknown primary	n = 4 0.0 (0.0 to 60.2)	n = 4 7.6 (1.3 to NE)	n = 4 7.6 (5.6 to NE)
Breast	n = 1 0.0 (0.0 to 97.5)	n = 1 3.1 (NE to NE)	n = 1 NR (NE to NE)
Glioblastoma	n = 1 0.0 (0.0 to 97.5)	n = 1 1.4 (NE to NE)	n = 1 NR (NE to NE)

NOTE. Data as of October 1, 2022 (median follow-up, 16.8 months). Excluding non–small-cell lung cancer and colorectal cancer.
Abbreviations: GEJ, gastroesophageal junction; NE, not evaluable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]Intrahepatic, n = 5; extrahepatic, n = 2; hilar, n = 1.

TABLE A5. Summary of BICR and Investigator-Assessed Disease Control Rate (full analysis set), Categorized by Tumor Type

	Disease Control Rate, No. (%)	
Tumor Type	BICR	Investigator-Assessed
All patients	(n = 57) 49 (86.0)	(n = 63) 55 (87.3)
Pancreatic cancer	(n = 21) 17 (81.0)	(n = 21) 17 (81.0)
Biliary tract cancer	(n = 12) 11 (91.7)	(n = 12) 11 (91.7)
Cholangiocarcinoma	n = 8 7 (87.5)	n = 8 7 (87.5)
Ampullary	n = 3 3 (100.0)	n = 3 3 (100.0)
Gallbladder	n = 1 1 (100.0)	n = 1 1 (100.0)
Other GI tumors	(n = 12) 10 (83.3)	(n = 16) 15 (93.8)
Appendiceal	(n = 7) 6 (85.7)	(n = 9) 9 (100.0)
Small bowel	(n = 2) 2 (100.0)	(n = 3) 3 (100.0)
GEJ/esophageal	(n = 3) 2 (66.7)	(n = 4) 3 (75.0)
Gynecologic tumors	(n = 7) 6 (85.7)	(n = 8) 8 (100.0)
Ovarian	(n = 4) 3 (75.0)	(n = 5) 5 (100.0)
Endometrial	(n = 3) 3 (100.0)	(n = 3) 3 (100.0)
Other tumors	(n = 5) 5 (100.0)	(n = 6) 4 (66.7)
Unknown primary	(n = 4) 4 (100.0)	(n = 4) 3 (75.0)
Breast	(n = 1) 1 (100.0)	(n = 1) 1 (100.0)
Glioblastoma	(n = 0) NA	(n = 1) 0 (0.0)

Abbreviations: BICR, blinded independent central review; GEJ, gastroesophageal junction; NA, not applicable.

TABLE A6. Summary of TEAEs (all grades) in ≥10% of Patients With *KRAS*^{G12C}-Mutated Solid Tumors (safety population)

	Overall Solid Tumors (n = 63), No. (%)					
TEAE[a]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4[b]	Grade 5[c]
Any TEAE	63 (100)	5 (7.9)	16 (25.4)	29 (46.0)	6 (9.5)	7 (11.1)
Most frequent TEAEs,[d] No. (%)						
Diarrhea	39 (61.9)	25 (39.7)	12 (19.0)	1 (1.6)	1 (1.6)	0 (0.0)
Fatigue	38 (60.3)	17 (27.0)	14 (22.2)	7 (11.1)	0 (0.0)	0 (0.0)
Nausea	38 (60.3)	25 (39.7)	11 (17.5)	2 (3.2)	0 (0.0)	0 (0.0)
Vomiting	29 (46.0)	23 (36.5)	5 (7.9)	1 (1.6)	0 (0.0)	0 (0.0)
Anemia	22 (34.9)	4 (6.3)	13 (20.6)	5 (7.9)	0 (0.0)	0 (0.0)
Abdominal pain	20 (31.7)	9 (14.3)	7 (11.1)	4 (6.3)	0 (0.0)	0 (0.0)
Peripheral edema	20 (31.7)	16 (25.4)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increase	18 (28.6)	13 (20.6)	5 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	17 (27.0)	9 (14.3)	8 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	16 (25.4)	7 (11.1)	9 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	15 (23.8)	12 (19.0)	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
AST increase	14 (22.2)	11 (17.5)	0 (0.0)	2 (3.2)	1 (1.6)	0 (0.0)
Blood alkaline phosphatase increase	10 (15.9)	5 (7.9)	4 (6.3)	1 (1.6)	0 (0.0)	0 (0.0)
Pyrexia	10 (15.9)	7 (11.1)	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
Dysgeusia	9 (14.3)	8 (12.7)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	9 (14.3)	5 (7.9)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolongation	9 (14.3)	3 (4.8)	2 (3.2)	4 (6.3)	0 (0.0)	0 (0.0)
Flatulence	9 (14.3)	8 (12.7)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalemia	9 (14.3)	5 (7.9)	1 (1.6)	3 (4.8)	0 (0.0)	0 (0.0)
Pruritus	9 (14.3)	5 (7.9)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decrease	9 (14.3)	6 (9.5)	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal distension	8 (12.7)	6 (9.5)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increase	8 (12.7)	3 (4.8)	2 (3.2)	3 (4.8)	0 (0.0)	0 (0.0)
Headache	8 (12.7)	7 (11.1)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypomagnesemia	8 (12.7)	7 (11.1)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	8 (12.7)	3 (4.8)	2 (3.2)	3 (4.8)	0 (0.0)	0 (0.0)
Arthralgia	7 (11.1)	6 (9.5)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	7 (11.1)	2 (3.2)	5 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	7 (11.1)	4 (6.3)	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	7 (11.1)	1 (1.6)	5 (7.9)	1 (1.6)	0 (0.0)	0 (0.0)
Hypertension	7 (11.1)	2 (3.2)	2 (3.2)	3 (4.8)	0 (0.0)	0 (0.0)
Lipase increase	7 (11.1)	2 (3.2)	1 (1.6)	4 (6.3)	0 (0.0)	0 (0.0)
Lymphocyte count decrease	7 (11.1)	1 (1.6)	5 (7.9)	1 (1.6)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation	4 (6.3)	—	—	—	—	—
TEAEs leading to dose reduction	29 (46.0)	—	—	—	—	—
TEAEs leading to dose interruption	41 (65.1)	—	—	—	—	—

NOTE. Data as of October 1, 2022 (median follow-up, 16.8 months). TEAE includes all reported adverse events, regardless of whether or not related to treatment. Excluding non–small-cell lung cancer and colorectal cancer.

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0; as per the Methods section).

[b]Grade 4 TEAEs also included decreased neutrophil count (n = 1), febrile neutropenia (n = 1), sepsis (n = 1), hemorrhagic anemia (n = 1), and obesity (n = 1).

[c]Grade 5 TEAEs included malignant neoplasm progression (n = 5), cardiorespiratory arrest (n = 1), and myocardial infarction (n = 1).

[d]Occurring in ≥10% of patients.

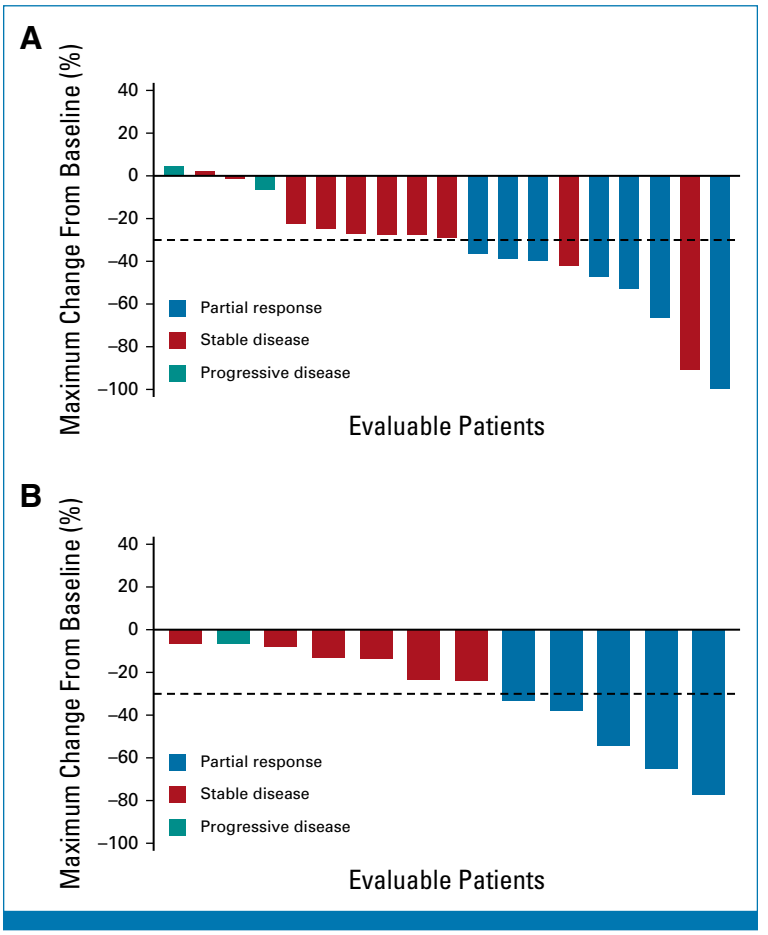

FIG A1. Waterfall plot of maximum percentage tumor change from baseline in patients with (A) PDAC and (B) BTC cancers. BTC, biliary tract cancer; PDAC, pancreatic ductal adenocarcinoma.

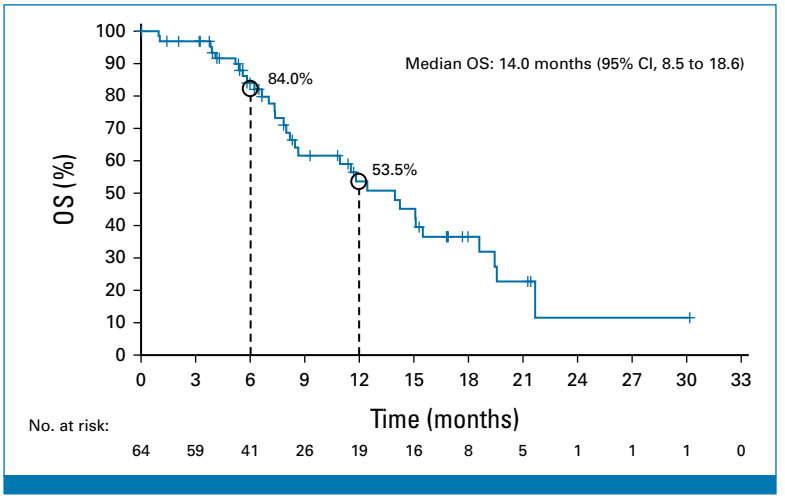

FIG A2. OS in patients with *KRAS*^{G12C}-mutated solid tumors[a] (N = 64). Data as of October 1, 2022 (median follow-up, 16.8 months). [a]Excluding non–small-cell lung cancer and colorectal cancer. OS, overall survival.