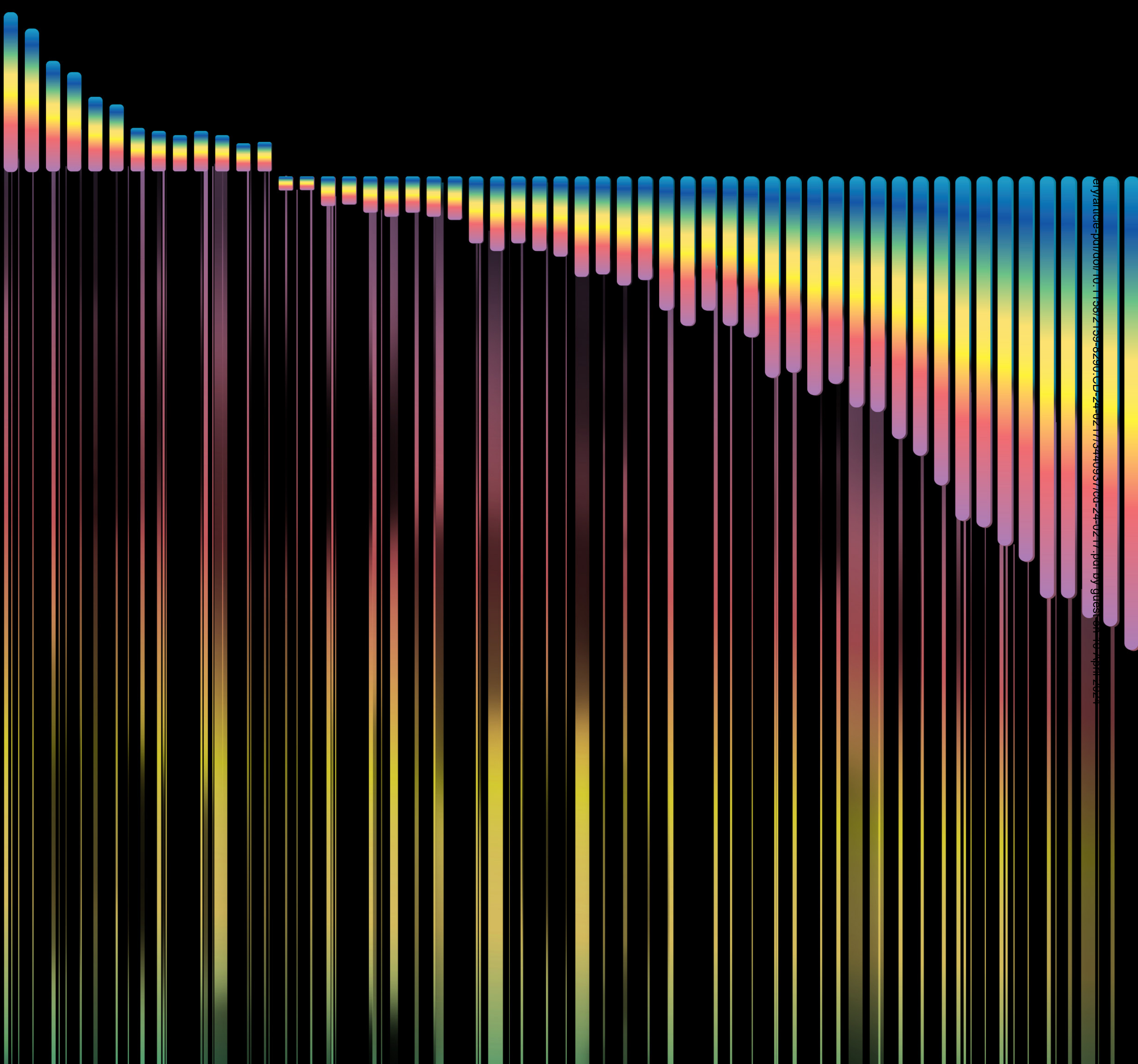
RESEARCH ARTICLE

Efficacy and Safety of Adagrasib plus Cetuximab in Patients with *KRAS*^{G12C}-Mutated Metastatic Colorectal Cancer

Rona Yaeger[1], Nataliya V. Uboha[2], Meredith S. Pelster[3], Tanios S. Bekaii-Saab[4], Minal Barve[5], Joel Saltzman[6], Joshua K. Sabari[7], Julio A. Peguero[8], Andrew Scott Paulson[9], Pasi A. Jänne[10], Marcia Cruz-Correa[11], Kenna Anderes[12], Karen Velastegui[12], Xiaohong Yan[12], Hirak Der-Torossian[12], Samuel J. Klempner[13], and Scott E. Kopetz[14]



ABSTRACT Adagrasib, an irreversible, selective KRAS^{G12C} inhibitor, may be an effective treatment in *KRAS*^{G12C}-mutated colorectal cancer, particularly when combined with an anti-EGFR antibody. In this analysis of the KRYSTAL-1 trial, patients with previously treated *KRAS*^{G12C}-mutated unresectable or metastatic colorectal cancer received adagrasib (600 mg twice daily) plus cetuximab. The primary endpoint was objective response rate (ORR) by blinded independent central review. Ninety-four patients received adagrasib plus cetuximab. With a median follow-up of 11.9 months, ORR was 34.0%, disease control rate was 85.1%, and median duration of response was 5.8 months (95% confidence interval [CI], 4.2–7.6). Median progression-free survival was 6.9 months (95% CI, 5.7–7.4) and median overall survival was 15.9 months (95% CI, 11.8–18.8). Treatment-related adverse events (TRAEs) occurred in all patients; grade 3–4 in 27.7% and no grade 5. No TRAEs led to adagrasib discontinuation. Exploratory analyses suggest circulating tumor DNA may identify features of response and acquired resistance.

SIGNIFICANCE: Adagrasib plus cetuximab demonstrates promising clinical activity and tolerable safety in heavily pretreated patients with unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer. These data support a potential new standard of care and highlight the significance of testing and identification of *KRAS*^{G12C} mutations in patients with colorectal cancer.

INTRODUCTION

KRAS^{G12C} mutations occur in 3% to 4% of colorectal cancer cases and are associated with poor prognosis (1, 2). Adagrasib is a selective, irreversible inhibitor of KRAS^{G12C} and has favorable properties, including long half-life (23 hours), dose-dependent pharmacokinetics, and central nervous system penetration (3–5). Adagrasib was granted accelerated approval by the FDA for the treatment of adult patients with locally advanced or metastatic *KRAS*^{G12C}-mutated non–small cell lung cancer who have received at least one prior systemic therapy (6).

In colorectal cancer, adaptive resistance to KRAS^{G12C} inhibition can occur via EGFR-mediated reactivation of the MAPK pathway (7). Preclinical data suggest that dual EGFR/KRAS^{G12C} blockade mitigates adaptive resistance in *KRAS*^{G12C}-mutated colorectal cancer cell lines (7). In a phase I cohort ($n = 32$) of KRYSTAL-1, adagrasib plus cetuximab yielded higher clinical activity than adagrasib monotherapy in patients with *KRAS*^{G12C}-mutated metastatic colorectal cancer. Objective response rate (ORR) was 46% [95% confidence interval (CI), 28–66) and 19% (95% CI, 8–33), respectively; median progression-free survival (PFS) was 6.9 months (95% CI, 5.4–8.1) and 5.6 months (95% CI, 4.1–8.3), respectively; per investigator assessment (8). Adagrasib, in combination with cetuximab, has received FDA breakthrough therapy designation for the treatment of patients with *KRAS*^{G12C}-mutated advanced colorectal cancer that has progressed after previous treatment (9). Adagrasib, in combination with cetuximab or panitumumab, is recommended for patients with previously treated advanced or metastatic *KRAS*^{G12C}-mutated colorectal cancer by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines); adagrasib may also be considered as monotherapy if a patient is unable to tolerate an anti-EGFR antibody due to toxicity (10, 11).

Here, we report pooled data from the phase I and phase II cohorts of the KRYSTAL-1 trial for previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic colorectal cancer who received adagrasib plus cetuximab. To contextualize the results obtained with combination therapy, we include an additional phase II adagrasib monotherapy cohort distinct from the adagrasib monotherapy cohort previously described (8). Finally, we provide exploratory evidence supporting a role for circulating tumor DNA (ctDNA) as a tool to define biomarkers of response and molecular resistance.

RESULTS

Patients

As of June 30, 2023, 94 patients with *KRAS*^{G12C}-mutated colorectal cancer had received ≥1 dose of study treatment across phase I ($n = 32$) and phase II ($n = 62$) combination cohorts. Median follow-up was 11.9 months (30.0 months for the

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [2]Division of Hematology and Oncology, Department of Medicine, University of Wisconsin, Madison, Wisconsin. [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee. [4]Department of Medical Oncology and Hematology, Mayo Clinic, Scottsdale, Arizona. [5]Mary Crowley Cancer Research Center, Dallas, Texas. [6]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, Ohio. [7]Division of Medical Oncology, Perlmutter Cancer Center, New York University Langone Health, New York, New York. [8]Department of Research, Oncology Consultants PA, Houston, Texas. [9]Department of Medical Oncology, Texas Oncology – Baylor Charles A. Sammons Cancer Center, Dallas, Texas. [10]Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts. [11]PanOncology Trials, San Juan, Puerto Rico. [12]Mirati Therapeutics, a wholly owned subsidiary of Bristol Myers Squibb Company, San Diego, California. [13]Division of Hematology-Oncology, Massachusetts General Cancer Center, Boston, Massachusetts. [14]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas.

S.J. Klempner and S.E. Kopetz are the co-senior authors of this article. R. Yaeger and N.V. Uboha are the co-lead authors of this article.

Corresponding Authors: Rona Yaeger, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. E-mail: yaegerr@mskcc.org; and Nataliya V. Uboha, Department of Medicine, Division of Hematology & Oncology, University of Wisconsin, 600 Highland Avenue, Madison, WI 53792. E-mail: nvuboha@medicine.wisc.edu

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Table 1. Demographics and baseline characteristics of previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC receiving adagrasib plus cetuximab.

	Adagrasib + cetuximab CRC cohort (*N* = 94)
Median age, y (range)	57 (24–75)
Female, *n* (%)	50 (53.2)
Race, *n* (%)	
White	67 (71.3)
Black or African American	13 (13.8)
Asian	5 (5.3)
Other[a]	9 (9.6)
Ethnicity, *n* (%)	
Hispanic or Latino	16 (17.0)
Not Hispanic or Latino	75 (79.8)
Missing	3 (3.2)
ECOG PS, *n* (%)	
0	48 (51.1)
1	46 (48.9)
Sidedness of primary tumor, *n* (%)[b]	
Left-sided	32 (51.6)
Right-sided	19 (30.6)
Synchronous left- and right-sided	5 (8.1)
Missing/unknown	6 (9.7)
Metastatic disease per BICR, *n* (%)	93 (98.9)
Lung	67 (71.3)
Liver	60 (63.8)
Bone	13 (13.8)
Adrenal	2 (2.1)
Brain	1 (1.1)
Prior lines of systemic anticancer therapy	
Median (range)	3 (1–9)
1/2/3/≥4, %	8 (8.5)/34 (36.2)/29 (30.9)/23 (24.5)
Prior systemic anticancer therapy, *n* (%)[c]	
Fluoropyrimidine	94 (100)
Oxaliplatin	93 (98.9)
Anti-VEGF mAb	90 (95.7)
Irinotecan	89 (94.7)
Fluoropyrimidine, oxaliplatin, anti-VEGF mAb, and irinotecan	84 (89.4)
Trifluridine/tipiracil	11 (11.7)
Regorafenib	8 (8.5)
Anti–PD-1/PD-L1	8 (8.5)
Anti-EGFR mAb	3 (3.2)
KRAS^{G12C} inhibitor	1 (1.1)
Concurrent molecular alterations, *n*/m (%)[d]	
EGFR amplification	2 of 81 (2.5)
NTRK fusion	1 of 80 (1.3)
TP53 mutation	59 of 80 (73.8)
PIK3CA mutation	14 of 80 (17.5)

NOTE: Data as of June 30, 2023.
Abbreviations: BICR, blinded independent central review; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability-high; mAb, cetuximab; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a]Includes one American Indian or Alaska native patient, one Puerto Rican patient, and seven patients with race unknown.
[b]Sidedness of primary tumor location was reported only for phase II. Percentages are calculated on the basis of *N* = 62.
[c]Patients may be counted toward more than one regimen.
[d]*n* = number of patients with the molecular alteration; m = number of patients with definitive test result. No *BRAF*^{V600E} (0 of 90), MSI-H/dMMR (0 of 73), or *HER2* (*ERBB2*; 0 of 81) alterations were reported.

Table 2. Overall efficacy summary with adagrasib plus cetuximab in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC[a].

	Adagrasib + cetuximab CRC cohort (*N* = 94)	
	Per BICR	Per investigator
ORR, *n* (%)	32 (34.0)	40 (42.6)
95% CI	24.6–44.5	32.4–53.2
BOR, *n* (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	32 (34.0)	40 (42.6)
Stable disease	48 (51.1)	41 (43.6)
Progressive disease	6 (6.4)	5 (5.3)
Not evaluable	8 (8.5)	8 (8.5)
DCR, *n* (%)	80 (85.1)	81 (86.2)
95% CI	76.3–91.6	77.5–92.4
Median DOR, months	5.8	5.9
95% CI	4.2–7.6	5.5–7.6
Median PFS, months	6.9	6.9
95% CI	5.7–7.4	5.9–7.4
Median OS, months	15.9	
95% CI	11.8–18.8	

NOTE: Data as of June 30, 2023 (median follow-up: 11.9 months).

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; ORR, objective response rate; PFS, progression-free survival.

[a]All endpoints were measured in the FAS (*N* = 94).

phase I cohort and 10.0 months for the phase II cohort). Median (range) age was 57 (24–75) years; median (range) prior lines of systemic therapy was 3 (1–9). All patients received prior fluoropyrimidine, 98.9% prior oxaliplatin, 95.7% prior anti-VEGF treatment, and 94.7% prior irinotecan (Table 1). Median (range) duration of treatment with adagrasib was 7.4 (0.03–36.4) months. Seventeen patients started cetuximab intravenously weekly (400 mg/m^2 loading dose followed by 250 mg/m^2), seven of whom later switched to treatment every 2 weeks (500 mg/m^2). Seventy-seven patients started with cetuximab treatment every 2 weeks (500 mg/m^2), consistent with the cetuximab U.S. prescribing information (12). Median (range) duration of treatment with cetuximab was 7.1 (0.2–34.5) months. As of data cutoff, treatment was ongoing in 18 of 94 (19.1%) patients. A total of 38 of 94 (40.4%) patients continued adagrasib plus cetuximab beyond disease progression, 10 of 94 (10.6%) patients continued adagrasib only beyond disease progression, and one patient continued treatment with cetuximab only beyond disease progression. The participants in this trial were representative of the broader population of patients with *KRAS*^{G12C}-mutated colorectal cancer (Supplementary Table S1). See Supplementary Appendix for details of the adagrasib monotherapy cohort (Supplementary Table S2).

Efficacy

Overall, 94 patients with measurable disease at baseline received ≥1 dose of study treatment. The ORR as assessed by blinded independent central review (BICR) was 34.0% (95% CI, 24.6–44.5) and disease control rate (DCR) was 85.1% (95% CI, 76.3–91.6; Table 2; Fig. 1A–C). Median duration of response (DOR) was 5.8 months (95% CI, 4.2–7.6) and median PFS was 6.9 months (95% CI, 5.7–7.4; Table 2; Fig. 1D). The ORR as assessed by investigator was 42.6% (95% CI, 32.4–53.2), DCR was 86.2% (95% CI, 77.5–92.4), and median DOR was 5.9 months (95% CI, 5.5–7.6; Table 2). Median overall survival (OS) was 15.9 months (95% CI, 11.8–18.8; Table 2; Fig. 1E). Separate efficacy data, per BICR, for the phase I and phase II cohorts, as well as for the pooled data from both cohorts are shown in the Supplementary Appendix (Supplementary Table S3). In total, 36 patients (38.3%) received subsequent anticancer therapy. Of 49 patients who continued study treatment after disease progression, postprogression scans were available for 34 (33 who continued adagrasib and cetuximab and one who continued adagrasib alone). Continued tumor control was observed in many patients receiving treatment beyond progression (Supplementary Fig. S1), with tumor shrinkage observed versus baseline at the first postprogression scan for 18 of 33 patients (54.5%) continuing adagrasib plus cetuximab and 1 of 1 continuing adagrasib only.

Subgroup analyses of ORR (per BICR) for the pooled phase I and phase II adagrasib plus cetuximab combination data are shown in Fig. 2. For all subgroups, the range of 95% CIs overlapped the ORR for the overall population (34.0%). Subgroup analyses based on the presence of brain, bone, or adrenal metastases at baseline were omitted from the forest plot due to small patient numbers (less than five) in one of the subgroup categories.

For the adagrasib monotherapy cohort, ORR per BICR was 21.4% (95% CI, 10.3–36.8), median DOR was 15.2 months (95% CI, 2.8–not evaluable), median PFS was 4.1 months (95% CI, 2.8–6.5), and median OS was 12.2 months (95% CI, 8.1–15.2; see Supplementary Appendix for further detail; Supplementary Table S4; Supplementary Fig. S2A–S2D).

Safety

No new safety signals were observed in this larger dataset. The most frequent treatment-related adverse events (TRAEs) with adagrasib plus cetuximab included nausea (60.6%), vomiting (51.6%), diarrhea (48.9%), and dermatitis acneiform (47.9%; Table 3). Grade 3–4 TRAEs occurred in 27.7% of patients; there were no grade 5 TRAEs. TRAEs led to adagrasib dose reductions in 29.8% of patients and cetuximab dose reductions in 6.4% of patients. One patient required dose reduction of adagrasib and cetuximab. TRAEs led to discontinuation of cetuximab in eight patients (8.5%; Table 3), six of whom continued with adagrasib as a single agent; no TRAEs led to discontinuation of adagrasib. See Supplementary Appendix for the adagrasib monotherapy cohort safety data (Supplementary Table S5).

KRAS^{G12C} ctDNA Concordance, Kinetics, and Tumor Response

All 94 patients had a *KRAS*^{G12C} mutation detected in tumor tissue and 83 patients had available baseline plasma ctDNA for analysis. The concordance of *KRAS*^{G12C} mutation–positive status at baseline for patients with paired tumor and plasma samples was 83% (69 of 83) with the *KRAS*^{G12C} alteration

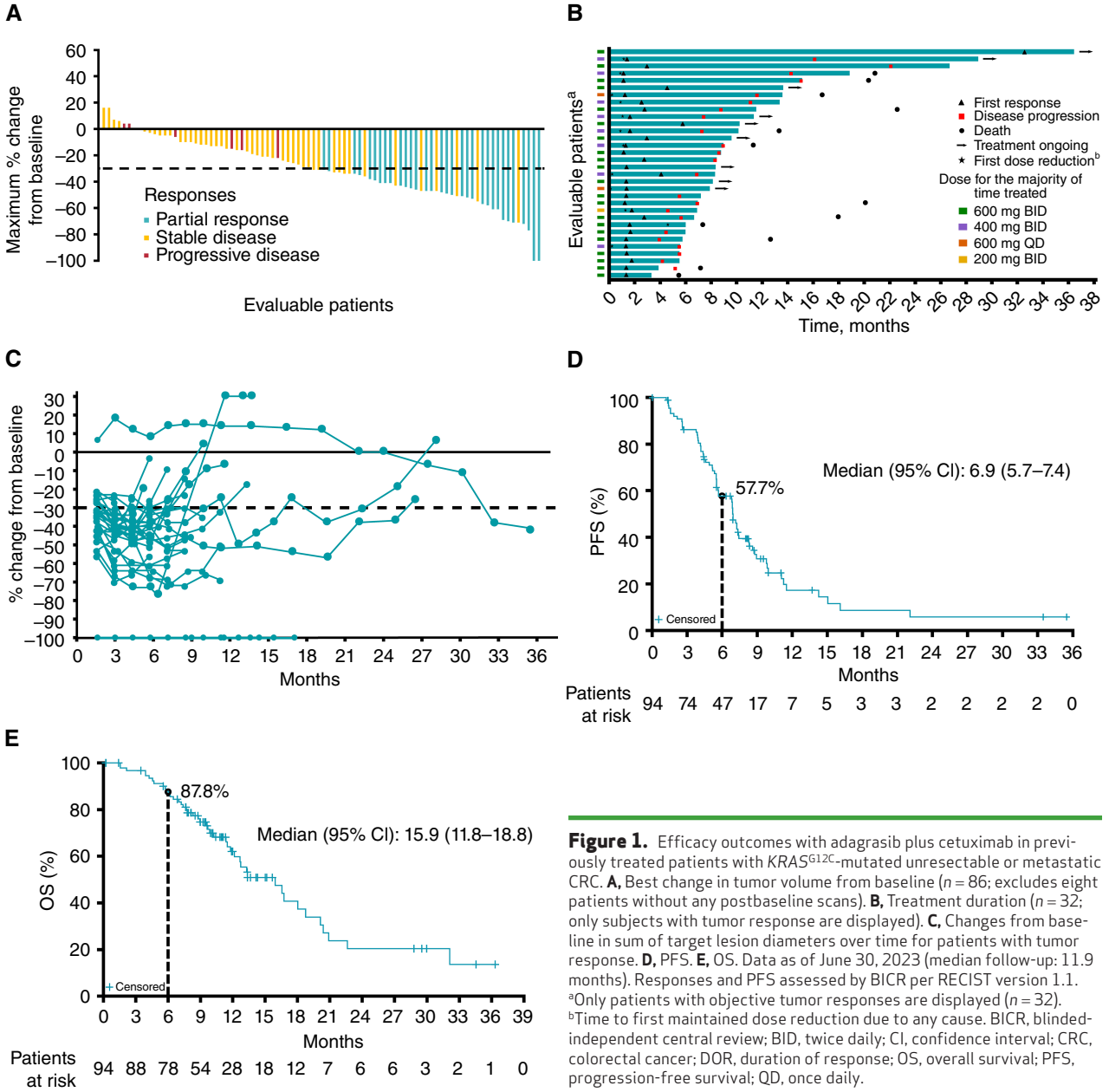

Figure 1. Efficacy outcomes with adagrasib plus cetuximab in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC. **A,** Best change in tumor volume from baseline ($n = 86$; excludes eight patients without any postbaseline scans). **B,** Treatment duration ($n = 32$; only subjects with tumor response are displayed). **C,** Changes from baseline in sum of target lesion diameters over time for patients with tumor response. **D,** PFS. **E,** OS. Data as of June 30, 2023 (median follow-up: 11.9 months). Responses and PFS assessed by BICR per RECIST version 1.1. [a]Only patients with objective tumor responses are displayed ($n = 32$). [b]Time to first maintained dose reduction due to any cause. BICR, blinded-independent central review; BID, twice daily; CI, confidence interval; CRC, colorectal cancer; DOR, duration of response; OS, overall survival; PFS, progression-free survival; QD, once daily.

detected in tissue but not ctDNA for 14 of 83 cases. ORR was 35% in the 83 patients with paired ctDNA/tissue, 39% in those with *KRAS*^{G12C} detected in ctDNA, and 14% in those where *KRAS*^{G12C} was not detected in ctDNA. Clearance of ctDNA of the targeted oncogene has been proposed as a potential pharmacodynamic marker, predictive of response to the matched therapy and of OS (13, 14). We therefore evaluated *KRAS*^{G12C} ctDNA at cycle 1 day 1 (C1D1) (baseline), C2D1 (4 weeks), and C4D1 (8 weeks), and associations of ctDNA clearance with response (Fig. 3). Clearance of *KRAS*^{G12C} ctDNA was defined as more than 90% decrease in the variant allele fraction based on prior defined thresholds (15). These analyses were only performed in phase I patients. Samples at baseline, C2D1, and C4D1 were available in 15 of 32 of these patients. ORR was 60% (9 of 15) in the evaluable population. At C4D1, 12 of 15 (80%) patients had a decrease in *KRAS*^{G12C} ctDNA by at least 90% and responses were seen in 67% (8 of 12) of these patients. Three patients had less than 90% clearance of *KRAS*^{G12C} at C4D1 and one response (1 of 3; 33%) was seen among these patients (Fig. 3).

Acquired Genomic Alterations by ctDNA

To identify potential mechanisms underlying acquired clinical resistance, we compared genomic alterations in plasma ctDNA at baseline with those in ctDNA collected at end of therapy (EOT). Paired plasma samples were available for 34 patients across the phase I and II adagrasib plus cetuximab combination therapy cohorts. A total of 25 patients (74%) had at least one acquired pathogenic alteration, with a total of 116 alterations identified overall. In 21 of

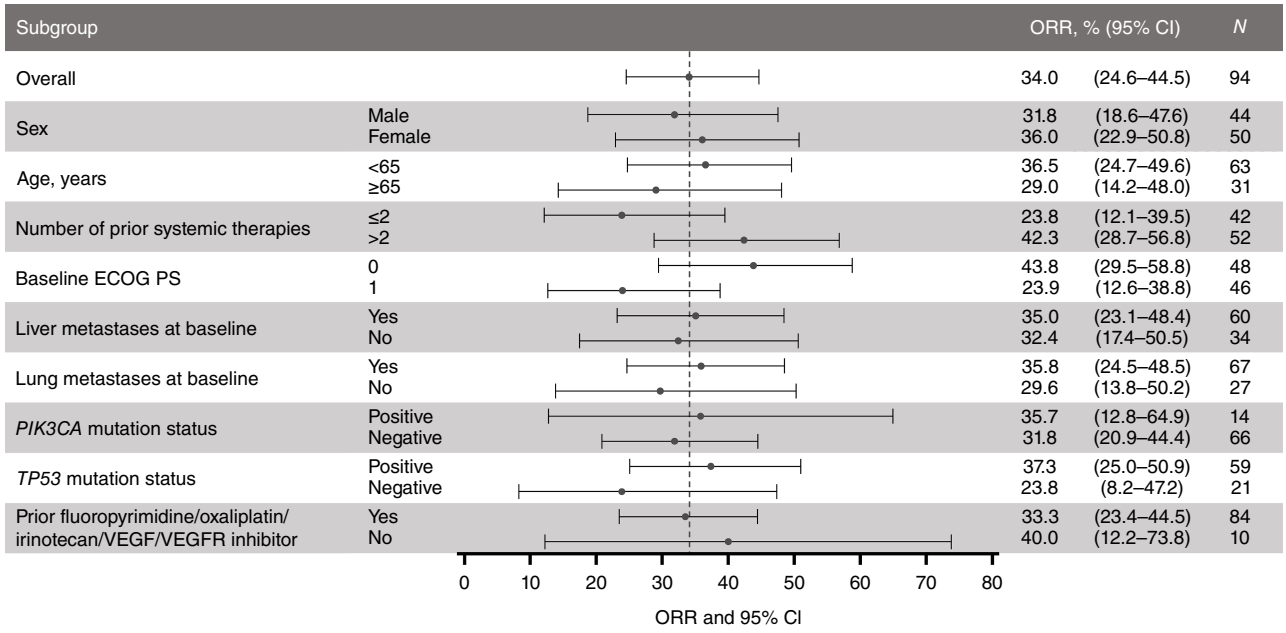

Figure 2. Subgroup analyses of ORR (in FAS per BICR) for patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC receiving adagrasib plus cetuximab. Data as of June 30, 2023 (median follow-up: 11.9 months). BICR, blinded-independent central review; CI, confidence interval; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; ORR, objective response rate.

25 cases, multiple acquired alterations were observed in the same patient (Fig. 4). Acquired alterations included *RTK* amplifications/fusions (12 of 34 patients; 35%), *EGFR* amplification (3 of 34; 9%), secondary mutations in *KRAS* (14 of 34; 41%), *KRAS* amplification (10 of 34; 29%), and mutations/fusions in other MAPK pathway genes (13 of 34; 38%).

DISCUSSION

Dual KRAS/EGFR inhibition with adagrasib plus cetuximab demonstrated promising clinical activity in patients with heavily pretreated (≥3 lines of therapy) unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer from the KRYSTAL-1 trial. ORR was 34.0%, median DOR was 5.8 months, median PFS was 6.9 months, and median OS was 15.9 months. Consistent with a previous report (8), in this study, ORR, median PFS, and median OS with adagrasib plus cetuximab were numerically higher than observed with adagrasib monotherapy. The combination of adagrasib plus cetuximab was tolerable, with no new safety concerns identified; most TRAEs were grade 1–2 in severity. Adagrasib-related AEs resulted in adagrasib dose reduction in 29.8% of patients and many patients continued to derive benefit after dose reduction. Some patients continued study treatment beyond RECIST progression and, among these, some appeared to obtain a degree of ongoing disease control. However, there are no prospective data on this treatment approach and it remains investigational.

The efficacy data reported here are consistent with data showing synergistic activity of KRAS^{G12C} and EGFR inhibitors in *KRAS*^{G12C}-mutated colorectal cancer cell lines (7, 16). Similarly, phase I/II data for other KRAS^{G12C} inhibitors in colorectal cancer demonstrated greater activity in combination with anti-EGFR antibodies versus monotherapy (17–21). Recent findings from a phase III study in the third-line setting (CodeBreaK 300) showed a PFS benefit with sotorasib (960 mg once daily) when combined with panitumumab versus standard of care [median PFS 5.6 months vs. 2.2 months; HR, 0.49 (95% CI, 0.30–0.80; $P = 0.006$); ref. 22]. In addition, ORR was higher in patients treated with sotorasib plus panitumumab (26.4%; 95% CI, 15.3–40.3) than in those treated with standard of care (0%; 95% CI, 0.0–6.6; ref. 22).

These data support adagrasib plus cetuximab as a potential therapy for heavily pretreated patients with unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer, where treatment options are limited (8), and are currently under review by the FDA. The low efficacy of current late-line standard of care trifluridine/tipiracil plus bevacizumab (SUNLIGHT trial; median PFS 5.6 months; ORR 6%), fruquintinib (median PFS 3.7 months; ORR 2%), or regorafenib (median PFS 1.9 months; ORR 1%) underscores the high unmet need in heavily pretreated patients (23–25). However, it should be noted that these trials included a molecularly unselected population, while this study only includes patients with *KRAS*^{G12C}-mutated colorectal cancer, a population with a generally worse prognosis (26). No subgroup analysis has been presented for trifluridine-tipiracil plus bevacizumab, fruquintinib, or regorafenib in patients with *KRAS*^{G12C}-mutated colorectal cancer.

There are multiple series highlighting the potential of ctDNA for both baseline genotyping in colorectal cancer and defining resistance mechanisms to targeted therapies (27–29). In our study population, baseline *KRAS*^{G12C} was detected

Table 3. Summary of TRAEs with adagrasib plus cetuximab in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC.

	Adagrasib + cetuximab CRC cohort ($N = 94$)				
TRAEs, *n* (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	94 (100)	8 (8.5)	60 (63.8)	22 (23.4)	4 (4.3)
Most frequent TRAEs, *n* (%)[a]					
Nausea	57 (60.6)	35 (37.2)	20 (21.3)	2 (2.1)	0
Vomiting	48 (51.1)	30 (31.9)	18 (19.1)	0	0
Diarrhea	46 (48.9)	31 (33.0)	14 (14.9)	1 (1.1)	0
Dermatitis acneiform	45 (47.9)	28 (29.8)	15 (16.0)	2 (2.1)	0
Fatigue	40 (42.6)	23 (24.5)	16 (17.0)	1 (1.1)	0
Dry skin	32 (34.0)	24 (25.5)	8 (8.5)	0	0
Hypomagnesemia	27 (28.7)	17 (18.1)	7 (7.4)	2 (2.1)	1 (1.1)[b]
Headache	25 (26.6)	14 (14.9)	8 (8.5)	3 (3.2)	0
Rash	21 (22.3)	11 (11.7)	8 (8.5)	2 (2.1)	0
TRAEs leading to dose reduction, *n* (%)					
Adagrasib	28 (29.8)	–	–	–	–
Cetuximab	6 (6.4)	–	–	–	–
TRAEs leading to dose interruption, *n* (%)					
Adagrasib	34 (36.2)	–	–	–	–
Cetuximab	33 (35.1)	–	–	–	–
TRAEs leading to discontinuation, *n* (%)					
Adagrasib	0	–	–	–	–
Cetuximab	8 (8.5)	–	7 (7.4)[c]	–	1 (1.1)[d]

NOTE: Data as of June 30, 2023 (median follow-up: 11.9 months).

Abbreviation: ALT, alanine aminotransferase; CRC, colorectal cancer; TRAE, alanine aminotransferase.

[a]Occurring in ≥20% of patients.

[b]Other grade 4 TRAEs were cetuximab-related infusion-related reaction, neutrophil count decrease, and hyperkalemia ($n = 1$ each). There were no grade 5 TRAEs.

[c]TRAEs (grade 1–2) that resulted in discontinuation of cetuximab were: cetuximab-related infusion-related reaction ($n = 3$); malaise ($n = 1$); ALT increase ($n = 1$); dermatitis acneiform ($n = 1$); and flushing ($n = 1$). Of these, 5 patients continued with adagrasib as a single agent.

[d]Cetuximab-related infusion-related reaction, this patient continued with adagrasib as a single agent.

in ctDNA for 69 of 83 patients, with 83% concordance between paired tumor samples. This highlights the possible utility of liquid biopsies for molecular genotyping, facilitating more rapid patient access to targeted therapy options in the future (30). In an exploratory analysis of plasma ctDNA kinetics, among patients treated with adagrasib plus cetuximab in the phase I portion, the ORR for those with a ≥90% decrease in *KRAS*^{G12C} ctDNA at 8 weeks (67%) was higher than that for those with <90% clearance of *KRAS*^{G12C} ctDNA at this timepoint (33%). While several variables can influence ctDNA detection and the optimal early timepoint is not known, our data further support that early, profound decrease is a favorable feature. In an exploratory analysis, we observed a diverse spectrum of acquired genomic alterations in patients treated with adagrasib in combination with cetuximab. This is in line with previous reports of acquired *KRAS* mutations and acquired RTK/RAS/MAPK/PI3K pathway alterations following concurrent KRAS^{G12C} and EGFR inhibition in colorectal cancer (31, 32).

Limitations of this study include the nonrandomized, open-label trial design as well as the absence of a comparator arm.

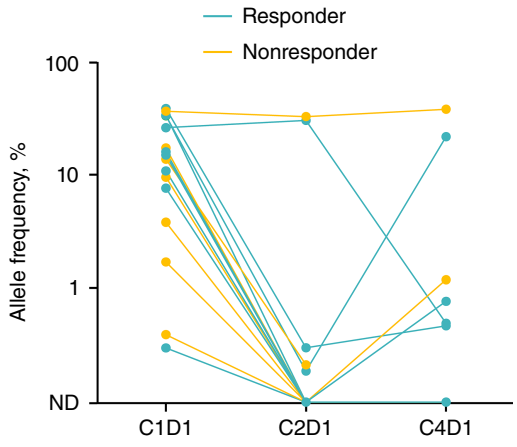

Figure 3. *KRAS*^{G12C} ctDNA clearance in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC receiving adagrasib plus cetuximab ($n = 15$). Response according to BICR. BICR, blinded independent central review; C, cycle; CRC, colorectal cancer; ctDNA, circulating tumor DNA; D, day; ND, not detected.

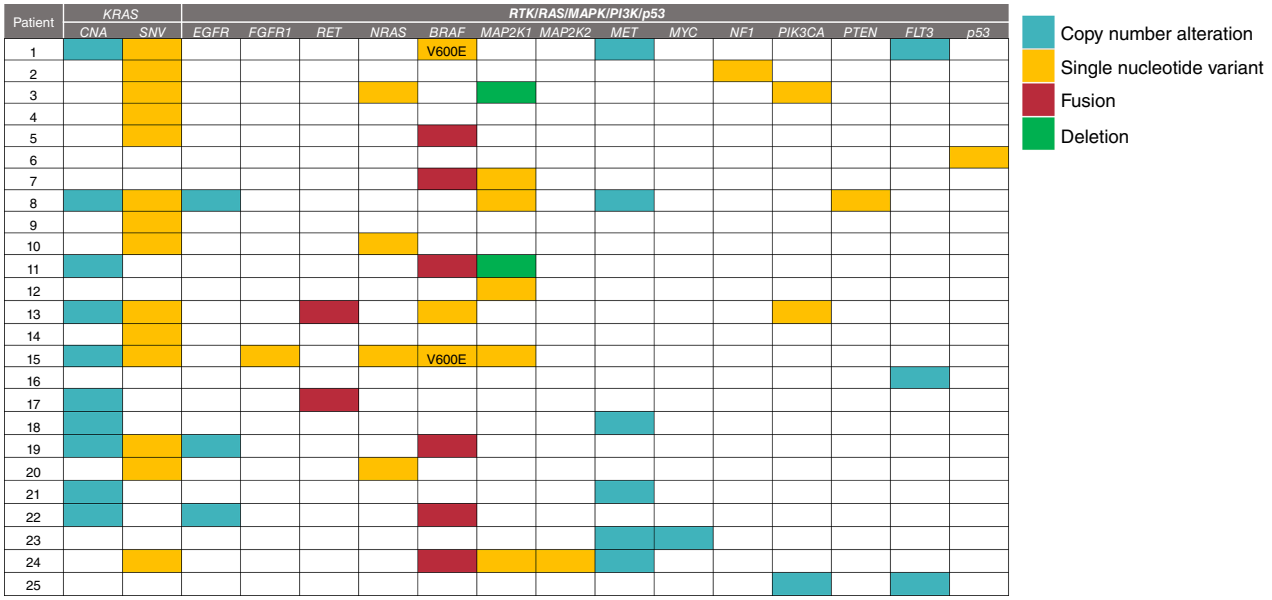

Figure 4. Acquired genomic alterations in previously treated patients with *KRAS*^{G12C}-mutated unresectable or metastatic CRC receiving adagrasib plus cetuximab; alterations present at EOT, that were not present at baseline. CNA, copy number alteration; EOT, end of therapy; SNV, single nucleotide variant.

The proportion of patients with lung metastases was high in our cohort (71.3%) and higher than that for liver metastases (63.8%), although *RAS* mutations have been associated with increased tendency for lung involvement in colorectal cancer (33–35). In the context of a non-randomized study, it is not possible to determine whether factors such as this may have impacted the outcomes observed, however, the patient population in this study was representative of later-line colorectal cancer in the United States and responses were observed across all subgroups analyzed.

As observed in large genomic studies (36), *KRAS* mutations are enriched in microsatellite stable (MSS) tumors relative to microsatellite instability-high (MSI-H) tumors and rarely cooccur with actionable oncogenic drivers for which approved immunotherapy and targeted therapy options exist. Although our study did not exclude patients with MSI-H or deficient mismatch repair (dMMR) colorectal cancer, all patients enrolled had MSS tumors. While we were not able to specifically test the efficacy of adagrasib plus cetuximab in *KRAS*^{G12C}-mutated colorectal cancer with MSI-H/dMMR, we expect that this subset would also benefit from this combination, similar to the success of *BRAF*^{V600E}-targeted therapy in MSI-H and MSS colorectal cancer. The efficacy of second-line adagrasib plus cetuximab versus standard of care is being investigated in the phase III KRYSTAL-10 trial (NCT04793958; ref. 16). These findings emphasize the clinical importance of testing for *KRAS*^{G12C} mutations in patients with unresectable or metastatic colorectal cancer to identify those eligible for this combination therapy.

Conclusion

In heavily pretreated patients with unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer, dual blockade of KRAS^{G12C}/EGFR by adagrasib plus cetuximab demonstrated encouraging clinical activity, was well tolerated, and is now recommended in the NCCN Guidelines®. These data support potential registration of adagrasib plus cetuximab as a late-line treatment for patients with unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer.

METHODS

Study Oversight

This open-label, nonrandomized, multicenter, multiple-expansion cohort phase I/II study was designed by employees of the sponsor, Mirati Therapeutics, a wholly owned subsidiary of Bristol Myers Squibb Company, and the investigators. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines (37, 38). The protocol was approved by the relevant institutional review boards or ethics committees; all 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.

Study Design

Full study details have been published previously (4, 5, 8, 39). The KRYSTAL-1 colorectal cancer cohorts included phase I and phase II cohorts in which the safety and efficacy of adagrasib plus cetuximab were assessed in patients with previously treated unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer. Patients received adagrasib 600 mg orally twice daily and cetuximab intravenously weekly (400 mg/m^2 loading dose followed by 250 mg/m^2; phase I) or every 2 weeks (500 mg/m^2; phase I and phase II) until disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients experiencing clinical benefit per the investigator could continue treatment despite confirmed radiographic progression. For the phase II adagrasib monotherapy cohort, study design, eligibility criteria, and endpoints are detailed in the Supplementary Methods.

Patients

Patients (aged ≥18 years of age) with previously treated, histologically confirmed, unresectable or metastatic *KRAS*^{G12C}-mutated colorectal cancer and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 were eligible for inclusion. Patients enrolled in the phase I and phase II cohorts had no available treatment with curative intent and were ineligible for, declined, or had no available standard of care treatment options; patients enrolled in the phase II expansion cohort had previously had to have received fluoropyrimidine, irinotecan, oxaliplatin, and a VEGF/VEGFR inhibitor. Patients with untreated or active brain metastases were excluded; patients with stable, treated brain metastases were eligible. Patients with prior therapy targeting *KRAS*^{G12C} mutations were excluded in the phase II portion.

Assessments and Endpoints

The primary endpoint of the phase I portion was safety. The primary endpoint of the phase II portion was confirmed ORR as assessed by BICR according to RECIST v1.1. Secondary endpoints of the phase I portion included ORR, DOR, and PFS, all per BICR, as well as OS. Secondary endpoints of the phase II portion included DOR and PFS, both per BICR, OS, and safety. *KRAS*^{G12C} mutations were identified in tumor tissue (phase I and phase II) and/or ctDNA (phase I) by preapproved methods (PCR or NGS platforms) and laboratories. Additional baseline genomic alterations were assessed from anonymized testing reports that had been uploaded into the electronic data capture system. The reports were reviewed by the sponsor for the presence of certain genomic alterations, namely *TP53*, *PIK3CA*, *BRAF*, *EGFR*, *NTRK*, and *HER2* (*ERBB2*), and for MSI/MMR status. Disease was evaluated at baseline and every 6 weeks during the study by CT scan or MRI. Patients with tumor response had a confirmatory assessment at least 4 weeks after the initial response. AEs were monitored throughout the study until 28 days after the last dose of study treatment and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Exploratory Translational Analyses

KRAS*^{G12C} *ctDNA Kinetics. Serial plasma samples were collected (before C1D1 treatment and at the beginning of C2 and C4) and analyzed using droplet digital PCR to assess the effect of treatment on ctDNA clearance of *KRAS*^{G12C}-variant alleles. Cycle length was defined as 28 days. Clearance of *KRAS*^{G12C} ctDNA was defined as more than 90% decrease in the variant allele fraction based on prior defined thresholds (15). These data were only collected for the phase I cohort and are not available for the phase II cohort.

Acquired Genomic Alterations at EOT. Targeted hybrid capture NGS (Agilent Resolution ctDx FIRST 109 gene panel; https://www.resolutionbio.com/assays/Resolution-ctDx-FIRST.html) was performed on ctDNA obtained at baseline and EOT. Acquired genomic alterations were characterized for pathogenicity and defined as absent at baseline and present at EOT. All clearly inactivating mutations for known tumor suppressor genes were included. Well-established, annotated, clearly recurrent mutations were confirmed by COSMIC. For inclusion, point mutations that were potential variants of unknown significance required evidence of recurrence in COSMIC (≥5 instances) plus structural impact assessment by SIFT and mutation assessor.

Subgroup Analyses. Subgroup analyses of ORR (per BICR) were conducted for the following baseline characteristics: sex; age (<65 vs. ≥65); number of prior systemic therapies (≤2 vs. >2); baseline ECOG PS (0 vs. 1); presence of liver, lung, brain, bone, or adrenal metastases at baseline (yes vs. no for each metastatic site); *PIK3CA* and *TP53* status (positive vs. negative); and patients treated with prior fluoropyrimidine, oxaliplatin, irinotecan, and VEGF/VEGFR inhibitor (all treatments; yes vs. no).

Statistical Analyses

In the phase I cohort, seven patients were initially enrolled to receive adagrasib plus cetuximab; if the number of patients with dose-limiting toxicity observed among these patients warranted further enrollment, approximately 30 patients could be enrolled to fully characterize safety. In the phase II combination cohort, a sample size of 60 patients was planned to demonstrate a target ORR of ≥30% with a 95% CI excluding the ORR of <5% for standard of care in this setting (Clopper–Pearson method). The safety population included all patients who received ≥1 dose of any study treatment. The full analysis set included all patients with measurable disease at baseline who received ≥1 dose of adagrasib plus cetuximab. ORR was determined by BICR according to RECIST v1.1. DOR, PFS, and OS were estimated using the Kaplan–Meier method.

Data Sharing Statement

The Bristol Myers Squibb data sharing policy (https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html) is compliant with ICMJE guidelines. Bristol Myers Squibb will honor legitimate requests for clinical trial data from qualified researchers. Data will be shared with external researchers whose proposed use of the data has been approved. Complete deidentified patient data sets will be eligible for sharing 2 years after completion of the study. Before data are released, the researcher(s) must sign a Data Sharing Agreement, after which the deidentified and anonymized datasets can be accessed within a secured portal.

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Authors' Contributions

R. Yaeger: Data curation, investigation, writing–original draft, writing–review and editing. **N. Uboha:** Resources, data curation, investigation, writing–original draft, project administration, writing–review and editing. **M.S. Pelster:** Data curation, investigation, writing–original draft, writing–review and editing. **T.S. Bekaii-Saab:** Conceptualization, resources, writing–original draft, writing–review and editing. **M. Barve:** Resources, investigation, writing–original draft, writing–review and editing. **J. Saltzman:** Resources, writing–original draft, writing–review and editing. **J.K. Sabari:** Conceptualization, supervision, investigation, writing–original draft, writing–review and editing. **J.A. Peguero:** Investigation, writing–original draft, writing–review and editing. **A.S. Paulson:** Resources, data curation, supervision, validation, investigation, writing–original draft, project administration, writing–review and editing. **P.A. Jänne:** Resources, writing–original draft, writing–review and editing. **M. Cruz-Correa:** Supervision, investigation, writing–original draft, project administration, writing–review and editing. **K. Anderes:** Conceptualization, investigation, writing–original draft, project administration, writing–review and editing. **K. Velastegui:** Data curation, investigation, writing–original draft, writing–review and editing. **X. Yan:** Formal analysis, writing–original draft, writing–review and editing. **H. Der-Torossian:** Conceptualization, visualization, methodology, writing–original draft, writing–review and editing. **S.J. Klempner:** Resources, data curation, investigation, writing–original draft, writing–review and editing. **S.E. Kopetz:** Conceptualization, resources, data curation, supervision, investigation, writing–original draft, writing–review and editing.

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