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Wild-Type *KRAS* Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose
Panitumumab, a fully human antibody against the epidermal growth factor receptor (EGFR), has activity in a subset of patients with metastatic colorectal cancer (mCRC). Although activating mutations in KRAS, a small G-protein downstream of EGFR, correlate with poor response to anti-EGFR antibodies in mCRC, their role as a selection marker has not been established in randomized trials.

Patients and Methods
KRAS mutations were detected using polymerase chain reaction on DNA from tumor sections collected in a phase III mCRC trial comparing panitumumab monotherapy to best supportive care (BSC). We tested whether the effect of panitumumab on progression-free survival (PFS) differed by *KRAS* status.

Results
KRAS status was ascertained in 427 (92%) of 463 patients (208 panitumumab, 219 BSC). *KRAS* mutations were found in 43% of patients. The treatment effect on PFS in the wild-type (WT) *KRAS* group (hazard ratio [HR], 0.45; 95% CI: 0.34 to 0.59) was significantly greater ($P < .0001$) than in the mutant group (HR, 0.99; 95% CI, 0.73 to 1.36). Median PFS in the WT *KRAS* group was 12.3 weeks for panitumumab and 7.3 weeks for BSC. Response rates to panitumumab were 17% and 0%, for the WT and mutant groups, respectively. WT *KRAS* patients had longer overall survival (HR, 0.67; 95% CI, 0.55 to 0.82; treatment arms combined). Consistent with longer exposure, more grade III treatment-related toxicities occurred in the WT *KRAS* group. No significant differences in toxicity were observed between the WT *KRAS* group and the overall population.

Conclusion
Panitumumab monotherapy efficacy in mCRC is confined to patients with WT *KRAS* tumors. *KRAS* status should be considered in selecting patients with mCRC as candidates for panitumumab monotherapy.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) has been validated as a therapeutic target in several human tumors, including colorectal cancer (CRC).[1-4] Ligand occupancy of the EGFR activates the RAS/RAF/MAPK, STAT, and PI3K/AKT signaling pathways, which together modulate cellular proliferation, adhesion, angiogenesis, migration, and survival.[5,6] The anti-EGFR targeted antibodies cetuximab and panitumumab administered as monotherapy in CRC have shown response and disease stabilization rates of approximately 10% and 30%, respectively.[2,3] Although EGFR expression is used for patient selection, clinical experience shows that the level of EGFR expression as measured by immunohistochemistry does not predict clinical benefit.[2,7-9]

KRAS, the human homolog of the Kirsten rat sarcoma-2 virus oncogene, encodes a small GTP-binding protein that acts as a self-inactivating signal transducer by cycling from GDP- to GTP-bound states in response to stimulation of a cell surface receptor, including EGFR.[10,11] *KRAS* can harbor oncogenic mutations that yield a constitutively active protein.[10-13] Such mutations are found in approximately 30% to 50% of CRC tumors and are common in other tumor types.[12,14-19] Several studies have indicated that the presence of mutant *KRAS* in lung and CRC tumors correlates with poor prognosis,[14,17,18,20] and is associated with lack of response to EGFR inhibitors.[15,16,19,21,22] These published reports investigating the role of *KRAS* as a selection

marker for EGFR inhibitor treatment were based on tumor samples from uncontrolled studies and included patients treated with anti-EGFR antibodies alone or in combination with irinotecan. Given the possible prognostic role of *KRAS* mutational status, these uncontrolled studies could not isolate the relative effect of antibody treatment on outcome by *KRAS* status from the prognostic implications of *KRAS* as a marker of poor clinical outcome in CRC.

We assessed the predictive role of *KRAS* in a phase III, randomized trial comparing panitumumab monotherapy with best supportive care (BSC) in patients with chemotherapy-refractory metastatic CRC.[3] The primary objective of the biomarker analyses was to determine whether the effect of panitumumab monotherapy on progression-free survival (PFS) differed between patients whose tumors contain mutant versus wild-type (WT; ie, nonmutated) *KRAS*.

PATIENTS AND METHODS

Trial Design and Patient Population

The design of this controlled, panitumumab monotherapy study has been previously described.[3] Briefly, patients with metastatic CRC with EGFR expression in $\geq$ 1% of tumor cells (assessed by immunohistochemistry) and documented evidence of disease progression after failure of fluoropyrimidines and prespecified exposure to oxaliplatin and irinotecan were randomly assigned to panitumumab 6 mg/kg plus BSC every 2 weeks or BSC alone. BSC patients could receive panitumumab after disease progression. Tumor status was assessed radiographically every 4 to 8 weeks from week 8 until disease progression using the Response Evaluation Criteria in Solid Tumors by blinded central review. The primary end point was PFS, defined as the interval from random assignment to radiologic progression or death. Secondary end points included objective response rate, overall survival (OS), and safety. All patients, including those with unassessable or missing assessments, were included in the response rate analysis. A best response of stable disease was determined at or after week 8 from random assignment. At enrollment, patients provided informed consent for study procedures including research on archived paraffin-embedded tumor samples (mostly from primary tumor resection) for identification of predictive biomarkers. The study protocol was approved by the ethics board at each research center.

Assay to Detect Mutant KRAS

Formalin-fixed, paraffin-embedded tumor sections were deparaffinized and air dried, and DNA was isolated using proteinase K and a DNeasy mini-spin column (Qiagen, Valencia, CA). Mutant *KRAS* was detected using a validated *KRAS* mutation kit (DxS Ltd, Manchester, United Kingdom) that identifies seven somatic mutations located in codons 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) using allele-specific real-time polymerase chain reaction.[23-25] A central laboratory (HistoGeneX, Antwerp, Belgium) validated the assay for analytic and diagnostic performance, established acceptance criteria, included appropriate quality controls for each assay, and performed the *KRAS* analysis in a blinded fashion.

Statistical Analysis

The primary objective of the biomarker analyses was to examine whether the relative effect of panitumumab compared with BSC on PFS differed in patients with tumors bearing mutant versus WT *KRAS*. Additional objectives included examining whether panitumumab improved PFS, OS, and response rate in the WT *KRAS* group compared with the BSC group. Safety was assessed in both *KRAS* groups. Analyses were limited to patients with known *KRAS* status and were categorized by randomized treatment for efficacy and safety. Adverse events were graded per the National Cancer Institute Common Toxicity Criteria version 2.0 with the exception of selected skin toxicities, which were graded using version 3.0. Statistical analyses were performed at Amgen Inc. All analyses were prespecified in a statistical analysis plan before *KRAS* mutation assessment.

A quantitative-interaction test[26] at a two-sided 5% level was used to compare the PFS log-hazard ratio (HR; panitumumab relative to BSC) from a Cox model with covariates for the randomization factors between the WT and mutant *KRAS* groups. Based on an assessable sample size of 380 patients and assuming 60% WT prevalence, power was estimated at more than 99% if the HR was 1.0 in the mutant *KRAS* group and at 87% if the HR was 0.80 in the mutant *KRAS* group, assuming an overall HR of 0.54 among all patients. Kaplan-Meier methods were used to estimate PFS and OS. Conditional on a significant interaction test, sequential testing at a 5% level of PFS, followed by OS and overall response rate, were planned within the WT *KRAS* group between panitumumab versus BSC. A log-rank test was used for PFS, Wilcoxon for OS, and a generalized Cochran-Mantel-Haenszel test for response rate, each stratified by the randomization factors.

Maximum change in tumor burden per blinded central radiology review was summarized by treatment in each *KRAS* group. Propensity-score sensitivity analyses were performed to assess bias due to exclusion of patients with unknown *KRAS* status.

RESULTS

Patients

Of the 463 patients originally enrolled,[3] 427 (92%) were included in the *KRAS* analyses (208 and 219 in the panitumumab and BSC arms, respectively; Fig 1). *KRAS* status could not be determined in 18 patients because of unavailable samples and in an additional 18 patients whose samples had insufficient or poor-quality DNA. *KRAS* mutations were identified in 184 (43%) of 427 patients (84 [40%] and 100 [46%] in the panitumumab and BSC arms, respectively). In the BSC arm, 76% of patients with WT *KRAS* and 77% of patients with mutant *KRAS* received panitumumab in a cross-over protocol, after a median PFS time in the original study (investigator assessment) of 7.1 weeks (95% CI, 7.0 to 7.6) and 6.3 weeks (95% CI, 5.1 to 7.1) for patients in the WT and mutant *KRAS* groups, respectively.

Baseline patient characteristics were balanced between the WT and mutant *KRAS* groups for both panitumumab and BSC (Table 1). The distribution of specific *KRAS* mutations was similar between treatment arms (Table 2).

Efficacy

Primary end point: PFS. Similar to previously described results in the intent-to-treat population,[3] a statistically significant improvement in PFS was observed in the *KRAS* assessable group between panitumumab and BSC (HR, 0.59; 95% CI, 0.48 to 0.72). Median PFS time was 8.0 weeks for panitumumab and 7.3 weeks for BSC. The relative effect of panitumumab versus BSC on PFS was significantly greater among patients with WT *KRAS* (HR, 0.45; 95% CI, 0.34 to 0.59; median PFS of 12.3 weeks for panitumumab *v* 7.3 weeks for BSC) compared with patients with mutant *KRAS*, in whom no panitumumab benefit was observed (HR, 0.99; 95% CI, 0.73 to 1.36; median PFS of 7.4 weeks for panitumumab *v* 7.3 weeks for BSC; Fig 2). The quantitative-interaction test comparing the magnitude of the relative treatment effect on PFS between WT and mutant *KRAS* groups was statistically significant ($P < .0001$). Consistent results were obtained with propensity-score adjusted HRs. PFS was significantly greater for panitumumab versus BSC in the WT *KRAS* group (stratified log-rank test $P < .0001$; Fig 2). In all sensitivity analyses performed in the WT *KRAS* subset, PFS favored the panitumumab arm. In particular, to compensate for potential tumor-ascertainment bias in favor of the BSC arm, an interval-censored sensitivity analysis was performed

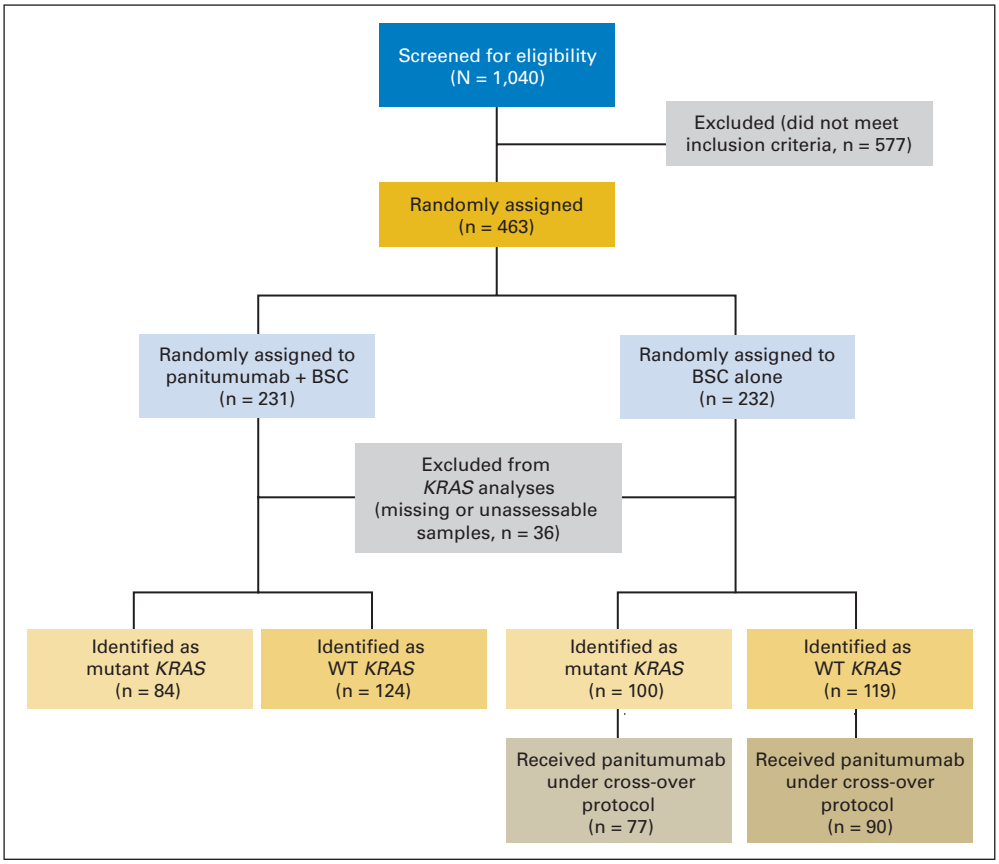

Fig 1. CONSORT diagram. BSC, best supportive care; WT, wild-type.

whereby radiologic event times were moved to the closest assessment time prespecified in the protocol. These analyses showed HR = 0.44 (95% CI, 0.30 to 0.63) and median PFS times of 16 and 8 weeks for panitumumab and BSC, respectively. Across all subsets examined, the treatment effect of panitumumab on PFS in the WT *KRAS* group was consistent with the primary analysis (Fig 3). Of 168 BSC patients receiving panitumumab after progression, PFS was significantly longer among patients with WT versus patients with mutant *KRAS* (HR, 0.32; 95% CI, 0.22 to 0.45; median PFS time of 16.4 weeks for WT and 7.9 weeks for mutant; online-only Fig A1A).

Response rate. Best overall response data were unassessable or missing for 35 of 231 patients receiving panitumumab and for 53 of 232 BSC patients (this included 16 of 124 patients receiving panitumumab with WT *KRAS*, 16 of 119 BSC patients with WT *KRAS*, 15 of 84 patients receiving panitumumab in the mutant *KRAS* group, and 32 of 100 BSC patients in the mutant *KRAS* group). In the *KRAS* assessable group, response rate for panitumumab was 10%, stable disease was 25%, and disease progression was 50%. For *KRAS* assessable patients in the BSC arm, 0% had a response, 10% had stable disease, and 68% had disease progression. No responders were identified in the panitumumab mutant *KRAS* group (100% positive predictive value for nonresponse in the mutant group). In contrast, in the panitumumab WT *KRAS* group 21 of 124 patients had a partial response (17%; 95% CI, 11% to 25%; Fig 4). Median time to response was 7.9 weeks (range, 7.0 to 15.6 weeks), and median duration of response was 19.7 weeks (range, 7.9 to 88.7 weeks).

In the WT *KRAS* group, 42 patients receiving panitumumab (34%) and 14 BSC patients (12%) had stable disease (Fig 4). In the mutant *KRAS* group, stable disease was observed in 10 (12%) and eight patients (8%) in the panitumumab and BSC arms, respectively. Consistent results with PFS and response were observed when examining the magnitude of effect on target lesions for individual patients. For the WT *KRAS* group, 61% of patients receiving panitumumab with available target lesion measurements (62 of 101 in the WT group) had a target lesion decrease, including the majority of patients with stable disease (Fig 4). In contrast, in the mutant *KRAS* group, only 5% of patients receiving panitumumab (three of 62) had minor tumor reductions. For the BSC patients in both *KRAS* groups, 3% of patients (six of 178) had some degree of tumor reduction.

Of 168 BSC patients in the *KRAS* assessable group that crossed over to receive panitumumab on progression, 20 (12%) experienced a response (including one patient with a complete response), and 55 (33%) had stable disease. All responders had WT *KRAS*, for a response rate of 20 of 91 (22%; 95% CI, 14% to 32%).

OS. At the time of these analyses, a total of 391 *KRAS* assessable patients (92%) had died (186 [89%] patients receiving panitumumab and 205 [94%] BSC patients). Median follow-up time was 14.1 months for the remaining 36 patients. No statistically significant OS difference was observed between treatment arms among all patients (HR, 0.97; 95% CI, 0.79 to 1.18), or in either of the *KRAS* groups; the HR for OS was 1.02 (95% CI, 0.75 to 1.39) and 0.99 (95% CI, 0.75 to 1.29) for the mutant and WT *KRAS* groups, respectively. OS was longer overall in the WT group than in the mutant group adjusting for stratification factors and randomized treatment (HR, 0.67; 95% CI, 0.55 to 0.82; both arms combined; Fig 5). Multivariate analysis showed that WT *KRAS* status was a predictor for OS in both the

Table 1. Patient Demographics and Baseline Characteristics by *KRAS* Status

Characteristic	Mutant				Wild-Type			
	Panitumumab		BSC		Panitumumab		BSC	
	No.	%	No.	%	No.	%	No.	%
No. of patients	84		100		124		119	
Sex								
Male	47	56	64	64	83	67	76	64
Race/ethnicity								
White	84	100	97	97	122	98	118	99
Baseline age, years								
Median	62.0		62.0		62.5		63.0	
Minimum	27		27		29		32	
Maximum	79		83		82		81	
Primary diagnosis								
Colon cancer	53	63	65	65	86	69	82	69
Rectal cancer	31	37	35	35	38	31	37	31
ECOG performance status								
0	43	51	37	37	53	43	40	34
1	28	33	47	47	56	45	62	52
≥ 2*	13	15	16	16	15	12	17	14
Cells with EGFR membrane staining								
1% to < 10%	20	24	23	23	31	25	29	24
10% to 100%	63	75	77	77	93	75	89	75
Highest membrane staining intensity								
3+ (strong)	17	20	17	17	25	20	22	18
2+ (moderate)	42	50	51	51	69	56	58	49
1+ (weak)	24	29	32	32	30	24	39	33
0	1	1	0	0	0	0	0	0
Prior adjuvant chemotherapy								
Yes	27	32	40	40	50	40	32	27
Prior lines of chemotherapy								
2	54	64	74	74	79	64	63	53
3	23	27	24	24	41	33	49	41

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
*Of patients treated with BSC, one patient with wild-type *KRAS* status and one patient with mutant *KRAS* status had an ECOG performance status score of 3.

panitumumab (HR, 0.64; $P = .004$) and BSC (HR, 0.68; $P = .007$) arms. Similar results for OS were observed among the 168 BSC patients receiving panitumumab after progression (HR, 0.65; 95% CI, 0.47 to 0.90; median OS time of 6.8 months for WT *v* 4.5 months for mutant; online-only Fig A1B). For the 51 BSC patients who did not cross-over to panitumumab, no difference in OS was observed between WT and mutant *KRAS* groups (median OS time of 1.9 and 2 months, respectively).

Table 2. Distribution of *KRAS* Mutations By Treatment Arm

KRAS Mutation	Total (N = 184)		Panitumumab (n = 84)		BSC (n = 100)	
	No.	%	No.	%	No.	%
12Ala	15	8.2	8	9.5	7	7.0
12Asp	70*	38.0	34	40.5	36	36.0
12Arg	3*	1.6	0	0.0	3	3.0
12Val	40	21.7	15	17.9	25	25.0
12Cys	14	7.6	7	8.3	7	7.0
12Ser	14	7.6	5	6.0	9	9.0
13Asp	29	15.8	15	17.9	14	14.0

Abbreviations: BSC, best supportive care; Ala, alanine; Asp, aspartic acid; Arg, arginine; Val, valine; Cys, cysteine; Ser, serine.
*Two mutations were detected in one specimen.

Exposure and Safety

The mean number of panitumumab infusions was 10.0 (median, 8.0) and 4.9 (median, 4.0) in WT and mutant *KRAS* groups, respectively. In the mutant *KRAS* group, 100% of patients receiving panitumumab and 84% of BSC patients had an adverse event. In the WT *KRAS* group, these numbers were 100% and 90%, respectively. By maximum grade and by *KRAS* group, a higher incidence of grade 3 or 4 adverse events (44% *v* 28%) and treatment-related grade 3 adverse events (25% *v* 12%) was observed in the panitumumab WT versus mutant *KRAS* groups, respectively. In the *KRAS* assessable population, 37% of patients had a grade 3 or 4 event, and 20% of patients had a treatment-related grade 3 or 4 adverse events. The incidence of adverse events leading to withdrawal in the panitumumab arm was 7% and 5% for the WT and mutant *KRAS* groups, respectively; 2% of WT *KRAS* patients and 1% of mutant *KRAS* patients withdrew for panitumumab-related events.

Grade 3 integument-related events occurred in 20% of all *KRAS* assessable patients (in 25% of WT *KRAS* patients and in 13% of mutant *KRAS* patients). In the mutant *KRAS* group, 1% of patients

had a grade 4 integument-related event; there were no grade 4 events in the WT group. The time to any integument-related event or to an event grade 2 or higher was similar in both *KRAS* groups, suggesting that incidence differences for integument toxicity were due to differential exposure. Consistent with previous reports,[2,3] patients with the worst grade skin toxicity in the WT *KRAS* group appeared to experience better PFS and OS (data not shown). In the panitumumab arm, a higher incidence of diarrhea of any grade was observed (WT *KRAS* 24%; mutant *KRAS* 19%) but grade 3 diarrhea was comparable between groups (WT *KRAS* 2%; mutant *KRAS* 1%). The incidence of hypomagnesemia reported as an adverse event of any grade was 3% and 0% for WT and mutant *KRAS* groups, respectively. One grade 2 infusion reaction was reported as an adverse event in a patient with mutant *KRAS*.

DISCUSSION

These results show that *KRAS* mutations predict for lack of clinical benefit to panitumumab therapy. The presence of a control arm made it possible to study the relative effect of panitumumab monotherapy by *KRAS* mutational status independent of the potential prognostic influence of *KRAS* mutations on outcomes, enabling us to conclude that the clinical benefit observed in the *KRAS* unselected population was entirely derived from the *KRAS* WT population. Given the crossover design, conclusions are limited to the effect of *KRAS* mutational status on PFS and tumor response end points and not to OS. Indeed, the majority of BSC patients received panitumumab on disease progression early in the trial in both *KRAS* groups (median

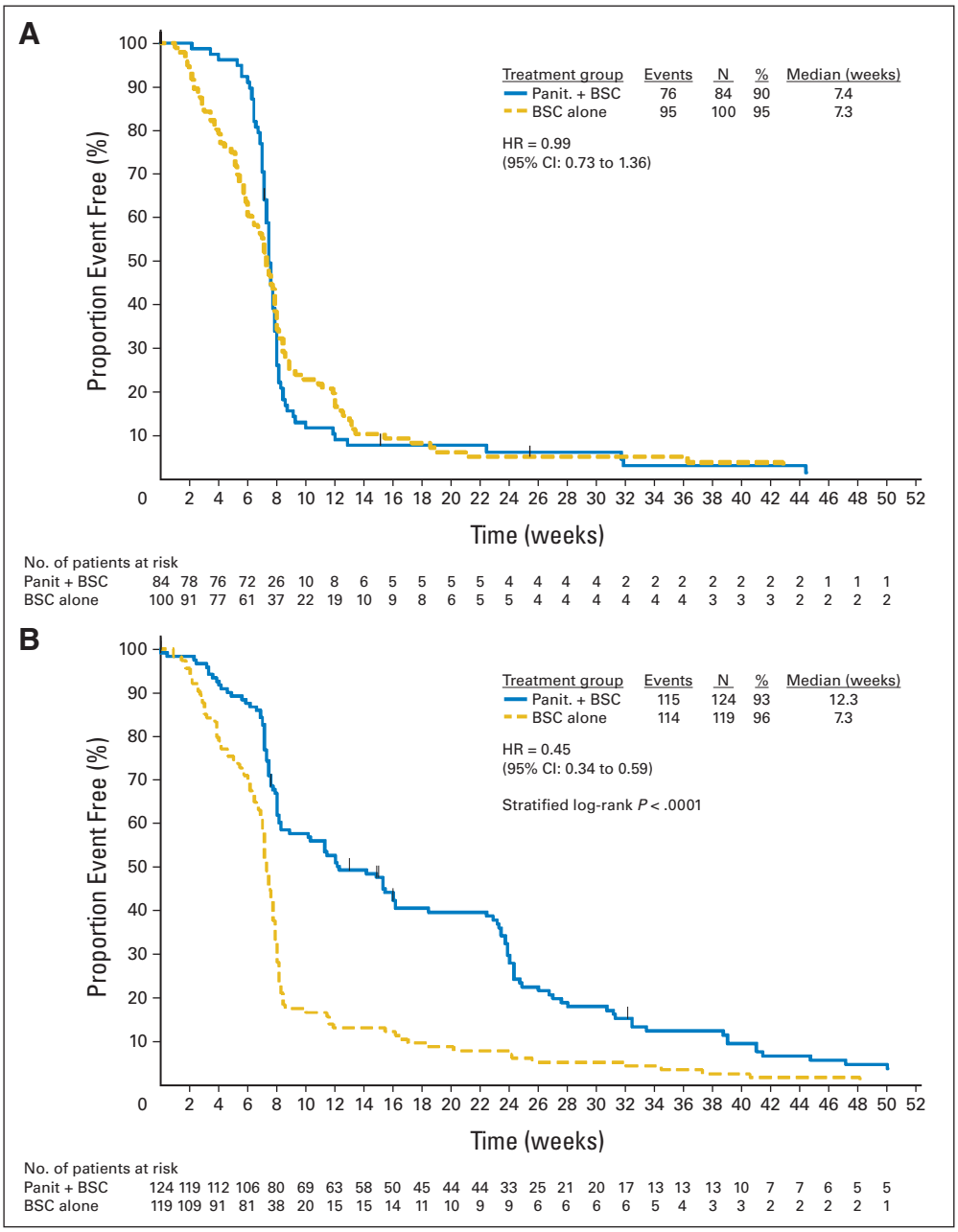

Fig 2. Progression-free survival by treatment within *KRAS* groups. Progression-free survival by randomized treatment in (A) mutant and (B) wild-type *KRAS* groups. Hazard ratios (HR) are shown for panitumumab (panit.) versus best supportive care (BSC) adjusted for randomization factors (Eastern Cooperative Oncology Group score, geographic region).

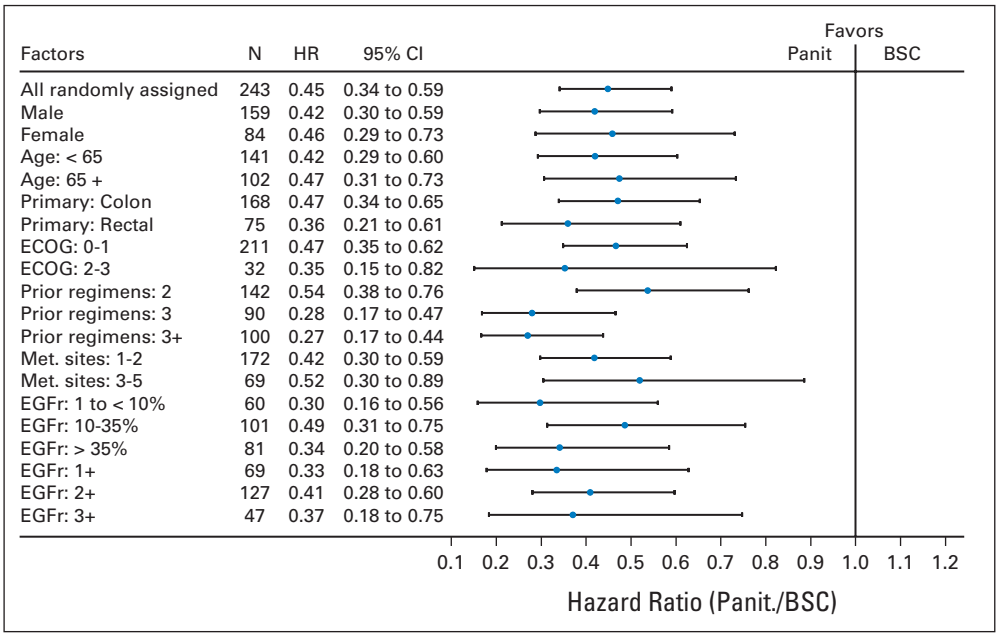

Fig 3. Subset analyses of progression-free survival in the *KRAS* wild-type group. Hazard ratio (HR; blue circle) and 95% CI (horizontal lines) adjusted for randomization factors for panitumumab (panit.) versus best supportive care (BSC). N, sample size; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; Met, metastatic; EGFr, epidermal growth factor receptor; 1+, weak; 2+, moderate; 3+, strong.

time to cross-over was 7.1 weeks), and, importantly, there was demonstrated benefit of panitumumab after cross-over in patients with WT *KRAS* tumors. The difference in OS in favor of the WT *KRAS* group in both treatment arms observed in our study may have reflected a potential prognostic value of *KRAS* mutational status in CRC or differential sensitivity to panitumumab treatment between *KRAS* groups.

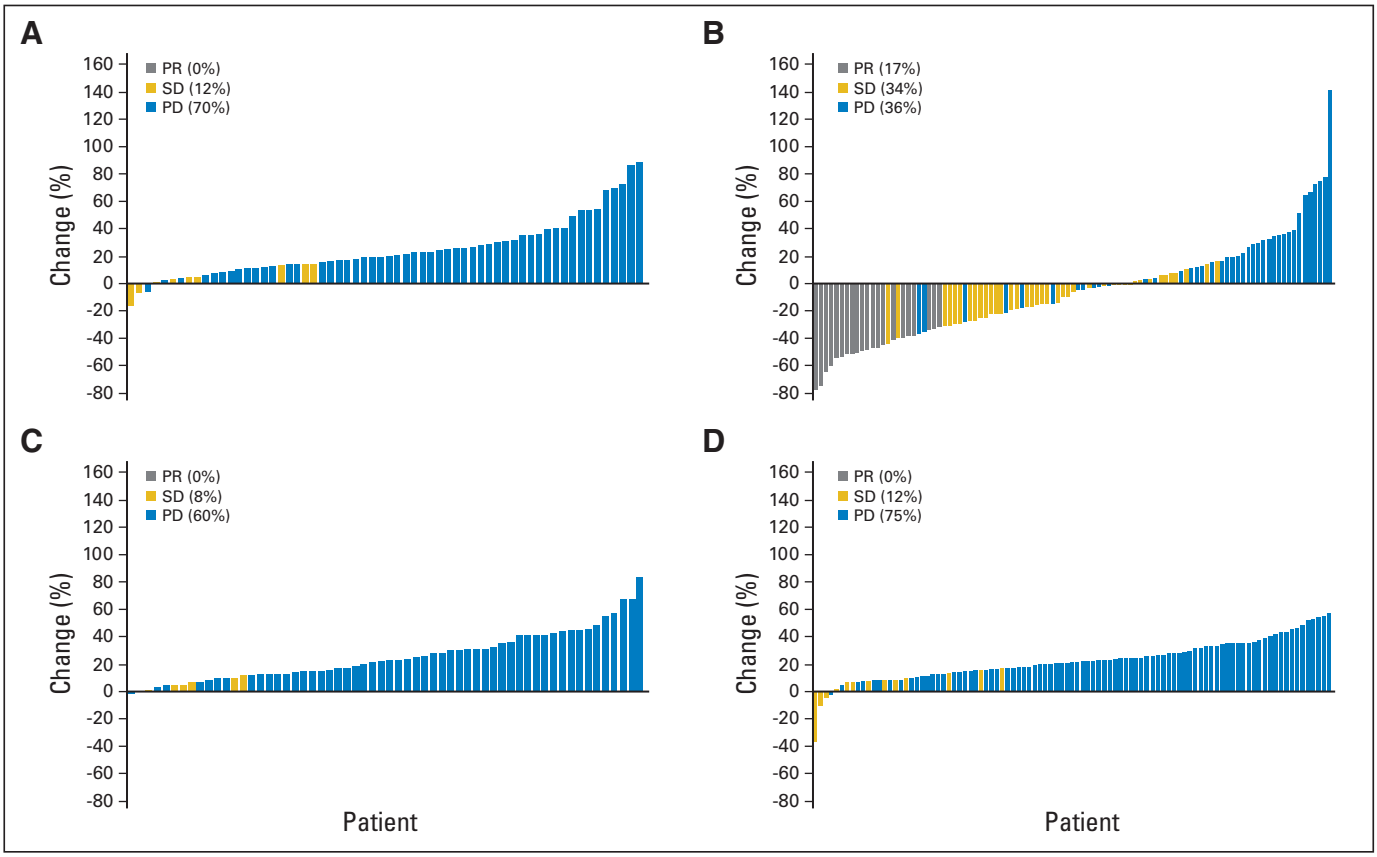

Fig 4. Waterfall plots showing maximum percent decrease in target lesions (blinded central radiology). (A) Patients receiving panitumumab, mutant *KRAS*. (B) Patients receiving panitumumab, wild-type (WT) *KRAS*. (C) Best supportive care (BSC) patients, mutant *KRAS*. (D) BSC patients, WT *KRAS*. Percentages are best response within each *KRAS* group, excluding missing or nonassessable postbaseline tumor assessments. PR, partial response (gray); SD, stable disease (yellow); PD, progressive disease (blue).

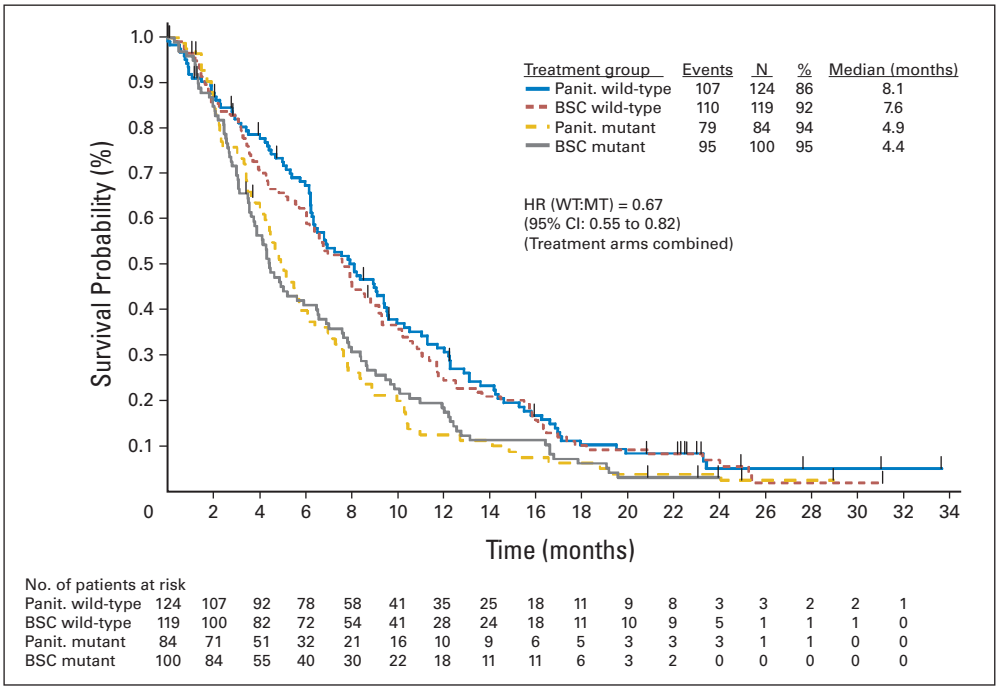

Fig 5. Kaplan-Meier curves for overall survival by treatment and *KRAS* status. Hazard ratio (HR) for wild-type (WT) versus mutant (MT) KRAS status adjusted for randomized treatment and randomization factors. Panit, panitumumab; BSC, best supportive care; events, deaths; N, sample size.

Although these analyses were conducted retrospectively, several aspects relating to the methodology lend robustness to the results. First, the hypothesis that *KRAS* mutations may confer primary resistance to anti-EGFR antibodies was generated independently from previous trials. Second, to avoid inflation of type-1 error, samples were only subjected to one biomarker analysis, that of *KRAS* mutation. Third, the analyses were sufficiently powered and prespecified in a statistical analysis plan before knowledge of *KRAS* outcome. Fourth, testing was performed by an independent laboratory without patient-level knowledge of randomization or clinical outcomes. Fifth, the magnitude of the interaction observed is substantial. These considerations, together with consistency with previous studies, and the recognized biologic plausibility of the hypothesis, strongly support the validity of our results and conclusions.

To our knowledge, these are the first results arising from a randomized, controlled trial showing that the state of a signaling molecule downstream of a target plays a crucial role in predicting clinical benefit to a targeted therapeutic. These results also illustrate that the presence of a therapeutic target in itself may be insufficient to predict response to therapy in tumors with multiple molecular alterations. The high positive predictive value (100% for lack of objective response rate) for mutant *KRAS* suggests that inhibition of the RAS/RAF/MAPK signaling pathway is primarily responsible for the clinical activity of panitumumab in metastatic CRC, and raises the possibility that mutant *KRAS* may be predictive in other tumor types. Indeed, EGFR inhibitors have shown modest or no activity in pancreatic cancer, a disease with a high prevalence of *KRAS* mutations,[4,27] and in patients with lung cancer whose tumors harbor *KRAS* mutations.[22,28]

In our study, WT *KRAS* status was shown to be required but not sufficient to confer sensitivity to panitumumab monotherapy. The mechanisms of primary and treatment-emergent resistance to panitumumab in patients with WT *KRAS* tumors are unknown. With regard to primary resistance, EGFR may not be a dominant oncogenic pathway in some tumors, regardless of *KRAS* status. In addition, while *KRAS* mutations occur early in the development of CRC,[29-31] they may also be subsequently acquired, leading to tumor cell heterogeneity. Moreover, while the assay employed in our study is known to detect more than 90% of known activating *KRAS* mutations in CRC, it would have missed additional mutations in codons 12 and 61. Other potential mechanisms of resistance include activation of additional tyrosine kinase receptors, such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and insulin-like growth factor 1 receptor[7]; activating mutations of additional signaling proteins downstream of the EGFR, such as PI3K,[33] and Src,[34] or downstream of KRAS such as RAF[15,35]; and loss-of-function mutations of tumor-suppressor genes such as phosphatase and tensin homolog (*PTEN*).[33] Elucidating mechanisms of resistance to panitumumab will prove important for the selection of therapeutic combinations to maximize clinical benefit. In addition to ascertaining resistance mechanisms, other biomarkers such as EGFR gene copy number and expression levels of EGFR ligands in tumor cells may be useful to further refine the responder population.[32,36]

The current results apply to the setting of panitumumab monotherapy and indicate that *KRAS* status should be considered when selecting mCRC patients as candidates for this treatment. Studies are currently underway to assess prospectively whether *KRAS* mutations also influence response to panitumumab in combination with chemotherapy in earlier lines of therapy. In addition to the relevance of these results to the current use and to the future development of anti-EGFR antibodies, these findings may have implications for the development of oncology therapeutics directed against other targets known to signal though the RAS/RAF/MAPK pathway.[37,38]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

