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ORIGINAL REPORT

Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Panitumumab is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR). We compared the activity of panitumumab plus best supportive care (BSC) to that of BSC alone in patients with metastatic colorectal cancer who had progressed after standard chemotherapy.

Patients and Methods
We randomly assigned 463 patients with 1% or more EGFR tumor cell membrane staining, measurable disease, and radiologic documentation of disease progression during or within 6 months of most recent chemotherapy to panitumumab 6 mg/kg every 2 weeks plus BSC (n = 231) or BSC alone (n = 232). Tumor assessments by blinded central review were scheduled from week 8 until disease progression. The primary end point was progression-free survival (PFS). Secondary end points included objective response, overall survival (OS), and safety. BSC patients who progressed could receive panitumumab in a cross-over study.

Results
Panitumumab significantly prolonged PFS (hazard ratio [HR], 0.54; 95% CI, 0.44 to 0.66, [$P < .0001$]). Median PFS time was 8 weeks (95% CI, 7.9 to 8.4) for panitumumab and 7.3 weeks (95% CI, 7.1 to 7.7) for BSC. Mean (standard error) PFS time was 13.8 (0.8) weeks for panitumumab and 8.5 (0.5) weeks for BSC. Objective response rates also favored panitumumab over BSC; after a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC ($P < .0001$). No difference was observed in OS (HR, 1.00; 95% CI, 0.82 to 1.22), which was confounded by similar activity of panitumumab after 76% of BSC patients entered the cross-over study. Panitumumab was well tolerated. Skin toxicities, hypomagnesaemia, and diarrhea were the most common toxicities observed. No patients had grade 3/4 infusion reactions.

Conclusion
Panitumumab significantly improved PFS with manageable toxicity in patients with chemorefractory colorectal cancer.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with approximately 1 million new cases diagnosed yearly.[1] Although current use of irinotecan, oxaliplatin, and bevacizumab with long-time standards fluourouracil and leucovorin as first- or second-line treatment for metastatic colorectal cancer have resulted in median survival rates greater than 18 months,[2-14] most patients develop resistance to these therapies and die of their disease. Therefore, there is a need for new active treatment options in this setting.

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arm was not included. Other studies with new agents (eg, tipifarnib, a farnesyl transferase inhibitor) compared with BSC did not show activity in refractory colorectal cancer.[21]

Panitumumab binds to EGFR and prevents receptor dimerization, EGFR-tyrosine autophosphorylation, and activation of downstream signaling molecules, resulting in the inhibition of cellular proliferation and tumor growth and in the induction of apoptosis.[15,19] In phase II studies, panitumumab monotherapy for the treatment of chemorefractory colorectal cancer was active and well tolerated.[13,14,16] To fully evaluate the effect of panitumumab monotherapy in patients with chemorefractory metastatic colorectal carcinoma, we designed this randomized phase III study of panitumumab administered at 6 mg/kg every 2 weeks plus BSC compared with BSC alone.

PATIENTS AND METHODS

Patients

Eligible patients had pathologic diagnosis of metastatic colorectal adenocarcinoma and radiologic documentation of disease progression during or within 6 months following the last administration of fluoropyrimidine, irinotecan, and oxaliplatin. To ensure adequate exposure to prior chemotherapy, average dose-intensity of irinotecan ($\geq$ 65 mg/m^2 per week) and of oxaliplatin ($\geq$ 30 mg/m^2 per week) were required. Both criteria of disease progression and dose-intensity were confirmed retrospectively and centrally.

Other key eligibility criteria included: 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, two or three prior chemotherapy regimens for metastatic colorectal cancer, and 1% or more EGFR-positive membrane staining in evaluated tumor cells (primary or metastatic) by immunohistochemistry (DAKO, Carpinteria, CA) prospectively read centrally (after a protocol amendment; 10% or more in the original protocol). Exclusion criteria included symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis, systemic chemotherapy or radiotherapy within 30 days before random assignment, and prior anti-EGFR agents.

The study protocol was approved by the independent ethics committee at participating study centers, and all patients provided written, informed consent before any study-related procedures were performed.

Study Design and Treatment Schedule

This is a phase III, multicenter, randomized controlled trial. The study was not blinded because of the expected skin toxicity related to panitumumab administration. Patients were randomly assigned 1:1 to receive panitumumab plus BSC (panitumumab) or BSC alone (BSC). Random assignment was stratified by ECOG performance status (0 or 1 *v* 2) and region (Western Europe *v* Central and Eastern Europe *v* the rest of the world [Canada, Australia, and New Zealand]). Panitumumab was administered by a 60-minute intravenous infusion at 6 mg/kg once every 2 weeks until patients progressed or unacceptable toxicity developed. Premedication was not required. BSC was defined as the best palliative care per investigator excluding antineoplastic agents.

Objective tumor response was evaluated by central radiology review using modified Response Evaluation Criteria in Solid Tumors[22] at weeks 8, 12, 16, 24, 32, 40, and 48, and every 3 months thereafter until disease progression, and confirmed no less than 4 weeks after the criteria for response were first met. At the discretion of the investigator, patients could be evaluated for radiographic tumor assessment after developing symptoms consistent with disease progression.

All patients were followed for survival approximately every 3 months up to 2 years after random assignment. BSC patients determined by the investigator to have disease progression were eligible to receive panitumumab under a separate study. The cross-over study was included based on prior evidence of activity with panitumumab[15,16,23] and cetuximab.[18,20] Radiographic assessments in the cross-over study were performed by local review.

Statistical Analysis

The primary study end point was progression-free survival (PFS) by blinded central radiology assessment. PFS time was calculated from the day of random assignment until radiologic progression or death. The primary analysis of PFS included tumor assessments after cross over to panitumumab for BSC patients if disease progression was not centrally confirmed while the patient received BSC alone. Cosecondary study end points were best objective response by blinded central review and overall survival (OS) time. OS was calculated from the day of random assignment until death, censoring patients at the last day known to be alive. Additional descriptive secondary end points included time to and duration of response. Safety end points included the incidence of adverse events, infusion reactions, and antipanitumumab antibody formation.

The primary analysis set included all patients randomly assigned (all randomly assigned set). PFS was analyzed at the 5% significance level using a log-rank test stratified by baseline ECOG performance status and region. The study had 90% power for a two-sided 1% significance level test given a hazard ratio (HR; panitumumab relative to BSC) of 0.67. The sample size goal was 430 patients, with an event goal of 362 patients with progressive disease by central review or death. A 1% test of objective response at the primary analysis and a 4% test of OS were prespecified conditional on a significant PFS difference. The primary analysis of OS and an update of objective response rates and duration of response were conducted after a minimum of 12 months of follow-up.

Prospective sensitivity analyses for PFS assessed (1) inclusion of events only in the initial treatment phase (excluding data after cross over in the BSC group), (2) local radiology review, and (3) secondary analysis sets. A post-hoc analysis was performed that imputed unscheduled assessments of radiologic disease progression to the closest scheduled assessment to reduce time ascertainment bias (interval censored).

Kaplan-Meier methodology was used to estimate PFS, OS, and time to and duration of response, including 95% CI for event-free rates and differences in rates. The 95% CI for time-to-event quartiles were calculated per Brookmeyer and Crowley.[24] HRs for PFS and OS were estimated with a Cox proportional hazards regression model adjusted for the randomization factors.

Exploratory subset analyses were conducted for PFS by demography, disease characteristics, EGFR membrane positive staining level (1, 2, 3) or quantity (1% to $<$ 10%, 10% to 100%), and severity of skin-related toxicity. Objective response rates also were assessed by EGFR categories and skin toxicity severity. For all skin toxicity severity analyses, a landmark approach including only patients who were progression free for 28 days or more was used to allow for time to onset. The methods and results of patient-reported outcome assessments are reported online in Appendix B.

Serum antipanitumumab antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA; Amgen, Thousand Oaks, CA) with a sensitivity of 10 ng/mL. The ELISA included an acid dissociation step to disrupt antibody-panitumumab complexes before detection. All programming was performed with SAS version 8 or 9 (SAS Institute, Cary, NC) and StatXact version 6 (Cytel Inc, Cambridge, MA).

RESULTS

Patients

From January 2004 to June 2005, 1,040 patients were screened. Of these, 463 patients were enrolled and randomly assigned (231 to panitumumab and 232 to BSC; Fig 1). Of all patients screened, 38% of patients were ineligible because they did not meet a laboratory-inclusion criterion, and 27% specifically did not meet EGFR-staining criteria. The most common reason for discontinuation was disease progression (75% of patients enrolled onto panitumumab, and 85% of patients enrolled onto BSC). Median follow-up was approximately 35 weeks (range, 15 to 76). In the BSC group, 176 (76%) patients received panitumumab in a cross-over protocol. The median time to

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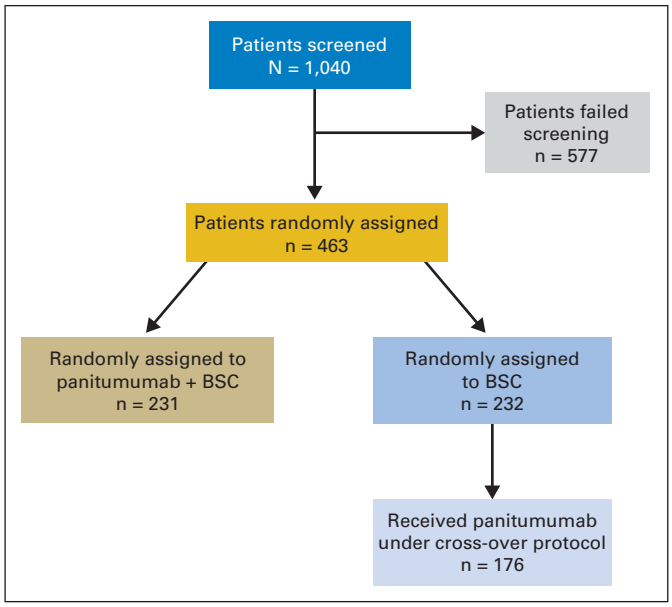

Fig 1. Consolidated Standards of Reporting Trials diagram. BSC, best supportive care.

cross over was 7 weeks (range, 6.6 to 7.3). The median follow-up after cross over was 61 weeks (range, 18 to 103).

Baseline characteristics were balanced between the two groups (Table 1). All but one patient had received at least two prior lines of chemotherapy; 37% had three prior lines of chemotherapy. By immunohistochemistry, nearly half of the patients had EGFR-staining intensity of 2+.

Efficacy

Progression-free survival. A statistically significant improvement in PFS was observed favoring the panitumumab group compared with the BSC group ($P < .0001$, stratified log-rank test, all randomly assigned analysis set; Fig 2). Patients receiving panitumumab had a 46% decrease in the relative progression rate compared with patients receiving BSC (HR, 0.54; 95% CI, 0.44 to 0.66). At week 8, the PFS rates were 49% for panitumumab and 30% for BSC, and a 95% CI for the difference in PFS rates favored panitumumab at all scheduled assessments from weeks 8 to 32.

Median PFS time was 8 (95% CI, 7.9 to 8.4) weeks for panitumumab and 7.3 (95% CI, 7.1 to 7.7) weeks for BSC. Mean (standard error) PFS time was 13.8 (0.8) weeks for panitumumab and 8.5 (0.5) weeks for BSC.

Consistent with the primary analysis, PFS favored panitumumab in all sensitivity analyses (HR range, 0.41 to 0.63; Table A1, online only). These included an interval-censored analysis to compensate for time ascertainment bias. In this analysis, which imputed radiologic disease progression to the nearest scheduled assessment time point, the HR for PFS continued to favor panitumumab (HR, 0.61).

Across all variables examined, the treatment effect on PFS was consistent with that of the primary analysis (Fig 3). By EGFR membrane–staining categories, PFS favored panitumumab (HR range, 0.47 to 0.62), and objective response rates were similar to those in the primary analyses (5% to 10%).

Table 1. Demographics and Baseline Characteristics

Characteristic	Panitumumab Plus BSC (n = 231)		BSC Alone (n = 232)		All Patients (N = 463)	
	No.	%	No.	%	No.	%
Sex						
Men	146	63	148	64	294	63
Women	85	37	84	36	169	37
Race/ethnicity						
White	229	99	228	98	457	99
Other	2	1	4	2	6	1
Age, years						
Median	62		63		62	
Minimum	27		27		27	
Maximum	82		83		83	
Primary diagnosis						
Colon cancer	153	66	157	68	310	67
Rectal cancer	78	34	75	32	153	33
ECOG performance status						
0	107	46	80	34	187	40
1	94	41	115	50	209	45
2	29	13	35	15	64	14
3	1	0	2	1	3	1
Cells with EGFR membrane staining*						
1% to < 10%	57	25	57	25	114	25
10% to 100%	172	74	174	75	346	75
Intensity of EGFR staining†						
3+, strong	47	20	41	18	88	19
2+, moderate	122	53	113	49	235	51
1+, weak	60	26	78	34	138	30
0	0	0	0	0	0	0
Prior adjuvant chemotherapy‡	86	37	78	34	164	35
Prior lines of chemotherapy§						
2 lines	230	100	232	100	462	100
3 lines	84	36	88	38	172	37

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

*By central laboratory immunohistochemistry (DAKO pharmDX; DAKO, Carpinteria, CA). Two patients in the panitumumab group and one patient in the BSC group had < 1% EGFR membrane staining.

†Of those patients with ≥1% EGFR membrane staining by immunohistochemistry.

‡Does not include prior lines of treatment for metastatic colorectal cancer.

§Six percent of patients in each group received more than three prior lines of therapy. These patients were enrolled before a protocol amendment that limited entry criteria to two to three prior lines of therapy.

Objective Response

In the primary analysis, objective response rates favored panitumumab versus BSC, and the difference in response rates was statistically significant ($P < .0001$). After a 12-month minimum follow-up, 22 (10%) patients in the panitumumab group had an objective response (all partial responses). No patients in the BSC group had an objective response. Median time to response was 7.9 (range, 6.7 to 15.6) weeks and median duration of response was 17.0 (range, 7.9 to 76.7) weeks. An additional 62 (27%) patients in the panitumumab group and 23 (10%) patients in the BSC group had a best response of stable disease. Similar activity was observed in the cross-over group.

It is known from previous studies that disease stabilization in chemorefractory metastatic colorectal cancer is clinically meaningful.[10,20] To explore the role of stable disease on the treatment effect of

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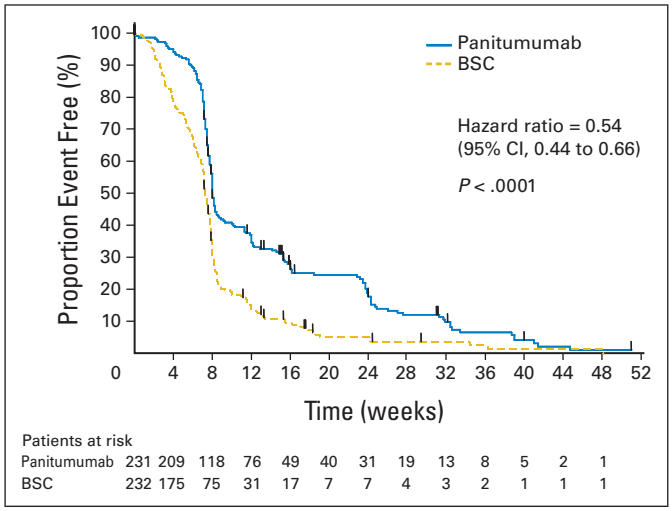

Fig 2. Progression-free survival (all randomly assigned analysis set). BSC, best supportive care.

panitumumab on PFS, an analysis was conducted removing responding patients from the panitumumab group. Using this approach, the HR for PFS was 0.63 (95% CI, 0.52 to 0.77; $P < .0001$), indicating that approximately 80% (1 − 0.63/1 − 0.54) of the treatment effect on PFS was due to nonresponders.

Overall Survival

In the primary analysis of OS, a total of 380 (82%) had died (186 [81%] patients in the panitumumab group and 194 [84%] patients in the BSC group). The minimum follow-up time was 52 weeks, with a median follow-up time of 72 weeks for all patients (range, 52 to 113 weeks). No significant difference was observed between groups (HR, 1.00; 95% CI, 0.82 to 1.22; $P = .81$, stratified log-rank test; Fig 4A).

Subset Analyses

Among patients in the panitumumab group, PFS appeared to favor patients with a worst severity of grade 2 to 4 versus grade 1 skin toxicity (HR, 0.62; 95% CI, 0.44 to 0.88). Nineteen (86%) of 22 responders had a maximum skin toxicity severity of either grade 2 or 3, and the remaining three (14%) responders had a maximum skin-toxicity severity of grade 1. Additionally, OS favored patients with a skin toxicity of grade 2 to 4 versus grade 1 (Fig 4B).

Safety

The incidence of frequent adverse events is provided in Table 2. Two patients did not receive panitumumab and were included in the BSC group for safety analyses. Skin-related toxicities occurred in 90% of patients in the panitumumab group and in 9% of patients in the BSC group. One patient in the panitumumab group discontinued treatment because of grade 2 dermatitis acneiform.

Deaths on study (including the long-term follow-up period) occurred in 186 (81%) patients in the panitumumab group and 194 (84%) patients in the BSC group. Nearly all deaths were related to disease progression. There were no treatment-related deaths.

In the panitumumab group, 36% of patients had declines in blood magnesium levels versus 1% in the BSC group. Grade 3 or 4 hypomagnesemia occurred in 3% of patients and required magnesium supplementation.

One patient discontinued treatment because of a grade 2 hypersensitivity reaction. Of 185 (83%) of 224 patients with both a baseline and post baseline sample available for testing, no patients tested positive for antipanitumumab antibodies.

DISCUSSION

This study was designed to assess the efficacy of an anti-EGFR antibody administered as monotherapy in a randomized setting. The rate

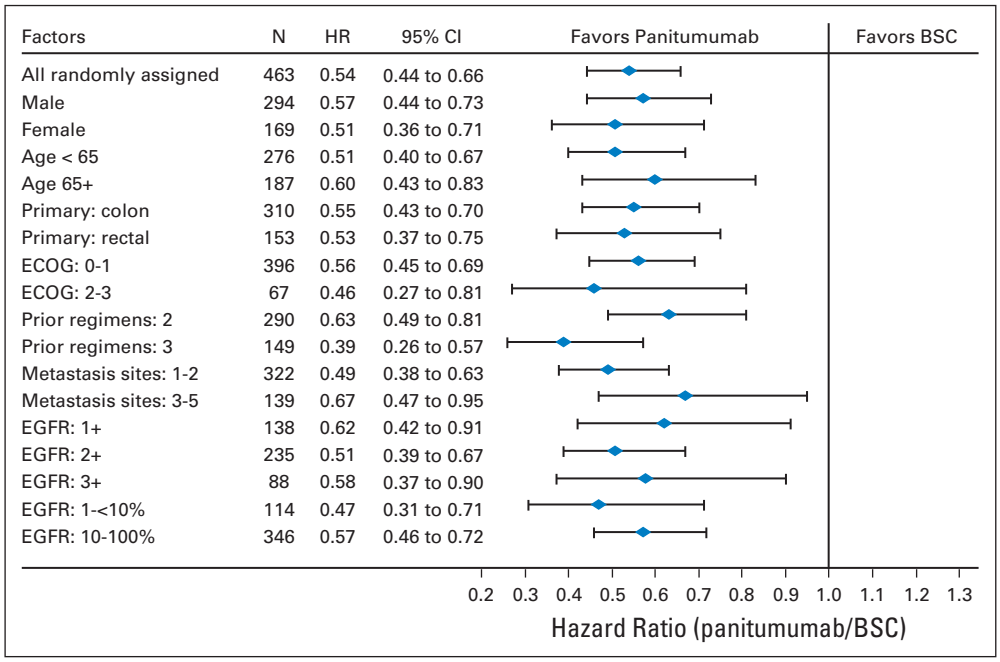

Fig 3. Subset analyses of progression-free survival (PFS). Hazard ratios (HR) for PFS and the 95% CIs for HRs are shown and represented by the diamond and horizontal line, respectively. The HR for the all randomly assigned analysis was adjusted for randomization factors, as described. All other HRs were unadjusted.

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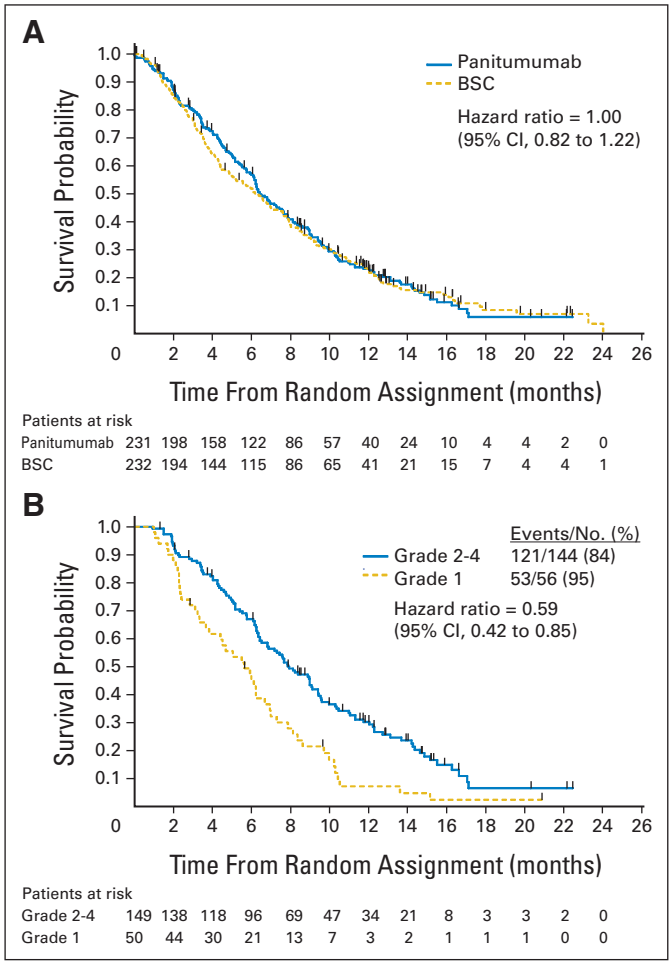

Fig 4. (A) Overall survival (OS)—primary analysis (all randomly assigned analysis set). (B) OS by worst severity of skin-related toxicity. Hazard ratio (grade 2-4 relative to grade 1) was adjusted for randomization factors as described.

of disease progression based on the HR was approximately half in the panitumumab group versus the BSC group. The upper bound of the 95% CI for the PFS HR excluded a PFS rate reduction of less than 33%, which was the hypothesized treatment effect. Sensitivity analyses confirmed the results of the primary analysis. Importantly, a meaningful treatment effect was observed despite the fact that 20 patients on BSC had central progression after cross over.

As expected for patients with advanced refractory disease, more than half progressed in both groups by week 8, the first scheduled visit. Therefore, the difference between median PFS times between groups was small. Although the absolute effect of panitumumab is relatively small, the magnitude of the improvement in PFS as measured by the HR of PFS for panitumumab relative to the BSC control compares favorably with those of recent trials leading to important advances in the treatment of metastatic colorectal cancer, including those testing novel agents in earlier lines of therapy.[6,7,20,25]

The study design was subject to a potential bias favoring panitumumab because of its open-label nature, the availability of panitumumab in the cross-over study, and unscheduled radiographic assessments for patients with symptoms consistent with progressive disease. However, detection bias was mitigated by a blinded central radiology review, and BSC patients were followed in the cross-over study for central progression when investigator assessment of radiologic progression was not centrally confirmed. The post-hoc sensitivity analysis, including imputations of unscheduled assessments for disease progression, also indicated that the treatment effect of panitumumab was likely not confounded by ascertainment bias.

The response rate observed in this study is similar to previously reported response rates of 8.5% to 11.6% in irinotecan and oxaliplatin refractory patients treated with cetuximab monotherapy.[20,25a] Interpretation of the time-to-progression results were limited by the lack of an adequate control for the monotherapy arm in those studies.

Evaluation of response rates alone may underestimate the overall treatment effect of targeted therapies. Despite modest effects on response rates, panitumumab resulted in a clinically significant improvement in PFS. In a post-hoc analysis, PFS in the panitumumab group was similar for patients with either a partial response or stable disease (data on file, Amgen). Moreover, an exploratory analysis excluding patients that experienced a response in the panitumumab group showed that 80% of the overall treatment effect as measured by the HR of PFS was retained. These data suggest that stable disease was associated with significant clinical benefit in these patients.

No differences in OS were observed in this study. The high rate and rapidity of cross over of the BSC patients and the similar activity of panitumumab seen in the cross-over population likely confounded the survival data. To evaluate the cross-over effect, we conducted an exploratory analysis on survival that censored BSC patients who subsequently responded (confirmed or otherwise) after cross over (30 of 176 patients) at the time they received their first dose of panitumumab (data on file, Amgen). In this exploratory analysis, the HR shifted from 1.00 in the primary analysis to 0.86, suggesting that had a cross over not been allowed, a treatment effect on OS may have been observed.

Even though the data have yet to be published, it was recently reported that the primary end point of OS was met in the NCIC CTG CO.17 phase III trial comparing cetuximab with BSC in metastatic colorectal cancer.[25b] Although information on poststudy treatment after progression is not available, that study did not allow for cross over onto active treatment and was conducted in regions where access to cetuximab was limited. Appropriately designed studies with panitumumab are under way to further investigate whether panitumumab treatment improves OS in metastatic colorectal cancer.

Skin rash is a characteristic toxicity of most EGFR inhibitors. Consistent with previous reports, we found an association between clinical efficacy and rash severity.[18,20,26] The incidence of skin toxicity in panitumumab-treated patients is dose-related; however, we have not observed a correlation between dose and severity. The time to worst grade of rash did not differ from the time to any grade of rash (15 *v* 12 days, respectively; data on file, Amgen). Furthermore, whereas skin rash appears to be a pharmacodynamic marker of on-target activity associated with clinical benefit, it also often develops in patients who do not benefit from treatment. Other factors such as the dimerization of erbB family members in tumor cells,[26] EGFR gene copy number or mutations,[26,27] K-*ras* mutations,[27,28] and activation levels of downstream targets[29,30] may influence tumor response to anti-EGFR monoclonal antibodies. The role of these and other potential markers are currently under investigation.

Consistent with the fully human nature of panitumumab, we saw a low incidence of infusion reactions and no antibody formation. This important observation supports the current belief that fully human antibodies have the lowest risk for immunogenicity.[31] Further

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Table 2. Any Grade Adverse Events in at Least 10% of Patients and Corresponding Grade 3/4 Events

	Panitumumab Plus BSC (n = 229)						BSC Alone (n = 234)					
	Any Grade		Grade 3		Grade 4		Any Grade		Grade 3		Grade 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients with at least one adverse event - n	229	100	75	33	4	2	202	86	41	18	4	2
Erythema	146	64	12	5	0	0	2	1	0	0	0	0
Dermatitis acneiform	142	62	17	7	0	0	2	1	0	0	0	0
Pruritus	130	57	5	2	0	0	5	2	0	0	0	0
Skin exfoliation	56	24	5	2	0	0	0	0	0	0	0	0
Fatigue	55	24	10	4	0	0	34	15	7	3	0	0
Paronychia	55	24	3	1	0	0	0	0	0	0	0	0
Abdominal pain	52	23	17	7	0	0	39	17	8	3	3	1
Anorexia	50	22	7	3	1	0	43	18	5	2	0	0
Nausea	50	22	2	1	0	0	36	15	1	0	0	0
Diarrhea	48	21	3	1	0	0	26	11	0	0	0	0
Rash	46	20	2	1	0	0	2	1	0	0	0	0
Skin fissures	45	20	2	1	0	0	1	0	0	0	0	0
Constipation	44	19	6	3	0	0	21	9	2	1	0	0
Vomiting	42	18	5	2	0	0	28	12	2	1	0	0
Dyspnea	33	14	9	4	2	1	31	13	8	3	0	0
Pyrexia	33	14	0	0	0	0	29	12	4	2	1	0
Asthenia	33	14	6	3	1	0	27	12	5	2	0	0
Cough	31	14	1	0	0	0	17	7	0	0	0	0
Back pain	24	10	4	2	0	0	16	7	0	0	0	0
Edema peripheral	24	10	2	1	0	0	13	6	1	0	0	0
General physical health deterioration	23	10	11	5	5	2	8	3	2	1	3	1

NOTE. Two patients in the panitumumab group did not receive panitumumab and were included in the BSC group for all safety analyses.
Abbreviation: BSC, best supportive care.

experience with fully human antibodies is needed to understand their long-term immunogenic potential.

This study did not evaluate the efficacy of panitumumab in patients who progressed after bevacizumab treatment or in patients with undetectable EGFR tumor expression levels. At the time of enrollment, bevacizumab had not yet been approved.[32] Given the different mechanisms of action, cross-resistance of panitumumab with this agent is not expected. Studies evaluating panitumumab activity in patients who progressed after receiving bevacizumab and in patients with EGFR-negative tumors are currently ongoing.

In conclusion, this study demonstrates that panitumumab given every 2 weeks is effective and well tolerated in patients with advanced colorectal cancer that had progressed after standard chemotherapy. Panitumumab represents a new treatment option that can improve PFS with manageable toxicity in patients with chemorefractory metastatic colorectal cancer. These results warrant investigation of panitumumab in combination with earlier lines of therapy in colorectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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®).