Panitumumab Monotherapy in Patients With Previously Treated Metastatic Colorectal Cancer

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Supported by Immunex Corp., a wholly owned subsidiary of Amgen Inc., Thousand Oaks, CA.

Alan Venook has received honoraria and research funding from Amgen. Simon Tchekmedyian has received research funding from Amgen. Imtiaz Malik is a consultant and advisor to Genentech, Amgen, and Pfizer, receives honoraria from Roche, Bristol-Myers Squibb, Imclone, and Genentech, and receives research funding from Sanofi-Aventis, Roche, and Pfizer. Lynn Navale is an employee of Amgen. Rafael Amado is an employee of Amgen. Neal Meropol has received consulting fees unrelated to this study from Amgen.

Prior Presentations: Meropol NJ, Berlin J, Hecht JR, et al. Multicenter study of ABX-EGF monotherapy in patients with metastatic colorectal cancer. Presented at the 39th annual meeting of the American Society of Clinical Oncology, Chicago, Illinois, May 31-June 3, 2003. Hecht JR, Patnaik A, Malik I, et al. ABX-EGF monotherapy in patients (pts) with metastatic colorectal cancer (mCRC): an updated analysis. Presented at the 40th annual meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, June 5–8, 2004. Malik I, Hecht JR, Patnaik A, et al. Safety and efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer (mCRC). Presented at the 41st annual meeting of the American Society of Clinical Oncology, Orlando, Florida, May 13–17, 2005. Berlin J, Van Cutsem E, Peeters M, et al. Safety and efficacy of panitumumab monotherapy in the treatment of metastatic colorectal cancer (mCRC)-summary of results across clinical studies. Presented at the 31st Congress of the European Society for Medical Oncology, Istanbul, Turkey, September 29–October 3, 2006.

BACKGROUND. The safety and efficacy of the fully human antibody panitumumab was evaluated in patients with metastatic colorectal cancer refractory to available therapies.

METHODS. This phase 2 open-label, multicenter study of panitumumab enrolled patients with metastatic colorectal cancer who had progressed on chemotherapy that included a fluoropyrimidine and irinotecan or oxaliplatin, or both. All patients had tumors with $\geq$10% 1+ epidermal growth factor receptor (EGFr) staining by immunohistochemistry. Patients were stratified into 2 strata (high or low staining intensity) and received intravenous panitumumab 2.5 mg/kg weekly 8 of every 9 weeks until disease progression or unacceptable toxicity.

RESULTS. In all, 148 patients received panitumumab, 105 in the high EGFr stratum, 43 in the low EGFr stratum. Overall response by central review was 9% (95% confidence interval [CI], 5%–15%) and was similar between strata. An additional 29% of patients had stable disease. Median progression-free survival was 14 weeks (95% CI, 8–16) and median overall survival was 9 months (95% CI, 6–10). Toxicities were manageable, with skin toxicity reported in 95% of patients (5% grade 3 or 4). Four patients discontinued therapy because of toxicity. No antipanitumumab antibodies were detected. One patient had an infusion reaction but was able to continue therapy.

CONCLUSIONS. Panitumumab given weekly was well tolerated and had single-agent activity in previously treated patients with colorectal cancer. Dermatologic toxicity was common but rarely severe. Ongoing studies will determine panitumumab activity earlier in the course of treatment for colorectal cancer and in combination with other antineoplastic agents. ***Cancer*** **2007;110:980–7.** © *2007 American Cancer Society.*

KEYWORDS: panitumumab, epidermal growth factor receptor, human monoclonal antibody, colorectal cancer.

We thank the patients who participated in this study. We also acknowledge the study coordinators at each of the sites and the following individuals at Amgen Inc.: Monica MacDonald, RN, and Nancy Kenyon, BS, for study management, Tab Hoda, MBBS, for data management, Michael Hagendoorn, MS, for programming support, Bing-Bing Yang, PhD, and Peggy Lum, BS, for pharmacokinetic analyses, Michael Mullenix, PhD, for immunologic analyses, and Mee Rhan Kim, PhD, for assistance with the preparation of the article.

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Received March 8, 2007; revision received April 20, 2007; accepted April 27, 2007.

DOI 10.1002/cncr.22915
Published online 1 August 2007 in Wiley InterScience (www.interscience.wiley.com).

Despite significant improvements in prevention, approximately 148,000 patients will develop colorectal cancer annually and 55,000 will die of the disease, rendering it the second most common cause of cancer death in the US.[1] Over the past decade the introduction of new agents such as irinotecan,[2] oxaliplatin,[3] and bevacizumab (an antibody against vascular endothelial growth factor)[4,5] have prolonged survival, yet nearly all tumors eventually progress. A recent therapeutic approach for the treatment of colorectal cancer is the development of monoclonal antibodies against the epidermal growth factor receptor (EGFr).

The EGFr is a member of the erbB transmembrane tyrosine kinase receptor family that is involved in multiple cellular processes including growth, differentiation, migration, and apoptosis and which may be dysregulated in malignant cells.[6,7] Expression of the EGFr is common in colorectal cancers and is correlated with a worse outcome.[8] Preclinical studies with anti-EGFr agents have demonstrated growth inhibition of colorectal cancer cells in vitro and in vivo.[7,9] Trials with cetuximab, a chimeric immunoglobulin G1 (IgG1) antibody, demonstrated antitumor activity in patients with colorectal cancer who had previously failed cytotoxic chemotherapy. Cetuximab is currently indicated in this setting either in combination with irinotecan or as monotherapy.[10,11] Toxicity was tolerable, with frequent skin rash and occasional infusion reactions.

The murine component of chimeric monoclonal antibodies is recognized as a potential source of immunogenicity and toxicity. Therefore, various strategies have been developed to minimize or eliminate murine content. The XenoMouse is genetically engineered to express only human immunoglobulins.[12] This technology was used to produce fully human antibodies in mice immunized with A431 cells that express high levels of EGFr. A resulting product, panitumumab (ABX-EGF), is a fully human IgG2 monoclonal antibody.[13] This high-affinity antibody blocks EGFr-ligand binding and causes internalization of the receptor.[14,15] Preclinical studies showed that panitumumab inhibited proliferation in multiple EGFr-expressing cancer cell lines and inhibited growth of xenografts.[13]

A phase 1 study of panitumumab given weekly (QW), every 2 weeks (Q2W), and every 3 weeks (Q3W) in patients with solid malignancies showed no dose-limiting toxicities; all patients receiving more than 2 mg/kg QW developed a rash. From pharmacokinetic evaluation, a loading dose was not required, inter- and intrapatient variability was low, and clearance was saturable. Five patients responded, all with colorectal cancer (n = 39; 13%), and an additional 7 (18%) patients with colorectal cancer had stable disease.[16,17] The QW dose for phase 2 testing was selected based on expected target trough concentrations consistent with receptor saturation. We therefore conducted a phase 2 trial of panitumumab in colorectal cancer patients whose tumors had progressed on chemotherapy.

MATERIALS AND METHODS

Study Design

This was a multicenter, open-label, nonrandomized phase 2 trial of panitumumab monotherapy for the treatment of colorectal cancer in patients with EGFr-expressing metastatic colorectal cancer. Patients were assigned to 1 of 2 strata based on the level of EGFr tumor membrane expression as determined by an immunohistochemical kit (Dako, Carpinteria, Calif). In Stratum A, patients had tumors with an EGFr staining intensity of 2+ or 3+ in greater than 10% of evaluated tumor cells (high EGFr expression). In Stratum B, patients had tumors with an EGFr staining intensity of 2+ or 3+ in less than 10% of evaluated tumor cells (low EGFr expression; also required was the sum of EGFr staining intensity of 1+, 2+, or 3+ in greater than 10% of evaluated tumor cells). Stratum B was added as a protocol amendment; this allowed for evaluation of the relation between high and low EGFr tumor expression levels with panitumumab antitumor activity.

Eligibility

Eligible patients were $\geq$18 years old, had pathologically confirmed metastatic adenocarcinoma of the colon or rectum, had bidimensionally measurable disease, and a tumor tissue sample available for immunohistochemical measurement of EGFr expression. Patients had previously received 1 or more fluoropyrimidine-based chemotherapy regimens and either irinotecan, oxaliplatin, or both. Patients also had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate hematologic and organ function: absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L; serum creatinine $\leq$2.2 mg/dL; alkaline phosphatase $\leq$3 times the upper limit of normal; AST and ALT both $\leq$3 times the upper limit of normal ($\leq$5 times if liver metastases were present); and bilirubin $\leq 1.5 \times$ upper limit of normal. Patients who had previously received an EGFr-targeting agent or chemotherapy other than a fluoropyrimidine, irinotecan, or oxaliplatin were excluded from the study.

Institutional review boards for each participating center approved the study before initiation and patients granted written informed consent before any study-related procedures were performed.

Treatment

Panitumumab was produced using a hybridoma expression system and was provided by Immunex Corp. (a fully owned subsidiary of Amgen Inc., Thousand Oaks, Calif). Panitumumab was administered intravenously over 60 minutes at 2.5 mg/kg QW for 8 weeks followed by a 1-week rest (9-week cycle) until disease progression or drug intolerability. Premedication was not required.

Panitumumab infusions were withheld in the event of severe skin toxicity, including skin desquamation or exfoliation involving greater than 25% of body surface area, generalized urticaria, or other skin reactions requiring narcotics, systemic steroids, or other intolerable toxicity. If the toxicities were resolved (ie, patient no longer required systemic steroids or narcotics for rash, desquamation, or exfoliation was reduced to $<$25% of body surface area and was improving, and skin-related toxicity resolved to $\leq$grade 2) within 3 weeks of a missed dose, panitumumab could be reinstated at 1.5 mg/kg QW and increased to 2.0 mg/kg weekly subsequently as tolerated. If the toxicity still met the dose-limiting criteria after 3 weeks or subsequently recurred after reinstitution of therapy, treatment would be permanently discontinued.

Assessments

Physical examination, performance status, and a serum sample for antihuman panitumumab antibodies were taken once per course at Week 1. Vital signs were monitored before panitumumab infusion, during, and at intervals after the completion of infusion. Scans for tumor assessment were taken during the ninth week and every 9 weeks thereafter. Response was assessed by centralized independent review (RadPharm, Princeton, NJ) using the RECIST criteria.[18] Responses were confirmed $\geq$4 weeks after the response criteria were first met. Stable disease was assessed at the first scheduled assessment. Disease control rates were the sum of the objective response and stable disease rates.

Serum antipanitumumab antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA) with a sensitivity of 10 ng/mL (Amgen). The ELISA included an acid dissociation step to disrupt antibody-panitumumab complexes before detection.

For pharmacokinetic analyses, serum panitumumab samples were obtained both pre- and post-dose at specified timepoints throughout the study.

Statistical Analysis

The primary endpoint was objective tumor response after the initial 8-week treatment. After the addition of Stratum B, the sample size was increased from 100 patients to 150 patients; this increased the study power from 80% to 91% and would produce a 2-sided 95% confidence interval (CI) of 5.2% to 14.8% for the objective response rate at 8 weeks if a point estimate of 10% was to be observed.[19]

Secondary endpoints included best overall objective tumor response, progression-free survival, overall survival, incidence of adverse events, and pharmacokinetics. All patients who received at least 1 dose of study drug were included in the efficacy and safety analyses. Fisher exact test was used to compare response rates between strata. Time-to-event outcomes were analyzed using the Kaplan-Meier method, with standard censoring rules; a 2-sided log rank test was used to compare progression-free survival and overall survival between strata. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) v. 2.0.

Exploratory analyses evaluating the association of worst grade of skin toxicity with objective response, progression-free survival, and overall survival were conducted. Patients were included in these analyses if they were progression-free for at least 28 days (to avoid lead-time bias). Day 28 was selected because skin-rash onset was frequently observed before Day 28.

RESULTS

Patient Characteristics

Between March 2002 and July 2003, 150 patients from 380 screened candidates were enrolled among 17 institutions. The most common reasons for screen failure were the inability to meet the EGFr staining criterion (52% of patients) and inadequate hepatic function (15% of patients). Two patients never received treatment with panitumumab; 1 patient did not have adequate hepatic function and the other patient was lost to follow-up. Thus, 148 patients were assessed for safety and efficacy. One hundred five patients (71%) had high EGFr expression levels (Stratum A) and 43 patients (29%) had low EGFr expression (Stratum B).

Baseline demographics and disease characteristics were similar between the 2 strata (Table 1). Most patients were male and white; all patients had an

TABLE 1
Demographics and Disease Characteristics

	Stratum A high EGFr+ (N = 105)	Stratum B low EGFr+ (N = 43)	All patients (N = 148)
Sex no. (%)			
Men	63 (60)	20 (47)	83 (56)
Women	42 (40)	23 (53)	65 (44)
Age, y			
Median (min, max)	58.0 (21, 79)	62.0 (29, 88)	59.5 (21, 88)
Ethnicity no. (%)			
White	85 (81)	35 (81)	120 (81)
Black	9 (9)	5 (12)	14 (9)
Asian	6 (6)	2 (5)	8 (5)
Other	5 (4)	1 (2)	6 (5)
ECOG score no. (%)			
0	29 (28)	8 (19)	37 (25)
1	76 (72)	35 (81)	111 (75)
Primary tumor no. (%)			
Colon	74 (70)	32 (74)	106 (72)
Rectum	31 (30)	11 (26)	42 (28)
Months from primary diagnosis			
Median (min, max)	21.4 (5, 117)	27.2 (4, 88)	24.2 (4, 117)
Prior radiotherapy, no. (%)	30 (29)	18 (42)	48 (32)
Primary chemotherapy no. (%)			
Fluoropyrimidine	105 (100)	43 (100)	148 (100)
Irinotecan	100 (95)	40 (93)	140 (95)
Oxaliplatin	44 (42)	28 (65)	72 (49)
Fluoropyrimidine and irinotecan	61 (58)	14 (33)	75 (51)
All 3 agents	39 (37)	26 (60)	65 (44)
Tumor cells with positive EGFr staining %			
Median (min, max)	90 (25, 100)	40 (10, 100)	90 (10, 100)
Maximum staining intensity no. (%)			
3+ (strong)	64 (61)	2 (5)	66 (45)
2+ (moderate)	41 (39)	12 (28)	53 (36)
1+ (weak)	0 (0)	29 (67)	29 (20)

EGFr indicates epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group.

ECOG score of 0 or 1. The median age was 59.5 years. The number of previous chemotherapy regimens ranged from 1 to 7. All patients had received a fluoropyrimidine (most commonly 5-fluorouracil), 95% had received irinotecan, and 49% had received oxaliplatin. Seventy-five patients (51%) had received a fluoropyrimidine and irinotecan (double failures), and 65 patients (44%) had received all 3 agents together or in various combinations (triple failures).

Efficacy

Objective response rates

After 8 weeks of treatment, 10 of 148 patients (7%; 95% CI, 3–12) had a partial response by central review (Table 2). The overall response rate by central assessment was 9% (95% CI, 5–15) (Table 2). The overall stable disease rate was 29% and the overall disease control rate was 38%. The response rates were not significantly different by EGFr staining stratum ($P = .20$ by Fisher 2-sided exact test; by central review, 7% for high EGFr+ and 14% for low EGFr+). Response and stable disease rates by local assessment were similar.

An exploratory analysis was performed on both prior chemotherapy subgroups, double failures (n = 75 patients), and triple failures (n = 65 patients). Across the entire study the response rate was 8% (95% CI, 3–17) in the double failures and 11% (95% CI, 4–21) in the triple failures. These rates were similar to the overall study response rate.

Progression-free and overall survival

At the time of this analysis, 95% of patients had a progression-free survival event and 89% of patients had a death event. Median progression-free survival time was 14 (95% CI, 8–16) weeks. No significant differences in progression-free survival were observed between Stratum A (high EGFr) and Stratum B (low EGFr) (Fig. 1, top). Median overall survival time was 8.6 (95% CI, 5.9–9.8) months with no differences observed between strata (Fig. 1, bottom).

An exploratory analysis examined the association of skin toxicity with outcome. Of the 13 responders, 2 patients had a maximum grade of 0–1, and 11 had a maximum grade of 2–4. Among nonresponders, 60 patients had a maximum grade of 0–1 and 65 had a maximum grade of 2–4. Patients with a maximum skin toxicity of grade 2–4 had better progression-free survival (hazard ratio [HR], 0.67; 95% CI, 0.50–0.90) and overall survival (HR, 0.72; 95% CI, 0.54–0.97) compared with those with a maximum grade of 0–1 (Fig. 2).

Safety

The most common adverse events are shown in Table 3. Four patients (3%) died during treatment; none of these deaths were considered related to panitumumab. One patient had an infusion reaction with severe dyspnea, flushing, and rigors after the second infusion of panitumumab and received meperidine, lorazepam, and diphenhydramine. This patient received 2 additional weekly infusions of panitumumab with premedication without further events.

As expected given the biology of EGFr inhibitors, skin-related adverse events were common, but were seldom severe. The most common toxicities involving the integument were rash, pruritus, dry skin, and dermatitis (Table 3). Overall, 95% of patients experienced a skin-related toxicity during treatment; these rashes were generally described as follicular, macular, and/or papular. Most were grade 1 or 2 in severity.

TABLE 2
Objective Response Rates

	Central assessment			Local assessment		
	Stratum A: high EGFr+ (N = 105)	Stratum B: Low EGFr+ (N = 43)	All patients (N = 148)	Stratum A: high EGFr+ (N = 105)	Stratum B: low EGFr+ (N = 43)	All patients (N = 148)
Objective response rate at week 8 no. (%)*	5 (5)	5 (12)	10 (7)	11 (10)	3 (7)	14 (9)
Overall objective response rate no. (%)						
Complete response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	7 (7)	6 (14)	13 (9)	12 (11)	4 (9)	16 (11)
Stable disease	36 (34)	7 (16)	43 (29)	39 (37)	14 (33)	53 (36)
Progressive disease	35 (33)	24 (56)	59 (40)	46 (44)	24 (56)	70 (47)
Unevaluable†	1 (1)	1 (2)	2 (1)	2 (2)	0 (0)	2 (1)
Not done‡	26 (25)	5 (12)	31 (21)	6 (6)	1 (2)	7 (5)

EGFr indicates epidermal growth factor receptor.

* Partial responses; All responses were confirmed 4 weeks after response criteria were first met.

† Unevaluable, poor quality scans, missing image windows, assessment of SD or PR prior to 8 weeks.

‡ Not done, scans were not available (patients discontinued treatment before their first assessment or did not come in for the disease assessment).

Four patients required narcotic analgesics to treat rash-associated pain and 5 were given systemic steroids for symptomatic relief. Four patients required permanent discontinuation because of nailbed infection or rash. Four patients required dose alterations because of rash and pruritus. Eye-related toxicities occurred in 27 (18%) of patients, with the most frequent being conjunctivitis in 6% of patients.

Median time to worst skin-related toxicity was 12 (95% CI, 9–14) days. Median duration of grade 3 and 4 skin-related toxicities was 20 (95% CI, 10-NE) days.

Fatigue was reported in approximately 50% of patients and was grade 3 or higher in 9% of patients. Mild-to-moderate nausea, diarrhea, abdominal pain, and vomiting were also observed. Mild transient decreases in serum potassium were seen in 13% of patients. Serum magnesium levels were not formally collected in this study; however, hypomagnesemia was reported in 4 patients (3%): 3 with grade 1 severity and 1 with grade 2 severity.

Eight patients (5%) discontinued treatment because of an adverse event. In 4 (3%) of these patients the events were considered related to panitumumab: grade 3 fatigue, grade 1 nailbed infection, grade 3 rash, and grade 2 rash. The other events were either unrelated disorders or manifestations of the primary disease.

Of the 148 treated patients, 142 had a predose baseline sample for antibody evaluation. No baseline sample tested seropositive for antihuman panitumumab antibodies. One hundred seven patients had 1 or more postdose samples (taken either during treatment or during follow-up) tested for antipanitumumab antibodies. None were detected in any samples.

Pharmacokinetics

Serum panitumumab concentrations throughout the study are shown in Figure 3. After 1 dose of panitumumab the mean trough concentration (C_{min}) was above the IC_{90} from xenograft models.[16] Mean concentrations of panitumumab at steady state were approximately 55 μg/mL at trough and 120 μg/mL at peak. No apparent differences in the pharmacokinetics of panitumumab were observed between the strata.

DISCUSSION

These data demonstrate that panitumumab as a single agent has clinical activity in patients with pretreated metastatic colorectal cancer. In 148 patients receiving weekly panitumumab, the response rate was 9% and progression-free survival was 14 weeks. The number of prior regimens did not appear to affect the response rate. Treatment was well tolerated, with mild to moderate skin rash being common. These clinical results appear similar to those observed with cetuximab, with single-agent response rates of 8.8 to 10.8%.[10,11] Furthermore, Van Cutsem et al.[20] recently described results of a randomized clinical trial of panitumumab compared with best supportive care that showed an improvement in progression-free survival with panitumumab. On the basis of the results of this randomized trial,

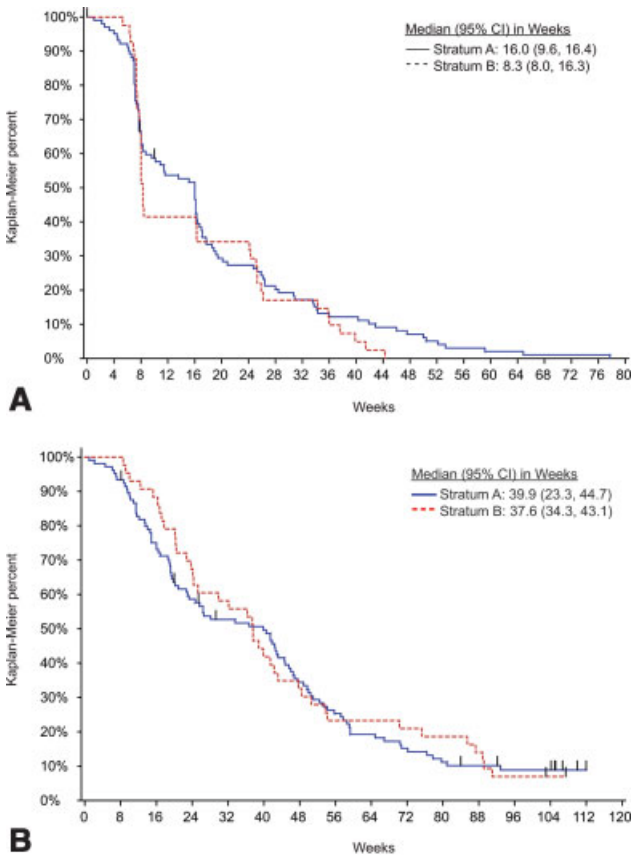

FIGURE 1. Upper: Progression-free survival by stratum, measured from the date of the first dose of panitumumab to the first date of observed progression or death. Stratum A, solid line; Stratum B, dashed line. Censored observations are indicated by a vertical tick mark. Lower: Overall survival by stratum, measured from the date of the first dose of panitumumab to date of death. Stratum A, solid line; Stratum B, dashed line. Censored observations are indicated by a vertical tick mark.

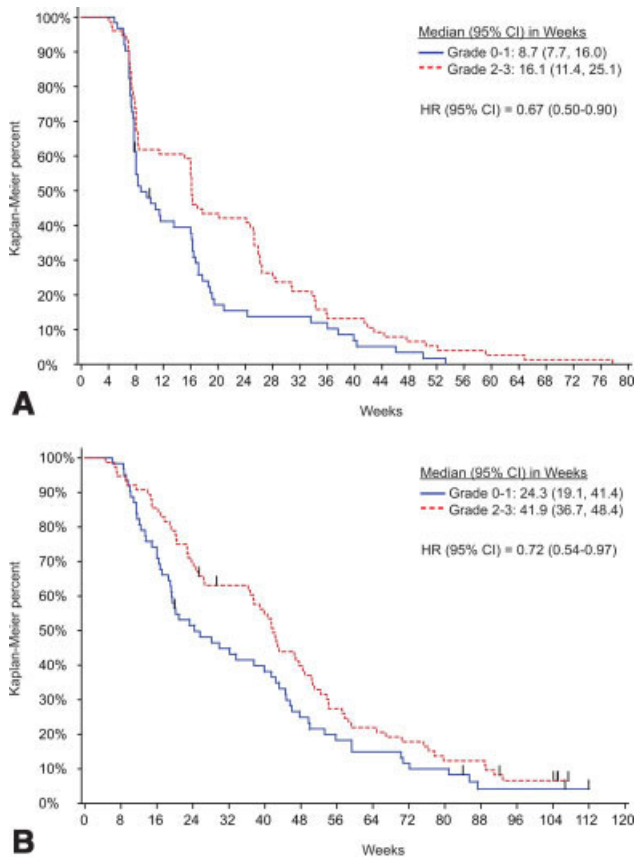

FIGURE 2. Upper: Progression-free survival by worst grade of skin toxicity. Patients were included if they were progression-free for at least 28 days (to avoid lead-time bias). Censored observations are indicated by a vertical tick mark. Lower: Overall survival by worst grade of skin toxicity.

panitumumab was recently approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer in patients who progressed after fluoropyrimidine-, irinotecan-, and oxaliplatin-containing chemotherapy.[21] As with cetuximab, the incidence and severity of rash in our study appears to be associated with response and progression-free survival, whereas EGFr staining level does not.[22]

Treatment with panitumumab resulted in few severe toxicities. Fatigue was the only grade 3–4 event that occurred in greater than 5% of patients. Integumentary side effects, presumably because of EGFr inhibition in skin,[7] are nearly universal but rarely lead to drug discontinuation. Treatment of EGFr rash usually consists of antibiotics or topical steroids but remains anecdotal and is ripe for rigorous investigation.

Panitumumab is the first fully human anti-EGFr antibody to reach advanced clinical evaluation in patients with cancer. It was developed with the rationale that a fully human antibody would be less immunogenic.[13] Monotherapy with the chimeric antibody cetuximab results in severe infusion reactions in 3% of patients.[23] No antipanitumumab antibodies were detected in this study. Only a single infusion reaction was reported, which did not require treatment discontinuation.

The selection of a weekly dose and schedule of panitumumab for this study was largely based on xenograft modeling data and safety results from the phase 1 monotherapy panitumumab study available at the time of study inception.[16,17] The approved dosage of panitumumab is 6.0 mg/kg Q2W.[21] Current clinical data suggest similar activity with both schedules in refractory metastatic colorectal cancer patients.[20,24]

One important limitation to this study is the discrepancy in missing scans as reported by central versus local review, 21% versus 5%, respectively (Table

TABLE 3
Any and Treatment-Related Adverse Events

	Any event* (N = 148)			Treatment-Related event (N = 148)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Patients with any event, no. (%)	148 (100)	61 (41)	11 (7)	142 (96)	17 (11)	1 (1)
Fatigue	75 (51)	13 (9)	0 (0)	41 (28)	4 (3)	0 (0)
Nausea	58 (39)	5 (3)	0 (0)	23 (16)	1 (1)	0 (0)
Diarrhea	53 (36)	3 (2)	0 (0)	32 (22)	1 (1)	0 (0)
Abdominal pain	44 (30)	5 (3)	0 (0)	9 (6)	0 (0)	0 (0)
Anorexia	40 (27)	2 (1)	1 (1)	18 (12)	0 (0)	0 (0)
Vomiting	40 (27)	5 (3)	0 (0)	10 (7)	2 (1)	0 (0)
Constipation	37 (25)	2 (1)	0 (0)	4 (3)	0 (0)	0 (0)
Cough	26 (18)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)
Dyspnea	21 (14)	4 (3)	0 (0)	3 (2)	1 (1)	0 (0)
Peripheral edema	21 (14)	2 (1)	0 (0)	5 (3)	0 (0)	0 (0)
Pyrexia	21 (14)	1 (1)	0 (0)	6 (4)	0 (0)	0 (0)
Arthralgia	20 (14)	1 (1)	0 (0)	2 (1)	0 (0)	0 (0)
Integumentary toxicity no. (%)						
Rash	119 (80)	5 (3)	0 (0)	116 (78)	5 (3)	0 (0)
Pruritus	50 (34)	2 (1)	0 (0)	50 (34)	2 (1)	0 (0)
Dry skin	38 (26)	0 (0)	0 (0)	38 (26)	0 (0)	0 (0)
Stomatitis	26 (18)	0 (0)	0 (0)	21 (14)	0 (0)	0 (0)
Dermatitis acneiform	24 (16)	0 (0)	0 (0)	24 (16)	0 (0)	0 (0)
Skin desquamation	19 (13)	0 (0)	0 (0)	19 (13)	0 (0)	0 (0)
Paronychia	16 (11)	0 (0)	0 (0)	15 (10)	0 (0)	0 (0)

* Included both related and unrelated events. Graded NCI-CTCAE v. 2.0.

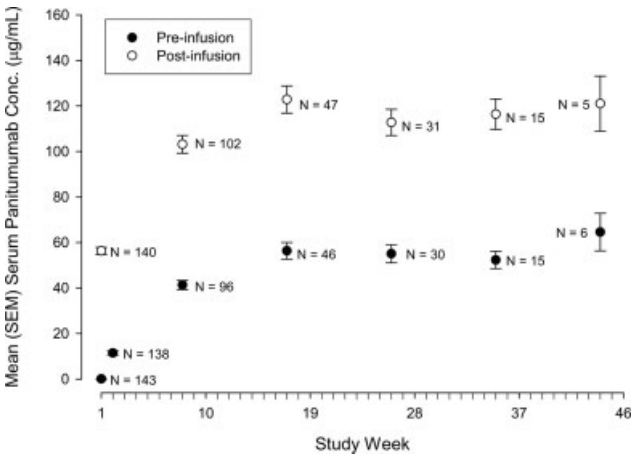

FIGURE 3. Serum panitumumab pharmacokinetics with 2.5 mg/kg weekly dose of panitumumab.

2). The missing assessments by central review were a consequence of multiple factors, including scans not sent by the investigator to the central facility, inadequate treatment duration, and/or early disease progression. This did not affect the response rate, as per protocol, patients with missing scans were considered nonresponders and all 148 patients treated were included in the denominator for response rate calculations.

Ongoing clinical development of panitumumab in patients with colorectal cancer will address the activity of combinations with chemotherapy, less frequent dosing schedules, and use as initial treatment of metastatic disease.[16,25–27] Given preclinical and clinical evidence of augmented activity when EGFr and VEGF inhibitors are administered together,[28,29] a randomized phase 3 trial was undertaken to examine the addition of panitumumab to standard chemotherapy and bevacizumab in previously untreated metastatic colorectal cancer (the PACCE trial).[30] A recent press release from the study sponsor based on an interim analysis indicated a negative effect on progression-free and overall survival with the addition of panitumumab[31]; the implications of this announcement for the development of antibody combinations must await full data presentation and analysis.

Because EGFr monoclonal antibodies appear to benefit only a minority of patients, there is a pressing need to identify the characteristics of patients and tumors most likely to respond to this treatment. Skin rash appears to serve as a surrogate pharmacodynamic marker, but cannot be used for patient selection. As EGFr expression by immunohistochemistry

is not predictive,[22,26,32] alternate markers are being sought. Although EGFr mutations have been associated with response in lung cancers to small molecule TK inhibitors, these mutations are uncommon in colorectal cancer.[33–36] Preliminary evidence that *EGFr* gene amplification, lack of *KRAS* mutation, or ligand expression may predict for response to anti-EGFr antibodies has been suggested and requires confirmation.[37–39] Given the myriad of treatment options, each with modest activity, there is a great opportunity and need to conduct studies that will help guide the rational selection of these agents for individual patients.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* 2006;56:106–130.
2. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med.* 2000;343:905–914.
3. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2004;22:23–30.
4. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350: 2335–2342.
5. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group study E3200. *J Clin Oncol.* 2007;25:1539–1544.
6. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol.* 2001;2:127–137.
7. Mendelsohn J. Targeting the epidermal growth factor receptor for cancer therapy. *J Clin Oncol.* 2002;20:1S–13S.
8. Mayer A, Takimoto M, Fritz E, et al. The prognostic significance of proliferating cell nuclear antigen, epidermal growth factor receptor, and mdr gene expression in colorectal cancer. *Cancer.* 1993;71:2454–2460.
9. Cohen SJ, Cohen RB, Meropol NJ. Targeting signal transduction pathways in colorectal cancer—more than skin deep. *J Clin Oncol.* 2005;23:5374–5385.
10. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337–345.
11. Saltz LB, Meropol NJ, Loehrer PJ Sr, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol.* 2004;22:1201–1208.
12. Mendez MJ, Green LL, Corvalan JR, et al. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nat Genet.* 1997;15:146–156.
13. Yang XD, Jia XC, Corvalan JR, et al. Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy. *Cancer Res.* 1999;59:1236–1243.
14. Lynch DH, Yang XD. Therapeutic potential of ABX-EGF: a fully human anti-epidermal growth factor receptor monoclonal antibody for cancer treatment. *Semin Oncol.* 2002;29:47–50.
15. Foltz I, King CT, Liang M. Panitumumab induces internalization of the epidermal growth factor receptor (EGFr). AACR-NCI-EORTC International Conference. Molecular Targets and Cancer Therapeutics (Proceedings). 2005:B43. Abstract B43.
16. Weiner LM, Belldegrun A, Rowinsky E, et al. Updated results from a dose and schedule study of Panitumumab (ABX-EGF) monotherapy, in patients with advanced solid malignancies. *J Clin Oncol.* 2005;23(suppl 16):3059a. Abstract 3059.
17. Foon KA, Yang XD, Weiner LM, et al. Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal growth factor receptor antibody. *Int J Radiat Oncol Biol Phys.* 2004;58:984–990.
18. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–216.
19. Collette D. Modelling Binary Data. London: Chapman and Hall; 1991.
20. Van Cutsem E, Peeters M, Siena S, et al. Open-label, randomized, phase 3 clinical trial of panitumumab plus best supportive care versus best supportive care in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007;25:1658–1664.
21. Vectibix. Prescribing Information. Amgen, Thousand Oaks, CA; 2006.
22. Meropol NJ. Epidermal growth factor receptor inhibitors in colorectal cancer: it's time to get back on target. *J Clin Oncol.* 2005;23:1791–1793.
23. Erbitux. Prescribing Information, Imclone Systems, Branchburg, NJ; 2006.
24. Berlin J, Van Cutsem E, Peeters M, et al. Safety and efficacy of panitumumab monotherapy in the treatment of metastatic colorectal cancer (mCRC)-summary of results across clinical studies. Ann Oncol 31st ESMO Conference Proceedings. 2006:326O. Abstract 326O.
25. Berlin J, Neubauer M, Swanson P, et al. Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing $>$ 10% epidermal growth factor receptor (EGFr). *J Clin Oncol.* 2006;24(suppl 18):3548. Abstract 3548.
26. Hecht JR, Mitchell E, Baranda J, et al. Panitumumab activity in metastatic colorectal cancer (mCRC) patients (pts) with low or negative tumor epidermal growth factor receptor (EGFr) levels: an updated analysis. *J Clin Oncol.* 2007;24(suppl 18):3547a. Abstract 3547.
27. Hecht JR, Posey J, Tchekmedyian S, et al. Panitumumab in combination with 5-fluorouracil, leucovorin, and irinotecan (IFL) or FOLFIRI for first-line treatment of metastatic colorectal cancer (mCRC). *Proc Gastrointestinal Cancers Symposium.* 2006:237. Abstract 237.
28. Shaheen RM, Ahmad SA, Liu W, et al. Inhibited growth of colon cancer carcinomatosis by antibodies to vascular endothelial and epidermal growth factor receptors. *Br J Cancer.* 2001;85:584–589.
29. Saltz LB, Lenz H, Hochster H, et al. Randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer. *J Clin Oncol.* 2005;23(suppl 16):3508. Abstract 3508.

30. Wainberg Z, Hecht JR. A phase III randomized, open-label, controlled trial of chemotherapy and bevacizumab with or without panitumumab in the first-line treatment of patients with metastatic colorectal cancer. *Clin Colorectal Cancer.* 2006;5:363–367.
31. Amgen Discontinues Vectibix(TM) Treatment In PACCE Trial Evaluating Vectibix(TM) As Part Of Triple Combination Regimen. Available at URL: http://www.amgen.com/media/media_pr_detail.jsp?releaseID=977186.
32. Chung KY, Shia J, Kemeny NE, et al. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol.* 2005;23:1803–1810.
33. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004;350:2129–2139.
34. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med.* 2005;2:e73.
35. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. *J Clin Oncol.* 2005;23:2556–2568.
36. Barber TD, Vogelstein B, Kinzler KW, et al. Somatic mutations of EGFR in colorectal cancers and glioblastomas. *N Engl J Med.* 2004;351:2883.
37. Moroni M, Veronese S, Benvenuti S, et al. Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorecta cancer: a cohort study. *Lancet Oncol.* 2005;6:279–286.
38. Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res.* 2006;66:3992–3995.
39. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-RAS mutation status are associated with disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol.* In press.