

# Epidermal Growth Factor Receptor Monoclonal Antibodies for the Treatment of Metastatic Colorectal Cancer

Gary W. Jean, Pharm.D., and Sachin R. Shah, Pharm.D.

Treatment of metastatic colorectal disease has evolved over the last decade. Two epidermal growth factor receptor (EGFR) monoclonal antibodies—cetuximab and panitumumab—have been developed in an effort to provide yet another therapeutic option. The EGFR is a transmembrane glycoprotein, expressed constitutively throughout the body and found on many epithelial tissues. The monoclonal antibodies bind to and inhibit the activation of the receptor in the body. This inhibition prevents tumor cell growth, angiogenesis, invasion, and metastasis, and induces apoptosis. Cetuximab and panitumumab exhibit nonlinear pharmacokinetics. Both monoclonal antibodies are approved for the treatment of refractory metastatic colorectal cancer. Cetuximab in combination with irinotecan has significantly better response rates and progression-free survival compared with those of cetuximab or irinotecan alone. Cetuximab and panitumumab as monotherapy have shown significantly better response rates and progression-free survival compared with best supportive care in patients refractory to irinotecan and oxaliplatin. In the Cetuximab Combined with Irinotecan in First Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial, treatment-naïve patients received cetuximab in combination with the chemotherapy regimen infusional leucovorin, fluorouracil, and irinotecan (FOLFIRI) or FOLFIRI alone; the difference in progression-free survival was statistically significant but suggested only a modest benefit over FOLFIRI alone (8.9 vs 8 mo,  $p=0.036$ ). Results of a preplanned analysis of the first 231 events in the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial favored the control group (chemotherapy regimen with folinic acid [leucovorin], fluorouracil, and oxaliplatin [FOLFOX] plus bevacizumab) instead of the control group plus panitumumab. For clinical consideration, many trials have shown that the intensity or absence of EGFR expression is not a clinically significant predictor of outcomes. Development and intensity of a rash are suggested to be a positive predictor of outcomes in patients. The most common adverse events of EGFR monoclonal antibody therapy are rash, diarrhea, and hypomagnesemia. Other serious but not common adverse events include hypersensitivity reactions and pulmonary toxicity. The availability of EGFR monoclonal antibodies has provided another weapon in the arsenal to treat refractory metastatic colorectal cancer. They have shown safety and efficacy in combination with other chemotherapy regimens and as monotherapy; however, their use as metastatic colorectal cancer therapy needs to be further explored.

**Key Words:** cetuximab, panitumumab, epidermal growth factor receptor, EGFR, monoclonal antibodies, metastatic colorectal cancer, adverse events.  
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Colorectal cancer is the third most common cancer among men and women in the United States and has the third highest mortality rate.<sup>1</sup> In 2007, 153,760 new diagnoses of colorectal cancer were expected to be reported in the United States.<sup>1</sup> Twenty percent of these patients will have metastatic disease at the time of diagnosis. Also, 14.9% of patients with stage II or III colon cancer will relapse or have metastatic disease at 3 years after adjuvant chemotherapy.<sup>2</sup> More than 52,180 patients were expected to die from colorectal cancer in 2007.<sup>1</sup> The mortality rate has been decreasing steadily, at an average of 1.83% over the past 20 years.<sup>3</sup> Agents such as irinotecan, oxaliplatin, and bevacizumab have significantly improved progression-free survival and overall survival in patients with metastatic colorectal cancer over the last decade.<sup>4-6</sup> Progression-free survival is an important end point, as it shows how long these agents keep the cancer under remission. Even after significant improvement in care, most patients will eventually relapse. Therefore, a need exists for newer agents that have novel mechanisms of action.

The epidermal growth factor receptor (EGFR) is a transmembrane cell surface receptor that is expressed on a variety of tissues including the lungs, skin, hair follicles, and gastrointestinal tract. It is a receptor tyrosine kinase that has activity in the signaling pathway promoting cell growth, differentiation, proliferation, and

inhibition of apoptosis. The EGFR is stimulated by transforming growth factor (TGF)- $\alpha$  and epidermal growth factor (EGF). Approximately 25–77% of tumor cells associated with colorectal cancer overexpress EGFR.<sup>7,8</sup> Overexpression of EGFR results in angiogenesis, invasion, and metastasis.<sup>9</sup> Two monoclonal antibodies are available for the treatment of colorectal cancer that inhibit EGFR, and both cetuximab and panitumumab have been approved for the treatment of refractory metastatic colorectal cancer.

To gain a better understanding of EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer, a literature search using the PubMed-MEDLINE database (January 1966–May 2007) and American Society of Clinical Oncology (ASCO), ASCO–Gastrointestinal Cancer Symposium, and American Association for Cancer Research abstracts (2003–2007) was performed to identify relevant articles. The search included the terms cetuximab, panitumumab, and colorectal. In addition, references from articles were screened for other relevant literature. A press release issued in March 2007 for a panitumumab trial was also reviewed.

### Pharmacology

The EGFR is expressed constitutively throughout the body and found on many epithelial tissues. The EGFR is a 170-kD transmembrane glycoprotein. It has EGF- and TGF- $\alpha$ -dependent intracellular tyrosine kinase activity. It has three major regions consisting of extracellular, transmembrane, and cytoplasmic domains. The EGF and TGF- $\alpha$  binding induces homodimerization of the EGFR or heterodimerization of EGFR family members (EGFR<sub>1</sub>–EGFR<sub>4</sub>). This receptor dimerization results in the phosphorylation of tyrosine kinases associated with this receptor.<sup>10</sup> Epidermal growth factor is important for the progression of cancer, using mechanisms such as the proliferation of tumor cells, inhibition of apoptosis, angiogenesis, invasion, and metastasis.<sup>9</sup>

Both monoclonal antibodies, cetuximab and panitumumab, bind to the extracellular domain of EGFR and compete with ligand binding to the receptor. They have a high affinity for the EGFR, which prevents the binding of the endogenous EGF and TGF- $\alpha$  to the receptor.<sup>9,11</sup> For example, cetuximab has a 2-log higher affinity for the EGFR when compared with EGF and TGF- $\alpha$ .<sup>12</sup> Binding of the EGFR monoclonal antibodies ultimately results in the inhibition of cell growth

From the School of Pharmacy, Texas Tech University Health Sciences Center, Dallas, Texas (both authors).

Address reprint requests to Sachin R. Shah, Pharm.D., BCOP, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, School of Pharmacy, 4500 South Lancaster, Building 7, Room 119A, Dallas, TX 75216.

(in G1 phase), angiogenesis, tumor cell invasion, and metastasis. It also induces apoptosis and downregulation of the EGFR.<sup>9, 13, 14</sup> The EGFR monoclonal antibodies all have been shown to augment the antitumor effects of chemotherapy and radiation therapy. In the human tumor cell xenograph model, EGFR monoclonal antibodies markedly augmented the antitumor effects of cisplatin, doxorubicin, paclitaxel, topotecan, and irinotecan.<sup>15–18</sup> Cetuximab in combination with irinotecan has shown enhanced growth inhibition in tumors insensitive to irinotecan or cetuximab alone.<sup>17</sup> The mechanisms that appear to contribute to the enhanced cytotoxicity of cetuximab in chemotherapy or radiation therapy are programmed cell death, reduced angiogenesis, and tumor cell invasion. Cetuximab is suggested to enhance programmed cell death by inhibiting the cell survival pathway and DNA repair mechanism.<sup>17</sup>

Cetuximab is a recombinant, human-mouse chimeric immunoglobulin-G1 monoclonal antibody that binds specifically to the EGFR—human epidermal growth receptor-1 on both normal and tumor cells.<sup>14</sup> Cetuximab is 65–95% human antibodies consisting of a murine antigen-binding variable region fused with human constant domains.<sup>19</sup> Panitumumab is the first fully human monoclonal antibody for the inhibition of EGFR. It is a recombinant human immunoglobulin-G2  $\kappa$  monoclonal antibody that binds EGFR.<sup>13</sup>

### Pharmacokinetics and Pharmacodynamics

The EGFR monoclonal antibodies are administered intravenously. Cetuximab's maximum concentration ( $C_{max}$ ) after a loading dose infusion of 400 mg/m<sup>2</sup> over 2 hours is a mean of 184  $\mu$ g/ml (range 92–327  $\mu$ g/ml). A 1-hour infusion of the maintenance dose of 250 mg/m<sup>2</sup> produces a mean  $C_{max}$  of 140  $\mu$ g/ml (range 120–170  $\mu$ g/ml). In a phase I trial, the area under the plasma concentration–time curve (AUC) was recorded at levels of 12,520–17,337  $\mu$ g•hour/ml between weeks 1 and 4, when patients received the recommended dosage.<sup>9</sup> The AUC of cetuximab increased in a greater than dose-proportional manner when the dose increased from 20 to 400 mg/m<sup>2</sup>. With use of the recommended dosage regimen, patients usually reach steady state by the third weekly infusion, resulting in mean peak and trough concentrations across two studies that ranged from 168–235  $\mu$ g/ml and 41–85  $\mu$ g/ml, respectively.<sup>9, 14</sup> The

same two phase I trials revealed that cetuximab has a mean volume of distribution that is approximately equivalent to plasma volume at intravenous doses of 20–100 mg/m<sup>2</sup> (45.2–61.9 ml/kg).<sup>9, 14</sup>

Similar to cetuximab, panitumumab exhibited nonlinear pharmacokinetics when it was evaluated alone in clinical trials. The AUC was found to increase in a greater than dose-proportional manner; however, at doses greater than 2 mg/kg, the AUC increased in an approximately proportional manner.<sup>11, 13</sup> According to the package insert, the mean  $C_{max}$  after the recommended dosage of 6 mg/kg once every 2 weeks is 213  $\pm$  59  $\mu$ g/ml, and the mean  $\pm$  SD AUC after the same dosage is 1306  $\pm$  374  $\mu$ g•day/ml. Also determined was that after the recommended dosage and interval, steady-state concentrations were attained by the third infusion.<sup>13</sup>

The EGFR is expressed on tumor cells as well as normal cells, which include the liver and skin. Cetuximab and panitumumab have been hypothesized to be removed through internalization of the drug-receptor complex.<sup>9</sup> Overall, clearance of both drugs decreases with increasing doses, suggesting saturation of the metabolic pathway.<sup>18</sup> In a phase I study of cetuximab, a small difference in clearance was observed with 200- and 400-mg/m<sup>2</sup> doses.<sup>18</sup> The clearance of the drug decreased from 0.08 to 0.02 L/hour/m<sup>2</sup> as the dose increased from 20 to 200 mg/m<sup>2</sup>, and it appeared to plateau with greater than 200-mg/m<sup>2</sup> doses.<sup>14</sup> Similarly, during pharmacokinetic evaluation of panitumumab, the clearance was found to decrease from 30.6 to 4.6 ml/day/kg as the dose increased from 0.75 to 9 mg/kg.<sup>13</sup> During clinical trials, it was revealed that female patients have a 25% lower intrinsic clearance of cetuximab; however, this difference does not warrant a modification in the dose.<sup>14</sup> The elimination half-life of cetuximab after a 2-hour infusion of 400 mg/m<sup>2</sup> was a mean of 4 days (range 1.7–9.8 days).<sup>14</sup> The elimination half-life of panitumumab is approximately 7.5 days (range 3.6–10.9 days; Table 1).<sup>20</sup> The differences in the half-lives of these two monoclonal antibodies may be responsible for once-weekly dosing of cetuximab versus every-other-week dosing of panitumumab. However, a couple of studies suggest that cetuximab 500 mg/m<sup>2</sup> alone or in combination with irinotecan could be given every 2 weeks in the future.<sup>21, 22</sup> The need for dosage modification was evaluated in a variety of conditions including race-ethnicity, sex, and mild renal and hepatic impairment, and no need for

**Table 1. Comparison of Cetuximab and Panitumumab Pharmacokinetic Parameters<sup>9, 13, 14, 18, 20</sup>**

Parameter	Cetuximab	Panitumumab
Peak concentration ( $\mu\text{g/ml}$ )	168–235 <sup>a</sup>	154–272 <sup>b</sup>
AUC ( $\mu\text{g}\cdot\text{day/ml}$ )	522–722	1306
Volume of distribution (ml/kg)	45.2–61.9	41.8
Elimination half-life (days)	4	~7.5
Clearance (ml/kg/day)	9.0	4.9

Data are mean or range of means from the referenced articles.

AUC = area under the concentration-time curve.

<sup>a</sup>After a steady-state 2-hr infusion of 400 mg/m<sup>2</sup> and a 1-hr infusion of 250 mg/m<sup>2</sup>.

<sup>b</sup>After a steady-state 6-mg/kg, 1-hr infusion.

any modification was found.<sup>13</sup>

One group evaluated the addition of cetuximab to irinotecan and the effects on the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38).<sup>23</sup> In this phase I trial that included eight patients, the addition of cetuximab had no clinically relevant effect on the concentration and pharmacokinetics of irinotecan and its potent metabolite, SN-38. In another study, panitumumab was administered with an irinotecan-based regimen.<sup>24</sup> In this phase II trial, no pharmacokinetic interaction or alteration in irinotecan concentration was seen when panitumumab was administered in combination with the chemotherapy regimen irinotecan, fluorouracil, and leucovorin (IFL) or infusional leucovorin, fluorouracil, and irinotecan (FOLFIRI).<sup>24</sup>

## Clinical Trials

### Previously Treated Patients

Irinotecan, oxaliplatin, and bevacizumab in combination with long-time standard of care fluorouracil and leucovorin have shown significant improvement in the survival rate as first- or second-line therapy in patients with metastatic colorectal cancer compared with fluorouracil alone.<sup>4–6</sup> However, most patients will develop resistance to these therapies. The EGFR monoclonal antibodies have been investigated as another active treatment option in these previously treated patients with metastatic colorectal cancer. The efficacy of cetuximab has been investigated in many phase II and phase III trials.

In the pivotal phase III Bowel Oncology with Cetuximab Antibody (BOND) trial, cetuximab plus irinotecan was evaluated in patients with irinotecan-refractory metastatic colorectal

cancer.<sup>25</sup> It was a randomized, open-label, multicenter trial conducted in 56 centers in 11 European countries. Patients were considered eligible if they had received at least 6 weeks of irinotecan and had documented progression of disease during receipt of this regimen. Patients were also required to have immunohistochemical evidence of EGFR protein expression either in the primary tumor or in a metastatic lesion. The trial randomly assigned 329 patients to receive cetuximab plus irinotecan (218 patients) or cetuximab alone (111 patients). Cetuximab was administered at an initial loading dose of 400 mg/m<sup>2</sup> followed by weekly infusions of 250 mg/m<sup>2</sup>. In the combination group, irinotecan was given at the same dosage as the patient's previous therapy. Patients were continued on the treatment until disease progression or severe adverse event. The primary objective of the study was to compare tumor response based on an intent-to-treat analysis.

Most patients in the trial were male, and the median age was 59 years. Approximately 88% of the patients had Karnofsky performance status score of 80 or higher. In addition, 63% of the patients had previously received oxaliplatin therapy. Results revealed that the combination therapy was superior to the monotherapy, with a response rate of 22.9% (95% confidence interval [CI] 17.5–29.1%) versus 10.8% (95% CI 5.7–18.1%,  $p=0.007$ ). The stable disease rates were 33% and 22%, respectively. The median time to progression was significantly longer in the combination group, at 4.1 months compared with 1.5 months in the monotherapy group. The study revealed a non-statistically significant median overall survival of 8.6 months in the combination group versus 6.9 months in the monotherapy group. Fifty-six (50%) of the patients in the monotherapy group received additional irinotecan after disease progression. Approximately 39% of those patients had partial response or stable disease after receiving the additional irinotecan, which could be responsible for the absence of a significant difference in the overall survival rate.

A cetuximab and irinotecan combination was also evaluated against irinotecan alone in patients with refractory metastatic colorectal cancer, in the Erbitux Plus Irinotecan in Colorectal Cancer (EPIC) trial.<sup>26</sup> This phase III trial included 1298 patients and reported a significantly better response rate (16% vs 4%,  $p<0.0001$ ) and progression-free survival (4 vs 2.6 mo,  $p<0.0001$ ) when the cetuximab-irinotecan combination was

used in a second-line setting compared with irinotecan alone. All patients in the study had failed first-line therapy with oxaliplatin and fluoropyrimidine. The trial, however, failed to show significant improvement in overall survival, probably due to 42% of patients in the irinotecan monotherapy group crossing over to the cetuximab combination group.

The National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG) have completed a phase III randomized cetuximab monotherapy trial in previously treated patients.<sup>27</sup> The trial compared the efficacy of cetuximab monotherapy plus best supportive care with best supportive care alone in patients with EGFR-positive colorectal cancer. Patients were required to have failed irinotecan and oxaliplatin therapy before enrollment. The trial enrolled 572 patients from November 2003–August 2005, and the results were presented at the 2007 American Association for Cancer Research annual meeting. The study showed significantly better time to tumor progression and overall survival in the cetuximab group. The hazard risk for time to tumor progression was 0.68 (95% CI 0.57–0.80,  $p < 0.0001$ ) in favor of cetuximab. The median overall survival was 6.1 and 4.6 months ( $p = 0.005$ ) in the cetuximab and best supportive care–alone group, respectively. Objective response rate of 6.6% was reported in the cetuximab group. This is the first study, to our knowledge, to show statistically significant improvement in overall survival with monoclonal antibodies alone in patients with refractory colorectal cancer.

The BOND and NCIC-CTG–AGITG trials confirmed the results of cetuximab combination and monotherapy phase II trials.<sup>28–30</sup> Two phase II trials evaluated cetuximab monotherapy in patients with refractory colorectal cancer that expressed EGFR.<sup>29, 30</sup> Both trials included patients who failed prior irinotecan-based regimens. In the one trial,<sup>30</sup> all 346 patients had previously progressed while receiving an oxaliplatin-based regimen, compared with 14% of the 57 patients in the other study.<sup>29</sup> These two trials had response rates of 11.6% and 9%, respectively. The response rates of these phase II trials were similar to the 10.8% response rate reported in the cetuximab monotherapy group of the BOND trial.<sup>25</sup> The progression-free survival was consistent, at 1.4 months in both trials. The overall median survival rates were reported to be

6.6 and 6.4 months, respectively.<sup>29, 30</sup> An Italian phase II trial evaluated cetuximab in combination with irinotecan in patients with EGFR-expressing tumors.<sup>28</sup> Fifty-five patients failed both the first-line therapy of an oxaliplatin-based regimen and then the irinotecan-based regimen as a second-line therapy. In this trial, patients received irinotecan at a dosage of 90 mg/m<sup>2</sup>/week. Overall, patients had a 25.4% response rate and a median survival of 9.8 months.

The Monoclonal Antibody Erbitux in a European Pre-License (MABEL) study,<sup>31</sup> which is an ongoing, multicenter, noncontrolled study of cetuximab plus irinotecan in a setting similar to the Italian phase II study,<sup>28</sup> should further strengthen the evidence for efficacy of cetuximab in the refractory setting. To our knowledge, this will be the largest study in this patient population (> 1400 patients).

Similar to cetuximab, panitumumab monotherapy also has been evaluated (Table 2).<sup>32</sup> In this pivotal phase III trial, panitumumab was evaluated in patients with metastatic colorectal cancer refractory to fluoropyrimidine, irinotecan, and oxaliplatin. It was a randomized, open-label, controlled multicenter study. Patients were required to express at least 1% or higher EGFR staining per immunohistochemistry. Patients were randomly assigned to receive panitumumab 6 mg/kg once every 2 weeks (231 patients) or best supportive care (232 patients). The primary end point of the study was progression-free survival. The baseline demographics were similar between the two groups. The overall median age of patients in the trial was 62 years, and 85% of the patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Also, 35% of the patients had been previously treated with adjuvant chemotherapy.

In an intent-to-treat analysis, panitumumab was significantly more effective than best supportive care. The panitumumab group had a 46% decrease in risk of progression compared with best supportive care (hazard ratio 0.54, 95% CI 0.44–0.66). Overall, median progression-free survival was 8 weeks in the panitumumab group and 7.3 weeks in the best supportive care group ( $p < 0.0001$ ). Mean progression-free survival was 13.8 weeks for patients receiving panitumumab and 8.5 weeks for those receiving only best supportive care ( $p < 0.0001$ ). Patients receiving panitumumab had a statistically significant improved response rate of 10% compared with those getting best supportive care. None of the patients in the best supportive care group

**Table 2. Pivotal Phase III Trials of Cetuximab and Panitumumab in Previously Treated Patients with Metastatic Colorectal Cancer**

Characteristic	Cetuximab Trial <sup>a, 25</sup>		Panitumumab Trial <sup>a, 32</sup>	
	Cetuximab + Irinotecan (n=218)	Cetuximab Only (n=111)	Panitumumab + Best Supportive Care (n=231)	Best Supportive Care Only (n=232)
	Percentage of Patients			
Male	66	57	63	64
Cells with EGFR staining				
1 to < 10%	43.1	36.9	25	25
10–100%	56.9	63.1	74	75
≥ 2 previous treatments	81.2	75.6	100	100
Overall response rate	23 <sup>a</sup>	11	10 <sup>a</sup>	0
	Median			
Age (yrs)	59	58	62	63
Progression-free survival (mo)	4.1 <sup>b</sup>	1.5	2.0 <sup>b, c</sup>	1.8 <sup>c</sup>
Overall survival (mo)	8.6	6.9	6.5 <sup>c</sup>	6.5 <sup>c</sup>

EGFR = epidermal growth factor receptor.

<sup>a</sup>In the cetuximab trial, 63% of the patients received a previous oxaliplatin-based regimen, whereas in the panitumumab trial, 100% of the patients did.<sup>b</sup>Statistically significant difference between groups.<sup>c</sup>Approximate value.

responded. No statistically significant difference was noted in overall survival, which could be explained by the fact that most patients (76%) in the best supportive care group were given panitumumab after disease progression.

The EGFR monoclonal antibodies are also being studied in combination with oxaliplatin, fluorouracil, and bevacizumab-based regimens.<sup>33–35</sup> Safety and efficacy of cetuximab have been evaluated with FOLFOX4 (folinic acid [leucovorin], infusional fluorouracil, and oxaliplatin [different dosing regimen than with FOLFOX]), FOLFIRI, and bevacizumab in these small trials. All of these regimens have shown activity and safety of cetuximab in patients with refractory metastatic cancer. Addition of bevacizumab to irinotecan and cetuximab showed a favorable response rate of 37% (BOND 2 trial), compared with 23–25% reported in previous trials of cetuximab plus irinotecan alone.<sup>25, 28, 34</sup> The same trial showed that the addition of bevacizumab to cetuximab can improve the response rate to 20%, compared with 11% in the previously reported trial.<sup>25, 34</sup> The bevacizumab-irinotecan-cetuximab group (43 patients) had a median survival of 14.5 months compared with 11.4 months in the bevacizumab-cetuximab group (40 patients).<sup>34</sup>

#### Treatment-Naïve Patients

Promising results of EGFR monoclonal antibodies in the setting of refractory metastases

have led to their evaluation as first-line therapy. There are two phase III trials evaluating the efficacy of EGFR monoclonal antibodies in treatment-naïve patients with metastatic colorectal cancer.<sup>36, 37</sup> In the Cetuximab Combined with Irinotecan in First Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial, EGFR-positive, treatment-naïve patients were randomly assigned to receive FOLFIRI plus cetuximab (608 patients) or FOLFIRI alone (609 patients).<sup>36</sup> The response rate was significantly higher in the cetuximab group, at 46.9% compared with 38.7% in the FOLFIRI-alone group. Cetuximab also resulted in significantly better progression-free survival at 8.9 months (95% CI 8–9.5 mo) compared with 8 months (95% CI 7.6–9 mo) in the FOLFIRI-alone group ( $p=0.036$ ). The response rate and progression-free survival of the FOLFIRI regimen are consistent with the results of previously published phase III trials of FOLFIRI.<sup>38–40</sup> Overall, both treatments were well tolerated, with the cetuximab regimen reporting higher rates of grade 3–4 neutropenia, diarrhea, and skin reaction adverse events. The CRYSTAL trial suggested a modest clinical benefit of cetuximab as first-line therapy compared with bevacizumab, which is used in clinical practice today.<sup>4, 36, 41</sup>

The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial did not suggest a benefit of panitumumab as first-line therapy. In a March 22, 2007 press release, the manufacturer of panitumumab announced the discontinuation

of the phase III trial, which compared panitumumab plus standard first-line treatment with first-line treatment alone.<sup>37</sup> Patients were randomly assigned to receive oxaliplatin and irinotecan-based chemotherapy and bevacizumab with or without panitumumab. The decision to discontinue was made based on a preliminary review of a preplanned evaluation of efficacy after the first 231 events, which were defined as death or disease progression. Statistical analysis revealed a significant difference in progression-free survival in favor of the control group. Based on this information, the manufacturer conducted an unplanned overall survival analysis to that point, which was consistent with the aforementioned progression-free survival data.

There are many phase II trials of EGFR monoclonal antibodies in combination with other chemotherapy regimens as first-line treatment of metastatic colorectal cancer. Of these, four have reported progression-free survival and safety of the regimens.<sup>24, 42-44</sup> Similar to the panitumumab PACCE trial, cetuximab has been evaluated in combination with an oxaliplatin and bevacizumab regimen. The difference is that cetuximab was evaluated in a small (67 patients), nonrandomized, noncontrolled trial.<sup>44</sup> Cetuximab was given with modified FOLFOX6 (same agents as in FOLFOX4, but agents are given at different dosages and duration) and bevacizumab. Of the 58 evaluable patients, the study showed a response rate of 55% and a median progression-free survival of 9.6 months. Similarly, cetuximab in combination with capecitabine 850 mg/m<sup>2</sup> twice/day for 14 days with irinotecan (XELIRI) showed an overall response rate of 40% and a median duration of response of 8.8 months in 55 evaluable patients.<sup>43</sup> Another group evaluated the safety and tolerability of adding cetuximab to irinotecan-fluorouracil-folinic acid. In this small trial, they evaluated 21 patients with untreated metastatic colorectal cancer expressing EGFR.<sup>42</sup> Cetuximab was given with either low- or high-dose fluorouracil at either 1500 or 2000 mg/m<sup>2</sup>, plus irinotecan 280 mg/m<sup>2</sup>/week. Six patients received low-dose fluorouracil, and 15 patients received high-dose fluorouracil. The study showed dose-limiting toxicities in the low-dose fluorouracil group and three dose-limiting toxicities in the high-dose group (two patients had grade 3 diarrhea and one patient had grade 4). The study had a median time to progression of 9.9 months and median survival of 33 months.

In a phase II trial, panitumumab was evaluated

as a first-line agent for the treatment of metastatic colorectal cancer.<sup>24</sup> This was a noncontrolled, two-part trial evaluating panitumumab in combination with IFL (part 1) or in combination with FOLFIRI (part 2). The study was divided because of toxicity issues that developed with the original regimen in part 1. The study was small, with only 19 patients in part 1 and 24 patients in part 2. With respect to the secondary end points, the study found that nine patients and eight patients had partial responses in parts 1 and 2, respectively. Progression-free survival was found to be 5.6 and 10.9 months in the two groups, respectively. Overall median survival was 17 months in part 1 and 22.5 months in part 2.

Several phase III trials of cetuximab and panitumumab in treatment-naïve and previously treated patients with metastatic colorectal cancer are ongoing; these will provide additional efficacy and safety information of EGFR monoclonal antibodies (Table 3).<sup>45-47</sup>

## Clinical Considerations

### Expression of Epidermal Growth Factor Receptor

Expression of EGFR has been reported in most colorectal cancer diagnoses. Both EGFR monoclonal antibodies are approved for use in patients with tumors that have been determined to express EGFR.<sup>13, 14</sup> However, data from the BOND trial<sup>25</sup> and the other two phase II trials<sup>29, 30</sup> show that intensity of EGFR staining does not correlate with efficacy. Also, the panitumumab trial did not show an appreciable difference in the hazard ratio in patients with less than or more than 10% EGFR expression of evaluated cells.<sup>32</sup> These findings may relate to the absence of data indicating the prognostic value of EGFR and colorectal tumor response. One group of authors evaluated 16 EGFR-negative patients treated with cetuximab plus irinotecan (14 patients) or cetuximab alone (two patients) who were refractory to previous chemotherapy.<sup>48</sup> This study, although small, identified a 25% response rate. Another study showed a 30% response rate in 10 EGFR-negative patients treated with irinotecan and cetuximab.<sup>49</sup> A third study showed an 11% response rate in nine EGFR-negative patients treated with cetuximab alone.<sup>30</sup> These findings suggest that EGFR-negative tumors have the potential to respond to EGFR monoclonal antibody therapy and that EGFR immunohistochemistry before therapy does not appear to be needed.

Table 3. Ongoing Phase III Trials of Epidermal Growth Factor Receptor Monoclonal Antibodies in Patients with Metastatic Colorectal Cancer<sup>45-47</sup>

Study Design	Study Population	Trial Name and/or Identifier <sup>a</sup>	Treatment Regimens
Randomized, open-label, active-control, parallel-assignment, safety and efficacy	Previously treated	EXPLORE, NCT00061815	Group 1: FOLFOX + cetuximab Group 2: FOLFOX
Randomized, multicenter	Previously treated	NCT00499369	Group 1: Irinotecan or FOLFIRI, + cetuximab Group 2: Irinotecan or FOLFIRI, + cetuximab + low-dose bevacizumab Group 3: Irinotecan or FOLFIRI, + cetuximab + high-dose bevacizumab
Randomized, open-label, multicenter	Treatment naïve	CALGB 80405, NCT00265850	Group 1: FOLFOX or FOLFIRI, + bevacizumab Group 2: FOLFOX or FOLFIRI, + cetuximab Group 3: FOLFOX or FOLFIRI, + cetuximab + bevacizumab
Randomized, open-label, active-control, parallel-assignment, efficacy	Treatment naïve	NCT00145314	Group 1: FLOX Group 2: FLOX + cetuximab
Randomized, open-label, placebo-controlled, parallel-assignment, safety and efficacy	Treatment naïve	CAIRO 2, NCT00208546	Group 1: Capecitabine + oxaliplatin + bevacizumab Group 2: Same as group 1 + cetuximab
Randomized, open-label	Treatment naïve	NCT00482222	Before surgery: Group 1: OxMdG or CAPOX Group 2: OxMdG or CAPOX + cetuximab After surgery: Same as groups 1 and 2
Randomized, open-label, active-control	Treatment naïve	NCT00077233	Group 1: FOLFIRI Group 2: FOLFIRI + cetuximab Group 3: FOLFOX Group 4: FOLFOX + cetuximab
Randomized, open-label, noncontrolled, parallel-assignment, safety and efficacy	Treatment naïve	USOnc 252, NCT00252564	Group 1: FOLFOX + bevacizumab Group 2: FOLF + cetuximab + bevacizumab
Randomized	Treatment naïve	COIN, NCT00182715	Group 1: OxMdG or XELOX Group 2: Group 1 + cetuximab Group 3: Group 1 for 12 wks, then a break, then resume at disease progression
Randomized, open-label, active control	Previously treated	NCT00389870	Group 1: Irinotecan Group 2: Irinotecan + cyclosporine Group 3: Irinotecan + panitumumab
Randomized, open-label, active-control, parallel-assignment	Previously treated	NCT00339183	Group 1: FOLFIRI  Group 2: FOLFIRI + panitumumab
Randomized, open-label, active-control, parallel-assignment, safety and efficacy	Treatment naïve	PRIME, NCT00364013	Group 1: FOLFOX Group 2: FOLFOX + panitumumab

EXPLORE = Cetuximab plus FOLFOX for colorectal cancer; FOLFOX = oxaliplatin over 2 hrs, folinic acid (leucovorin) over 2 hrs, fluorouracil over 46–48 hrs; FOLFIRI = irinotecan over 30–90 min, leucovorin over 2 hrs, and fluorouracil over 46–68 hrs; CALGB = Cancer and Leukemia group B; FLOX = fluorouracil, leucovorin, and oxaliplatin; CAIRO = Capecitabine, Irinotecan, and Oxaliplatin trial; OxMdG = leucovorin over 2 hrs, oxaliplatin over 2 hrs, fluorouracil over 46 hrs; CAPOX or XELOX = oxaliplatin over 2 hrs, oral capecitabine twice/day for 2 wks; USOnc = US Oncology; FOLF = biweekly infusion of fluorouracil, and folinic acid (leucovorin); COIN = Continuous Chemotherapy plus Cetuximab or Intermittent Chemotherapy; and PRIME = Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic CRC to Determine Efficacy.

<sup>a</sup>ClinicalTrials.gov identifier.



### Appearance of Rash

Unlike EGFR expression, an association between appearance or intensity of rash and efficacy has been observed in patients treated with EGFR monoclonal antibodies.<sup>25, 29, 30, 32, 49</sup> Post hoc analysis of the BOND trial showed a significantly better response rate of 13% in patients having a skin reaction compared with 0% in patients with no skin reaction. This difference in response rates was also consistent in the combination group. The median overall survival was also found to be prolonged in patients with skin reaction (8–9 vs 2.5–3 mo).<sup>25</sup> In addition, patients with a grade 3 or 4 rash had better response rates compared with those with a grade 1 or 2 rash (59% vs 20% cetuximab-irinotecan and 25% vs 11% cetuximab alone).

The same relationship was seen in the panitumumab study.<sup>32</sup> Patients receiving panitumumab who had grade 2–4 skin toxicity revealed a statistically significant (41%) reduction in death, compared with those with a grade 1 skin reaction. A pooled analysis of five panitumumab clinical trials showed 8.5 versus 4.5 months median survival in patients with grade 2–4 skin toxicity versus those with grade 1.<sup>50</sup> Although rash appears to be a good prognostic factor in responsiveness of the tumor, its interpretation remains a challenge. Rash appears in responders as well as in nonresponders.<sup>25, 32</sup> The EVEREST trial—a cetuximab dose-escalation study in patients with metastatic colorectal cancer with no or slight skin reactions while receiving cetuximab standard-dose treatment—is currently evaluating the efficacy of cetuximab and irinotecan.<sup>47</sup> The study is designed to increase the cetuximab dosage in an escalation group if the patient does not have a grade 2 or higher rash at the third week of treatment.

### Adverse Effects

As a class, the EGFR monoclonal antibodies are relatively well tolerated either as monotherapy or in combination with chemotherapy. They are not associated with typical chemotherapy-induced myelosuppression, mucositis, nausea and/or vomiting, or alopecia. The most common adverse events reported are rash, diarrhea, and hypomagnesemia.<sup>13, 14, 25, 32, 51</sup> Some of the more serious issues that require dosage adjustment or discontinuation include infusion-related reactions, dermatologic conditions, and pulmonary toxicity.<sup>25, 32</sup>

### Rash

Although skin reactions have been reported in 80–90% of patients receiving EGFR monoclonal antibodies, the severe grade 3 or 4 acne-type (acneiform) rash is reported in only 5–9% of patients.<sup>29, 30</sup> The rash usually manifests itself on the face, upper chest, and back; however, it is not limited to these areas.<sup>14, 29</sup> Most patients develop the rash in the first 3 weeks of therapy, which is reversible upon discontinuation. Acne-like rash can be managed with topical and/or systemic therapy. Clindamycin phosphate 1% gel can be used for the inflammatory pustular lesions.<sup>52</sup> It also can be combined with benzoyl peroxide 5% gel. In severe cases, antibiotics such as tetracycline, minocycline, or doxycycline should be used. For dry skin, a moisturizing cream or ointment is recommended.<sup>52</sup>

### Diarrhea

Diarrhea is more common in patients who are receiving the combination of irinotecan and cetuximab; however, it has also been reported with EGFR monoclonal antibody monotherapy.<sup>25, 30</sup> The cetuximab package insert reports diarrhea in 72% of patients, with 22% experiencing grade 3 or 4 diarrhea when cetuximab is given in combination with irinotecan. When cetuximab was given as monotherapy, 28% experienced diarrhea, 2% of whom had grade 3 or 4 toxicity.<sup>14</sup> Panitumumab has shown similar data: 21% of patients experienced some form of diarrhea, and 2% had grade 3 or 4 toxicity.<sup>13</sup> Patients should be educated regarding adequate fluid intake and administration of loperamide in the event of diarrhea. If patients develop diarrhea, loperamide every 2–4 hours should be used until 12 hours have passed after the last episode of diarrhea. In particular, patients taking irinotecan could have an increased risk of delayed diarrhea.

### Hypomagnesemia

Hypomagnesemia was not identified as a common adverse event of EGFR monoclonal antibody therapy at the time of the cetuximab registrational trial. Postmarketing analyses have now shown that cetuximab and panitumumab therapy can be associated with severe hypomagnesemia.<sup>32, 51, 53, 54</sup> Retrospective analyses of cetuximab trials have shown a frequency of 50–65%, and a prospective phase III trial of panitumumab has shown a 36% overall rate of hypomagnesemia. Cases of severe grades 3 and 4

hypomagnesemia have been reported in 10–27% of patients receiving cetuximab and 3% of patients receiving panitumumab.<sup>32, 51, 54</sup> At times, patients may also present with accompanying hypocalcemia and hypokalemia.<sup>32, 51, 53, 54</sup> In the cases of severe hypomagnesemia, intravenous replacement was often required.<sup>13</sup> Most cases of hypomagnesemia were identified at 6–8 weeks of EGFR monoclonal antibody therapy. One study reported that it might take up to 4 weeks to recover after discontinuation of cetuximab.<sup>54</sup> Magnesium wasting syndrome with inappropriate urine excretion is the suggested mechanism, per one group of authors.<sup>51</sup> Inhibition of EGFR in the nephron may reversibly impair function of the proteins involved in active transport of extracellular magnesium.

### Hypersensitivity

The randomized phase III EPIC trial released its safety data of cetuximab in combination with irinotecan as second-line therapy (800 patients).<sup>55</sup> A total of 3629 chemotherapy cycles were administered to patients, with a median of 4 cycles/patient. Overall, 4% of the patients had infusion reactions to cetuximab. Four patients (0.5%) experienced severe infusion reactions, but none was fatal.<sup>26</sup> The package insert reports a similar finding and that 90% of reactions occur during the first infusion.<sup>14</sup> With panitumumab, 1% of infusion reactions were grade 3 or 4, with an overall frequency of 3%.<sup>13</sup> Unlike with cetuximab, however, the use of premedication was not standardized in panitumumab clinical trials, since it is a fully human antibody.<sup>13</sup> Also, one case report indicates panitumumab was given successfully to a patient with a previous severe reaction to cetuximab.<sup>56</sup>

### Other Adverse Events

Other common adverse events reported with EGFR monoclonal antibodies are fatigue, asthenia, dyspnea, paronychia (infection of the nail fold surrounding the nail plate), abdominal pain, nausea, and anorexia.<sup>13, 14, 25, 32</sup> Ocular toxicity was reported with panitumumab in 15% of patients. Ocular events include conjunctivitis, ocular hyperemia, increased lacrimation, and eye or eyelid irritation.<sup>13</sup> Interstitial lung disease was reported in three of 633 cetuximab-treated patients (< 0.5%), one case of which actually resulted in death. Two of the patients had preexisting pulmonary fibrosis that resulted in exacerbations while taking cetuximab and

irinotecan.<sup>14</sup> For panitumumab, there was a similar occurrence, with less than 1% of patients experiencing interstitial lung disease; however, once a fatality was associated with interstitial lung disease, patients with preexisting lung disease were excluded from the studies. Both EGFR monoclonal antibodies are pregnancy category C drugs, and no drug interaction has been studied or identified with other agents.<sup>13</sup>

### Dosage and Administration

Cetuximab carries a United States Food and Drug Administration–approved indication for use in combination with irinotecan for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based therapy. It is also approved as a monotherapy in the event patients are intolerant to irinotecan. The recommended dosing is for patients to receive a 400-mg/m<sup>2</sup> loading dose by a 2-hour infusion followed by weekly infusions of 250 mg/m<sup>2</sup> over 1 hour.<sup>14</sup>

Panitumumab is indicated for use in patients with metastatic colorectal cancer who express EGFR with disease progression while receiving or after fluorouracil, oxaliplatin, and irinotecan-based therapy. Panitumumab is dosed at 6 mg/kg and is infused over 1 hour every 2 weeks. If doses greater than 1000 mg are required, they should be administered over 90 minutes instead.<sup>13</sup>

It is recommended that patients receive intravenous diphenhydramine 50 mg before administration of cetuximab to prevent possible infusion-related reactions.<sup>14</sup> The use of premedication with panitumumab was not standardized in the clinical trial, and therefore, treatment with a histamine antagonist is not required.<sup>11, 13</sup>

No dosage adjustment is suggested for cetuximab or panitumumab in the setting of hepatic or renal impairment. Dosage adjustment is recommended in the setting of infusion-related reactions or dermatologic toxicity. If the patient experiences either grade 1 or 2 infusion reactions, the infusion rate should be reduced by 50%. If the reaction is severe grade 3 or 4, then EGFR monoclonal antibodies should be discontinued permanently. In the event of severe dermatologic toxicity, subsequent infusions should be held until improvement to at least grade 2 toxicity. Subsequent doses of panitumumab should be reduced to 50% of the scheduled dose. The cetuximab dose can be reduced to 150 mg/m<sup>2</sup> based on the severity of dermatologic toxicity.<sup>13, 14</sup>

## Conclusion

The availability of EGFR monoclonal antibodies has broadened the therapies available for metastatic colorectal cancer. Cetuximab and panitumumab have demonstrated efficacy against metastatic colorectal cancer previously resistant to multiple chemotherapy regimens, including irinotecan and oxaliplatin. In particular, cetuximab, with or without irinotecan, has been evaluated extensively in phase III (BOND, EPIC, and NCIC) and phase II trials. It has shown significant activity as second- or third-line treatment of metastatic colorectal cancer. However, panitumumab monotherapy has been evaluated primarily as a third-line therapy. In addition, cetuximab has significant synergistic activity when administered in combination with irinotecan. Based on the BOND and EPIC trials, cetuximab in combination with irinotecan has better efficacy compared with cetuximab and irinotecan alone. Therefore, combination treatment should be a first option unless the patient is not a good candidate for irinotecan in a refractory setting.

Based on the CRYSTAL trial, cetuximab has shown improved activity as first-line therapy with FOLFIRI. The role of EGFR monoclonal antibodies in the treatment of chemotherapy-naïve patients needs to be further evaluated, as bevacizumab is the standard monoclonal antibody in combination with irinotecan or oxaliplatin-based chemotherapy. Multiple interim analyses have proved the safety of EGFR monoclonal antibodies in combination with various chemotherapy regimens. Because of the specificity, EGFR monoclonal antibodies are less cytotoxic compared with chemotherapy. Skin reaction, diarrhea, hypomagnesemia, and infusion reactions are the adverse events to be monitored when administering EGFR monoclonal antibodies.

The value of EGFR expression and rash as a prognostic indicator needs to be further established. Expression of EGFR is not likely to determine tumor response. Patients who develop rash are likely to respond better; however, rash also develops in individuals who do not respond. The optimal EGFR monoclonal antibody dosage in patients without rash needs to be further evaluated. Clinical trials published to date have not included patients with metastatic colorectal cancer refractory to bevacizumab. We hope future EGFR monoclonal antibody studies will provide answers to these questions.

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