# Targeting colorectal cancer with human anti-EGFR monoclonocal antibodies: focus on panitumumab

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**Abstract:** The human anti-epidermal growth factor receptor (EGFR) monoclonal antibody, panitumumab, represents a significant advance in the treatment of colorectal cancer. The strategy to target this receptor is based on sound cancer biology demonstrating its essential role in colorectal carcinogenesis. Panitumumab, unlike its predecessor, cetuximab, is fully human and thus reduces the incidence of hypersensitivity reactions. But, in several clinical trials, unexpected toxicities have become more apparent, raising concerns of how readily panitumumab can succeed cetuximab. This paper reviews the development of this agent and the pivotal clinical trials that help our understanding of its optimal use in colorectal cancer treatment.

**Keywords:** colorectal cancer, chemotherapy, panitumumab, oxaliplatin, irinotecan, bevacizumab, cetuximab

## Colorectal cancer (CRC)

Colorectal cancer ranks second in overall cancer deaths for men and women in the US with 148,810 new cases diagnosed and roughly 50,000 fatalities expected in 2008 (Jemal et al 2008). Approximately 40% of these patients will develop metastatic disease and require systemic treatment. Advances in the number and types of active chemotherapy agents in colorectal cancer have been witnessed, although their optimal use remains to be established. Their initial evaluation in the metastatic setting will allow subsequent testing in earlier stage disease with the potential of curing a greater number of colorectal cancer patients.

## Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR; HER1 or c-ErbB-1) is a member of the HER family of receptor tyrosine kinases (TKs; including HER2, HER3, and HER4) (Citri and Yarden 2006). The EGFR is a transmembrane receptor with an intracellular TK domain that is activated by several growth factors, mainly EGF and transforming growth factor-$\alpha$. With ligand binding, receptor dimerization occurs, and the receptor is activated via autophosphorylation of the associated TK domain. An intracellular signal transduction cascade is initiated with the subsequent phosphorylation of Ras, and other downstream signaling pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol- 3-kinase (PI3K)/AKT cascades. Ultimately, transcriptional activity is increased and multiple biologic processes are activated such as anti-apoptosis, chemotherapy resistance, angiogenesis, and metastasis (Baselga 2001). The EGFR is constitutively expressed in many human cancers, including 60%–80% of CRCs. Over-expression of EGFR correlates with poor prognosis, increased risk of metastasis, and drug resistance (Mendelson 2002). The malignant processes regulated by EGFR highlight the inhibition of receptor function as a potential therapeutic approach in colorectal cancer.

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The development of EGFR inhibitors has led to the emergence of two classes of compounds: (1) monoclonal antibodies (MoAbs) directed against the extracellular domain of the EGFR (eg, cetuximab, panitumumab [ABX-EGF], and matuzumab [EMD 7200]); and (2) specific small-molecule inhibitors of the intracellular TK domain of EGFR (eg, erlotinib and gefitinib). In general, the latter class of compounds, unlike in lung cancer, have shown minimal activity in colorectal cancer. This is largely due to the low incidence of mutations in the ATP site of the EGFR TK domain (0.34% or 1 mutated tumor in 293 analyzed) (Barber et al 2004).

The first monoclonal antibody to demonstrate activity in colorectal cancer was cetuximab. It is a chimeric immunoglobulin G (IgG1) monoclonal antibody consisting of human and murine sequences. The IgG1 subclass, in comparison with other IgG subclasses, can elicit antibody-dependent cellular cytotoxicity (ADCC) which theoretically contributes an immune-mediated anti-cancer effect. The murine peptide sequences are noteworthy as they introduce the risk of hypersensitivity reactions; about 2% of patients experience grade 4 anaphylaxis. This can be considerably higher, 21%, in certain geographic regions (O'Neil et al 2007). In addition, human anti-mouse antibodies against cetuximab can also be generated which could potentially inactivate the agent upon subsequent administrations. Cetuximab was approved in the US as a single agent or in combination with irinotecan for the treatment of EGFR-positive metastatic CRC refractory to irinotecan-based treatment (Cunningham et al 2004; Saltz et al 2004). This approval was based on several studies that demonstrated a unique ability of cetuximab to reverse irinotecan resistance. More recent trials have shown cetuximab to be superior in terms of progression-free survival (PFS) and overall survival (OS) vs best supportive care in patients refractory to multiple lines of therapy (Jonker et al 2007). In addition, when used in the first-line or second-line settings, addition of cetuximab to chemotherapy results in improvements in PFS (Sobrero et al 2008; Van Cutsem et al 2007a).

These early trials with cetuximab served as proof-of-principle in validating the use of anti-EGFR monoclonal antibodies in the treatment of CRC. This success led to the development and emergence of successive monoclonal antibodies that were humanized and less likely to induce anti-mouse directed hypersensitivity reactions. An improved safety profile without any loss in efficacy was presumed which would allow these subsequent generation compounds to be fully interchangeable into chemotherapeutic regimens in which cetuximab had previously demonstrated benefit. Unfortunately, these predictions were not validated in recent trials as unexpected, excess toxicities were encountered, as discussed below.

## Panitumumab

Panitumumab is a high-affinity (Kd = 5 × 10–11 M), fully human IgG2 monoclonal antibody with specificity for the ligand-binding region of EGFR (Yang et al 2001). This represents an approximate 8-fold greater affinity compared with cetuximab (Kd = 0.39 nM). The binding of panitumumab to EGFR completely blocks its association with ligands and activation of downstream kinase cascades. Panitumumab was constructed using XenoMouse® technology, a genetically engineered mouse whose immunoglobulin heavy and κ light chain loci are substituted with human immunoglobulin genes. Unlike cetuximab, panitumumab contains no murine protein sequences and thereby significantly reduces the risk for hypersensitivity reactions.

The antineoplastic effects of panitumumab have been demonstrated in mouse models using xenografts from various tumor types (Yang et al 2001; Foon et al 2004). Panitumumab prevents xenograft formation and completely eradicates established tumors (as large as up to 1.2 $cm^3$). When panitumumab is combined with chemotherapeutic agents, such as platinums, inhibition of tumor growth and eradication of carcinoma cells in in vitro and in vivo models has also been demonstrated. In addition, the inhibition of tumor growth is sustained for up to an impressive 8 months after discontinuation of therapy (Baselga and Mendelson 1997).

Early clinical evaluation included a phase I study (Weiner et al 2005) of panitumumab that revealed the agent to be active in several advanced solid tumors, in particular, metastatic CRC. In the trial, sequential cohorts of patients with EGFR-expressing cancers (at least 1+ in ≥10% of tumor cells) were administered 4 infusions of panitumumab that varied in dosage and treatment schedule. In each case, the drug was administered intravenously for 1 hour without premedication. Dosing and treatment schedules were 0.01–5.0 mg/kg once a week (qw), 6.0 mg/kg once every 2 weeks (q2w), and 9.0 mg/kg once every 3 weeks (q3w). Although this dose-finding study was not designed to evaluate efficacy, it was immediately evident that panitumumab was active in colorectal cancer, as 5 of the 6 recorded partial responses were among patients with this disease (overall response rate 12.8%). As anticipated, skin-related events (grade 3/4), a class effect of EGFR inhibitors, dominated the observed toxicities. This intensity of rash was dose dependent up to 2.0 mg/kg qw. Overall, the grade 3/4 toxicity rate was 10% and no maximum tolerable dose was

defined. No hypersensitivity reactions or human anti-human antibody (HAHA) formation was observed. Pharmacokinetic exposure was comparable for all treatment schedules.

The encouraging phase I results led to a phase II trial of weekly panitumumab 2.5 mg/kg as monotherapy in previously treated, refractory patients with metastatic CRC (Malik et al 2005). Some patients had received up to 4 lines of prior therapy. The study design included 2 cohorts based on EGFR staining intensity. A total of 148 patients were treated, with 15 patients having confirmed partial responses (10%) and 54 patients (36.5%) stable disease. Importantly, these outcomes are similar to the results seen with cetuximab monotherapy. The median OS was 9.4 months and time to progression was 2.5 months. Overall the safety analysis demonstrated that panitumumab as monotherapy was well tolerated with a grade 3/4 rate of 14% (21 of 148 patients) being registered. The most frequently reported grade 3/4 treatment-related adverse events were rash (n = 11; 7%), fatigue (n = 4), vomiting (n = 2), nausea (n = 1), and pruritus (n = 1). Skin toxicity overall was reported in 141 patients (95%; 5% grade 3/4), with 2 patients discontinuing treatment. Only 1 grade 3 infusion-related reaction occurred, which did not require dose modification or treatment interruption.

The pivotal confirmation of the earlier observations of clinical benefit with panitumumab in CRC was a phase III trial (Van Cutsem et al 2007b) that randomized 463 metastatic patients between panitumumab (6.0 mg/kg q2w) and best supportive care (n = 231) vs best supportive care alone (n = 232). Eligible patients were required (veritable third-line setting), through prior radiologic confirmation, to be refractory to fluoropyrimidine, irinotecan, and oxaliplatin treatment (third-line setting) and to have tumors expressing EGFR in ≥1% of cancer cells examined. The primary endpoint of the trial was progression-free survival with secondary endpoints including overall survival, objective response, and duration of and time to response. The study clearly demonstrated superiority of panitumumab over best supportive care (BSC) in terms of progression-free survival (panitumumab 8 weeks vs BSC 7.3 weeks, hazard ratio (HR) of 0.54 (95% CI 0.44, 0.66; $p < 0.0001$). This PFS benefit though did not translate into an overall survival advantage for panitumumab-treated patients (6.5 months for both arms, HR 1.00; 95% CI 0.82–1.22; $p = 0.81$). It is important to recognize that the trial allowed patients initially assigned to BSC to cross over to receive panitumumab upon progression; 76% of BSC patients crossed over to receive panitumumab. When the hazard ratio was recalculated after censoring for patients who crossed over, a modest, but still non-significant, trend in survival was observed (HR 0.78; 95% CI 0.61–1.01). Eight percent of patients achieved a response while 28% had stable disease. The toxicity profile for panitumumab in the trial was similar to that in the earlier reported studies.

With the activity of panitumumab in colorectal cancer having been confirmed, subsequent studies were performed to assess the dependence of EGFR expression on clinical outcome (Berlin et al 2007; Hecht et al 2007a; Mitchell et al 2007). Two phase II trials of panitumumab in the third-line setting in metastatic CRC patients were conducted that were stratified by EGFR expression. In one trial, the percentage of tumor cells positive for EGFR expression had to be negative (<1%) or low (1%–9%) and in the other trial, high (≥10%). It should be noted that EGFR status was defined by immunohistochemical methods which previously were shown to be of limited utility in predicting outcome (Chung et al 2005; Lenz et al 2006). Patients received at least 2 prior treatment regimens consisting of a fluoropyrimidine, irinotecan, and oxaliplatin. In these studies, patients received 6.0 mg/kg of panitumumab q2w until tumor progression or drug intolerability. The primary endpoint of the study was objective response which, recently updated after central review, was seen in 5% and 8% in the two cohorts, negative/low and high, respectively. Only partial responses were seen. Stable disease was seen in 30% of all patients (32% negative/low EGFR-expression patients and 29% in the high group). PFS was 8.0 weeks in both groups. The toxicity profile for panitumumab was consistent with that of previous reports. Dermatologic toxicity of any grade was seen in 93%–97% of patients and of grade 3 or higher in 15%–21% of individuals. Importantly, 2 panitumumab-related deaths were reported; one patient had a pulmonary embolism and another had a myocardial infarction and cerebrovascular accident.

Further development of panitumumab required testing whether it could be combined with conventional chemotherapy agents active in CRC and specifically which agents. A phase II trial designed to address this key question incorporated panitumumab into irinotecan-containing regimens, either IFL or FOLFIRI (Berlin et al 2007). The primary objective was to assess the safety of the regimens as first-line treatment in patients with metastatic CRC. Secondary objectives included response rate, PFS, and OS. Patients received panitumumab (2.5 mg/kg qw × 6) with IFL (irinotecan 125 mg/m$^2$, leucovorin 20 mg/m$^2$, and bolus 5-FU 500 mg/m$^2$) or with FOLFIRI (irinotecan 180 mg/m$^2$, leucovorin 400 mg/m$^2$, and bolus 5-FU 400 mg/m$^2$ followed by a 46-hour infusion of 5-FU 2,400–3,000 mg/m$^2$ q2w × 3). Patients were required to have measurable metastatic CRC, no prior treatment

for advanced disease, and EGFR expression in ≥10% of evaluated tumor cells. The objective response rate was 46% (9 of 19) for patients receiving the panitumumab-IFL regimen and 42% (8 of 24) for those receiving panitumumab-FOLFIRI. The PFS for patients treated with panitumumab and either FOLFIRI or IFL were 10.9 months and 5.6 months, respectively. The superiority of panitumumab and FOLFIRI was not indicative of a specific pharmacologic interaction but was attributable to known differences in toxicity and survival between the two 5-FU schedules, infusional vs bolus administration. The addition of panitumumab to FOLFIRI, compared with IFL, was more favorable especially in regards to the incidence of grade 3/4 diarrhea (25% vs 58%, respectively). Serious adverse events were observed and included thromboembolic events – pulmonary embolism (3 patients), congestive heart failure, chest pain, and significant hypomagnesemia. No infusion reactions or panitumumab-induced HAHA formation were reported. Overall survival data are not yet available for the trial.

Whether panitumumab could be incorporated into first-line treatment regimens for metastatic colorectal patients represented the next question, which has been explored in a large, multicenter phase III study, the PACCE trial (Panitumumab Advanced Colorectal Cancer Evaluation) (Hecht et al 2007b). This study was predicated upon intriguing results from the BOND2 trial in which the dual biologic approach of bevacizumab combined with cetuximab yielded significant activity in refractory colorectal cancer patients (Saltz et al 2007). In order to assess the impact of combining bevacizumab and cetuximab with front-line standard regimens, a larger trial, the US Intergroup (CALGB 80405) study, is ongoing. Similarly, the PACCE trial was designed to substitute cetuximab with panitumumab and test the biologic agents in both oxaliplatin-based (80%) and irinotecan-based (20%) regimens. The results from an interim analysis were recently presented and included the 812 patients randomized to an oxaliplatin-containing regimen and bevacizumab without (Arm A) or with panitumumab (Arm B). The primary endpoint was PFS with secondary endpoints including response rate, time to treatment failure, OS, and safety profile. Standard eligibility criteria were followed; EGFR testing was not required. As the trial proceeded, it became apparent that the dual biologic-containing Arm B was more toxic than the control arm. Specifically, higher grade 4 (28% vs 19%) and grade 5 (6% vs 3%) toxicities were seen. In total about 19% of patients stopped treatment with panitumumab due to serious adverse events. In terms of the actual toxicities, a higher rate of diarrhea, dehydration, electrolyte imbalance, and infections was seen and, when coupled to the known skin toxicities, this multitude of side effects created a difficult-to-tolerate regimen. There also was a higher death on study rate of 35% (Arm B) vs 27% (Arm A); statistical significance was not reported.

The toxicities and intolerability of the dual biologic regimen affected clinical outcomes. No improvement in response was seen (Arm A 41% vs Arm B 39%) and, importantly, the PFS (Arm A 10.5 vs Arm B 9 mos, HR = 1.29, 95% CI 1.05–1.58) and OS (Arm A not reached vs 18.6 mos, HR = 1.44, 95% CI 1.10–1.88) were inferior as of data cutoff April 2007. In an effort to explain these unexpected results, several analyses were performed including the amount of exposure patients on study experienced to the specific drugs. In the experimental arm, more dose delays and reductions were seen especially with the use of bolus 5FU. Importantly, the oxaliplatin dose was relatively maintained between the two arms (Arm A 88% vs Arm B 84%). A higher number of patients in the panitumumab-containing combination discontinued therapy due to progressive disease than their counterparts (Arm A 27% vs Arm B 36%). The investigators summarized that these findings demonstrated an unfavorable therapeutic index for the combined biologic regimen due to the reduction in PFS and increased toxicity. The question as to whether a biological synergy exists between panitumumab and bevacizumab or whether toxicity is simply potentiated with the combination remains to be answered. At present, data from trials combining only the two biologic agents without chemotherapy are not available.

The role of panitumumab in the treatment of CRC remains to be defined. Despite setbacks, panitumumab may prove useful, although further work is required to determine how it can be safely combined with standard chemotherapy regimens such as FOLFOX or FOLFIRI. In addition, the setting (first-line, second-line) and the types of patients who benefit most need further evaluation. Ongoing trials will either corroborate or refute the earlier findings. Toward this end, a large European phase III trial is evaluating the combination of panitumumab and FOLFOX as first-line therapy in patients with metastatic disease. This is an important trial as the combination of an oxaliplatin-containing regimen and panitumumab deserves to be explored. Another outstanding issue is whether the appropriate dose was selected. It needs to be highlighted that similar activity has been observed at the 6.0 mg/kg q2w vs 2.5 mg/kg qw raising the question of whether 5 mg/kg q2w (83% of the present dose) is more tolerable.

## Panitumumab predicitive markers

In effort to predict which patients will benefit from panitumumab, several retrospective analyses have been conducted. One consistently interesting observation with EGFR inhibitors is that rash intensity correlates with survival outcomes (Cunningham et al 2004; Saltz et al 2004). In the panitumumab vs BSC trial (Van Cutsem et al 2007b), overall survival of patients with grade ≥2 events is superior to that of patients who have grade 1 adverse events (hazard ratio, 0.61; 95% CI 0.40–0.95). This observation has been consistently reported in trials with EGFR inhibitors reflective of its being a class effect. In addition, EGFR expression as measured by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) is being evaluated although, as noted above, the former is not particularly useful (Chung et al 2005; Pippas et al 2005).

A more compelling approach to identifying patients who will benefit from panitumumab is to assess the status of the K-ras oncogene. This gene encodes a 21 kDa RAS protein which functions as a GTPase involved in signal transduction (Bos 1989; Fearon and Vogelstein 1990). Mutations in K-ras occur early on in carcinogenesis resulting in constitutively activated protein that perpetually drives cellular proliferation. In colorectal cancers, K-ras mutations are frequent (20%–50%), and the great majority of the mutations are clustered in two codons, 12 and 13. The utility of K-ras assessment in the context of panitumumab monotherapy was recently demonstrated with archived tissues from the panitumumab vs BSC study (Amado et al 2008). Roughly 92% of patients were evaluable for K-ras analysis of which 57% were K-ras wild-type or non-mutated and 43% mutated K-ras. Importantly, in the wild-type K-ras patients treated with panitumumab, the median PFS was 12.3 vs 7.3 weeks in the BCS-receiving patients (HR = 0.45, 95% CI 0.34–0.59, $p < 0.0001$). In the mutated K-ras patients, PFS was identical 7.4 vs 7.3 weeks, HR = 0.99 (95% CI 0.73–1.36). Even in the K-ras wild-type patients who initially were assigned to BSC and later crossed-over to panitumumab, a better PFS was observed. In addition, response rates were 17% in the wild-type K-ras patients and 0% in their mutated K-ras counterparts.

These types of retrospective analyses allow for the prediction of patients most likely to benefit from panitumumab and fuel future studies that can prospectively examine the true magnitude of this benefit. A tantalizing hypothesis is that the 40% survival benefit seen in WT-ras patients with panitumuab can be transferred into the first-line setting and rival the survival advantage observed with bevacizumab.

# Conclusions

Significant progress in the treatment of colorectal cancer has been made as new drugs have proven beneficial to metastatic colorectal cancer patient. Biologic agents that target specific vulnerabilities within cancer cells are amongst these newer treatments. The anti-EGFR inhibitor, panitumumab, has demonstrable efficacy in refractory patients especially in regards to PFS. Its utility in other stages of disease and in other subsets of patients is under evaluation. The incorporation of panitumumab into first- and second-line regimens is also currently being tested. In addition, an important predictive biomarker, wild-type K-ras, has been identified and will assist in the pre-selection of patients most likely to benefit from panitumumab. This type of discovery will eventually allow chemotherapy to be tailored to an individual patient, an important milestone in the treatment of colorectal cancer.

# Disclosures

Neither author has any conflicts of interest to disclose.

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