



Panitumumab

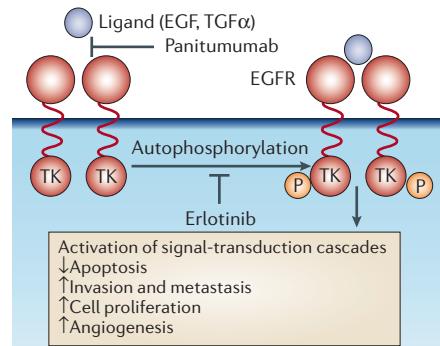
## FRESH FROM THE PIPELINE

## Panitumumab

Chris Easley and Peter Kirkpatrick

In September 2006, panitumumab (Vectibix; Amgen), a fully human antibody against the epidermal growth factor receptor (EGFR), was approved by the FDA for the treatment of patients with EGFR-expressing metastatic colorectal cancer with disease progression on or following fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

In the past 5 years there have been considerable advances in the therapy of colorectal cancer (CRC)<sup>1</sup>, which has been estimated to be the fourth largest cause of cancer deaths worldwide<sup>2</sup>. In particular, the addition of the cytotoxic drugs irinotecan (Camptosar; Pfizer) and oxaliplatin (Eloxatin; Sanofi-Aventis), and the antibody bevacizumab (Avastin; Genentech/Roche), which targets vascular endothelial growth factor (VEGF), to established first-line regimens based on cytotoxic fluoropyrimidines has been shown to significantly prolong survival in metastatic CRC<sup>1</sup>. Furthermore, cetuximab (Erbitux; ImClone/Bristol-Myers Squibb), an antibody against the epidermal growth factor receptor (EGFR), has been approved for the treatment of patients with EGFR-expressing metastatic CRC who are refractory or intolerant to irinotecan-based regimens<sup>3</sup>.



**Figure 1 | EGFR signalling and panitumumab.** Ligand binding to the EGFR causes receptor dimerization (either with another EGFR monomer or with another member of the ERBB family), leading to tyrosine kinase activation<sup>10</sup>. The resultant receptor autophosphorylation initiates signalling cascades involved in cell proliferation and survival<sup>10</sup>. Panitumumab blocks binding of ligands to EGFR. TGF $\alpha$ , transforming growth factor- $\alpha$ ; TK, tyrosine kinase.

**Basis of discovery**

Activation of EGFR, a member of the ERBB family of receptor tyrosine kinases, has been implicated in processes involved in tumour growth and progression<sup>4</sup> (FIG. 1). EGFR is expressed in a wide range of solid tumours, including CRC and non-small-cell lung cancers (NSCLC), which has led to considerable interest in its potential as a molecular anticancer target<sup>4,5</sup>.

Several approaches to targeting EGFR have been investigated, including small-molecule inhibitors of the intracellular tyrosine kinase domain, such as erlotinib (Tarceva; Genentech/OSI), which has been approved for the treatment of NSCLC, and monoclonal antibodies directed against the extracellular ligand-binding domain, such as cetuximab and panitumumab.

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of human EGFR<sup>3</sup>. Chimeric antibodies are potentially immunogenic as a result of their murine components, which might limit their efficacy by causing the production of antibodies against them or make hypersensitivity reactions more common, and so there have been efforts to develop strategies for generating fully human antibodies. One such strategy involves transgenic mouse strains in which human immunoglobulin (Ig) genes are introduced into mice that lack functional mouse Ig genes<sup>6</sup>, which was used to generate the anti-EGFR antibody panitumumab<sup>7,8</sup>.

**Drug properties**

Panitumumab is a recombinant, human IgG2K monoclonal antibody that binds with high affinity specifically to human EGFR<sup>7-9</sup>. Panitumumab blocks the binding of EGFR ligands (FIG. 1) to various EGFR-expressing human cancer cell lines, and inhibits EGF-dependent tumour-cell activation<sup>7-9</sup>. It showed potent activity as a monotherapy in xenograft mouse models of human EGFR-expressing cancers<sup>7-9</sup>, encouraging its clinical evaluation in such cancers, including CRC.

**Clinical data**

The safety and efficacy of panitumumab were studied in an open-label, randomized, controlled trial involving 463 patients with

EGFR-expressing metastatic carcinoma of the colon or rectum<sup>9</sup>. Patients were required to have progressed during or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin and irinotecan; this was confirmed by an independent review committee (IRC) for 75% of the patients<sup>9</sup>. All patients were also required to have EGFR expression, defined as at least 1+ membrane staining in  $\geq 1\%$  of tumour cells as assessed by the Dako EGFR pharmDx test kit<sup>9</sup>.

Patients were randomized 1:1 to receive panitumumab (6 mg per kg dose as an intravenous infusion once every 2 weeks) plus best supportive care (BSC) or BSC alone until investigator-determined disease progression<sup>9</sup>. Following investigator-determined disease progression, patients in the BSC-alone group were eligible to receive panitumumab and were followed until disease progression was confirmed by the IRC<sup>9</sup>. The analyses of progression-free survival (PFS), objective response and response duration were based on events confirmed by the IRC that were masked to treatment assignment<sup>9</sup>.

On the basis of the IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving panitumumab compared with those receiving BSC alone<sup>9</sup>. The mean PFS was 96 days in the panitumumab arm and 60 days in the BSC alone arm<sup>9</sup>. Of the 232 patients randomized to BSC alone, 75% of patients crossed over to receive panitumumab following investigator determination of disease progression, with the median time to crossover being 8.4 weeks<sup>9</sup>. In patients randomized to panitumumab, there were 19 partial responses identified by the IRC, corresponding to an overall response rate of 8%; no patient in the control arm had an objective response identified by the IRC<sup>9</sup>. The median duration of response was 17 weeks<sup>9</sup>. There was no difference in overall survival observed between the study arms<sup>9</sup>.

**Indications**

Panitumumab is approved by the FDA for the treatment of EGFR-expressing metastatic CRC with disease progression on or following fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens<sup>9</sup>. ▶

## ANALYSIS | METASTATIC COLORECTAL CANCER

► Analysing clinical issues related to antibody therapies for metastatic colorectal cancer is Leonard B. Saltz, M.D., Professor of Medicine, Weill Medical College of Cornell University, and Attending Physician, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, USA.

Monoclonal antibody (mAb)-containing therapies have become a standard part of therapy of metastatic colorectal cancer (CRC) in many parts of the world over the past 2 years. The anti-VEGF mAb bevacizumab has been shown to improve survival, progression-free survival, and response rate when added to front-line irinotecan/fluorouracil/leucovorin chemotherapy<sup>11</sup>. Another mAb, cetuximab, which targets EGFR, has shown a 23% response rate in patients with irinotecan-refractory colorectal cancer when used in combination with irinotecan, and an 8–11% response rate as a single agent<sup>12,13</sup>.

The recent FDA approval of the anti-EGFR mAb panitumumab as a single agent for the treatment of metastatic CRC has made available another targeted therapy for this disease, although it does not directly open up a new therapeutic avenue of attack. Whether cetuximab or panitumumab might have advantages relative to each other has yet to

be adequately addressed, because no head-to-head comparisons have been performed so far.

Cetuximab is chimeric in structure, with ~30% murine protein. Panitumumab is a fully human mAb and so would be anticipated to have a lower degree of hypersensitivity reactions (HSR). As reported in the label, panitumumab has a small, but not nonexistent rate of HSR (~4% overall incidence, and a ~1% incidence of severe or life-threatening HSRs). Cetuximab's label reports a 3% incidence of severe or life-threatening HSRs. In the absence of head-to-head comparisons, it is not certain if these differences are real, but on face value they would seem to be.

Panitumumab has been developed on an every 2-week schedule, whereas cetuximab so far has been largely used on a once-a-week schedule, although data suggest that the pharmacokinetics of 500 mg per m<sup>2</sup> of cetuximab every other week are quite similar to those of 250 mg per m<sup>2</sup> weekly<sup>14</sup>. As such, it is not clear whether there is a true advantage in scheduling of one drug over the other.

As cetuximab is an IgG1 antibody, it is potentially able to fix complement and initiate antibody-dependent cellular cytotoxicity (ADCC), whereas panitumumab, as an IgG2 antibody, would not have a significant ability to do so. Whether this

might have a meaningful clinical impact on the relative utility of these drugs also remains to be demonstrated. Another important question not yet addressed is whether or not, in irinotecan-refractory colorectal cancer, panitumumab will be more active in the presence of continued irinotecan, than as a single agent, as has been seen with cetuximab.

Given the similarities between these two agents, and the paucity of comparative data, there will be room for individual physician preference in selecting which anti-EGFR mAb to use. However, it would not be clinically defensible to offer panitumumab to a patient who has progressed through a cetuximab-based regimen, or vice versa, unless some unexpected data emerge suggesting that there is a significant non-cross resistance between these two mAbs.

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*doi:10.1038/nrd2204*

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## Box 1 | Market for therapies for metastatic colorectal cancer

Analysing the market for therapies for metastatic colorectal cancer (CRC) is Chris Easley, Engagement Manager, Product & Portfolio Development Practice, IMS Management Consulting, London, UK.

CRC. Colorectal cancer is the third most common cancer in developed countries; of the ~1,000,000 new cases diagnosed annually worldwide, 194,000 are in Europe and 150,000 in the United States. Although many cases of early-stage disease can be successfully treated via surgery, estimates suggest that at least 20% of patients present with CRC that has already metastasized. Improved screening and earlier diagnosis has led to a modest overall decrease in the death rate from CRC over the past 15 years; however, the 5-year relative survival rate for metastatic CRC is only around 10%, indicating the very high unmet therapeutic needs that exist for advanced-stage patients.

Various chemotherapy regimens (typically based on 5-fluorouracil) are in use; however, late-stage CRC treatment requires careful weighing of the potential benefits versus quality-of-life issues and the sometimes severe side effects experienced, even with newer agents such as irinotecan and oxaliplatin. Cetuximab was the first monoclonal antibody (mAb) targeting EGFR approved for EGFR-expressing CRC in patients refractory to, or intolerant of, irinotecan. Bevacizumab, a mAb directed against VEGF, is approved for first-line use in metastatic CRC alongside other chemotherapy drugs.

**Panitumumab.** Panitumumab was approved by the FDA in September 2006 following priority review. It is indicated for use in metastatic CRC patients with disease progression refractory to other chemotherapy regimens. Marketing applications were submitted to the EMEA, Health Canada, Australia and Switzerland during the second quarter of 2006. In addition to competition from bevacizumab, and potentially in the future erlotinib, panitumumab will directly take on cetuximab for market share. The benefit of panitumumab in terms of only requiring biweekly as opposed to weekly administration represents a convenience advantage for patients, and is also expected to translate into a lower price level compared with its main rival. Analysts' 2010 sales forecasts for panitumumab range from US\$850–920 million, although to reach its full potential it will need to achieve uptake in additional tumour types to CRC, such as NSCLC and renal cancer; Phase II trials have already been initiated in the United States for these indications.