Panitumumab the first fully human monoclonal antibody: from the bench to the clinic

Michael Cohenuram and Muhammad Wasif Saif

Panitumumab (formerly known as ABX-EGF) is the first fully human monoclonal antibody to epidermal growth factor receptor to enter clinical trials for the treatment of solid tumors. Like cetuximab (Erbitux; BMS), it is directed against the extracellular ligand-binding domain of the receptor and results in blockade of the essential downstream signaling pathways that are known to govern apoptosis, proliferation and differentiation of both normal and neoplastic cell types in a wide array of tissues. It has a very high affinity for epidermal growth factor receptor and has been generally well tolerated and associated with very few infusion reactions. As a fully human agent, panitumumab has not been associated with the formation of any antibodies directed against it that has been evidenced by a very reliable pharmacokinetic profile with possible dosing schedules ranging from 1 to 3 weeks. Similar to other agents targeting the epidermal growth factor receptor pathway, a rash has been the primary toxicity and is dose dependent up to 2.5 mg/kg at which dose 100% of all patients have been affected. The anti-tumor activity of panitumumab has been tested *in vitro* and *in vivo,* and inhibition of tumor growth has been observed in numerous cancer models, particularly lung, kidney and colorectal. It has been efficacious and well tolerated both as monotherapy and in combination with other chemotherapeutic agents. Several phase I trials, two phase II trials and most recently a phase III trial in pretreated colorectal cancer have been carried out to date. Currently, there is also a randomized phase III trial (Panitumumab Advanced Colorectal Cancer Evaluation Study) investigating the role of panitumumab in the first-line treatment of colorectal cancer. No unfavorable drug–drug interactions have been observed nor has there been any effect on the pharmacokinetics of drugs with which it is being used. Recent progress in preclinical and clinical studies of panitumumab is reviewed. *Anti-Cancer Drugs* 18:7–15 © 2007 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2007, **18**:7–15

Keywords: colorectal cancer, cetuximab (Erbitux), epidermal growth factor, panitumumab

Section of Medical Oncology, Yale University School of Medicine, New Haven, Connecticut, USA.

Correspondence to M.W. Saif, Section of Medical Oncology, Yale University School of Medicine, 333 Cedar Street, FMP 116, New Haven, CT 06520, USA. Tel: +1 203 737 1875; fax: +1 203 785 3788; e-mail:wasif.saif@yale.edu

Received 6 July 2006 **Revised** 20 August 2006

Introduction

Agents targeting the epidermal growth factor receptor (EGFR) pathway offer promise for the treatment of patients with advanced disease, particularly when the intent of standard chemotherapy is palliation. EGFR is overexpressed in numerous types of solid tumors, including colorectal cancer (CRC). [1] EGFR activation is associated with proliferation, anti-apoptosis and metastatic spread, making this pathway a particularly compelling target for rational drug design. [1] Currently, there are two classes of anti-EGFR agents: the monoclonal antibodies directed toward the extracellular EGFR domain (cetuximab, panitumumab) and small-molecule tyrosine kinase (TK) inhibitors, which inactivate the receptor enzyme activity (gefitinib, erlotinib) [1].

EGFR (HER1 or ErbB1) belongs to the ErbB family of related cell membrane receptors. [1–3] The other members of this family include: HER2/*neu* (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). [1–3] These receptors are transmembrane glycoproteins consisting of an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and a cytoplasmic domain containing the TK domain and a carboxy-terminal region with tyrosine autophosphorylation sites. [1–3] After receptor–ligand binding, dimerization and autophosphorylation of the receptor TK, a complex series of signal transduction pathways are activated, and downstream signaling molecules such as mitogen-activated protein kinase, AKT and phosphatidylinositol 3′-kinase are known to effect key tumorigenic processes such as proliferation, differentiation, migration/motility, adhesion, prevention of apoptosis, enhanced survival and gene transcription [1,2].

EGFR is expressed on nearly all normal cells, particularly those of epithelial origin such as the liver, skin and gastrointestinal tract, but not on hematopoietic cells [3,4]. The level of expression is highly variable in normal tissues. [4] The EGFR signal is strictly regulated in normal cells [1,2]. In malignant cells, EGFR TK may be inappropriately activated and drives uncontrolled cancer

0959-4973

growth as well as angiogenesis and metastatic tumor spread [1,2]. This excessive signaling in tumor cells may be the result of EGFR overexpression, increased production of receptor ligands, heterodimerization with other ErbB receptors, transactivation of heterologous signaling networks within the cell, activating mutations or loss of regulatory mechanisms for receptor signaling [5,6]. In the 1980s, EGFR was identified as a cellular oncogene with homology to the v-*erb*-b viral oncogene and investigators began to explore the possibility of blocking this receptor to inhibit tumor growth [2]. The inhibition of cell growth resulting from blockade of EGFR is characterized by G_1 cell cycle arrest that has been attributed to blockade-induced upregulation/accumulation of the cyclin-dependent kinase inhibitors $p27^{kip1}$ and/or $p21^{cip1/waf1}$ [5,6].

Cetuximab is a chimeric IgG1 monoclonal antibody (MAb) that selectively binds EGFR. In addition to the effects of blocking the EGFR signaling pathways, immunologic effects, such as cell-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, may contribute to cetuximab's mechanism of action [5]. Cetuximab has demonstrated activity and survival benefits in combination with cytotoxic chemotherapy in phase II trials in patients with CRC, and in phase III trials in combination with both cytotoxics and radiotherapy in squamous cell carcinoma of the head and neck [7–11]. The most common side-effect of cetuximab is a rash. Allergic and anaphylactoid reactions have been reported with cetuximab administration [7–11]. The development of human anti-chimeric antibodies (HACAs) has been reported in four of 120 patients (3.3%); three of the four patients had neutralizing antibodies [12]. Other humanized MAbs against EGFR with demonstrated activity against solid tumors include: EMD72000 (matuzumab), OSAG101/Theraloc (nimotuzumab) and h-R3 (TheraCIM), which are further detailed in Table 1.

Panitumumab

Panitumumab is distinct from the other anti-EGFR MAbs under study in several important ways. As the first fully human MAb, the risk of an immunogenic reaction, while reduced with chimeric or humanized MAbs, is virtually eliminated [13,14]. Panitumumab is administered with no loading dose or premedication. Panitumumab has high affinity and specificity for the EGFR, exhibiting dose-dependent pharmacokinetics (PKs) and a 50% inhibitory concentration, substantially lower than that of cetuximab. Activity in a variety of solid tumors has been reported [15–20].

Much progress has been made in the generation of MAbs with therapeutic potential since the initial development of hybridoma technology nearly three decades ago [21]. The early MAbs were fully murine proteins, which elicited a humoral immune response in humans; human anti-mouse antibodies. This reaction limited the safety and efficacy of MAbs, particularly with respect to repeat administrations. Chimeric antibodies, which contain a human antibody constant region with a murine variable region, offered some improvement. At approximately 34% mouse origin, however, chimeric antibodies are still potentially immunogenic [14]. Humanized antibodies, which contain 5–10% murine proteins, have been created by fusing a murine variable or hypervariable region to human constant region [13]. Although clearly less immunogenic, humanized MAbs are still capable of eliciting a humoral immune response.

Fully human MAbs can be expected to produce minimal, if any, immunogenic response, and may be more suitable for the chronic treatment and management of patients with cancer. Generation of a fully human MAb has been accomplished via several different technologies such as the creation of a transgenic strain of mouse, known as XenoMouse; a product of crossbreeding between mice designed to be homozygous for deletions in their own heavy and light chain loci with other mice transfected with yeast vectors bearing human heavy and light chains [13].

In-vitro and preclinical activity of panitumumab

The treatment of athymic mice with panitumumab 0.2 mg intraperitoneally twice weekly for 3 weeks completely prevented the formation of EGFR-over-expressing human epidermoid carcinoma A431 xenografts

Table 1 Monoclonal antibodies directed against epidermal growth factor receptor

Monoclonal antibody	Description	Status	Additional comments
Cetuximab (C225)	chimeric IgG1	approved for CRC approved for head and neck cancer phase II NSCLC and others	rash common rare anaphylactoid reactions hypomagnesemia is on target effect
Matuzumab (EMD72000)	humanized IgG1	phase I and II for CRC phase II for recurrent ovarian cancer phase II for NSCLC phase II for esophogastric cancer	q3 week dosing possible headache and fever at high doses have been dose limiting maximally tolerated dose has been determined
Nimotuzumab TheraCIM (h-R3)	humanized IgG1	currently under study in head and neck cancer gliomas pancreatic cancer	being studied in conjunction with radiotherapy

CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

[22]. Furthermore, administration of panitumumab at low doses for 3 weeks without concomitant chemotherapy or radiation fully eliminated tumors as large as 1.2 cm^3 and a total dose of 0.6 mg was successful in extirpating tumors in 65% of the inoculated mice. Although similar results have been reported with other EGFR-targeted agents, the fact that no tumor recurrences have been noted for more than 8 months after the last antibody injection in any of the animals makes the results with panitumumab unprecedented [23–28]. The authors of the study suggest that this further reflects the capacity of panitumumab to effect total tumor cell eradication [22].

In addition to the demonstrated inhibition of growth in EGFR-overexpressing cell lines, such as A431 and MDA-MB-468, panitumumab has also been shown to inhibit growth of other cancers with significantly lower levels of EGFR expression [13]. Similar results were observed in the renal, breast, pancreatic, ovarian, prostate and CRC human tumor xenografts with varying EGFR expression [13]. The magnitude of tumor growth inhibition achieved following panitumumab treatment, however, seemed to relate to a threshold EGFR level as significant growth inhibition of xenografts expressing at least 17 000 receptors per cell were noted, whereas xenografts expressing 11 000 or fewer receptors per cell seemed not to be affected by panitumumab treatment [13].

Further studies using the A431 tumor model demonstrated that panitumumab administered concomitantly with cytotoxic chemotherapy produced additive anti-tumor effects. The A431 inoculated nude mice were either treated with placebo, cisplatin 50 μg, panitumumab 30 μg or combined cisplatin and panitumumab. Significant divergence in mean tumor volumes was seen by day 18 and by day 47; the cohort receiving combined treatment had a tumor volume that was approximately 25% of those treated with panitumumab alone and approximately 10% of the group receiving cisplatin monotherapy [13,29].

Pharmacokinetics in animal models

Pharmacologic studies of panitumumab in mice and non-human primates have been used to simulate the PK profiles in humans and predict effective dosing regimens. Clearance (CL) of panitumumab in mice, in which the MAb is not cross-reactive, was slow and linear. In contrast, in cynomolgus monkeys, in which there is expected to be a degree of cross-reactivity, CL decreased from 20 ml/kg/day at a dose of 0.6 mg/kg down to approximately 8 ml/kg/day at a dose of 6 mg/kg and only decreased to approximately 5 ml/kg/day when the dose was further increased by a magnitude of 10. On the basis of the rapid CL seen in the monkeys at non-saturating doses, human CL was similarly anticipated to be non-linear owing to the role of the EGFR itself as a mode of MAb CL [30]. The dose-schedule determined for phase I studies was based on allometric scaling of the aforementioned data [31].

Clinical studies panitumumab

Two phase I and two phase II studies (one monotherapy and one in combination with chemotherapy) for metastatic CRC have been conducted. Additionally, interim analyses of two ongoing phase II studies were presented at the 2006 American Society of Clinical Oncology (ASCO) Meeting.

Phase I studies

Rowinsky *et al.* [32] performed a phase I study of panitumumab to determine the anti-tumor activity of panitumumab in previously treated patients with metastatic renal cell carcinoma, and to characterize its toxicity, immunogenicity, PKs and pharmacodynamics. Eighty-eight patients were treated with panitumumab doses of 1.0, 1.5, 2.0 or 2.5 mg/kg weekly with no loading dose. Major responses occurred in three patients, and two patients had minor responses. Forty-four patients (50%) also had stable disease (SD) at their first 8-week assessment and the median progression-free survival (PFS) was 100 days [95% confidence interval (CI), 58–140 days]. An acneiform rash was the principal toxicity and occurred in 68, 95, 87 and 100% of patients who received at least three doses of panitumumab at 1.0, 1.5, 2.0 and 2.5 mg/kg/week, respectively. The rash was noted to reach maximal intensity between weeks 3 and 5, and then steadily abated despite continued treatment. Of the patients receiving 2.5 mg/kg, 75% experienced grade 2 and 3 skin reactions compared with 32–52% of those being treated with the lower dose levels. A trend indicated that the severity of the rash may relate to PFS. The other most frequent toxicities were asthenia, unspecified pain and back pain, none of which were dose related nor were they dose limiting. The hypothesized intrinsic lack of immunogenicity to this fully human MAb was supported by the fact that no human anti-human antibodies (HAHAs) were detected. Panitumumab PKs fit a model that incorporated both linear and saturable EGFR-mediated CL mechanisms, and interindividual variability was low. Steady states increased non-linearly with the dose and the half-life derived as a secondary parameter when the receptor-mediated CL pathway was saturated at 15.9 days. At both the 2.0 and 2.5 mg/kg/week dose levels, concentrations throughout treatment exceeded those estimated to saturate non-linear CL and inhibit xenograft growth by 90%, and concentrations achieved with 1.5 mg/kg/week approached this as well.

A second phase I trial by Figlin *et al.* [33] using doses ranging from 0.1 mg/kg up to 2.5 mg/kg was performed with 43 patients with multiple tumor types; renal ($n = 10$), prostate ($n = 13$), non-small-cell lung cancer (NSCLC) ($n = 7$), pancreatic ($n = 3$), esophageal ($n = 3$)

and CRC ($n = 7$). Patients received up to 4 weekly doses, and those evidencing response or stability were eligible to continue to receive treatment every other week for 6 additional months or until disease progression. Biologic activity was seen even with low doses, including one patient with esophageal cancer treated with the lowest dose that had SD for 7 months. A partial response (PR) of 10 months duration was seen in one patient with colorectal cancer treated with 2.5 mg/kg. The incidence of rash in patients receiving 2.0 or 2.5 mg/kg approached 100%. Overall, panitumumab was well tolerated and no allergic reactions, infusion-related or serious adverse events were observed. Moreover, no HAHAs were detected.

Weiner *et al.* updated the data reported by Figlin *et al.*, treating an additional 50 patients, with updated report at the 2005 ASCO Meeting. Sequential cohorts were enrolled to receive four infusions of panitumumab monotherapy at different dose levels ranging from 0.01 to 5.0 mg/kg once per week, 6.0 mg/kg every 2 weeks and 9.0 mg/kg every 3 weeks [34]. Ninety-six patients were enrolled and treated (CRC $n = 39$, lung $n = 14$, pancreatic $n = 3$, prostate $n = 21$, renal $n = 15$, esophageal $n = 3$ and anal cancer $n = 1$). Grade 3 or 4 toxicities were observed in 10% of patients with 7% being grade 3 skin toxicity. No maximally tolerated dose was reached and PKs were noted to be stable over the range of dosing schedules. Of particular note, five of the 39 CRC patients achieved PR.

Phase II studies

Phase II trial of panintumumab as monotherapy in patients with chemorefractory metastatic colorectal cancer. The primary end point of this study was to assess the OR with secondary objectives to evaluate the safety and efficacy of panitumumab in patients with CRC following 8 weeks of therapy including response rates and PFS and overall survival (OS) [35,36]. Assessment based on level of EGFR expression was also carried out. Patients enrolled into the study had measurable disease, an Eastern Cooperative Oncology Group performance status of no higher than 1 and had failed therapy with a fluoropyrimidine with irinotecan or oxaliplatin or both. A total of 148 evaluable patients were entered into this study. One hundred percent of the patients had received prior treatment with a fluoropyrimidine, 96% with irinotecan and 49% with oxaliplatin. Patients received a weekly dose of 2.5 mg/kg over 1 h and no loading dose or premedications. Patients were allowed to continue on panitumumab as long as there were clinical benefits and no unacceptable toxicities.

Panitumumab was generally well tolerated, with rash and fatigue being the most commonly reported adverse events in the trial. The rash was typically a maculopapular acneiform rash appearing on the face and trunk within 1–3 weeks of beginning of panitumumab therapy. The rash persisted, usually without worsening, through the duration of treatment. Only four patients discontinued treatment owing to skin toxicity. Grade 3 toxicities were infrequent and there were no reported grade 4 events. Only one patient had a grade 3 infusion reaction and this did not result in any interruption of treatment. In the testing of 107 patients to date, no HAHA formation has been detected.

By Response Evaluation Criteria In Solid Tumors criteria with central review, 9% (13) of patients were found to have responded after 8 weeks of therapy. Overall, 29% of patients had SD with a median duration of response of 5.2 months and a median OS of 9.4 months. No meaningful difference was seen when the results were broken down into the two cohorts as based on immunohistochemical demonstration of EGFR expression.

A retrospective analysis to determine the effect of prior regimens on response to panitumumab did not show any significant difference in response between patients who had received three prior agents as opposed to two. Similar to other studies with EGFR-related agents, there was a trend toward a correlation between clinical response and severity of the rash; approximately 62% of those with at least a grade 2 rash had either a PR or SD.

Phase II trial in combination with either IFL or FOLFIRI as first-line therapy for metastatic colorectal cancer. This phase II study was performed to assess both the safety and efficacy of panitumumab when given in combination with IFL (Saltz regimen: irinotecan 125 mg/m^2, leucovorin 20 mg/m^2 and 5-FU 500 mg/m^2 on days 1, 8, 15 and 22) as first-line therapy in metastatic CRC patients [37,38]. All patients were required to have EGFR expression of 2+ or 3+ in 10% or more by immunohistochemistry. The first 19 patients received panitumumab in combination with IFL weekly for 4 weeks of each 6-week treatment cycle. On the basis of the data from the first few patients and the change in the standard of care from bolus to infusional 5-FU, the decision was made to amend the protocol to include another regimen, FOLFIRI (irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and 5-FU as a 400 mg/m^2 bolus followed by 2.4–3 g/m^2 over 46 h) [37,38].

Among 19 patients who received panitumumab with IFL, diarrhea was the most common non-skin toxicity observed in this study and skin toxicity was seen in 100% of the participants. Both of these toxicities were expected on the basis of the mechanism of action of these agents. Sixteen percent experienced a grade 3 skin reaction and there were no grade 4 dermatologic reactions. Forty-seven percent experienced grade 3 diarrhea and only one patient experienced grade 4 diarrhea.

Forty-seven percent of the patients on this trial had a response. Five additional patients (26%) had SD. The combination of chemotherapy and panitumumab had a disease control rate (OR + SD) of 74% in this study. The median PFS was 5.6 months and the OS was 17 months.

The patients enrolled into the second part of this study received panitumumab combined with FOLFIRI [38]. Twenty-four patients were entered into part 2 of the study. Initial safety and efficacy results were first presented at the 2005 European Conference on Clinical Oncology Meeting and more updated at the 2006 GI ASCO Meeting, the latter of which included analyses of both parts of the study. In keeping with the greater tolerability of FOLFIRI as opposed to IFL, fewer patients experienced grade 3 or 4 diarrhea; six (25%) and 0 (0%), respectively. All patients experienced skin-related toxicity, grade 3 reactions were seen in four (17%) of the patients and there were no grade 4 dermatologic reactions.

Similar to the results of part 1 of the trial, the disease control rate was 79%, with 33% achieving a PR and 46% exhibiting SD. Median PFS is 10.9 months, whereas survival data is not yet mature.

Phase II studies of pretreated patients with metastatic colorectal cancer stratified on the basis of the level of epidermal growth factor receptor expression

Interim analyses of two ongoing multicenter phase II studies are investigating panitumumab monotherapy in patients whose disease has progressed despite treatment with two or more regimens with fluoropyrimidines; irinotecan and oxaliplatin were recently presented at the 2006 ASCO meeting [39,40]. Patients with tumors expressing EGFR in more than 10% of cells are being enrolled into one of the studies. The other study is investigating the efficacy of panitumumab in patients with metastatic CRC whose tumors express low levels of EGFR (1–9%) or who have EGFR-negative (below 1% expression) tumors.

In the study of low and non-expressers of EGFR, 88 of a planned 150 patients have been enrolled and 23 patients have been treated for a sufficient period of time to be included in a safety and efficacy analysis [39]. Two of the 11 patients whose tumor was negative for EGFR had a PR, whereas one of 12 low expressers achieved a PR. An additional 30% achieved SD with a median PFS of 7.9 weeks. In the study of high expressers, 91 patients have thus far been treated with plans to accrue an additional 209 patients. Thirty-nine patients in this trial were included in the efficacy set [40]. Three patients obtained a PR with durations of response between 12 and 14 weeks. An additional eight patients had SD.

Safety profiles for the two studies are fairly equivalent. In both studies, greater than 90% of the patients experienced an adverse event and between 19 and 24% were grade 3 or higher. Not surprisingly, the predominant toxicity was dermatologic with 92% affected in one study and 96% in the other. Hypomagnesemia was also common; 8 and 12%. In the study of low expressers, there were three infusion reactions with one patient discontinuing treatment as a result. In the study of high expressers, there was one hypersensitivity reaction but the patient was able to continue on with the treatment with appropriate premedications. No HAHA formation has been observed in either study.

Phase III study of panitumumab as monotherapy in patients with metastatic colorectal cancer

Mature results from a large, multicenter phase III study comparing panitumumab monotherapy versus best supportive care in patients with pretreated metastatic CRC were recently presented at plenary session of the Annual Meeting of the American Association for Cancer Research [41]. This study of 463 patients was powered to detect a 33% difference in PFS, but the actual figure far exceeded this with a risk reduction of 46% that was statistically significant with $P < 0.000000001$. The overall response rate was 36 versus 10% in the control arm with a median duration of response of 17 weeks. At 6 months, PFS was 18 versus 5% and at 8 months, this difference was still maintained: 10 versus 4%. All responses were evaluated by an independent, central review. Results are summarized in Table 2.

Although no difference has been noted in OS, this is likely to have been confounded by the fact that 75% of those on the best supportive care arm crossed over to panitumumab with impressive results. Of the 174 patients who crossed over to the treatment arm, there was a 9% PR and 32% with SD. Toxicities have been in keeping with what has been seen with earlier trials and there were no grade 3 or 4 infusion reactions. On the basis of these results, Amgen and Abgenix were allowed to file a Biologic License Application for panitumumab, which was accepted and the drug has now been granted priority status by the Food and Drug Administration.

Table 2 Summary of results of phase III trial comparing panitumumab monotherapy versus BSC in patients with metastatic colorectal cancer previously treated with irinotecan and oxaliplatin

	Panitumumab ($n=232$)	BSC ($n=231$)
PFS at 24 weeks (%)	18	5
PFS at 32 weeks (%)	10	4
RR (%)	8	0
SD (%)	28	10
ORR (%)	36	10
Median duration of response (weeks)	17	NA

BSC, best supportive care; PFS, progression-free survival; RR, response rate; SD, stable disease; ORR, overall response rate.

Ongoing studies

Study of panitumumab in CRC proceeds in a number of ongoing trials. As noted, accrual continues in the two studies analyzing safety and efficacy of panitumumab on the basis of levels of EGFR expression. A large, randomized phase III trial, the Panitumumab Advanced Colorectal Cancer Evaluation Study (PACCE), is investigating the role of panitumumab in the first-line therapy of metastatic colorectal cancer. There are two separate cohorts. The first is 800 patients receiving FOLFOX and bevacizumab with or without panitumumab. The second cohort with 200 patients will receive FOLFIRI in addition to the aforementioned biologic agents. The primary analysis will be PFS in the FOLFOX cohort [42]. Additionally, a phase I study is underway to evaluate panitumumab given concurrently with the novel agent AMG 706, an oral drug with activity against multiple TKs including vascular endothelial growth factor, platelet-derived growth factor and Kit [43].

Pharmacokinetics

The PKs of panitumumab has been determined in a number of trials at varying doses and for multiple indications. As mentioned earlier, it has been demonstrated that CL of panitumumab is mediated by two separate pathways [29,30]. The EGFR itself acts as a sink with CL decreasing in a dose-dependent manner [31,32]. Once the receptor becomes saturated, the reticular–endothelial system assumes a greater role and the PK becomes linear [32]. Intersubject variability is low with interpatient coefficients of variation for areas under the curve below 20% even at high doses [44]. On the basis of observations of both clinical safety data and biomarkers of EGFR occupancy (rash and PK), 2.5 mg/kg has been determined to be the optimal weekly dose [32]. Of significant interest is the data from studies employing flexible dosing schedules that demonstrated the trough level for 6 mg/kg q2w and 9 mg/kg q3w to be similar to the aforementioned optimal weekly dose [34,45]. The consistency and stability of the PK over time is consistent with the absence of immunogenicity of panitumumab [33]. Finally, no apparent drug interactions have been observed when panitumumab has been given concurrently with other cytotoxic agents [20,38,46]. Summary of PK studies of panitumumab is given in Table 3 [20,30–32,34,37,38,45–47].

Comparison between panitumumab and cetuximab (Erbitux)

No prospective comparative study between panitumumab and cetuximab has been conducted at present [48]. Although no HAHAs to panitumumab have yet been observed, development of human anti-chimeric antibodies has been reported in up to 3% of those receiving cetuximab with a significant number of these antibodies having a neutralizing effect [12]. Thus far there have only been five infusion reactions to panitumumab reported in clinical trials and in only one instance did this result in any treatment interruptions [36,39,40]. Additionally, panitumumab has been able to be administered without premedication, whereas it is recommended that H1 antagonists be administered before cetuximab infusion, and epinephrine, corticosteroids, intravenous anti-histamines, bronchodilators and oxygen should be readily available (Erbitux package insert). In Cunningham's multicenter randomized control trial comparing cetuximab alone versus cetuximab given in combination with irinotecan, four of 329 patients had severe anaphylactic reactions characterized by the rapid onset of airway obstruction, urticaria and hypotension [9]. Although most of these infusion reactions occurred during the initial infusion, severe reactions have also been seen with later treatments and it is recommended that all patients receiving cetuximab be observed for at least 1 h after their infusion (Erbitux package insert).

The skin reaction is an on-target effect, as it is seen with significant frequency with both panitumumab and

Table 3 PK studies of panitumumab

Study	Summary of results	References
Preclinical in-vivo animal-based studies	clearance mediated by both the reticular–endothelial system and epidermal growth factor receptor itself; both linear and nonlinear minimal interpatient variation optimal weekly dose 2.5 mg/kg at which clearance is near its minimum and EGFR is near saturation	Roskos *et al.* [30,31]
Phase I in patients with metastatic renal cell cancer	clinical data nearly identical and thus confirming findings from pre-clinical studies	Rowinsky *et al.* [32]
Phase I study in advanced cancer	doses of 6 mg/kg q2w and 9 mg/kg q3w safe and feasible trough levels consistent and predictable and similar to that found for weekly dosing at 2.5 mg/kg no MTD reached	Weiner [34], Arends and Yang [45]
Phase II study in metastatic CRC	stable PK when given in conjunction with IFL PK of irinotecan unaffected no increase in toxicity	Hecht *et al.* [37,38,46,47]
Phase II study in advanced NSCLC	safe and well tolerated when given in conjunction with paclitaxel and carboplatin no PK interactions	Crawford [20]

PK, pharmacokinetic; CRC, colorectal cancer; MTD, maximally tolerated dose; IFL, irinotecan 125 mg/m^2, leucovorin 20 mg/m^2 and 5-FU 500 mg/m^2; NSCLC, non-small-cell lung cancer.

cetuximab. Cetuximab has, however, additionally demonstrated several unique toxicities. In the aforementioned study by Cunningham, almost 10% of patients treated with cetuximab monotherapy developed significant asthenia and three of 774 patients have developed severe cases of interstitial lung disease (Erbitux package insert). Both cetuximab and panitumumab have been associated with hypomagnesaemia, which is thought to be an on-target effect of the drug class owing to strong EGFR expression in the loop of Henle [49].

Although panitumumab has been demonstrated to have a significantly higher affinity for the EGFR ($K_D = 0.05$ versus 0.39 nmol/1), cetuximab has also been found to saturate the systemic CL at dose levels that are easily tolerable [10]. Both drugs have demonstrated reliability with minimal interpatient variability and dose-dependent, non-linear PK. Neither of the MAbs has been found to have adverse interactions with concurrent cytotoxic chemotherapies either in terms of their PK or their toxicities, and thus are felt to be both safe and efficacious, both alone and in multidrug regimens [7–10,19,35,36,43,46,50]. Of the two drugs, only panitumumab has currently demonstrated flexible dosing schedules [34,45].

As noted above, panitumumab has demonstrated efficacy in a wide range of solid tumors. Similarly, cetuximab has been found to be efficacious and indeed is in widespread clinical use in solid tumors ranging from CRC to head and neck to NSCLC. Both panitumumab and cetuximab have been tested as monotherapy in patients with metastatic CRC that was refractory to standard first-line and second-line regimens with results listed in Table 4 [8,34,35,45]. Only panitumumab has been studied in a phase III setting versus best supportive care and thus is discussed separately.

Both groups were heavily pretreated and while inclusion criteria for the cetuximab group mandated demonstrated progression during or within 3 months of irinotecan-based therapy, 96% of those in the panitumumab study had similarly failed irinotecan. There may, however, have been significant differences in the baseline clinical characteristics between the two studies as suggested by the fact that the median survival time seen in the panitumumab study exceeded that seen in the study of cetuximab and irinotecan. Regardless, both drugs have established efficacy with statistical significance even in patients with advanced disease that has proved resistant to multiple treatment regimens.

Table 4 Comparison of results of monotherapy with either panitumumab or cetuximab in previously treated patients with metastatic CRC

Features	Panitumumab [35]	Cetuximab [8]
Efficacy		
OR (%)	10	11
TTP (months)	2.5	1.5
OS (months)	9.4	6.9
Acneiform rash		
Overall incidence (all grades)	70–100	89
≥ Grade 3 rash	3.4	5.2
HAHA/HACA (%)	0	3
Allergic reactions (%)		
Overall incidence	<1	3
Other toxicities (%)		
Interstitial lung disease	0	0.5
PK interactions with other chemotherapies	0	0
Affinity for EGFR (nmol/1)	0.05	0.39
Type of antibody	IgG2 100% human protein	IgG1 34% mouse protein
Premedications required	no	yes
Alternative dosing schedules	doses of 6 mg/kg q2w and 9 mg/kg q3w safe and feasible [34,45]	not conclusively studied

CRC, colorectal cancer; OR, objective response; TTP, time to progression; OS, overall survival; HAHA, human anti-human antibodies; HACA, human antichimeric antibodies; PK, pharmacokinetic; EGFR, epidermal growth factor receptor.

Discussion

Panitumumab is a fully human MAb directed against EGFR. Unlike its chimeric and humanized precursors, no immunogenicity has been observed and thus has demonstrated improved safety and reliable dose-dependent PK with an 50% inhibitory concentration lower than other EGFR antibodies already in widespread clinical use. Infusion reactions are markedly fewer, particularly in terms of anaphylactoid reactions, and no loading doses, close observation or premedications have been required. Panitumumab has demonstrated significant activity against a broad array of solid tumors including the renal, breast, pancreatic, ovarian, prostate and CRC, both *in vitro* and in phase I clinical trials. While a threshold level of EGFR expression was seen, it was quite low and the efficacy of panitumumab was otherwise not correlated with levels of expression. Phase I studies have demonstrated that panitumumab is well tolerated. Doses up to 5 mg/kg/week and up to 9 mg/kg q3w have been delivered without observing dose-limiting toxicities. In metastatic CRC, panitumumab has demonstrated significant activity alone and in combination with other chemotherapeutic drugs. PK has been well studied both in phase I and phase II trials, and there have been no PK interactions seen with drugs such as the fluoropyrimidines and irinotecan. Like other EGFR-targeted agents, an acneiform rash has been the most frequently exhibited toxicity, but only infrequently has it been a cause of treatment cessation. The rash tended to appear within the first one to two doses and typically resolved within 4 weeks of treatment cessation. Moreover, there are some data to suggest that the severity of the rash correlates with clinical outcome. Development proceeds and panitumumab is now being studied as part of a multidrug first-line regimen in a randomized phase III trial for metastatic CRC as well as in several phase 2 trials as a salvage regimen.

Conclusion

Panitumumab is the first fully human MAb directed against EGFR in clinical use. It has proven to be very well tolerated both alone and in combination with other cytotoxic chemotherapeutic agents. The PK of panitumumab has been well studied, and has been shown to be very predictable over a wide range of doses and dosing intervals. Panitumumab has demonstrated efficacy both as monotherapy and with standard chemotherapeutic agents in a wide variety of cancer types including NSCLC, renal and CRC. To date no HAHAs have been detected and unlike cetuximab, infusion reactions are infrequent and no premedications are required when administering panitumumab. The only significant toxicity has been a rash similar to that seen with other agents targeting the EGFR receptor and such reactions have been predominantly mild to moderate. In metastatic CRC, panitumumab has been safe and efficacious when given with other commonly used agents in this disease including irinotecan and fluorouracil. Current studies under way are looking at panitumumab in combination with FOLFOX–bevacizumab as well as with novel agents that have yet to come into common clinical practice.

References

1 Ritter CA, Arteaga CL. The epidermal growth factor receptor – tyrosine kinase: promising therapeutic target in solid tumors. *Semin Oncol* 2003; **30**:3–11.

2 Arteaga CL. The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. *J Clin Oncol* 2001; **19**:32s–40s.

3 Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor-receptor positive tumors. *Cancer* 2002; **94**:1593–1611.

4 Ennis BW, Lippman ME, Dickson RB. The EGF receptor system as a target for antitumor activity. *Cancer Invest* 1991; **9**:553–562.

5 Mendelsohn J. Targeting the epidermal growth factor receptor for cancer therapy. *J Clin Oncol* 2002; **20** (**Suppl 18**):1s–13s.

6 Woodburn JR. The epidermal growth factor receptor and its inhibition in cancer therapy. *Pharmacol Ther* 1999; **82**:241–250.

7 Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al.* Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. *N Engl J Med* 2006; **354**:567–578.

8 Saltz L, Meropol N, Loehrer PJ, Needle MN, Kpoit J, Mayer RJ. Phase II Trial of cetuximab in patients with refractory colorectal cancer that express the epidermal growth factor receptor. *J Clin Oncol* 2004; **22**:1201–1208.

9 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**:337–345.

10 Van Laethem JL, Raoul JL, Mitry E, Brezault C, Husseini F, Cals L, *et al.* Cetuximab in combination with biweekly irinotecan, infusional 5-fluorouracil and folinic acid in patients with metastatic colorectal cancer expressing the epidermal growth factor receptor. Preliminary safety and efficacy results. *Proc Am Soc Clin Oncol* 2003; **22**: abstr 1058.

11 Baselga J, Pfister D, Cooper MR, Cohen R, Burtness B, Bos M, *et al.* Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol* 2000; **18**:904–914.

12 Khazaeli MB, LoBuglio AF, Falcey JW, Paulter V, Fetzer M, Waksal H. Low immunogenicity of a chimeric monoclonal antibody (MAb), IMC-C225, used to treat epidermal growth factor receptor-positive tumors. *Proc Am Soc Clin Oncol* 2000; abstr 808.

13 Yang XD, Xiao-Chi J, Corvalan JRF, Wang P, Davis CG. Development of ABX-EGF, a fully human anti-EGF receptor monoclonal antibody, for cancer chemotherapy. *Crit Rev Oncol Hematol* 2001; **38**:17–23.

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** (**Suppl 4**):47–50.

15 Yang XD, Wang P, Fredlin P, Davis CG. ABX-EGF, a fully human anti-EGF receptor monoclonal antibody: inhibition of prostate cancer in vitro and in vivo. *Proc Am Soc Clin Oncol* 2002; abstr 245.

16 Wang P, Fredlin P, Davis CG, Yang XD. Therapeutic potential of ABX-EGF, fully human anti-EGF receptor monoclonal antibody, for the treatment of renal cell carcinoma. *Proc Am Soc Clin Oncol* 2002; abstr 761.

17 Schwartz G, Dutcher JP, Vogelzang NJ, Gollob J, Thompson J, Bokowski RM, *et al.* Phase 2 clinical trial evaluating the safety and effectiveness of ABX-EGF in renal cell cancer (RCC). *Proc Am Soc Clin Oncol* 2002; abstr 91.

18 Figlin RA, Belldegrun AS, Crawford J, Lohner M, Roskos L, Yang XD, *et al.* ABX-EGF, a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody (MAb) in patients with advanced cancer: phase 1 clinical results. *Proc Am Soc Clin Oncol* 2002; abstr 35.

19 Hecht R, Patnaik A, Malik I, Venook A, Berlin J, Croghans G, *et al.* ABX-EGF monotherapy in patients with metastatic colorectal cancer (mCRC): an updated analysis. *Proc Am Soc Clin Oncol* 2004; abstr 3511.

20 Crawford J, Sandler AB, Hammond LA, Schiller J, Belani C, Kozloff M, *et al.* ABX-EGF in combination with paclitaxel and carboplatin for advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2004; abstr 7083.

21 Kohler G, Milstein C. Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion. *Eur J Immunol* 1976; **6**:511–519.

22 Yang XD, Jia XC. 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.

23 Baselga J, Mendelsohn J. Type I receptor tyrosine kinases as targets for therapy in breast cancer. *J Mamm Gland Biol Neoplasia* 1997; **2**:165–174.

24 Mendelsohn J. Epidermal growth factor receptor inhibition by a monoclonal antibody as anticancer therapy. *Clin Cancer Res* 1997; **3**:2703–2707.

25 Ciardiello F, Caputo R, Bianco R, Damiano V, Pomatico G, De Placido S, *et al.* Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res* 2000; **6**:2053–2063.

26 Fan Z, Baselga J, Masui H, Mendelsohn J. Anti tumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus *cis*-diamminedichloroplatinum on well established A431 cell xenografts. *Cancer Res* 1993; **53**:4637–4642.

27 Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boma B, Cunningham A, *et al.* Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* 1997; **57**:4838–4848.

28 Fry DW. Inhibition of the epidermal growth factor receptor family of tyrosine kinases as an approach to cancer chemotherapy: progression from reversible to irreversible inhibitors. *Pharmacol Ther* 1999; **82**:207–218.

29 Foon K, Yang XD, Weiner LM, Belldegrun AS, Figlin RA, Crawford J, *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.

30 Roskos L, Arends R, Lohner M, Osborn K, Pasumarti R, Lu H, *et al.* Optimal dosing of Panitumumab (ABX-EGF) in cancer patients. *18th UICC International Cancer Congress*, abstr, 2002.

31 Roskos L, Lohner M, Schwab G. A biomathematical model of neoplastic cell growth and prediction on silico of effective doses of ABX-EGF in cancer patients. *Proc Am Assoc Cancer Res* 2001; **42**:833. (abstr 4471).

32 Rowinsky E, Schwartz GH, Gollob JA, Thompson JA, Vogelzang NJ, Figlin R, *et al.* Safety, pharmacokinetics and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J Clin Oncol* 2004; **22**:3003–3015.

33 Figlin RA, Belldegrun AS, Crawford J, Lohner M, Roskos L, Yang XD, *et al.* ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with advanced cancer: phase 1 clinical results. *Proc Am Soc Clin Oncol* 2002; abstr 35.

34 Weiner LM. Updated results from a dose and schedule study of Panitumumab (ABX-EGF) monotherapy in patients with advanced solid malignancies. *Proc Am Soc Clin Oncol* 2005; abstr 3059.

35 Hecht JR, Patnaik A, Malik I, Venook A, Berlin J, Croghan G, *et al.* ABX-EGF Monotherapy in patients with metastatic colorectal cancer: an updated analysis. *Proc Am Soc Clin Oncol* 2004; abstr 3511.

36 Malik I, Hecht JR, Patnaik A, Venook A, Berlin J, Croghan G, *et al.* Safety and Efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 2005; abstr 3520.

37 Berlin J, Malik I, Picus J. Panitumumab therapy with irinotecan, 5-fluorouracil, and leukovorin (IFL) in metastatic colorectal patients. *Proc Eur Soc Med Oncol* 2004; abstr 265PD.

38 Hecht J, Posey J, Tchekmedyian S, Hu E, Malik I, Yang L, *et al.* J. Panitumumab in combination with irinotecan, 5-fluorouracil, and leukovorin

(IFL) or FOLFIRI for first-line treatment of metastatic colorectal cancer. Program of the American Society of Clinical Oncology Gastrointestinal Cancers Symposium; San Francisco, abstr 237, 2006.
39 Hecht J, Mitchell E, Barada J, Malik I. Panitumumab antitumor activity in patients with metastatic colorectal cancer expressing low (1–9%) or negative levels of EGFR. *Proc Am Soc Clin Oncol* 2006; abstr 3547.
40 Berlin J, Neubauer M, Swanson P, Harker WG. Panitumumab antitumor activity in patients with metastatic colorectal cancer expressing greater than 10% EGFR. *Proc Am Soc Clin Oncol* 2006; abstr 3548.
41 Peeters M, Van Cutsem E, Siena S, Humblet Y, Alain Hendlisz A, *et al.* A Phase 3, multicenter, randomized controlled trial of panitumumab plus best supportive care (BSC) vs. BSC alone in patients with metastatic colorectal cancer. *Proc Am Assoc Cancer Res* 2006;**47**:A CP–1, abstr.
42 PACCE: a randomized, open-label, controlled, clinical trial of chemotherapy and bevacizumab with and without panitumumab in the first-line treatment of subjects with metastatic colorectal cancer. National Cancer Institute web site. Available at www.clinicaltrials.gov.ct/show/NCT00115765.
43 An open-label, dose-finding study to evaluate the safety of AMG 706 plus panitumumab plus chemotherapy in the treatment of subjects with metastatic colorectal cancer. National Cancer Institute web site. Available at www.clinicaltrials.gov.ct/show/NCT00115765.
44 Roskos L. Low pharmacokinetic variability facilitates optimal dosing of ABX-EGF in cancer patients. *Proc Am Soc Clin Onc* 2002; abstr 362.
45 Arends R, Yang B. Flexible dosing schedules of panintumumab (abx-egf) in cancer patients. *Proc Am Soc Clin Oncol* 2005; abstr 3089.
46 Hecht JR, Berlin J, Malik I, Picus J, Glisson S, Kozloff M, *et al.* Panitumumab therapy with irinotecan, 5-fluorouracil, and leukovorin (IFL) in metastatic colorectal patients: a pharmacokinetic analysis. Program of the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, Hollywood, abstr 259, 2005.
47 Yang B, Hecht JR, Malik I, Picus J, Glisson S, Kozloff M, *et al.* Pharmacokinetics of panitumumab and irinotecan were not altered after first line panitumumab therapy with irinotecan, 5-fluorouracol and leukovorin (IFL) in metastatic colorectal cancer patients. ESMO, abstr 311P, 2005.
48 Saif MW, Cohenuram M. Role of panitumumab in the management of metastatic colorectal cancer. *Clin colorectal cancer.* 2006 July; **6**:118–24.
49 Schrag D, Chung KY, Flombaum C, Saltz L. Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; **97**:1221–1224.
50 Chung KY, Shia J, Kemeny N, Shah M, Schwartz G, Tse A, *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.