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Panitumumab

In the Treatment of Metastatic Colorectal Cancer

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Contents

Abstract

▲ Panitumumab is a fully human immunoglobulin G2 monoclonal antibody highly selective for the epidermal growth factor receptor (EGFR), which is overexpressed in 25–77% of colorectal cancers. This overexpression is frequently associated with a poor prognosis.

▲ In a large, randomised, nonblind, multicentre phase III study in pretreated adult patients with metastatic colorectal cancer and EGFR staining in ≥1% tumour cells, panitumumab 6 mg/kg every 2 weeks plus best supportive care (BSC) was significantly ($p < 0.0001$) more effective in improving progression-free survival than BSC alone; recipients of panitumumab plus BSC had a 46% lower disease progression rate than those receiving BSC alone after a median follow-up of 19 weeks.

▲ Panitumumab 6 mg/kg every 2 weeks or 2.5 mg/kg/week, administered as monotherapy, produced partial response rates of 8–13% and stable disease rates of 21–30% in pretreated patients with metastatic colorectal cancer in three noncomparative, multicentre phase II studies.

▲ Preliminary phase II results also suggest a potential role for panitumumab as first-line therapy in combination with fluorouracil, folinic acid and irinotecan in patients with metastatic colorectal cancer.

▲ Panitumumab was generally well tolerated. Grade 3/4 skin-related toxicities were reported in 14% of patients receiving panitumumab plus BSC in the phase III study (versus 0% of patients receiving BSC alone). An analysis of pooled data found that high-affinity binding antibodies to panitumumab were detected in <1% of patients.

Features and properties of panitumumab (ABX-EGF; Vectibix™)	
Indication	
Treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer with disease progression on or following fluoropyrimidine-, irinotecan- and oxaliplatin-containing chemotherapy regimens	
Mechanism of action	
Fully human monoclonal antibody that is highly selective for the EGFR. It inhibits EGFR-activated cellular activities, including cell proliferation and survival, and pro-inflammatory cytokine and vascular endothelial growth factor production	
Dosage and administration	
Approved dosage (US)	6 mg/kg every 2 weeks
Clinical study dosage	6 mg/kg every 2 weeks and 2.5 mg/kg/week
Method of administration	Intravenous infusion
Pharmacokinetic profile of panitumumab 6 mg/kg every 2 weeks (at steady state)	
Mean peak concentration	213 μg/mL
Mean trough concentration	39 μg/mL
Mean area under the concentration-time curve	1306 μg • day/mL
Mean clearance	4.9 mL/kg/day
Mean elimination half-life	≈7.5 days
Most frequent adverse events (pooled analysis)	
Skin-related toxicities, abdominal pain, diarrhoea, fatigue, hypomagnesaemia, nausea, paronychia	

Approximately 655 000 deaths worldwide each year can be attributed to colorectal cancer.[1] The primary treatment option for patients with colorectal cancer is surgery;[2] however, approximately 50% of patients will subsequently develop metastases.[3,4] The prognosis for these patients is generally poor; median survival from diagnosis is 6–9 months[5] and the 5-year survival rate is <5%.[3] Nevertheless, quality of life, time to disease progression and overall survival in patients with metastatic colorectal cancer can be improved with the use of chemotherapy.[3,4]

Tumour growth is dependent upon the activation of cell membrane receptors, which indirectly control adhesion, motility and proliferation.[4] The epidermal growth factor receptor (EGFR), which is expressed on normal epithelial, glial, smooth muscle and stromal cells[4,6,7] and is involved in the regulation of cellular differentiation and proliferation,[3] is overexpressed in 25–77% of colorectal cancers.[6,8] This overexpression is frequently associated with a poor prognosis[3] and has been linked with a resistance to standard treatment.[9] Furthermore, activation of the EGFR has been found to stimulate tumour growth and progression (including proliferation, angiogenesis, invasion, metastasis and the inhibition of apoptosis).[10] By contrast, the inhibition of EGFR signalling by an EGFR antibody has been shown to reduce the level of DNA-dependent protein kinase (and its activity in the nucleus), which may result in tumour regression.[4]

The recent creation of genetically engineered transgenic mice (in which murine immunoglobulin genes have been replaced with human antibody genes) and advances in the formation of synthetic human antibody libraries have resulted in the generation of fully human (100% human protein sequences) monoclonal antibodies.[11-13] These novel monoclonal antibodies target specific molecular abnormalities and are believed to be associated with reduced anti-antibody response rates and, consequently, enhanced efficacy and safety profiles.[11,14]

This profile focuses on the pharmacology and clinical profile of the fully human IgG2 monoclonal antibody panitumumab (ABX-EGF; Vectibix™)[1] in patients with metastatic colorectal cancer.

1. Pharmacodynamic Profile

- Panitumumab has a high affinity (dissociation constant [K_D] = 5×10^{-11} mol/L) for the EGFR and blocks the binding of epidermal growth factor (EGF) and transforming growth factor-α to the receptor.[15] The binding of panitumumab to the EGFR results in the internalisation of the EGFR, the inhibition of cell growth, the induction of apoptosis, and a reduction in proinflammatory cytokine and vascular endothelial growth factor (VEGF) production.[16]
- Panitumumab was internalised, but not degraded, after binding to the EGFR.[17] In an *in vitro* study,[18] panitumumab induced 20–74% internalisation of the EGFR in various human cancer cell lines (A431, A549, H1975, HeLa) and significantly reduced total EGFR expression (versus the control antibody), but not total AKT expression, as measured by a Western blot analysis (values not stated).
- *In vitro*, panitumumab inhibited the spontaneous production of VEGF and interleukin-8 (IL-8),[17] both of which are known to be expressed as a result of EGFR activation via downstream signalling pathways.[19]
- The ligand-induced activation and auto-phosphorylation of EGFR in HT-29 colon carcinoma and A431 epidermoid carcinoma cells and xenograft models was reduced both *in vitro* and *in vivo* by panitumumab.[20]
- In an *in vivo* study,[13] panitumumab eradicated A431 epidermoid carcinoma xenografts in athymic mice; by contrast, tumour growth was not affected by a human IgG2 non-blocking anti-EGFR antibody (E7.5.2), suggesting that the anti-tumour activity of panitumumab may be related to its ability to block EGF binding.
- In the same study, panitumumab inhibited the growth of tumours expressing >17 000 EGFRs per

1 The use of trade names is for product identification purposes only and does not imply endorsement.

cell but had no effect on tumours expressing ≤11 000 EGFRs per cell.[13]

- Two *in vivo* studies evaluating panitumumab demonstrated significant inhibition of tumour growth in a HT-29 murine xenograft model of human colon cancer ($p < 0.005$ vs IgG2[20] and $p < 0.05$ vs baseline[21]).
- The inhibitory effects of panitumumab on tumour growth were increased by the addition of the tyrosine kinase inhibitor AMG 706[21] or irinotecan[20] in human tumour xenograft models in mice, with the effect of addition of AMG 706 to panitumumab being at least additive.[21]

2. Pharmacokinetic Profile

The pharmacokinetics of panitumumab administered at 2.5 mg/kg/week, 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks to patients with various solid tumours (including colorectal cancer) were evaluated in one phase I study,[22-24] one phase II study[25] and a dose-finding study.[26] Additional pharmacokinetic data are reported in the manufacturer's prescribing information.[16] Where stated, panitumumab was administered as a 1-hour intravenous infusion.[16,24-26]

- Based on the data from a phase I study[22] that indicated >80% saturation of EGFR-mediated clearance (CL) with panitumumab ≥1.5 mg/kg, predicted 90% saturation with a 2 mg/kg dose and observed that saturation of EGFR-mediated CL paralleled the incidence of skin rash, the optimal weekly dosage of panitumumab was determined to be 2.5 mg/kg/week.[23] In order to allow for more convenient administration, the pharmacokinetics of panitumumab 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks were evaluated.[23,24]
- Panitumumab demonstrated non-linear pharmacokinetics when administered as a single agent.[16] Following the infusion of a single dose of panitumumab, the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner (data not reported) and the CL decreased (from 30.6 to 4.6 mL/day/kg) as the dose of panitumumab increased from 0.75 to 9 mg/kg.[16] However, panitumumab AUC values increased in an approximately dose-proportional manner at doses >2 mg/kg.[16]
- Systemic exposure to panitumumab 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks was similar to that of panitumumab 2.5 mg/kg/week.[23,24] Mean AUC values were 853 and 1627 μg • day/mL following the administration of a single 6 mg/kg or 9 mg/kg dose of panitumumab (AUC value for the 2.5 mg/kg dose was not reported); mean maximum serum concentration (C_{max}) values were 147 and 227 μg/mL.[23]
- In a phase I study, mean steady-state trough serum concentrations (C_{trough}) were 49 and 45 μg/mL after the administration of panitumumab 6 mg/kg every 2 weeks (n = 17) or 9 mg/kg every 3 weeks (n = 23) [three doses in total].[23] These values were consistent with those predicted by a two-compartment model (53 and 47 μg/mL, respectively).[23]
- Throughout the dose-finding study, C_{max} and C_{trough} values with panitumumab 2.5 mg/kg/week exceeded those estimated to inhibit xenograft growth by 90% and saturate nonlinear CL in patients with metastatic renal cell cancer.[26] At steady state, serum C_{trough} values for the 2.0 and 2.5 mg/kg/week dosages exceeded the 90% inhibitory concentration (IC_{90}) [calculated from the xenograft models; no quantitative data reported] and, based on the clinical pharmacokinetic data, also exceeded the estimated IC_{90} of the nonlinear CL pathway (11.2 μg/mL).[26] Patients with metastatic renal cell cancer received panitumumab 1.0 (n = 22), 1.5 (n = 22), 2.0 (n = 23) or 2.5 (n = 21) mg/kg/week (with no loading dose) for up to five 8-week periods.[26]
- Steady-state concentrations were reached following the third infusion of the recommended dosage regimen (panitumumab 6 mg/kg every 2 weeks infused over 1 hour).[16] At steady state, mean C_{max} and C_{trough} values were 213 and 39 μg/mL and mean AUC was 1306 μg • day/mL.[16]
- In the dose-finding study, mean steady-state C_{max} concentrations for patients with metastatic renal cell cancer treated with panitumumab 1.0, 1.5, 2.0 and 2.5 mg/kg/week were 22.0, 42.2, 70.1 and 130 μg/mL, respectively; mean steady-state C_{trough}

values were 0.473. 9.69, 27.4 and 48.4 μg/mL, respectively.[26]

- Steady-state serum concentrations for panitumumab 2.5 mg/kg/week, in combination with irinotecan, fluorouracil and folinic acid (IFL), were reached at week 7 in a single-arm phase II study in 19 male and female patients.[25] C_{max} at steady state was 96.4 μg/mL; AUC during the first week was 165 μg • day/mL.[25] Treatment was administered for up to eight 6-week periods.[25]
- Panitumumab CL is dose dependent as a result of progressive saturation of the EGFR.[22] In a phase I study in 43 patients receiving panitumumab ≤2.5 mg/kg/week for ≤4 weeks, mean serum CL ranged from 52 mL/kg/day with the 0.2 mg/kg dose to 16 mL/kg/day with the 2 mg/kg dose.[22] This is supported by data from the dose-finding study in patients with metastatic renal cell cancer in which the mean CL of panitumumab decreased as the dosage increased (1.0 mg/kg/week [n = 20], 14 mL/kg/day; 1.5 mg/kg/week [n = 20], 11 mL/kg/day; 2.0 mg/kg/week [n = 19], 8.5 mL/kg/day; 2.5 mg/kg/week [n = 14], 4.8 mL/kg/day).[26]
- The mean elimination half-life and CL of panitumumab 6 mg/kg every 2 weeks at steady state was ≈7.5 days and 4.9 mL/kg/day.[16]
- Data from a population analysis indicate that age (21–88 years), EGFR staining intensity, gender, mild to moderate hepatic or renal dysfunction and race have no apparent impact on the pharmacokinetics of panitumumab.[16] However, formal pharmacokinetic studies of panitumumab have not yet been conducted in patients with hepatic or renal impairment.[16]

3. Therapeutic Efficacy

Pretreated Patients

The efficacy of panitumumab in the treatment of adult patients with metastatic colorectal cancer relapsing after or unresponsive to prior chemotherapy has been investigated in one randomised, nonblind, multicentre phase III[27] and three noncomparative, multicentre phase II[28-30] clinical studies. The study data are supplemented with data from the manufacturer's prescribing information.[16] The three phase II studies[28-30] evaluated panitumumab as monotherapy; in the phase III study,[27] patients were randomised to receive panitumumab monotherapy plus best supportive care (BSC; BSC included steroids, pain medication and therapy to improve quality of life) or BSC alone. Upon disease progression, patients in the BSC treatment arm of the phase III study[27] were eligible to enter a separate multicentre crossover study[31] and receive panitumumab. All of the studies have been published as abstracts and oral[27,31] or poster[28-30] presentations.

The dosage of panitumumab was 6 mg/kg every 2 weeks[27-29,31] or 2.5 mg/kg/week[30] administered as an intravenous infusion. Pretreated patients in the phase III and phase II clinical studies received a median of 5[16] and 4–8[28-30] infusions of panitumumab. The use of premedication in the clinical studies was not standardised;[16] there were no premedications required per protocol.[32] Patients were treated until disease progression,[27-31] drug intolerability[28-30] or treatment discontinuation.[31]

The studies enrolled male and female adult patients aged 21–88 years with metastatic colon (67–75% of patients) or rectal (25–33% of patients) cancer.[27-30] The main inclusion criteria included metastatic colorectal cancer with documented disease progression during or following chemotherapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.[27-30] In addition, where reported, patients were required to have EGFR staining (by immunohistochemistry [IHC]) in <1%,[29] 1–9%,[29] ≥1%[27] or ≥10%[28] of evaluable tumour cells or as follows:[30] cohort A: 2+/3+ in ≥10% of tumour cells; cohort B: sum of 1+, 2+ and 3+ in ≥10% of tumour cells, but with a sum of 2+ or 3+ in <10% of tumour cells (EGFR staining intensity: 0 = none; 1+ = weak; 2+ = moderate; 3+ = strong). Exclusion criteria for patients in the crossover study included no anti-tumour therapies, investigational agents, radiotherapy or systemic chemotherapy following completion of the phase III study and an interval of no more than 3 months from the last assessment in the phase III study.[31]

Where specified, the primary endpoint was progression-free survival (PFS),[27] objective response[30] through to week 16 (including confirmation ≥4 weeks after the response criteria were first met),[28,29] response duration[28,29] or safety.[31] Secondary endpoints included PFS,[28,29,31] overall survival,[27] time to response,[27-29,31] best[27] objective response rate,[31] response duration,[27,31] survival time[31] and duration of stable disease.[31] Tumour assessments and responses were reported in accordance with modified WHO[28,29] or modified[31] Response Evaluation Criteria in Solid Tumours Group (RECIST)[27,30] criteria.

- Panitumumab plus BSC (n = 231; intent-to-treat population) was significantly more effective than BSC alone (n = 232) in improving PFS in the randomised comparative phase III study.[27] After a median follow-up of 19 weeks, patients receiving panitumumab plus BSC had a 46% relative reduction in the rate of disease progression compared with those receiving BSC alone (hazard ratio [HR] 0.54; 95% CI 0.44, 0.66; p < 0.0001).[27]

- The positive effect of panitumumab plus BSC on PFS compared with BSC alone was also observed in the per-protocol population (n = 337) [HR 0.63; 95% CI 0.50, 0.80] and in various patient subgroups after subset analyses according to gender, age, primary tumour site, ECOG status score and number of prior regimens.[27]

- At week 8, 49% versus 30% of patients receiving panitumumab plus BSC versus BSC alone were progression-free; PFS rates were 18% versus 5% at week 24, 10% versus 4% at week 32 and 1% versus 1% at week 48.[27] Panitumumab plus BSC had no significant effect on overall survival (HR 0.93; 95% CI 0.73, 1.19); however, in interpreting this data it should be noted that 76% of patients in the BSC-alone treatment arm received panitumumab (in the crossover study[31]).[27]

- A partial response was observed in 8% versus 0% of patients treated with panitumumab plus BSC versus BSC alone (p < 0.0001) [figure 1].[27] Stable disease and disease control (objective response plus stable disease) were observed in 28% vs 10% and 36% vs 10% of patients, respectively.[27] Furthermore, panitumumab plus BSC was associated with a median time to response of 8 weeks and a median

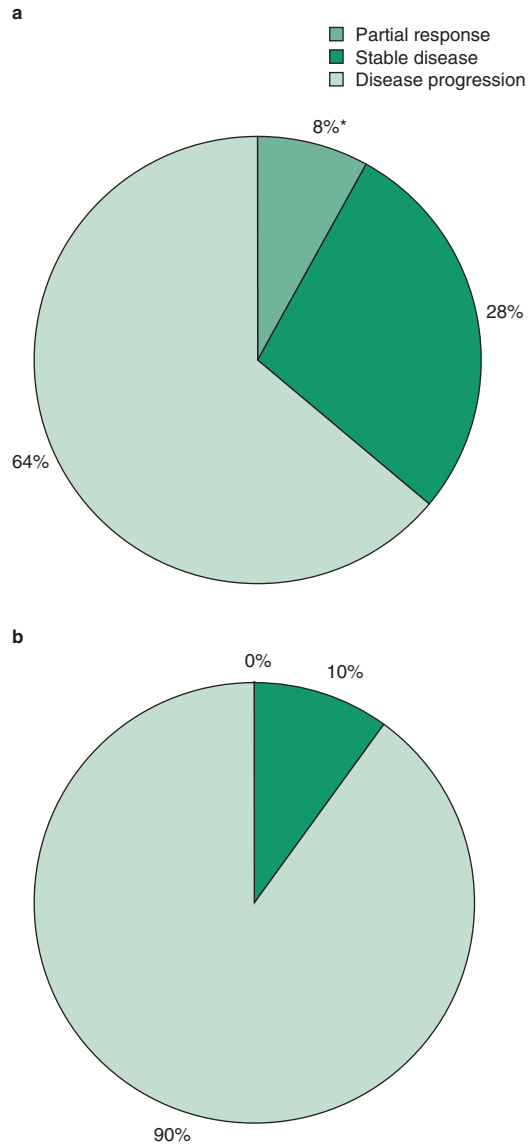

Fig. 1. Comparative efficacy of panitumumab plus best supportive care (BSC) versus BSC alone in patients with metastatic colorectal cancer relapsing after or unresponsive to standard chemotherapy. Partial response, stable disease and disease progression rates in a randomised, nonblind, multicentre phase III study in which patients received (**a**) panitumumab 6 mg/kg every 2 weeks plus BSC (n = 231) or (**b**) BSC alone (n = 232) until disease progression.[27] Data are for the intent-to-treat population. *p < 0.0001 vs BSC alone.

duration of response of 17 weeks (data for the BSC alone treatment group were not reported).[27]

- Of the 232 patients in the BSC treatment arm of the phase III study,[27] 76% (n = 176; intent-to-treat population) crossed over (mean time to crossover 7 weeks) to receive panitumumab therapy.[31] After a median follow-up (in the crossover study) of 12 weeks, complete response, partial response and stable disease were observed in 1%, 11% and 33% of patients. Moreover, panitumumab recipients had a median PFS of 8.1 weeks (95% CI 8.0, 12.4), a median time to response of 8 weeks and a median duration of response of 16 weeks.[31]
- Objective (partial) response rates of 8–13% were seen in the three noncomparative phase II studies.[28-30] Response rates with panitumumab 6 mg/kg every 2 weeks or 2.5 mg/kg/week are shown in figure 2. Where stated, time to response was 7.0–11.6 weeks,[28,29] duration of response was 4.1–18.1 weeks,[28-30] median overall survival was 37.6 weeks[30] and median PFS was 7.6–13.6 weeks.[28-30]
- The relationship between baseline EGFR gene expression levels and a clinical response to panitumumab is not yet clear,[30] despite preclinical evidence indicating a greater response in tumours expressing the gene (see section 1). It has been hypothesised that inhibitor-sensitive cells with low levels of EGFR staining may not register as positively using IHC compared with cells with high levels of EGFR staining.[33] If so, novel assays will be required to ascertain a threshold level for total and/or phosphorylated tumour EGFR (or other markers) that will predict a clinical benefit from EGFR-targeted therapy.[33]

Treatment-Naive Patients

One small, noncomparative, phase II study has investigated the efficacy of panitumumab 2.5 mg/kg/week (administered as a 1-hour intravenous infusion) in combination with fluorouracil, folinic acid and irinotecan (IFL or FOLFIRI regimen) in treatment-naive patients with metastatic colorectal cancer.[34-36] Reports of unacceptable IFL-related toxicity resulted in amendments to the study protocol

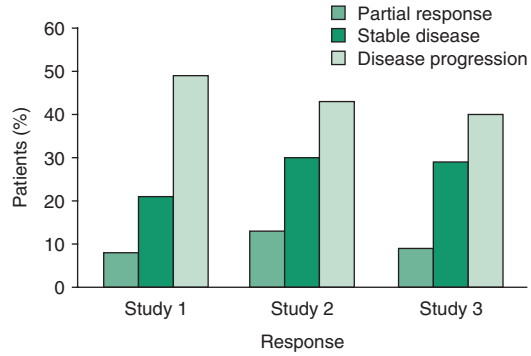

Fig. 2. Efficacy of panitumumab in patients with metastatic colorectal cancer relapsing after or unresponsive to standard chemotherapy. Partial response, stable disease and disease progression rates in three noncomparative, multicentre phase II studies in which patients received panitumumab monotherapy (study 1: 6 mg/kg every 2 weeks, n = 39;[28] study 2: 6 mg/kg every 2 weeks, n = 23;[29] study 3: 2.5 mg/kg/week, n = 148[30]). Where reported, 23%,[28] 13%[29] and 22%[30] of patients were unevaluable. Patients received a median of 4–8 infusions of panitumumab and were treated until disease progression or drug intolerability.[28-30] Data are for the per-protocol[28,29] or intent-to-treat[30] populations.

permitting the use of FOLFIRI.[34-36] Patients aged ≥18 years with an ECOG performance status of 0–1 and EGFR staining in ≥10% of tumour cells were included.[34] The primary endpoint was safety (see section 4); secondary endpoints included objective response, overall survival and PFS.[34] Tumour assessments and responses were reported in accordance with RECIST criteria.[34]

- Preliminary results indicate potential first-line efficacy for panitumumab 2.5 mg/kg/week in combination with FOLFIRI (n = 24).[34] Partial response and stable disease rates were observed in 33% and 46% of patients; median PFS was 10.9 months.[34]
- Partial response and stable disease rates were observed in 47% and 26% of patients receiving panitumumab 2.5 mg/kg/week in combination with IFL (n = 19); median PFS was 5.6 months.[34]

4. Tolerability

Discussion in this section focuses on the multicentre clinical studies in pretreated patients with metastatic colorectal cancer reviewed in section 3 (intent-to-treat analyses)[27-31] and a study in treatment-naive patients with metastatic colorectal cancer also discussed in section 3.[34] These data are

supplemented with data from the manufacturer's prescribing information.[16]

- Panitumumab was generally well tolerated.[27-31] In the randomised, multicentre phase III study, a higher incidence of skin-related toxicities (all grades) was observed in the panitumumab plus BSC (n = 229) versus BSC alone (n = 234) treatment groups (90% vs 6% of patients); grade 3/4 skin-related toxicities were reported in 14% versus 0% of patients (figure 3).[16] The incidence of skin rash is thought to be dose-dependent and related to the saturation of EGFR-mediated CL, indicating full receptor occupancy.[22]

- In the phase III study, other adverse events (all grades) reported in patients treated with panitumumab plus BSC versus BSC alone included fatigue (26% vs 15%), abdominal pain (25% vs 17%), paronychia (25% vs 0%), nausea (23% vs 16%), diarrhoea (21% vs 11%), constipation (21% vs 9%) and vomiting (19% vs 12%).[16] Hypomagnesaemia (all grades) was reported in 39% vs 2% of patients.[16]

- Panitumumab therapy was discontinued in one patient in the randomised comparative study because of a grade 2 hypersensitivity reaction.[27] No grade 3/4 infusion reactions were reported.[27] Infusion reactions (all grades) [including hypersensitivity reactions] occurred rarely (0.6–5% of patients) in the noncomparative studies.[28-30] No infusion reactions were reported in the crossover study.[31]

- According to an analysis of pooled tolerability data from 15 clinical studies evaluating panitumumab (n = 1467), the most common adverse events observed were abdominal pain, diarrhoea, fatigue, hypomagnesaemia, nausea, paronychia and skin rash (variable presentations).[16] A further analysis of pooled tolerability data found that 3% of patients (43/1336) receiving panitumumab experienced an infusion reaction; <1% (6/1336) of these reactions were severe (grade 3 or 4).[16]

- Panitumumab was generally well tolerated in the crossover study.[31] Treatment-related adverse events were reported in 93% of patients; the majority were mild or moderate in intensity and involved skin-related toxicities (all grades: 90% of patients;

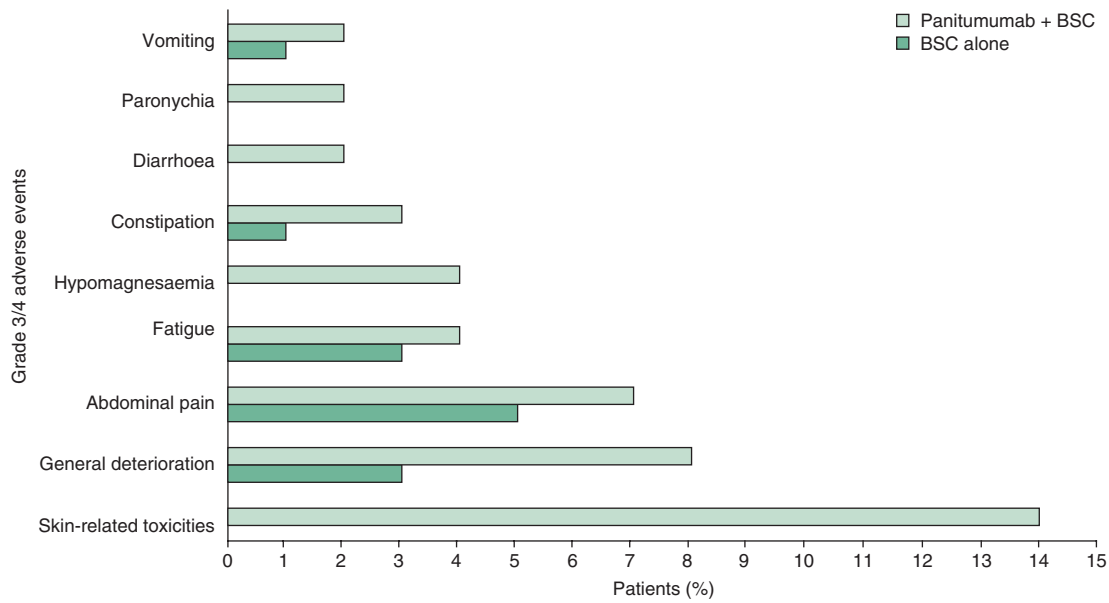

Fig. 3. Comparative tolerability profile of panitumumab in patients with metastatic colorectal cancer relapsing after or unresponsive to standard chemotherapy. The occurrence of treatment-emergent grade 3/4 adverse events in a randomised, multicentre phase III study in which patients received panitumumab 6 mg/kg every 2 weeks plus best supportive care (BSC) [n = 229] or BSC alone (n = 234).[16] Patients were treated until disease progression. Absent bars indicate an incidence of 0%. Data are for the intent-to-treat population.

grade 3 or 4: 13%).[31] Other treatment-related adverse events included paronychia (all grades: 20%; grade 3/4: 2%), eye-related adverse events (all grades: 11%; grade 3/4: 1%), diarrhoea (all grades: 9%; grade 3/4: 1%) and fatigue (all grades: 4%; grade 3/4: 0%).[31] Grade 3 and 4 adverse events occurred in 30% and 3% of patients; 3% of patients experienced grade 3 hypomagnesaemia.[31]

- In the noncomparative studies, 96%[28] and 94%[29] of patients treated with panitumumab alone experienced at least one treatment-related adverse event (all grades).
- Treatment-related skin reactions (mostly dermatitis acneiform, erythema or pruritus; all grades) occurred in 93–97% of patients in the noncomparative studies (n = 88–148).[28-30] Grade 3/4 skin reactions occurred in 7–21% of patients.[28-30]
- Where reported, the most common treatment-related adverse events (all grades) other than skin reactions in these studies were diarrhoea (15–22%),[28-30] fatigue (19–28%)[28-30] and nausea (10–16%).[28-30]
- Hypomagnesaemia of all grades (treatment-related[28,30] or not specified[29]) occurred in 10%,[28] 8%[29] and 2%[30] of patients receiving panitumumab in the noncomparative studies, with grade 3/4 events occurring in 1%,[28] 2%[29] and 0%[30] of patients.
- Where stated, study discontinuation because of an adverse event (all grades) occurred in 4–14%[28-30] of patients receiving panitumumab monotherapy. Serious treatment-related adverse events were reported in 2%[28] and 8%[29] of patients; 1%[28] and 3%[29] of patients withdrew from therapy because of serious treatment-related adverse events.
- Death (mostly due to disease) during treatment or within 30 days of the last dose of panitumumab occurred in 12%[28] and 6%[29] of patients. Treatment-related death was reported in 0–1%[28-30] of patients (pulmonary embolism,[28] myocardial infarction and cerebrovascular accident[29]).
- The incidence of the development of high-affinity binding antibodies to panitumumab, as detected by acid dissociation bridging enzyme-linked immunosorbent assay (ELISA), was <1% (2/612), according to an analysis of pooled tolerability data.[16]
- Intravenous panitumumab 2.5 mg/kg/week was generally well tolerated when given as first-line therapy in combination with FOLFIRI in a noncomparative study.[34] All patients (n = 24) had skin reactions (grade 3: 17% of patients); other common adverse events included diarrhoea (grade 3: 25%; grade 4: 0%) and treatment-related hypomagnesaemia (grade 4: 4%).[34] No panitumumab-induced human anti-human antibodies or severe infusion reactions were reported.[34]
- Grade 3 and 4 diarrhoea (the primary endpoint) was reported in 53% and 5% of patients receiving panitumumab 2.5 mg/kg/week in combination with IFL (n = 19).[34] Treatment-related adverse events included skin reactions (all grades: 100%; grade 3: 16% of patients; grade 4: 0%), hypokalaemia (grade 3: 16%), fatigue (grade 3: 11%), nausea (grade 3: 5%) and hypomagnesaemia (grade 4: 5%).[34] Toxicity related to the IFL regimen resulted in a study protocol amendment permitting the use of FOLFIRI.[34-36]

5. Dosage and Administration

Panitumumab is indicated for the treatment of patients with EGFR-expressing metastatic colorectal cancer who have disease progression on or following fluoropyrimidine-, irinotecan- and oxaliplatin-containing chemotherapy regimens.[16] The recommended dosage regimen is 6 mg/kg every 2 weeks, administered as an intravenous infusion over 1 hour; doses >1000mg should be administered over 1½ hours.[16] Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special populations.

6. Panitumumab: Current Status

Panitumumab has been approved in the US and is currently awaiting registration in Australia, Canada, the EU and Switzerland for the treatment of patients with EGFR-expressing metastatic colorectal cancer who have disease progression on or following fluoropyrimidine-, irinotecan- and oxaliplatin-containing chemotherapy regimens.[37] It is under clinical investigation as both monotherapy and in

combination with other anticancer agents for the treatment of patients with various types of cancer.[37]

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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