An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy


1Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium; 2Divisone Oncologia Falck, Ospedale Niguarda Cà Granda, Milan, Italy; 3Department of Medical Oncology, St-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; 4Department of Oncology-Hematology, Centre Hospitalier Notre Dame et Reine Fabiola, Charleroi, Belgium; 5Medical Oncology Service, Hospital Clinic de Barcelona, Ciberhct, Barcelona, Spain; 6Medical Oncology Unit 2, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 7Klinikum Mannheim; 8Medical Oncology, Ashford Cancer Centre, Ashford, Australia; 9Department of Gastroenterology, Istituto Clinico Humanitas, Rozzano, Milan, Italy; 10Department of Internal Medicine I and Cancer Center, Medical University of Vienna, Vienna, Austria; 11Algoma District Cancer Program at Sault Area Hospital, Sault Sainte Marie, Ontario, Canada; 12Clinical Development, Amgen Inc., Thousand Oaks, CA, USA; 13Medical Affairs Biostatistics, Amgen Ltd, Cambridge, UK; 14HepatoGastroenterology, Digestive Oncology Unit, Ghent University Hospital, Ghent, Belgium

Received 1 April 2007; revised 10 July 2007; accepted 11 July 2007

Background: A phase 3 study demonstrated that panitumumab, a human monoclonal anti-epidermal growth factor receptor antibody, significantly prolonged progression-free survival versus best supportive care (BSC) in patients with chemorefractory metastatic colorectal cancer.

Patients and methods: This open-label extension study evaluated panitumumab monotherapy in BSC patients with radiographically documented disease progression in the phase 3 study. Patients received panitumumab 6 mg/kg every 2 weeks. The primary end point was safety; efficacy was also evaluated.

Results: One hundred and seventy-six patients were randomly assigned to the BSC arm of the phase 3 study received ≥1 panitumumab dose in this extension study. Panitumumab was well tolerated. The most frequent treatment-related adverse events were skin toxic effects. Three (2%) patients had a grade 4 treatment-related adverse event. There were no infusion reactions. One (0.6%) patient had a complete response; 19 (11%) patients had a partial response; and 58 (33%) patients had stable disease. Median progression-free survival time was 9.4 [95% confidence interval (CI): 8.0–13.4) weeks. Median overall survival time was 6.3 (95% CI: 5.1–6.8) months. Anti-panitumumab antibodies were detected in 3 (4.2%) of 71 patients with a post-baseline sample.

Conclusions: These findings are comparable to those from the phase 3 study and support panitumumab monotherapy for chemorefractory colorectal cancer.

Key words: crossover, EGFr, extension study, fully human antibody, metastatic colorectal cancer, panitumumab

introduction

Colorectal cancer is the third leading cause of cancer-related deaths worldwide, with over 500 000 deaths occurring worldwide each year [1]. Combination therapy with fluorouracil/leucovorin, irinotecan, oxaliplatin, and bevacizumab has increased survival rates of patients with metastatic colorectal cancer [2–4]. Despite these improvements, disease relapse is almost universal, and therefore, there is a need for alternative treatments.

The epidermal growth factor receptor (EGFr) signal transduction pathway has long been established as playing a key growth-promoting role in a subset of epithelial tumors. Two monoclonal antibodies (mAb) targeting EGFr, panitumumab and cetuximab, are approved for the treatment of patients with metastatic colorectal cancer [5, 6]. Cetuximab, a chimeric antibody, is registered as monotherapy in the United States for the treatment of patients with irinotecan-refractory metastatic colorectal cancer in combination with irinotecan and in the United States also as monotherapy in patients intolerant to irinotecan [7]. Panitumumab, a fully human Immunoglobulin G2 mAb with a high affinity (Kd = 5 × 10-11 M) for human EGFr, is registered as monotherapy in the United States for the treatment of patients with metastatic colorectal cancer with disease progression during or following fluoropyrimidine-, irinotecan-, and oxaliplatin-containing chemotherapy regimens [8].

The antitumor activity of panitumumab was recently demonstrated in a large phase 3, randomized, controlled trial.
conducted in Europe, Australia, and Canada. Results from this trial demonstrated that panitumumab plus best supportive care (BSC) significantly reduced the rate of disease progression by ~40% compared with BSC alone in patients with metastatic colorectal cancer refractory to standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy [9]. BSC patients in that study who had disease progression were allowed to receive panitumumab by enrolling in an extension (crossover) study. Here, we present the efficacy and safety findings of panitumumab monotherapy from the extension study.

**patients and methods**

**study design and procedures**

The phase 3 study enrolled metastatic colorectal cancer patients with radiographically documented disease progression during or within 6 months after the most recent treatment with a standard fluoropyrimidine-, irinotecan-, and oxaliplatin-containing regimen at an adequate prespecified overall exposure (confirmed by an Independent Eligibility Review Committee) [9]. The extension study was a multicenter, open-label, single-arm trial assessing the efficacy and safety of panitumumab monotherapy in patients with metastatic colorectal cancer, who had radiographically documented disease progression while receiving BSC in the phase 3 study. In addition to documented disease progression, patients were required to complete the last assessment on the phase 3 study not >3 months before enrollment in the extension study, and in the interim could not have received systemic chemotherapy, radiotherapy, investigational agents, or antitumor therapies including approved antitumor small molecules and biologics. During this interval, patients could not have had a myocardial infarction, interstitial pneumonitis, or pulmonary fibrosis. Brain metastases, if present, were to be controlled and asymptomatic. Patients were also required to have adequate renal and hepatic functions and an Eastern Cooperative Oncology Group (ECOG) performance status of zero, one, or two at entry into the extension study. EGFr membrane expression in ≥21% of tumor cells was an eligibility criterion for the phase 3 study [9].

Panitumumab was administered i.v. at a dose of 6 mg/kg once every 2 weeks over 60–90 min until disease progression, unacceptable toxicity, or discontinuation because of investigator and/or patient request. Patients also received BSC. Patients who discontinued the extension study were to complete a safety follow-up visit 4 weeks after the last panitumumab infusion. Patients were followed for survival approximately every 3 months for up to 2 years from the randomization date into the phase 3 study.

The study protocols and informed consent forms were approved by the appropriate institutional review boards, and all patients signed a written consent form before initiation of the study-specific screening procedures.

**safety and efficacy assessments**

The primary end point of this study was safety, including the incidence of grade 3/4 adverse and treatment-related events, skin-related events, and antibody formation. Safety assessments were carried out every 2 weeks and at the safety follow-up visit 4 weeks after the last panitumumab infusion. Adverse events were graded using the National Cancer Institute—Common Toxicity Criteria version 2.0, with the exception of selected dermatological/skin toxic effects (erythema, rash, desquamation, and ulceration), which were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications [10].

Although no secondary end points were prespecified in the protocol, the efficacy of panitumumab monotherapy was explored by assessing progression-free survival, objective response rate, time to and duration of response, duration of stable disease (SD), and survival using the local investigators’ assessment of radiographic images. Patients were evaluated for tumor response every 8 weeks from the first dose of panitumumab and at the time of suspected disease progression according to a modified version of the Response Evaluation Criteria in Solid Tumors [11]. SD was first evaluated at the first scheduled assessment (week 8). Disease control rate was defined as the sum of objective response and SD rates. Tumor responses were confirmed ≥4 weeks after the criteria for response were first met. Patients with no response confirmation were considered nonresponders.

**statistical analyses**

The sample size was limited to the patients enrolled in the BSC arm of the phase 3 study [9] who met the eligibility criteria for both the phase 3 and extension studies (planned n = 200). Assuming a true event rate of 1%, the probability of at least one patient experiencing a given adverse event was 87% for a sample size of 200.

The primary analyses of efficacy and safety outcomes included all enrolled patients who received at least one dose of panitumumab. Time to response was calculated as the period from enrollment date to the first objective response. Duration of response was calculated only for the responders as the period from the first objective response to the first observation of disease progression or death due to disease progression. Duration of SD was calculated as the period from enrollment date to the first observation of disease progression or death due to disease progression; only patients who had at least one scan of SD as their best response were included. Progression-free survival time was calculated as the period from enrollment date to the first observed disease progression or death. Overall survival (OS) time was calculated as the period from enrollment date until death.

Descriptive statistics were calculated for the incidence of objective response [with two-sided 95% confidence intervals (CIs)], adverse events, laboratory values, changes in vital signs, and antibody measurements. Time-to-event outcomes were analyzed by Kaplan–Meier methods. For the analyses on OS, a minimum of 12 months of follow-up were included (data cut-off of March 2006). In addition, among patients with skin toxicity, the relationship between severity of skin toxicity and OS was evaluated using a Cox regression model adjusted for the phase 3 randomization factors, ECOG score, and geographic region. Patients were included in this analysis if they were progression free for at least 28 days to allow the worst severity of skin toxicity to manifest.

**detection of anti-panitumumab antibodies**

Serum samples were collected at screening and the safety follow-up visit. Two validated screening assays were used to test for the presence of anti-panitumumab antibodies. The first screening assay was a bridging enzyme-linked immunosorbent assay that included an acid dissociation step designed to reduce the interference from excess panitumumab in the serum samples (Amgen Inc., Thousand Oaks, CA) [12]. The second screening assay was Biacore-based direct bind immunoassay using surface plasmon resonance to directly detect antibody binding to immobilized panitumumab [13]. All samples testing positive in one or both of the screening assays were tested in a validated cell-based bioassay (Amgen Inc.) for the detection of antibodies capable of neutralizing panitumumab activity. The bioassay utilized the EGFr-expressing adherent human epidermoid carcinoma cell line A431 and measured the neutralization of panitumumab-mediated inhibition of EGFr phosphorylation by a serum containing anti-panitumumab antibodies [13].

**results**

**patients**

Of 232 patients who were randomly assigned to the BSC arm in the phase 3 study, 183 patients were screened for the
extension study. In the phase 3 study, 36 patients died because of disease progression, and 13 patients were not available for screening of the extension study because of consent withdrawal, discontinuation due to an adverse event (wound infection, supraventricular arrhythmia, and septic shock in one patient) or administrative decision, or lost to follow-up. Of the 183 patients, 177 patients were enrolled in the extension study (Figure 1); six patients did not meet the screening requirements because of disease-related or laboratory reasons. The median (95% CI) crossover time was 7.1 (6.7–7.3) weeks from randomization on the phase 3 trial. One patient died after enrollment on the extension study but before receiving panitumumab. Therefore, 176 patients received at least one dose of panitumumab and were included in the efficacy and safety analysis sets. As of February 2006, all patients had ended the treatment; the main reason for discontinuation was disease progression. Median (range) potential follow-up time (calculated from enrollment date in the extension study to the day of the last safety follow-up visit) was 61 (18–103) weeks.

Baseline patient demographics and disease characteristics were captured in the phase 3 study and were not measured again after enrollment into the extension study, except for body weight and ECOG status, which were reassessed at baseline of the extension study (Table 1). All patients had received prior irinotecan- and oxaliplatin-containing chemotherapy regimens.

**exposure to panitumumab**

A total of 1171 panitumumab infusions were administered across all 176 patients, with a median (range) number of 5 (1–29) infusions per patient. The median (range) duration of infusions was 60 (25–145) min.

**safety**

All patients experienced at least one adverse event. Most patients (92%) experienced adverse events that were considered related to panitumumab; 29 (16%) patients had a grade 3

treatment-related adverse event and three (2%) patients had a grade 4 treatment-related adverse event (acute renal failure, pulmonary embolism, erythema, and pustular acne). There were no fatal adverse events related to panitumumab. Treatment-related adverse events with an incidence of at least 5% are summarized in Table 2. The most frequent toxic effects were skin related and included erythema, pruritus, acne, rash, and paronychia. Median (range) time to first skin toxicity was 14 (0–72) days and the median (range) time to most severe skin toxicity was 15 (0–182) days. Treatment-related fatigue occurred in seven (4%) patients. No patient had grade 3 or 4 treatment-related fatigue.

Fifty-one patients (29%) experienced hypomagnesemia (per laboratory values captured as a shift change ≥1 grade from the baseline), with grade 3 and 4 hypomagnesemia being reported in five (3%) patients and two (1%) patients, respectively. One patient with grade 3 hypomagnesemia experienced tachycardia. Magnesium was given orally to 12 (7%) patients and i.v. to four (2%) patients. No patient withdrew from the study because of hypomagnesemia.

<table>
<thead>
<tr>
<th>Patient demographics and disease characteristics</th>
<th>Panitumumab (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 111 (63)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White or Caucasian 175 (99)</td>
</tr>
<tr>
<td>Japanese 1 (1)</td>
<td></td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>62 (32–83)</td>
</tr>
<tr>
<td>≥65 years 67 (38)</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td>Colon cancer 113 (64)</td>
</tr>
<tr>
<td>Rectal cancer 63 (36)</td>
<td></td>
</tr>
<tr>
<td>Number of prior chemotherapy regimens</td>
<td>Median (range) 2 (2–6)</td>
</tr>
<tr>
<td>Number of prior chemotherapy lines</td>
<td>1–2 114 (65%)</td>
</tr>
<tr>
<td>≥3 62 (35%)</td>
<td></td>
</tr>
<tr>
<td>Duration of BSC in the phase 3 study, weeks</td>
<td>0–2 16 (9)</td>
</tr>
<tr>
<td>3–6 45 (26)</td>
<td></td>
</tr>
<tr>
<td>7–10 89 (51)</td>
<td></td>
</tr>
<tr>
<td>11–20 21 (12)</td>
<td></td>
</tr>
<tr>
<td>20–47 5 (3)</td>
<td></td>
</tr>
<tr>
<td>Percentage of tumor cells with membrane EGFr staining</td>
<td>&lt;1% 1 (1)</td>
</tr>
<tr>
<td>1%–9% 45 (26)</td>
<td></td>
</tr>
<tr>
<td>10%–20% 53 (30)</td>
<td></td>
</tr>
<tr>
<td>21%–35% 19 (11)</td>
<td></td>
</tr>
<tr>
<td>&gt;35% 58 (33)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0 53 (30)</td>
</tr>
<tr>
<td>1 85 (48)</td>
<td></td>
</tr>
<tr>
<td>2 38 (22)</td>
<td></td>
</tr>
</tbody>
</table>

BSC, best supportive care; EGFr, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group.
Nausea 8 (5) 0 (0) 0 (0)
Conjunctivitis 10 (6) 1 (1) 0 (0)
Diarrhea 15 (9) 1 (1) 0 (0)
Skin exfoliation 22 (13) 1 (1) 0 (0)
Paronychia and other nail disorders 14 (8) 1 (1) 0 (0)
Any treatment-related adverse eventa 162 (92) 29 (16) 3 (2)
Erythema 112 (64) 8 (5) 1 (1)
Acneb 104 (59) 11 (6) 0 (0)
Pruritus 101 (57) 2 (1) 0 (0)
Rashc 93 (53) 8 (5) 0 (0)
Other skin manifestationsd 65 (37) 4 (2) 0 (0)
Patency of the other nail disorders 50 (28) 3 (2) 0 (0)
Skin exfoliation 22 (13) 1 (1) 0 (0)
Diarrhead 15 (9) 1 (1) 0 (0)
Conjunctivitise 10 (6) 1 (1) 0 (0)
Nausea 8 (5) 0 (0) 0 (0)

Table 2. Treatment-related adverse events occurring in at least 5% of patients

Table 3. Summary of panitumumab efficacy

Deaths
Overall, 145 (82%) of the 176 patients who crossed over to the extension study died either during the treatment period (10% of patients), within 30 days of treatment discontinuation (20% of patients), or after 30 days of receiving the last panitumumab infusion (52% of patients). All deaths during the treatment period but two (cerebrovascular events and possible systemic mycosis associated with fungal stomatitis) were attributed to disease progression; none of the deaths was considered related to panitumumab. The patient who developed fungal stomatitis discontinued the study because of a severe rectal hemorrhage. Fungal cultures were not carried out to confirm systemic mycosis. This patient received a single panitumumab infusion and did not experience skin toxicity.

Efficacy
Twenty (11%) patients had an objective response with panitumumab: one (0.6%) patient had a complete response and 19 (11%) patients had a partial response (Table 3). An additional 58 (33%) patients had a best response of SD, and the disease control rate was 44% (n = 78). Median (95% CI) progression-free survival time was 9.4 (8.0–13.4) weeks compared with the median progression-free survival time of

<table>
<thead>
<tr>
<th>Panitumumab (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best objective response, n (%)</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Disease progression</td>
</tr>
<tr>
<td>Unevaluablee</td>
</tr>
<tr>
<td>Not donef</td>
</tr>
<tr>
<td>Disease control, n (%)</td>
</tr>
<tr>
<td>Time to response</td>
</tr>
<tr>
<td>Median weeks (range)</td>
</tr>
<tr>
<td>Duration of responseg</td>
</tr>
<tr>
<td>Median weeks (range)</td>
</tr>
<tr>
<td>Duration of stable disease</td>
</tr>
<tr>
<td>Median weeks (range)</td>
</tr>
<tr>
<td>Progression-free survival timeh</td>
</tr>
<tr>
<td>Median weeks (95% CI)</td>
</tr>
<tr>
<td>Overall survival timei</td>
</tr>
<tr>
<td>Median months (95% CI)</td>
</tr>
</tbody>
</table>

*Patients who had only one assessment (recorded as stable disease); these assessments were before day 50 after enrollment and were considered unevaluable.
*There was no radiological scan available for the disease assessment.
*For the 20 responders (one complete response and 19 partial responses).
*Of these, at the time of study completion, 15 patients had disease progression and one patient had died because of disease progression.
*At the time of study completion, 158 (90%) patients had disease progression or had died of any cause.
*One hundred and forty-five (82%) patients died (most after the safety follow-up visit).
CI, confidence interval.
7.1 (6.9–7.4) weeks for the same subset of patients who received BSC in the phase 3 study (Figure 2). At the time of study completion, 145 patients (82%) had died mostly after the safety follow-up visit. After a minimum of 12 months of follow-up (data cut-off of March 2006), the median (95% CI) OS time was 6.3 (5.1–6.8) months (Figure 3A).

Response rates were similar on the basis of EGFr tumor cell membrane staining categories as measured by immunohistochemistry (data not shown). In an exploratory analysis of OS by the severity of skin toxicity, patients with grade 2–4 skin toxicity had a longer OS relative to those who had grade 1 skin toxicity [hazard ratio (95% CI) = 0.70 (0.47–1.05); Figure 3B]. This trend towards longer survival, however, did not reach statistical significance.

anti-panitumumab antibody formation

Of 176 patients treated with panitumumab in this study, 152 (86%) patients were tested for the presence of anti-panitumumab antibodies. Seventy-one of the 152 (47%) patients had at least one postdose sample available. Three patients (3 of 71; 4.2%) tested positive post-baseline for anti-panitumumab antibodies; one of these three patients (1.4%) tested positive for neutralizing antibodies in the bioassay.

discussion

The findings of this study indicated that panitumumab monotherapy was well tolerated and effective in patients with metastatic colorectal cancer with disease progression after standard chemotherapy. Most of the patients (76%) in the BSC arm of the phase 3 study crossed over to the extension study at a median time of 7.1 weeks after initial randomization in the phase 3 study.

The safety profile of panitumumab was consistent with the known effects of EGFr inhibitors and previous panitumumab studies [9, 14–17]. The most common treatment-related adverse events were associated with skin and s.c. tissue and were mostly mild or moderate in severity. Only a few patients (4%) discontinued panitumumab or withdrew from the study because of a treatment-related adverse event. Hypomagnesemia was frequent, but most events were grade 1 or 2. Hypomagnesemia has also been reported with cetuximab therapy and is considered to be a class effect with anti-EGFr antibodies [18].

Consistent with their mechanism of action, EGFr inhibitors are associated with skin-related toxic effects [19]. A positive association was observed between the severity of skin toxicity and OS of patients receiving panitumumab in both the phase 3 and extension studies [9]. Prospective studies including skin and tumor biopsies are needed to clarify this relationship.

There were no grade 3 or 4 infusion reactions and the incidence of antibody formation against panitumumab was low, suggesting that fully human antibodies are associated with a low risk of immunogenicity [20]. Although there was some detection of neutralizing antibodies, these do not appear to affect the safety or efficacy of panitumumab.

The efficacy outcomes of the extension study were generally comparable to those from patients receiving
panitumumab in the phase 3 study and previous panitumumab studies and were consistent with other anti-EGFR inhibitors in a similar patient population. Across panitumumab studies, the objective response rate ranged from 7% to 11% [9, 14, 16, 17]. Similarly, cetuximab monotherapy resulted in a response rate of 8.5%–11.6% in patients with metastatic colorectal cancer refractory to both irinotecan and oxaliplatin [15, 21].

In the extension study, the response rates to panitumumab were similar regardless of EGFr staining levels. Similar findings with regards to panitumumab activity and EGFr tumor staining were seen in previous panitumumab monotherapy studies [16, 17], suggesting that EGFr expression as measured by immunohistochemistry may have low predictive value for response to panitumumab in patients with metastatic colorectal cancer.

In the phase 3 study, there was no difference in OS times between the panitumumab and BSC patients (hazard ratio = 1.0) [9]. As expected with this refractory patient population, most patients in the BSC arm (76%) progressed early at a median of 7.1 weeks in the phase 3 study. The patients who crossed over to panitumumab were followed for survival on the BSC arm in the phase 3 study. Sensitivity analyses testing the effect of crossover of patients in the BSC arm to the current study indicated that the rapid crossover of the majority of patients and similar efficacy achieved after crossover may have been responsible for the lack of OS differences observed in the phase 3 study. However, this cannot be formally tested in this study design.

The findings described in this report demonstrate similar safety and efficacy of panitumumab to that observed in other monotherapy studies [9, 14, 16, 17], in a population that was chemotherapy refractory, had actively progressing disease (both criteria were adjudicated by central review in the phase 3 study), and had not been receiving active antitumor therapy when randomized to the BSC arm of the phase 3 study. While these findings indicate evidence of clinical activity in a most advanced patient population, the requirement for disease progression while on the phase 3 study, a basic inclusion criteria for entry in the current study, could have resulted in the selection of patients with the least adverse prognosis among those who received BSC in the phase 3 study.

In conclusion, the results of this study were comparable to the findings from previous panitumumab monotherapy trials, with manageable toxicity and similar response rates, duration of response, and progression-free survival. These findings support the use of panitumumab for the treatment of metastatic colorectal cancer after failure of standard irinotecan- and oxaliplatin-containing chemotherapy regimens.

funding
Amgen Inc., Thousand Oaks, CA.

acknowledgements
We gratefully thank the patients and their families for study participation. We thank the study staffs at each individual site and the following individuals from Amgen Inc.: C. Ravell, for study management; M. Wolf, for statistical analyses; M. Hagendoorn and D. Paterson, for programming support; S. Edgington and T. Hoda, for data management; and H. Moini, of Kendle International, for writing assistance on behalf of Amgen Inc.

references

