Synopsis of Study 20020408

Study Title:	An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer
Investigational Product:	Panitumumab (ABX-EGF)
Indication:	Treatment of subjects with metastatic colorectal cancer who had disease progression during or after prior standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy
Brief Description:	Multicenter, comparative study of panitumumab monotherapy at a dose of 6 mg/kg given once every 2 weeks plus best supportive care versus best supportive care alone in subjects with metastatic colorectal cancer who had documented disease progression during or after prior standard treatment with fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy.
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No:	20020408
BB-IND No:	8382
Study Phase:	Phase 3
Study Initiation Date:	16 January 2004 (first subject randomized)
Data Cut-off Date:	15 March 2007
Principal Investigators:	Multicenter study conducted in Europe, Canada, Australia, and New Zealand
Good Clinical Practice:	This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	10 September 2007

Name of the Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Amgen Inc. Thousand Oaks CA USA	Panitumumab (ABX-EGF)	rHuMAb-EGFr

Title of Study:
An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer

Investigator(s) and Study Center(s):
This was a multicenter study conducted at 81 institutions in Europe, Canada, Australia, and New Zealand.

Publication(s):
Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658-1664.

Van Cutsem E, Humblet Y, Canon J-L, et al. An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. Ann Oncol. 2007; doi: 10.1093/annonc/mdm399.

Study Period:	**Development Phase:**
16 January 2004 (first subject randomized) through 15 March 2007 (data cut-off date; enrollment was completed on 16 March 2005, and 1 subject was still receiving treatment in Study 20020408 at the time of the data cut-off)	Phase 3

Introduction and Objectives:
Panitumumab is a fully human IgG2 monoclonal antibody that is directed against the human epidermal growth factor receptor (EGFr). This phase 3 study was conducted to provide a controlled, 1:1 comparison of the efficacy and safety of panitumumab plus best supportive care (BSC) versus BSC alone in subjects with EGFr-expressing metastatic colorectal cancer who had documented disease progression during or after prior standard treatment with fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy.

The primary objective of this study was to assess whether panitumumab plus BSC improves progression-free survival compared with BSC alone in this subject population.

Secondary objectives were to evaluate survival time, objective response, duration of response, time to response, time to disease progression, time to treatment failure, duration of stable disease, patient-reported outcomes, and the safety profile of panitumumab plus BSC compared with BSC alone in this subject population.

Methodology:
This is an ongoing, multicenter, randomized, open-label, comparative study of panitumumab plus BSC versus BSC alone in subjects with metastatic colorectal cancer who had disease progression during or after treatment with prior, standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy. Subjects were randomly assigned in a 1:1 ratio to receive panitumumab plus BSC or BSC alone.

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Methodology (continued):
Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and geographic region (Western Europe versus Central and Eastern Europe versus rest of world). Panitumumab was administered as an intravenous (IV) infusion at a dose of 6 mg/kg given once every 2 weeks until disease progression, inability to tolerate investigational product, or other reason for discontinuation. BSC was defined as the best palliative care available as judged appropriate by the investigator (excluding antineoplastic chemotherapy). Subjects were to be evaluated for tumor response according to modified Response Evaluation Criteria in Solid Tumors (RECIST) at weeks 8, 12, 16, 24, 32, 40, and 48 and every 3 months thereafter until disease progression. Tumor responses were to be confirmed no less than 4 weeks after the criteria for response were first met. In addition to the investigator's assessments, scans of all subjects evaluated for tumor response were evaluated by a blinded Independent Review Committee. Subjects determined to have progressive disease by investigator assessment were discontinued from the treatment phase of the study. All subjects were to complete a safety follow-up visit at least 4 weeks after the last assigned treatment (for the panitumumab plus BSC group) or at any time within 4 weeks after the decision to withdraw from the treatment phase (for the BSC group). Subjects in the BSC alone group who had disease progression at any time were eligible to receive panitumumab 6 mg/kg administered once every 2 weeks as part of a separate protocol (Study 20030194). All subjects are being followed-up for survival approximately every 3 months for up to 2 years after their randomization into the study. Enrollment is complete, but 1 subject was still ongoing at the time of data cut-off. This clinical study report presents the final descriptive analysis of long-term efficacy and safety data planned to occur when the last subjects has completed the 2-year long term follow-up period.

Number of Subjects Planned:
Approximately 430 randomized subjects were planned.

Number of Subjects Enrolled:
Four hundred sixty-three subjects were enrolled into the panitumumab plus BSC group (n = 231) and BSC alone group (n = 232).

Sex:
146 (63%) men, 85 (37%) women (panitumumab plus BSC)
148 (64%) men, 84 (36%) women (BSC alone)

Mean (SD) Age:
61.2 (10.3) years (panitumumab plus BSC)
61.4 (10.8) years (BSC alone)

Ethnicity (Race):
229 (99%) white, 1 (< 1%) black, 1 (< 1%) Hispanic (panitumumab plus BSC)
228 (98%) white, 1 (< 1%) Hispanic, 2 (1%) Asian, 1 (< 1%) Japanese (BSC alone)

Diagnosis and Main Criteria for Eligibility:
Eligible subjects were men and women 18 years of age or older, competent to comprehend and sign an informed consent form, who had a pathologic diagnosis of colorectal adenocarcinoma with documented evidence of disease progression during or after prior treatment with a fluoropyrimidine, irinotecan, and oxaliplatin at an adequate prespecified overall exposure. Radiographic documentation of disease progression during or within 6 months after the most recent regimen was required for enrollment, and the time interval between documented tumor progression and study entry was not

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Diagnosis and Main Criteria for Eligibility (continued):
to exceed 6 months. Subjects also were required to have unidimensionally measurable disease (≥ 20 mm); an ECOG status of 0 to 2; EGFr expression in ≥ 1% of evaluated tumor cells; and adequate hematologic, renal, and hepatic function.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Panitumumab (rHuMab-EGFr), manufactured using the Chinese hamster ovary expression system (2-kL production scale), was supplied in single-use 10-mL glass vials containing 20 mg of panitumumab per mL, to be diluted in pyrogen-free 0.9% sodium chloride solution (USP/PhEur). Panitumumab was administered IV at a dose of 6 mg/kg once every 2 weeks. Infusions were administered through a peripheral line or indwelling catheter using a 0.22-micron in-line filter.

Duration of Treatment:
Subjects received panitumumab once every 2 weeks until disease progression, inability to tolerate investigational product, or other reasons for discontinuation.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
BSC was defined as the best palliative care available as judged appropriate by the investigator and institutional guidelines, including antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated. For the purposes of this study, BSC did not include antineoplastic chemotherapy.

Efficacy Endpoints:
Primary

- progression-free survival

Secondary

- survival and best objective response over time (co-secondary)
- duration of response
- time to response
- time to disease progression
- time to treatment failure
- duration of stable disease

Patient Reported Outcomes:

- time-adjusted area under the curve (AUC) for EUROQOL EQ-5D Index
- time-adjusted AUC for National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Colorectal Cancer (NCCN/FACT CRC) subscale
- time-adjusted AUC for other scales including the NCCN/FACT Physical and Functional Well being subscales, EORTC-QLQ-C30 Global Quality of Life subscale, Dermatology and De Novo “Bother” Life Quality Index 92 (DLQI92), and EUROQOL EQ-5D visual analog scale (VAS)

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Safety Endpoints:

- incidence of adverse events (including serious, grade 3, grade 4, and treatment related events)
- changes in laboratory values
- changes in vital signs
- incidence of anti-panitumumab antibody formation
- incidence and severity of integument and eye toxicity
- investigational product compliance and incidence of dose adjustments
- incidence of concomitant medications
- changes from baseline over time in ECOG performance status
- incidence of procedures (cytology, surgery, biopsies)

Statistical Methods:

The primary analysis of all efficacy endpoints was conducted using the All Enrolled (intent-to-treat) analysis set, which included all randomized subjects who signed the informed consent and were randomized into the study. A secondary analysis of the efficacy endpoints was done using the Adjudicated Prior Failures analysis set, which included subjects who were determined by an Independent Eligibility Review Committee to have developed progressive disease or relapsed during or after standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy (see Diagnosis and Main Criteria for Eligibility).

Progression-free survival was analyzed at the 5% significance level using a log-rank test stratified by the stratification factors of baseline ECOG performance status and geographic region. The primary analysis was based on the response assessment from a blinded review of radiographic scans by the Independent Review Committee. For subjects who withdrew because of disease progression that was not confirmed by the Independent Review Committee, radiographic data collected during the long-term follow-up (both treatment groups) or the extension protocol (Study 20030194) (BSC alone group) was used in the primary analysis of progression-free survival. If the log-rank test for progression-free survival was significant, the co-secondary endpoints of survival and best objective response rate over time were to be analyzed simultaneously. To control for multiple testing, survival was to be analyzed controlling at the 4% significance level, whereas response rate was to be analyzed at the 1% significance level. The primary analyses for progression-free survival and best objective response rate were to coincide; however, survival was to be analyzed sequentially, with the primary analysis planned to occur after the last subject had the opportunity to be followed for 1 year after randomization. A 1% significance test of survival was to be performed as an interim analysis, which was to coincide with the primary analysis of progression-free survival and objective response rate. The nominal significance level for the primary analysis of survival will be calculated to preserve an overall 4% significance level, based on the proportion of events shared between the interim and primary analysis (planned to occur after the last subject has had the opportunity to complete 1 year of long-term follow-up). All other efficacy endpoints were analyzed descriptively including point estimates and 95% confidence intervals.

The time-adjusted AUC values for the PRO scales were analyzed for weeks 8 to 16. Analysis of covariance was used to estimate differences between treatment groups, with main effects for treatment group, baseline PRO scale score, and the stratification

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Statistical Methods (continued):
variables of baseline ECOG performance status and geographic region. Summary statistics were calculated for all PRO scale scores and changes from baseline for each visit by treatment group and overall. Adverse events were grouped by system organ class and graded using National Cancer Institute (NCI) Common Toxicity Criteria version 2.0, with the exception of selected dermatological/skin toxicities, which were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with modifications. Descriptive statistics were calculated for all safety endpoints, including adverse events, laboratory values, vital signs, and antibody results. Results were provided by treatment group through the safety follow-up period.

A final descriptive analysis was planned to occur when all subjects had completed the 2-year long-term follow-up; the results of which are provided in this report.

Summary - Results:

This report reflects data as of 15 March 2007 and includes data for all subjects up to completion of the 2-year long term follow-up period and represents the final study report for this study.

Subject Disposition:
A total of 463 subjects were randomized into this study (231 subjects in the panitumumab plus BSC group and 232 subjects in the BSC alone group). Of the 231 subjects randomized to the panitumumab plus BSC group, 229 subjects (99%) received panitumumab at a dose of 6 mg/kg given once every 2 weeks during the study; 2 subjects died of disease progression within 1 day of randomization before receiving panitumumab. In accordance with the protocol, no subject in the BSC group received panitumumab during the treatment period of this study. At the time of the data cut-off (15 March 2007), 1 subject in the panitumumab plus BSC group was still on treatment. The median follow-up time was 29.6 weeks (range: 0 to 134.9) in the panitumumab plus BSC group and 31.8 weeks (range: 0.1 to 153.3) in the BSC alone group. A total of 177 subjects (76%) in the BSC alone group who had radiographic disease progression (as determined by the investigator) were subsequently enrolled in Study 20030194.

Efficacy Results:
In this final analysis, the rate of disease progression or death was reduced by approximately 43% in the panitumumab plus BSC group compared with BSC alone (hazard ratio = 0.574, 95% CI: 0.473, 0.697). Twenty-two subjects (10%) in the panitumumab plus BSC group and no subject in the BSC alone group had an objective response per modified RECIST criteria by central review (all partial responses). The effects of panitumumab on progression-free survival and objective response were consistent within subpopulations defined by age, sex, primary tumor type, ECOG performance status, and the quantity of tumor EGFr membrane staining or highest tumor EGFr membrane staining intensity. The median duration of response was 18.4 weeks (95% CI: 16.0, 25.3; range: 7.9, 88.7) (All Enrolled analysis set). An additional 61subjects (26%) in the panitumumab plus BSC group and 24 subjects (10%) in the BSC alone group had a best response of stable disease in the All Enrolled analysis set; the median duration of stable disease was 24.0 weeks (95% CI: 22.4, 27.3; range: 7.1, 95.1) and 17.6 weeks (95% CI: 15.4, 25.6; range: 11.4, 48.1), respectively, in these subjects. Consistent with the previous analyses, no survival benefit for subjects receiving panitumumab was identified at this final analysis.

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Patient-reported Outcomes Results:
Numerical differences between treatment groups favoring panitumumab were observed in the time-adjusted area under the curve from weeks 8 to 16 for HRQoL (as measured by the EUROQOL EQ-5D and EORTC-QLQ-C30 Global Quality of Life scales) and CRC cancer symptomology (as measured by the NCCN/FACT CRC scales), although none were clinically meaningful. As expected, the panitumumab plus BSC group had a lower time-adjusted AUC for the DLQI92, indicating that these subjects had more skin toxicity and were more embarrassed or bothered by their skin conditions than subjects in the BSC alone group. These results are consistent with the higher incidence of integument- and eye-related adverse events in the panitumumab plus BSC group. Thus, although subjects in the panitumumab plus BSC group were more bothered by skin toxicity relative to the BSC alone group, the overall effect on patient reported health-related quality of life remained numerically in favor of panitumumab plus BSC.

Safety Results:
The Safety analysis set included the same 463 subjects as the All Enrolled analysis set. However, 2 subjects in the panitumumab plus BSC group who did not receive at least 1 dose of panitumumab were analyzed in the BSC alone group (ie, according to actual treatment received). Two hundred twenty-nine subjects (100%) in the panitumumab plus BSC group and 205 subjects (88%) in the BSC alone group had at least 1 adverse event during the study. A low percentage of subjects had an adverse event leading to discontinuation of treatment in the panitumumab plus BSC (7%) and BSC alone (3%) groups. The percentage of subjects with severe (ie, grade 3) adverse events was higher in the panitumumab plus BSC group (33%) than in the BSC alone group (17%), primarily as a result of adverse events associated with integument and eye toxicity. Three percent of subjects in the panitumumab plus BSC group and 1% of subjects in the BSC group had adverse events with a worst grade of life-threatening (ie, grade 4). The incidence of serious adverse events was higher in the panitumumab plus BSC group (44%) than in the BSC alone group (26%); however, most of these events were associated with clinical disease progression (preferred terms corresponding to the primary tumor type such as “colorectal cancer” and “metastatic colorectal cancer” were to be reported as serious adverse events when the outcome was fatal). A higher incidence of these events was reported in the panitumumab plus BSC group during the treatment period, likely because more subjects in the BSC alone group had radiographic disease progression by investigator assessment and withdrew from study or crossed over to the extension protocol (Study 20030194). When all deaths up to the time of data cut-off were included, the percentage of deaths was 90% in the panitumumab plus BSC group, 94% in the BSC alone group for subjects who crossed over to Study 20030194, and 91% for subjects in the BSC alone group who did not cross over to Study 20030194. Only 3% of deaths (2% in the panitumumab plus BSC group and 1% in the BSC alone group) were not directly attributed to disease progression, and none were considered related to investigational product.

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Safety Results (continued):

Most subjects (90%) in the panitumumab plus BSC group had treatment-related adverse events. Most of these treatment-related adverse events were mild or moderate and were toxicities consistent with the known effects of EGFr inhibitors. Nineteen percent of subjects in the panitumumab plus BSC group had a severe (ie, grade 3) integument- and eye-related toxicity. Integument-related toxicities leading to study discontinuation were reported for 1 subject in the panitumumab plus BSC group (moderate dermatitis acneiform) and 1 subject in the BSC alone group (moderate jaundice). Even though jaundice would not typically be categorized as an integument toxicity (rather as a liver toxicity); it was conservatively included in this analysis because the preferred term of jaundice is included in the high-level and primary system organ class categories of "dermal and epidermal conditions NEC" and "skin and subcutaneous tissue disorders." In the panitumumab plus BSC group, 2 subjects received a narcotic and 13 subjects (6%) received systemic steroids for integument-related toxicities. Seventy-four subjects (32%) in the panitumumab plus BSC group and 5 subjects (2%) in the BSC alone group had integument- and eye-related toxicities that were infectious in nature.

No subject had an adverse event that the investigator reported as an “infusion reaction” or “infusion-related reaction”, although 1 subject had an infusion-associated event of moderate hypersensitivity. In a conservative, post hoc analysis of adverse event terms derived from Version 3.0 of the CTCAE (acute infusion reaction/cytokine release syndrome and allergic reaction/hypersensitivity occurring on the day of infusion and resolving the same day or the day after), potential infusion reactions occurred in 12 subjects, yielding a per-infusion incidence of 0.9% and a per-subject incidence of 5.2%. Only 5 subjects in the panitumumab plus BSC group had clinically significant vital sign changes (ie, $\geq$ 30%) in association with a potential infusion reaction. Consistent with the known effects of other EGFr inhibitors, median magnesium levels decreased during the study for subjects in the panitumumab plus BSC group compared with the BSC alone group. In the panitumumab plus BSC group, 6 subjects (3%) had a reduction in magnesium levels to grade 3, and 3 subjects (1%) had a reduction in magnesium levels to grade 4. Four subjects (all in the panitumumab plus BSC group) had adverse events of mild to severe hypomagnesemia or blood magnesium decreased. No subject withdrew from the study because of an adverse event of hypomagnesemia. No other clinically significant changes in laboratory values were observed in the panitumumab plus BSC group compared with the BSC alone group. A total of 224 subjects in the panitumumab plus BSC group were tested for anti-panitumumab antibodies (222 subjects [99%] at baseline and 184 subjects [82%] postbaseline), and 74 subjects (33%) had a follow-up sample collected $\geq$ 21 days after the last dose of panitumumab (ie, the duration of time considered appropriate for the evaluation of antibody formation). Three subjects tested positive for anti-panitumumab antibodies in the screening ELISA at baseline (week 1). All serum samples from these 3 subjects were negative for neutralizing antibodies in the bioassay. In the Biacore assay, 6 subjects tested positive for anti-panitumumab antibodies at baseline, 13 subjects tested positive at postdose time points (postbaseline), and 3 subjects tested positive at the end of study/follow-up time point. Of the subjects who tested positive in the biacore assay, 4 subjects tested positive for neutralizing antibodies in the bioassay.