Synopsis of Study 20030167	
Study Title:	A Phase 2, Multicenter, Single-arm Clinical Trial of ABX-EGF Monotherapy in Subjects With Metastatic Colorectal Cancer Following Treatment With Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemotherapy
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 oxaplatin chemotherapy
Brief Description:	Multicenter, single-arm, open-label study designed to evaluate the efficacy and safety of panitumumab monotherapy at a dose of 6 mg/kg given once every 2 weeks in subjects with metastatic colorectal cancer who had documented disease progression during or after fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy.
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No.:	20030167
IND No.:	8382
Study Phase:	Phase 2
Study Initiation Date:	01 March 2004 (first subject enrolled)
Data Cutoff Date:	22 December 2006 Data Cutoff Date (enrollment completed; 1 subject was still receiving treatment;,49 subjects remained in long-term follow-up)
Principal Investigators:	Eighty-seven study centers enrolled subjects in this study. Investigators are listed in Appendix 4.
Good Clinical Practice:	This study was conducted in accordance with the principles of the US Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/ guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	25 October 2007

Product: Panitumumab
Clinical Study Report: 20030167
Date: 25 October 2007

Name of Sponsor: Amgen, Inc., Thousand Oaks, CA

Name of Finished Product: Panitumumab (ABX-EGF)

Name of Active Ingredient: rHuMAb-EGFr

Title of Study: A Phase 2, Multicenter, Single-arm Clinical Trial of ABX-EGF Monotherapy in Subjects with Metastatic Colorectal Cancer Following Treatment with Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemotherapy

Investigator(s) and Study Center(s): This study is ongoing and is being conducted at 87 sites in the United States. A list of study centers and principal investigators is provided in Appendix 4.

Publication(s): None

Study Period: 01 March 2004 (first subject enrolled) to 22 December 2006, data cutoff (1 subject was still receiving treatment and 49 subjects remained in the long-term follow-up period)

Development Phase: Phase 2

Introduction and Objectives: Colorectal cancer accounts for a substantial portion of the cancer burden and constitutes a major health problem. Treatment of stage IV disease is palliative, except in subjects with isolated, resectable liver or lung metastases. Despite advances, metastatic colorectal carcinoma cannot be cured with currently available chemotherapy regimens, and there is a need for more effective therapies.

Panitumumab is a high-affinity, fully human monoclonal antibody directed against human epidermal growth factor receptor (EGFr) that blocks the ligands for epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) from binding to EGFr, inhibits tumor growth, and elicits both tumor regression and eradication of established tumors in murine xenograft tumor models (Yang et al 1999).

Data from an interim analysis of a phase 2 study (20025405) of panitumumab monotherapy in subjects with metastatic colorectal cancer who had failed prior standard chemotherapy (fluoropyrimidine and either irinotecan, oxaliplatin, or both) have shown that inhibition of the epidermal growth factor receptor (EGFr) pathway by panitumumab can result in objective (complete or partial) tumor responses (Meropol et al, 2003; Hecht et al, 2004).

The primary objectives of this study were to assess the objective response rate through week 16 (responses needed to be confirmed no less than 4 weeks after the criteria for response were first met) and the duration of response in subjects with metastatic colorectal cancer who were receiving panitumumab at the dose schedule of 6 mg/kg once every 2 weeks. Secondary objectives were to assess the effect of treatment with panitumumab on objective response rate throughout the study, time to response, progression-free survival time, time to disease progression, time to treatment failure, duration of stable disease, survival time, change in patient-reported outcomes (PRO), and the safety profile of panitumumab in this same patient population.

Methodology: This was a multicenter, open-label, single-arm, phase 2 clinical study examining the efficacy and safety of panitumumab administered as monotherapy in subjects with EGFr-expressing (positive membrane staining in ≥ 10% of evaluated tumor cells) metastatic colorectal cancer who had developed progressive disease or relapsed during or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy (see Diagnosis and Criteria for Eligibility for details on the number of previous lines of chemotherapy and the overall exposure eligible subjects must have received). Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg given once every 2 weeks until subjects developed progressive disease, were unable to tolerate panitumumab, or discontinued for other reasons (eg, administrative decision, consent withdrawn). Subjects were evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40, and 48 and every 3 months thereafter until disease progression. Subjects with symptoms suggestive of disease progression were to be evaluated for tumor

response at the time these symptoms occurred. Four weeks after the last panitumumab infusion received (regardless of the reason for discontinuation), subjects were to attend a safety follow-up visit. In addition, subjects were contacted to assess disease status and survival every 3 months through 24 months (the 24-month time period was calculated from the first day of panitumumab administration).

Number of Subjects Planned: The planned sample size was 300 subjects who were confirmed to be eligible by an Independent Eligibility Review Committee (IERC) for the purpose of the primary analysis (see Statistical Methods). Subjects were enrolled on the basis of investigator assessment only, then were retrospectively confirmed eligible by the IERC. To allow for an estimated IERC-determined ineligibility rate of 20%, the planned enrollment was set to approximately 375 subjects.

Number of Subjects Enrolled: One hundred eighty five subjects enrolled in the study and 182 were treated.

Sex: 100 men (54%) and 85 women (46%)

Age: mean (SD) = 59.6 (10.6) years

Ethnicity (Race): 144 Caucasian (78%), 19 Hispanic (10%), 15 black (8%), 4 Asian (2%), 1 Native Hawaiian (1%), and 2 Other Ethnicity (1%)

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women ≥ 18 years of age who had a pathological diagnosis of colorectal adenocarcinoma; had metastatic colorectal carcinoma; had a tumor expressing EGFr by immunohistochemistry (positive membrane staining in ≥ 10% of evaluated tumor cells); had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; had received treatment with fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy for metastatic colorectal cancer; and had documented evidence of disease progression during or after the most recent prior chemotherapy regimen. Subjects were to have received at least 2 but no more than 3 prior chemotherapy regimens for metastatic colorectal cancer. Subjects could have received prior radiotherapy but the index lesions should not have been irradiated. Radiographic documentation of disease progression during or within 6 months after the most recent chemotherapy regimen was required, and documented tumor progression was to have occurred ≤ 6 months before study entry. Subjects were not to have received prior anti-tumor therapies, including prior experimental agents or approved anti-tumor small molecules and biologics of short serum half-life (< 1 week), within 30 days before enrollment, or prior experimental or approved proteins/antibodies with longer serum half-life (eg, bevacizumab) within 6 weeks before enrollment; small-molecule EGFr tyrosine kinase inhibitors (eg, gefitinib) were permitted. Subject enrollment was based on investigator assessment.

Investigational Product, Dose and Mode of Administration: Panitumumab was supplied at a concentration of 20 mg/mL in single-use, 10-mL vials and diluted in a minimum volume of 100 mL pyrogen-free 0.9% sodium chloride solution, USP/PhEur. A dose of 6 mg/kg was administered by IV infusion once every 2 weeks.

Duration of Treatment: Panitumumab was administered once every 2 weeks until subjects developed progressive disease, were unable to tolerate panitumumab, or discontinued treatment for other reasons (eg, administrative decision). Subjects then attended a safety follow-up visit 4 weeks from the last panitumumab infusion. Subjects were subsequently contacted every 3 months from the last panitumumab infusion through month 24 to assess disease status and survival.

Reference Therapy, Dose and Mode of Administration: No reference therapy was used in this study.

Study Endpoints

Primary Efficacy Endpoints (centrally assessed):

- objective response rate through week 16 (responses needed to be confirmed no less than 4 weeks after the criteria for response were first met)
- duration of response

Secondary Efficacy Endpoints (centrally assessed, except as noted):

- objective response rate throughout study
- time to response
- progression-free survival
- time to disease progression
- time to treatment failure (not centrally assessed)
- duration of stable disease
- survival time (not centrally assessed)

Additional efficacy endpoints not defined in the protocol, but included in the statistical analysis plan were:

- change in the sum of the products of longest diameters of index lesions
- change in ECOG performance status

Safety Endpoints:

- incidence of adverse events (including all, serious, grade 3, grade 4, and treatment-related
- changes in laboratory values
- incidence of antibody formation

Additional safety endpoints not defined in the protocol, but included in the statistical analysis plan were:

- incidence of grade 3 and 4 laboratory toxicities
- change in vital signs (including blood pressure, respiration rate, resting pulse, and temperature)
- incidence and severity of integument and eye toxicities
- time to first, time to most severe, duration of, and duration of most severe integument and eye toxicity
- time to resolution of integument and eye toxicity after the last dose of investigational product
- incidence of infectious integument and eye toxicities
- incidence of acneiform rash
- incidence and severity of adverse events characteristic of infusion reactions

Primary Patient-reported Outcomes Endpoints:

- time adjusted area under the curve (AUC) for EUROQOL EQ-5D Index

- time adjusted AUC for NCCN/FACT CRC Subscale

The secondary patient-reported outcomes endpoints include time adjusted AUC for the following: NCCN/FACT physical well-being subscale; NCCN/FACT functional well-being subscale; 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.

Statistical Methods: For the primary endpoint, the rate of objective response through week 16 (including a confirmatory scan no less than 4 weeks after the criteria for response were first met), exact, 2-sided 95% confidence intervals were calculated. For time-to-event and duration endpoints, Kaplan-Meier curves and Kaplan-Meier quartiles (with 2-sided 95% confidence intervals) were generated.

Safety analyses were conducted for the Safety Set, consisting of all consented subjects who received $\geq$ 1 dose of panitumumab. Adverse event incidences (all, serious, grades 3, 4, 5 [fatal], and treatment-related), withdrawals due to adverse events, and the incidence of anti-panitumumab antibody formation were summarized. Adverse events were grouped by system organ class and graded using National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, with the exception of prespecified dermatologic/skin toxicities, which were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with modifications. Extent of exposure, laboratory analyte changes, and vital signs changes were summarized with descriptive statistics. Ad hoc and/or separate analyses were conducted on adverse events of special interest (ie, infusion reactions, integument and eye toxicities, stomatitis, pulmonary toxicity, cardiac toxicity, vascular toxicity, diarrhea, and hypomagnesemia).

Summary of Results:

Subject Disposition:

One hundred eighty-five subjects were enrolled and 182 subjects received at least 1 dose of panitumumab. Of the 181 subjects (98%) who ended treatment, 130 subjects (72%) ended treatment because of radiographically documented disease progression. One hundred thirty-two subjects (71%) completed the safety follow-up period, and the median follow-up time (from enrollment to the last on-study safety follow-up or long-term follow-up visit) was 27 weeks (range: 1 to 128 weeks). As of the data cutoff, 1 subject was still receiving treatment with panitumumab and 49 subjects (26%) were in the long term follow-up period.

Efficacy Results:

All subjects enrolled were treated on study regardless of the IERC review. However, only those subjects confirmed to be eligible by the IERC review were included in the primary efficacy analysis set (ie, the Adjudicated Prior Failure Analysis Set). The first primary endpoint of the study was objective tumor response through week 16. Of the 142 subjects in this analysis set, 5 were categorized as responders, based on an independent central assessment, resulting in an overall objective response rate of 3.5% (95% CI: 1.2, 8.0). All 5 subjects had a partial response (ie, no subject had a complete response). The co-primary endpoint in this study was duration of response. The Kaplan-Meier estimate of the median duration of response for the 5 subjects (by central assessment) was 14 weeks (95% CI: 12.0, 102.0).

Time to response was a secondary endpoint of this study. Summary statistics on time to response were generated for the 5 responding subjects in the Adjudicated Prior Failure Set who had an objective response based on central assessment. The median time to first objective response among these 5 responders was not estimable; however the range was 7 to 12 weeks. The objective response rate over the study period was the same as the objective response rate through week 16.

The median progression-free survival time or death was 7.3 weeks (95% CI: 7.1, 7.4 and 7.1, 7.6, respectively). The median time to treatment failure was 8 weeks (95% CI: 7.4, 8.1). One

hundred and eleven subjects (78%) died and the median survival time was 7.0 months (95% CI: 5.7, 8.0).

Safety Results:

Safety analyses were conducted on the Safety Set, consisting of all consented subjects who received ≥ 1 dose of panitumumab.

All subjects had an adverse event while on treatment or during the safety follow-up. Seventy-five subjects (41%) had a worst grade of severe (grade 3) event, and 10 subjects (5%) had a life-threatening (grade 4) event. Serious and fatal (grade 5) adverse events were experienced by 24 subjects (13%), each.

Overall, adverse events affecting the skin and subcutaneous tissue disorders system organ class were most common, occurring in 91% of the subjects. Almost all of the subjects (93%) had at least 1 adverse event that was considered by the investigator to be possibly related to treatment with panitumumab. These events included primarily skin and subcutaneous disorders (90%), gastrointestinal disorders (31%), and infections and infestations (26%).

The 5 most frequently occurring treatment-related adverse events were dermatitis acneiform (69%), erythema (61%), pruritus (52%), rash (23%), and fatigue (19%). The incidence of subjects with a worst grade of mild (grade 1) treatment-related adverse events was 20% and the incidence of moderate (grade 2) events was 46%. Severe (grade 3) treatment-related adverse events occurred in 44 subjects (24%) and life-threatening (grade 4) adverse events occurred in 5 subjects (3%). Eight subjects (4%) had serious treatment-related adverse events. A fatal (grade 5) adverse event of treatment-related pulmonary edema was reported for 1 subject, who also had a serious treatment-related adverse event of vocal cord paralysis.

Thirty-four subjects (19%) had adverse events that resulted in removal from treatment or removal from the study; these events were serious in 24 subjects. Adverse events leading to discontinuation in 12 subjects (7%) were reported as treatment-related; of these, 3 events were serious. Thirty-nine subjects (21%) had adverse events that resulted in dose alterations; most of these events were considered severe (grade 3) and occurred in the skin and subcutaneous tissue disorders system organ class.

The overall subject incidence of grade 3 laboratory toxicities was 24% and the subject incidence of grade 4 laboratory toxicities was 7%. Laboratory toxicities of grade 3 or 4 hypomagnesemia were reported for 18 subjects (10%). No reported grade 4 hematology laboratory abnormalities were reported.