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Product: Panitumumab
Clinical Study Report: 20040249 KRAS
Date: 13 June 2008

1. TITLE PAGE

Study Title:	A Randomized, Open-label, Controlled, Clinical Trial of Chemotherapy and Bevacizumab with and without Panitumumab in the First-line Treatment of Subjects with Metastatic Colorectal Cancer
Investigational Product:	Panitumumab
Indication:	First-line treatment of metastatic colorectal cancer
Brief Description:	The objective of this trial was to explore the safety and efficacy of panitumumab, an EGFr inhibitor, combined with oxaliplatin- and irinotecan-based chemotherapy plus bevacizumab, an angiogenesis inhibitor, in the first-line treatment of metastatic colorectal cancer.
Study Sponsor:	Amgen Inc., Thousand Oaks CA
Study No.:	20040249
IND No.:	BB-IND 8382
Study Phase:	3B
Study Initiation Date:	10 March 2005 (First subject enrolled)
Early Study Termination Date:	22 March 2007 (Panitumumab withdrawn from study)
Study Completion Date:	(long-term follow-up ongoing)
Date Cut-off Date	31 May 2007
Principal Investigators:	This study was conducted at 200 sites in the US. A list of investigators and sites is included in **Error! Reference source not found.**.
Clinical Study Manager:	Yvonne Denkins PhD Telephone: (805) 447-5928 Fax: (805) 375-8546
Good Clinical Practice:	This study was conducted in accordance with 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:	28 April 2008

2. SYNOPSIS

Name of Sponsor:	Amgen Inc.
Name of Finished Product:	Vectibix®
Name of Active Ingredient:	Panitumumab
Title of Study:	"A Randomized, Open-label, Controlled, Clinical Trial of Chemotherapy and Bevacizumab with and without Panitumumab in the First-line Treatment of Subjects with Metastatic Colorectal Cancer
Investigator(s) and Study Center(s):	Multicenter (see **Error! Reference source not found.**)
Publication(s):	None to date
Study Period:	Enrollment: 10 March 2005 through 19 October 2006 (Long-term follow-up ongoing)
Development Phase:	3B

Introduction and Objectives:

The PACCE study ("Panitumumab Advanced Colorectal Cancer Evaluation") was designed to study the efficacy and safety of combination chemotherapy and bevacizumab with or without panitumumab for the first-line treatment of metastatic colorectal cancer. The current standard of care is oxaliplatin- or irinotecan-based chemotherapy—both typically in combination with 5-fluorouracil and leucovorin, combined with bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF). Nonclinical and preliminary clinical studies have suggested that combining an EGFr inhibitor and a VEGF inhibitor may further improve efficacy. The key objective of this study was to assess whether the addition of panitumumab to oxaliplatin-based chemotherapy and bevacizumab could improve progression-free survival (and other efficacy measures) compared with oxaliplatin-based chemotherapy and bevacizumab alone in subjects receiving first-line treatment for metastatic colorectal cancer. Other objectives included the assessment of safety of panitumumab given concomitantly with oxaliplatin-based chemotherapy and bevacizumab, and the assessment of the safety and efficacy of panitumumab given concomitantly with irinotecan-based chemotherapy and bevacizumab compared with irinotecan-based chemotherapy and bevacizumab alone.

Methodology:

This was a multicenter, randomized, open-label, controlled clinical trial designed to test the contribution of panitumumab to the best standard of care for the first-line treatment of metastatic colorectal cancer. Subjects were first assigned by the investigator to receive either oxaliplatin-based or irinotecan-based chemotherapy, to be given with bevacizumab. Randomization to panitumumab or no panitumumab within each separate chemotherapy stratum was weighted 1:1. Subjects received their planned chemotherapy regimen, bevacizumab, and either panitumumab at a dose of 6 mg/kg Q2W or no panitumumab. Treatment continued until disease progression, unacceptable toxicity, death, or withdrawal of consent.

Number of Subjects Planned:

1000 total: 800 in oxaliplatin stratum, 200 in irinotecan stratum

Number of Subjects Enrolled:

1053 randomized: 823 in oxaliplatin stratum, 230 in irinotecan stratum

Sex:	598 men (57%), 455 women (43%)
Age:	Median 61 years (range: 22, 89)

Ethnicity (Race):	80% white, 10% black, 7% Hispanic, 3% other

Diagnosis and Main Criteria for Eligibility:

Stage IV adenocarcinoma of the colon or rectum without prior therapy for metastatic disease, at least 1 measurable lesion, ECOG of 0 or 1, 18 years or older, adequate hematologic status and organ function, no chemotherapy within 6 months of enrollment, no radiotherapy within 14 days of enrollment, no major surgery within 28 days of enrollment, signed informed consent.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Panitumumab 6 mg/kg every 2 weeks, given as an IV infusion over 30 to 60 minutes 1 hour before chemotherapy. Lot numbers used in this study were L004050, L004196, L004198, L004533, L005819, and L006482, and are listed by subject in **Error! Reference source not found.**.

Duration of Treatment:

Until disease progression, unacceptable toxicity, death, withdrawal of consent, or other reason for discontinuation

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

None; the open-label control group received first-line treatment without panitumumab

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Study Endpoints

Primary efficacy (oxaliplatin):	Progression-free survival
Other efficacy endpoints:	Week 12 objective response, overall best response, time to progression, time to treatment failure, overall survival
Safety endpoints:	Incidence of adverse events, standard laboratory variables, occurrence of anti-panitumumab antibodies

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Statistical Methods:

With the 1:1 randomization and 400 subjects each in the panitumumab and control arms of the oxaliplatin stratum, 462 progression events were required to detect a hazard ratio of 0.769 with at least 80% power for a 2-sided 0.05 level test. This hazard ratio, assuming exponential progression-free survival, would translate to a 30% improvement in median progression-free survival. Although the primary objective for the irinotecan stratum was to collect safety data, efficacy variables were also analyzed and week 12 response rate was designated as the primary efficacy endpoint. One hundred subjects per treatment arm in the irinotecan stratum would allow detection of a difference of 20% vs 40% in week-12 response rate with at least 80% power in a 2-sided 0.05 significance level test.

Three analysis sets were specified: intent-to-treat, safety evaluable, and per-protocol. For continuous endpoints, the mean, standard deviation or standard error, median, quartiles, minimum, and maximum were calculated. For discrete data, frequency and percent distributions were provided as appropriate. Tumor response was graded by modified-RECIST (response evaluation criteria in solid tumors) from central radiologic review. The intent-to-treat analysis set was used for all primary efficacy analyses. For time-to-event analyses, Kaplan-Meier plots, estimates of event-free probabilities, between-group differences in the probabilities, and associated 95% confidence limits (CL) were presented. The primary comparison of treatment effect and the effect of covariates were based on the Wald Chi-square test from the Cox proportional hazards regression model. For tumor response rate, number and percentage of subjects in each tumor response category were presented for each treatment group, along with 95% CL and between-group difference. A logistic regression model using treatment group and covariates corresponding to the randomization factors was employed; p-values and 95% CL were calculated using the Wald method.

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Standard procedures were used for the analysis and presentation of safety variables.

Summary of Results:

Subject Disposition:

For the oxaliplatin stratum, 823 subjects were randomized to either the panitumumab arm (413 subjects) or the control arm (410 subjects); these constituted the intent-to-treat analysis set. The safety analysis set consisted of 407 and 397 subjects, respectively. At the time of data cut-off, 776 of 804 subjects had discontinued first-line treatment; major reasons for discontinuation were, for panitumumab vs control, respectively, disease progression (28% vs 24%), adverse event (22% vs 22%), withdrawal of consent (15% vs 19%), and requirement for alternative treatment (9% vs 8%).

For the irinotecan stratum, 230 subjects were randomized to either the panitumumab arm (115 subjects) or the control arm (115 subjects); these constituted the intent-to-treat analysis set. The safety analysis set consisted of 111 and 113 subjects, respectively. At the time of data cut-off, 201 of 224 subjects had discontinued first-line treatment; major reasons for discontinuation were, for panitumumab vs control, respectively, disease progression (31% vs 23%), withdrawal of consent (13% vs 22%), adverse event (15% vs 5%), and requirement for alternative treatment (3% vs 11%).

Efficacy Results:

In a planned interim analysis of the primary endpoint conducted after 257 progression or death events had occurred in the oxaliplatin stratum, median progression-free survival in the panitumumab and control groups was 8.8 months (95% CL: 8.3, 9.5) vs 10.5 months (95% CL: 9.4, 12.0), respectively. Based on Cox regression analysis, the hazard ratio for progression or death for panitumumab vs control was 1.44 (95% CL: 1.13, 1.85, p = 0.004). As a result of this interim analysis, which revealed an unfavorable benefit-to-risk ratio in the oxaliplatin stratum, a decision was made as of 22 March 2007 to discontinue panitumumab as an investigational agent from both the oxaliplatin and irinotecan strata.

The analysis presented in this report (using a data cut-off of 31 May 2007) represents the final on-treatment efficacy and safety results from both the oxaliplatin and irinotecan strata. As was found in the previous interim analysis, median progression-free survival in the oxaliplatin stratum was shorter for the panitumumab group relative to control (10.0 months vs 11.4 months), with a hazard ratio for progression or death of 1.27 (95% CL: 1.06, 1.52). Overall best response rate was not different between groups: 46% (95% CL: 41, 51) for panitumumab vs 48% (95% CL: 43, 53) for control. Other efficacy endpoints (duration of response, time to progression, and time to treatment failure) were likewise either no different or worse for the panitumumab group. Overall survival was shorter in the panitumumab group, with a median of 19.4 months vs 24.5 months for control; the hazard ratio for death was 1.43 (95% CL: 1.11, 1.83).

Week 12 response rate in the irinotecan stratum (the primary efficacy endpoint for this stratum) was similar between groups: 25% (95% CL: 17, 33) for panitumumab vs 23% (95% CL: 16, 31) for control. For the other efficacy endpoints (overall response rate, progression-free survival, time to progression, and time to treatment failure), likewise no detectable differences between treatment groups were found. At the time of data cut-off, median survival was comparable between groups (20.7 vs 20.5 months for panitumumab vs control, respectively).

Safety Results:

Across both chemotherapy strata, more toxicity was seen in the panitumumab group, manifesting as a greater incidence of grade 3 and higher adverse events, a greater incidence of serious adverse events, and more overall deaths relative to the control group. Similar safety trends were seen for the oxaliplatin and irinotecan strata separately.

Within the panitumumab treatment group, 95% had 1 or more adverse events that were considered related to panitumumab. Twenty-six percent of subjects ended panitumumab treatment because of adverse events—although some of these continued first-line chemotherapy on study. The percent of subjects who discontinued all components of first-line treatment due to an adverse event was similar between treatment groups (panitumumab vs control) across both chemotherapy strata combined (22% vs 20%) and for the oxaliplatin stratum alone (23% vs 24%). However, the irinotecan stratum displayed a difference between treatment groups (17% vs 5%).

Serious adverse events were experienced by 59% in the panitumumab group vs 37% in the control, with higher incidences in the panitumumab group of dehydration, diarrhea, pulmonary embolism, nausea, and vomiting. Serious infections overall displayed a treatment difference (15% vs 9%); however, no one specific type of infection occurred at a high frequency. Nineteen percent of subjects receiving panitumumab experienced a serious event that was considered related to panitumumab, the most common of which were diarrhea, dehydration, and vomiting

More deaths occurred in the panitumumab group relative to the control group—all deaths (32% vs 25%), deaths attributed to disease progression (25% vs 20%), deaths due to adverse event (7% vs 4%), and deaths occurring on treatment (8% vs 3%). Of the 35 subjects who died on, or within 30 days of the last dose of first-line treatment (23 vs 12 subjects for panitumumab vs control), differences between treatment groups were noted in the number of deaths due to cardiac causes (10 vs 4 subjects), sepsis (6 vs 3 subjects), intestinal perforation (3 vs 0 subjects), and pulmonary embolism (3 vs 0 subjects).

No subject who was seronegative for anti-panitumumab antibodies at baseline became seropositive after exposure, and no sample at any time point was positive for neutralizing antibodies to panitumumab. Based on the investigator's assessment, 4% of subjects experienced an infusion reaction to panitumumab. Using a more conservative (inclusive) analysis, no difference was seen in the incidence of possible infusion reactions between the panitumumab group and control. Two percent of these possible infusion reaction were graded 3 or 4.

Among adverse events of special interest, higher incidences were observed in the panitumumab group (across both chemotherapy strata) of integument/eye events as a whole, diarrhea, hypomagnesemia, hypocalcemia, and mucositis/stomatitis, and to a lesser extent of cardiac, pulmonary, and vascular events (specifically pulmonary embolism). In the irinotecan stratum, diarrhea displayed, as expected, a higher overall incidence relative to the oxaliplatin stratum, as well as a higher incidence of grade 3 diarrhea in the panitumumab group relative to control.