2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: panitumumab

Title of Study: A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer

Investigator(s) and Study Center(s): This multicenter study was conducted at 190 centers in the United States, Australia, Western Europe, Eastern Europe, and Japan. A list of institutions and principal investigators is provided in Appendix 4.

Publication(s): Peeters M, Price T, Hotko Y, et al. Randomized phase 3 study of panitumumab with FOLFIRI vs FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *Eur J Cancer Suppl.* 2009;7:9. Abstract 14LBA.

Study Period: 30 June 2006 (first subject enrolled) through 30 April 2009 (data cutoff date, enrollment was completed on 13 March 2008); 16 subjects (13 in the *KRAS* Efficacy Analysis Set) were still receiving treatment in Study 20050181 at the time of data cutoff.

Development Phase: 3

Introduction and Objectives: Colorectal cancer (CRC) often is treated with chemotherapy regimens consisting of irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) or oxaliplatin, 5-FU, and leucovorin (FOLFOX). Malignancies of the colon and rectum are among those that express epidermal growth factor receptor (EGFR), and panitumumab, a high affinity, fully human IgG2 monoclonal antibody that is directed against human EGFR, has demonstrated efficacy when administered as a single agent in this setting.

Recent data from phase 3 controlled studies have shown that Kirsten rat Sarcoma-2 virus *(KRAS)* mutation status (wild-type vs mutant) may be an important predictive factor for response to antibodies directed against the EGFR in patients with metastatic CRC (mCRC). The availability of these data led to amendments to the protocol and Statistical Analysis Plan (SAP) for this study to prospectively evaluate the treatment effect of panitumumab in combination with chemotherapy in a wild-type *KRAS* population. The protocol and SAP amendments occurred before any *KRAS* testing and before the first planned efficacy analysis.

The primary objective of this study was to evaluate the treatment effect of panitumumab plus FOLFIRI on overall survival (OS) and progression-free survival (PFS) compared with FOLFIRI alone as second-line therapy for mCRC among subjects with wild-type *KRAS* tumors and mutant *KRAS* tumors. Secondary objectives were to evaluate overall objective response rate (ORR), time to progression, duration of response, and safety (subject incidence of adverse events and significant laboratory changes) among subjects with wild-type *KRAS* tumors and mutant *KRAS* tumors.

Methodology: This is an ongoing, multicenter, randomized, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFIRI chemotherapy relative to FOLFIRI alone as second-line treatment in subjects with mCRC. Eligible subjects were randomized in a 1:1 ratio to receive panitumumab plus FOLFIRI or FOLFIRI alone. Randomization was stratified by prior oxaliplatin exposure for mCRC (yes vs no), prior bevacizumab exposure for mCRC (yes vs no), and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2). To be eligible for the study, subjects needed to have

paraffin-embedded tumor tissue from the primary tumor or metastasis available for central biomarker testing; however, subject eligibility criteria were unselected for both *KRAS* mutational status and EGFR expression.

Subjects received panitumumab as an intravenous infusion at a dose of 6 mg/kg and FOLFIRI chemotherapy or FOLFIRI alone every 14 days until disease progression or unacceptable toxicity occurred. Subjects were to be evaluated for tumor response by both the investigator and by blinded central radiology review per modified Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks ± 1 week until disease progression. Subjects receiving panitumumab plus FOLFIRI who demonstrated objective response (complete or partial) or who had stable disease but became intolerant to chemotherapy or to panitumumab were permitted to continue panitumumab or chemotherapy, respectively, until disease progression or intolerance of study treatment. If withdrawal from study treatment occurred before disease progression (eg, due to unacceptable toxicities), tumor response and patient-reported outcome (PRO) assessments were continued until disease progression or the end of the study, whichever was earlier. Subjects with evidence of disease progression were discontinued from treatment and followed for safety 30 ± 3 days after the last study treatment administration and survival (every 3 months ± 28 days) until 30 months after the last subject was randomized.

Number of Subjects Planned: The planned sample size was approximately 1100 subjects.

Number of Subjects Enrolled: A total of 1186 subjects (591 panitumumab plus FOLFIRI, 595 FOLFIRI alone) were randomized.

Of the 1186 subjects, 1083 (91%) were evaluable for *KRAS* and were included in the *KRAS* Efficacy Analysis Set: 541 subjects (92%) in the panitumumab plus FOLFIRI arm and 542 subjects (91%) in the FOLFIRI alone arm:

- Wild-type *KRAS* Efficacy Analysis Set (303 panitumumab plus FOLFIRI, 294 FOLFIRI alone)
- Mutant *KRAS* Efficacy Analysis Set (238 panitumumab plus FOLFIRI, 248 FOLFIRI alone).

Wild-type *KRAS* Efficacy Analysis Set:

Sex:

Panitumumab plus FOLFIRI: 188 men (62%), 115 women (38%)

FOLFIRI alone: 191 men (65%), 103 women (35%)

Age:

Panitumumab plus FOLFIRI: Mean (SD) 60.4 (10.6) years

FOLFIRI alone: Mean (SD) 60.6 (10.3) years

Ethnicity (Race):

Panitumumab plus FOLFIRI: 294 white (97%), 1 black (< 1%), 5 Asian (2%), 3 other (1%)

FOLFIRI alone: 278 white (95%), 4 black (1%), 2 Hispanic (1%), 8 Asian (3%), 2 other (1%)

Mutant *KRAS* Efficacy Analysis Set:

Sex:

Panitumumab plus FOLFIRI: 133 men (56%), 105 women (44%)

FOLFIRI alone: 148 men (60%), 100 women (40%)

Age:

Panitumumab plus FOLFIRI: Mean (SD) 60.1 (10.5) years

FOLFIRI alone: Mean (SD) 61.6 (10.6) years

Ethnicity (Race):

Panitumumab plus FOLFIRI: 226 white (95%), 2 black (1%), 2 Hispanic (1%), 5 Asian (2%), 3 other (1%)

FOLFIRI alone: 238 white (96%), 1 black (< 1%), 1 Hispanic (< 1%), 6 Asian (2%), 2 other (1%)

The Wild-type *KRAS* Safety Analysis Set (302 panitumumab plus FOLFIRI, 294 FOLFIRI alone) and the Mutant *KRAS* Safety Analysis Set (237 panitumumab plus FOLFIRI, 246 FOLFIRI alone) included subjects in the *KRAS* Efficacy Analysis Sets who had received at least 1 dose of panitumumab or chemotherapy; overall demographic characteristics were similar between these analysis sets.

Diagnosis and Main Criteria for Eligibility: Subjects enrolled in this study were men and women 18 years of age or older with histologically or cytologically confirmed adenocarcinoma of the colon or rectum. Subjects were to have received 1 (and only 1) prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine-based chemotherapy, with radiographically documented disease progression per modified RECIST during or ≤ 6 months after the last dose of first-line chemotherapy. Subjects were required to have at least 1 unidimensionally measurable lesion of at least 20 mm per modified RECIST; an ECOG status of 0, 1, or 2; available paraffin-embedded tumor tissue from the primary tumor or metastasis for central analyses of EGFR and biomarker testing; and to have provided informed consent.

Subjects must have had no history or known presence of central nervous system metastases. Subjects were not to have undergone certain prior therapies including (but not limited to) irinotecan; EGFR inhibitors; systemic chemotherapy, hormonal therapy, immunotherapy, or proteins/antibodies (eg, bevacizumab) ≤ 30 days before randomization; radiotherapy ≤ 14 days before randomization; or other investigational therapies ≤ 30 days before randomization.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Panitumumab was administered at a dose of 6 mg/kg once every 2 weeks (Q2W). Panitumumab was provided at a concentration of 20 mg/mL in vials containing [redacted] mL of a sterile protein solution, to be diluted in pyrogen-free [redacted] % sodium chloride solution (USP/PhEur). [redacted]

Duration of Treatment: Panitumumab was to be administered until subjects developed disease progression or were unable to tolerate panitumumab. Any subject permanently discontinuing panitumumab was allowed to continue receiving FOLFIRI until disease progression or intolerance to FOLFIRI.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Components of the reference therapy, the FOLFIRI regimen (ie, irinotecan, 5-FU, and leucovorin) were obtained by each site according to routine institutional practice and prepared according to the most current package insert for the region.

Study Endpoints

Co-primary efficacy endpoints

- PFS
- OS

Secondary efficacy endpoints

- objective response rate
- time to progression
- duration of response

Tertiary efficacy endpoints

- time to response
- patient-reported outcomes

The primary safety endpoints were the incidence of adverse events and significant laboratory changes.

Statistical Methods:

The data cutoff date for the primary analysis of PFS was 08 April 2008, the date by which at least 380 PFS events (the target goal) in the Wild-type *KRAS* Efficacy Analysis Set occurred. The primary PFS analyses used tumor evaluation data from an independent blinded central radiology review, and secondary analyses used tumor evaluation per the investigator. The data cutoff date for the primary OS analysis and all other endpoints was 30 April 2009, the date by which at least 380 OS events (target goal) in the Wild-type *KRAS* Efficacy Analysis Set were projected to occur.

An overall 5% significance level was used to compare treatments with respect to both OS and PFS with a 4% and 1% level used to test OS and PFS, respectively. A log-rank test was used to compare treatments with respect to both OS and PFS stratified by the randomization factors. A hierarchical sequential testing procedure was used for each endpoint. If a significant difference in PFS was observed in the Wild-type *KRAS* Efficacy Analysis Set, PFS in the Mutant *KRAS* Efficacy Analysis Set was to be compared. Overall survival was tested independently of PFS using the same sequential testing procedure (ie, wild-type *KRAS* followed by mutant *KRAS* analysis sets).

Descriptive statistics were calculated for all other endpoints.

Summary of Results:

Subject Disposition:

Wild-type *KRAS* Efficacy Analysis Set: As of the data cutoff date (30 April 2009), the mean (SD) actual follow-up time was 56.1 (33.6) weeks in the panitumumab plus FOLFIRI arm and 51.1 (33.7) weeks in the FOLFIRI alone arm. A total of 295 subjects (97%) in the panitumumab plus FOLFIRI arm and 290 subjects (99%) in the FOLFIRI alone arm had discontinued chemotherapy; 296 subjects (98%) had discontinued panitumumab. A total of 295 subjects

(97%) in the panitumumab plus FOLFIRI arm and 290 subjects (99%) in the FOLFIRI alone arm had ended all treatment. The most common reason for ending panitumumab or chemotherapy treatment was disease progression.

Mutant *KRAS* Efficacy Analysis Set: The mean (SD) actual follow-up time was 49.4 (30.9) weeks in the panitumumab plus FOLFIRI arm and 46.0 (31.2) weeks in the FOLFIRI alone arm, which was a shorter duration than that in the Wild-type *KRAS* Efficacy Analysis Set. A total of 237 subjects (100%) in the panitumumab plus FOLFIRI arm and 245 subjects (99%) in the FOLFIRI alone arm had discontinued chemotherapy; 236 subjects (99%) had discontinued panitumumab. A total of 236 subjects (99%) in the panitumumab plus FOLFIRI arm and 245 subjects (99%) in the FOLFIRI alone arm had ended all treatment. The most common reason for ending panitumumab or chemotherapy treatment was disease progression.

Efficacy Results:

Wild-type *KRAS* Efficacy Analysis Set: At the time of the primary PFS analysis, 59% of subjects in the panitumumab plus FOLFIRI arm and 69% of subjects in the FOLFIRI alone arm had progressed or died. A statistically significant difference in PFS in favor of panitumumab was demonstrated (p = 0.0036, stratified log-rank test). The estimated median PFS times were 5.9 months (95% CI: 5.5, 6.7) in the panitumumab plus FOLFIRI arm and 3.9 months (95% CI: 3.7, 5.3) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The hazard ratio from a stratified Cox model was 0.732 (95% CI: 0.593, 0.903), favoring the panitumumab plus FOLFIRI arm.

A total of 66% of subjects in the panitumumab plus FOLFIRI arm and 70% of subjects in the FOLFIRI alone arm died during treatment or long-term follow up. The estimated median OS was 14.5 months (95% CI: 13.0, 16.0) in the panitumumab plus FOLFIRI arm and 12.5 months (95% CI: 11.2, 14.2) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The p-value for the stratified log-rank test did not achieve statistical significance (p = 0.1154). The hazard ratio from a stratified Cox model was 0.854 (95% CI: 0.702, 1.039), favoring the panitumumab plus FOLFIRI arm. In a post-hoc analysis, Kaplan-Meier estimated survival rates were higher (with confidence intervals excluding zero, not adjusted for multiplicity) for panitumumab plus FOLFIRI than for FOLFIRI alone at various timepoints in a 14-month interval where the survival curves were clearly separated between 6 and 20 months.

The objective response rate was 35% for subjects receiving panitumumab plus FOLFIRI and 10% for subjects receiving FOLFIRI alone (all partial responses). The odds ratio for objective response was 5.33 (95% CI: 3.21, 8.60), favoring the panitumumab plus FOLFIRI arm.

Mutant *KRAS* Efficacy Analysis Set: At the time of the primary PFS analysis, 68% of subjects in the panitumumab plus FOLFIRI arm and 65% of subjects in the FOLFIRI alone arm had progressed or died in the Mutant *KRAS* Efficacy Analysis Set. No statistically significant difference in PFS was observed between treatment arms (p = 0.1448, stratified log-rank test). The estimated median PFS times were 5.0 months (95% CI: 3.8, 5.6) in the panitumumab plus FOLFIRI arm and 4.9 months (95% CI: 3.6, 5.6) in the FOLFIRI alone arm, an absolute difference of 0.1 months. The hazard ratio from a stratified Cox model was 0.846 (95% CI: 0.677, 1.059), favoring the panitumumab plus FOLFIRI arm.

Per the SAP, the formal test of the treatment difference for OS at a 4% level was not performed because a significant difference was not demonstrated for OS in the Wild-type *KRAS* Efficacy Analysis Set. A similar proportion of subjects in each treatment arm died (76% panitumumab plus FOLFIRI, 78% FOLFIRI alone). The estimated median OS was 11.8 months (95% CI: 10.4, 13.3) in the panitumumab plus FOLFIRI arm and 11.1 months (95% CI: 10.3, 12.4) in the FOLFIRI alone arm, an absolute difference of 0.7 months. The hazard ratio for OS was 0.939 (95% CI: 0.764, 1.154), favoring the panitumumab plus FOLFIRI arm.

Objective responses were observed in 13% and 14% of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms, respectively (all partial responses). The odds ratio for objective response was 1.00 (95% CI: 0.56, 1.76).

Safety Results:

The safety profile of panitumumab added to FOLFIRI chemotherapy in the overall Safety Analysis Set was similar to that seen in the Wild-type and Mutant *KRAS* Safety Analysis Sets. Detailed results for the Wild-type and Mutant *KRAS* analysis sets are presented below.

Wild-type *KRAS* Safety Analysis Set: Almost all subjects experienced at least 1 adverse event during the study (100% panitumumab plus FOLFIRI, 98% FOLFIRI alone). The incidence of subjects with adverse events of grade 3 or higher was greater in the panitumumab plus FOLFIRI arm (76%) than in the FOLFIRI alone arm (58%). Adverse events of grade 3 or higher that differed by > 5% between the panitumumab plus FOLFIRI and FOLFIRI alone arms were consistent with those expected for EGFR inhibitors, including rash (15% vs 0%), dermatitis acneiform (9% vs 0%), and hypokalemia (7% vs 1%). Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events with a worst grade of 4 (19% vs 17%) or a worst grade of 5 (4% vs 6%). For subjects with grade 5 (fatal) adverse events, the primary cause of death was reported as disease progression by the investigator in 8 of 12 subjects (67%) in the panitumumab plus FOLFIRI arm and 6 of 18 subjects (33%) in the FOLFIRI alone arm. Few subjects in either treatment arm had grade 5 events that were considered related to panitumumab and/or chemotherapy by the investigator (2 panitumumab plus FOLFIRI, 4 FOLFIRI alone).

The incidence of serious adverse events was higher in the panitumumab plus FOLFIRI arm (41%) than in the FOLFIRI alone arm (31%), as was the incidence of serious adverse events considered related to treatment by the investigator (22% vs 16%). Overall, the most frequently reported serious, treatment-related adverse events were diarrhea (7% panitumumab plus FOLFIRI, 3% FOLFIRI alone), dehydration (3% panitumumab plus FOLFIRI, 1% FOLFIRI alone), pyrexia (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), vomiting (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), and febrile neutropenia (2% in each treatment arm).

Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events leading to discontinuation of chemotherapy (15% vs 13%) or removal from study (5% vs 4%). More subjects had adverse events leading to discontinuation of any study drug in the panitumumab plus FOLFIRI arm (21%) than in the FOLFIRI alone arm (13%), largely due to adverse events leading to discontinuation of panitumumab (16% in the panitumumab plus FOLFIRI arm). The most frequently reported adverse events leading to discontinuation of panitumumab were generally skin-related toxicities.

Three subjects (1%) receiving panitumumab had adverse events (one grade 2, two grade 4) with terms indicative of an infusion reaction reported by the investigator as related to panitumumab. As expected, the incidences of integument toxicities, stomatitis/oral mucositis, and hypomagnesemia, which are all known biological effects of EGFR inhibitors, were higher in subjects receiving panitumumab. Diarrhea was reported for 66% of subjects in the panitumumab plus FOLFIRI arm and 57% of subjects in the FOLFIRI alone arm. Most of the adverse events of diarrhea were grade 1 or 2, and few led to discontinuation of panitumumab (incidence of 1% in the panitumumab plus FOLFIRI arm) or chemotherapy (incidence of 1% in each treatment arm). Pulmonary, vascular, and cardiac toxicities occurred at a similar subject incidence in each treatment arm. No evidence of an altered safety profile was found in subjects testing positive for anti-panitumumab antibodies when compared to the safety profile of subjects testing negative.

Mutant *KRAS* Safety Analysis Set: Almost all subjects experienced at least 1 adverse event during the study (99% panitumumab plus FOLFIRI, 96% FOLFIRI alone). The incidence of subjects with adverse events of grade 3 or higher was greater in the panitumumab plus FOLFIRI arm (71%) than in the FOLFIRI alone arm (55%). Adverse events of grade 3 or higher with the

greatest differences between treatment arms were similar to those observed in the Wild-type *KRAS* Safety Analysis Set and included rash, dermatitis acneiform, and mucosal inflammation. Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events with a worst grade of 4 (16% vs 14%) or a worst grade of 5 (7% vs 5%). For subjects with grade 5 (fatal) adverse events, the primary cause of death was reported as disease progression by the investigator in 11 of 17 subjects (65%) in the panitumumab plus FOLFIRI arm and 6 of 13 subjects (46%) in the FOLFIRI alone arm. Two subjects (1 in each treatment arm) had grade 5 events that were considered related to chemotherapy by the investigator.

The incidence of serious adverse events was higher in the panitumumab plus FOLFIRI arm (37%) than in the FOLFIRI alone arm (30%), and the incidence of serious adverse events considered related to treatment by the investigator was 20% vs 16%, respectively. Overall, the most frequently reported serious, treatment-related adverse events were generally similar between treatment arms and included diarrhea (4% in each treatment arm), vomiting (3% in each treatment arm), nausea (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), and febrile neutropenia (2% panitumumab plus FOLFIRI, 3% FOLFIRI alone).

Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events leading to discontinuation of chemotherapy (13% vs 10%) or removal from study (5% vs 4%). More subjects had adverse events leading to discontinuation of any study drug in the panitumumab plus FOLFIRI arm (19%) than in the FOLFIRI alone arm (10%), largely due to adverse events leading to discontinuation of panitumumab (16% panitumumab plus FOLFIRI). The most frequently reported adverse events leading to discontinuation of panitumumab were generally skin-related toxicities.

One subject (< 1%) receiving panitumumab had an adverse event (grade 1) with terms indicative of an infusion reaction reported by the investigator as related to panitumumab. As was observed in the Wild-type *KRAS* Safety Analysis Set, the incidences of integument toxicities, stomatitis/oral mucositis, and hypomagnesemia and hypocalcemia were higher in subjects receiving panitumumab. Diarrhea was reported for 62% of subjects in the panitumumab plus FOLFIRI arm and 56% of subjects in the FOLFIRI alone arm. Most of the adverse events of diarrhea were grade 1 or 2, and few led to discontinuation of panitumumab or chemotherapy (incidence of 2% in the panitumumab plus FOLFIRI arm). Pulmonary and cardiac toxicities occurred at a similar subject incidence in each treatment arm. Vascular toxicities were reported for 22% of subjects in the panitumumab plus FOLFIRI arm and 17% of subjects in the FOLFIRI alone arm. The overall difference in the incidence of vascular toxicity between treatment arms was largely attributable to a higher incidence of peripheral edema (mostly grade 2) in the panitumumab plus FOLFIRI arm. No evidence of an altered safety profile was found in subjects testing positive for anti-panitumumab antibodies.

Conclusions:

In subjects with wild-type *KRAS* tumor status, panitumumab combined with FOLFIRI resulted in a statistically significant and clinically relevant increase in PFS when compared to FOLFIRI alone. A 2-month absolute improvement in median OS was observed in the panitumumab plus FOLFIRI arm relative to FOLFIRI alone; however, the overall difference between treatment arms did not achieve statistical significance. The objective response rate in subjects with wild-type *KRAS* tumor status was over 3-fold higher among subjects receiving panitumumab plus FOLFIRI compared with FOLFIRI alone.

In subjects with mutant *KRAS* tumor status, no differences in PFS, OS, or objective response rates were observed between treatment arms.

The safety profile of panitumumab (both overall and in subjects with wild-type or mutant *KRAS* tumor status) was consistent with that observed in previous studies of panitumumab and with other EGFR inhibitors administered in combination with irinotecan-based chemotherapy.

2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: panitumumab

Title of Study: A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer

Investigator(s) and Study Center(s): This multicenter study was conducted at 190 centers in the United States, Australia, Western Europe, Eastern Europe, and Japan. A list of institutions and principal investigators is provided in Appendix 4.

Publication(s): Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010; 28: 4706-4713.

Study Period: 30 June 2006 (first subject enrolled) through 02 September 2010 (data cutoff date).

Development Phase: 3

Introduction and Objectives: Colorectal cancer (CRC) often is treated with chemotherapy regimens consisting of irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) or oxaliplatin, 5-FU, and leucovorin (FOLFOX). Malignancies of the colon and rectum are among those that express epidermal growth factor receptor (EGFR), and panitumumab, a high affinity, fully human IgG2 monoclonal antibody that is directed against human EGFR, has demonstrated efficacy when administered as a single agent in this setting.

Recent data from phase 3 controlled studies have shown that Kirsten rat Sarcoma-2 virus *(KRAS)* mutation status (wild-type vs mutant) may be an important predictive factor for response to antibodies directed against the EGFR in patients with metastatic CRC (mCRC). The availability of these data led to amendments to the protocol and Statistical Analysis Plan (SAP) for this study to prospectively evaluate the treatment effect of panitumumab in combination with chemotherapy in a wild-type *KRAS* population. The protocol and SAP amendments occurred before any *KRAS* testing and before the first planned efficacy analysis.

The primary objective of this study was to evaluate the treatment effect of panitumumab plus FOLFIRI on overall survival (OS) and progression-free survival (PFS) compared with FOLFIRI alone as second-line therapy for mCRC among subjects with wild-type *KRAS* tumors and mutant *KRAS* tumors. Secondary objectives were to evaluate overall objective response rate (ORR), time to progression, duration of response, and safety (subject incidence of adverse events and significant laboratory changes) among subjects with wild-type *KRAS* tumors and mutant *KRAS* tumors.

The primary analyses of PFS (data cutoff of 08 April 2008) and OS (data cutoff of 30 April 2009) were presented in a clinical study report dated 15 December 2009. This report presents the final efficacy and safety results as of a cutoff date of 02 September 2010.

Methodology: This was a multicenter, randomized, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFIRI chemotherapy relative to FOLFIRI alone as second-line treatment in subjects with mCRC. Eligible subjects were randomized in a 1:1 ratio to receive panitumumab plus FOLFIRI or FOLFIRI alone. Randomization was stratified

by prior oxaliplatin exposure for mCRC (yes vs no), prior bevacizumab exposure for mCRC (yes vs no), and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2). To be eligible for the study, subjects needed to have paraffin-embedded tumor tissue from the primary tumor or metastasis available for central biomarker testing; however, subject eligibility criteria were unselected for both *KRAS* mutational status and EGFR expression.

Subjects received panitumumab as an intravenous infusion at a dose of 6 mg/kg and FOLFIRI chemotherapy or FOLFIRI alone every 14 days until disease progression or unacceptable toxicity occurred. Subjects were to be evaluated for tumor response by both the investigator and by blinded central radiology review per modified Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks ± 1 week until disease progression. Subjects receiving panitumumab plus FOLFIRI who demonstrated objective response (complete or partial) or who had stable disease but became intolerant to chemotherapy or to panitumumab were permitted to continue panitumumab or chemotherapy, respectively, until disease progression or intolerance of study treatment. If withdrawal from study treatment occurred before disease progression (eg, due to unacceptable toxicities), tumor response and patient-reported outcome (PRO) assessments were continued until disease progression or the end of the study, whichever was earlier. Subjects with evidence of disease progression were discontinued from treatment and followed for safety 30 ± 3 days after the last study treatment administration and survival (every 3 months ± 28 days) until 30 months after the last subject was randomized.

Number of Subjects Planned: The planned sample size was approximately 1100 subjects.

Number of Subjects Enrolled: A total of 1186 subjects (591 panitumumab plus FOLFIRI, 595 FOLFIRI alone) were randomized.

Of the 1186 subjects, 1083 (91%) were evaluable for *KRAS* and were included in the *KRAS* Efficacy Analysis Set: 541 subjects (92%) in the panitumumab plus FOLFIRI arm and 542 subjects (91%) in the FOLFIRI alone arm:

- Wild-type *KRAS* Efficacy Analysis Set (303 panitumumab plus FOLFIRI, 294 FOLFIRI alone)
- Mutant *KRAS* Efficacy Analysis Set (238 panitumumab plus FOLFIRI, 248 FOLFIRI alone).

Wild-type *KRAS* Efficacy Analysis Set:

Sex:

Panitumumab plus FOLFIRI: 188 men (62%), 115 women (38%)

FOLFIRI alone: 191 men (65%), 103 women (35%)

Age:

Panitumumab plus FOLFIRI: Mean (SD) 60.4 (10.6) years

FOLFIRI alone: Mean (SD) 60.6 (10.3) years

Ethnicity (Race):

Panitumumab plus FOLFIRI: 294 white (97%), 1 black (< 1%), 5 Asian (2%), 3 other (1%)

FOLFIRI alone: 278 white (95%), 4 black (1%), 2 Hispanic (1%), 8 Asian (3%), 2 other (1%)

Mutant *KRAS* Efficacy Analysis Set:

Sex:

Panitumumab plus FOLFIRI: 133 men (56%), 105 women (44%)

FOLFIRI alone: 148 men (60%), 100 women (40%)

Age:

Panitumumab plus FOLFIRI: Mean (SD) 60.1 (10.5) years

FOLFIRI alone: Mean (SD) 61.6 (10.6) years

Ethnicity (Race):

Panitumumab plus FOLFIRI: 226 white (95%), 2 black (1%), 2 Hispanic (1%), 5 Asian (2%), 3 other (1%)

FOLFIRI alone: 238 white (96%), 1 black (< 1%), 1 Hispanic (< 1%), 6 Asian (2%), 2 other (1%)

The Wild-type *KRAS* Safety Analysis Set (302 panitumumab plus FOLFIRI, 294 FOLFIRI alone) and the Mutant *KRAS* Safety Analysis Set (237 panitumumab plus FOLFIRI, 247 FOLFIRI alone) included subjects in the *KRAS* Efficacy Analysis Sets who had received at least 1 dose of panitumumab or chemotherapy; overall demographic characteristics were similar between these analysis sets.

Diagnosis and Main Criteria for Eligibility: Subjects enrolled in this study were men and women 18 years of age or older with histologically or cytologically confirmed adenocarcinoma of the colon or rectum. Subjects were to have received 1 (and only 1) prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine-based chemotherapy, with radiographically documented disease progression per modified RECIST during or ≤ 6 months after the last dose of first-line chemotherapy. Subjects were required to have at least 1 unidimensionally measurable lesion of at least 20 mm per modified RECIST; an ECOG status of 0, 1, or 2; available paraffin-embedded tumor tissue from the primary tumor or metastasis for central analyses of EGFR and biomarker testing; and to have provided informed consent.

Subjects must have had no history or known presence of central nervous system metastases. Subjects were not to have undergone certain prior therapies including (but not limited to) irinotecan; EGFR inhibitors; systemic chemotherapy, hormonal therapy, immunotherapy, or proteins/antibodies (eg, bevacizumab) ≤ 30 days before randomization; radiotherapy ≤ 14 days before randomization; or other investigational therapies ≤ 30 days before randomization.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Panitumumab was administered at a dose of 6 mg/kg once every 2 weeks (Q2W). Panitumumab was provided at a concentration of 20 mg/mL in vials containing [redacted] mL of a sterile protein solution, to be diluted in pyrogen-free [redacted]% sodium chloride solution (USP/PhEur). [redacted]

Duration of Treatment: Panitumumab was to be administered until subjects developed disease progression or were unable to tolerate panitumumab. Any subject permanently discontinuing panitumumab was allowed to continue receiving FOLFIRI until disease progression or intolerance to FOLFIRI.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Components of the reference therapy, the FOLFIRI regimen (ie, irinotecan, 5-FU, and leucovorin) were obtained by each site according to routine institutional practice and prepared according to the most current package insert for the region.

Study Endpoints

Co-primary efficacy endpoints

- PFS
- OS

Secondary efficacy endpoints

- objective response rate
- time to progression
- duration of response

Tertiary efficacy endpoints

- time to response
- patient-reported outcomes

The primary safety endpoints were the incidence of adverse events and significant laboratory changes.

Statistical Methods:

The primary PFS and OS analyses have been reported previously. Subsequent to the primary analyses, all subjects were to be followed for survival for up to approximately 30 months after the last subject was randomized. At that time, the final analysis of OS was to be performed, but no formal hypothesis testing of efficacy or safety endpoints was planned. In addition, descriptive estimates of key comparative efficacy and safety analyses were to be updated to assess the overall relative treatment profile. Results from the final analyses are presented in this updated clinical study report.

Summary of Results:

Subject Disposition:

Wild-type *KRAS* Efficacy Analysis Set: As of the data cutoff date (02 September 2010), the mean (SD) actual follow-up time was 66.7 (46.5) weeks in the panitumumab plus FOLFIRI arm and 60.1 (48.0) weeks in the FOLFIRI alone arm. All 596 subjects (302 panitumumab plus FOLFIRI and 294 FOLFIRI alone) had ended all treatment. The most common reason for ending panitumumab or chemotherapy treatment was disease progression.

Mutant *KRAS* Efficacy Analysis Set: The mean (SD) actual follow-up time was 55.2 (40.8) weeks in the panitumumab plus FOLFIRI arm and 51.4 (40.6) weeks in the FOLFIRI alone arm, which was a shorter duration than that in the Wild-type *KRAS* Efficacy Analysis Set. All 484 subjects (237 panitumumab plus FOLFIRI and 247 FOLFIRI alone) had ended all treatment. The most common reason for ending panitumumab or chemotherapy treatment was disease progression.

Efficacy Results:

The results of the final analysis support the efficacy conclusions from the primary analysis. In subjects with wild-type *KRAS* tumors, PFS and objective response were improved with the addition of panitumumab to FOLFIRI relative to FOLFIRI alone, with a trend toward improvement in OS. In subjects with mutant *KRAS* tumor status, no meaningful differences in PFS, OS, or objective response rates were observed between treatment arms.

Wild-type *KRAS* Efficacy Analysis Set: At the time of the final data cutoff date, 283 subjects (93%) in the panitumumab plus FOLFIRI arm and 274 subjects (93%) in the FOLFIRI alone arm had progressed or died. The estimated hazard ratio for PFS from a stratified Cox proportional hazards regression model was 0.820 (95% CI: 0.692, 0.972), favoring the panitumumab plus FOLFIRI arm. The p-value for the stratified log-rank test was 0.0231. The median PFS was

6.7 months (95% CI: 5.8, 7.4) in the panitumumab plus FOLFIRI arm and 4.9 months (95% CI: 3.8, 5.5) in the FOLFIRI alone arm, an absolute difference of 1.8 months.

A total 267 subjects (88%) in the panitumumab plus FOLFIRI arm and 256 subjects (87%) in the FOLFIRI alone arm died during treatment or long-term follow-up. The estimated hazard ratio for OS from a stratified Cox proportional hazards regression model was 0.922 (95% CI: 0.775, 1.098), favoring the panitumumab plus FOLFIRI arm. The p-value for the stratified log-rank test was 0.3660. The median OS was 14.5 months (95% CI: 13.0, 16.1) in the panitumumab plus FOLFIRI arm and 12.5 months (95% CI: 11.2, 14.2) in the FOLFIRI alone arm, an absolute difference of 2.0 months.

The objective response rate was 36% for subjects receiving panitumumab plus FOLFIRI and 10% for subjects receiving FOLFIRI alone (with 1 complete response in the panitumumab plus FOLFIRI arm). The odds ratio for objective response was 5.50 (95% CI: 3.32, 8.87), favoring the panitumumab plus FOLFIRI arm.

Mutant *KRAS* Efficacy Analysis Set: At the time of the final data cutoff, 229 subjects (96%) in the panitumumab plus FOLFIRI arm and 237 subjects (96%) in the FOLFIRI alone arm had progressed or died. The estimated hazard ratio for PFS from a stratified Cox proportional hazards regression model was 0.945 (95% CI: 0.784, 1.139). The p-value for the stratified log-rank test was 0.5611. The median PFS was 5.3 months (95% CI: 4.2, 5.7) in the panitumumab plus FOLFIRI arm and 5.4 months (95% CI: 4.0, 5.6) in the FOLFIRI alone arm, an absolute difference of 0.1 months.

A total of 221 subjects (93%) in the panitumumab plus FOLFIRI arm and 225 subjects (91%) in the FOLFIRI alone arm died during treatment or long-term follow-up. The estimated hazard ratio for OS from a stratified Cox proportional hazards regression model was 0.934 (95% CI: 0.773 1.129). The p-value for the stratified log-rank test was 0.4815. The median OS was 11.8 months (95% CI: 10.4, 13.3) in the panitumumab plus FOLFIRI arm and 11.1 months (95% CI: 10.3, 12.4) in the FOLFIRI alone arm, an absolute difference of 0.7 months.

Objective responses were observed in 13% and 15% of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms, respectively (all partial responses). The odds ratio for objective response was 0.93 (95% CI: 0.53, 1.63).

Safety Results:

Safety results in this final analysis were nearly identical to those observed at the time of the primary OS analysis. The safety profile of panitumumab added to FOLFIRI chemotherapy in the overall Safety Analysis Set was similar to that seen in the Wild-type and Mutant *KRAS* Safety Analysis Sets. Detailed results for the Wild-type and Mutant *KRAS* analysis sets are presented below.

Wild-type *KRAS* Safety Analysis Set: Almost all subjects experienced at least 1 adverse event during the study (100% panitumumab plus FOLFIRI, 98% FOLFIRI alone). The incidence of subjects with adverse events of grade 3 or higher was greater in the panitumumab plus FOLFIRI arm (77%) than in the FOLFIRI alone arm (59%). Adverse events of grade 3 or higher that differed by > 5% between the panitumumab plus FOLFIRI and FOLFIRI alone arms were consistent with those expected for EGFR inhibitors, including rash (15% vs 0%), dermatitis acneiform (9% vs 0%), and hypokalemia (7% vs 1%). Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events with a worst grade of 4 (20% vs 17%) or a worst grade of 5 (4% vs 6%). Few subjects in either treatment arm had grade 5 events that were considered related to panitumumab and/or chemotherapy by the investigator (2 panitumumab plus FOLFIRI, 4 FOLFIRI alone).

The incidence of serious adverse events was higher in the panitumumab plus FOLFIRI arm (41%) than in the FOLFIRI alone arm (31%), as was the incidence of serious adverse events

considered related to treatment by the investigator (22% vs 16%). Overall, the most frequently reported serious, treatment-related adverse events were diarrhea (6% panitumumab plus FOLFIRI, 3% FOLFIRI alone), dehydration (3% panitumumab plus FOLFIRI, 1% FOLFIRI alone), pyrexia (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), vomiting (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), and febrile neutropenia (2% in each treatment arm).

Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events leading to discontinuation of chemotherapy (16% vs 14%) or removal from study (5% vs 4%). More subjects had adverse events leading to discontinuation of any study drug in the panitumumab plus FOLFIRI arm (22%) than in the FOLFIRI alone arm (14%), largely due to adverse events leading to discontinuation of panitumumab (16% in the panitumumab plus FOLFIRI arm). The most frequently reported adverse events leading to discontinuation of panitumumab were generally skin-related toxicities.

Three subjects (1%) receiving panitumumab had adverse events (one grade 2, two grade 4) with terms indicative of an infusion reaction reported by the investigator as related to panitumumab. As expected, the incidences of integument toxicities, stomatitis/oral mucositis, and hypomagnesemia, which are all known biological effects of EGFR inhibitors, were higher in subjects receiving panitumumab. Diarrhea was reported for 66% of subjects in the panitumumab plus FOLFIRI arm and 57% of subjects in the FOLFIRI alone arm. Most of the adverse events of diarrhea were grade 1 or 2, and few led to discontinuation of panitumumab (subject incidence of 1% in the panitumumab plus FOLFIRI arm) or chemotherapy (subject incidence of 2% in the panitumumab plus FOLFIRI arm and 1% in the FOLFIRI alone arm). Pulmonary, vascular, and cardiac toxicities occurred at a similar subject incidence in each treatment arm.

Mutant *KRAS* Safety Analysis Set: Almost all subjects experienced at least 1 adverse event during the study (99% panitumumab plus FOLFIRI, 96% FOLFIRI alone). The incidence of subjects with adverse events of grade 3 or higher was greater in the panitumumab plus FOLFIRI arm (71%) than in the FOLFIRI alone arm (55%). Adverse events of grade 3 or higher with the greatest differences between treatment arms were similar to those observed in the Wild-type *KRAS* Safety Analysis Set and included rash, dermatitis acneiform, and mucosal inflammation. Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events with a worst grade of 4 (16% vs 14%) or a worst grade of 5 (7% vs 5%). Two subjects (1 in each treatment arm) had grade 5 events that were considered related to chemotherapy by the investigator.

The incidence of serious adverse events was higher in the panitumumab plus FOLFIRI arm (37%) than in the FOLFIRI alone arm (30%), and the incidence of serious adverse events considered related to treatment by the investigator was 20% vs 16%, respectively. Overall, the most frequently reported serious, treatment-related adverse events were generally similar between treatment arms and included diarrhea (4% in each treatment arm), vomiting (3% in each treatment arm), nausea (2% panitumumab plus FOLFIRI, 1% FOLFIRI alone), febrile neutropenia (2% panitumumab plus FOLFIRI, 3% FOLFIRI alone), and neutropenia (1% panitumumab plus FOLFIRI, 2% FOLFIRI alone).

Similar percentages of subjects in the panitumumab plus FOLFIRI and FOLFIRI alone arms had adverse events leading to discontinuation of chemotherapy (14% vs 11%) or removal from study (6% vs 4%). More subjects had adverse events leading to discontinuation of any study drug in the panitumumab plus FOLFIRI arm (19%) than in the FOLFIRI alone arm (11%), largely due to adverse events leading to discontinuation of panitumumab (16% panitumumab plus FOLFIRI). The most frequently reported adverse events leading to discontinuation of panitumumab were generally skin-related toxicities.

One subject (< 1%) receiving panitumumab had an adverse event (grade 1) with terms indicative of an infusion reaction reported by the investigator as related to panitumumab. As was observed in the Wild-type *KRAS* Safety Analysis Set, the incidences of integument toxicities, stomatitis/oral mucositis, and hypomagnesemia and hypocalcemia were higher in subjects receiving

panitumumab. Diarrhea was reported for 62% of subjects in the panitumumab plus FOLFIRI arm and 56% of subjects in the FOLFIRI alone arm. Most of the adverse events of diarrhea were grade 1 or 2, and few led to discontinuation of panitumumab or chemotherapy (incidence of 2% in the panitumumab plus FOLFIRI arm). Pulmonary and cardiac toxicities occurred at a similar subject incidence in each treatment arm. Vascular toxicities were reported for 21% of subjects in the panitumumab plus FOLFIRI arm and 18% of subjects in the FOLFIRI alone arm. The overall difference in the incidence of vascular toxicity between treatment arms was largely attributable to a higher incidence of peripheral edema (mostly grade 1 or 2) in the panitumumab plus FOLFIRI arm.

Conclusions:

The results of the final analysis support the efficacy and safety conclusions from the primary analysis. In subjects with wild-type *KRAS* tumor status, PFS and objective response were improved with the addition of panitumumab to FOLFIRI relative to FOLFIRI alone, with a trend toward improvement in OS. In subjects with mutant *KRAS* tumor status, no meaningful differences in PFS, OS, or objective response rates were observed between treatment arms.

The safety profile of panitumumab (both overall and in subjects with wild-type or mutant *KRAS* tumor status) was consistent with that observed in previous studies of panitumumab and with other EGFR inhibitors administered in combination with irinotecan-based chemotherapy.