2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: Panitumumab

Title of Study: A Multi-center, Open-label, Randomized, Phase 2 Clinical Trial Evaluating Safety and Efficacy of FOLFIRI with Either Panitumumab or Bevacizumab as Second-line Treatment in Subjects with Metastatic Colorectal Cancer with Wild-type *KRAS* tumors

Investigator(s) and Study Center(s): This study was conducted at 89 centers in the United States. Study centers and investigators are listed in Appendix 4.

Publications:

Hecht JR, Dakhil, SR, Saleh MN. Pooled safety results from SPIRITT: A multicenter, open-label, randomized, phase II study of FOLFIRI with panitumumab (pmab) or bevacizumab (bev) as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC). *J Clin Oncol.* 2011;29:(suppl 4). Abstract 477.

Cohn AL, Krishnan K, Hecht JR. SPIRITT: A multicenter, open-label, randomized, phase II clinical trial evaluating safety and efficacy of FOLFIRI with either panitumumab or bevacizumab as second-line treatment in patients with metastatic colorectal cancer (mCRC) with wild-type KRAS tumors. *J Clin Oncol*. 2010;28:15s(suppl). Abstract TPS195.

Hecht JR, Cohn AL. SPIRITT: a study of second-line treatment of metastatic colorectal cancer with FOLFIRI plus panitumumab or bevacizumab. *Commun Oncol*. 2008;5(suppl 16):1–4.

Study Period: 29 November 2006 through 10 May 2012 data cutoff (data were collected through 15 February 2012 for subjects who had discontinued the study before then)

Development Phase: 2

Objectives:

The primary objective of this study was to estimate the treatment effect of panitumumab plus irinotecan, infusional 5-FU, and leucovorin (FOLFIRI) compared to bevacizumab plus FOLFIRI on progression-free survival (PFS). Secondary objectives were to evaluate objective response rate, duration of response, time to response, time to progression, disease control, and overall survival.

Methodology: This phase 2, multicenter, open-label, randomized, two-arm study was designed to estimate the treatment effect of panitumumab in combination with FOLFIRI compared to bevacizumab in combination with FOLFIRI in subjects with metastatic colorectal cancer (mCRC) who had failed first-line therapy with at least 4 doses of oxaliplatin-based chemotherapy and bevacizumab. After data became available demonstrating that the treatment effect of anti-epidermal growth factor receptor (EGFR) agents was limited to patients with wild-type Kirsten rat Sarcoma-2 virus (*KRAS)* mCRC, the study was amended to enroll only subjects with wild-type *KRAS* tumors. Eligible subjects were randomized in a 1:1 ratio to receive panitumumab 6 mg/kg plus FOLFIRI once every 2 weeks (Q2W) or bevacizumab 5 mg/kg or 10 mg/kg plus FOLFIRI Q2W. Randomization was stratified by the reason for first-line treatment failure (progression vs toxicity) and by intended bevacizumab dose (5 mg/kg vs 10 mg/kg). The intended bevacizumab doses were ascertained from sites at the time of site initiation.

Subjects were treated with all or any components of second-line treatment until the occurrence of unacceptable adverse events, disease progression, death, loss to follow up, or study withdrawal by the subject, investigator, or sponsor. Tumor response was evaluated by blinded central radiology review per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and by the investigator using either modified RECIST version 1.0 or clinical assessment.

After subjects permanently discontinued all components of second-line treatment, they were to undergo a safety follow-up assessment 30 (± 7) days after the last dose. Subjects ending second-line treatment before disease progression were followed for PFS (radiographic disease assessment) every 12 weeks (± 14 days) from the safety follow-up visit until disease progression,

initiation of a new therapy for mCRC, or until approximately 100 PFS events were observed in subjects with wild-type *KRAS* tumors. Subjects were also followed for survival every 12 weeks (± 14 days) from the safety follow-up assessment until approximately 100 PFS events were observed in subjects with wild-type *KRAS* tumors.

Number of Subjects Planned: A minimum of 176 subjects with wild-type *KRAS* mCRC

Number of Subjects Enrolled: 266 total; 182 with wild-type *KRAS* mCRC

Diagnosis and Main Criteria for Eligibility:

Eligible subjects were men and women ≥ 18 years of age with a diagnosis of unresectable metastatic adenocarcinoma of the colon or rectum. Subjects enrolled after protocol Amendment 1 were to have wild-type *KRAS* tumor status confirmed by a central laboratory or a local laboratory that was certified by Clinical Laboratory Improvement Amendments (prior to Amendment 1, subjects were enrolled without regard to *KRAS* status; see Section 7.11). All subjects were required to have failed prior first-line oxaliplatin-based chemotherapy with bevacizumab (at least 4 doses of this combination) and to have an Eastern Cooperative Oncology Group performance status of 0 or 1. Complete inclusion and exclusion criteria are provided in the protocol (Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Panitumumab was administered by IV infusion at a dose of 6 mg/kg over 1 hour ± 15 minutes on day 1 of each Q2W cycle before the administration of chemotherapy. [redacted]

Reference Therapy, Dose, and Mode of Administration, Manufacturing Batch Number: Bevacizumab was obtained by each site according to routine institutional practice, and administered at a dose of either 5 mg/kg Q2W or 10 mg/kg Q2W, depending on physician choice and institutional standard of care.

All components of FOLFIRI were obtained by each site according to routine institutional practice. The premedication regimen for FOLFIRI chemotherapy was at the discretion of the investigator and/or according to institutional guidelines.

Duration of Treatment: Subjects were to receive all or any of the second-line treatment components until the occurrence of unacceptable adverse events, disease progression, death, loss to follow up, or study withdrawal.

Study Endpoints:

Primary Efficacy Endpoint:

The primary endpoint was PFS

Secondary Efficacy Endpoints:

- overall survival (OS)
- objective response rate
- duration of response
- time to response
- time to progression
- disease control rate

Safety Endpoints:

- incidence, severity, and relationship to treatment of treatment-emergent adverse events (all, serious, maximum Common Terminology Criteria for Adverse Events (CTCAE) grades, relationship to study medications)
- change in selected laboratory values (magnesium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, absolute neutrophil count, hemoglobin, platelet count)

- changes in blood pressure, including the presence of hypertension at baseline and the incidence of hypertension during second-line treatment (systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg)

[redacted]

Statistical Methods: The primary goal of the statistical analysis was to obtain a point estimate and associated 95% confidence interval (CI) for the treatment effect of panitumumab on PFS (ie, panitumumab vs bevacizumab in combination with FOLFIRI). No formal hypothesis testing was planned. Data were analyzed by *KRAS* status, but the primary focus was on subjects with wild-type *KRAS* mCRC.

PFS was defined as the days from the date of randomization to the date of radiographic disease progression (per modified RECIST version 1.0) or death within 60 days after the last evaluable tumor assessment or randomization date (whichever was later). Subjects not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment date. The primary estimation of PFS and OS was analyzed by *KRAS* status using the Full Analysis Set (ie, randomized subjects who provided informed consent and received at least 1 dose of panitumumab or bevacizumab). The timing for the primary assessment of PFS was event-driven and was conducted when at least 100 subjects with wild-type *KRAS* in the Full Analysis Set had met the definition for PFS. The primary assessment of objective response, time to response, and duration of response by *KRAS* status was based on subjects in the Full Analysis Set who had at least 1 unidimensionally measurable lesion at baseline based on central (for central tumor response analysis) and investigator (for local tumor response analysis) radiographic assessment. Assessment of safety endpoints utilized the Safety Analysis Set. All safety evaluations were performed by known *KRAS* status (wild-type and mutant) and for all subjects.

The primary estimation of PFS was based on radiographic assessments by blinded central review. The hazard ratio for PFS (panitumumab relative to bevacizumab, in combination with FOLFIRI) was estimated using a Cox model stratified by the randomization factors. The point estimate and corresponding 95% CIs were provided. A descriptive p-value according to a Wald test for a null treatment effect (ie, hazard ratio = 1) for panitumumab compared to bevacizumab in combination with FOLFIRI was provided using the stratified Cox model with treatment as a covariate. Kaplan-Meier curves were generated to estimate PFS by randomized treatment group within each *KRAS* group (wild-type and mutant).

OS was evaluated based on Kaplan-Meier estimates of event-free rates at 3-month intervals. The proportion of subjects within each category of overall objective response (complete response, partial response, stable disease, progressive disease, unevaluable, not done) and with an objective response (confirmed complete response or partial response) were summarized by treatment group within each known KRAS group and overall. An exact 95% CI for the objective response rate was provided by treatment group within each known KRAS group (wild-type and mutant). Wilson's score method with continuity correction was used to calculate the 95% CIs for the difference in rates

For continuous variables, the mean, standard deviation, median, and range were provided. For categorical variables, the frequency and percentage in each category were presented. The CI for all binomial rates was based on an exact method, and the CI for between-group differences was estimated using Wilson's score method with continuity correction. For time-to-event endpoints, the Kaplan-Meier point estimates and 95% CIs were calculated by randomized treatment at protocol-specified assessment time points and for event time quartiles.

Summary of Results:

Subject Disposition:

Of the 266 randomized subjects, 264 received study medication and were included in the Full Analysis Set (133 panitumumab plus FOLFIRI, 131 bevacizumab plus FOLFIRI).
Two hundred fifty subjects had available *KRAS* status, including 182 subjects with wild-type *KRAS* tumors and 68 subjects with mutant *KRAS* tumors; 14 subjects were unevaluable for *KRAS* status.

Among the 182 subjects with wild-type *KRAS* tumors, 91 were randomized to and received panitumumab plus FOLFIRI arm and 91 were randomized to and received bevacizumab plus FOLFIRI arm. As of the data cutoff dates, 90 subjects in each treatment arm had ended study treatment, and 1 subject in each treatment arm was still receiving study treatment. The most common reason for ending treatment was disease progression, which occurred more frequently in the panitumumab plus FOLFIRI arm compared with the bevacizumab plus FOLFIRI arm (56 subjects [62%] vs 47 subjects [52%]). Rates of treatment discontinuation because of adverse events were similar in the two treatment arms (12 [13%] vs 14 [15%]). Eighty-nine subjects (98%) receiving panitumumab plus FOLFIRI and 90 subjects (99%) receiving bevacizumab plus FOLFIRI had ended the study as of the data cutoff dates (3 [2 panitumumab plus FOLFIRI and 1 bevacizumab plus FOLFIRI] still participating). In each arm, the most common reason for ending the study was death (58 [64%] vs 63 [69%]).

Among the 68 subjects with mutant *KRAS* tumors, 36 and 33 subjects were randomized to the panitumumab plus FOLFIRI and bevacizumab plus FOLFIRI arms, respectively; all but 1 subject in the bevacizumab plus FOLFIRI arm received study drug. All subjects (100%) with mutant *KRAS* tumors have ended second-line treatment and the study. The most common reason for ending second-line treatment was disease progression (19 [53%] vs 17 [53%]). The most common reason for ending the study was death (32 [89%] vs 23 [72%]).

Baseline Demographics:

	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab (N = 91)	Bevacizumab (N = 91)	Panitumumab (N = 36)	Bevacizumab (N = 32)
Sex				
Men	62 (68%)	58 (64%)	20 (56%)	23 (72%)
Women	29 (32%)	33 (36%)	16 (44%)	9 (28%)
Mean (SD) Age, years	59.4 (12.4)	58.9 (10.6)	59.3 (9.0)	58.9 (8.7)
Ethnicity (Race)				
White	66 (73%)	68 (75%)	30 (83%)	20 (63%)
Black	17 (19%)	13 (14%)	4 (11%)	5 (16%)
Hispanic	4 (4%)	5 (5%)	1 (3%)	4 (13%)
Asian	4 (4%)	5 (5%)	0 (0%)	2 (6%)
American Indian/ Alaska Native	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (3%)

Efficacy Results:

Wild-type *KRAS* Tumors

Among subjects with wild-type *KRAS* mCRC, the estimated PFS hazard ratio from a stratified Cox proportional hazards regression model using central review was 1.01 (95% CI: 0.68, 1.50; descriptive p-value = 0.97). The estimated median PFS was 7.7 months (95% CI: 5.7, 11.8) in the panitumumab plus FOLFIRI arm and 9.2 months (95% CI: 7.8, 10.6) in the bevacizumab plus FOLFIRI arm, an absolute difference of 1.5 months. Hazard ratios from secondary and sensitivity analyses were consistent with the primary analysis.

As of the data cutoff dates, 66 subjects (73%) in the panitumumab plus FOLFIRI arm and 68 subjects (75%) in the bevacizumab plus FOLFIRI arm had died. The estimated OS hazard ratio from a stratified Cox proportional hazards regression model was 1.06 (95% CI: 0.75, 1.49; descriptive p-value = 0.75). The estimated median overall survival was 18.0 months (95% CI: 13.5, 21.7) in the panitumumab plus FOLFIRI arm and 21.4 months (95% CI: 16.5, 24.6) in the bevacizumab plus FOLFIRI arm; an absolute difference of 3.4 months. More subjects in the bevacizumab plus FOLFIRI arm (54%) than the panitumumab plus FOLFIRI arm (26%) received

subsequent anti-EGFR monoclonal antibody therapy. Subsequent anti-vascular endothelial growth factor (VEGF) therapy was administered to similar percents of subjects in each treatment arm (20% panitumumab plus FOLFIRI vs 24% bevacizumab plus FOLFIRI).

The objective response rate was higher in the panitumumab plus FOLFIRI arm (32%; 95% CI: 23%, 43%) compared with the bevacizumab plus FOLFIRI arm (19%; 95% CI: 11%, 29%). One complete response and 27 partial responses were observed in the panitumumab plus FOLFIRI arm compared with no complete responses and 16 partial responses in the bevacizumab plus FOLFIRI arm.

Mutant *KRAS* Tumors

Among subjects with mutant *KRAS* tumors, the estimated PFS hazard ratio by central review was 1.65 (95% CI: 0.84, 3.23), and the estimated OS hazard ratio was 1.35 (95% CI: 0.80, 2.27). The objective response rate by central assessment was 12% (95% CI: 3%, 27%) in the panitumumab plus FOLFIRI arm compared with 3% (95% CI: <1%, 17%) in the bevacizumab plus FOLFIRI arm.

Safety Results:

Wild-type KRAS Tumors

All 91 subjects (100%) in the panitumumab plus FOLFIRI arm and 90 of 91 subjects (99%) in bevacizumab plus FOLFIRI arm had at least 1 adverse event during the study. Diarrhea (68 subjects [75%] panitumumab plus FOLFIRI vs 63 subjects [69%] bevacizumab plus FOLFIRI), fatigue (54 [59%] vs 55 [60%]), nausea (53 [58%] vs 59 [65%]), vomiting (38 [42%] vs 33 [36%]), and neutropenia (34 [37%] vs 43 [47%]) were among the most frequently reported events in both treatment arms. Other common adverse events in the panitumumab plus FOLFIRI arm were those known to be associated with panitumumab and as well as other EGFR inhibitors, such as rash (52 [57%] vs 8 [9%]) and hypomagnesemia (39 [43%] vs 12 [13%]).

The subject incidence of adverse events with worst grade 3 or higher was greater in the panitumumab plus FOLFIRI arm (77 [85%]) than in the bevacizumab plus FOLFIRI arm (65 subjects [71%]). This difference was caused by an imbalance in worst grade 4 events, which were more common in subjects receiving panitumumab plus FOLFIRI (29 [32%]) than in subjects receiving bevacizumab plus FOLFIRI (9 [10%]). Grade 4 adverse events that were reported with at least 5% higher subject incidence in the panitumumab plus FOLFIRI arm relative to the bevacizumab plus FOLFIRI arm were pulmonary embolism (7 [8%] vs 2 [2%]) and hypomagnesemia (5 [5%] vs 0 [0%]). Six subjects (7%) in each treatment arm had fatal adverse events during the treatment period. The most common fatal adverse events were rectal cancer (2 [2%] panitumumab plus FOLFIRI vs 0 [0%] bevacizumab plus FOLFIRI) and mCRC (1 [1%] vs 2 [2%]).

Serious adverse events were reported in 42 subjects (46%) in the panitumumab plus FOLFIRI arm and 30 subjects (33%) in the bevacizumab plus FOLFIRI arm. The most commonly reported serious adverse events were pulmonary embolism (7 [8%] vs 1 [1%]), dehydration (6 [7%] vs 4 [4%]), and diarrhea (5 [5%] vs 4 [4%]).

Twenty-six subjects (29%) in the panitumumab plus FOLFIRI arm and 23 subjects (25%) in the bevacizumab plus FOLFIRI arm discontinued any component of study treatment because of an adverse event. The most common adverse events leading to discontinuation of treatment in subjects receiving panitumumab plus FOLFIRI were rash (5 [5%] vs 0 [0%]), dermatitis acneiform (3 [3%] vs 0 [0%]), and mucosal inflammation (3 [3%] vs 0 [0%]). In subjects receiving bevacizumab plus FOLFIRI, nausea (2 [2%] vs 3 [3%]) and fatigue (0 [0%] vs 3 [3%]) were the most common reasons for discontinuing treatment.

As expected, the subject incidence of adverse events that are known biological effects of EGFR inhibitors, such as skin disorders (83 [91%]) vs 51 [56%]), eye disorders (31 [34%] vs 7 [8%]), hypokalemia (33 [36]% vs 17 [19%]), and hypomagnesemia (40 [44%] vs 12 [13%]), was higher in the panitumumab plus FOLFIRI arm relative to the bevacizumab plus FOLFIRI arm. Venous thromboembolic events also were more common in the panitumumab plus FOLFIRI arm (15 [16%]) compared with the bevacizumab plus FOLFIRI arm (5 [5%]), mostly due to differences in pulmonary embolism (9 [10%] vs 2 [2%]) and deep vein thrombosis (7 [8%] vs 2 [2%]).

Noninfectious diarrhea was the most commonly reported adverse event and occurred with a slightly higher frequency in the panitumumab plus FOLFIRI arm (68 [75%]) compared with the bevacizumab plus FOLFIRI arm (63 [69%]).

Mutant *KRAS* Tumors

Although the protocol was amended to enroll only subjects with wild-type *KRAS* mCRC, 68 subjects with mutant KRAS status who were enrolled before the amendment received study medication (36 panitumumab plus FOLFIRI vs 32 bevacizumab plus FOLFIRI). The safety profile in the mutant *KRAS* dataset was generally similar to that observed in the wild-type *KRAS* dataset.

Conclusions:

In this estimation study of panitumumab or bevacizumab in combination with FOLFIRI as second-line treatment of wild-type *KRAS* mCRC, the PFS hazard ratio was 1.01 (95% CI: 0.68, 1.50) and the OS hazard ratio was 1.06 (95% CI: 0.75, 1.49). More frequent use of subsequent anti-EGFR therapy in the bevacizumab plus FOLFIRI arm relative to the panitumumab plus FOLFIRI arm may have limited the ability to observe differences in OS. The observed objective response rate for subjects with wild-type *KRAS* mCRC was higher in the panitumumab plus FOLFIRI arm than in the bevacizumab plus FOLFIRI arm.

The safety profile in both treatment arms was similar to previously reported studies, and treatment discontinuation rates due to adverse events were similar between treatment arms. No new safety signals were observed, and the study data provided no evidence of a change in the benefit:risk profile of panitumumab in combination with irinotecan-based chemotherapy.