2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: panitumumab

Title of Study: A Single-arm Multicenter Phase 2 Study of Panitumumab in Combination with Irinotecan/5-fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer

Investigator(s) and Study Center(s): This study was conducted at 36 sites in Austria, Belgium, France, Germany, and Sweden. Names of the principal investigators and site addresses are provided in Appendix 4.

Publication(s): None as of the date of this report.

Study Period: 09 May 2007 (first subject enrolled) through 18 June 2009 (data cutoff date); 8 subjects were still receiving treatment in Study 20060314 at the time of data cutoff.

Development Phase: Phase 2

Introduction and Objectives: Irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) or oxaliplatin, 5-FU, and leucovorin (FOLFOX) are chemotherapy regimens commonly used in the first-line treatment of metastatic colorectal cancer (mCRC). 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.

The primary objective of this study was to estimate the effect of *KRAS* mutation status (Wild-type versus Mutant) on objective response rate and other measures of efficacy for subjects treated with panitumumab in combination with a chemotherapy regimen of irinotecan, 5-FU, and leucovorin (FOLFIRI) as first-line therapy for mCRC. The secondary objective was to describe the safety profile of this combination therapy in the first-line setting including the incidence of adverse events and significant changes in laboratory parameters. [redacted]

Methodology: This was a phase 2, single-arm, open-label multicenter study designed to estimate the objective response rate and other measures of efficacy for subjects treated with panitumumab in combination with FOLFIRI as first-line regimen for previously untreated mCRC. Subjects received 6 mg/kg of panitumumab as an intravenous infusion just before the administration of chemotherapy on day 1 of each cycle (14 days) until subjects were diagnosed with radiographic disease progression, at which time subjects were withdrawn from the treatment phase. If a subject stopped the FOLFIRI regimen due to toxicity, the subject was allowed to continue with panitumumab monotherapy until disease progression, at which time the treatment phase ended for that subject.

Number of Subjects Planned: The planned sample size was approximately 150 subjects.

Number of Subjects Enrolled: A total of 154 subjects were enrolled. Of these, 86 (56%) evaluable subjects expressed Wild-type *KRAS* status and 59 (38%) evaluable subjects expressed Mutant *KRAS* status.

Sex: 99 subjects (68%) men, 46 subjects (32%) women

Age, Mean (SD): 62.8 (10.6) years

Ethnicity (Race): 141 subjects (97%) white, 2 subjects (1%) black or African American, 1 subject (1%) each Hispanic or Latino and Japanese.

Diagnosis and Main Criteria for Eligibility: Male or female subjects ≥ 18 years of age with histologically or cytologically-confirmed and radiologically-measurable metastatic colorectal adenocarcinoma. Additional inclusion criteria were measurable disease per the modified Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, and adequate hematologic, renal, hepatic, and metabolic function.

Subjects were excluded if they received prior systemic therapy for the treatment of metastatic colorectal carcinoma, with the exception of adjuvant fluoropyrimidine-based chemotherapy given at least 6 months before enrollment. Subjects with central nervous system metastases or those with significant cardiovascular disease were also excluded. Additionally subjects were excluded who received prior anti-EGFR antibody therapy, treatment with small molecule EGFR tyrosine kinase inhibitors, or had prior radiotherapy within 14 days before screening, and for which all signs of early radiological toxicity have not abated.

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: Subjects received panitumumab and FOLFIRI until a diagnosis of disease progression was made. If a subject withdrew FOLFIRI due to toxicity then subjects were allowed to continue with panitumumab monotherapy until disease progression.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: A reference therapy was not used during this study.

Study Endpoints

Efficacy: The primary efficacy endpoint was the incidence of either a confirmed complete or partial response (objective response). Non-responders were considered subjects who discontinued prematurely without a postbaseline tumor response assessment or who did not meet the criteria for an objective response by the analysis cutoff date.

The secondary efficacy endpoints were:

- Objective response by 17 weeks
- Disease control rate (DCR)
- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Time to progression (TTP)

- Duration of stable disease (DOSD)
- Time to treatment failure
- Time to disease relapse following surgical intervention (TTDR)
- Resection rate

Safety Endpoints:

- Incidence and severity of adverse events
- Changes in laboratory values
- Change in vital signs
- Investigational medicinal product complete and incidence of dose adjustments
- Incidence of concomitant medications
- Changes from baseline over time in ECOG performance status

Exploratory Endpoints:

[redacted]

Statistical Methods: The efficacy results were reported using descriptive statistics. All efficacy data was stratified by *KRAS* mutation status. The analyses were based on radiographic images collected during the study and reviewed by the investigator. Any scan that was rated as unevaluable by the investigator was omitted from the analysis.

For continuous endpoints, the mean, standard error (for efficacy endpoints) or standard deviations (SD), median, 25th percentile, 75th percentile, minimum and maximum were provided. For discrete data, the frequency and percent distributions were provided.

For the primary endpoint, objective response rate was reported by *KRAS* mutation status along with 2-sided exact 95% confidence intervals (CIs) for the *KRAS* Tumor Response Analysis Set. The cumulative objective response rate over time was also presented for responding subjects. The number and percentage of best tumor response was tabulated to support the primary analysis. The objective response rate was also summarized overall using the Full Analysis Set.

Wilson's score method with continuity correction was used to calculate a 95% CI for the difference between rates across *KRAS* mutation groups.

A logistic regression model was employed to estimate the effect of *KRAS* mutation status on objective response rate. The odds ratio and 95% CI using the Wald method was provided. The model may have included covariates other than EGFR staining.

The analysis of all secondary endpoints was performed using the *KRAS* Tumor Response Analysis Set and overall using the Full Analysis Set. Subgroup analyses may have been performed.

Summary of Results: A total of 169 subjects were screened, of whom 154 were enrolled. All 154 subjects were included in the Full Analysis Set; 145 subjects were evaluable for *KRAS* status (the Primary Analysis Set). Of these, 85 subjects (55%) had measurable disease per RECIST with wild-type *KRAS* tumors and 58 subjects (38%) had measurable disease per RECIST with mutant *KRAS* tumors, comprising the *KRAS* Tumor Response Evaluable Analysis Set. The most frequent reasons that subjects were not evaluable for *KRAS* status were lack of tumor tissue availability or test failure.

Subject Disposition: As of the data cutoff date of 18 June 2009, a total of 150 subjects (97%) in the Full Analysis Set ended treatment with either panitumumab or FOLFIRI (97% with Wild-type *KRAS* and 100% with Mutant *KRAS*). A total of 147 Subjects (95%) discontinued panitumumab (94% Wild-type *KRAS*, 98% Mutant). The most common reason for discontinuing panitumumab treatment was disease progression per radiographic evidence (53 subjects, 36% [31% Wild-type, 45% Mutant]). A total of 149 subjects (97%) discontinued FOLFIRI chemotherapy (95% Wild-type, 100% Mutant). Disease progression per radiographic evidence (50 subjects, 34% [26% Wild-type, 44% Mutant] was the most common reason for ending FOLFIRI. Eight subjects were still receiving at least 1 component of the combination treatment at the time of data cutoff. The mean (SD) actual follow-up time was 37.7 (15.7) weeks (39.5 weeks Wild-type, 35.8 weeks Mutant).

Efficacy Results: In the Full Analysis Set, 76 subjects (49%) had either a complete or partial tumor response. The objective response rate was 49.3% (95%CI: 41.2, 57.6). Secondary analyses were consistent with the findings in the primary analysis. The disease control rate was 90.8% (95% CI: 85.0, 94.9). The median duration of response was 9.2 months (95% CI: 7.3, 13.0). The median time to initial objective response for subjects who responded was 1.9 months (1.3, 7.8). The median PFS time was 7.6 months (95% CI: 7.3, 8.9). The median time to disease progression was 7.8 months (95%CI: 7.3, 9.2). The median duration of stable disease was 5.9 months (95%CI: 5.6, 7.3). The median time to treatment failure was 6.2 months (5.8, 6.9).

In the Primary Analysis Set, a higher percentage of subjects with Wild-type *KRAS* than compared with Mutant *KRAS* had either a complete or partial tumor response. The objective response rate for subjects in the Wild-type *KRAS* group was 56.5% (95% CI: 45.3, 67.2) and 37.9% (95% CI: 25.5, 51.6) for subjects in the Mutant *KRAS* group.

The difference in rates between the 2 *KRAS* groups was 18.5 (95% CI: 0.8, 34.6). The odds ratio for objective response rate was 2.12 (95% CI: 1.02, 4.45), favoring the Wild-type *KRAS* group. Secondary analyses were consistent with the findings in the primary analysis. The median duration of response was longer for subjects with Wild-type *KRAS* compared with subjects in the Mutant *KRAS* group (13.0 months [95% CI: 9.3, 13.0] and 7.4 months [95% CI: 5.4, 8.8], respectively). The median PFS times were 8.9 months (95% CI: 7.6, 14.3) in the Wild-type *KRAS* group and 7.2 months (95% CI: 5.6, 7.8) in the Mutant *KRAS* group. The median time to disease progression also favored the Wild-type *KRAS* group, 11.2 months (95%CI: 7.6, 14.8), over the Mutant *KRAS* group, 7.3 months (95% CI: 5.7, 8.9). There was little difference between the *KRAS* groups in the disease control rate and time to initial objective response and the median duration of response was comparable in both groups. The median time to treatment failure was longer in the Wild-type *KRAS* group than in the Mutant *KRAS* group.

Safety Results: In the Safety Analysis Set, the mean (SD) average dose of panitumumab delivered was 5.78 (0.49) mg/kg. A total of 116 subjects (75%) had panitumumab dose changes; the most frequent reason was weight change. In the KRAS Safety Analysis Set, the median dose of panitumumab administered was approximately 6.0 mg/kg for the first 12 cycles for both KRAS mutation groups, and ranged from 4.80 to 6.00 mg/kg from cycle 13 to cycle 35 for subjects with Wild-type KRAS and 5.12 to 6.05 mg/kg from cycle 13 to 26 for subjects with Mutant KRAS. A total of 66 subjects (77%) in the Wild-type KRAS group and 44 subjects (75%) in the Mutant KRAS group had panitumumab dose changes.

In the Safety Analysis Set, all subjects received irinotecan and 5-FU bolus continuous infusion. The mean (SD) relative dose intensity for irinotecan was 83.42 (12.94) and for 5-FU bolus was 84.28 (12.92). The median number of cycles delivered for panitumumab was 11.5 (range: 1 to 35) and the median number of cycles delivered for chemotherapy was 12.0 (range: 1 to 35).

In the KRAS Safety Analysis Set, the cumulative dose delivered for chemotherapy (any component) was longer in the Wild-type KRAS group than in the Mutant KRAS group. The mean (SD) relative dose intensity for irinotecan was 84.18 (12.50) in the Wild-type KRAS group and 83.18 (13.64) in the Mutant KRAS group, for 5-FU bolus was 84.53 (13.33) in the Wild-type KRAS group and 84.08 (12.78) in the Mutant KRAS group, and for 5-FU continuous infusion 86.37 (13.76) in the Wild-type KRAS group and 85.26 (14.82) in the Mutant KRAS group. The median number of delays was 2 per subject in both KRAS mutation status groups.

All subjects experienced at least 1 adverse event during the study. As would be expected for subjects with mCRC receiving FOLFIRI chemotherapy, diarrhea, nausea, dry skin, rash fatigue and vomiting were among the most frequently reported adverse events overall and the incidences were similar in both KRAS groups.

In the Safety Analysis Set, 73% of subjects had an adverse event that was grade 3 or 4. The most frequently reported adverse events were diarrhea, neutropenia, acne and rash, pulmonary embolism, and paronychia. The subject incidence of adverse events that were grade 3 was greater in the Wild-type KRAS group (51%) than in the Mutant KRAS group (42%). However, the subject incidence of grade 4 or higher adverse events was greater in the Mutant KRAS group (39%) compared with the Wild-type KRAS group (30%). Adverse events with the greatest differences between the Wild-type and Mutant KRAS groups (ie, > 5%) included dry skin, rash, neutropenia, alopecia, and conjunctivitis; however due to the small number of subjects in each KRAS group, these results should be interpreted with caution.

Overall, 13 subjects (8%) had fatal adverse events; 7 subjects with Wild-type KRAS and 6 subjects with Mutant KRAS. The fatal adverse events in the Wild-type group were death, hematemesis, hepatic failure, intestinal obstruction, multi-organ failure, rectal hemorrhage and septic shock. The fatal adverse events in the Mutant KRAS group were mCRC (2 subjects), general health deterioration, subileus, and vena cava thrombosis.

Overall, 84 subjects (55%) had serious adverse events, of these 43 subjects (28%) had events considered related to treatment by the investigator. The incidence of serious adverse events was higher in the Wild-type KRAS group (59%) than in the Mutant KRAS group (47%). Serious adverse events with the greatest difference between the Wild-type KRAS group and the Mutant KRAS group were diarrhea (16% vs 8%) and pulmonary embolism (6% vs 10%). The incidence of serious adverse events considered related to treatment by the investigator was also higher in the Wild-type KRAS group (30%) than in the Mutant KRAS group (22%). Overall, the most frequently reported serious, treatment-related adverse events were diarrhea (15% Wild-type KRAS, 8% Mutant KRAS), vomiting (3% Wild-type KRAS, 2% Mutant KRAS), neutropenia (2% Wild-type KRAS, 3% Mutant KRAS), and dehydration, fatigue, and pulmonary embolism (2% each KRAS group).

Twenty-nine percent of all subjects had adverse events that led to discontinuation of any study drug, of these 13% were considered serious. Twenty percent of the subjects had treatment-related adverse events that led to discontinuation of any study drug, 5% of these were considered serious. More subjects in the Mutant KRAS group had adverse events leading to discontinuation of panitumumab than in the Wild-type KRAS group (29% versus 22%) and more subjects in the Wild-type group (21%) than in the Mutant KRAS group (20%) had adverse events leading to discontinuation of all chemotherapy. The most frequently reported adverse events leading to discontinuation of panitumumab were generally skin-related toxicities.

In the Safety Analysis Set, almost all subjects (99%) had adverse events of interest. The most frequently reported were integument toxicities (98%), specifically skin toxicities (97%) then followed by diarrhea (79%). There was no infusion reaction reported as an adverse event. In the KRAS Safety Analysis Set, the greatest difference between the KRAS groups was observed in eye toxicities (45% Wild-type, 29% Mutant), hair (31% Wild-type, 51% Mutant), and stomatitis/oral mucositis (45% Wild-type, 63% Mutant).

Grade 4 diarrhea occurred in 5% of subjects with Wild-type KRAS status and no subjects in the Mutant KRAS group.

The overall incidence of pulmonary, vascular, and cardiac toxicities occurred at a similar subject incidence in the Wild-type and Mutant KRAS groups.

Conclusions:

In subjects with mCRC treated with a first-line therapy of panitumumab in combination with a chemotherapy regimen of irinotecan, 5-FU, and leucovorin (FOLFIRI), a higher objective response rate was observed in subjects with Wild-type *KRAS* compared with subjects with Mutant *KRAS*. The secondary analyses such as duration of response, progression-free survival time and time to disease progression favored the Wild-type *KRAS* group and which were consistent with the findings from the primary analysis. However, it should be noted that without a concurrent control group, it was difficult to distinguish whether the differences observed in *KRAS* mutation status were because *KRAS* mutation status had prognostic value or predictive value.

The safety profile of panitumumab was consistent with that observed with cetuximab administered in combination with irinotecan-based chemotherapy.

2. SYNOPSIS

Background: Study 20060314 was a phase 2, single-arm, open-label, multicenter study designed to estimate the objective response rate (ORR) and other measures of efficacy for subjects treated with panitumumab in combination with irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) as first-line regimen for previously untreated metastatic colorectal cancer (mCRC). In the primary analysis, a higher percentage of subjects with wild-type Kirsten rat sarcoma-2 viral oncogene (*KRAS*) exon 2 tumors had either a complete response (CR) or partial response (PR) compared with mutant *KRAS* exon 2 tumors (56% versus 38%, respectively) (Primary Analysis clinical study report [CSR], 11 March 2010). The difference in ORR between the 2 *KRAS* exon 2 strata was 18.5% (95% confidence interval [CI]: 0.8%, 34.6%). The unadjusted common treatment odds ratio was 2.12 (95% CI: 1.02, 4.45).

Results: In this predefined supplemental biomarker analysis, additional rat sarcoma viral oncogene homolog (*RAS*) mutations beyond *KRAS* exon 2 (*KRAS* exon 3, 4 and neuroblastoma *RAS* viral oncogene [*NRAS*] exon 2, 3, and 4) and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) exon 15 were examined with respect to panitumumab treatment effects on ORR and other measures of efficacy, and safety in subjects with mCRC. The *RAS* ascertainment rate was 93% overall (143 of 154 enrolled subjects). All enrolled subjects who had received at least 1 dose of panitumumab and whose *RAS* status could be assessed were included in the *RAS* Efficacy Analysis Set. Key efficacy results for *RAS* Efficacy Analysis Sets are shown in the Table 2-1 below.

The difference in the ORR between the wild-type and mutant *RAS* strata was 17.7% (95% CI: 0.3%, 33.8%). The odds ratio for objective response in subjects with wild-type versus mutant *RAS* tumors was 2.05 (95% CI: 0.99, 4.23). The estimated hazard ratio (wild-type versus mutant *RAS*) from a Cox proportional hazards regression model for duration of response was 0.155 (95% CI: 0.065, 0.367), for PFS was 0.370 (95% CI: 0.237, 0.576), and for time to disease progression was 0.345 (95% CI: 0.215, 0.554).

Table 2-1. Key Efficacy Results by *RAS* Efficacy Analysis Sets

	RAS Analysis		*KRAS* exon 2 analysis	
	Panitumumab plus FOLFIRI N = 143		Panitumumab plus FOLFIRI N = 145	
	Wild-type *RAS* (N = 69)	Mutant *RAS* (N = 74)	Wild-type *KRAS* Exon 2 (N = 86)	Mutant *KRAS* Exon 2 (N = 59)
Objective tumor response[a]				
Subjects responding – n (%)	40 (59)	30 (41)	48 (56)	22 (38)
Response Rate (95% CI)- %	58.82 (46.23, 70.63)	41.10 (29.71, 53.23)	56.47 (45.28, 67.20)	37.93 (25.51, 51.63)
Difference in rates (95% CI) - %	17.73 (0.25, 33.83)		18.54 (0.84, 34.63)	
Unadjusted common treatment odds ratio[b] (95% CI)	2.05 (0.99, 4.23)		2.12 (1.02, 4.45)	
Duration of response (months)[c]				
Subjects with disease progression	15 (38)	24 (80)	13 (27)	16 73)
Median time (95% CI)	13.0 (9.3, 15.7)	5.8 (3.9, 7.8)	13.0 (9.3, 13.0)	7.4 (5.4, 8.8)
Hazard ratio[d] (95% CI)	0.155 (0.065, 0.367)		0.283 0.130, 0.614	
Progression-free survival (months)[e]				
Subjects with disease progression/died – n (%)	38 (55)	61 (82)	44 (51)	48 (81)
Median time (95% CI)	11.2 (7.6, 14.8)	7.3 (5.8, 7.5)	8.9 (7.6, 14.3)	7.2 (5.6, 7.8)
Hazard ratio[d] (95% CI)	0.370 0.237, 0.576		0.464 0.306, 0.703	
Time to disease progression (months)				
Subjects with disease progression – n (%)	34 (49)	55 (74)	36 (42)	45 (76)
Median time (95% CI)	13.2 (7.8, 17.0)	7.3 (6.1, 7.6)	11.2 (7.6, 14.8)	7.3 (5.7, 8.9)
Hazard ratio[d] (95% CI)	0.345 0.215, 0.554		0.395 0.252, 0.618	

CI = confidence interval; FOLFIRI = irinotecan, 5-fluorouracil, and leucovorin; *KRAS* = Kirsten rat sarcoma-2 viral oncogene; *RAS* = rat sarcoma viral oncogene homolog; RECIST = Response Evaluation Criteria In Solid Tumors

Disease assessments were based on investigator review of scans using modified-RECIST v1.0 criteria.

[a] A subject was considered a responder if the best response was either a complete or partial response. Objective tumor response was calculated using Tumor Response Analysis Set. Two subjects with evaluable *RAS* data (1 subject with wild-type *RAS* tumors and 1 subject with mutant *RAS* tumors) did not have measurable disease as per modified RECIST and therefore were excluded from this analysis. Wild-type *RAS* N = 68; mutant *RAS* N = 73; wild-type *KRAS* exon 2 N = 85; mutant *KRAS* exon 2 N = 58.

[b] Odds ratio is presented as wild-type : mutant strata.

[c] Duration of response is calculated using Tumor Response Analysis Set: Responders; wild-type *RAS* N = 40; mutant *RAS* N = 30; wild-type *KRAS* exon 2 N = 48; mutant *KRAS* exon 2 N = 22.

[d] Hazard ratios are presented as wild-type : mutant strata.

[e] Progression-free survival time is defined as time from date of enrollment to date of first disease progression per modified-RECIST criteria or death.

Source: Table 14-4.2.1, Table 14-4.5.1, Table 14-4.8.1, Table 14-4.9.1; Table 14-4.2.1, Table 14-4.12.1, Table 14-4.21.1, and Table 14-4.28.1 of Primary Analysis CSR, 11 March 2010.

For subjects with wild-type *KRAS* exon 2 and mutant *RAS* (subjects with newly identified tumor *RAS* alterations beyond *KRAS* exon 2), the ORR was 46.7% (95% CI: 21.3%, 73.4%). The estimated median duration of response was 3.9 months (95% CI: 3.5, not estimable), estimated median PFS time was 7.3 months (95% CI: 5.3, 7.6), and the estimated median time to disease progression was 7.3 months (95% CI: 5.6, 8.9).

Safety Results:

All enrolled subjects who received at least 1 dose of panitumumab and whose *RAS* status could be assessed were included in *RAS* Safety Analysis Set (69 subjects with wild-type *RAS* tumors and 74 subjects with mutant *RAS* tumors). All subjects in the *RAS* Safety Analysis Set had at least 1 adverse event. The most frequently reported adverse events in both the *RAS* strata were diarrhea (wild-type 80% versus mutant 78%) and nausea (52% versus 58%). The subject incidence of adverse events with ≥ 10% difference in either of the 2 *RAS* strata (wild-type versus mutant) were dry skin (48% versus 36%), conjunctivitis (35% versus 12%), alopecia (28% versus 43%), neutropenia (23% versus 49%), vomiting (23% versus 35%), skin toxicity (19% versus 7%), mucosal inflammation (17% versus 36%), Palmar-plantar erythrodysesthesia syndrome (12% versus 24%), and cough (3% versus 14%), respectively. Conjunctivitis was the only adverse event with ≥ 20% higher incidence in the wild-type *RAS* stratum than in the mutant *RAS* stratum (35% versus 12%), respectively.

On-treatment fatal adverse events were reported in 3 subjects (4%) with wild-type *RAS* tumors and 7 subjects (9%) with mutant *RAS* tumors. In subjects with wild-type *RAS* tumors, the fatal adverse events reported were hepatic failure, intestinal obstruction, and septic shock (1 subject each). In subjects with mutant *RAS* tumors, the fatal adverse events reported were mCRC, multi-organ failure, rectal hemorrhage, subileus, and vena cava thrombosis (1 subject each). The only fatal adverse event reported in more than 1 subject was in the mutant *RAS* strata by the preferred term of 'death' (2 subjects). These on-treatment fatal adverse events were previously reported for subjects with *KRAS* exon 2 tumors. Fatal adverse events considered by the investigator to be treatment-related in the wild-type *KRAS* exon 2 strata were hematemesis and rectal hemorrhage (1 subject each). One subject had a fatal adverse event considered by the investigator to be treatment-related in the mutant *KRAS* exon 2 strata (vena cava

thrombosis). Hematemesis was not reported as a fatal adverse event in either of the 2 *RAS* strata.

Adverse events leading to discontinuation of panitumumab were reported in 15 subjects (22%) with wild-type *RAS* tumors and 14 subjects (19%) with mutant *RAS* tumors. Adverse events leading to discontinuation of panitumumab reported in > 1 subject in either of the 2 *RAS* strata (wild-type versus mutant) were rash (3 [4%] each), paronychia (3 [4%] versus 0 [0%]), conjunctivitis (2 [3%] versus 0 [0%]), acne (1 [1%] versus 2 [3%]), and pulmonary embolism (0 [0%] versus 2 [3%]).

Adverse events leading to discontinuation of FOLFIRI were reported in 15 subjects (22%) in wild-type *RAS* strata and 8 subjects (11%) in the mutant *RAS* strata. Adverse events leading to discontinuation of FOLFIRI reported in > 1 subject in either of the 2 *RAS* strata (wild-type versus mutant) were paronychia (4 [6%] versus 0% [0%]), diarrhea (2 [3%] each), and catheter related infection (2 [3%] versus 0 [0%]).

Serious adverse events were reported in 40 subjects (58%) in the wild-type *RAS* stratum and 38 subjects (51%) in the mutant *RAS* stratum. The frequent serious adverse events (occurring in ≥ 5% of subjects in either of the 2 *RAS* strata) were diarrhea (13 [19%]) and pulmonary embolism and vomiting (4 [6%] each) in the wild-type *RAS* stratum; and pulmonary embolism (7 [9%]) and diarrhea (6 [8%]) in the mutant *RAS* stratum.

In the wild-type *RAS* stratum, 38 subjects (55%) had grade 3 adverse events, 18 subjects (26%) had grade 4 adverse events, and 3 subjects (4%) had grade 5 adverse events. In the mutant *RAS* stratum, 29 subjects (39%) had grade 3 adverse events, 21 subjects (28%) had grade 4 adverse events, and 7 subjects (9%) had grade 5 adverse events. Similar observations in incidence of grade 3, 4, and 5 adverse events were seen in subjects with wild-type and mutant *KRAS* exon 2 tumors, respectively (Primary Analysis CSR, 11 March 2010).

The most frequently reported adverse events of interest in the wild-type and mutant *RAS* strata were integument toxicities (68 [99%] versus 72 [97%]) and diarrhea (55 [80%] versus 58 [78%]), respectively. The integument toxicities (wild-type versus mutant *RAS* strata) reported were skin (68 [99%] versus 71 [96%]), eye (36 [52%] versus 22 [30%]), hair (21 [30%] versus 36 [49%]), nail (20 [29%] versus 28 [38%]), and cheilitis (2 [3%] in each stratum). Skin anti-epidermal growth factor receptor effect is an identified risk associated with panitumumab treatment. The other adverse events of interest reported with ≥ 5% difference in incidence between either of the 2 *RAS* strata (wild-type versus

mutant) were hypomagnesemia (17 [25%] versus 14 [19%]), pulmonary toxicity (12 [17%] versus 18 [24%]), and stomatitis/oral mucositis (30 [43%] versus 45 [61%]), respectively. Infusion reactions (wild-type versus mutant *RAS* strata) predefined as United States prescribing information was 0% versus 3%; per Common Terminology Criteria for Adverse Events was 19% versus 8%; and as per adverse event reporting by the investigator was 0% in both the *RAS* strata.

Conclusions

- An improved panitumumab treatment effect was observed for ORR and PFS in subjects with wild-type *RAS* tumors compared with mutant *RAS* tumors. The odds ratio for objective response in subjects with wild-type versus mutant *RAS* tumors was 2.05 (95% CI: 0.99, 4.23) and the PFS hazard ratio was 0.370 (95% CI: 0.237, 0.576).
- For ORR, the magnitude of the improvement between the wild-type and mutant *RAS* tumors was less when compared with the magnitude of the improvement between the wild-type and mutant *KRAS* exon 2 tumors (odds ratio = 2.12 [95% CI: 1.02, 4.45]); however, for PFS the reverse was true; the magnitude of improvement between the wild-type and mutant *RAS* tumors was greater when compared with the magnitude of the improvement between the wild-type and mutant *KRAS* exon 2 tumors (hazard ratio = 0.464 [95% CI: 0.306, 0.703]).
- A clinical benefit was observed in subjects with wild-type *RAS* tumors compared to subjects with mutant *RAS* tumors for duration of response (hazard ratio 0.155 [95% CI: 0.065, 0.367]) and time to disease progression (hazard ratio 0.345 [95% CI: 0.215, 0.554]).
- [redacted]
- The safety profile observed in subjects with wild-type *RAS* tumors was consistent with that previously reported for subjects with wild-type *KRAS* exon 2 tumors. In general, the safety profile observed across biomarker analysis sets in this study was consistent with what has been observed in other studies using panitumumab and FOLFIRI chemotherapy in a mCRC population.
- No new safety signals for panitumumab were observed and no new toxicities were identified in this refined *RAS* population administered panitumumab with FOLFIRI chemotherapy.