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 Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

Investigators and Study Centers: This study was conducted at 133 sites in western, central and eastern Europe; Canada; Australia; and South America.

Study Period: 23 August 2006 (first subject randomized) through 24 January 2013 (data analysis cutoff date for MRT *KRAS* re-testing analysis)

Development Phase: 3

Methodology:

This phase 3, multicenter, open-label, randomized clinical trial was conducted to assess the efficacy of panitumumab in combination with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy compared with FOLFOX alone for initial treatment of metastatic colorectal cancer (mCRC) in subjects with wild-type Kirsten rat sarcoma-2 viral oncogene (*KRAS*) tumors and subjects with mutant *KRAS* tumors. For the primary, final, and OS update analyses, *KRAS* mutation status was assessed using the investigational-use only/laboratory-developed test (IUO) kit, and efficacy and safety results by *KRAS* mutation status were reported in the 20050203 Progression-free Survival, 20050203 Overall Survival, 20050203 Final Analysis, and 20050203 OS Update Analysis clinical study reports. Results of analyses to test concordance between the IUO and market-ready test (MRT) kits were presented in the 20050203 and 20050181 therascreen® *KRAS* RGQ PCR Kit *KRAS* Bridging Study Report (bridging study part 1). For the 20050203 MRT *KRAS* re-testing analysis (bridging study part 2), available samples from the approximately 40% of subjects not included in the bridging study part 1 were tested using the MRT kit; efficacy and safety results by MRT *KRAS* status for both the bridging study part 1 and part 2 are presented in this report.

The primary objective of this prospectively defined, retrospective analysis was to evaluate the predictive value of MRT *KRAS* status on progression-free survival (PFS) (per central review) and overall survival (OS) for the treatment effect of panitumumab plus FOLFOX compared to FOLFOX alone as first-line therapy for mCRC, and the treatment effect on PFS (per central review) and OS among subjects with MRT *KRAS* wild-type tumors. The secondary objective was to evaluate the treatment effect on PFS (per central review) and OS among subjects with MRT *KRAS* mutant tumors, and on 60-day PFS and objective response rate (ORR) by MRT *KRAS* status.

Summary of Results:

Subject Disposition:

MRT *KRAS* status was available for 1017 of 1183 randomized subjects (86%); 569 subjects were included in the MRT Wild-type *KRAS* Efficacy Analysis Set, 448 in the MRT Mutant *KRAS* Efficacy Analysis Set, and 166 in the MRT Unevaluable *KRAS* Efficacy Analysis Set. Overall, 1014 (86%) subjects had valid *KRAS* results from both the IUO and MRT kits.

Efficacy Results:

A quantitative interaction test was conducted to compare the magnitude of the relative treatment effect on PFS between the MRT Wild-type and Mutant *KRAS* Efficacy Analysis Sets. Within each analysis set, the relative treatment effect was estimated by the log-hazard ratio (panitumumab plus FOLFOX vs FOLFOX alone) stratified by the randomization factors. The results from the primary analysis indicated a significant interaction between treatment and *KRAS* status on PFS ($p = 0.0149$) and OS ($p = 0.0316$).

In the MRT Wild-type *KRAS* Efficacy Analysis Set, median PFS and OS times were greater in the panitumumab plus FOLFOX arm than in the FOLFOX alone arm. The estimated PFS and OS hazard ratios and the odds ratio for ORR favored the panitumumab plus FOLFOX arm. The treatment effect on PFS and OS favored the panitumumab plus FOLFOX arm in all subgroups defined by prespecified baseline covariates, except for ECOG performance score 2 and age ≥ 75 years. Results for the final analysis and OS update snapshots were similar to those for the primary analysis snapshot.

	MRT Wild-type *KRAS* Efficacy Analysis Set					
	Primary Analysis Snapshot		Final Analysis Snapshot		OS Update Snapshot	
	Panitumumab Plus FOLFOX (N = 281)	FOLFOX Alone (N = 288)	Panitumumab Plus FOLFOX (N = 281)	FOLFOX Alone (N = 288)	Panitumumab Plus FOLFOX (N = 281)	FOLFOX Alone (N = 288)
PFS						
Median PFS (95% CI)–months	9.4 (9.2, 11.1)	8.0 (7.5, 9.3)	9.7 (9.2, 11.2)	8.9 (7.5, 9.9)	9.9 (9.2, 11.4)	9.2 (7.6, 10.0)
P-value[a]	0.0762		0.0637		0.1110	
Hazard ratio[b]	0.826 (0.669, 1.021)		0.841 (0.700, 1.010)		0.864 (0.722, 1.034)	
OS						
Median OS (95% CI)–months	25.4 (20.7, 28.7)	20.7 (17.8, 23.8)	25.2 (20.3, 28.3)	20.7 (17.8, 23.8)	25.2 (20.2, 27.8)	20.6 (17.7, 23.8)
P-value[a]	0.1381		0.2014		0.0551	
Hazard ratio[b]	0.842 (0.670, 1.058)		0.877 (0.716, 1.074)		0.834 (0.693, 1.004)	
60-day PFS[c]						
Median 60-day PFS (95% CI)–months	9.7 (9.2, 11.3)	8.0 (7.5, 9.4)	9.6 (9.2, 11.2)	8.1 (7.5, 9.5)	9.6 (9.2, 11.2)	8.1 (7.5, 9.5)
P-value[a]	0.0452		0.0233		0.0233	
Hazard ratio[b]	0.795 (0.635, 0.996)		0.789 (0.643, 0.969)		0.789 (0.643, 0.969)	
ORR						
N	274	284	274	284	274	284
Rate (95% CI)–%	57.30 (51.21, 63.23)	47.54 (41.60, 53.52)	59.49 (53.42, 65.35)	47.54 (41.60, 53.52)	59.49 (53.42, 65.35)	47.54 (41.60, 53.52)
Odds ratio[d]	1.49 (1.06, 2.13)		1.63 (1.16, 2.35)		1.63 (1.16, 2.35)	
P-value	0.0223		0.0048		0.0048	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; *KRAS* = Kirsten rat sarcoma-2 viral oncogene; MRT = market-ready test; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Results are given with 95% confidence intervals in parentheses.

[a]P-value is based on a 2-sided log-rank test stratified by region (Western Europe, Canada, and Australia vs. Rest of World) and ECOG performance score (0 or 1 vs. 2).

[b]The Cox proportional hazard ratio is stratified by region and ECOG performance score. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab plus FOLFOX relative to FOLFOX alone.

[c] 60-day death rule for progression-free survival time is defined as the time from the randomization date to date of first disease progression per modified-RECIST criteria or death; subjects not meeting these criteria by the analysis data cutoff date will have their PFS time censored at their last evaluable disease assessment date; subjects without disease progression who died more than 60 days after the last tumor assessment or randomization date whichever happened later, PFS time will be censored at their last evaluable disease assessment date or randomization date whichever happened later within 60 days from last evaluable disease assessment date or randomization date whichever happened later.

[d]The odds ratio is defined as the odds of having an objective response in the panitumumab plus arm relative to the odds on the FOLFOX alone arm.

In the MRT Mutant *KRAS* Efficacy Analysis Set, median PFS and OS times were greater in the FOLFOX alone arm than in the panitumumab plus FOLFOX arm. The estimated PFS and OS hazard ratios and the odds ratio for ORR favored either the FOLFOX alone arm or neither arm. The treatment effect on PFS and OS across subgroups favored either the FOLFOX alone arm or neither arm. Results for the final analysis and OS update snapshots were similar to those for the primary analysis snapshot.

	MRT Mutant *KRAS* Efficacy Analysis Set					
	Primary Analysis Snapshot		Final Analysis Snapshot		OS Update Snapshot	
	Panitumumab Plus FOLFOX (N = 225)	FOLFOX Alone (N = 223)	Panitumumab Plus FOLFOX (N = 225)	FOLFOX Alone (N = 223)	Panitumumab Plus FOLFOX (N = 225)	FOLFOX Alone (N = 223)
PFS						
Median PFS (95% CI)–months	7.3 (6.3, 8.0)	8.6 (7.6, 9.3)	7.4 (6.3, 8.1)	9.0 (7.7, 9.6)	7.4 (6.3, 8.1)	9.0 (7.7, 9.6)
P-value[a]	0.0933		0.0752		0.0798	
Hazard ratio[b]	1.206 (0.969, 1.500)		1.195 (0.981, 1.456)		1.190 (0.979, 1.446)	
OS						
Median OS (95% CI)–months	15.8 (13.4, 18.1)	18.7 (15.7, 21.0)	15.8 (13.4, 18.1)	18.2 (15.7, 20.9)	15.8 (13.4, 18.1)	18.2 (15.7, 20.9)
P-value[a]	0.1180		0.1891		0.2497	
Hazard ratio[b]	1.200 (0.955, 1.510)		1.150 (0.934, 1.416)		1.124 (0.921, 1.372)	
60-day PFS[c]						
Median 60-day PFS (95% CI)–months	7.3 (6.3, 7.9)	8.6 (7.5, 9.3)	7.3 (6.3, 7.8)	8.7 (7.6, 9.4)	7.3 (6.3, 7.8)	8.7 (7.6, 9.4)
P-value[a]	0.1080		0.0607		0.0607	
Hazard ratio[b]	1.210 (0.959, 1.525)		1.234 (0.990, 1.538)		1.234 (0.990, 1.538)	
ORR						
N	219	214	219	214	219	214
Rate (95% CI)–%	38.81 (32.32, 45.61)	41.12 (34.46, 48.03)	39.27 (32.76, 46.08)	41.59 (34.91, 48.50)	39.27 (32.76, 46.08)	41.59 (34.91, 48.50)
Odds ratio[d]	0.90 (0.60, 1.35)		0.90 (0.60, 1.35)		0.90 (0.60, 1.35)	
P-value	0.6663		0.6642		0.6642	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; *KRAS* = Kirsten rat sarcoma-2 viral oncogene; MRT = market-ready test; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Results are given with 95% confidence intervals in parentheses.

[a]P-value is based on a 2-sided log-rank test stratified by region (Western Europe, Canada, and Australia vs. Rest of World) and ECOG performance score (0 or 1 vs. 2).

[b]The Cox proportional hazard ratio is stratified by region and ECOG performance score. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab plus FOLFOX relative to FOLFOX alone.

[c] 60-day death rule for progression-free survival time is defined as the time from the randomization date to date of first disease progression per modified-RECIST criteria or death; subjects not meeting these criteria by the analysis data cutoff date will have their PFS time censored at their last evaluable disease assessment date; subjects without disease progression who died more than 60 days after the last tumor assessment or randomization date whichever happened later, PFS time will be censored at their last evaluable disease assessment date or randomization date whichever happened later within 60 days from last evaluable disease assessment date or randomization date whichever happened later.

[d]The odds ratio is defined as the odds of having an objective response in the panitumumab plus arm relative to the odds on the FOLFOX alone arm.

Safety Results:

Safety results obtained with *KRAS* mutation status assessed using the MRT kit were consistent with those observed in the primary analysis for OS, the final analysis, and the OS update analysis obtained using the IUO kit. In the MRT Unevaluable *KRAS* Safety Analysis Set, although the incidence of on-treatment fatal adverse events was greater in the panitumumab plus FOLFOX arm (11 subjects [13%]) than in the FOLFOX alone arm (3 subjects [4%]), these incidences were similar to those previously reported for the Unevaluable *KRAS* Safety Analysis Set in the primary analysis for OS (using the IUO kit) (6 subjects [13%] vs 1 subject [3%], respectively).

Subject Incidence of Adverse Events – n (%)	Panitumumab Plus FOLFOX	FOLFOX Alone
MRT Wild-type *KRAS* Safety Analysis Set	N = 278	N = 285
On-treatment fatal adverse event	12 (4)	17 (6)
Serious adverse event	117 (42)	100 (35)
Leading to permanent discontinuation of any study drug	69 (25)	40 (14)
MRT Mutant *KRAS* Safety Analysis Set	N = 222	N = 222
On-treatment fatal adverse event	16 (7)	8 (4)
Serious adverse event	105 (47)	69 (31)
Leading to permanent discontinuation of any study drug	49 (22)	30 (14)
MRT Unevaluable *KRAS* Safety Analysis Set	N = 85	N = 77
On-treatment fatal adverse event	11 (13)	3 (4)
Serious adverse event	40 (47)	29 (38)
Leading to permanent discontinuation of any study drug	18 (21)	14 (18)

FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; *KRAS* = Kirsten rat sarcoma-2 viral oncogene; MRT = market-ready test.

Conclusions:

This report presents the results of the MRT *KRAS* re-testing analysis with assessment of *KRAS* mutation status generated using the MRT kit. The primary and final analyses of PFS and OS and the OS update analysis by *KRAS* mutation status using the IUO kit were reported previously. The sample ascertainment rate for MRT *KRAS* status was 86% (1017 of 1183 randomized subjects).

Results from the primary analysis using a quantitative interaction test indicated a significant interaction between treatment and *KRAS* status on PFS (p = 0.0149) and OS (p = 0.0316).

In the MRT Wild-type *KRAS* Efficacy Analysis Set, PFS was greater in the panitumumab plus FOLFOX arm than in the FOLFOX alone arm (median PFS [95% CI]: 9.4 months [9.2, 11.1] vs 8.0 months [7.5, 9.3]; hazard ratio: 0.826 [95% CI: 0.669, 1.021]). PFS favored the panitumumab plus FOLFOX arm for subjects in most of the subgroups analyzed. Median OS time was greater in the panitumumab plus FOLFOX arm than in the FOLFOX alone arm (median OS [95% CI]: 25.4 months [20.7, 28.7] vs 20.7 months [17.8, 23.8]; hazard ratio: 0.842 [95% CI: 0.670, 1.058]). Response rates were high in both treatment arms. The hazard ratio (95% CI) for the 60-day death rule PFS time was 0.795 (0.635, 0.996), favoring the panitumumab plus FOLFOX arm.

In the MRT Mutant *KRAS* Efficacy Analysis Set, PFS was inferior for those receiving panitumumab plus FOLFOX compared to those receiving FOLFOX alone (median PFS [95% CI]: 7.3 months [6.3, 8.0] vs 8.6 months [7.6, 9.3]; hazard ratio: 1.206 [95% CI: 0.969, 1.500]). OS was also inferior for those receiving panitumumab plus FOLFOX (median OS [95% CI]: 15.8 months [13.4, 18.1] vs 18.7 months [15.7, 21.0]; hazard ratio: 1.200 [95% CI: 0.955, 1.510]). The treatment effect across subgroups either favored either the FOLFOX alone arm or neither arm. The hazard ratio (95% CI) for the 60-day death rule PFS time was 1.210 (0.959, 1.525), favoring the FOLFOX alone arm.

The OS event rate in the MRT Wild-type *KRAS* Efficacy Analysis Set was 53% for the primary analysis snapshot and 80% for the OS update snapshot, and the treatment effect on OS favored the panitumumab plus FOLFOX arm over the FOLFOX alone arm in both cases (descriptive p-values: 0.1381 and 0.0551, respectively).

Safety results were consistent with those observed in the primary analysis for OS, the final analysis, and the OS update analysis using the IUO kit. No new safety risks were identified with the MRT *KRAS* re-testing analysis.

Results from the descriptive analyses presented in this report are consistent with the findings from the primary, final, and OS update analyses using the IUO kit and support the efficacy and safety conclusions drawn previously.