2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix® (no trade name exists for conatumumab)

Name of Active Ingredient: panitumumab and conatumumab

Title of Study: A Phase 1b/2 Trial of AMG 655 in Combination with Panitumumab in Subjects with Metastatic Colorectal Cancer

Investigator(s) and Study Center(s): This study was conducted at 10 centers in the United States and Western Europe (Belgium and France). Centers and principal investigators are listed in Appendix 4.

Publication(s):

Rougier P, Infante J, Van Laethem J, et al. A phase Ib/II trial of AMG 655 and panitumumab (pmab) for the treatment (tx) of metastatic colorectal cancer (mCRC): Safety results. *J Clin Onco*l. 2009;27(15 suppl 1):4130.

Peeters M, Infante JR, Rougier P, et al. Phase 1b/2 trial of conatumumab and panitumumab (pmab) for the treatment (tx) of metastatic colorectal cancer (mCRC): Safety and efficacy. Presented at: Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, Florida.

Study Period: 14 January 2008 *(d*ate first subject enrolled in part 1) to 04 November 2010 (date last subject completed follow-up)

Development Phase: 1b (part 1)/2 (part 2)

Objectives:

The primary objective of part 1 of this study was to identify a tolerable dose of conatumumab (AMG 655) in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs) in subjects with metastatic colorectal cancer (mCRC). The primary objective of part 2 was to evaluate the objective response rate (ORR) stratified by v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS)* status (wild-type vs mutant) in subjects with mCRC treated with the combination of panitumumab and the tolerable dose of conatumumab identified in part 1.

The secondary objectives were to evaluate the effect of the combination of panitumumab and conatumumab overall and stratified by *KRAS* status (wild-type vs mutant) on the incidence of adverse events and clinical laboratory abnormalities, incidence of human anti-panitumumab antibodies (HAPA) and anti-conatumumab antibodies, objective response (alternate doses in part 1), duration of response, time to response, disease control rate (including complete and partial response or stable disease), progression-free survival (PFS), and overall survival in subjects with mCRC.

[redacted]

Methodology:

This was an exploratory phase 1b/2, global, multicenter, single-arm, 2-part (phase 1b and 2) study of conatumumab in combination with panitumumab in subjects with mCRC. In part 1, up to 3 doses of conatumumab (10, 3, and 1 mg/kg) were to be tested in a de-escalation manner to determine a tolerable dose administered intravenously (IV) once every 2 weeks (Q2W) in combination with panitumumab (6 mg/kg). Once a tolerable dose of conatumumab was identified, then enrollment into part 2 initiated. Subjects in part 2 were treated with the combination determined to be tolerable in part 1. All subjects in parts 1 and 2 received treatment until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated by the

data review team (DRT). Following completion of treatment, subjects were followed for disease progression (if not the reason for ending treatment) and survival for up to 2 years after the last subject was enrolled.

At regular, prespecified intervals during the treatment period and at a safety follow-up visit 30 (+3) days after the end of treatment, adverse events, concomitant medications, vital signs, and clinical laboratory parameters were evaluated; tumor response was assessed radiographically using modified Response Evaluation Criteria in Solid Tumors (RECIST); and samples for biomarker, anti-drug antibodies, and pharmacokinetic assays were obtained. Pharmacokinetics and anti-drug antibody samples were also obtained at a follow-up visit 60 (+14) days after the end of treatment. If the last antibody sample taken after the last dose of investigational product was positive for HAPA or positive for neutralizing human anti-conatumumab antibodies, then additional antibody samples were collected at each 3 month long-term follow-up visit until the antibody levels were negative for HAPA or negative for neutralizing human anti-conatumumab antibodies, until the antibody levels returned to baseline, until the subject withdrew consent, or until the subject died. Subjects were also followed for disease progression (if radiographic disease progression was not the reason for ending treatment), until disease progression or the subject began another anticancer treatment, and for survival every 3 months (± 28 days) for up to 2 years after the last subject was enrolled.

Number of Subjects Planned: Approximately 47 to 65 total: 6 to 27 in part 1 and 38 to 41 in part 2, depending on the number of conatumumab dose levels evaluated in part 1

Number of Subjects Enrolled: 53

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum; radiographically documented disease progression per modified RECIST during or ≤ 6 months following treatment with fluoropyrimidine, irinotecan, and/or oxaliplatin chemotherapy for mCRC; ≥ 1 unidimensionally measurable lesion measuring ≥ 20 mm in 1 dimension per modified RECIST; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and hematologic, renal, hepatic, and metabolic function within appropriate limits who received up to 3 prior chemotherapy regimens for mCRC and had available archived paraffin-embedded tumor tissue from the primary tumor or metastasis.

Subjects must not have had prior treatment with anti-EGFR inhibitors, systemic chemotherapy or radiotherapy, antitumor therapies, investigational products, or surgery within protocol-specified time periods; a history of central nervous system metastases or interstitial lung disease; clinically significant cardiovascular disease; or active inflammatory/other bowel disease causing chronic diarrhea.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: In this study, investigational product referred to either panitumumab or conatumumab. Panitumumab was supplied in single-use vials containing [redacted] mL of a sterile, colorless, [redacted] mg/mL protein solution. Conatumumab was supplied in single-use vials containing [redacted] mL of a sterile, frozen, [redacted] mg/mL liquid solution.

Panitumumab 6 mg/kg was administered by infusion pump using an in-line filter infusion set up over 60 ± 15 minutes (or 90 ± 15 minutes for doses > 1000 mg). After the completion of the panitumumab infusion, conatumumab was administered by infusion pump over 60 ± 15 minutes. If a dose of panitumumab and/or conatumumab was well tolerated (ie, without any serious infusion-related reactions), then subsequent IV infusions could have been administered over 30 ± 10 minutes. Lot numbers for panitumumab and conatumumab used in this study are provided in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: none

Duration of Treatment: Subjects were administered panitumumab and conatumumab Q2W until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated by the DRT. If 1 of the 2 investigational products was permanently discontinued, the other investigational product could have been continued per protocol at the investigator's discretion.

Study Endpoints:

Primary Endpoints:

- Part 1: incidence of DLTs
- Part 2: ORR

Secondary Endpoints for part 1 and 2:

- incidence of all adverse events and clinical laboratory abnormalities
- incidence of HAPA and anti-conatumumab antibodies
- time to response
- duration of response
- disease control (includes complete and partial response or stable disease)
- PFS
- overall survival

Exploratory Endpoints:

[redacted]

Statistical Methods:

Tolerability was assessed by the DRT in part 1 based on the incidence of DLTs among DLT-evaluable subjects (ie, subjects who received ≥ 2 doses of panitumumab and conatumumab as scheduled [ie, weeks 1 and 3] and had completed 4 weeks [28 days] of treatment, or had a DLT within the first 4 weeks [28 days] of treatment).

Overall safety was evaluated in part 1 and 2 for all enrolled subjects who received ≥ 1 dose of investigational product (ie, panitumumab or conatumumab) (Safety Analysis Set).

The primary analysis set for the evaluation of efficacy (ORR) included all subjects in the Safety Analysis Set in part 1 and 2 who initiated the dose of conatumumab selected in part 1. The primary analysis of efficacy included data after a minimum potential follow-up of 24 weeks after the last subject was enrolled. ORR was to be analyzed by *KRAS* status (wild-type vs mutant) based on a posterior distribution of the ORR, given observed data and prior distributions for ORR in each strata based on historical panitumumab data. [redacted] The secondary efficacy endpoints were analyzed descriptively, and Kaplan-Meier curves were also estimated for duration of response, PFS, and overall survival.

Summary of Results:

Subject Disposition:

A total of 58 subjects were screened of whom 53 were enrolled and 52 received both panitumumab and conatumumab at 10 study centers in the United States and Western Europe. Of the 52 subjects who received panitumumab and conatumumab, 19 subjects (37%) were wild-type *KRAS*, 25 subjects (48%) were mutant *KRAS*, and 8 subjects (15%) were unevaluable *KRAS*. All 52 subjects who received panitumumab and conatumumab ended both study drugs;

there were no ongoing subjects still in long-term follow-up. A total of 28 subjects (53%) completed the 30-day safety visit and 21 subjects (40%) completed the 60-day follow-up visit. The most common reason for ending the study was death (48 subjects, 91%) and the most common reason for ending investigational product was disease progression for both panitumumab (47 subjects [90%]) and conatumumab (47 subjects [90%]).

Baseline Demographics:

Demographic characteristics were generally similar among the wild-type, mutant, and unknown *KRAS* strata. Overall, 48% of subjects were men and 52% were women. There was a greater percentage of women (68%) than men (32%) in the wild-type *KRAS* stratum; where the opposite was noted in the mutant *KRAS* stratum (men [56%], women [44%]) and unknown *KRAS* stratum (men [63%], women [38%]). Most subjects (90%) were white (wild-type *KRAS*: 84%; mutant *KRAS*: 96%; unknown *KRAS*: 88%) and the median age was 62.0 years (range 29 to 87) with a median age of 62 years (range: 30 to 77) in the wild-type *KRAS* stratum, 63.0 years (range: 38 to 87) in the mutant *KRAS* stratum, and 59.0 years (range: 29 to 76) in the unknown *KRAS* stratum.

Baseline disease characteristics were generally similar among the wild-type, mutant, and unknown *KRAS* strata. Most subjects (69%) had a primary diagnosis of colon cancer [redacted]; the other subjects (31%) had a primary diagnosis of rectal cancer [redacted]. Most subjects (77%) had > 1 site of metastatic disease [redacted]. All subjects had an ECOG performance status of 0 or 1 and nearly all subjects (92%) had prior surgery for CRC [redacted].

Efficacy Results:

No subject in either *KRAS* strata (wild-type or mutant) had an objective response (confirmed complete or partial response). The posterior probability of the pre-specified absolute increase of 25% in ORR for the combination of panitumumab and conatumumab suggested that the combination therapy was not promising for further study. The disease control rate (overall objective response of complete response, partial response, or stable disease) was 44% (95% confidence interval [CI]: 21.5, 69.2) in the wild-type *KRAS* stratum and 16% (95% CI: 4.5, 36.1) in the mutant *KRAS* stratum. The difference (95% CI) in disease control rate was 28% (95% CI: -1.9, 54.9). Median PFS in months was longer in the wild-type *KRAS* stratum (2.3 months [95% CI: 1.6, 5.3]) compared with the mutant *KRAS* stratum (1.6 months [95% CI: 1.5, 1.8]). Based on the Kaplan-Meier estimates, the probability of being event-free (disease progression or death) was higher for subjects in the wild-type *KRAS* stratum at 8, 16, and 24 weeks. A similar percentage of subjects died in the wild-type *KRAS* stratum (95%) compared with the mutant *KRAS* stratum (92%). The median overall survival time was longer in the wild-type *KRAS* stratum (8.7 months [95% CI: 3.2, 14.9]) compared with the mutant *KRAS* stratum (4.4 months [95% CI: 3.4, 8.5]).

Safety Results:

Based on the DLT evaluable set of subjects during part 1 of the study (N = 5), no DLTs were experienced and the 10 m/kg dose was used for the part 2 portion of the study.

Most subjects (98%) had at least 1 adverse event during the study. The overall incidence of subjects with grade 3 or higher adverse events was 50% (26 subjects), with the greatest percentage in the unknown *KRAS* stratum [redacted] followed by mutant *KRAS* stratum [redacted] and wild-type *KRAS* stratum [redacted]. Of the adverse events that were grade 3 or higher in severity, most of the events were grade 3 (16 subjects [31%]), with few events of grade 4 (4 subjects [8%]) and grade 5 (6 subjects [12%]). Eleven subjects (21%) experienced grade 3 or higher adverse events that were assessed by the investigator as treatment-related and few occurred in > 1 subject (rash: 3 subjects; folliculitis, hypomagnesemia, nausea, and vomiting: 2 subjects each).

Six subjects (12%) had fatal (ie, grade 5) adverse events and died within 30 days of the last dose of investigational product or the 30-day safety follow-up visit [redacted]. The fatal adverse events were in the setting of disease progression and none were assessed by the investigator as related to investigational product.

Four subjects had an adverse event that resulted in discontinuation of investigational product [redacted]). None of the adverse events that resulted in discontinuation of investigational product were assessed by the investigator as related to panitumumab and 2 subjects [redacted] had adverse events that were assessed by the investigator as related to conatumumab (1 subject with pelvic fluid collection and pneumoperitoneum and 1 subject with performance status decreased and worsening of mCRC).

Overall, 25 subjects (48%) had a serious adverse event. The subject incidence rate was greater in subjects in the mutant *KRAS* stratum [redacted] and the unknown *KRAS* stratum [redacted] compared with the subjects in the wild-type *KRAS* stratum [redacted]; however, this difference appeared to be due to a number of individual adverse events occurring in 1 subject each. Overall, 8 subjects (15%) had a treatment-related serious adverse event. The subject incidence rate was greater in the mutant *KRAS* stratum [redacted] and the unknown *KRAS* stratum [redacted] compared with the wild-type *KRAS* stratum [redacted]; as with the all serious adverse event totals, this difference was primarily due to a number of individual adverse events occurring in 1 subject each. Few treatment-related serious adverse events occurred in > 1 subject overall and included pyrexia [redacted] and vomiting [redacted].

Adverse events of interest in the context of panitumumab administration included infusion reactions, integument and eye toxicities, diarrhea, dehydration, stomatitis/oral mucositis, hypomagnesemia, hypocalcemia, hypokalemia, pulmonary toxicities, vascular toxicities, cardiac toxicities, impaired or delayed wound healing, acute renal failure, and severe cutaneous adverse reactions. Adverse events of interest in the context of conatumumab administration included infusion reactions, hyponatremia, hypomagnesemia, increased amylase, and increased lipase. Infusion reactions per the CTCAE definition occurred in a total of 14 subjects (27%) and occurred within each stratum [redacted] all of which were grade 1 and 2. One subject [redacted] had an infusion reaction that was reported by the investigator as related to investigational product and no subjects had an infusion reaction as specified in the Vectibix USPI Integument and eye toxicities, which are known biological effects of EGFR inhibitors, were commonly reported (42 subjects [81%]) and occurred within each stratum [redacted] Of the subjects with a resolved integument toxicity, the median duration was 50 days (range: 11 to 221). Diarrhea was reported in 17% (9 subjects) of all subjects and occurred in each *KRAS* stratum [redacted]. Dehydration was reported in 1 subject [redacted] Stomatitis/oral mucositis occurred in 25% of all subjects and also occurred in each *KRAS* stratum [redacted] The subject incidence of hypomagnesemia was greater in the wild-type *KRAS* strata [redacted] and the unknown *KRAS* strata [redacted] compared with the mutant *KRAS* strata [redacted]; most events were grade 1 and no serious adverse events occurred. One subject [redacted] experienced hypocalcemia, 4 subjects [redacted] experienced hypokalemia. One subject [redacted] experienced increased amylase and 2 subjects [redacted] experienced increased lipase. The overall incidence of pulmonary, vascular, and cardiac toxicities was 2% [redacted], 2% [redacted] and 4% [redacted] respectively. One subject [redacted] experienced a grade 2 event of anuria (adverse event category of acute renal failure). No adverse events of hyponatremia, delayed or impaired wound healing or severe cutaneous reactions were reported.

Overall, no differences were noted by KRAS status for grade 3 or higher hematology and serum chemistry laboratory toxicities. Laboratory values that increased to grade 3 in the Safety Analysis Set included alkaline phosphatase (9 subjects [17%]), total bilirubin (6 subjects [12%]), aspartate aminotransferase (AST) (5 subjects [10%]), alanine aminotransferase (ALT) (4 subjects [8%]), and amylase and glucose (1 subject [2%], each). Laboratory values that increased to grade 4 in the Safety Analysis Set included lipase (2 subjects [4%]), and amylase, calcium and magnesium

(1 subject [2%], each). Laboratory values that decreased to grade 3 in the Safety Analysis Set included lymphocytes (6 subjects [12%]), hemoglobin (4 subjects [8%]), magnesium (3 subjects [6%]), and bicarbonate, calcium, phosphorus and sodium (1 subject [2%], each). Laboratory values that decreased to grade 4 in the Safety Analysis Set included absolute neutrophil count (ANC) (7 subjects [13%]), calcium (2 subjects [4%]), and magnesium and lymphocytes (1 subject [2%], each). Most shifts from baseline in hematology and serum chemistry laboratory values were grade 1 or 2.

No clinically significant changes from baseline in vital signs were observed during the study.

Pharmacokinetic Results:

[redacted]

Anti-panitumumab and Anti-conatumumab Antibody Assay Results:

A total of 52 subjects (37 subjects with a postbaseline sample) were evaluable for anti-panitumumab antibodies. Two subjects (5.4%) developed anti-panitumumab binding antibodies following panitumumab administration. Both subjects had tumors expressing mutant *KRAS*. One of these subjects exhibited a transient antibody response that was no longer detectable at the 30-day safety follow-up visit. The other subject tested positive for binding antibodies only at the last time point tested. The presence of antibodies capable of neutralizing panitumumab was not detected in any subjects in the study.

A total of 51 subjects (37 subjects with a postbaseline sample) were evaluable for anti-conatumumab antibodies. No subject developed anti-conatumumab antibodies following conatumumab administration. One subject was positive for binding anti-conatumumab antibodies before dosing; according to testing strategy, this sample was not tested for the presence of neutralizing antibodies. Postdose samples were not available for antibody analysis for this subject.

The analysis of the impact of immunogenicity on safety was based on the medical review and assessment of the incidence of adverse events (including serious adverse events), potential infusion reactions, number of doses received, and reason for ending study treatment subjects. Although the analysis of the impact of immunogenicity on safety was limited to 3 subjects (1 subject with pre-existing anti-conatumumab antibodies and 2 subjects who developed anti-panitumumab antibodies), there was no evidence of an altered safety profile found in the subjects who tested positive for antibodies compared to the safety profile of subjects who tested negative.

Conclusions:

No DLTs were observed in the 5 DLT evaluable subjects during part 1 of the study; thus, the 10 mg/kg dose of conatumumab was chosen for part 2 of the study.

Results of this study combining part 1 and 2 data indicate that the combination treatment of conatumumab and panitumumab is not promising in the treatment of subjects with mCRC. Safety findings were generally consistent with the safety profiles of each molecule observed in previous studies of these investigational products.