2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: Panitumumab

Title of Study: A Phase 3 Randomized Trial of Chemotherapy With or Without Panitumumab in Patients with Metastatic and/or Recurrent Squamous Cell Carcinoma of the Head and Neck

Investigator(s) and Study Center(s): This study was conducted at 126 centers in the regions of Asia Pacific, North America, South America, Western Europe, and Eastern Europe. Centers and principal investigators are listed in Appendix 4.

Publication(s): The following abstracts have been published:

Stöhlmacher J, Davidenko I, Winquist E, et al. SPECTRUM, a phase III trial for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) receiving chemotherapy with or without panitumumab: interim pooled safety analysis. *EJC Supplements*. 2009;7(2):474-475.

Vermorken J, Stöhlmacher J, Davidenko I, et al. Primary efficacy and safety results of spectrum, a phase 3 trial in patients (PTS) with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) receiving chemotherapy with or without panitumumab (PMAB). *Annals of Oncology*. 2010;21;viii-12.

Vermorken J, Stöhlmacher J, Davidenko I, et al. An analysis of safety in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) receiving chemotherapy (CT) with or without panitumumab (pmab) in a phase III clinical trial (SPECTRUM). *J Clin Oncol*. 2009;27(1):6050.

Vermorken J, Stöhlmacher J, Oliner K, et al. Safety and efficacy of panitumumab (pmab) in HPV positive (+) and HPV negative (−) recurrent/metastatic (r/m) squamous cell carcinoma of the head and neck (SCCHN): analysis of the phase 3 SPECTRUM trial. *European Journal Cancer*. 2011;47(suppl 2):13.

Study Period: 25 May 2007 (date first subject enrolled) to 14 May 2010 (data cutoff date); 3 subjects were still in the treatment period or the safety follow-up period at the time of data cutoff.

Development Phase: Phase 3

Objectives: The primary objective of the study was to assess whether panitumumab plus chemotherapy improves overall survival (OS) compared with chemotherapy alone as first-line treatment for metastatic and/or recurrent squamous cell carcinoma of the head and neck (SCCHN). Secondary objectives were to evaluate progression-free survival (PFS), objective response rate, duration of response, time to progression, and safety. Tertiary objectives included evaluation of time to response and patient-reported outcomes (PROs) using the validated EuroQol EQ-5D health state index score and overall health rating. [redacted]

Methodology: This is an ongoing, multicenter, open-label, randomized comparative study evaluating the efficacy of panitumumab in combination with cisplatin and 5-fluorouracil (5-FU) relative to cisplatin and 5-FU alone as first-line treatment in subjects with metastatic and/or recurrent SCCHN. Eligible subjects were randomized in a 1:1 ratio to receive panitumumab plus chemotherapy or chemotherapy alone. Randomization was stratified by prior treatment (newly diagnosed/previously untreated with chemotherapy and/or radiotherapy for metastatic SCCHN vs recurrent disease), site of primary tumor (hypopharynx/oral cavity vs oropharynx/larynx), and performance status (Eastern Cooperative Oncology Group [ECOG] 0 vs 1).

Subjects received panitumumab as an intravenous (IV) infusion at a dose of 9 mg/kg plus cisplatin/5-FU chemotherapy or cisplatin/5-FU alone every 21 days until disease progression or for a maximum of 6 cycles. Carboplatin was substituted for cisplatin in subjects who developed grade 2 neurotoxicity (based on the Common Terminology Criteria for Adverse Events v3.0

[CTCAE]) or at the first occurrence of a creatinine clearance < 50 mL/min. Subjects randomized to the panitumumab plus chemotherapy arm who had not progressed after completion of 6 cycles of chemotherapy could continue on panitumumab monotherapy until disease progression, intolerability, withdrawal, or death. In the event any or all components of the treatment regimen (ie, cisplatin/carboplatin, 5-FU, or panitumumab) were discontinued for intolerability in the absence of disease progression during any of the 6 planned cycles, subjects could continue with the remaining component(s) for the remainder of the 6 planned cycles or until disease progression, intolerability, withdrawal, or death.

Response evaluation was performed by the investigator per a modified version of the Response Evaluation Criteria in Solid Tumors guidelines every 6 weeks (± 1 week). Responding disease was to be confirmed no less than 4 weeks after the criteria for response were first met. If withdrawal from study treatment occurred prior to disease progression (eg, unacceptable toxicity), tumor response assessments were to continue every 6 weeks (± 1 week) until disease progression or the end of the study, whichever was earlier.

Number of Subjects Planned: 650

Number of Subjects Enrolled: 657

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 SCCHN or its variants of the oral cavity, oropharynx, hypopharynx, or larynx. Diagnosis of metastatic disease and/or recurrent disease was to have followed locoregional therapy and determined to have been incurable by surgery or radiotherapy. Subjects were required to have an ECOG performance status of 0 or 1.

Subjects were excluded if they had a history of prior systemic chemotherapy for SCCHN as part of the initial multimodality treatment for locally advanced disease if completed < 6 months prior to randomization, prior cisplatin containing induction chemotherapy followed by cisplatin containing chemoradiotherapy, prior anti-epidermal growth factor receptor (EGFR) antibody therapy, or treatment with small molecule EGFR inhibitors.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Panitumumab was provided at a concentration of 20 mg/mL in vials containing [redacted] cc of a sterile protein solution to be diluted in pyrogen-free [redacted] % sodium chloride solution (USP). Panitumumab 9 mg/kg was administered as an IV infusion before chemotherapy every 21 days (± 3 days). The manufacturing batch numbers of panitumumab used in this study are provided in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Components of the reference therapy, cisplatin/carboplatin, and 5-FU were obtained by each site according to routine institutional practice and prepared according to the most current package insert for the region. Cisplatin 100 mg/m^2 was infused IV over 1 to 2 hours (± 15 minutes) on day 1 of each of chemotherapy cycle. Continuous IV infusion of 5-FU 1000 mg/m^2/day occurred on days 1 to 4 (96 hours, ± 8 hours). If necessary to substitute carboplatin for cisplatin, carboplatin was administered to achieve an area under the curve (AUC) of 5 mg/mL•min, based on the Calvert formula, on day 1 of each chemotherapy cycle over 30 minutes (± 15 minutes).

Duration of Treatment: Panitumumab was to be administered until subjects developed disease progression or for a maximum of 6 cycles. Subjects who were randomized to the panitumumab plus chemotherapy arm and who had not progressed after completing 6 cycles of chemotherapy or became intolerant to chemotherapy could continue on panitumumab monotherapy until disease progression, intolerability, withdrawal, or death occurred.

Study Endpoints: The primary endpoint was OS, defined as the time from randomization to the date of death.

Secondary endpoints were:

- Efficacy: PFS, objective response rate, duration of response, and time to progression.
- Safety: incidence of adverse events, significant laboratory changes, and human anti-panitumumab antibody formation.

Tertiary endpoints were:

- time to response and PROs using EuroQol EQ-5D health state index score and overall health rating.

Exploratory endpoints were:

- [redacted]

Statistical Methods: The primary goal of the statistical analysis was to determine if there was a difference in OS between the 2 treatment groups. Six hundred-fifty subjects (325 per arm) were to be randomized to achieve 470 events (death) for analysis of OS. Randomization was stratified by prior treatment (newly diagnosed/previously untreated with chemotherapy and/or radiotherapy for metastatic SCCHN vs recurrent disease), site of primary tumor (hypopharynx/oral cavity vs oropharynx/larynx), and performance status (ECOG 0 vs 1). An overall 5% significance level was used to compare treatments with respect to OS in the Intention-to-Treat (ITT) Analysis Set. A stratified log-rank test with stratification on the randomization factors was used to compare OS between the 2 randomized treatment groups.

Summary of Results:

Subject Disposition:

A total of 765 subjects were screened and 657 subjects were included in the ITT Analysis Set; 327 subjects were randomized to panitumumab plus chemotherapy and 330 were randomized to chemotherapy alone. Of the 657 subjects in the ITT Analysis Set, 650 (99%) subjects were included in the Safety Analysis Set (325 subjects in each arm). As of the data cutoff date of 14 May 2010, 550 (84%) subjects in the ITT Analysis Set had ended the study, including 267 (82%) subjects in the panitumumab plus chemotherapy arm and 283 (86%) subjects in the chemotherapy alone arm. Three (1%) subjects in the panitumumab plus chemotherapy arm were continuing to receive panitumumab monotherapy. For subjects included in the ITT Analysis Set, a total of 219 (67%) subjects in the panitumumab plus chemotherapy arm and 231 (70%) subjects in the chemotherapy alone arm completed the safety follow-up. The most common reason for ending the study was death (483 [74%] subjects), which was similar for both arms. The most common reason for not completing safety follow-up was also death (panitumumab plus chemotherapy: 48 [15%] subjects; chemotherapy alone: 40 [12%] subjects).

Baseline Demographics:

Sex: 570 (87%) subjects were male; 87 (13%) subjects were female

Age: mean (standard deviation): 58.1 (8.2) years

Ethnicity/Race: White or Caucasian: 539 (82%) subjects; Asian: 55 (8%) subjects; Hispanic or Latino: 25 (4%) subjects; Japanese: 20 (3%) subjects; Black or African American: 6 (1%) subjects; other: 9 (1%) subjects; unknown/missing: 2 (< 1%) subjects; Aborigine: 1 (< 1%) subject

Baseline demographics were balanced between arms.

ECOG Performance Status: 0: 196 (30%) subjects; 1: 455 (69%) subjects; 2: 6 (1%) subjects

Primary Tumor Site: larynx: 195 (30%) subjects; oral cavity: 191 (29%) subjects; oropharynx: 182 (28%) subjects; hypopharynx: 89 (14%) subjects

Efficacy Results:

Overall survival was compared between arms using the log-rank test stratified by the randomization factors at an overall 5% significance level. After adjusting for an efficacy interim analysis, the nominal significance level for the primary analysis was 0.0471.

A total of 242 (74%) subjects in the panitumumab plus chemotherapy arm and 241 (73%) subjects in the chemotherapy alone arm had died as of the data cutoff on 14 May 2010. Median OS was 11.1 months (95% confidence interval [CI]: 9.8, 12.2) in the panitumumab plus chemotherapy arm and 9.0 months (95% CI: 8.1, 11.2) in the chemotherapy alone arm, an absolute difference of 2.1 months. However, the stratified log-rank test that compares the survival distributions of the 2 treatment groups was not statistically significant

(p value: 0.1403). The estimated hazard ratio was 0.873 (95% CI: 0.729, 1.046), favoring the panitumumab plus chemotherapy arm.

Because the OS difference was not statistically significant, secondary efficacy endpoints and subgroup analyses were not formally tested for statistical significance. Thus, p-values associated with these endpoints are provided for descriptive purposes only.

The treatment effect of panitumumab plus chemotherapy relative to chemotherapy alone for OS was evaluated in subpopulations defined by the baseline covariates. Overall survival favored the panitumumab plus chemotherapy arm for subjects with an involuntary weight loss within the last 6 months prior to randomization > 5% (p-value: 0.0278). However, the test for interaction between baseline weight loss and treatment was not statistically significant; therefore, there is no evidence that the effect of panitumumab differs by degree of baseline weight loss. No p-values < 0.05 were observed for the other subpopulations evaluated.

A total of 290 (89%) subjects in the panitumumab plus chemotherapy arm and 275 (83%) subjects in the chemotherapy alone arm had progressed or died as of the data cutoff on 14 May 2010. Median PFS was 5.8 months (95% CI: 5.6, 6.6) in the panitumumab plus chemotherapy arm and 4.6 months (95% CI: 4.1, 5.4) in the chemotherapy alone arm, an absolute difference of 1.2 months. The stratified log-rank test p-value was 0.0036. The estimated hazard ratio was 0.780 (95% CI: 0.659, 0.922), favoring the panitumumab plus chemotherapy arm.

The analysis for objective response was performed on the Evaluable for Tumor Response Analysis Set. An objective response was determined for 101 subjects (36.33% response rate [95% CI: 30.67, 42.29]) in the panitumumab plus chemotherapy arm and for 73 subjects (25.35% response rate [95% CI: 20.43, 30.78]) in the chemotherapy alone arm, an absolute difference in rates of 10.98%. The odds ratio was 1.69 (95% CI: 1.15, 2.44), favoring the panitumumab plus chemotherapy arm (stratified exact test p-value: 0.0065).

The median duration of response for subjects with an objective response was 5.6 months (95% CI: 4.8, 6.2) in the panitumumab plus chemotherapy arm and 5.7 months (95% CI: 4.7, 6.2) in the chemotherapy alone arm.

The median time to progression was 6.8 months (95% CI: 5.9, 6.9) in the panitumumab plus chemotherapy arm and 5.6 months (95% CI: 5.2, 5.8) in the chemotherapy alone arm, an absolute difference of 1.2 months. The stratified log-rank test p-value was 0.0014. The estimated hazard ratio was 0.718 (95% CI: 0.585, 0.880), favoring the panitumumab plus chemotherapy arm.

The median time to response for subjects with an objective response was 6.1 weeks (range 2.4 to 32.7 weeks) in the panitumumab plus chemotherapy arm and 6.7 weeks (range 4.6 to 31.0 weeks) in the chemotherapy alone arm.

Safety Results:

In the Safety Analysis Set, 320 (98%) subjects in each treatment arm reported at least 1 adverse event. As would be expected for subjects that receive chemotherapy, adverse events of nausea, neutropenia, vomiting, anemia, decreased appetite, and fatigue frequently occurred (> 25%) in both arms. Adverse events that occurred at a > 5% higher incidence in the panitumumab plus chemotherapy arm compared with the chemotherapy alone arm were rash, hypomagnesemia, diarrhea, dermatitis acneiform, pruritus, dry skin, paronychia, weight decreased, acne, skin fissures, erythema, hypocalcemia, and conjunctivitis, which are events known to be associated with panitumumab treatment.

Overall, 267 (82%) and 255 (78%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively, experienced grade 3 or higher adverse events. Grade 3 or higher adverse events that occurred at a > 5% higher incidence in the panitumumab plus chemotherapy arm compared with the chemotherapy alone arm were hypomagnesemia and rash.

Forty-eight (15%) and 41 (13%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively, died as a result of a fatal adverse event during treatment or within 33 days of the last dose of either panitumumab plus chemotherapy or chemotherapy alone. The primary cause of death was reported as disease progression in 25% (12/48) and 41% (17/41) of subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively. The subject incidence of early fatal adverse events (ie, those that

occurred within the first 30 days of the first dose of either panitumumab plus chemotherapy or chemotherapy alone) was similar between arms (panitumumab plus chemotherapy: 14 [4%] subjects; chemotherapy alone: 13 [4%] subjects). Fatal adverse events were deemed by the investigator as possibly related to treatment in 14 (4%) and 8 (2%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively. Five (2%) subjects had panitumumab-related fatal events: myocardial infarction, cardiac failure, cerebrovascular accident, acute renal failure, and hemorrhagic diarrhea.

Serious adverse events occurred in 157 (48%) and 139 (43%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. Serious adverse events reported in at least 5% of subjects in the panitumumab plus chemotherapy arm included febrile neutropenia (panitumumab plus chemotherapy: 6%; chemotherapy alone: 4%), dehydration (panitumumab plus chemotherapy: 5%; chemotherapy alone: 2%), and anemia (panitumumab plus chemotherapy: 5%; chemotherapy alone: 5%). There were no serious adverse events with at least a 5% difference between the 2 arms.

Adverse events led to removal from the study for 30 (9%) and 21 (6%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively, and led to discontinuation of any study drug (ie, panitumumab or chemotherapy) in 81 (25%) and 70 (22%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively. A total of 45 (14%) subjects in the panitumumab plus chemotherapy arm discontinued panitumumab due to an adverse event. Rash was the most common reason for discontinuation of panitumumab (5 [2%] subjects). Some component of chemotherapy was discontinued due to an adverse event in 66 (20%) and 70 (22%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively. Peripheral neuropathy and hypoacusis (6 [2%] subjects, each) and deafness (5 [2%] subjects) were the most common reasons for discontinuation of chemotherapy in the panitumumab plus chemotherapy arm. Renal failure (6 [2%] subjects) and deafness and tinnitus (5 [2%] subjects, each) were the most common reasons for discontinuation of chemotherapy in the chemotherapy alone arm.

Adverse events of interest for panitumumab have been identified by Amgen via evidence summarized from basic research, information from nonclinical investigations, observed in similar drugs in class, epidemiologic data on disease indications, early clinical development, and safety data that supported the original indication. Adverse events of interest for panitumumab include infusion reactions, integument and eye toxicities, diarrhea, dehydration, stomatitis/oral mucositis, hypomagnesemia, hypocalcemia, hypokalemia, pulmonary, vascular, cardiac, impaired or delayed wound healing, acute renal failure, and severe cutaneous adverse reactions. The terms for the adverse events of interest were predefined and included in the statistical analysis plan for the study. Adverse events identified as infusion reaction events of interest using the US package insert occurred in 9 (3%) and 5 (2%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. Adverse events identified as infusion reaction events of interest using the investigator assessed definitions occurred in 4 (1%) and 1 (<1%) subject in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. Adverse events identified as infusion reaction events of interest using the CTCAE definition occurred in 35 (11%) and 20 (6%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. A serious infusion reaction event of interest of hypersensitivity was reported for 2 subjects in the panitumumab plus chemotherapy arm. Integument and eye toxicities, which are known adverse drug reactions of EGFR inhibitors, were the most commonly occurring adverse event of interest (panitumumab plus chemotherapy: 267 [82%] subjects; chemotherapy alone: 78 [24%] subjects). Adverse events suggestive of diarrhea, dehydration, and stomatitis/oral mucositis events of interest occurred in 130 (40%) vs 78 (24%), 27 (8%) vs 13 (4%), and 130 (40%) vs 117 (36%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively. Adverse events suggestive of hypomagnesemia events of interest occurred in 140 (43%) and 71 (22%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. Adverse events suggestive of hypocalcemia events of interest occurred in 44 (14%) and 22 (7%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. Adverse events suggestive of hypokalemia events of interest occurred in 56 (17%) and 46 (14%) subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively. The subject incidence of adverse events suggestive of pulmonary, vascular, and cardiac adverse events of interest was similar between the treatment

groups. Adverse events that were identified as events of interest using the acute renal failure Standard Medical Dictionary for Regulatory Affairs Query search criteria occurred in 50 (15%) and 69 (21%) subjects in the panitumumab plus chemotherapy arm and the chemotherapy alone arm, respectively.

Overall, hematology laboratory results were similar between the panitumumab plus chemotherapy and the chemotherapy alone arms, and no notable trends were observed.

Pharmacokinetic Results:

After administration of 9 mg/kg panitumumab every 3 weeks, the mean steady state pre-infusion (trough) and post-infusion (peak) concentrations from cycle 4 and onward were 29.9 ± 18.3 µg/mL and 228 ± 99 µg/mL, respectively, which were within the ranges of previously observed values in subjects with advanced solid malignancies receiving panitumumab as monotherapy (Study 20030138) and were consistent with the predicted values of the population pharmacokinetic analysis (Study 108471).

Patient-reported Outcome Results:

Patient-reported outcome analyses did not show differences between arms in the time-adjusted AUC from study day 1 through day 1 of the last chemotherapy cycle for the EQ-5D health state index score (least-squares adjusted mean difference of 0.007; 95% CI: -0.016, 0.030) or the EQ-5D visual analog scale (least-squares adjusted mean difference of -0.119; 95% CI: -1.645, 1.407).

Anti-panitumumab Antibody Assay Results:

There were no neutralizing anti-panitumumab antibodies detected in any subject as of the data cutoff date of 14 May 2010. Fifteen subjects had pre-existing anti-panitumumab binding antibodies and 3 subjects developed anti-panitumumab binding antibodies. The analysis of the impact of immunogenicity on safety was evaluated for the antibody-positive subjects through review and assessment of adverse events (including serious adverse events), potential infusion reactions, number of doses received, and reason for ending study treatment. There was no evidence of a change in safety profile found in subjects who tested positive for anti-panitumumab antibodies when compared to that of subjects who tested negative.

Conclusions:

In conclusion, although there was a trend of improved OS for subjects with metastatic and/or recurrent SCCHN who received panitumumab in combination with cisplatin and 5-FU relative to cisplatin and 5-FU alone, results did not meet the predetermined threshold for statistical significance. A trend of improved PFS and objective response rate was also noted, with results favoring subjects receiving panitumumab. This study evaluated a global, geographically broad population of subjects with metastatic and/or recurrent SCCHN (enrolling at 126 centers in 26 countries). Heterogenecity in tumor biology (human papillomavirus status) and medical practice standards, including extent/intensity of prior therapy and post-study treatment received, was greater than in studies restricted to smaller regions (Vermorken et al, 2008). Each of these factors could potentially have had an impact on the OS observed during this study. No new safety risks for panitumumab were identified. The adverse event profile was consistent with EGFR inhibitor therapy in combination with platinum-based chemotherapy plus 5-FU and with that observed in studies with panitumumab administered at doses of 6.0 mg/kg every 2 weeks.