2. SYNOPSIS

Name of Sponsor: Amgen, Ltd

Name of Finished Product: Vectibix®

Name of Active Ingredient: panitumumab

Title of Study: A Phase 2 Randomized Trial of Radiotherapy Plus Panitumumab Compared to Chemoradiotherapy in Subjects with Unresected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Investigators and Study Centers: The study was conducted at 22 centers in North America, Western Europe, and Eastern Europe. A complete list of investigators and sites is included in Appendix 4.

Publication: Giralt J, Trigo JM, Nuyts S, et al. A phase 2, randomized trial (CONCERT-2) of panitumumab (pmab) plus radiotherapy compared with chemoradiotherapy (CRT) in patients (pts) with unresected, locally advanced squamous cell carcinoma of the head and neck (LASCCHN). *Ann Oncol*. 2012 (suppl). Abstract 1016O.

Study Period: 30 November 2007 (first subject enrolled) to 16 December 2011 (last subject completed followup)

Development Phase: 2

Objectives:

The primary objective of the study was to estimate, with prespecified precision, the difference in local-regional control (LRC) rate at 2 years in subjects receiving chemoradiotherapy (CRT) or panitumumab plus radiotherapy (PRT) as first-line treatment for locally advanced squamous cell carcinoma of the head and neck (SCCHN). The secondary objective was to estimate the difference between the 2 treatment regimens (CRT vs PRT) on other measures of clinical benefit, including LRC duration, overall response rate (ORR), progression-free survival (PFS), overall survival (OS); and safety. Tertiary objectives were to estimate the difference in health-related quality of life (HRQoL) and performance status in subjects receiving PRT or CRT. [redacted].

Methodology: This open-label, randomized, multicenter study was conducted in subjects with pathologically confirmed SCCHN. Eligible subjects were randomly assigned in a 3:2 ratio to receive either PRT or CRT. Randomization was stratified by: site of primary tumor (hypopharynx or oral cavity vs oropharynx or larynx), radiotherapy delivery modality (intensity modulated radiotherapy vs 3-dimensional conformal radiotherapy), nodal status (N0 vs N+), and tumor stage (T1-3 vs T4). Subjects received 70-72 gy of radiotherapy over approximately 6 to 6.5 weeks, with panitumumab administered on days 1, 22, and 43 of radiotherapy (PRT arm) and cisplatin administered on days 1 and 22 of radiotherapy (CRT arm). Disease status was assessed clinically at 30 ± 7 days and clinically and radiographically at 60 ± 7 days. Radiologic assessments were performed per a modification of the World Health Organization criteria. Additional tumor assessments (radiographic and clinical) were made at 6 months (± 2 weeks), 12 ± 1 months, 18 ± 1 months and 24 ± 1 months from randomization and then every 6 ± 3 months thereafter until disease progression or end of study.

Number of Subjects Planned: 150

Number of Subjects Enrolled: 152 (90 PRT, 62 CRT)

Diagnosis and Main Criteria for Eligibility: Men and women aged ≥ 18 years with previously untreated, histologically or cytologically confirmed, Stage III or Stage IVa-b (M0) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were enrolled into the study. Subjects were required to have bidimensionally measurable disease ≥ 10 mm in at least 1 dimension, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, renal, hepatic, and metabolic function. Subjects were excluded if the primary tumor was in the nasopharynx, sinuses, salivary gland, or skin, if prophylactic tracheostomy was required, or if they had received prior treatment for locally advanced SCCHN (anti-epidermal

growth factor receptor [EGFR] antibody therapy, small molecule tyrosine kinase inhibitors of EGFR, radiotherapy, systemic chemotherapy or surgery [except nodal sampling or biopsy]).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Panitumumab 9.0 mg/kg was administered as a 60 ± 15 minute intravenous infusion every 3 weeks on days 1, 22, and 43 of radiotherapy (3 doses total). Lot numbers: [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Cisplatin 100 mg/m^2 was administered on days 1 and 22 of radiotherapy (2 doses total).

Duration of Treatment: Treatment was administered for approximately 6 to 6.5 weeks. Subjects were followed until disease progression or the end of the study, which was not to exceed 60 months from the date that the first subject was randomized.

Study Endpoints:

Primary Efficacy Endpoint: LRC rate at 2 years

Secondary Efficacy Endpoints:

- Duration of LRC
- LRC at 6 months and at 1 year
- PFS
- OS
- Rate of complete response by 6 months
- ORR by 6 months

Safety Endpoints:

- Incidence of death on or within 30 days of last protocol-defined treatment
- Protocol treatment delivery (percentage and timing of planned dose delivery) of:
  - Radiotherapy
  - Cisplatin (if applicable)
  - Panitumumab (if applicable)
- Incidence and severity of prespecified protocol-specific adverse events (ie, events commonly associated with the treatment of head and neck cancer)
- Incidence and severity of all other adverse events
- Significant changes in laboratory values
- Incidence of human anti-panitumumab antibody formation (if applicable)

Tertiary Endpoints:

- HRQoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and Quality of Life Questionnaire Head and Neck module (completed by subject)
- Performance status as measured by the Performance Status Scale for Head and Neck Cancer (completed by investigator)

[redacted]

Statistical Methods:

The main objective of the study was to estimate the efficacy and safety of PRT as compared to CRT in a locally advanced SCCHN population; no formal hypothesis testing was performed. The treatment effect of PRT as compared to CRT and the associated 2-sided 95% confidence intervals (CIs) were estimated for all efficacy endpoints.

For the primary endpoint of LRC rate at 2 years, Kaplan-Meier estimates and the associated 95% CIs were calculated for each randomized treatment arm and for the difference in the 2-year LRC rate between the two treatment arms. A 95% CI with a half-width no wider than 16% was desired for the treatment difference between the 2 arms.

For duration of LRC, PFS, and OS, the hazard ratio and the associated 2-sided 95% CI were estimated from an unstratified Cox proportional hazard model and a Cox proportional hazard

model stratified by randomization factors. For ORR and complete response by 6 months, Wilson's score method with continuity correction was used to calculate the 2-sided 95% CIs for the mean difference between treatment groups.

All safety analyses were presented in tabular format with the appropriate summary statistics for each treatment arm. Prespecified protocol-specific adverse events commonly associated with treatment of head and neck cancer were identified and tabulated.

[redacted]

Summary of Results:

Subject Disposition:

All 152 randomized subjects (90 PRT and 62 CRT) were included in the Intent to Treat Analysis Set. Of these subjects, 151 received at least 1 dose of study medication and were included in the Efficacy and Safety Analysis Sets; 1 subject did not receive study medication for administrative reasons. Additionally, 1 subject who was randomized to the PRT arm received radiotherapy, but died before receiving panitumumab; this subject is included in the PRT arm for efficacy analyses and the CRT arm for safety analyses.

All 151 subjects who received study medication have ended treatment and the study. Eighty subjects (53%) completed the study (41 [46%] PRT vs 39 [63%] CRT), and 71 subjects (47%) discontinued the study (48 [53%] vs 23 [37%]). In both treatment arms, the most common reason for discontinuing the study was death (38 [42%] vs 18 [29%]).

Seventy-four subjects (82%) in the PRT arm received all 3 panitumumab infusions. Reasons for discontinuation of panitumumab were adverse event (8 [9%]), death (4 [4%]), protocol-specified criteria (3 [3%]), and other (1 [1%]). Fifty-eight subjects (94%) in the CRT arm received both cisplatin infusions. Reasons for discontinuing cisplatin were adverse event (3 [5%]) and administrative decision (1 [2%]). Most subjects in both treatment arms completed radiotherapy treatments (85 [94%] PRT vs 60 [97%] CRT).

[redacted]

Baseline Demographics:

Sex: 127 (84%) men, 24 (16%) women

Age: mean (standard deviation) 57 (8) years

Ethnicity/Race: 147 (97%) white, 4 (3%) Hispanic/Latino

Efficacy Results:

Overall, the LRC rate at 2 years was 61% (95% CI: 47%, 72%) in the CRT arm and 51% (95% CI: 40%, 62%) in the PRT arm. Median PFS time was 17 months (95% CI: 12.0, 27.0) in the PRT arm and not estimable (NE) in the CRT arm; the PFS hazard ratio from an unstratified Cox proportional hazards model was 1.73 (95% CI: 1.07, 2.81; p = 0.03), favoring the CRT arm. The hazard ratio for duration of LRC was 1.61 (95% CI: 0.98, 2.66; p = 0.06), and the hazard ratio for OS was 1.59 (95% CI: 0.91, 2.79; p = 0.10), favoring the CRT arm. The odds ratio for ORR at 6 months was 1.28 (95% CI: 0.44, 4.04; p = 0.81).

[redacted] The PFS hazard ratio was 1.22 (95% CI: 0.30, 4.86; p = 0.78), and the OS hazard ratio was 2.80 (95% CI: 0.31, 25.07; p = 0.36). All subjects had a response at 6 months (100% each arm per investigator review; unadjusted odds ratio and p-value NE). [redacted]

In the HPV Negative Efficacy Analysis Set, the LRC rate at 2 years was higher in the CRT arm (61% [95% CI: 41%, 76%]) compared with the PRT arm (45% [95% CI: 29%, 59%]). Median PFS

time was 15 months (95% CI: 8.4, 23.9) in the PRT arm and NE in the CRT arm; the PFS hazard ratio from an unstratified Cox proportional hazards model was 2.04 (95% CI: 1.05, 3.96; p = 0.04), favoring the CRT arm. Trends in favor of the CRT arm were also observed for the endpoints of duration of LRC (hazard ratio 1.90 [95% CI: 0.94, 3.81]; p = 0.07) and OS (hazard ratio 1.93 [95% CI: 0.90, 4.16]; p = 0.09). ORR at 6 months per investigator review was similar in the 2 treatment arms (78% PRT vs 80% CRT; unadjusted odds ratio 0.88 [95% CI: 0.23, 3.10; p = 1.00).

Safety Results:

Overall

All 151 subjects reported adverse events during the study. In general, skin toxicity was more common in the PRT arm whereas hematologic toxicity and nausea/vomiting were more common in the CRT arm. Adverse events with the greatest differences in subject incidence between the PRT arm and the CRT arm (PRT minus CRT) were rash (48 [54%] vs 2 [3%]), dermatitis acneiform (15 [17%] vs 0 [0%]), and pruritis (14 [16%] vs 0 [0%]). Adverse events with the greatest differences in subject incidence between the CRT arm and the PRT arm (CRT minus PRT) were nausea (19 [21%] PRT vs 27 [44%] CRT), neutropenia (0 [0%] PRT vs 12 [19%] CRT), and dysguesia (18 [20%] PRT vs 21 [34%] CRT).

Grade 3 and higher adverse events were reported in 76 subjects (85%) receiving PRT and 50 subjects (81%) receiving CRT. Grade 3 and higher adverse events that were more common in the PRT arm compared with the CRT arm were dermatitis (14 [16%] PRT vs 0 [0%] CRT), radiation skin injury (21 [24% vs 7 [11%]), stomatitis (14 [16%] vs 3 [5%]), rash (8 [9%] vs 0 [0%]), dysphagia (35 [39%] vs 20 [32%]), and radiation mucositis (6 [7%] vs 1 [2%]). Grade 3 and higher adverse events that were more common in the CRT arm compared with the PRT arm were neutropenia (0 [0%] PRT vs 8 [13%] CRT), odynophagia (7 [8%] vs 12 [19%]), and febrile neutropenia (0 [0%] vs 5 [8%]).

Five subjects (6%) in the PRT arm and 2 subjects (3%) in the CRT arm died on treatment (from first dose of study treatment to 30 days after last dose). Fatal adverse events reported in the PRT arm were sudden death (2 subjects), pneumonia (1 subject), death (not otherwise specified; 1 subject), and septic shock (1 subject). Fatal adverse events reported in the CRT arm were pneumonia (1 subject) and cardio-respiratory arrest (1 subject). Two fatal adverse events in the PRT arm, both reported as sudden death, were considered related to panitumumab by the investigator.

Serious adverse events were reported more frequently in the CRT arm relative to the PRT arm (30 [34%] PRT vs 25 [40%] CRT). Among subjects receiving PRT, the most frequently reported serious adverse events were dysphagia (7 [8%] vs 3 [5%]) and mucosal inflammation (6 [7%] vs 6 [10%]). No serious adverse events were reported with ≥ 5% higher subject incidence in the PRT arm relative to the CRT arm. In addition to mucosal inflammation, the most frequently reported serious adverse events in the CRT arm were febrile neutropenia (0 [0%] PRT vs 4 [6%] CRT) and neutropenia (0 [0%] PRT vs 3 [5%] CRT).

Only 1 subject (PRT) was reported as ending the study due to an adverse event; the adverse event was death, not otherwise specified. Discontinuation of any study treatment because of adverse events was reported in 12 subjects (13%) receiving PRT and 3 subjects (5%) receiving CRT. The most commonly reported adverse events leading to any treatment discontinuation in the PRT arm were dermatitis (3 [3%] PRT vs 0 [0%] CRT) and radiation skin injury (3 [3%] PRT vs 0 [0%] CRT). In the CRT arm, no adverse event preferred terms leading to any treatment discontinuation were reported in > 1 subject.

Adverse events of interest for panitumumab include eye disorders, ocular infections, stomatitis/oral mucositis, hypomagnesemia, hypocalcemia, hypokalemia, noninfectious diarrhea, dehydration infusion reactions skin disorders (excluding radiation-related skin disorders), skin infections, and severe cutaneous adverse reactions (SCARs). As would be expected with administration of anti-EGFR therapy in this setting, the most common adverse events of interest (per the narrow search strategy) in the PRT arm were stomatitis/oral mucositis (81 [91%] PRT vs 57 [92%] CRT) and skin disorders (81 [91%] vs 20 [32%]). Events suggestive of acute renal failure were more common in the CRT arm (6 [10%]) than in the PRT arm (2 [2%]). The subject incidence of cardiac arrhythmia (1 [1%] PRT vs 1 [2%] CRT), venous thromboembolic events

(1 [1%] vs 0 [0%]), arterial thromboembolic events (0 [0%] vs 1 [2%]), ischemic heart disease (0 [0%] vs 1 [2%]), and events suggestive of vasculitis (1 [1%] vs 0 [0%]) were low and similar in the 2 treatment arms. No subjects had unspecified/mixed vessel type thromboembolic events, SCARs, infusion reactions, or events suggestive of interstitial lung disease or impaired wound healing.

No subjects tested positive for antibodies capable of neutralizing panitumumab.

[redacted] Safety Analysis Set reported adverse events. Adverse events with the greatest differences in subject incidence between the PRT arm and the CRT arm (PRT minus CRT) were rash (9 [60%] PRT vs 0 [0%] CRT), dysphagia (13 [87%] vs 4 [44%]), and odynophagia (7 [47%] vs 1 [11%]). Adverse events with the greatest differences between the CRT and PRT arms (CRT minus PRT) were tinnitus (0 [0%] vs 3 [33%]) and oropharyngeal pain (2 [13%] vs 4 [44%]).

Fourteen subjects (93%) receiving PRT and 7 subjects (78%) receiving CRT had grade 3 or higher adverse events. Grade 3 and higher adverse events that were more common in the PRT arm relative to the CRT arm and occurred in > 1 subject in the PRT arm were dysphagia (7 [47%] PRT vs 1 [11%] CRT), radiation skin injury (5 [33%] vs 0 [0%]), stomatitis (5 [33%] vs 0 [0%]), and mucosal inflammation (7 [47%] vs 3 [33%]). Neutropenia (0 [0%] vs 2 [22%]) was the only grade 3 or higher adverse event reported in more than a single subject in the CRT arm. No deaths were reported in the HPV Positive Safety Analysis Set.

A total of 6 subjects (40%) receiving PRT and 3 subjects (33%) receiving CRT had serious adverse events. Serious adverse events reported in > 1 subject in the PRT arm were mucosal inflammation (3 [20%] vs 0 [0%]) and dehydration (2 [13%] vs 0 [0%]). No serious adverse event preferred term was reported in > 1 subject in the CRT arm.

As in the Safety Analysis Set, stomatitis/oral mucositis (15 [100%] vs 9 [100%]) and skin disorders (15 [100%] vs 5 [56%]) were the most frequently reported events. Skin disorders and skin infections (5 [33%] vs 0 [0%]) were more common in the PRT relative to the CRT arm.

[redacted] Safety Analysis Set reported adverse events. Adverse events with the greatest differences in subject incidence between the PRT arm and the CRT arm (PRT minus CRT) were rash (22 [49%] PRT vs 1 [3%] CRT), constipation (14 [31%] vs 4 [13%]), dermatitis (14 [31%] vs 4 [13%]), acne (8 [18%] vs 0 [0%]), and pruritus (8 [18%] vs 0 [0%]). Adverse events with the greatest differences between the CRT and PRT arms (CRT minus PRT) were nausea (7 [16%] PRT vs 12 [40%] CRT) and leukopenia (0 [0%] vs 5 [17%]).

Thirty-eight subjects (84%) receiving PRT and 23 subjects (77%) receiving CRT had grade 3 or higher adverse events. Grade 3 and higher adverse events that were more common in the PRT arm relative to the CRT arm were dermatitis (10 [22%] PRT vs 0 [0%] CRT), radiation skin injury (12 [27%] vs 5 [17%]), and radiation mucositis (5 [11%] vs 1 [3%]). Grade 3 and higher adverse events that were more common in the CRT arm relative to the PRT arm were leukopenia (0 [0%] PRT vs 2 [7%] CRT), neutropenia (0 [0%] vs 2 [7%]), syncope (0 [0%] vs 2 [7%]), mucosal inflammation (13 [29%] vs 11 [37%]), odynophagia (3 [7%] vs 5 [17%]), and febrile neutropenia (0 [0%] vs 3 [10%]).

Grade 5 (fatal) adverse events were reported in 3 subjects (7%) receiving PRT and 1 subject (3%) receiving CRT. Fatal adverse events reported in the PRT arm were sudden death (2 subjects) and death not otherwise specified (1 subject). Pneumonia was the cause of death for the 1 subject receiving CRT.

Fourteen subjects (31%) receiving PRT and 12 subjects (40%) receiving CRT had serious adverse events. No serious adverse events were reported with ≥ 5% higher subject incidence in the PRT arm relative to the CRT arm. Febrile neutropenia (0 [0%] PRT vs 2 [7%] CRT) and neutropenia (0 [0%] vs 2 [7%]) were reported with ≥ 5% higher subject incidence in the CRT arm relative to the PRT arm.

The most frequently reported events were stomatitis/oral mucositis (40 [89%] vs 27 [90%]) and skin disorders (39 [87%] vs 7 [23%]). Skin disorders, skin infections (6 [13%] vs 1 [3%]), and eye disorders (4 [9%] vs 1 [3%]) were more common in the PRT arm relative to the CRT arm.

Conclusions: In this estimation study, the primary endpoint did not support further investigation of panitumumab as a substitution for cisplatin in chemoradiotherapy regimens for locally advanced SCCHN. No new safety signals for panitumumab were detected in the study.