2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: panitumumab

Title of Study: A Phase 2, Randomized Trial of Chemoradiation With or Without Panitumumab in Subjects With Unresected Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN).

Investigator(s) and Study Center(s): This study was conducted at 42 sites in the United States, Italy, Spain, Hungary, Germany, Finland, Canada, Mexico, and Hong Kong.

Publication(s): Giralt J, Fortin A, Mesia R, et al. A phase II, randomized trial (CONCERT-1) of chemoradiotherapy (CRT) with or without panitumumab (pmab) in patients (pts) with unresected, locally advanced squamous cell carcinoma of the head and neck (LASCCHN). *J Clin Oncol*. 2012;30. Abstract 5502.

Study Period: 26 October 2007 (first subject enrolled) to 26 April 2011

Development Phase: Phase 2

Objectives: The primary objective of this study was to estimate, with pre-specified precision, the difference in local-regional control (LRC) rate at 2 years in subjects receiving panitumumab plus chemoradiation (PCRT) or chemoradiotherapy (CRT) alone as first-line treatment for locally advanced squamous cell carcinoma of the head and neck (SCCHN). The secondary objectives were to estimate the difference between 2 treatment regimens (PCRT versus CRT) for other measures of clinical benefit, including LRC, objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety.

Methodology

This study was a phase 2, multicenter, open-label, randomized study designed to explore the addition of panitumumab to current standard therapy (standard fractionation radiotherapy [RT] plus cisplatin).

Subjects with pathologically confirmed locally advanced SCCHN were randomized in a 2:3 ratio to receive either standard fractionation RT and 100 mg/m^2 cisplatin (CRT -arm 1) or standard fractionation RT, 75 mg/m^2 cisplatin, and 9 mg/kg panitumumab (PCRT - arm 2). Randomization was stratified by site or tumor (hypopharynx or oral cavity versus oropharynx or larynx), RT delivery modality (Intensity Modulated Radiotherapy [IMRT] versus 3D-Conformal Radiotherapy [3D-CRT]), nodal status (N0 versus N+), and tumor stage (T1-3 versus T4).

Each subject's planned modality of RT (IMRT or 3D-CRT) was declared before randomization. Once eligible subjects were enrolled, RT was administered as 2 Gray (Gy) fractions daily for 5 days a week for 7 consecutive weeks (35 fractions). In the CRT arm, subjects received cisplatin (100 mg/m^2) on days 1, 22, and 43 of RT. In the PCRT arm, subjects received cisplatin (75 mg/m^2) on days 1, 22, and 43 of RT and panitumumab (9 mg/kg) as a 60 ± 15 minute intravenous (IV) infusion every 3 weeks (Q3W) on days 1, 22, and 43 of RT.

Radiologic assessments were performed per a modification of the World Health Organization (WHO) criteria. After completion of RT, subjects were assessed clinically at 30 ±7 days and clinically and radiographically at 60 ± 7 days for disease status. 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.

A neck dissection was required for subjects with persistent clinical or radiographic evidence of residual nodal disease by 60 ± 7 days after completion of RT and was optional for subjects with N2 or N3 disease at pretreatment who achieved a complete response in the neck. The option to perform neck dissection was to have been prospectively defined for each subject prior to initiation

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of study treatment. Additionally, providing paraffin-embedded tumor tissue for biomarker analysis to determine human papilloma virus (HPV) status from archived tumor tissue or from screening biopsy was optional.

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

Number of Subjects Enrolled: 153 subjects were enrolled.

Sex: 20 women (13%), 133 men (87%)

Median Age: 57 years (range: 39 to 77)

Ethnicity (Race): 137 (90%) White, 12 (8%) Asian, 3 (2%) Hispanic or Latino, 1 (1%) Black or African American

Diagnosis and Main Criteria for Eligibility

Eligible subjects were men or women ≥ 18 with histologically or cytologically confirmed SCC of oropharynx, oral cavity, hypopharynx, or larynx, with Stage III or Stage IVa-b (M0) disease according to the American Joint Committee on Cancer Staging Manual (6th edition), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and bidimensionally measurable disease ≥ 10 mm in at least 1 dimension. The subject also had to have adequate hematologic, renal, hepatic, and metabolic function.

Subjects were excluded if the primary tumor was of the nasopharynx, sinuses, salivary gland or skin. Subjects must not have had prior or concomitant malignancy other than SCCHN (except non-melanomatous skin cancer or in situ cervical cancer), unless they were treated with curative intent with no evidence of disease for ≥ 3 years or required prophylactic tracheostomy. Subjects were excluded if they had prior anti- endothelial growth factor receptor (EGFR) therapy or treatment with small molecule tyrosine kinase inhibitors of EGFR, prior surgery for SCCHN (except nodal sampling or biopsy for study disease), prior RT in the planned field, prior systemic chemotherapy for the study cancer, or major or minor surgery within 28 days and 14 days of screening, respectively (with the exception of feeding tube placement, dental extractions, central venous catheter placement, biopsies [endoscopic or otherwise], and nodal sampling).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: In arm 2, panitumumab was administered by IV infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with 0.2 – or 0.22-micron pore size in-line filter infusion set-up at a dose of 9 mg/kg every 3 weeks. [redacted]

Duration of Treatment: The treatment duration was a maximum of 7 weeks if there were no treatment breaks. Subjects were followed for at least 2 years from randomization.

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

Study Endpoints

The primary endpoint was the LRC rate at 2 years.

The secondary efficacy endpoints were duration of LRC, LRC rate at 6 months and 1 year, PFS, OS, and ORR by 6 months. The secondary safety endpoints were the incidence of death on or within 30 days of last protocol-defined treatment, protocol treatment delivery of RT, CRT, and panitumumab (if applicable), incidence and severity of adverse events commonly associated with treatment of head and neck cancer, the incidence and severity of all other adverse events, significant changes in laboratory values, [redacted]

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A supplemental Statistical Analysis Plan was written to estimate the efficacy as well as safety of PCRT compared with CRT in subsets of subjects with tumors that were positive or negative for HPV.

Statistical Methods

No formal hypothesis was planned in this study. The treatment effect of PCRT compared with CRT alone and the associated 95% confidence intervals (CI) were estimated for all efficacy endpoints. For the primary endpoint of LRC rate at 2 years, a 95% CI with half-width no wider than 16% for the treatment difference between the 2 arms was desired in this study.

For LRC rates, Kaplan-Meier (KM) estimates and the associated 2-sided 95% CI were calculated by randomized treatment group for each treatment arm to determine the difference between the 2 treatment arms. For duration of LRC, PFS, and OS the hazard ratio (HR) 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 (CR) 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.

The supplemental Statistical Analysis Plan described additional analyses to estimate the treatment effect of PCRT compared with CRT and the associated 2-sided 95% CIs within the HPV subsets for all efficacy endpoints. In addition, whether the relative effect of PCRT compared with CRT alone on LRC rate at 2 years, OS, and PFS were significantly different between subjects who had HPV+ and HPV- tumors was also examined.

Summary of Results

Subject Disposition

Of the 153 subjects enrolled and randomized to treatment, 150 subjects received study drug and were and included in the Intent-to-treat (ITT) Analysis Set, 87 subjects in the PCRT arm and 63 subjects in the CRT arm. As of the data cutoff date, 86 subjects (56%) completed the study including the 24-month period after the last subject was randomized (46 subjects [52%] in the PCRT arm and 40 subjects [63%] in the CRT arm). Reasons for not completing the study in the PCRT and CRT arms were death (32 subjects [36%] and 15 subjects [23%], respectively), consent withdrawn (5 subjects [6%] and 7 subjects [11%], respectively), administrative decision and lost to follow-up (2 subjects [2%] and 0 subjects, respectively), and (3 subjects [3%] and 0 subjects, respectively).

A total of 67 subjects (75%) completed all 3 treatments of panitumumab. The most common reasons for discontinuing panitumumab were adverse events (15 subjects [17%]) and partial withdrawal of consent (2 subjects [2%]). A total of 71 subjects (80%) in the PCRT arm and 45 subjects (70%) in the CRT arm completed all 3 treatments of cisplatin. Adverse events led to the discontinuation of cisplatin in 14 subjects (16%) and 13 subjects (20%) in the PCRT and CRT arms, respectively. In the CRT arm, 3 subjects (5%) discontinued cisplatin because of protocol-specified criteria and 2 subjects (3%) withdrew full consent. Most subjects completed RT, 76 subjects (85%) in the PCRT arm and 59 subjects (92%) in the CRT arm. The most common reason for ending RT was adverse events experienced by 6 subjects (7%) and 3 subjects (5%), respectively.

The actual median follow-up time was 107 weeks in the PCRT arm and 110 weeks in the CRT arm.

A total of 99 subjects (65%) were included in the HPV Efficacy analysis set; 42 subjects (27%) had HPV+ tumors, 57 subjects (37%) had HPV- tumors, and 51 subjects (33%) had tumors that were unevaluable for HPV status. As of the data cutoff date, a similar percentage of subjects in the HPV+ and HPV- subjects in the HPV Efficacy analysis set ended the study (98% and 96%,

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respectively). Death was the most common reason for not completing the study in the HPV+ and HPV- analysis sets (19% and 33%, respectively).

Efficacy Results

Subjects were considered to be in LRC if there was no evidence of active disease in the previously affected/irradiated head and neck area. LRC could have been achieved at any time following completion of treatment unless disease progression in the local-regional area occurred or the subject received subsequent anti-tumor therapy. The KM estimate of the LRC rate at 2 years, in the Efficacy Analysis Set, was 61% (95% CI: 50%, 71%) for the PCRT arm and 68% (95% CI: 54%, 78%) for the CRT arm. The difference between the PCRT arm and the CRT arm was -7% (95% CI: -23%, 9%).

In HPV+ subjects, the KM estimate of the LRC rate at 2 years was 77% (95% CI: 55%, 89%) for the PCRT arm and 87% (95% CI: 56%, 96%) for the CRT arm. The difference between the PCRT arm and the CRT arm was -10% (95% CI: -34%, 14%).

In HPV- subjects, the KM estimate of the LRC rate at 2 years was 62% (95% CI: 43%, 76%) for the PCRT arm and 68% (95% CI: 44%, 83%) for the CRT arm. The KM estimate of difference between the PCRT arm and the CRT arm) was -6% (95% CI: -32%, 20%).

In the Efficacy Analysis Set, the KM estimate of the median duration of LRC was 34 months (95% CI: 29, not estimable) for the PCRT arm and not estimable for the CRT arm. The difference between the PCRT arm and the CRT arm was -6% (95% CI: -32%, 20%). For PFS, the median KM estimate was not estimable in either treatment arm. The median KM estimate for OS in the PCRT arm was 34 months (95% CI: 32, not estimable); the median in the CRT arm was not estimable (95% CI: 35; not estimable). The ORR rates by 6 months were 71% (95% CI: 61%, 80%) in the PCRT arm and 82% (95% CI: 70%, 91%) in the CRT arm for subjects that were evaluable for central tumor response. The difference between the PCRT arm and the CRT arm was 11% (95% CI: -24.56, 4.14). For subjects with a CR by 6 months, the CR rate in the PCRT arm was 20.69% (95% CI: 12.75, 30.71) and 19.35% (95% CI: 10.42, 31.37) in the CRT arm. The difference in CR rate by 6 months was (PCRT - CRT) 1.33% (95% CI: -13.23, 14.71).

Safety Results

The Safety Analysis Set included 150 subjects, 87 subjects in the PCRT arm and 63 subjects in the CRT arm.

All subjects in the PCRT arm (87 [100%]) and CRT arm (63 [100%]) experienced treatment-emergent adverse events. Of these, 37 subjects (43%) in the PCRT arm and 20 subjects (32%) in the CRT arm had a serious adverse event. A total of 74 subjects (85%) in the PCRT arm and 43 subjects (68%) in the CRT arm had an adverse event that was grade 3 or higher.

The most common adverse events in the PCRT arm with at least a 5% difference subject incidence between treatment groups (PCRT arm; CRT arm) included rash (46%, 2%), acne (18%, 2%), and pruritus (15%, 0%); the most common adverse events in the CRT arm with at least a 5% difference in subject incidence between treatment groups were tinnitus (9%, 19%), radiation skin injury (68%, 83%), and dysgeusia (24%, 43%). Radiation skin injury and renal failure were the most common serious adverse event with the greatest difference between treatment groups (6% PCRT; 0 CRT and 0 PCRT; 5% CRT, respectively). The most common grade 3 or higher adverse events in the PCRT arm with at least a 5% difference in subject incidence between treatment arms (PCRT arm; CRT arm) included mucosal inflammation (55%, 24%), radiation skin injury (28%, 13%), and dysphagia (40%, 27%); the most common grade 3 or higher adverse event in the CRT arm with at least a 5% difference in subjects incidence between treatment groups was neutropenia (2%, 11%).

On-treatment fatal adverse events, for any cause, which occurred between the first dose day through 30 days after the last dose of study drug were experienced by 4 subjects (5%) in the PCRT arm and 2 (3%) in the CRT arm. In the PCRT arm the following deaths occurred: circulatory collapse (2 subjects); staphylococcal sepsis (1 subject); and cardio-respiratory arrest (1 subject). In the CRT arm, the deaths were myocardial infarction (1 subject) and acute renal

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failure (1 subject). One of the events of circulatory collapse and acute renal failure were considered related to PCRT and CRT treatment, respectively. The only event that occurred within the first 30 days of study treatment was myocardial infarction. All of these deaths occurred in the setting of pre-existing condition or current disease state.

The overall subject incidence of adverse events of interest (EOI) by worst grade (using a narrow search strategy) for subjects in the PCRT arm was 100% and 95% for subjects in the CRT arm. The subject incidence rates of grade 3 or higher EOIs were 77% and 41%, respectively. The most common grade 3 or higher EOIs (> 10% subject incidence in either treatment group) (PCRT arm, CRT arm) were stomatitis/oral mucositis (67%, 35%) and skin disorders (29%, 0). Almost all subjects had prespecified adverse events (99% PCRT; 97% CRT); mucosal inflammation was the most commonly reported in both treatment arms (82% PCRT; 71% CRT).

Conclusions

No notable difference was seen between the PCRT and CRT treatment groups for the primary endpoint of LRC rate at 2 years. The KM estimate of the LRC rate at 2 years, in the Efficacy Analysis Set, was 61% (95% CI: 50%, 71%) for the PCRT arm and 68% (95% CI: 54%, 78%) for the CRT arm. The lack of improvement in efficacy with the addition of panitumumab to CRT was observed in the Overall Efficacy Analysis Set and for the HPV+ and HPV- subgroups for all efficacy endpoints. Increased toxicity (attributable to on-target effects of EGFR inhibition) in the PCRT arm compared with the CRT arm was also observed; this included an increased incidence of high-grade oral mucositis/stomatitis and an increased incidence of skin toxicity in the PCRT arm. The limitations of this study included a small sample size and a difference in the dose of CRT between the arms.

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