2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 706/Vectibix®

Name of Active Ingredient: motesanib/panitumumab

Title of Study: An Open-label, Multicenter, Dose-finding Study to Evaluate the Safety and Tolerability of AMG 706 or Panitumumab When Administered With Induction Chemotherapy (IC) and/or Chemo-radiotherapy (CRT) in the Treatment of Subjects With Loco-regionally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN).

Investigator(s) and Study Center(s): This study was conducted at 6 sites in Spain, France, and Belgium.

Publication(s): None as of the date of this report.

Study Period: 27 December 2005 (first subject enrolled) to 22 May 2010.

Development Phase: Phase 1b

Introduction and Objectives:

Approximately 90% of head and neck cancers over-express endothelial growth factor receptor (EGFR), and therefore treatments targeting this receptor are of interest in squamous cell carcinoma of the head and neck (SCCHN). Preclinical models have demonstrated radiosensitization following molecular inhibition of EGFR signaling (Huang and Harari et al, 2000). A phase 3 clinical trial in patients with locoregionally advanced SCCHN demonstrated prolonged survival with the addition of cetuximab (a chimeric mAb to the EGFR) to radiotherapy (RT), with minimal additive toxicity (Bonner et al, 2004). These findings suggest that EGFR blockage may be important in enhancing the response to radiotherapy.

Cetuximab has been shown to enhance the anti-tumor effect of cisplatin in preclinical models, and has shown benefit when combined with cisplatin in platinumrefractory patients with recurrent/metastatic SCCHN (Baselga et al, 2002).

Increased expression of vascular endothelial growth factor receptor (VEGF) is seen in many different cancers including SCCHN, and inhibition of angiogenesis diminishes growth of tumors in SCCHN animal models. In addition, preclinical studies in SCCHN xenografts have demonstrated that the combination of an anti-angiogenic agent and ionizing radiation produces synergistic tumor growth inhibition (Gorski et al, 1999). A phase I study incorporating bevacizumab, a monoclonal antibody directed against VEGF, with chemoradiotherapy (CRT) has demonstrated tolerability and efficacy in SCCHN patients with poor prognosis (Cohen et al, 2004).

The primary objective of this study was to characterize the safety profile and tolerability of the combinations of CRT plus panitumumab or induction chemotherapy (IC) and CRT plus panitumumab or CRT plus AMG 706 in subjects undergoing IC followed by CRT for locoregionally advanced SCCHN. The secondary objective were to determine the maximum tolerated dose (MTD) of panitumumab (up to 2.5 mg/kg every week in combination with CRT; to determine the MTD of AMG 706 (up to 125 mg every week, given orally); to evaluate the pharmacokinetic profiles of panitumumab when given with CRT or IC and CRT; to evaluate the pharmacokinetic profiles of AMG 706 when given with CRT; and to evaluate the subject incidence of dose-limiting toxicities (DLTs). The tertiary objectives were to assess the incidence of unacceptable interruption of radiation therapy; to describe the objective response rate (ORR) in each dose cohort; and to investigate the long term effects (disease outcome and survival) of adding panitumumab or AMG 706 to CRT, or adding panitumumab to IC and CRT. [redacted]

Methodology: This study was a phase 1b, multicenter, open-label, sequential-cohort-escalation study designed to explore the addition of panitumumab at different phases of treatment in subjects with locally advanced SCCHN undergoing docetaxel (T) + cisplatin (P) + 5-fluorouracil (F) chemotherapy regimen (TPF) IC followed by CRT and the addition of AMG 706 to CRT following IC.

Each subject underwent 2 phases of treatment, which were identical irrespective of the cohort that a subject was assigned to, namely an IC phase (three or four 21-day cycles of TPF followed by a CRT phase (standard fraction RT with carboplatin).

Once eligible subjects were enrolled, subjects in all cohorts received a maximum of 3 or 4 cycles of TPF IC. On day 1 of each 21-day cycle, subjects received the TPF regimen: docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), then 5-fluorouracil (750 mg/m^2). 5-fluorouracil was administered continuously, as an infusion, and repeated days 2 to 5.

During the CRT phase, subjects in cohorts A and B began investigational product administration for 1 week (7 ± 2 days) before receiving CRT. In the absence of toxicity, subjects in cohort C did not have a planned break in panitumumab administration, ie, panitumumab was administered on day 1 of CRT (21 days after day 1 of the last IC cycle).

All subjects who were candidates for chemoradiotherapy received a radiosensitizing dose of carboplatin, which was administered to target an area under the curve (AUC) of 1.5 mg/mL•min (Calvert Formula) once weekly on day 1, 2, or 3 of RT. RT was administered as standard fractions, 5 days per week for 7 weeks. Subjects were to receive a total dose of 70 Gray (Gy) administered as 2 Gy/day in 35 fractions over 7 weeks.

The cohorts were:

Cohort A
Dose Level A1: TPF IC followed by CRT plus panitumumab 1.5 mg/kg every week (n = 3-6)
Dose Level A2: TPF IC followed by CRT plus panitumumab 2.5 mg/kg every week (n = 3-6)

Cohort B
Dose Level B1: TPF IC followed by CRT plus AMG 706 50 mg QD PO (n = 3-6)
Dose Level B2: TPF IC followed by CRT plus AMG 706 125 mg QD PO (n = 3-6)

Cohort C
TPF IC plus panitumumab 9 mg/kg Q3W followed by CRT plus panitumumab 2.5 mg/kg QW (n = 3-18). Dose of panitumumab QW during CRT was determined in cohort A.

At the start of the study only the CRT stream was open. Cohorts A and B started first with the aim of identifying the MTD for panitumumab and AMG 706 respectively when administered in the CRT phase. Thereafter, cohort C was to open with the aim of exploring the safety and tolerability of panitumumab at the safe dose determined from cohort A when given throughout IC and CRT.

Subjects in cohorts A and B and were considered evaluable for DLT after the 56-day investigational product treatment period without significant deviation from the study procedures that could affect the interpretation of the data. For subjects in cohort C, the same consideration for evaluability applied, except they were considered evaluable for DLT after the 21-day investigational product treatment period.

MTD was defined at the highest dose level at which 0 of 3 or ≤ 1 of 6 evaluable subjects had a DLT within the defined period for safety review. If the MTD was not identified from these cohorts then additional cohorts may have been added. Dose exploration was not to exceed panitumumab 2.5 mg/kg every week or 9 mg/kg every 3 weeks, or AMG 706 125 mg orally every day.

Number of Subjects Planned: The planned sample size was 21 to 57 subjects.

Number of Subjects Enrolled: 41 subjects were enrolled.

Sex: 5 women (12%), 36 men (88%)

Median Age: 55 years (range: 26 to 74)

Ethnicity (Race): 41 (100%) White

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18, but ≤ 80 years of age with histologically or cytologically confirmed SCCHN of oropharynx, oral cavity, hypopharynx, larynx, or squamous cell cancer of unknown origin with cervical node involvement, with no evidence of distant metastasis (tumor-node-metastasis [TNM] stages T3-4, and N, M0) or nasopharynx (TNM stages T3-4, N3, M0) locally advanced and determined to be incurable by surgery or radiotherapy alone. Subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measureable disease or evaluable (non-measureable) disease per modified Response Evaluation Criteria in Solid Tumors (RECIST) guideline. The subject also had to have adequate hematologic, renal, hepatic, and metabolic function.

Subjects were excluded if they had treatment for SCCHN with any antineoplastic treatment, had SCCHN of the paranasal sinus, or larynx and were a candidate for organ preservation. Subjects must not have had symptomatic central nervous system involvement, prior malignancy other than SCCHN (except in situ basal cell carcinoma or in situ cervical cancer), unless they were treated with curative intent with no evidence of disease for ≥ 3 years. Subjects were excluded if they had a history of venous thrombosis within 1 year of enrollment, a history of bleeding, hypercoagulopathy, pulmonary hemorrhage or hemoptysis of > 15 mL blood tinged sputum/24 hours, major surgery within 28 days of screening, clinically significant cardiac disease within 12 months of enrollment, uncontrolled hypertension (or if on hypertensive medication, must be stable), symptomatic peripheral neuropathy (grade ≥ 2), a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis, or pulmonary fibrosis on screening chest computed tomography (CT)-scan, known positivity of human immunodeficiency virus, hepatitis C virus, chronic active hepatitis B infection, or any comorbid disease that would increase risk of toxicity.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: In cohort A, panitumumab was administered by intravenous (IV) infusion pump through a peripheral line or indwelling catheter using 0.2 – or 0.22-micron in-line filter infusion set-up at a dose of 1.5 mg/kg (cohort A1) or 2.5 mg/kg (cohort A2) every week. In cohort C, panitumumab was administered at a dose of 9 mg/kg every 3 weeks. Panitumumab was supplied in single-use 10-mL vials containing 20 mg of panitumumab per mL, to be diluted in pyrogen-free [redacted]% sodium chloride solution (USP). The manufacturing batch numbers of panitumumab used in this study are [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

In cohort B, AMG 706 was administered orally (PO) at a dose of 50 mg (cohort B1) or 125 mg (cohort B2) every day. AMG 706 was supplied as bottles of 30 tablets in 25 mg or 100 mg strengths. The manufacturing batch numbers of AMG 706 25 mg tablet used in this study are [redacted], [redacted], and [redacted]. The manufacturing batch numbers of AMG 706 100 mg tablets used in this study are [redacted], and [redacted].

Duration of Treatment: In each cohort, treatment duration was a maximum of 31 weeks including screening and safety follow up.

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

Study Endpoints

The primary endpoint was the incidence of adverse events.

The secondary endpoint was the incidence of DLTs and pharmacokinetic profiles (concentration over time) of AMG 706 and panitumumab when each was given with CRT or both IC and CRT (panitumumab only)

Tertiary endpoints included:

- the incidence of interruptions in RT > 7 consecutive days
- the incidence of chemotherapy dose reductions during the IC phase
- the incidence of delay in commencing the CRT phase
- objective response rate over the entire study
- overall survival
- progression-free survival

[redacted]

Statistical Methods: This study was exploratory and no hypothesis testing was performed. If the number of subjects allowed, descriptive statistics were provided such that categorical variables may have been presented using counts and percentages and continuous data may have been reported using means, medians, standard deviations, minimum, and maximum. Graphical presentation, including patient profiles of safety data were presented for adverse events, DLTs, abnormalities in laboratory data, vital sign measurements, and electrocardiograms together with supportive investigational product, IC and CRT data. Data were presented by cohort, dose level, and phase.

Summary of Results

Subject Disposition: Of the 46 subjects screened for this study 41 subjects were enrolled. A total of 34 subjects (83%) completed the study and 7 subjects (17%) discontinued the study. Reasons for study discontinuation were administrative decision (3 subjects [7%]), death (2 subjects [5%]), and adverse event and ineligibility determined (1 subject [2%] each).

Of the 41 subjects, 31 subjects (76%) completed the IC phase; the most common reasons for not completing the IC phase were administrative decision and adverse event (3 subjects [7%] each). Of the 30 subjects in the CRT phase, a total of 26 subjects (63%) completed the CRT phase; the most common reason for not completing the CRT phase was adverse event (2 subjects [5%]).

Efficacy Results: In cohort A1, 5 of the 7 subjects (71%) (95% CI: 29.0, 96.3) were responders; 2 subjects (29%) had a CR and 3 subjects (43%) had a PR. In cohort A2, 2 of the 6 subjects (33%) (95% CI: 4.3, 77.7) were responders, both with a best response of PR. In cohort B1, 6 of the 7 subjects (81%) (95% CI: 42.1, 99.6) were responders; 1 subject (14%) with CR and 5 subjects (71%) with a PR. In cohort B2, 5 of the 6 subjects (83%) (95%CI: 35.9, 99.6) were responders with a best response of PR. In cohort C, 2 of 4 subjects (50%) (95%CI: 50.0 6.8, 93.2) had a best response of PR. Three subjects (33%) who withdrew from the study before being assigned to panitumumab or AMG 706 had a best response of PR (95%CI: 7.5, 70.1). The median time to response ranged from 5.1 weeks in cohort A2 to 8.9 weeks in cohort B1.

Pharmacokinetic Results: Eighteen subjects from Cohorts A1 (8 subjects), A2 (6 subjects), and C (4 subjects) had pharmacokinetic samples collected for panitumumab concentration measurement. Fourteen subjects from Cohorts B1 (7 subjects) and B2 (7 subjects) had pharmacokinetic samples collected for AMG 706 concentration measurement. The mean (SD) trough panitumumab concentration from Week 21 and onward during the CRT phase were 7.29 (8.00) and 22.5 (8.48) µg/mL for subjects in cohortA1 and cohortA2, respectively.

In cohort C, the mean (SD) trough panitumumab concentration during the CRT phase was 25.9 (13.2) µg/mL.

The mean AMG 706 concentration profiles overlapped considerably on Week 17 between subjects in cohortB1 and cohortB2. C_{max} and AUC_{24hr} were similar between subjects who received AMG 706 at 50 and 125 mg QD. Comparing with subjects who received AMG 706 as monotherapy, the exposure is slightly lower but within the range for the 50 mg QD cohort. The exposure for the 125 mg QD cohort is lower than expected. The reason for low exposure is unclear; however, the data need to be interpreted with caution given limited sample size.

The mean (SD) total and unbound platinum concentrations in plasma after cisplatin administration were 3.21 (0.35) and 2.38 (0.30) µg/mL, respectively on Week 1 and were 4.07 (1.16) and 2.80 (1.04) µg/mL, respectively on Week 4. The mean (SD) docetaxel plasma concentrations after docetaxel administration were 1.88 (0.47) and 1.21 (0.87) µg/mL on Weeks 1 and 4, respectively.

Safety Results:

In the IP safety analysis set, all 32 subjects (100%) had treatment-emergent adverse events. A total of 15 subjects (47%) had treatment-emergent adverse events with a worst grade of 3 and 14 subjects (44%) had a worst grade of 4. The most common treatment-emergent adverse events were mucosal inflammation (22 subjects [69%]), alopecia (19 subjects [59%]), and diarrhea and nausea (18 subjects [56%] each). Twenty subjects (63%) had serious treatment-emergent adverse events. Six subjects (19%) had serious treatment-emergent adverse events with a worst grade of 3 and 13 subjects (44%) had a worst grade of 4.

In cohort A1, 8 subjects (100%) had treatment-emergent adverse events. The most frequent treatment-emergent adverse events were mucosal inflammation (7 subjects [88%]), nausea (5 subjects [63%]), and alopecia and dysphagia (4 subjects [50%] each). In cohort A2, 6 subjects (100%) had treatment-emergent adverse events. The most frequent treatment-emergent adverse events were asthenia (6 subjects [100%]), mucosal inflammation (5 subjects [83%]), and dysphagia (4 subjects [67%]). In cohort B1, 7 subjects (100%) had treatment-emergent adverse events. The most frequent were dysphagia (6 subjects [86%]), mucosal inflammation (5 subjects [71%]), diarrhea, decreased appetite, vomiting, asthenia, alopecia, and dry mouth (4 subjects [57%] each). In cohort B2, 7 subjects (100%) had treatment-emergent adverse events. The most frequent were diarrhea and decreased appetite (6 subjects [86%] each), nausea and alopecia (5 subjects [71%] each), and vomiting and mucosal inflammation (4 subjects [57%] each). In cohort C, 4 subjects (100%) had treatment-emergent adverse events. The most frequent were nausea and vomiting (4 subjects [100%] each) and febrile neutropenia, neutropenia, diarrhea, pain, pyrexia, decreased appetite, alopecia, and rash (3 subjects [75%] each).

In the IC phase safety analysis set, 40 subjects (98%) had treatment-emergent adverse events. A total of 8 subjects (20%) had treatment-emergent adverse events with a worst grade of 3 and 13 subjects (32%) had a worst grade of 4. The most common treatment-emergent adverse events were diarrhea (22 subjects [54%]), alopecia (21 subjects [51%]), and nausea and decreased appetite (18 subjects [44%] each). Two subjects (5%) had fatal adverse events. Twenty subjects (49%) had serious treatment-emergent adverse events. Five subjects (12%) had serious treatment-emergent adverse events with a worst grade of 3, 13 subjects (32%) had a worst grade of 4 and 2 subjects had serious treatment-emergent adverse events with a worst grade of 5.

There were 9 subjects who withdrew before they were assigned to an IP cohort and all of them (100%) experienced treatment-emergent adverse events. The most frequent events were diarrhea, mucosal inflammation, and nausea (5 subjects [56%] each) and asthenia, decreased appetite, and alopecia (4 subjects [44%]).

In cohort A1, 8 subjects (100%) experienced treatment-emergent adverse events. The most frequent were nausea (5 subjects [63%]) and mucosal inflammation and alopecia (4 subjects [50%] each). In cohort A2, 6 subjects (100%) had treatment-emergent adverse events; the most frequent included asthenia (5 subjects [83%]) and mucosal inflammation (3 subjects [50%]). In

cohort B1, 6 subjects (86%) had treatment-emergent adverse events; the most frequent included diarrhea, vomiting, and decreased appetite, (4 subjects [57%] each) and hypokalemia and alopecia (3 subjects [43%] each). In cohort B2, 7 subjects (100%) had treatment-emergent adverse events; the most frequent included diarrhea and decreased appetite, and alopecia (5 subjects [71%] each) and oral pain, stomatitis, and fatigue (3 subjects [43%]). In cohort C, 4 subjects (100%) had treatment-emergent adverse events; the most frequent events were febrile neutropenia, diarrhea, nausea, vomiting, and alopecia (3 subjects [75%] each).

In the IP safety analysis set during the CRT phase, 29 subjects (97%) had treatment-emergent adverse events. A total of 18 subjects (60%) had treatment-emergent adverse events with a worst grade of 3 and 4 subjects (13%) had a worst grade of 4. The most common adverse events were mucosal inflammation (21 subjects [70%]), dysphagia (15 subjects [50%]), and rash (11 subjects [37%]) (Tab. Eight subjects (27%) had serious treatment-emergent adverse events. Three subjects (10%) each had serious treatment-emergent adverse events with a worst grade of 3 or 4.

In cohort A1, 8 subjects (100%) experienced treatment-emergent adverse events; the most frequent were mucosal inflammation (7 subjects (88%), radiation skin injury, dysphagia, decreased appetite, dermatitis (3 subjects [38%]). In cohort A2, 5 subjects (83%) had treatment-emergent adverse events; the most frequent were mucosal inflammation (4 subjects [67%]) and dysphagia, anemia, asthenia, and rash (3 subjects [50%] each). In cohort B1, 7 subjects (100%) had treatment-emergent adverse events; the most common were dysphagia (6 subjects [86%]), mucosal inflammation (5 subjects [71%]), and vomiting, asthenia, and rash (3 subjects [43%] each). In cohort B2, 7 subjects (100%) had treatment-emergent adverse events; the most frequent were nausea (5 subjects [71%]), vomiting, mucosal inflammation, and decreased appetite (4 subjects [57%] each), radiation skin injury, diarrhea, and dysphagia, (3 subjects [43%] each). In cohort C, 2 subjects (100%) had treatment-emergent adverse events; the most frequent were nausea, pyrexia, dizziness, and rash (2 subjects [100%] each).

Two subjects (50%) in cohort C experienced DLTs during the IC phase, suggesting this combination cannot be given safely at full dose during this treatment phase and 3 subjects (10%) (1 in cohort A1, 1 in cohort A2, and 1 in cohort B2) experienced DLTs in the CRT phase.

Conclusions:

The addition of single-targeted agents (panitumumab or AMG 706) to TPF IC and CRT as sequential therapy were tolerated in subjects with locally advanced SCCHN. The reported adverse event profile observed with panitumumab or AMG 706 plus IC and CRT sequential therapy was consistent with the events expected in sequential combination IC and CRT therapy alone. In this small phase 1 trial, the subject incidence of adverse events and their respective grade of severity did not increase with increased dose exposure of panitumumab or AMG 706.

The combination of TPF IC with sequential CRT is an aggressive therapy and investigators should carefully evaluate the performance status and any pre-exisiting comorbid conditions before selecting subjects as candidates for future clinical trials. This regimen would not be considered outside of the clinical trial setting. [redacted].