2. SYNOPSIS

Name of Sponsor: Amgen

Name of Finished Product: N/A

Name of Active Ingredient: conatumumab (AMG 655) and ganitumab (AMG 479)

Title of Study: A Phase 1b/2 Open Label, Dose Escalation Study of AMG 655 in Combination with AMG 479 in Subjects with Advanced, Refractory Solid Tumors

Investigators and Study Centers: This international study was conducted at 16 centers in the United States and Spain.

Publication: Chawla S, Lockhart AC, Azad N, et al. Efficacy and safety of conatumumab plus AMG 479 in patients with advanced sarcoma [poster]. CTOS 16th Annual Meeting; Paris, France; 11-13 November 2010. Abstract 890126.

Study Period: 16 January 2009 to 10 August 2011

Development Phase: Phase 1b/2

Objectives

Primary Objectives

Part 1: to identify a dose of conatumumab in combination with ganitumab that was safe and tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: to estimate the efficacy, as measured by the objective response rate (ORR) (confirmed complete response and partial response using modified Response Evaluation Criteria in Solid Tumors [RECIST]), of conatumumab in combination with ganitumab

Secondary Objectives

Part 1:

- to evaluate the safety and tolerability of conatumumab in combination with ganitumab
- to evaluate anti-conatumumab antibody formation and anti-ganitumab antibody formation
- to evaluate the pharmacokinetics (PK) of conatumumab and of ganitumab

Part 2:

- to estimate the efficacy of conatumumab in combination with ganitumab, as measured by time to response, duration of response, and progression-free survival (PFS)
- to evaluate the safety and tolerability of conatumumab in combination with ganitumab
- to evaluate anti-conatumumab antibody formation and anti-ganitumab antibody formation
- to evaluate the PK of conatumumab and of ganitumab

Methodology: This was a multicenter, open-label, 2-part, phase 1b/2 study of conatumumab in combination with ganitumab.

Part 1 was a dose-escalation segment to identify a dose of conatumumab in combination with ganitumab 18 mg/kg every 3 weeks (Q3W) that was safe and tolerable as determined by the incidence of DLT. The maximum dose of conatumumab planned was 15 mg/kg Q3W.

Part 2 of the study opened after a dose of conatumumab had been identified that was safe and tolerated based on the incidence of DLT in part 1. Part 2 evaluated the safety and estimated the efficacy (as measured by ORR) of conatumumab at the dose selected in part 1 in combination with ganitumab for the treatment of subjects with advanced non-small cell lung cancer (NSCLC) (cohort 1: nonsquamous histology; cohort 2: squamous histology), colorectal cancer (CRC) (cohort 3), pancreatic cancer (cohort 4), ovarian cancer (cohort 5), and sarcoma (cohort 6). Enrollment into the 6 cohorts occurred in parallel, independent of one another. Enrollment into cohort 2 (squamous NSCLC) and cohort 5 (ovarian cancer) was suspended due to a decision to not move forward with development of the combination treatment of conatumumab and

ganitumab in these disease settings due to low tumor response in 2 other previously enrolled cohorts (CRC and sarcoma).

In parts 1 and 2, conatumumab and ganitumab were administered Q3W until disease progression, intolerable adverse event, death, withdrawal of consent, or administrative decision for up to 24 months from the date of first study treatment (day 1). Subjects who had completed 24 months of conatumumab and/or ganitumab treatment and who continued to benefit from treatment could have been eligible for continued treatment with conatumumab and/or ganitumab by extension protocol or as provided for by the local country's regulatory mechanism.

This clinical study report summarizes data from part 1 of the study (data cutoff date: 10 August 2011), the primary analysis from part 2 of the study (data cutoff date: 01 September 2010), and the final analysis from part 2 of the study (data cutoff date: 10 August 2011). At the time of the final analysis, the last 2 subjects receiving protocol-specified treatment in the study met eligibility criteria and were enrolled into an extension protocol for continued treatment. Thus, no subject was on treatment and no subject remained in the study at the time of the final analysis.

Number of Subjects Planned: Approximately 99 to 108 (part 1: approximately 9 to 18 DLT-evaluable subjects; part 2: approximately 90 response-evaluable subjects)

Number of Subjects Enrolled: 9 subjects were enrolled in part 1; 80 subjects were enrolled in part 2 (78 subjects received investigational product).

Diagnosis and Main Criteria for Eligibility

Key Inclusion Criteria

- histologically or cytologically confirmed, locally advanced or metastatic, treatment-refractory solid tumors (part 1)
- histologically or cytologically confirmed, locally advanced or metastatic NSCLC (squamous or nonsquamous cell carcinoma; up to 2 prior treatment regimens), CRC (up to 2 prior treatment regimens), pancreatic cancer (up to 1 prior treatment regimen), ovarian cancer (up to 2 prior treatment regimens), or sarcoma (up to 2 prior treatment regimens) (part 2)
- measurable disease according to modified RECIST (at least 1 measurable lesion) (part 2)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- life expectancy ≥ 3 months
- ≥ 16 years of age
- adequate organ function (including hematological, renal, and hepatic) and glycemic function (for subjects with known diabetes)

Key Exclusion Criteria

- presence of uncontrolled central nervous system disease
- any prior or synchronous malignancy (except for non-melanoma skin cancer or in situ cervical cancer) other than the study disease unless treated with curative intent with no evidence of disease ≥ 3 years before enrollment (part 2)
- systemic chemotherapy, hormonal therapy, immunotherapy, or experimental or approved anticancer proteins/antibodies therapy ≤ 28 days before enrollment, except in part 1, subjects could have continued approved hormonal therapy as medically indicated
- prior treatment with death receptor agonists (eg, rhApo2L/TRAIL [AMG 951], apomab, mapatumumab, lexatumumab, or CS-1008)
- prior treatment with insulin-like growth factor receptor antagonists (eg, CP-751, 871, MK0646, AVE1642, or IMC-A12)
- any clinically significant medical or psychiatric condition, comorbid disease, addictive disorder, or laboratory abnormality, including cardiovascular disease or chronic obstructive pulmonary disease, which may increase the risks associated with study participation or study treatments, could interfere with the safe delivery of study treatment, or increase risk of toxicity

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number

Part 1

- cohort 1: ganitumab 18 mg/kg plus conatumumab 1 mg/kg intravenous (IV) on day 1 of each Q3W cycle
- cohort 2: ganitumab 18 mg/kg plus conatumumab 3 mg/kg IV on day 1 of each Q3W cycle
- cohort 3: ganitumab 18 mg/kg plus conatumumab 15 mg/kg IV on day 1 of each Q3W cycle

Part 2

- ganitumab 18 mg/kg plus conatumumab at the dose selected in part 1 (up to 15 mg/kg) IV on day 1 of each Q3W cycle

Conatumumab and ganitumab lot numbers are provided in Listing 14-1.2, Part 1 FA and in Listing 14-1.2, Part 2 FA.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No placebo or comparator groups were used in this study.

Duration of Treatment: up to 24 months from the date of first study treatment

Study Endpoints

Primary Efficacy Endpoint

- Part 2: ORR (confirmed complete response and partial response by modified RECIST)

Secondary Efficacy Endpoints

- Part 2: time to response, duration of response, and PFS

Primary Safety Endpoints

- Part 1: the incidence of adverse events and clinical laboratory abnormalities defined as DLT

Secondary Safety Endpoints

- Part 1: the incidence of adverse events and laboratory abnormalities not defined as DLT
- Part 2: the incidence of adverse events and laboratory abnormalities

Other Secondary Endpoints

- Parts 1 and 2: the incidence of anti-conatumumab antibody formation and anti-ganitumab antibody formation
- Parts 1 and 2: PK parameters of conatumumab and ganitumab

Statistical Methods

Data from part 1 and part 2 were analyzed separately. The primary analysis occurred after all subjects had the opportunity to complete 4 cycles of treatment, using a data cutoff date of 01 September 2010. The final analysis occurred after all subjects had progressed, died, or terminated the study for other reasons (part 1 and part 2), using a data cutoff date of 10 August 2011. The proportion of subjects with an objective response with corresponding 80% and 95% exact confidence intervals using the Clopper-Pearson method was presented for each cohort in part 1 and part 2. Progression-free survival was summarized using Kaplan-Meier curves and estimates.

Serum conatumumab and ganitumab concentrations were to be tabulated with descriptive statistics by study parts and cancer type cohorts.

The safety analyses included DLTs (part 1 and part 2); adverse events; clinical laboratory tests; and clinically significant changes in vital signs, electrocardiograms, and ECOG performance

status. The incidence of subjects developing anti-conatumumab antibodies or anti-ganitumab antibodies in at least 1 time point were summarized by cohort and time point.

Summary of Results

Subject Disposition: In part 1 of the study, 9 subjects were enrolled and received study treatment (3 subjects per dose group: conatumumab 1 mg/kg, conatumumab 3 mg/kg, and conatumumab 15 mg/kg, each administered with ganitumab 18 mg/kg Q3W). As of the final analysis, 5 (56%) subjects had discontinued the study due to death; the remaining 4 (44%) subjects discontinued after withdrawing consent (2 subjects) or due to loss to follow-up (2 subjects). The most common reason for subjects discontinuing protocol-specified treatment was disease progression (8 of the 9 subjects [89%]), and the reason was death for the remaining subject.

In part 2, 80 subjects were enrolled and 78 were treated. As of the final analysis, 6 (8%) subjects completed the study and 74 (93%) discontinued the study, most commonly due to death (40 subjects; 50%). The most common reason for subjects discontinuing an investigational product was disease progression (conatumumab: 78% of subjects; ganitumab: 76% of subjects).

Baseline Demographics

Sex: [redacted]; part 2 - 39 men (50%), 39 women (50%)

Age: part 1 - mean age [redacted] (range: [redacted]); part 2 - mean age 58.8 years (range: 29 to 83)

Ethnicity/Race: [redacted]; part 2 - 65 white (83%), 6 black (8%), 5 Asian (6%), 1 Hispanic (1%), 1 Japanese (1%)

Efficacy Results: In part 1, 1 subject (11%) with advanced, metastatic myxofibrosarcoma in the conatumumab 1 mg/kg + ganitumab 18 mg/kg dose group was an objective responder, with a confirmed partial response. In part 2, at the time of the primary analysis, no subjects were objective responders, although 1 subject in the CRC disease cohort had an unconfirmed partial response after 14 cycles of treatment as of the cutoff date for the analysis. As of the date of the final analysis of part 2, 1 subject (1%) in the CRC disease cohort had an objective response (confirmed partial response) and 27 (35%) subjects in part 2 of the study achieved stable disease.

The efficacy endpoints that were summarized included PFS for part 1 (final analysis) and part 2 (primary and final analyses) and overall survival for the part 1 final analysis and part 2 final analysis. The median PFS at all 3 analysis points was 1.6 months. The survival data in both part 1 and part 2 were not mature, with almost half of the subjects censored; the median time to death was 11.0 months and 8.7 months, respectively; and the 6-month survival rate was 74.1% and 58.3%, respectively.

[redacted]

Pharmacokinetic Results: In part 1, following IV infusion of conatumumab at 1, 3, or 15 mg/kg Q3W in combination with ganitumab at 18 mg/kg Q3W, conatumumab serum concentrations increased approximately linearly with increase of dose, and ganitumab serum concentrations were generally similar across cohorts.

In part 2, following IV infusion of conatumumab at 15 mg/kg Q3W in combination with ganitumab at 18 mg/kg Q3W, there was no apparent difference in either conatumumab or ganitumab exposures across cohorts in subjects with different types of advanced, solid, refractory tumors. Slight drug accumulation was observed in both conatumumab and ganitumab under the Q3W regimen.

Safety Results: In part 1 of the study, no subjects experienced DLTs. All 9 subjects experienced at least 1 treatment-emergent adverse event; the 3 most commonly reported events were fatigue (4 subjects [44%]), dyspnea (3 subjects [33%]), and anemia (3 subjects [33%]). The subject incidence of treatment-emergent adverse events of grade ≥ 3 was 56%. Dyspnea was the only event reported in 2 (22%) subjects. A total of 4 (44%) subjects experienced 1 or more serious adverse events. The adverse event for 1 (11%) of these 4 subjects was fatal (dyspnea, which was not considered related to either investigational product but rather due to disease progression). No treatment-emergent adverse event led to discontinuation of the study or protocol-specified treatment. The subject incidence of shifts in laboratory values from baseline grade 0 to 2 to postbaseline grade 3 or 4 was low (2 subjects).

In the absence of DLTs in part 1 of the study, the conatumumab dose chosen for use in part 2 was the maximum targeted dose, 15 mg/kg. The part 2 summaries of treatment-emergent adverse events in the primary analysis and final analysis were comparable; there were few changes noted between the data cutoff dates for the primary and final analyses, and no new safety signals were noted. The incidence of treatment-emergent adverse events was 91% in both analyses. Treatment-emergent adverse events reported most frequently in the final analysis (> 20%) in part 2 included fatigue (30 subjects [38%]), decreased appetite (24 subjects [31%]), chills (22 subjects [28%]), and nausea (19 subjects [24%]). The incidence of treatment-emergent adverse events of grade ≥ 3 was also unchanged between the primary and final analyses: adverse events of grade ≥ 3 were reported in 28 subjects (36%). Those reported in ≥ 2 subjects were dyspnea (5% [4 subjects]), deep vein thrombosis (4% [3 subjects]), fatigue (4% [3 subjects]), and thrombocytopenia (4% [3 subjects]).

Serious treatment-emergent adverse events in part 2 of the study were reported in 19 subjects (24%) in the primary analysis and 20 subjects (26%) in the final analysis. Three subjects (4%) experienced fatal adverse events in the primary analysis, none of which were considered related to investigational product: 1 subject with respiratory distress, 1 subject with malignant neoplasm progression, and 1 subject with acute respiratory failure. No additional subjects experienced fatal adverse events at the time of the final analysis.

No treatment-emergent adverse events led to study discontinuation during part 2 of the study. Four subjects (5%) discontinued ganitumab due to adverse events and 3 subjects (4%) discontinued conatumumab as of the primary analysis. No additional discontinuations occurred at the time of the final analysis.

The subject incidence of shifts in laboratory values from baseline grade 0 to 2 to postbaseline grade 3 was low during part 2 of the study: as of the final analysis, 9 subjects had such shifts in chemistry values and 9 subjects had shifts in hematology values. For most subjects with worsening shifts to grade 3, the grade 3 value occurred only once. There were no shifts to grade 4.

Analyses of antibody data at the primary analysis showed that 1 subject (nonsquamous NSCLC) tested positive for anti-ganitumab antibodies after receiving treatment but tested negative for neutralizing antibodies.

Conclusions: No DLTs were reported in part 1 of this study; thus, the dose of conatumumab selected for part 2 was 15 mg/kg. Treatment with the combination of conatumumab 15 mg/kg plus ganitumab 18 mg/kg Q3W demonstrated a safety profile that was consistent with the known safety profile of both conatumumab and ganitumab. No new safety signals associated with either investigational product were observed. Efficacy data based on the treatment of subjects with refractory solid tumors demonstrated a low response rate, with an ORR of 1% (1 subject). While the part 2 statistical hypothesis for demonstrating treatment activity (ie, at least 3 objective responses out of 15 evaluable subjects in at least 1 cohort) was thus rejected in 4 of 6 cohorts, no conclusion can be drawn in the squamous NSCLC and ovarian cancer cohorts due to premature suspension of enrollment. In addition, the median PFS was 1.6 months following treatment with conatumumab combined with ganitumab. The pharmacokinetics of conatumumab was linear and did not appear to be affected by ganitumab coadministration. The pharmacokinetics of ganitumab was generally comparable when in combination with different dose levels of conatumumab, indicating little impact of conatumumab coadministration on the pharmacokinetics of ganitumab. Based on the limited number of subjects, there was no remarkable difference in

either conatumumab or ganitumab concentrations across cohorts in subjects with different types of advanced solid refractory tumors.