## 2. SYNOPSIS

**Name of Sponsor:** Amgen Inc., Thousand Oaks, CA USA

**Name of Finished Product:** Conatumumab (AMG 655)

**Name of Active Ingredient:** Fully human monoclonal agonist antibody (immunoglobulin class $G_1$ [$IgG_1$]) against human DR5

**Title of Study:** A Phase 1b/2 Study of AMG 655 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Non-Small Cell Lung Cancer

**Investigator(s) and Study Center(s):** Part 1 of this study was conducted at 5 study centers in Europe and Australia. Part 2 was conducted at 41 study centers in North America, Eastern and Western Europe, and Australia. Investigators are listed in Appendix 4.

**Publication(s):** None

**Study Period:** 8 August 2007 (first subject enrolled, part 1), total of 12 subjects enrolled in part 1 and 172 subjects in part 2, 112 subjects continuing in study as of data cut-off date of 9 April 2009.

**Development Phase:** 1b/2

**Introduction and Objectives:**

Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL) is a transmembrane protein that is a member of the Tumor Necrosis Factor (TNF) super-family of cytokines expressed on a wide variety of normal human tissues (Pitti et al, 1996; Wiley et al, 1995). TRAIL specifically binds to 4 distinct cell surface receptors that are constitutively expressed on both normal tissues and transformed (cancer) cells. Two of these receptors, TRAIL receptor 1 (TR1, also known as death receptor 4 [DR4]) and TRAIL receptor 2 (TR-2, also known as death receptor 5 [DR5]), contain a cytoplasmic death domain and can transduce an apoptotic signal into the cell (Almasan and Ashkenazi, 2003; Ashkenazi, 2002). A wide variety of transformed cell lines are sensitive to TRAIL-induced apoptosis. Most normal cells are resistant to ligand or receptor agonist, antibody-induced apoptosis even though they express both DR4 and DR5 (Eggert et al, 2001; Griffith et al, 1998).

Conatumumab (also known as AMG 655) is a fully human monoclonal agonist antibody that binds to DR5 and mimics the effect of endogenous TRAIL, triggering death of ligand sensitive cells. A phase 1 clinical study of conatumumab monotherapy (up to 20 mg/kg) in subjects with advanced tumors refractory to standard treatment demonstrated that conatumumab was generally well tolerated. A maximum tolerated dose was not reached and no dose-limiting toxicities were observed. At least 2 subjects showed evidence of clinical activity as demonstrated by a RECIST response or disease stabilization of substantial duration. This report presents results of a phase 1b/2 clinical study investigating the safety, tolerability, and preliminary efficacy of conatumumab treatment in combination with paclitaxel and carboplatin for subjects with advanced non-small-cell lung cancer (NSCLC).

The primary objectives of this study were as follows:

- Part 1 (Phase 1b)

  Determine the maximum tolerated dose up to a target dose of 15 mg/kg of conatumumab that can be administered in combination with paclitaxel/carboplatin.

- Part 2 (Phase 2)

  Estimate the efficacy of conatumumab as assessed by progression-free survival (PFS) time (at 2 doses selected in part 1) in combination with paclitaxel/carboplatin.

The secondary objectives were as follows:

- Part 1 (Phase 1b)
  - Evaluate the safety and tolerability of escalating doses of conatumumab in combination with paclitaxel/carboplatin.
  - Evaluate parameters of clinical benefit as measured by objective response rate, duration of response, time-to-response, PFS, and overall survival.
  - Evaluate the pharmacokinetics of conatumumab.
  - Evaluate anti-conatumumab antibody formation.
- Part 2 (Phase 2)
  - Estimate the clinical benefit of conatumumab in combination with paclitaxel/carboplatin as measured by overall objective response rate, duration of response, time-to-response, and overall survival.
  - Evaluate the safety and tolerability of conatumumab in combination with paclitaxel/carboplatin.
  - Evaluate the pharmacokinetics of conatumumab.
  - Evaluate anti-conatumumab antibody formation.

This CSR is written based on the results of the primary analysis (data cut-off 09 April 2009) except for the analysis of overall survival from part 2. At the time of primary analysis, only 59 deaths occurred, and the last subject randomized had only 5 months of follow-up. The median survival for stage IIIb/IV subjects receiving carboplatin and paclitaxel is generally 9 months. The overall survival data is analyzed based on a data cut-off date of 25 January 2010 to have more than 12 months of follow-up and around 70% of deaths. The prognostic and predictive effects of Fc-Gamma Receptor 3A subtypes and DR5 expression are analyzed on the data cut of 25 January 2010.

**Methodology:**

Subjects who met the eligibility criteria and provided written consent were enrolled and received study treatment in this 2-part study. In part 1, the open-label, dose-escalation segment, conatumumab was tested in 2 sequential dose levels consisting of 6 subjects each. The starting dose was 5 mg/kg administered by intravenous infusion on day 1 of each 21-day cycle (up to 6 cycles) after treatment with paclitaxel/carboplatin. After data safety review at this dose level,

the next 6 subjects were treated at 15 mg/kg conatumumab using the same dosing schedule (ie, after receipt of chemotherapy infusions).

Part 2 was a multicenter, randomized, double-blind, placebo-controlled, phase 2 segment wherein subjects were randomized at a 1:1:1 ratio to 1 of 3 treatment arms. Arm 1 was paclitaxel/carboplatin plus 15 mg/kg conatumumab, arm 2 was paclitaxel/carboplatin plus 3 mg/kg conatumumab, and arm 3 was paclitaxel/carboplatin plus placebo.

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and disease stage (IIIb or IV/recurrent). Paclitaxel (200 mg/m$^2$) and carboplatin (AUC = 6 mg/mL•minute) in combination with conatumumab (arm 1 and arm 2) or placebo (arm 3) were administered on day 1 of each 21-day cycle for up to 6 cycles.

Radiological imaging to evaluate tumor response was performed every 6 weeks (± 7 days) from study day 1 (independent of treatment cycle) until disease progression.

Visits during the chemotherapy cycles and during the monotherapy phase were performed every 3 weeks ± 3 days. After the last dose of protocol-specified therapy, each subject was followed for 30 days (+3 days) or until the resolution of any treatment emergent adverse events and at least 60 days (+14 days) for anti-conatumumab antibody formation and conatumumab pharmacokinetics.

All subjects were to be followed up to 36 months after the last subject on the study was randomized.

Additional details of the study design and investigational plan are provided in Section 7.

**Number of Subjects Planned:** The planned sample size was 12 to 18 subjects in part 1 and 150 subjects (50 subjects randomized 1:1:1 to each of 3 arms) in part 2.

**Number of Subjects Enrolled:** 12 subjects were enrolled in part 1 and 172 subjects in part 2.

- **Sex:** [redacted] in part 1; 116 (67%) men and 56 (33%) women in part 2
- **Age:** Mean age [redacted] in part 1; mean age 59.9 years (range 27 to 81 years) in part 2
- **Ethnicity (Race):** [redacted] in part 1; 97% White/Caucasian, 1% Hispanic/Latino, and 2% Asian in part 2

**Diagnosis and Main Criteria for Eligibility:**

The main inclusion criteria for study subjects included, but were not limited to, men or women ≥ 18 years old (using adequate birth control) with histologically or cytologically confirmed advanced NSCLC defined as stage IIIB with malignant pleural effusion, stage IV, or recurrent disease and an ECOG performance status ≤ 1. Eligible subjects must not have had previous chemotherapy or chemoradiation for NSCLC, untreated or symptomatic central nervous system metastases, and must not have been under treatment or previously treated with biologic, small-molecule immunotherapy or other agents to treat advanced NSCLC.

A complete list of inclusion/exclusion criteria is provided in Section 7.5.

**Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number:**

Conatumumab and conatumumab placebo were considered investigational products in this study. Conatumumab was provided as a sterile, clear, colorless protein solution in single-use glass vials,

containing 3.0 mL of study medication with a concentration of 30 mg/mL. Conatumumab was diluted in [redacted] or [redacted] in a minimum [redacted] and administered by continuous intravenous infusion via controlled infusion pump over 60 minutes (for the first 2 cycles in part 1 and the first dose in part 2) and over 30 minutes for subsequent doses. The following dose levels were evaluated: 5 and 15 mg/kg (part 1); 3 and 15 mg/kg (part 2).

Conatumumab lot numbers [redacted] were used for part 1 of the study. Conatumumab lot numbers for part 2 of the study are provided in Listing 14-1.4, Part 2.

Placebo (part 2 only) was provided as sterile, clear, colorless solution in single-use glass vials (identical to those used for conatumumab) containing 3.0 mL of vehicle. Placebo was diluted in [redacted] or [redacted] in a minimum volume of [redacted] and administered by continuous intravenous infusion via controlled infusion pump over 60 minutes (for the first dose in part 2) and over 30 minutes for subsequent doses. Placebo lot numbers are provided in Listing 14-1.4, Part 2.

**Duration of Treatment:** Selection of a dose for part 2 was expected to occur over an 8-month period in part 1. The subject accrual period for part 2 (randomized segment) was estimated to be approximately 12 months. The maximum duration of the study was expected to be approximately 56 months as measured from the first subject enrolled in part 1 until approximately 36 months from the last subject randomized in part 2.

**Reference Therapy, Dose and Mode of Administration, and Manufacturing Batch Number:** Supplies of standard chemotherapy used in this study (paclitaxel [200 mg/m$^2$ infused over 3 hours ± 30 minutes] and carboplatin [AUC = 6.0 mg/mL•min infused over 30 ± 10 minutes] were obtained by investigators and administered intravenously based on approved product labeling in the region. Lot numbers were not collected.

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**Study Endpoints:**

- **Primary:** Part 1—the incidence of adverse events and clinical laboratory abnormalities defined as dose limiting toxicities; part 2—PFS (based on modified RECIST criteria or clinical progression)

- **Secondary:** Parts 1 and 2—objective response rate (complete and partial response as measured by RECIST with modification), duration of response, time-to-response, overall survival, PFS (part 1 only), PFS based on RECIST only (part 2 only), the incidence of adverse events and clinical laboratory abnormalities not defined as dose limiting toxicities, the incidence of anti-conatumumab antibody formation, and conatumumab pharmacokinetic parameters

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**Statistical Methods:** The data cut-off date for the primary analysis is 09 April 2009. Because only 59 deaths had occurred and the last subject randomized had only 5 months of follow-up at the 09 April 2009 cut-off, the overall survival data is analyzed based on a data cut-off date of 25 January 2010 to ensure more than 12 months of follow-up and around 70% of deaths present in the database.

All analyses were conducted separately for subjects in parts 1 and 2 of the study. Appropriate summary statistics were provided for all safety, efficacy, pharmacokinetic, antibody, and exploratory data by treatment group and time point, as appropriate. For continuous variables, the mean, standard deviation, median, first and third quartiles, minimum, and maximum were calculated. For categorical variables, the frequency and percentage in each category were displayed. Kaplan-Meier estimates were provided for time-to-event endpoints. Graphical summaries of selected endpoints were also presented. For any variable, baseline was defined as the last assessment prior to the first dose of study specified treatment (unless specified otherwise). Significance levels described were to be 2-sided, unless otherwise stated.

Two-sided 80% and 95% confidence intervals (CIs) were to be used to assess efficacy endpoints. No adjustments were to be made for multiple comparisons.

Efficacy Analyses:

The efficacy analysis was conducted on the safety analysis set (part 1) and full analysis set (part 2). The analysis of the tumor response endpoints (objective response rate, best overall response, disease control rate, sum of the target lesions, and duration of response and time-to-response) included the subset of subjects within the safety (part 1) and full analysis sets (part 2) that have measurable disease at baseline. Additionally, the analysis of duration of response and time-to-response were performed only on those subjects with an objective response. Sensitivity analyses were conducted for efficacy endpoints in part 2 of the study if greater than or equal to 10% of subjects in either treatment group have prespecified important deviations thought to impact the efficacy results by using a per protocol (PP) analysis set.

*Progression-free Survival Analysis of Part 1*:

For part 1 subjects, PFS was summarized using the Kaplan-Meier method. The definition of PFS time for part 1 subjects is described in the SAP. Censoring was handled in accordance with the primary censoring strategy defined for the primary analysis.

*Primary Analysis (Part 2)*:

The primary method of analysis used a stratified Cox's proportional hazards model, stratified by ECOG status (0 or 1) and disease stage (IIIb or IV/recurrent) (in accordance with the final pooling strategy) as collected via IVRS at the time of randomization. The estimated hazard ratios were presented together with associated 80% and 95% CIs for the following treatment comparisons.

1. Arm 1 (high dose of conatumumab, 15 mg/kg) and arm 2 (low dose of conatumumab, 3mg/kg) combined relative to arm 3 (placebo)

2. Arm 1 (high dose of conatumumab, 15 mg/kg) relative to arm 3 (placebo)

3. Arm 2 (low dose of conatumumab, 3mg/kg planned) relative to arm 3 (placebo); these analyses were also repeated without stratification for the stratification factors

*Secondary Analysis (Part 2)*:

The primary PFS analyses (Kaplan-Meier, Cox proportional hazard models, piecewise Cox model, and Tarone's trend test) were repeated, excluding clinical progression as an event, and for overall survival. In this instance, PFS was calculated for those subjects who have a disease progression based on RECIST criteria only. If ≥ 10% of subjects had different baseline values for the stratification factors recorded on the eCRF compared with the data collected by IVRS at the time of randomization, the stratified Cox proportional model and stratified Tarone's test were repeated for the primary PFS endpoint (including radiological and clinical progression) and the analyses were stratified by the baseline values of the stratification factors recorded on the eCRF.

*Sensitivity Analysis due to Time or Ascertainment Bias (Part 2)*:

To investigate the impact of any imbalances in the timing and frequency of disease assessments or in the number of deaths that were remote from the last disease assessment between treatment arms, sensitivity analyses (specified in the SAP) were conducted on the primary PFS endpoint (unless stated otherwise) after making the stated adjustments to the calculation of the PFS time.

*Analyses of Subsets and Covariates (Part 2)*:

[redacted]

*Multivariate Analysis (Part 2)*:

[redacted]



Safety:

The safety analyses included DLTs (part 1), adverse events, clinically significant changes in vital signs, ECGs, clinical laboratory tests, and the presence of antibodies to conatumumab. All safety analyses were descriptive in nature, and there were no specified tests for treatment comparisons.

Pharmacokinetics:

Serum conatumumab and plasma paclitaxel and carboplatin concentrations were tabulated, and descriptive statistics (means, standard deviations, median, minimums, and maximums) were calculated for each sampling time point using WinNonlin. All serum or plasma concentrations below the quantification limit (BQL) were set to 0.

**Summary of Results:**

Subject Disposition:

*Part 1*:

A total of 13 subjects were screened and 12 subjects were enrolled at 5 investigative centers in Australia, Belgium, and Spain. Six subjects received the 5 mg/kg conatumumab dose and 6 subjects received the 15 mg/kg conatumumab dose. One subject in the 5 mg/kg dose group was ongoing in the study at the time of data cut-off, but has discontinued all protocol-specified therapy due to disease progression. The remaining 11 subjects discontinued the study due to death (10 subjects) or protocol deviation (1 subject). The mean time on study was 9.30 and 8.36 months for subjects in the 5 mg/kg and 15 mg/kg dose groups, respectively. The 2 conatumumab dose groups were generally similar in terms of demography and baseline characteristics. The one exception was in tumor cell type where 3 of the 6 subjects in the 5 mg/kg dose group had squamous cell histology and no subjects in the 15 mg/kg dose group had squamous cell histology.

*Part 2*:

A total of 172 subjects were randomized at 41 investigative centers in 4 regions: 27 in Australia, 10 in North America (Canada), 75 in Eastern Europe (Czech Republic, Hungary, and Poland), and 60 in Western Europe (Belgium, France, and Spain). Fifty-seven were randomized to receive conatumumab 3 mg/kg plus cotherapy, 56 were randomized to receive conatumumab 15 mg/kg plus cotherapy, and 59 were randomized to receive placebo plus cotherapy, where cotherapy was paclitaxel and carboplatin. Five subjects did not receive investigational product; 3 subjects were in the 15 mg/kg conatumumab group, 1 subject was in the 3 mg/kg conatumumab group, and 1 subject was in the placebo group. Investigational product was discontinued in 74% of subjects in the conatumumab arms, most often as the result of disease progression (53% of total subjects; range of 48 to 56% across treatment groups). This was similarly the case for the cotherapies alone arm. Overall, 34 subjects in the 3 mg/kg conatumumab dose group, 36 subjects in the 15 mg/kg conatumumab dose group, and 41 subjects in the placebo dose group are still on study. At the time of data cut-off, 71 of these subjects have discontinued all protocol-specified therapy, 35 are still receiving investigational product after completing cotherapy, and 5 are still receiving investigational product after discontinuing cotherapy early. The mean time on study was comparable between treatment groups (5.6 months for the conatumumab 3 mg/kg dose group, 5.8 months for the conatumumab 15 mg/kg dose group, and 5.9 months for the placebo dose group).

All subjects randomized presented with NSCLC; the histological subtype of NSCLC was identified as adenocarcinoma in 50% of subjects, squamous cell carcinoma in 26% of subjects, other histological type in 16% of subjects, large cell carcinoma in 6% of subjects, and bronchoalveolar carcinoma in 2% of subjects. The histological subtypes were balanced among the treatment groups. Ninety-one percent of subjects had stage IV disease at enrollment, and, per protocol, all subjects had ECOG performance status of 0 or 1 with 70% having ECOG 1. The treatment groups were balanced for each of these demographic and disease characteristics.

Efficacy Results:

*Part 1*:

There were too few subjects (10/12 subjects who died) to draw any meaningful conclusions regarding the PFS or survival data. One subject from the 5 mg/kg conatumumab dose group and 3 from the 15 mg/kg conatumumab dose group had objective responses.

*Part 2*:

There were no statistically significant or clinically meaningful differences between treatment groups for the primary endpoint of PFS, based on both primary and secondary analyses. The results of sensitivity analyses demonstrated that these results were robust. The median PFS time (Kaplan-Meier) for the combined conatumumab groups was 5.3 months versus 5.5 months for the placebo group. The stratified hazard ratio (95% CIs) for PFS for the combined conatumumab group versus placebo was 1.03 (0.70, 1.50).

Secondary endpoints (which included objective response, duration of response, time to response, disease control rate, and sum of longest tumor diameter) also demonstrated no statistically significant or clinically meaningful differences between the treatment groups.

There were no statistically significant differences among treatment groups for overall survival. The updated analysis of overall survival revealed a median survival time of 12.3, 11.4, and 7.8 months for the 3 mg/kg conatumumab group, 15 mg/kg conatumumab group, and placebo group, respectively. The unstratified hazard ratios (95% CIs) for overall survival were 0.80 (0.52, 1.24) and 0.84 (0.54, 1.30) for the 3 mg/kg and 15 mg/kg conatumumab groups versus placebo, respectively.

Results from the forward stepwise progression analysis of prognostic factors indicated that the inclusion of gender and ECOG were statistically significant (p = 0.009 and 0.013, respectively). The hazard ratio (95% CIs) for gender (female vs male) was 0.58 (0.38, 0.87) and for ECOG (1 vs 0) was 1.69 (1.11, 2.55). A piecewise model of overall survival suggested that conatumumab demonstrated a more pronounced trend of overall survival improvement after 6 months compared to the first 6 months of the study.



Safety Results:

*Part 1*:

Treatment-emergent adverse events (TEAEs) were reported for all 12 subjects. The most frequently reported TEAEs were fatigue, arthralgia, myalgia, dyspnea, nausea, anorexia, alopecia, and neutropenia. There appeared to be no differences in the frequencies, severities, or timeframe of these TEAEs with dose, except for a higher incidence of nausea (5 subjects versus 2 subjects) and vomiting (4 subjects versus 0 subjects) in the 15 mg/kg conatumumab dose group than the 5 mg/kg conatumumab dose group.

Most of the treatment-related adverse events (TRAEs), which occurred in all subjects, were judged by the investigator to be related to chemotherapy rather than conatumumab. Those TRAEs reported as being at least possibly related to conatumumab were fatigue (8 events in 3 subjects); lung infiltration (2 subjects); muscular weakness, blurred vision, and hyponatremia (2 events in 1 subject each); and increased lipase, increased blood amylase, rash, pulmonary embolism, mucosal inflammation, hypokalemia, anorexia, hypoesthesia, peripheral edema, pain in extremity, nausea, and alopecia (1 subject each). All of the TRAEs reported as being at least possibly related to conatumumab were grade 1 or 2 in severity with the exception of pulmonary embolism, hyponatremia, and increased lipase.

Grade 3 to 4 TEAEs consisted of myelosuppressive effects, nervous system effects, drug hypersensitivity, gastrointestinal effects, infections, musculoskeletal effects, and pulmonary effects.

The only grade 3 TEAE that was considered a DLT for conatumumab was grade 3 hyponatremia. This event was reported in 1 subject in the 15 mg/kg conatumumab group, and the event resolved to grade 1 after discontinuation of paclitaxel, carboplatin, and conatumumab. Other grade 3 to 4 TEAEs that were considered possibly related to conatumumab administration were grade 3 increased lipase and grade 4 pulmonary embolism, which occurred in 1 subject each.

The TEAE for grade 4 pulmonary embolism, which was reported as an SAE, occurred on day 4 of the study during cycle 1 and was considered related to both conatumumab and paclitaxel/carboplatin chemotherapy.

Nine SAEs were reported in 3 subjects. In general, these SAEs were related to respiratory symptoms and included dysnpea, cough, hydropneumothorax, pyothorax, and respiratory tract infection. Dyspnea was the most frequently reported SAE, occurring in a total of 2 subjects. The only SAEs that were considered related to conatumumab treatment were hypokalemia and hyponatremia (the latter identified as a DLT), which led to discontinuation of conatumumab treatment in 1 subject in the 15 mg/kg conatumumab dose group.

No subjects were withdrawn from the study due to TEAEs. One subject in the 15 mg/kg conatumumab dose group who experienced a DLT (hyponatremia) during the study discontinued investigational product and chemotherapy due to TEAEs of hyponatremia, hypokalemia, respiratory tract infection, pyothorax, and hydropneumothorax. Paclitaxel and carboplatin cotherapy was discontinued in 3 other subjects due to TEAEs of neutropenia (1 subject in the 5 mg/kg conatumumab dose group), peripheral sensory neuropathy (1 subject in the 5 mg/kg conatumumab dose group), and peripheral neuropathy (1 subject in the 15 mg/kg conatumumab dose group).

Of the 12 subjects enrolled in the study, 1 subject died due to an adverse event (an event of cardiac failure in a subject in the 15 mg/kg conatumumab dose group). This event was reported by the investigator as unrelated to treatment with conatumumab or chemotherapy.

No subjects tested positive for anti-conatumumab antibodies.

No trends in laboratory hematology or chemistry values were noted. Other safety data, such as vital signs, ECGs, ECOG performance status, and concomitant medications, also show no clear safety signals.

*Part 2*:

Overall, the percentage of subjects reporting at least 1 TEAE was lower in the 3 mg/kg conatumumab group (89%) compared with the 15 mg/kg conatumumab and placebo groups (96% and 95%, respectively). The most frequently reported TEAEs across all treatment groups included alopecia, fatigue, nausea, dyspnea, neutropenia, and anorexia. There appeared to be a higher incidence of TEAEs reported for thrombocytopenia and insomnia (3 mg/kg and 15 mg/kg) and diarrhea (15 mg/kg) in conatumumab-treated subjects and a higher incidence of TEAEs for constipation and weight decrease in placebo-treated subjects.

In general, the most frequently reported TRAEs were consistent with those most often reported from the overall TEAEs presentation, and most were judged by the investigator to be related to chemotherapy rather than conatumumab.

The incidences of grade 3 to 4 TEAEs were generally balanced between the treatment groups, with the exception of a higher incidence in the conatumumab treatment groups of grade 3 to 4 TEAEs for anemia (11%, 9%, and 2% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively), thrombocytopenia (12%, 8%, and 2% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively), and a higher incidence in the placebo group of grade 3 to 4 TEAEs for anorexia (0%, 0%, and 5% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively).

Overall, treatment-emergent SAEs were reported in 37%, 32%, and 37% of subjects in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively. The most frequently reported events included events of dyspnea, neutropenia, anemia, and pyrexia, which each occurred in ≤ 5% of all subjects. In general, these serious adverse events were evenly distributed across the treatment groups. SAEs that were attributed to study treatment occurred in

5 subjects and included hypotension, renal impairment, and small bowel obstruction (3 mg/kg conatumumab); dysnpea and pulmonary embolism (conatumumab 15 mg/kg); and atrial fibrillation and dyspepsia (placebo).

Two subjects in the safety analysis set were withdrawn from the study due to adverse events of febrile neutropenia (1 subject in the placebo dose group) and decreased platelet count (1 subject in the 15 mg/kg conatumumab dose group). Overall, 18 subjects discontinued investigational product due to TEAEs. TEAEs that led to discontinuation of study medication occurred in 17% of subjects in the 15 mg/kg conatumumab group compared with 7% of subjects in the 3 mg/kg conatumumab group and 9% of subjects in the placebo group. Neutropenia was the most frequently reported TEAE leading to discontinuation of conatumumab. Twenty subjects discontinued paclitaxel and carboplatin cotherapy due to TEAEs. As with investigational product discontinuation, a higher proportion of subjects in the 15 mg/kg conatumumab dose group (19%) experienced TEAEs resulting in discontinuation of chemotherapy compared with subjects in the 3 mg/kg conatumumab dose group (9%) or placebo group (9%). Again, neutropenia was the most frequent cause of discontinuation of chemotherapy.

Thirteen subjects experienced fatal TEAEs; these events were reported for 4 subjects in the 3 mg/kg conatumumab group, 4 subjects in the 15 mg/kg conatumumab group, and 5 subjects in the placebo group. The types of fatal TEAEs were similar across the 3 treatment groups and included respiratory and cardiovascular events along with multiorgan failure and general deterioration. None of the TEAEs that resulted in death were attributed to the use of conatumumab; they were considered related to the subjects underlying disease or concomitant chemotherapy.

Events of interest that were analyzed during this study included infusion-related reactions, hyponatremia and hypomagnesemia, elevations in amylase and lipase, and immunogenicity (anti-conatumumab antibody) testing. Infusion-related reactions were defined in 2 ways: investigator-identified and sponsor-identified. The latter consisted of hypersensitivity terms and CTCAE Version 3.0 defined terms for cytokine release syndrome that occurred on the day of dosing or the day after dosing with a duration of ≤ 2 days. The most frequently reported events of sponsor-identified, infusion-related reactions within the conatumumab dose groups were dyspnea, nausea, vomiting, and pyrexia. The investigator-identified terms included mostly TRAEs that were attributed to conatumumab or chemotherapy administration but were not necessarily related to the infusion of a biologic.

The incidences of TEAEs for hypomagnesemia and hyponatremia were low and all were grade 1 or 2 with the exception of a grade 3 TEAE, which was reported in 1 placebo subject for hyponatremia.

Elevations in lipase and amylase were not frequently reported as TEAEs. Laboratory data reported a low but similar incidence of grade 3 to 4 increases in these enzymes across the conatumumab and placebo treatment groups. There were no clinical sequelae associated with the increases in amylase and lipase.

Analyses of laboratory data showed shifts from normal baseline values to grade 3 to 4 postbaseline values for hematologic parameters such as ANC, WBC, and platelets. This was an expected effect of paclitaxel and carboplatin therapy, and the incidence of these grade 3 to 4 shifts was similar across the treatment groups. Analysis of chemistry values showed a low incidence of grade 3 to 4 values with no clear imbalances across the treatment groups.

Other safety data including vital signs, ECGs, ECOG performance status, and concomitant medications showed no clear safety signals across treatment groups.

Other Evaluations:

*Pharmacokinetics:* Based on pharmacokinetic analysis from subjects receiving intravenous infusions of 3, 5, or 15 mg/kg conatumumab every 3 weeks (Q3W) in combination with paclitaxel and carboplatin, conatumumab exhibited approximately linear pharmacokinetics. Conatumumab concentration data observed after coadministration with paclitaxel and carboplatin were similar to those observed in the first-in-human (FIH) study where conatumumab was administered as a monotherapy, indicating no impact of paclitaxel and carboplatin on conatumumab exposures. In addition, small differences of paclitaxel and carboplatin exposures between placebo and conatumumab-treated groups were observed, indicating little impact on paclitaxel and carboplatin exposures following treatment with conatumumab.

*Antibody Assays:* Of the few (7 subjects) positive anti-conatumumab immunoassay results, all were either detected prior to conatumumab treatment or were negative for neutralizing antibodies based on the cell-based bioassay. There were no adverse events associated with positive antibody results.

*Biomarker results*: There may be a small difference in overall survival for patients in the conatumumab + cotherapy arm who carry the V allele (FV or VV) on FCGR3A 158; however, the small sample size precluded any conclusions. No notable difference between treatment arms in PFS time or objective response rate was observed when stratified by FCGR3A 158 genotype.

No difference in cell death analytes between the conatumumab + cotherapy group and the cotherapy alone group was observed; however, the small sample size and window of detection limited definitive conclusions. No dose-dependent increase in any of the cell death markers was observed in phase 2 patients. There was no correlation between increase in cell death analytes and responses or histology subtypes. There was also no correlation between increase in cell death analytes and FCGR3A genotypes.

**Conclusions:**

The overall conclusions of the study are as follows:

Part 1:

- One DLT (hyponatremia) was reported at the 15 mg/kg of conatumumab dose; however, a maximally tolerated dose (MTD) was not reached in this study.
- Conatumumab at both the 5 mg/kg and 15 mg/kg doses was generally well tolerated when given in combination with paclitaxel and carboplatin.
- Evidence of clinical benefit was demonstrated in 4 (1 complete response and 3 partial responses) of 12 subjects although the contribution of conatumumab could not be determined without a comparator arm.

Part 2:

- There was no evidence of treatment effect of conatumumab on PFS when administered in combination with paclitaxel/carboplatin.
- The overall survival results as of 25 January 2010, demonstrated a longer median overall survival time in the combined conatumumab + cotherapy group (11.4 months) compared with the placebo + cotherapy group (7.8 months). The unstratified hazard ratios (95% CIs) for overall survival were 0.80 (0.52, 1.24) and 0.84 (0.54, 1.30) for the 3 mg/kg and 15 mg/kg conatumumab groups versus placebo, respectively. This effect was more pronounced after patients were in the study for > 6 months. It should be noted that the median overall survival

for the placebo group is at the lower end of the expected result for this cotherapy regimen in this patient population.

- Conatumumab at the 3 mg/kg and 15 mg/kg doses was generally well tolerated when administered in combination with carboplatin and paclitaxel. There were no new or exacerbated safety signals when conatumumab, at doses of 3 and 15 mg/kg, was added to advanced NSCLC standard-of-care chemotherapy.

## SYNOPSIS

**Name of Sponsor:** Amgen Inc., Thousand Oaks, CA USA

**Name of Finished Product:** Conatumumab (AMG 655)

**Name of Active Ingredient:** Fully human monoclonal agonist antibody (immunoglobulin class $G_1$ [$IgG_1$]) against human DR5

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**Title of Study:** A Phase 1b/2 Study of AMG 655 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Non-Small-Cell Lung Cancer

**Investigators and Study Centers:** Part 2 of the study was conducted at 41 study centers in North America, Eastern and Western Europe, and Australia. The principal investigators are listed in Attachment 2.

**Publication(s):** Pan Y, Haddad V, Sabin T, et al. Predictive value of Fc gamma receptor IIIa genotype in response to conatumumab in three phase II studies [abstract]. 2011 ASCO Annual Meeting Proceedings, Abstract 3103. J Clin Oncol, 2011:29(suppl).

**Study Period:** The first subject was enrolled in part 2 of the study on 28 January 2008 and the last subject's safety follow-up visit in part 2 of the study was 23 March 2011.

**Development Phase:** Phase 1b/2

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**Introduction and Objectives:**

Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL) is a type 2 trans-membrane protein that is a member of the Tumor Necrosis Factor (TNF) superfamily of cytokines expressed on a wide variety of normal human tissues (Pitti et al, 1996; Wiley et al, 1995). TRAIL specifically binds to 4 distinct cell surface receptors that are constitutively expressed on both normal tissues and transformed (cancer) cells. Two of these receptors, TRAIL receptor 1 (TR1) (also known as death receptor 4 [DR4]) and TRAIL receptor 2 (TR2) (also known as death receptor 5 [DR5]), contain a cytoplasmic death domain and can transduce an apoptotic signal into the cell (Almasan and Ashkenazi, 2003; Ashkenazi, 2002). A wide variety of transformed cell lines are sensitive to TRAIL-induced apoptosis. Most normal cells are resistant to ligand or receptor agonist, antibody-induced apoptosis even though they express both DR4 and DR5 (Eggert et al, 2001; Griffith et al, 1998).

Conatumumab (also known as AMG 655) is a fully human monoclonal agonist antibody that binds to DR5 and mimics the effect of endogenous TRAIL, triggering death of ligand sensitive cells. Activating DR5 may be an effective anti-cancer therapy in humans. There is also evidence that TRAIL receptor agonists act cooperatively with existing cancer therapies, including targeted agents.

Part 1 of this study identified a dose of conatumumab (15 mg/kg) in combination with paclitaxel and carboplatin that was acceptable as determined by the incidence of dose limiting toxicity (DLT).

The primary objective for part 2 of the study was to:

- Determine if treatment with conatumumab in combination with paclitaxel/carboplatin improves progression-free survival (PFS) compared with treatment with placebo in combination with paclitaxel/carboplatin in subjects with advanced non-small-cell lung cancer (NSCLC).

The secondary objectives for part 2 of the study were to evaluate:

- the clinical benefit of conatumumab in combination with paclitaxel/carboplatin as measured by overall objective response rate (ORR), duration of response, time-to-response, and overall survival (OS)
- the safety and tolerability of conatumumab in combination with paclitaxel/carboplatin
- the pharmacokinetics (PK) of conatumumab
- anti-conatumumab antibody formation

**Methodology:**

The primary analyses of PFS (data cutoff of 09 April 2009) and OS (data cutoff of 25 January 2010) were presented in the primary clinical study report (CSR) dated 28 June 2010. The current report summarizes the final study results as of a cut-off date of 02 June 2011. Table 1 summarizes the data cuts used for each of the data types summarized in the primary and final CSRs:

**Table 1. Data Cut-off Dates for Each Data Type Summarized in the Primary and Final Clinical Study Reports**
**Study 20060295**

| | Primary CSR | | Final CSR |
|---|---|---|---|
| Data type | 09 April 2009 Data cut-off | 25 January 2010 Data cut-off | 02 June 2011 Data cut-off |
| Subject Disposition | X | — | X |
| Demographic and baseline characteristics | X | — | X |
| Efficacy - PFS, ORR | X | — | X |
| Efficacy - OS | X | X | X |
| Efficacy - duration of response, time to response | X | — | — |
| Safety - AEs, labs, EOIs | X | — | X[a] |
| Safety - ECOG, vital signs, ECGs, concomitant meds | X | — | — |
| PRO | X | X | — |
| PK | X | — | X[b] |
| Antibody | X | — | X |
| Biomarker | X | — | — |

[a] = Due to changes in the search strategies for EOIs, different analyses are provided in the final report.
[b] = Only PK data for new samples not analyzed in the primary CSR are included in the final CSR.
"—" = no data analysis performed, PFS = progression free survival, ORR = objective response rate, OS = overall survival, AE = adverse events, ECOG = Eastern Cooperative Oncology Group, ECG = electrocardiogram, EOI = events of interest, PRO = patient reported outcomes, PK = pharmacokinetics.

The purpose of this synopsis report is to provide the final subject disposition, efficacy, safety, PK, and antibody results for part 2 of the study. Final results from part 1 of the study and preliminary results from part 2 were previously presented in the primary report (dated 28 June 2010).

Part 2 of the study was a multicenter, randomized, double-blind, placebo-controlled study and evaluated the safety and efficacy of the combination of paclitaxel and carboplatin with conatumumab in subjects with advanced non-small-cell lung cancer. Subjects were randomized at a 1:1:1 ratio to 1 of 3 treatment arms. The first arm was paclitaxel/carboplatin plus 15 mg/kg conatumumab, the second arm was paclitaxel/carboplatin plus 3 mg/kg conatumumab, and the third arm was paclitaxel/carboplatin plus placebo. Subjects were to receive paclitaxel/carboplatin and conatumumab or placebo for up to 6 cycles followed by conatumumab or placebo monotherapy until disease progression, intolerability, withdrawal of consent, or 30 months from the first administration of study treatment.

Randomization was stratified by Eastern Cooperative oncology Group (ECOG) performance status (0 or 1) and disease stage (IIIb or IV/recurrent). Paclitaxel (200 mg/m$^2$) and carboplatin (AUC = 6 mg/mL•minute) in combination with conatumumab or placebo were administered on day 1 of each 21-day cycle for up to 6 cycles. "Conatumumab arm" and "placebo arm" refer to the investigational product; all subjects in both treatment arms also were administered paclitaxel and carboplatin at the doses specified.

Radiological imaging was performed every 6 weeks (± 7 days) from study day 1 until disease progression. Any subject who discontinued study treatment prior to disease progression or death continued to have radiological imaging performed every 6 weeks (± 7 days) during the long-term follow-up period to assess disease status until disease progression, start of a new treatment, death, withdrawal of consent, administrative decision to withdraw, or the end of the study, whichever was earlier.

Visits during the chemotherapy cycles and during the monotherapy phase were performed every 3 weeks ± 3 days. After the last dose of protocol-specified therapy, each subject was followed for 30 days (+3 days) or until the resolution of any TEAEs, and at least 60 days (+14 days) for anti-conatumumab antibody formation and conatumumab PK.

All subjects were to be followed up to 36 months after the last subject on the study was randomized.

**Number of Subjects Planned:** The planned sample size in part 2 was 150 subjects (50 randomized 1:1:1 to each of 3 arms).

**Number of Subjects Enrolled:** A total of 172 subjects were randomized in part 2 of the study: 56 in the 15 mg/kg conatumumab plus cotherapy arm, 57 in the 3 mg/kg conatumumab plus cotherapy arm, and 59 in the placebo plus cotherapy arm.

**Diagnosis and Main Criteria for Eligibility:** Study subjects were adults (≥ 18 years old) with histologically or cytologically confirmed advanced NSCLC defined as stage IIIb with malignant pleural effusion, stage IV, or recurrent disease. Subjects were to use adequate birth control and have an ECOG performance status of 0 or 1. Eligible subjects must not have been under treatment with or received previous treatment with chemotherapy, chemoradiation, biologic, small-molecule immunotherapy, or other agents to treat advanced NSCLC. Eligible subjects must not have untreated or symptomatic central nervous system metastases.

**Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number:** Conatumumab was provided as a sterile, clear, colorless protein solution in single-use glass vials, containing 3.0 mL of study medication with a concentration of 30 mg/mL. Conatumumab was diluted in [redacted] or [redacted] in a minimum [redacted], and administered by continuous intravenous infusion via controlled infusion pump over 60 minutes (for the first dose in part 2) and over 30 minutes for subsequent doses.

The doses of conatumumab selected for part 2 of the study (3 and 15 mg/kg) were selected by the Data Review Team following review of both the part 1 data and data from the first conatumumab clinical study (Study 20050171). Conatumumab lot numbers used in part 2 of the study are provided in Listing 14-1.1, P2.

Placebo (part 2 only) was provided as sterile, clear, colorless solution in single-use glass vials (identical to those used for conatumumab) containing 3.0 mL of vehicle. Placebo was diluted in [redacted] or [redacted] in a minimum volume of [redacted] and administered by continuous intravenous infusion via controlled infusion pump over 60 minutes (for the first dose in part 2) and over 30 minutes for subsequent doses. Placebo lot numbers are provided in Listing 14-1.1, P2.

**Duration of Treatment:** Subjects were to receive paclitaxel/carboplatin and conatumumab or placebo for up to 6 cycles, followed by conatumumab or placebo monotherapy until disease progression, intolerability, withdrawal of consent, or 30 months from the first administration of study treatment.

**Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number:** Supplies of standard chemotherapy used in this study (paclitaxel [200 mg/m$^2$ infused over 3 hours ± 30 minutes] and carboplatin [AUC = 6.0 mg/mL•min infused over 30 ± 10 minutes] were obtained by investigators and administered intravenously based on approved product labeling in the region. Lot numbers were not collected.

**Study Endpoints:**

**Efficacy Endpoints:**

The following is a complete list of endpoints from the part 2 study. As indicated below, some of these endpoints were presented in the primary analysis CSR (dated 28 June 2010) and are not included in the present report.

**Primary endpoints**

- PFS

**Secondary endpoints**

- ORR (complete and partial response as measured by modified Response Evaluation Criteria in Solid Tumors version 1.0 [RECIST])
- Duration of response (presented in primary CSR)
- Time to response (presented in primary CSR)
- OS
- Incidence of adverse events and clinical laboratory abnormalities not defined as DLTs.
- Incidence of anti-conatumumab antibody formation
- Conatumumab PK parameters

**Statistical Methods:**

The primary PFS and OS analyses and the statistical methodologies for those analyses, have been reported previously in the primary analysis report, dated 28 June 2010. Subsequent to the primary analyses, all subjects were to be followed for survival for up to approximately 30 months after the last subject was randomized. At that time, the final analysis of OS was to be performed, but no formal hypothesis testing of efficacy or safety endpoints was planned. In addition, descriptive estimates of key comparative efficacy and safety analyses were to be updated to assess the overall relative treatment profile. Results from the final analyses are presented in this updated clinical study report, and comparisons have been made back to the primary report where applicable.

Appropriate summary statistics were provided for all safety, efficacy, pharmacokinetic, antibody, and exploratory data by treatment group and time point. For continuous variables, the mean, standard deviation, median, first and third quartiles, minimum, and maximum were calculated. For categorical variables, the frequency and percentage in each category were displayed. Kaplan-Meier estimates were provided for time-to-event endpoints. Graphical summaries of selected endpoints were also presented. For any variable, baseline was defined as the last assessment prior to the first dose of study specified treatment (unless specified otherwise). Significance levels described were to be 2-sided, unless otherwise stated. Two-sided 80% and 95% confidence intervals (CIs) were to be used to assess efficacy endpoints. No adjustments were to be made for multiple comparisons.

The goal of the primary analyses of part 2 was to estimate the treatment effect on PFS among subjects receiving conatumumab in combination with paclitaxel/carboplatin compared with subjects receiving paclitaxel/carboplatin alone (placebo). The timing of the primary analysis was event driven based upon the pre-specified goal for the target number of PFS events and was planned when 120 subjects experienced a PFS event. For the primary analysis, hazard ratios and corresponding 80% and 95% CIs were estimated for the following treatment comparisons using a stratified Cox's proportional hazard model.

1. Conatumumab 15 mg/kg and conatumumab 3 mg/kg combined relative to placebo

2. Conatumumab 15 mg/kg relative to placebo

3. Conatumumab 3 mg/kg relative to placebo

The strength of the conatumumab dose response for PFS in part 2 was assessed by testing a null hypothesis that the hazard rates were the same vs an ordered alternative using Tarone's trend test stratified by the stratification factors. The analysis was repeated with adjustment for the stratification factors.

Secondary endpoints were ORR and OS. The proportion of subjects with an objective response (a confirmed complete response or partial response) was presented by treatment arm. The analysis of OS was performed in accordance with the methodologies described above for PFS.

Safety endpoints were assessed by the incidence of adverse events; clinically-significant changes in clinical laboratory tests, and the presence of antibodies to conatumumab. Sponsor-defined adverse events of interest were infusion-related reactions, hyponatremia, hypomagnesemia, elevated amylase, elevated lipase, and venous thromboembolic events. Each adverse event of interest has been summarized using both narrow (more specific) and broad (includes narrow) search strategies.

Serum conatumumab and plasma paclitaxel and carboplatin concentrations were tabulated, and descriptive statistics (means, standard deviations, median, minimums, and maximums) were calculated for each sampling time point using WinNonlin. All serum or plasma concentrations below the quantification limit (BQL) were set to 0. Because the primary analysis report included a complete PK report, only data for seven new PK samples collected since the primary analysis cut-off are summarized in this report.

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**Summary of Results:**

**Subject Disposition:**

In part 2 of the study, 172 subjects were randomized at 41 investigative centers in 3 regions: 37 in Canada and Australia, 75 in Eastern Europe (Czech Republic, Hungary, and Poland), and 60 in Western Europe (Belgium, France, and Spain). Fifty-seven were randomized to receive conatumumab 3 mg/kg plus cotherapy, 56 were randomized to receive conatumumab 15 mg/kg

plus cotherapy, and 59 were randomized to receive placebo plus cotherapy, where cotherapy was paclitaxel and carboplatin. Five subjects did not receive investigational product; 3 subjects were in the 15 mg/kg conatumumab group, 1 subject was in the 3 mg/kg conatumumab group, and 1 subject was in the placebo group.

At the time of the primary report, 34 subjects in the 3 mg/kg conatumumab dose group, 36 subjects in the 15 mg/kg conatumumab dose group, and 41 subjects in the placebo dose group were still on study. Thirty-five of these subjects were still receiving investigational product after completing cotherapy, and 5 subjects were still receiving investigational product after discontinuing cotherapy early. At the time of the final report, all subjects had discontinued from the study and all subjects had discontinued study treatment.

In the final analysis, the most common reason for study discontinuation was death, which occurred in 85% of subjects overall, and was similar in incidence in the combined conatumumab (86%) and placebo (85%) groups (Table 14-1.1, P2). The most common reason for discontinuation of investigational product was disease progression, which occurred in 73% of subjects overall and was similar in incidence in the combined conatumumab (73%) and placebo (75%) groups. Similar proportions of subjects in the conatumumab (10%) and placebo (7%) groups discontinued investigational product due to adverse events. Forty-seven percent of subjects discontinued carboplatin or paclitaxel cotherapies prior to receiving 6 cycles of treatment; the primary reason for discontinuation of cotherapies was disease progression (22% each for paclitaxel and carboplatin in the conatumumab group, and 22% each in the placebo group) followed by adverse events (11% for paclitaxel and 10% for carboplatin). A higher percentage of subjects in the conatumumab group than the placebo group discontinued paclitaxel (13% vs 7%) or carboplatin (12% vs 7%) due to an adverse event (Table 14-1.2, P2).

There were 116 (67%) men and 56 (33%) women in the study and the majority of subjects (97%) were white. The mean (SD) age was 59.9 (9.2) years and 69% of subjects were < 65 years of age (Table 14-2.1, P2). All subjects randomized presented with NSCLC; the histological subtype of NSCLC was identified as adenocarcinoma in 51% of subjects, squamous cell carcinoma in 26% of subjects, other histological type in 15% of subjects, large cell carcinoma in 6% of subjects, and bronchoalveolar carcinoma in 2% of subjects. Ninety-one percent of subjects had stage IV disease at enrollment, and, per protocol, all subjects had ECOG performance status of 0 or 1 with 70% having ECOG 1 performance status. In general, the treatment groups were balanced for each of these demographic and disease characteristics (Table 14-2.3, P2).

**Efficacy Results:**

The results of the final analysis support the efficacy conclusions from the primary analysis. The addition of conatumumab to paclitaxel and carboplatin did not result in consistent or durable improvement in PFS, OS, or ORR that could be considered clinically relevant in this population of subjects with advanced NSCLC. A comparison of the efficacy results between the primary report and the final analysis are provided in Table 2, Table 3, and Table 4 for the endpoints of PFS, OS, and ORR, respectively.

Progression Free Survival

At the time of the primary analyses for PFS in part 2 of the study, which was performed once 120 subjects had reached a PFS event; a total of 39 (68%) events (progression or death) occurred in the 3 mg/kg conatumumab group, 38 (68%) events occurred in the 15 mg/kg conatumumab group, and 43 (73%) events occurred in the placebo group. The final analysis of PFS, which was performed at study completion, showed a total of 52 (91%) events occurred in the 3 mg/kg conatumumab group, 55 (98%) events occurred in the 15 mg/kg conatumumab group, and 57 (97%) events occurred in the placebo group (Table 14-4.2, P2). Most of the PFS events were due to clinical progression or progression by RECIST (81%, 86%, and 88% in the conatumumab 3 mg/kg, conatumumab 15 mg/kg and placebo groups, respectively), with lower incidences of PFS events due to death (10%, 12%, and 9% in the conatumumab 3 mg/kg,

conatumumab 15 mg/kg, and placebo groups, respectively) (Listing 14.4-1, P2). Similar to the primary analysis of PFS, the final analysis of PFS showed no statistically significant or clinically meaningful differences between treatment groups for the primary endpoint of PFS. The median PFS time (Kaplan-Meier) in the final analysis was 5.4 months for the 3 mg/kg conatumumab group, 4.8 months for the 15 mg/kg conatumumab group, and 5.3 months for the placebo group. The stratified hazard ratio (95% CIs) for PFS for the conatumumab 3 mg/kg group vs placebo was 0.82 (0.56, 1.20) and for the conatumumab 15 mg/kg group vs placebo was 0.89 (0.61, 1.30) (Table 14-4.2, P2). Table 2 compares the PFS results from the primary analysis to the final analysis. The Kaplan-Meier plot for the final PFS results is provided in Figure 1.

**Table 2. Analysis of Progression Free Survival (Full Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) |
| Censored - n (%) | 18 (32) | 18 (32) | 16 (27) | 5 (9) | 1 (2) | 2 (3) |
| Events[a] - n (%) | 39 (68) | 38 (68) | 43 (73) | 52 (91) | 55 (98) | 57 (97) |
| Events of Progression | 34 (59) | 32 (57) | 38 (64) | 46 (81) | 48 (86) | 52 (88) |
| Events of Death | 5 (9) | 6 (11) | 5 (9) | 6 (10) | 7 (12) | 5 (9) |
| Progression Free Survival[b] (months) | | | | | | |
| Median (K-M) | 5.4 | 4.8 | 5.5 | 5.4 | 4.8 | 5.3 |
| 80% CI (K-M) | 5.0, 5.8 | 4.1, 6.0 | 4.4, 5.7 | 5.0, 6.0 | 4.0, 5.8 | 4.4, 5.6 |
| 95% CI (K-M) | 4.1, 6.4 | 3.2, 7.0 | 4.3, 5.7 | 4.1, 6.3 | 3.2, 6.5 | 4.2, 5.7 |
| Q1, Q3 (K-M) | 2.8, 7.0 | 2.6, 8.4 | 2.9, 7.1 | 2.8, 7.3 | 2.6, 8.4 | 2.8, 6.9 |
| Min, Max | 0.0, 11.1 | 0.1, 9.7 | 0.3, 10.0 | 0.0, 29.9 | 0.1, 16.6 | 0.0, 29.0 |
| Stratified Hazard Ratio [c, g] | 1.06 | 1.00 | | 0.82 | 0.89 | |
| 80% CI | (0.80, 1.42) | (0.75, 1.33) | | (0.64, 1.05) | (0.70, 1.14) | |
| 95% CI | (0.68, 1.66) | (0.64, 1.55) | | (0.56, 1.20) | (0.61, 1.30) | |
| Un-stratified Hazard Ratio [c] | 0.94 | 0.94 | | 0.87 | 0.93 | |
| 80% CI | (0.71, 1.26) | (0.71, 1.25) | | (0.68, 1.11) | (0.73, 1.19) | |
| 95% CI | (0.61, 1.46) | (0.61, 1.46) | | (0.59, 1.26) | (0.64, 1.35) | |
| Stratified Log-Rank Test | | | | | | |
| Normal Score | 0.198 | 0.002 | | -0.979 | -0.755 | |
| p-value [d, f] | 0.843 | 0.999 | | 0.328 | 0.450 | |
| Un-Stratified Log-Rank Test | | | | | | |
| Normal Score | -0.215 | -0.203 | | -0.728 | -0.429 | |
| p-value [d] | 0.830 | 0.839 | | 0.467 | 0.668 | |
| Stratified Tarone Test | | | | | | |
| Z Statistic | | 0.4294 | | | -0.6567 | |
| Two-sided p-value [e, f] | | 0.668 | | | 0.511 | |
| Un-Stratified Tarone Test | | | | | | |
| Z Statistic | | -0.0215 | | | -0.4327 | |
| Two-sided p-value [e] | | 0.983 | | | 0.665 | |

**Table 2. Analysis of Progression Free Survival (Full Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) |

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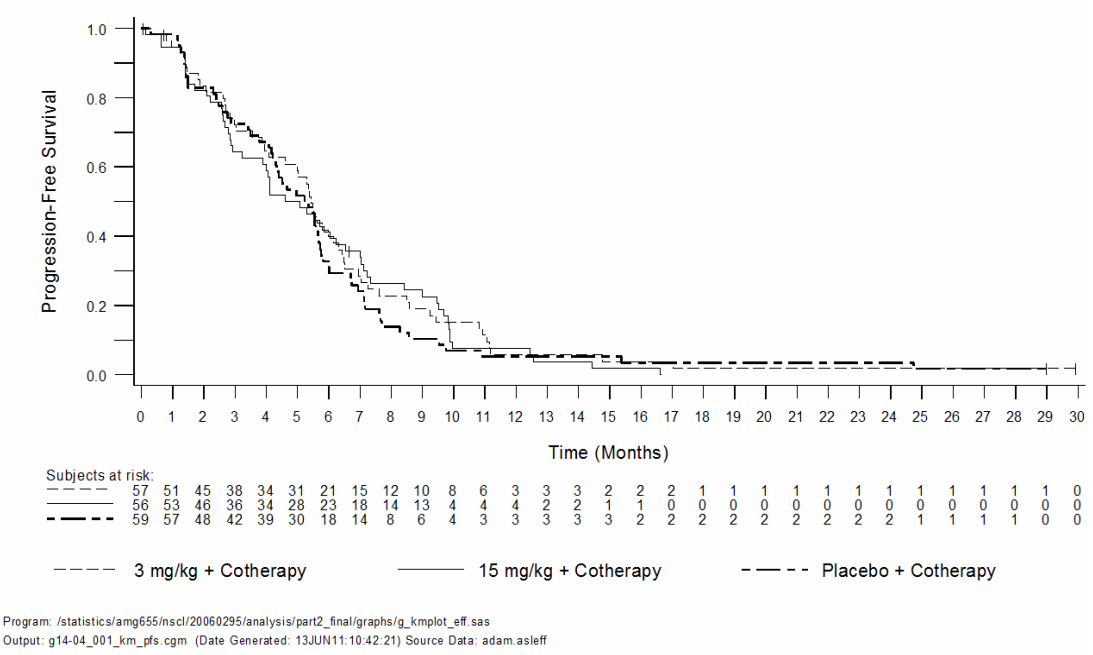
Note: The cotherapies are Paclitaxel and Carboplatin; K-M = Kaplan-Meier estimate; CI = Confidence Interval.
[a] Events are clinical progressions, radiological progressions or deaths.
[b] Progression-free survival time is calculated as the number of days from randomization to the first assessment of disease progression (as classified by modified RECIST or clinical progression) or death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer progression free survival time for AMG 655 relative to placebo.
[d] A normal score < 0 indicates fewer than expected events for AMG 655 relative to placebo, and therefore a longer progression free survival time.
[e] Indicates the strength of the dose response. A Z-Statistic < 0 indicates that the PFS time increases with dose of AMG 655. A Z-Statistic > 0 indicates that the PFS time decreases with dose of AMG 655.
[f] Stratification factor is per primary pooling strategy: Disease Stage (IIIb or IV/recurrent)
*Source: Table 14-4.1, P2; Listing 14-4.3, P2 (primary analysis);Table 14-4.02, P2; Listing 14-4.1, P2 (final analysis)*

**Figure 1. Kaplan-Meier Plot of Progression Free Survival Per Investigator Review - Part 2 (Full Analysis Set) Final Analysis**

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Output: g14-04_001_km_pfs.cgm (Date Generated: 13JUN11:10:42:21) Source Data: adam.asleff

Overall Survival

At the time of primary analysis data cut-off (09 April 2009), the OS data were too immature to draw meaningful conclusions. Thus, an updated survival analysis was performed (as of 25 January 2010) and included in the primary report. At the time of this updated survival analysis, a total of 37 (65%) events (deaths) occurred in the 3 mg/kg conatumumab group, 38 (68%) events occurred in the 15 mg/kg conatumumab group, and 44 (75%) events occurred in the placebo group.

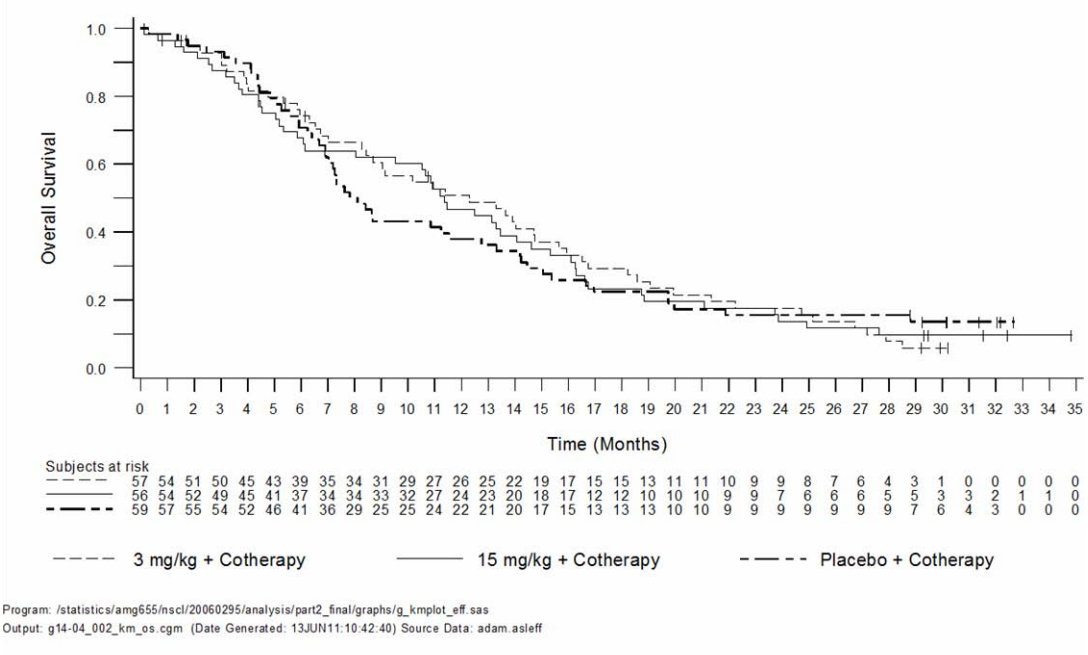
The final analysis of OS, which was performed at study completion, showed a total of 49 (86%) events occurred in the 3 mg/kg conatumumab group, 48 (86%) events occurred in the 15 mg/kg conatumumab group, and 50 (85%) events occurred in the placebo group. The median OS time was 12.3 and 11.4 months for the 3 mg/kg and 15 mg/kg conatumumab treatment groups, respectively. Median OS time in the placebo group was less than both conatumumab groups with duration of 8.0 months. The unstratified hazard ratios (95% CIs) for OS were 0.98 (0.66, 1.45) and 1.00 (0.68, 1.49) for the 3 mg/kg and 15 mg/kg conatumumab groups vs placebo, respectively (Table 14-4.3, P2). Table 3 compares the OS results from the updated primary analysis to the final analysis. The Kaplan-Meier plot for the final OS results is provided in Figure 2.

**Table 3. Analysis of Overall Survival (Full Analysis Set)**

| | Updated Primary Analysis (25 January 2010) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 56) n (%) | Placebo + Cotherapy (N = 59) n (%) |
| Censored - n (%) | 20 (35) | 18 (32) | 15 (25) | 8 (14) | 8 (14) | 9 (15) |
| Events[a] - n (%) | 37 (65) | 38 (68) | 44 (75) | 49 (86) | 48 (86) | 50 (85) |
| Overall Survival (months)[b] | | | | | | |
| Median (K-M) | 12.3 | 11.4 | 7.8 | 12.3 | 11.4 | 8.0 |
| 80% CI (K-M) | 9.0, 14.0 | 10.5, 13.3 | 7.2, 10.8 | 9.0, 14.0 | 10.5, 13.3 | 7.3, 10.8 |
| 95% CI (K-M) | 8.4, 14.8 | 8.0, 14.1 | 7.0, 11.5 | 8.4, 15.6 | 8.0, 14.1 | 6.9, 12.7 |
| Q1, Q3 (K-M) | 5.9, 18.6 | 4.5, 18.8 | 5.6, 15.4 | 5.9, 19.1 | 4.5, 16.8 | 5.6, 16.7 |
| Min, Max | 0.3, 19.9 | 0.1, 20.8 | 0.3, 19.7 | 0.3, 30.2 | 0.1, 34.8 | 0.1, 32.7 |
| Un-stratified Hazard Ratio [c] | 0.80 | 0.84 | | 0.98 | 1.00 | |
| 80% CI | (0.60, 1.07) | (0.63, 1.12) | | (0.75, 1.26) | (0.78, 1.30) | |
| 95% CI | (0.52, 1.24) | (0.54, 1.30) | | (0.66, 1.45) | (0.68, 1.49) | |
| Un-Stratified Log-Rank Test | | | | | | |
| Normal Score | -1.074 | -0.661 | | -0.097 | -0.038 | |
| p-value[d] | 0.283 | 0.509 | | 0.923 | 0.969 | |
| Un-Stratified Tarone Test | | | | | | |
| Z Statistic | | -0.6746 | | | -0.1906 | |
| Two-sided p-value[e] | | 0.500 | | | 0.849 | |

Note: The cotherapies are Paclitaxel and Carboplatin; K-M = Kaplan-Meier estimate; CI = Confidence Interval.
[a] Events are deaths.
[b] Overall survival time is calculated as the number of days from randomization to death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival time for AMG 655 relative to placebo.
[d] Indicates the strength of the dose response.
[e] Indicates the strength of the dose response. A Z-Statistic < 0 indicates that the overall survival time increases with dose of AMG 655. A Z-Statistic > 0 indicates that the overall survival time decreases with dose of AMG 655.
*Source: Table 14-4.18, UPA (updated primary analysis); Table 14-4.03, P2 (final analysis)*

**Figure 2. Kaplan-Meier Plot of Overall Survival - Part 2 (Full Analysis Set) Final Analysis**

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Output: g14-04_002_km_os.cgm (Date Generated: 13JUN11:10:42:40) Source Data: adam.asleff

Objective Response Rate

In both the primary analysis and the final analysis, the ORR was similar between the treatment groups. The final analysis showed an ORR of 29% (16/55) in the 3 mg/kg conatumumab group, 27% (15/56) in the 15 mg/kg conatumumab group, and 25% (14/56) in the placebo group (Table 14-4.1, P2). Table 4 compares the ORR and best overall response results between the primary analysis and the final analysis.

**Table 4. Summary of Objective Response and Best Overall Response per Investigator Review (Full Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| | AMG 655 3mg/kg (Q3W) + Cotherapy (N = 57) | AMG 655 15mg/kg (Q3W) + Cotherapy (N = 56) | Placebo + Cotherapy (N = 59) | AMG 655 3mg/kg (Q3W) + Cotherapy (N = 57) | AMG 655 15mg/kg (Q3W) + Cotherapy (N = 56) | Placebo + Cotherapy (N = 59) |
| Number of subjects with measurable disease at baseline | 55 | 56 | 56 | 55 | 56 | 56 |
| Number of objective responders[a] n (%) | 15 (27) | 14 (25) | 14 (25) | 16 (29) | 15 (27) | 14 (25) |
| Best overall response assessment[b] n (%) | | | | | | |
| Confirmed CR | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Confirmed PR | 14 (25) | 14 (25) | 14 (25) | 15 (27) | 15 (27) | 14 (25) |
| SD | 27 (49) | 28 (50) | 29 (52) | 26 (47) | 28 (50) | 29 (52) |
| Unconfirmed CR | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Unconfirmed PR | 2 (4) | 3 (5) | 7 (13) | 2 (4) | 3 (5) | 7 (13) |
| PD | 7 (13) | 8 (14) | 9 (16) | 7 (13) | 7 (13) | 9 (16) |
| Unknown[c] | 6 (11) | 6 (11) | 4 (7) | 6 (11) | 6 (11) | 4 (7) |

Note: The cotherapies are Paclitaxel and Carboplatin.
[a] A responder is defined as a confirmed partial or complete tumor response.
[b] A best overall response of SD requires a radiologically determined response of SD or better no earlier than study day 35.
[c] Unknown indicates no post-baseline assessment or unevaluable.
*Source: Table 14-4.32, P2 (primary analysis); Table 14-4.01, P2 (final analysis)*



**Safety Results:**

Safety results in the final analysis were nearly identical to those observed at the time of the primary analysis. Based on the final Safety Analysis Set, there were no new safety signals identified when conatumumab, at doses of 3 and 15 mg/kg, was added to advanced NSCLC standard-of-care chemotherapy (paclitaxel and carboplatin). Detailed safety results are presented below for the key safety parameters presented in the final analysis, with comparisons made to the primary analysis results when similar data presentations were available.

All Treatment Emergent Adverse Events

Based on the final analyses of adverse events, the overall percentage of subjects reporting at least 1 treatment emergent adverse event (TEAE) was lower in the 3 mg/kg conatumumab group (89%) compared with the 15 mg/kg conatumumab and placebo groups (96% and 95%, respectively). The most frequently reported TEAEs (≥ 10% in any treatment arm) are presented in Table 5. TEAEs with notably higher incidence rates in the conatumumab groups than the placebo group were thrombocytopenia, anemia, dyspnea, neutropenia, cough, insomnia, rash, (both the 3 and 15 mg/kg conatumumab groups) headache, diarrhea, and vomiting (15 mg/kg conatumumab group only). TEAEs with notably higher incidence rates in the placebo group than the conatumumab groups were constipation, weight decrease, nausea, and arthralgia. As noted

in Table 5, there were no notable differences between the primary analysis and final analysis in the incidence rates of individual TEAEs.

**Table 5. Most Frequently Reported (≥ 10%) Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency - Part 2 (Safety Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of Subjects reporting at least one AE | 51 (89) | 51 (96) | 54 (95) | 51 (89) | 51 (96) | 54 (95) |
| Alopecia | 26 (46) | 26 (49) | 24 (42) | 26 (46) | 26 (49) | 24 (42) |
| Fatigue | 17 (30) | 18 (34) | 20 (35) | 17 (30) | 19 (36) | 21 (37) |
| Nausea | 15 (26) | 14 (26) | 19 (33) | 15 (26) | 14 (26) | 20 (35) |
| Dyspnoea | 16 (28) | 13 (25) | 10 (18) | 16 (28) | 14 (26) | 10 (18) |
| Neutropenia | 15 (26) | 12 (23) | 11 (19) | 15 (26) | 13 (25) | 11 (19) |
| Decreased Appetite (anorexia in PA) | 15 (26) | 8 (15) | 15 (26) | 15 (26) | 9 (17) | 14 (25) |
| Anaemia | 13 (23) | 12 (23) | 10 (18) | 15 (26) | 12 (23) | 9 (16) |
| Diarrhoea | 10 (18) | 16 (30) | 9 (16) | 10 (18) | 16 (30) | 9 (16) |
| Asthenia | 12 (21) | 12 (23) | 11 (19) | 12 (21) | 12 (23) | 11 (19) |
| Vomiting | 11 (19) | 13 (25) | 10 (18) | 11 (19) | 13 (25) | 10 (18) |
| Cough | 12 (21) | 10 (19) | 8 (14) | 12 (21) | 10 (19) | 8 (14) |
| Constipation | 8 (14) | 8 (15) | 14 (25) | 8 (14) | 8 (15) | 13 (23) |
| Thrombocytopenia | 11 (19) | 11 (21) | 3 (5) | 11 (19) | 12 (23) | 3 (5) |
| Neuropathy Peripheral | 7 (12) | 11 (21) | 8 (14) | 7 (12) | 11 (21) | 8 (14) |
| Arthralgia | 6 (11) | 6 (11) | 11 (19) | 6 (11) | 7 (13) | 12 (21) |
| Myalgia | 8 (14) | 8 (15) | 8 (14) | 8 (14) | 8 (15) | 8 (14) |
| Paraesthesia | 12 (21) | 3 (6) | 9 (16) | 12 (21) | 3 (6) | 9 (16) |
| Pyrexia | 8 (14) | 8 (15) | 7 (12) | 8 (14) | 8 (15) | 7 (12) |
| Peripheral Sensory Neuropathy | 5 (9) | 7 (13) | 9 (16) | 5 (9) | 7 (13) | 9 (16) |
| Insomnia | 9 (16) | 8 (15) | 3 (5) | 9 (16) | 8 (15) | 3 (5) |

**Table 5. Most Frequently Reported (≥ 10%) Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency - Part 2 (Safety Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Chest Pain | 9 (16) | 5 (9) | 5 (9) | 9 (16) | 5 (9) | 5 (9) |
| Headache | 3 (5) | 9 (17) | 4 (7) | 3 (5) | 9 (17) | 5 (9) |
| Back Pain | 4 (7) | 4 (8) | 5 (9) | 4 (7) | 6 (11) | 6 (11) |
| Rash | 6 (11) | 5 (9) | 2 (4) | 6 (11) | 5 (9) | 2 (4) |
| Pain In Extremity | 6 (11) | 1 (2) | 3 (5) | 6 (11) | 3 (6) | 4 (7) |
| Weight Decreased | 3 (5) | 3 (6) | 7 (12) | 3 (5) | 3 (6) | 7 (12) |
| Dizziness | 6 (11) | 3 (6) | 3 (5) | 6 (11) | 3 (6) | 3 (5) |

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Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6-27, P2 (Primary analysis); Table 14-6.4, P2 (final analysis)*

The percentage of subjects reporting at least 1 treatment-related TEAE was also lower in the 3 mg/kg conatumumab group (82%) compared with the 15 mg/kg conatumumab and placebo groups (92% and 89%, respectively) (Table 14-6.5, P2). The most frequently reported treatment-related TEAEs across all treatment groups were consistent with those most often reported from the overall TEAE presentation and included alopecia, fatigue, nausea, and neutropenia. The incidence of treatment related TEAEs for cough and dyspnea were lower than the incidence of all TEAEs for cough and dyspnea indicating that the majority of these TEAEs were considered unrelated to study treatment. Most of the treatment-related TEAEs were judged by the investigator to be related to chemotherapy (ie, carboplatin and paclitaxel) rather than conatumumab.

Grade ≥ 3 Treatment Emergent Adverse Events

The incidence rates of grade ≥ 3 TEAEs were generally similar between the treatment groups, with the exception of a higher incidence in the conatumumab treatment groups of grade 3 to 5 TEAEs for anemia (11%, 9%, and 2% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively), thrombocytopenia (12%, 8%, and 2% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively), and a higher incidence in the placebo group of grade ≥ 3 to 5 TEAEs for decreased appetite (0%, 0%, and 5% in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively). As noted in Table 6, there were no notable differences between the primary analysis and final analysis in the incidence rates of individual grade ≥ 3 TEAEs.

**Table 6. Most Frequently Reported (≥ 5%) Grade ≥ 3 Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency - Part 2 (Safety Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of subjects reporting at least one grade ≥ 3 TEAE | 33 (58) | 31 (58) | 36 (63) | 34 (60) | 33 (62) | 37 (65) |
| Neutropenia | 8 (14) | 5 (9) | 9 (16) | 8 (14) | 5 (9) | 9 (16) |
| Anaemia | 6 (11) | 5 (9) | 1 (2) | 6 (11) | 5 (9) | 1 (2) |
| Thrombocytopenia | 7 (12) | 4 (8) | 1 (2) | 7 (12) | 4 (8) | 1 (2) |
| Dyspnoea | 4 (7) | 3 (6) | 4 (7) | 4 (7) | 3 (6) | 3 (5) |
| Chest Pain | 2 (4) | 1 (2) | 3 (5) | 2 (4) | 2 (4) | 3 (5) |
| Fatigue | 1 (2) | 2 (4) | 3 (5) | 1 (2) | 2 (4) | 3 (5) |
| Asthenia | 1 (2) | 1 (2) | 3 (5) | 1 (2) | 1 (2) | 3 (5) |
| Back Pain | 0 (0) | 2 (4) | 1 (2) | 0 (0) | 3 (6) | 1 (2) |
| Pleural Effusion | 1 (2) | 0 (0) | 2 (4) | 1 (2) | 0 (0) | 3 (5) |
| Decreased Appetite (anorexia in PA) | 0 (0) | 0 (0) | 3 (5) | 0 (0) | 0 (0) | 3 (5) |

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6-35, P2 (primary analysis); Table 14-6.9, P2 (final analysis)*



Serious Treatment Emergent Adverse Events

Overall, treatment-emergent serious adverse events (SAEs) were reported in 37%, 34%, and 39% of subjects in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively. The most frequently reported SAEs included respiratory events (dyspnea, pulmonary embolism, and pleural effusion), hematologic events (neutropenia and anemia), pyrexia, and chest pain. With the exception of chest pain which was only reported as an SAE in subjects receiving conatumumab and pleural effusion which was only reported as an SAE in subjects receiving placebo, these SAEs occurred at similar frequencies across the treatment groups (Table 14-6.14, P2). SAEs that were attributed to study treatment occurred in 5 subjects and included hypotension, renal impairment, and small bowel obstruction (3 mg/kg conatumumab); dyspnea and pulmonary embolism (conatumumab 15 mg/kg); and atrial fibrillation and dyspepsia (placebo) (Listing 14-6.2, P2). As noted in Table 7, there were no notable differences between the primary analysis and final analysis in the incidence rates of individual SAEs.

**Table 7. Most Frequently Reported (> 2%) Serious Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency - Part 2 (Safety Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of Subjects reporting at least one SAE | 21 (37) | 17 (32) | 21 (37) | 21 (37) | 18 (34) | 22 (39) |
| Dyspnoea | 5 (9) | 1 (2) | 3 (5) | 5 (9) | 1 (2) | 2 (4) |
| Neutropenia | 3 (5) | 0 (0) | 3 (5) | 3 (5) | 0 (0) | 3 (5) |
| Anaemia | 2 (4) | 2 (4) | 1 (2) | 2 (4) | 2 (4) | 1 (2) |
| Pyrexia | 1 (2) | 3 (6) | 1 (2) | 1 (2) | 3 (6) | 1 (2) |
| Pulmonary Embolism | 2 (4) | 1 (2) | 1 (2) | 2 (4) | 1 (2) | 2 (4) |
| Chest Pain | 3 (5) | 1 (2) | 0 (0) | 3 (5) | 1 (2) | 0 (0) |
| Thrombocytopenia | 2 (4) | 1 (2) | 1 (2) | 2 (4) | 1 (2) | 1 (2) |
| Febrile neutropenia | 0 (0) | 1 (2) | 2 (4) | 1 (2) | 1 (2) | 2 (4) |
| Pneumonia | 1 (2) | 1 (2) | 2 (4) | 1 (2) | 1 (2) | 2 (4) |
| Pleural Effusion | 0 (0) | 0 (0) | 3 (5) | 0 (0) | 0 (0) | 4 (7) |
| Respiratory failure | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 2 (4) |
| Lung infection | 0 (0) | 2 (4) | 0 (0) | 0 (0) | 2 (4) | 0 (0) |

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6.36, P2 (primary analysis); Table 14-6.14, P2 (final analysis)*



Fatal Treatment Emergent Adverse Events

Thirteen subjects experienced fatal TEAEs; these events were reported for 4 subjects in the 3 mg/kg conatumumab group, 4 subjects in the 15 mg/kg conatumumab group, and 5 subjects in the placebo group (Table 14-6.1, P2). The types of fatal TEAEs were similar across the 3 treatment groups and included respiratory failure or cardiopulmonary failure (4 subjects), general deterioration or disease progression (3 subjects), multiorgan failure (3 subjects), pulmonary infection or pneumonia (2 subjects), and cardiac failure (1 subject). None of the fatal TEAEs were attributed to the use of conatumumab but were considered related to the subjects underlying disease or concomitant chemotherapy (Listing 14-6.2, P2). Two of the fatal TEAEs that were reported in the primary report were updated as follows: the fatal TEAE for Subject [redacted] was changed from sepsis to cardiac failure and the fatal TEAE for Subject [redacted] was changed from cardiac arrest to respiratory failure. As noted in Table 8, there were no notable differences between the primary analysis and final analysis in the incidence rates of individual fatal TEAEs.

**Table 8. Subject Incidence of Fatal Treatment-emergent Adverse Events in the Safety Analysis Set - Part 2**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of subjects reporting at least 1 fatal adverse event | 4 (7) | 4 (8) | 5 (9) | 4 (7) | 4 (8) | 5 (9) |
| Multi-Organ failure | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 1 (2) |
| Non-Small Cell Lung Cancer | 1 (2) | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) |
| Respiratory failure | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 2 (5) |
| Cardiopulmonary failure | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Lung infection | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Pneumonia | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Sepsis | 1 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Cardiac Arrest | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 0 (0) |
| General Physical condition abnormal | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Cardiac failure | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6.43, P2, (Primary analysis); Listing 14-6.2, P2 (Final analysis)*



Treatment Emergent Adverse Events Leading to Study Withdrawal or Discontinuation of Therapy

One subject in the safety analysis set was withdrawn from the study due to an adverse event (ascites caused by disease progression); this subject was in the 15 mg/kg conatumumab dose group. Twenty-eight subjects discontinued protocol specified treatment (investigational product or chemotherapy) due to TEAEs; 14 of these subjects discontinued both investigational product and chemotherapy due to TEAEs (Table 14-6.1, P2 and Listing 14-6.4, P2).

TEAEs that led to discontinuation of investigational product (conatumumab or placebo) occurred in 21 subjects (6 subjects in the 3 mg/kg conatumumab group, 9 subjects in the 15 mg/kg conatumumab group, and 6 subjects in the placebo group). Neutropenia (3 subjects), febrile neutropenia (2 subjects), thrombocytopenia (2 subjects), respiratory failure (2 subjects), and chest pain (2 subjects) were the most frequently reported TEAEs leading to discontinuation of investigational product. All TEAEs that led to discontinuation of investigational product are summarized by treatment group for both the primary analysis and final analysis in Table 9. Adverse events that led to discontinuation of investigational product that were not previously reported in the primary report were febrile neutropenia, thrombocytopenia, non-small-cell lung cancer, cerebral ischemia, and ascites.

**Table 9. Subject Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product in the Safety Analysis Set - Part 2**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of subjects reporting at least 1 adverse event | 4 (7) | 9 (17) | 5 (9) | 6 (11) | 9 (17) | 6 (11) |
| Neutropenia | 1 (2) | 2 (4) | 0 (0) | 1 (2) | 2 (4) | 0 (0) |
| Febrile neutropenia | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 1 (2) |
| Thrombocytopenia | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 1 (2) | 0 (0) |
| Chest pain | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 1 (2) | 0 (0) |
| Respiratory failure | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 1 (2) |
| Adverse drug reaction | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Asthenia | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| General physical health deterioration | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Drug hypersensitivity | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Metastases to central nervous system | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 0 (0) | 0 (0) |
| Non-Small Cell Lung Cancer | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Hemiparesis | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Ischaemic cerebral infarction | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Cerebral ischemia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) |
| Pleural effusion | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Pulmonary embolism | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Ascites | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6.38, P2, (Primary analysis) and Listing 14-6.4, P2 (Final analysis)*

TEAEs that led to discontinuation of chemotherapy (paclitaxel and carboplatin) occurred in 21 subjects (5 subjects in the 3 mg/kg conatumumab group, 10 subjects in the 15 mg/kg conatumumab group, and 6 subjects in the placebo group). Neutropenia, thrombocytopenia, asthenia, and respiratory failure were the most frequent causes of discontinuation of chemotherapy, occurring in 4 subjects, 3 subjects, 2 subjects, and 2 subjects, respectively. Overall, most of the events that led to discontinuation of chemotherapy were the same events that led to discontinuation of conatumumab. All TEAEs that led to discontinuation of chemotherapy are summarized for both the primary analysis and final analysis in Table 10.

Polyneuropathy, an event that was reported in a subject receiving placebo, was the only TEAE that led to discontinuation of chemotherapy that was not previously reported in the primary report.

**Table 10. Subject Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Chemotherapy in the Safety Analysis Set - Part 2**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of subjects reporting at least 1 adverse event | 5 (9) | 10 (19) | 5 (9) | 5 (9) | 10 (19) | 6 (11) |
| Neutropenia | 1 (2) | 3 (6) | 0 (0) | 1 (2) | 3 (6) | 0 (0) |
| Thrombocytopenia | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 2 (4) | 0 (0) |
| Asthenia | 1 (2) | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) |
| Respiratory failure | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 1 (2) |
| Anaemia | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Drug hypersensitivity | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| General physical health deterioration | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Ischaemic cerebral infarction | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Platelet count decreased | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Pneumonia | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Pulmonary embolism | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Adverse drug reaction | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Febrile neutropenia | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Neuropathy peripheral | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Polyneuropathy | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) |

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6.39, P2, (Primary analysis) and Listing 14-6.4, P2 (Final analysis)*

Events of Interest

The overall incidence of adverse events of interest (infusion reactions, hyponatremia, hypomagnesemia, elevated amylase, elevated lipase, and venous thromboembolic events) was higher for the conatumumab 15 mg/kg group (66%) than the conatumumab 3 mg/kg (58%) and placebo (58%) groups when using the broad search strategy (Table 14-6.23, P2). The most frequent individual category of adverse events of interest was hypomagnesemia (conatumumab 3mg/kg: 54%, conatumumab 15 mg/kg: 60%, placebo: 53%), which consisted mostly of non-specific events such as fatigue (occurring in 30%, 36%, and 37% of subjects in the 3 mg/kg conatumumab, 15 mg/kg conatumumab, and placebo groups, respectively) and asthenia (occurring in 21%, 23%, and 19% of subjects in the 3mg/kg conatumumab, 15 mg/kg

conatumumab, and placebo groups, respectively). Infusion reactions were the second most frequently occurring adverse event of interest and occurred at similar frequencies in the 3 treatment groups (conatumumab 3mg/kg: 18%, conatumumab 15 mg/kg: 15%, placebo: 19%).

Using a narrow search strategy, the overall incidence of adverse events of interest was higher for the placebo group (25%), than the conatumumab 3 mg/kg group (18%), and conatumumab 15 mg/kg group (11%) (Table 14-6.22, P2). The differences among treatment groups were mostly due to a greater incidence of infusion reactions in the placebo and conatumumab 3 mg/kg groups compared with the conatumumab 15 mg/kg group (Table 14-6.20, P2). All other adverse events of interest were generally similar between the 2 conatumumab dose groups and the placebo group. The categorical frequencies of adverse events of interest based on the narrow search strategy are summarized for both the primary and final analysis in Table 11. Due to different search strategies used for events of interest in the primary report compared with the final report, the categorical frequencies of most events of interest cannot be compared back to the primary report.

**Table 11. Incidence of Treatment-Emergent Adverse Events of Interest: Narrow Search Terms - Part 2 (Safety Analysis Set)**

| | Primary Analysis (09 April 2009) | | | Final Analysis (02 June 2011) | | |
|---|---|---|---|---|---|---|
| Preferred Term | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) | AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57) n (%) | AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53) n (%) | Placebo + Cotherapy (N = 57) n (%) |
| Number of subjects reporting any adverse event of interest | - | - | - | 10 (18) | 6 (11) | 14 (25) |
| Increased serum amylase and lipase | 2 (4) | 1 (2) | 1 (2) | 2 (4) | 1 (2) | 1 (2) |
| Hypomagnesemia | 1 (2) | 3 (6) | 4 (7) | 3 (5) | 3 (6) | 5 (9) |
| Hyponatremia | 1 (2) | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 1 (2) |
| Infusion reaction | - | - | - | 4 (7) | 1 (2) | 6 (11) |
| Investigator assessed Infusion Reaction as IP-related | - | - | - | 0 (0) | 1 (2) | 1 (2) |
| Venous thromboembolic events | - | - | - | 3 (5) | 3 (6) | 3 (5) |

- Indicates data not available in primary report for comparisons.

Note: The cotherapies are Paclitaxel and Carboplatin
Note: Adverse events were coded using the MedDRA dictionary V14.0 and graded using CTCAE

*Source: Table 14-6.72, P2; Table 14-6.74, P2; Table 14-6.76, P2 (primary analysis); and Table 14-6.22, P2 (final analysis)*

Laboratory Data

Incidences of grade ≥ 3 postbaseline values for hematology parameters were similar across the 3 treatment groups (Table 14-7.2, P2); decreases in these parameters are expected effects of paclitaxel and carboplatin therapy. Analysis of chemistry values showed a low incidence of grade ≥ 3 values with no clear differences across the treatment groups (Table 14-7.2, P2). Shifts from baseline in National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) toxicity grades for laboratory evaluations were similar among the treatment arms (Table 14-7.5, P2). The frequencies of all grade ≥ 3 laboratory values are summarized for both the primary analysis and final analysis in Table 12. The overall trends are similar between the 2 analyses; the only difference in incidence greater than 5% between the primary and final analysis was absolute neutrophil count (ANC) in the placebo group (7% in the primary analysis vs 14% in the final analysis).

**Table 12. Incidence of All NCI-CTC Grade ≥ 3 Laboratory Values**
**Part 2 (Safety Analysis Set)**

| Category<br>Analyte | Primary Analysis (09 April 2009)<br>AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57)<br>n (%) | Primary Analysis (09 April 2009)<br>AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53)<br>n (%) | Primary Analysis (09 April 2009)<br>Placebo + Cotherapy (N = 57)<br>n (%) | Final Analysis (02 June 2011)<br>AMG 655 3 mg/kg (Q3W) + Cotherapy (N = 57)<br>n (%) | Final Analysis (02 June 2011)<br>AMG 655 15 mg/kg (Q3W) + Cotherapy (N = 53)<br>n (%) | Final Analysis (02 June 2011)<br>Placebo + Cotherapy (N = 57)<br>n (%) |
|---|---|---|---|---|---|---|
| **Hematology** | | | | | | |
| ANC | 5 (9) | 5 (9) | 4 (7) | 7 (12) | 7 (13) | 8 (14) |
| Hemoglobin | 3 (5) | 1 (2) | 2 (4) | 3 (5) | 1 (2) | 2 (4) |
| Lymphocytes | 13 (23) | 9 (17) | 13 (23) | 13 (23) | 9 (17) | 14 (25) |
| Platelets | 3 (5) | 1 (2) | 1 (2) | 3 (5) | 2 (4) | 1 (2) |
| WBC | 2 (4) | 2 (4) | 2 (4) | 4 (7) | 2 (4) | 4 (7) |
| **Chemistry** | | | | | | |
| ALT | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 1 (2) | 0 (0) |
| Amylase | 1 (2) | 0 (0) | 3 (5) | 2 (4) | 0 (0) | 3 (5) |
| AST | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Calcium | 2 (4) | 2 (4) | 1 (2) | 2 (4) | 2 (4) | 1 (2) |
| Glucose | 8 (14) | 9 (17) | 6 (11) | 5 (9) | 8 (15) | 5 (9) |
| Lipase | 2 (4) | 3 (6) | 3 (5) | 3 (5) | 3 (6) | 3 (5) |
| Magnesium | 2 (4) | 1 (2) | 2 (4) | 1 (2) | 1 (2) | 1 (2) |
| Phosphorous | 1 (2) | 0 (0) | 1 (2) | 2 (4) | 0 (0) | 1 (2) |
| Potassium | 2 (4) | 2 (4) | 1 (2) | 2 (4) | 2 (4) | 3 (5) |
| Sodium | 2 (4) | 2 (4) | 4 (7) | 2 (4) | 2 (4) | 4 (7) |
| **Coagulation** | | | | | | |
| INR | 2 (4) | 1 (2) | 0 (0) | 2 (4) | 1 (2) | 0 (0) |
| PTT | 0 (0) | 1 (2) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |

Note: The cotherapies are Paclitaxel and Carboplatin.
Note: Based on the NCI-CTCAE Version 3.0.
*Source: Table 14-7.77; Table 14-7.78; Table 14-7.79 (primary analysis); and Table 14-7.1, P2 (final analysis)*

**Other Evaluations:**

Pharmacokinetics

Based on PK analysis performed at the time of the primary report in subjects receiving intravenous infusions of 3, 5, or 15 mg/kg conatumumab every 3 weeks (Q3W) in combination with paclitaxel and carboplatin, conatumumab exhibited approximately linear PK. Conatumumab concentration data observed after coadministration with paclitaxel and carboplatin were similar to those observed in the first-in-human study where conatumumab was administered as monotherapy, indicating no impact of paclitaxel and carboplatin on conatumumab exposures. In addition, small differences of paclitaxel and carboplatin exposures between placebo and conatumumab-treated groups were observed, indicating little impact on paclitaxel and carboplatin exposures following treatment with conatumumab.

Seven new PK samples have been collected since the primary PK analysis was performed; all of these 7 new samples were collected at later cycles or during follow-up visits and thus have no impact on PK parameters derived from the intensive PK profiles in cycle 1. A summary of the concentration values for these samples is included in Attachment 8.

Antibody Assays

A low incidence of immunogenicity to conatumumab was observed in this study. Samples from 4 subjects tested positive for antibodies binding to conatumumab only prior to dosing with conatumumab, and samples from 5 out of 177 subjects tested positive for binding antibodies only at 1 time point postdose. Samples for 1 subject (Subject [redacted]) tested positive for both binding and neutralizing antibodies at cycle 5, day 1, but were negative for both types of conatumumab antibodies at earlier and later time points (Attachment 9). A review of this subject's TEAEs showed none were reported around this period of time (cycle 5, day 1) that were considered to be associated with the positive antibodies (the only TEAEs reported for this subject during the study were neutropenia and thrombocytopenia).

**Conclusions:**

Based on the final study results for part 2 of the study, the addition of conatumumab to paclitaxel and carboplatin did not result in consistent or durable improvement in PFS, OS, or ORR that could be considered clinically relevant in this population of subjects with advanced NSCLC. Based on the final safety analysis set, no new safety signals were observed for the combination of conatumumab 3 or 15 mg/kg with advanced NSCLC standard-of-care chemotherapy (paclitaxel and carboplatin). Higher rates of adverse events such as thrombocytopenia and insomnia are most likely due to the addition of conatumumab to the chemotherapy. Additionally, there was no impact of paclitaxel and carboplatin on conatumumab exposure and there was little impact of conatumumab administration on paclitaxel and carboplatin exposures. A low incidence of immunogenicity to conatumumab was observed in this study. The overall conclusions of the final study analyses are similar to those drawn in the primary report.