2. SYNOPSIS

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

Name of Finished Product:

Name of Active Ingredient: Ganitumab (AMG 479), rilotumumab (AMG 102)

Title of Study: A Phase 1b/2 Trial of AMG 479 or AMG 102 in Combination With Platinum-based Chemotherapy as First-line Treatment for Extensive Stage Small Cell Lung Cancer

Investigator(s) and Study Center(s): Part 1 of this study was conducted at 12 centers in the United States, Belgium, France, Spain, United Kingdom, and India; part 2 of this study was conducted at 46 centers in Europe, Asia, the United States, and India. Study centers and investigators are listed in Appendix 4.

Publication(s): None

Study Period: 02 December 2008 to 11 April 2012

Development Phase: 1b/2

Objectives:

Primary Objectives

Part 1: to identify a dose of ganitumab in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of rilotumumab in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that could be administered safely and was tolerated as determined by the incidence of dose-limiting toxicities (DLTs).

Part 2: to estimate the relative treatment effect of ganitumab (at the dose selected in part 1) in combination with chemotherapy (as determined in part 1) and of rilotumumab (at the dose selected in part 1) in combination with chemotherapy compared with placebo plus chemotherapy, as measured by the respective hazard ratios for overall survival.

Secondary Objectives

Part 1:

- to evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- to evaluate safety as assessed by the incidence of anti-ganitumab antibody formation and anti-rilotumumab antibody formation
- to evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and minimum observed serum concentration (C_{min}) for ganitumab and for rilotumumab

Part 2:

- to evaluate clinical benefit as assessed by the objective response rate (per modified Response Evaluation Criteria in Solid Tumors [RECIST]), duration of response, time to progression, progression-free survival, median overall survival, and overall survival rates at 10, 12, 24, and 36 months
- to evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- to evaluate safety as assessed by the incidence of anti-ganitumab antibody formation and anti-rilotumumab antibody formation
- to evaluate PK as assessed by C_{max} and C_{min} for ganitumab and for rilotumumab
- to estimate the effect of ganitumab and of rilotumumab on subjects' health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

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[redacted]

Methodology: This study was composed of 2 parts.

Part 1 was an open-label, 4-arm, dose de-escalation, phase 1b study of ganitumab and rilotumumab, each in combination with 2 different chemotherapies, to determine the safety, tolerability, and PK profile and to identify respective doses of ganitumab and of rilotumumab in combination with chemotherapy that would be safe and tolerated based on the incidence of DLTs observed within the first 21 days of starting study treatment. The 4 main cohorts included:

- Ganitumab combined with etoposide and carboplatin (cohort 1)
- Ganitumab combined with etoposide and cisplatin (cohort 2)
- Rilotumumab combined with etoposide and carboplatin (cohort 3)
- Rilotumumab combined with etoposide and cisplatin (cohort 4)

The first dose cohorts explored the target doses of ganitumab 18 mg/kg (cohorts 1a and 2a) and rilotumumab 15 mg/kg (cohorts 3a and 4a) every 3 weeks (Q3W). No dose escalation beyond the target doses was to occur. However, in case of unexpected toxicity with the combination of chemotherapy and ganitumab or rilotumumab at the respective target doses, dose de-escalation could occur (doses of ganitumab could be de-escalated to 9 mg/kg Q3W or 4.5 mg/kg Q3W [cohorts 1c and/or 2c]; doses of rilotumumab could be de-escalated to 7.5 mg/kg Q3W or 3.0 mg/kg Q3W [cohorts 3c and/or 4c]). The Amgen safety review team (SRT) reviewed all completed part 1 data, as well as emerging data from other studies involving ganitumab or rilotumumab, to make a recommendation about the treatment regimens to be used in part 2.

In part 2, subjects were double-blind randomized in a 1:1:1 ratio, stratified by gender (men, women) and chemotherapy (etoposide and carboplatin or etoposide and cisplatin) to receive 1 of the following:

- Arm A: ganitumab (at the dose selected in part 1) with chemotherapy
- Arm B: rilotumumab (at the dose selected in part 1) with chemotherapy
- Arm C: placebo with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1)

An Amgen data review team (DRT), independent of the study team, was to perform unblinded reviews of the safety data after at least 30 and 60 subjects had been randomized and had the opportunity to complete the first cycle of study treatment (safety interim analysis).

During part 1 and part 2, 4 to 6 cycles of chemotherapy were to be given. During the study, radiological assessments for disease status were performed according to modified RECIST. Imaging included computed tomography (CT) or magnetic resonance imaging (MRI) of the brain (at screening, then as needed), chest, abdomen, and all other sites of disease. Subjects who completed 4 to 6 cycles of chemotherapy or who discontinued chemotherapy early were to continue to receive investigational product (ganitumab, rilotumumab, or placebo) monotherapy (maintenance).

This clinical study report summarizes primary analysis data from part 1 and part 2 of the study using a data cutoff date of 11 April 2012.

Number of Subjects Planned: Part 1: 24 to 108 subjects (approximately 6 to 9 subjects per dose cohort); part 2: 180 subjects (60 per treatment arm)

Number of Subjects Enrolled: Part 1: 28 subjects (cohort 1: 6 subjects; cohort 2: 8 subjects; cohort 3: 6 subjects; cohort 4: 8 subjects); part 2: 185 subjects (arm A: 62 subjects; arm B: 62 subjects; arm C: 61 subjects)

Diagnosis and Main Criteria for Eligibility: In part 1 and part 2 of the study, the main inclusion criteria included histologically or cytologically confirmed small cell lung cancer (SCLC), extensive stage; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; life expectancy ≥ 3 months; and men or women ≥ 18 years of age.

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

Part 1: In cohorts 1 and 2, ganitumab was to be administered intravenously (IV) over 60 minutes at 18 mg/kg Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin). The ganitumab dose could be de-escalated to 9 mg/kg Q3W or 4.5 mg/kg Q3W based on the incidence of DLTs. In cohorts 3 and 4, rilotumumab was administered IV over 60 minutes at 15 mg/kg Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin). The rilotumumab dose could be de-escalated to 7.5 mg/kg Q3W or 3 mg/kg Q3W based on the incidence of DLTs.

Part 2: Ganitumab was to be administered IV over 60 minutes at the dose selected in part 1 Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin). Rilotumumab was to be administered IV over 60 minutes at the dose selected in part 1 Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin).

Ganitumab and rilotumumab lot numbers are provided in Listing 14-1.5, P1 PA and Listing 14-1.5, P2 PA.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

Part 2: Placebo was to be administered IV over 60 minutes following administration of chemotherapy (etoposide plus carboplatin or cisplatin).

Placebo lot numbers are provided in Listing 14-1.5, P2 PA.

Cotherapy: In part 1 and part 2, chemotherapy was administered prior to administration of investigational product (ganitumab, rilotumumab, or placebo). Etoposide was to be administered IV over 90 minutes at 100 mg/m^2; carboplatin was to be administered IV over 30 minutes at area under the concentration-time curve (AUC) = 5 mg/mL•min; and cisplatin was to be administered IV over 60 minutes at 75 mg/m^2.

Duration of Treatment: Every 3 weeks (Q3W) for up to 24 months from the date of first study treatment administration (study day 1). Study treatment was to cease if a subject withdrew consent or experienced disease progression, death, or unacceptable toxicity or based on administrative decision by the investigator or Amgen. After stopping study treatment, subjects were to be followed every 3 months for up to 36 months to assess disease status and survival. Subjects who had completed 24 months of investigational product could be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism.

Study Endpoints

Primary Endpoints

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities defined as DLT

Part 2:

- Overall survival

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-ganitumab and anti-rilotumumab antibody formation
- PK (C_{max} and C_{min} for ganitumab and rilotumumab)

Part 2:

- Progression-free survival
- Time to progression
- Objective response rate
- Duration of response

- Median overall survival and overall survival rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-ganitumab and anti-rilotumumab antibody formation
- PK (C_{max} and C_{min}) for ganitumab and rilotumumab
- Change in patient-reported outcomes as assessed with the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13)

[redacted]

Statistical Methods: Data from part 1 and part 2 were analyzed separately. The primary analysis occurred when approximately 130 deaths had occurred. The data cutoff date for the primary analysis was 11 April 2012.

Efficacy data for part 1 were listed by subject.

For part 2, the primary efficacy endpoint was overall survival, analyzed using a Cox regression model stratified by randomization stratification factors (chemotherapy and gender) and controlled for the lactate dehydrogenase (LDH) level. A Wald chi-square test provided a descriptive p-value for the hazard ratio. Both 80% and 95% confidence intervals (CIs) for the hazard ratio for treatment comparison were provided. A stratified log-rank test was provided for each pair of treatment groups (arm A versus arm C and arm b versus arm C) for a descriptive comparison. Kaplan-Meier curves were also generated for each treatment group.

Analyses of the secondary endpoint of progression-free survival were performed in accordance with the methodologies described for overall survival. The proportion of subjects with an objective response (complete or partial response per modified RECIST, confirmed by subsequent assessment) was presented as a binominal rate for each treatment group in part 2 of the study. The Wilson's score method with continuity correction was used to estimate the differences and corresponding 80% and 95% CIs for the differences in the objective response rates for arms A and C and arms B and C.

[redacted]

Patient-reported outcome data from the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were summarized descriptively.

A mixed-effects piecewise linear model was to be generated to compare the treatment groups from baseline through the safety follow-up assessment. Randomization stratification factors and prespecified covariates were included as covariates in the model.

The safety analyses included DLTs (part 1), adverse events, clinical laboratory tests, and clinically significant changes in vital signs and electrocardiograms for part 1 and part 2. The incidences of subjects developing anti-ganitumab and anti-rilotumumab antibodies in at least 1 time point were also listed.

Summary of Results

Subject Disposition

In part 1, a total of 28 subjects were enrolled; 27 subjects received at least 1 dose of investigational product, at least 1 dose of etoposide, and at least 1 dose of one of the platinum therapies: 6 subjects in the ganitumab plus etoposide/carboplatin cohort, 7 subjects in the ganitumab plus etoposide/cisplatin cohort, 6 subjects in the rilotumumab plus etoposide/carboplatin cohort, and 8 subjects in the rilotumumab plus etoposide/cisplatin cohort (1 subject in the ganitumab plus etoposide/cisplatin cohort did not receive investigational product or either of the chemotherapies). As of the data cutoff date, no subjects in part 1 of the study remained on treatment. The most common reason for discontinuing investigational product in the 4 cohorts was disease progression (50% each).

In part 2 of the study, a total of 185 subjects were randomized into the study (full analysis set): 62 subjects in the ganitumab plus chemotherapies treatment arm, 62 subjects in the rilotumumab plus chemotherapies treatment arm, and 61 subjects in the placebo plus chemotherapies treatment arm. The number of subjects who received at least 1 dose of all protocol-specified treatment in the ganitumab, rilotumumab, and placebo treatment arms was 59, 61, and 59, respectively. As of the data cutoff, 1 subject in the ganitumab treatment arm was continuing protocol-specified therapy, 28 (15%) subjects overall remained in the study, and 157 (85%) subjects overall had discontinued the study. The most common reason for discontinuing the study in all 3 arms was death (79%, 73%, and 77%, respectively). The reason for discontinuing investigational product was most often disease progression in the 3 treatment arms (ganitumab: 42 [68%] subjects; rilotumumab: 38 [61%] subjects; placebo: 45 [74%] subjects).

Baseline Demographics

Sex: part 1 – 17 men (61%), 11 women (39%); part 2 – 142 men (77%), 43 women (23%)

Age: part 1 – mean age 59.4 years (range: 40 to 76); part 2 – mean age 60.1 years (range: 33 to 79)

Ethnicity/Race: part 1 – 22 Caucasian (79%), 6 Asian (non-Japanese) (21%); part 2 – 152 Caucasian (82%), 32 Asian (non-Japanese) (17%), 1 other (1%)

Efficacy Results

For ganitumab, in part 1 of the study, 1 subject in the ganitumab/cisplatin cohort achieved a complete response (duration of response was 239 days) and 2 subjects achieved partial responses (duration of response of 83 days and 100 days). Stable disease was documented for 3 subjects in the ganitumab/carboplatin cohort and 2 subjects in the ganitumab/cisplatin cohort.

In part 2 of the study, at the time of the primary analysis, the median (95% CI) overall survival time (the primary efficacy endpoint) was comparable in the ganitumab and placebo treatment arms: 10.7 (8.1, 14.1) months for ganitumab and 10.8 (9.4, 11.9) months for placebo. Of note, as described in the statistical analysis plan (Appendix 2), the median overall survival in the placebo treatment arm was assumed to be 9.5 months; whereas the results from this analysis shown here indicate that this figure was just within the upper bound of the 95% CI above. The overall survival analysis was based on a percentage of events (deaths) in the 2 treatment arms of 79% and 75% for ganitumab and placebo, respectively. The overall survival hazard ratio (95% CI), stratified by gender and chemotherapy and controlled by baseline LDH, was 0.95 (0.62, 1.46) for the ganitumab treatment arm compared with placebo (p-value: 0.609).

In the univariate analysis of baseline covariates (all subjects in the 3 treatment groups), baseline ECOG status of 0 versus 1, 2, baseline LDH ≤ upper limit of normal (ULN) versus > ULN, and age < 65 versus ≥ 65 years demonstrated a significant association with overall survival and, thus, could have prognostic relevance. The hazard ratio (95% CI) and p-value were 1.68 (1.11, 2.53) and 0.014 for baseline ECOG of 1 or 2 compared to ECOG of 0, 1.55 (1.11, 2.17) and 0.010 for baseline LDH > ULN compared to LDH ≤ ULN, and 1.48 (1.02, 2.14) and 0.037 for age ≥ 65 years compared to age < 65 years.

Progression-free survival analyses (a secondary efficacy endpoint) showed median (95% CI) progression-free survival times for the ganitumab and placebo treatment arms that were comparable at 5.5 (4.4, 5.7) months and 5.4 (4.6, 5.8) months, respectively. The hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 1.03 (0.70, 1.52) for the ganitumab treatment arm compared with placebo (p-value: 0.780).

The objective response rate was similar between the ganitumab and placebo treatment arms: for ganitumab, the percentage (95% CI) of responders was 62.90% (49.69, 74.84; 39 subjects) and for placebo was 59.02% (45.68, 71.45; 36 subjects). The unstratified odds ratio (95% CI) for ganitumab relative to placebo was 1.18 (0.54, 2.59).

For rilotumumab, in part 1 of the study, in the rilotumumab/carboplatin cohort, the best overall response was partial response for 3 subjects; the duration of the responses ranged from 89 to 188 days. In the rilotumumab/cisplatin cohort, the best overall response was partial response for 4 subjects; duration of response ranged from 126 to 338 days.

In part 2 of the study, for the primary efficacy endpoint of overall survival, the median (95% CI) overall survival time in the rilotumumab treatment arm was 12.2 (8.8, 14.6) months compared with 10.8 (9.4, 11.9) months in the placebo treatment arm. Of note, as described in the statistical analysis plan (Appendix 2), the median overall survival in the placebo treatment arm was assumed to be 9.5 months; whereas the results from this analysis shown here indicate this figure was just within the upper bound of the 95% CI above. The percentage of events (deaths) in the 2 treatment arms was 73% and 75% for rilotumumab and placebo, respectively. The overall survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 0.86 (0.56, 1.34) for the rilotumumab treatment arm compared with placebo (p-value: 0.298).

In the univariate analysis of baseline covariates (all subjects in the 3 treatment groups), baseline ECOG status of 0 versus 1, 2, baseline LDH ≤ ULN versus > ULN, and age < 65 versus ≥ 65 years demonstrated a significant association with overall survival, and thus could have prognostic relevance. The hazard ratio (95% CI) and p-value were 1.68 (1.11, 2.53) and 0.014 for baseline ECOG of 1 or 2 compared to ECOG of 0, 1.55 (1.11, 2.17) and 0.010 for baseline LDH > ULN compared to LDH ≤ ULN, and 1.48 (1.02, 2.14) and 0.037 for age ≥ 65 years compared to age < 65 years.

For the secondary endpoint of progression-free survival, in part 2 of the study, the median (95% CI) progression-free survival time in the rilotumumab treatment arm was comparable to that in the placebo treatment arm (5.4 [4.4, 5.7] months and 5.4 [4.6, 5.8] months, respectively). The progression-free survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 1.03 (0.69, 1.52) for the rilotumumab treatment arm compared with placebo (p-value: 0.797).

The percentage of objective responders in the rilotumumab treatment arm (42 subjects, 67.74% [54.66, 79.06]) was numerically higher than that in the placebo treatment arm (36 subjects, 59.02% [45.68, 71.45]). The unstratified odds ratio (95% CI) for rilotumumab was 1.45 (0.65, 3.26) relative to placebo, which favored rilotumumab.

Patient-reported Outcome Results

There was little evidence of a treatment effect (ganitumab or rilotumumab compared with placebo) on patient-reported outcome measures (EORTC QLQ-C30 and EORTC QLQ-LC13), indicating that these treatments did not negatively impact quality of life in these subjects compared with placebo.

Pharmacokinetic Results

The PK data of ganitumab and rilotumumab were analyzed for 74 and 75 subjects, respectively, that included data from both part 1 and part 2. The PK data of etoposide, carboplatin, and cisplatin from subjects that participated in the intensive PK assessment were analyzed with pooled data from both study parts.

Ganitumab: Following the 18-mg/kg Q3W regimen, the mean pre- and end-of-infusion concentrations of ganitumab in cycle 3 were 16.9 and 337 µg/mL, respectively. The steady state achieved in cycle 3 with the anticipated level of accumulation based on the known PK properties of ganitumab. The accumulation of ganitumab, assessed by C_{max}, between cycles 1 and 3 was

less than 1.2-fold. The ganitumab concentrations are comparable when combined with either etoposide/carboplatin or etoposide/cisplatin.

Rilotumumab: Following the 15-mg/kg Q3W regimen, the mean pre- and end-of-infusion concentrations of rilotumumab in cycle 3 were 121 and 428 µg/mL, respectively. Different from ganitumab, which has a shorter half-life, the PK steady state of rilotumumab should be achieved in cycle 5, based on the known PK properties. Because the same PK sampling schedule had to be applied to both ganitumab and rilotumumab arms in a blinded study, and no PK samples were collected in cycle 5, the steady-state peak and trough concentrations could not be assessed in this study. The accumulation of rilotumumab, assessed by C_{max}, between cycles 1 and 3 was less than 1.5-fold. The rilotumumab concentrations are comparable when combined with either etoposide/carboplatin or etoposide/cisplatin.

Chemotherapy Agents: [redacted]

Safety Results

For ganitumab, in part 1 of the study, DLTs were reported for 1 subject in the ganitumab/carboplatin cohort: serious grade 4 events of neutropenia and thrombocytopenia. These events were considered to be related to all of the protocol-specified treatments; all treatments were discontinued as a result of the events. Based on the occurrence of DLTs in 1 subject in the ganitumab cohorts overall in part 1, the target dose of 18 mg/kg for ganitumab combined with chemotherapies was determined to be safe and tolerable for part 2 of the study. All of the subjects in the ganitumab/carboplatin cohort and 6 (86%) subjects in the ganitumab/cisplatin cohort experienced at least 1 treatment-emergent adverse event. The treatment-emergent adverse events reported most frequently (> 50% in either the ganitumab/carboplatin or the ganitumab/cisplatin cohort) were headache (67%, 43%, respectively), anemia (67%, 29%), thrombocytopenia (67%, 14%), pyrexia (67%, 14%), diarrhea (67%, 0%), neutropenia (50%, 57%), nausea (33%, 57%), and alopecia (33%, 57%). Adverse events considered to be related to treatment were reported in 83% of subjects in the ganitumab/carboplatin cohort and 57% of subjects in the ganitumab/cisplatin cohort. Serious adverse events were reported in 83% of subjects in the ganitumab/carboplatin cohort and 29% of subjects in the ganitumab/cisplatin cohort. One subject (ganitumab/carboplatin) experienced a fatal adverse event of septic shock in the setting of neutropenia, which was assessed as not related to investigational product. No subjects in either of the ganitumab cohorts were withdrawn from the study as a result of a treatment-emergent adverse event. Two subjects in the ganitumab/carboplatin cohort discontinued investigational product and the chemotherapies due to adverse events, and 1 subject in the ganitumab/cisplatin cohort discontinued etoposide and cisplatin due to an adverse event. The most frequently occurring adverse events of interest for ganitumab (≥ 50%) were thrombocytopenia (ganitumab/carboplatin: 67%; ganitumab/cisplatin: 14%) and neutropenia (50%, 57%). No significant trends in hematology or chemistry laboratory parameters were observed in part 1. In the ganitumab/carboplatin cohort, 1 subject tested positive postbaseline for anti-ganitumab antibodies. No subject tested positive for neutralizing antibodies.

In part 2 of the study, the subject incidence of treatment-emergent adverse events was comparable between the ganitumab and placebo treatment arms: 58 (98%) subjects and 57 (97%) subjects, respectively. The events reported in more than 30% of subjects in either arm were neutropenia (ganitumab: 69%; placebo: 71%), nausea (41%, 22%), alopecia (41%, 27%), anemia (39%, 36%), and vomiting (19%, 31%). Fifty-eight percent of subjects in the ganitumab treatment arm and 75% of subjects in the placebo treatment arm had at least 1 worst grade 3 or 4 adverse event. The subject incidence of adverse events considered to be related to treatment was similar between the ganitumab treatment arm (95% of subjects) and the placebo treatment arm (92% of subjects). Serious adverse events occurred in 39% of subjects in the ganitumab arm and 36% of subjects in the placebo arm. Seven (12%) subjects in the ganitumab treatment arm and 3 (5%) subjects in the placebo treatment arm experienced fatal adverse events. In the ganitumab arm, the events were aspiration, febrile neutropenia, neoplasm malignant, gastroenteritis, febrile neutropenia, and pulmonary hemorrhage (reported in 2 subjects); in the placebo arm, the events were septic shock, gastric ulcer hemorrhage, and SCLC stage unspecified. The only event assessed as related to investigational product was the event of gastric ulcer hemorrhage (also related to the chemotherapies). Ten percent of subjects in the ganitumab treatment arm and 2% of subjects in the placebo treatment arm discontinued the study as a result of a treatment-emergent adverse event. Investigational product was discontinued due to adverse events for 12% of subjects in the ganitumab treatment arm and 19% of subjects in the placebo treatment arm; etoposide was discontinued in 7% and 12% of subjects, respectively; and platinum therapy was discontinued in 8% and 12% of subjects. The most frequent ganitumab adverse events of interest included neutropenia, which was reported at 75% in both the ganitumab and placebo treatment arms, and thrombocytopenia, reported in 24% and 12%, respectively. There were no significant trends in hematology or chemistry laboratory parameters. At baseline, 5 (9%) subjects in the ganitumab arm and 7 (12%) subjects in the placebo arm tested positive for anti-ganitumab antibodies prior to dosing; postbaseline, 1 (2%) subject and 2 (4%) subjects, respectively, tested positive for anti-ganitumab antibodies only postbaseline. No neutralizing antibodies were detected in any of these subjects. Medical review of the adverse events experienced by these subjects indicated that these events were unlikely to have resulted from the presence of anti-ganitumab antibodies.

For rilotumumab, in part 1 of the study, the treatment-emergent adverse events reported most frequently (> 50% in either the rilotumumab/carboplatin or the rilotumumab/cisplatin cohort) were neutropenia (83%, 63%, respectively), fatigue (67%, 0%), nausea (50%, 63%), and alopecia (50%, 63%). Adverse events considered to be related to treatment were reported in 83% of subjects in the rilotumumab/carboplatin cohort and 88% of subjects in the rilotumumab/cisplatin cohort. Serious adverse events were reported for 67% of subjects in the rilotumumab/carboplatin cohort and 88% of subjects in the rilotumumab/cisplatin cohort. One subject in the rilotumumab/carboplatin cohort experienced a fatal adverse event of pulmonary embolism (not related to investigational product); 2 subjects in the rilotumumab/cisplatin cohort experienced fatal adverse events, 1 of pulmonary embolism (related to investigational product) and 1 of superior vena cava syndrome (not related). Seventeen percent of subjects from the rilotumumab/carboplatin cohort and 25% of subjects from the rilotumumab/cisplatin cohort were withdrawn from the study as a result of an adverse event; all were grade 5 events. Investigational product was discontinued due to adverse events for 17% of subjects in the rilotumumab/carboplatin cohort and 38% of subjects in the rilotumumab/cisplatin cohort; etoposide was discontinued in 33% and 25% of subjects, respectively; and platinum therapy was discontinued in 33% and 25% of subjects, respectively. The most frequently occurring adverse events of interest for rilotumumab (≥ 50%) were venous thromboembolic events (rilotumumab/carboplatin: 33%; rilotumumab/cisplatin: 63%) and neutropenia (83%, 63%). No subject in either of the rilotumumab cohorts experienced a DLT; thus, the dose of 15 mg/kg rilotumumab combined with chemotherapies was determined to be safe and tolerable for part 2 of the study. No significant trends in hematology or chemistry laboratory parameters were observed in part 1. On treatment, no subject tested positive for anti-rilotumumab antibodies.

In part 2 of the study, the subject incidence of treatment-emergent adverse events was comparable between the rilotumumab and placebo treatment arms: 61 (100%) subjects and 57 (97%) subjects, respectively. Those events reported in more than 30% of subjects in either arm were neutropenia (rilotumumab: 59%; placebo: 71%), anemia (34%, 36%), and vomiting

(10%, 31%). Sixty-two percent of subjects in the rilotumumab treatment arm and 75% of subjects in the placebo treatment arm had at least 1 worst grade 3 or 4 adverse event. The incidence of related adverse events was comparable between rilotumumab (92% of subjects) and placebo (92% of subjects). Serious adverse events were reported at similar incidences in the rilotumumab (38% of subjects) and placebo (36% of subjects) treatment arms. During part 2, the deaths for 6 (10%) subjects in the rilotumumab treatment arm and 3 (5%) subjects in the placebo treatment arm resulted from fatal adverse events. In the rilotumumab arm, 2 events (febrile neutropenia and cardiac arrest) were assessed as related to investigational product as well as the chemotherapies, and the other 4 (cerebrovascular accident, pancytopenia, pneumonia, SCLC stage-unspecified) were either not related or were related to the chemotherapies only. In the placebo arm, 1 event (gastric ulcer hemorrhage) was related to investigational product as well as the chemotherapies; the other events (septic shock, SCLC stage-unspecified) were assessed as not related to any treatment. Five percent of subjects in the rilotumumab treatment arm and 2% of subjects in the placebo treatment arm discontinued the study as a result of a treatment-emergent adverse event; all were grade 5 events. Investigational product was discontinued as a result of 1 or more treatment-emergent adverse events for 16% of subjects in the rilotumumab treatment arm and 19% of subjects in the placebo treatment arm; etoposide was discontinued in 13% of subjects and 12% of subjects, respectively; and platinum therapy was discontinued in 18% of subjects and 12% of subjects, respectively. The rilotumumab events of interest that were reported most frequently were neutropenia, reported at 64% in the rilotumumab treatment arm and 75% in the placebo treatment arm, and thrombocytopenia, reported in 31% and 12% of subjects, respectively. There were no significant trends in hematology or chemistry laboratory parameters. No anti-rilotumumab antibodies were detected in any of the subjects.

Conclusions

For ganitumab, treatment at a dose of 18 mg/kg when combined with etoposide plus carboplatin or etoposide plus cisplatin showed comparable efficacy to placebo plus chemotherapy with respect to overall survival, progression-free survival, and tumor response. The safety profile for the combination of ganitumab with etoposide plus carboplatin or cisplatin was consistent with the emerging safety profile of ganitumab and the chemotherapy background in this population of subjects with extensive-disease SCLC. The overall incidence of adverse events in the ganitumab group was similar to that in the placebo group.

For rilotumumab, treatment at a dose of 15 mg/kg when combined with etoposide plus carboplatin or etoposide plus cisplatin suggested a trend toward improvement in overall survival and objective response but appeared to be comparable to placebo with respect to progression-free survival, clinical benefit rate, and duration of response. The safety profile for the combination of rilotumumab and etoposide plus carboplatin or cisplatin was consistent with the emerging safety profile of rilotumumab and the chemotherapy background in this population. The overall incidence of adverse events in the rilotumumab group was similar to that in the placebo group.

The serum concentrations of ganitumab and rilotumumab in combination of etoposide, carboplatin, and cisplatin in SCLC patients were within the expected range, indicating that the PK of ganitumab and rilotumumab was not affected in the presence of cotherapy with these agents. Plasma concentrations of etoposide, carboplatin, and cisplatin were comparable with or without ganitumab or rilotumumab in this study, indicating that the PK of these chemotherapeutic agents was not affected in the presence of ganitumab or rilotumumab. An association was shown between low IGF-BP2 baseline levels and favorable objective response in the ganitumab treatment group.

2. SYNOPSIS

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

Name of Finished Product:

Name of Active Ingredient: Ganitumab (AMG 479), rilotumumab (AMG 102)

Title of Study: A Phase 1b/2 Trial of AMG 479 or AMG 102 in Combination With Platinum-based Chemotherapy as First-line Treatment for Extensive Stage Small Cell Lung Cancer

Investigator(s) and Study Center(s): Part 1 of this study was conducted at 12 centers in the United States, Belgium, France, Spain, United Kingdom, and India; part 2 of this study was conducted at 46 centers in Europe, Asia, the United States, and India. Study centers and investigators are listed in Section 16.1.4.

Publication(s): None

Study Period: 02 December 2008 to 01 May 2012

Development Phase: 1b/2

Objectives:

Primary Objectives

Part 1: to identify a dose of ganitumab in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of rilotumumab in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that could be administered safely and was tolerated as determined by the incidence of dose-limiting toxicities (DLTs).

Part 2: to estimate the relative treatment effect of ganitumab (at the dose selected in part 1) in combination with chemotherapy (as determined in part 1) and of rilotumumab (at the dose selected in part 1) in combination with chemotherapy compared with placebo plus chemotherapy, as measured by the respective hazard ratios for overall survival.

Secondary Objectives

Part 1:

- to evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- to evaluate safety as assessed by the incidence of anti-ganitumab antibody formation and anti-rilotumumab antibody formation
- to evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and minimum observed serum concentration (C_{min}) for ganitumab and for rilotumumab

Part 2:

- to evaluate clinical benefit as assessed by the objective response rate (per modified Response Evaluation Criteria in Solid Tumors [RECIST]), duration of response, time to progression, progression-free survival, median overall survival, and overall survival rates at 10, 12, 24, and 36 months
- to evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- to evaluate safety as assessed by the incidence of anti-ganitumab antibody formation and anti-rilotumumab antibody formation
- to evaluate PK as assessed by C_{max} and C_{min} for ganitumab and for rilotumumab

- to estimate the effect of ganitumab and of rilotumumab on subjects' health-related quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Methodology: This study was composed of 2 parts.

Part 1 was an open-label, 4-arm, dose de-escalation, phase 1b study of ganitumab and rilotumumab, each in combination with 2 different chemotherapies, to determine the safety, tolerability, and PK profile and to identify respective doses of ganitumab and of rilotumumab in combination with chemotherapy that would be safe and tolerated based on the incidence of DLTs observed within the first 21 days of starting study treatment. The 4 main cohorts included:

- Ganitumab combined with etoposide and carboplatin (cohort 1)
- Ganitumab combined with etoposide and cisplatin (cohort 2)
- Rilotumumab combined with etoposide and carboplatin (cohort 3)
- Rilotumumab combined with etoposide and cisplatin (cohort 4)

The first dose cohorts explored the target doses of ganitumab 18 mg/kg (cohorts 1a and 2a) and rilotumumab 15 mg/kg (cohorts 3a and 4a) every 3 weeks (Q3W). No dose escalation beyond the target doses was to occur. However, in case of unexpected toxicity with the combination of chemotherapy and ganitumab or rilotumumab at the respective target doses, dose de-escalation could occur (doses of ganitumab could be de-escalated to 9 mg/kg Q3W or 4.5 mg/kg Q3W [cohorts 1c and/or 2c]; doses of rilotumumab could be de-escalated to 7.5 mg/kg Q3W or 3.0 mg/kg Q3W [cohorts 3c and/or 4c]).

In part 2, subjects were double-blind randomized in a 1:1:1 ratio, stratified by gender (male, female) and chemotherapy (etoposide and carboplatin or etoposide and cisplatin) to receive 1 of the following:

- Arm A: ganitumab (at the dose selected in part 1) with chemotherapy
- Arm B: rilotumumab (at the dose selected in part 1) with chemotherapy
- Arm C: placebo with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1)

During part 1 and part 2, 4 to 6 cycles of chemotherapy were to be given. During the study, radiological assessments for disease status were performed according to modified RECIST. Imaging included computed tomography or magnetic resonance imaging of the brain (at screening, then as needed), chest, abdomen, and all other sites of disease. Subjects who completed 4 to 6 cycles of chemotherapy or who discontinued chemotherapy early were to continue to receive investigational product (ganitumab, rilotumumab, or placebo) monotherapy (maintenance).

This clinical study report summarizes final analysis data from part 2 of the study using a data from the final data lock of 01 May 2013.

Number of Subjects Planned: Part 1: 24 to 108 subjects (approximately 6 to 9 subjects per dose cohort); part 2: 180 subjects (60 per treatment arm).

Diagnosis and Main Criteria for Eligibility: In part 1 and part 2 of the study, the main inclusion criteria included histologically or cytologically confirmed small cell lung cancer (SCLC), extensive stage; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; life expectancy ≥ 3 months; and men or women ≥ 18 years of age.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Part 1: In cohorts 1 and 2, ganitumab was to be administered intravenously (IV) over 60 minutes at 18 mg/kg Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin). The ganitumab dose could be de-escalated to 9 mg/kg Q3W or 4.5 mg/kg Q3W based on the incidence of DLTs. In cohorts 3 and 4, rilotumumab was administered IV over 60 minutes at 15 mg/kg Q3W following administration of chemotherapy (etoposide plus carboplatin or

cisplatin). The rilotumumab dose could be de-escalated to 7.5 mg/kg Q3W or 3 mg/kg Q3W based on the incidence of DLTs.

Part 2: Ganitumab was to be administered IV over 60 minutes at the dose selected in part 1 Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin). Rilotumumab was to be administered IV over 60 minutes at the dose selected in part 1 Q3W following administration of chemotherapy (etoposide plus carboplatin or cisplatin).

Ganitumab and rilotumumab lot numbers are provided in Section 16.1.6.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
Part 2: Placebo was to be administered IV over 60 minutes following administration of chemotherapy (etoposide plus carboplatin or cisplatin).

Placebo lot numbers are provided in Section 16.1.6.

Manufacturing batch numbers are provided in Section 16.1.6.

Cotherapy: In part 1 and part 2, chemotherapy was administered prior to administration of investigational product (ganitumab, rilotumumab, or placebo). Etoposide was to be administered IV over 90 minutes at 100 mg/m^2; carboplatin was to be administered IV over 30 minutes at area under the concentration-time curve (AUC) = 5 mg/mL•min; and cisplatin was to be administered IV over 60 minutes at 75 mg/m^2.

Duration of Treatment: Every 3 weeks for up to 24 months from the date of first study treatment administration (study day 1). Study treatment was to cease if a subject withdrew consent or experienced disease progression, death, or unacceptable toxicity or based on administrative decision by the investigator or Amgen. After stopping study treatment, subjects were to be followed every 3 months for up to 36 months to assess disease status and survival. Subjects who had completed 24 months of investigational product could be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism.

Study Endpoints:

Primary Endpoints

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities as defined as DLT.

Part 2:

- Overall survival

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as DLT.
- The incidence of anti-ganitumab and anti-rilotumumab antibody formation.
- Pharmacokinetics (C_{max} and C_{min} for ganitumab and rilotumumab).

Part 2:

- Progression-free survival.
- Time to progression.
- Objective response rate.
- Duration of response.
- Median overall survival and overall survival rates at 10,12, 24, and 36 months.

- The incidence of adverse events and laboratory abnormalities.
- The incidence of anti-ganitumab and anti-rilotumumab antibody formation.
- Pharmacokinetics (C_{max} and C_{min}) for ganitumab and rilotumumab.
- Change in patient-reported outcomes as assessed with the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13).

Statistical Methods:

Data from part 1 and part 2 were analyzed separately. The primary analysis occurred when approximately 130 deaths had occurred. The data cutoff date for the primary analysis was 11 April 2012. The data cutoff date for the final analysis was 01 May 2013.

Efficacy data for part 1 were listed by subject.

For part 2, the primary efficacy endpoint was overall survival, analyzed using a Cox regression model stratified by randomization stratification factors (chemotherapy and gender) and controlled for the lactate dehydrogenase (LDH) level. A Wald chi-square test provided a descriptive p-value for the hazard ratio. Both 80% and 95% confidence intervals (CIs) for the hazard ratio for treatment comparison were provided. A stratified log-rank test was provided for each pair of treatment groups (arm A versus arm C and arm b versus arm C) for a descriptive comparison. Kaplan-Meier curves were also generated for each treatment group.

Analyses of the secondary endpoint of progression-free survival were performed in accordance with the methodologies described for overall survival. The proportion of subjects with an objective response (complete or partial response per modified RECIST, confirmed by subsequent assessment) was presented as a binominal rate for each treatment group in part 2 of the study. The Wilson's score method with continuity correction was used to estimate the differences and corresponding 80% and 95% CIs for the differences in the objective response rates for arms A and C and arms B and C.

Serum concentrations of ganitumab and rilotumumab were analyzed for C_{max} and C_{min}, and plasma concentrations of etoposide, cisplatin, and carboplatin were analyzed for C_{max} and AUC.

[redacted]

Patient-reported outcome data from the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were summarized descriptively.

A mixed-effects piecewise linear model was to be generated to compare the treatment groups from baseline through the safety follow-up assessment. Randomization stratification factors and prespecified covariates were included as covariates in the model.

The safety analyses included DLTs (part 1), adverse events, clinical laboratory tests, and clinically significant changes in vital signs and electrocardiograms for part 1 and part 2. The incidences of subjects developing anti-ganitumab and anti-rilotumumab antibodies in at least 1 time point were also listed.

Summary of Results:

In the primary analysis clinical study report (CSR), dated 31 May 2013, data were presented for part 1 and 2 of the study based on a data cutoff date of 11 April 2012. The results presented in this final CSR include all the subjects in part 2 based on a final data lock date of 01 May 2013, triggered by the last subject ending the study.

Subject Disposition:

As described in the primary analysis CSR, a total of 185 subjects were randomized into part 2 of study (full analysis set). There were 62 subjects in the ganitumab plus chemotherapies treatment arm, 62 subjects in the rilotumumab plus chemotherapies treatment arm, and 61 subjects in the placebo plus chemotherapies treatment arm. The number of subjects who received at least

1 dose of all protocol-specified treatment in the ganitumab, rilotumumab, and placebo treatment arms was 59, 61, and 59, respectively. At the time of the primary analysis, 1 subject in the ganitumab treatment arm was continuing protocol-specified therapy and 28 (15%) subjects overall remained in the study and have since discontinued the study. The 1 subject in the ganitumab treatment arm who was still receiving treatment at the time of the primary analysis discontinued ganitumab due to disease progression. Of the 28 subjects who were on study at the time of the primary analysis, 1 subject withdrew consent, 19 subjects died, and 8 subjects discontinued due to other reasons. The most common reason for discontinuing the study in all 3 arms was death (87%, 87%, and 85%, respectively in the ganitumab, rilotumumab and placebo treatment arms). The reason for discontinuing investigational product was most often disease progression in the ganitumab (n= 43; 69%), rilotumumab (n=38; 61%) and placebo (n=45; 74%) subjects).

Baseline Demographics:

Baseline demographics and disease characteristics for subjects in the final analysis of part 2 of the study were consistent with those previously discussed in the primary analysis CSR.

Sex: 142 males (77%) and, 43 females (23%)

Age: mean age of 60.1 years (range: 33 to 79)

Ethnicity/Race: 152 Caucasian (82%), 32 Asian (non-Japanese; 17%), 1 other (1%)

Efficacy Results:

Ganitumab

In part 2 of the study, at the time of the final analysis, the median (95% CI) overall survival time (the primary efficacy endpoint) was 10.7 (8.1, 14.1) months for ganitumab and 10.8 (9.4, 11.9) months for placebo (no change from primary analysis). In the analysis of overall survival there were 54 (87%) and 51 (84%) deaths in the ganitumab and placebo treatment arms, respectively. The overall survival hazard ratio (95% CI), stratified by gender and chemotherapy and controlled by baseline LDH was 1.01 (0.67, 1.52) for the ganitumab treatment arm compared with placebo (p-value = 0.787).

Progression-free survival analyses (a secondary efficacy endpoint) showed median (95% CI) progression-free survival times for the ganitumab and placebo treatment arms that were unchanged from the primary analysis at 5.5 (4.4, 5.7) months and 5.4 (4.6, 5.8) months, respectively. The progression free survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 1.03 (0.70, 1.52) for the ganitumab treatment arm compared with placebo (p-value: 0.780).

The objective response rate (percentage [95% CI] of responders) in the ganitumab treatment arm was 63% (50, 75; 39 subjects) and for placebo treatment arm was 59% (46, 71; 36 subjects). The unstratified odds ratio (95% CI) for ganitumab relative to placebo treatment arm was 1.18 (0.54, 2.59).

Rilotumumab

In the final analysis of part 2 of the study, for the primary efficacy endpoint of overall survival, the median (95% CI) overall survival time in the rilotumumab treatment arm was 12.2 (8.8, 14.6) months compared with 10.8 (9.4, 11.9) months in the placebo treatment arm (unchanged from the primary analysis). In the analysis of overall survival, there were 54 (87%) and 51 (84%) deaths in the rilotumumab and placebo treatment arms, respectively. The overall survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 0.91 (0.60, 1.39) for the rilotumumab treatment arm compared with placebo (p-value = 0.384).

In the univariate analysis of baseline covariates (all subjects in the 3 treatment groups), baseline ECOG status of 0 versus 1, 2, baseline LDH ≤ upper limits of normal (ULN) versus > ULN, and age < 65 versus ≥ 65 years demonstrated a significant association with overall survival, and thus could have prognostic relevance.

For the secondary endpoint of progression-free survival, in part 2 of the study, the median (95% CI) progression-free survival time in the rilotumumab and placebo treatment arms were 5.4 (4.4, 5.7) months and 5.4 (4.6, 5.8) months, respectively. The progression-free survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was unchanged from the primary analysis at 1.03 (0.69, 1.52) for the rilotumumab treatment arm compared with placebo (p-value: 0.797).

The objective response rate (percentage [95% CI] of responders) in the rilotumumab treatment arm was 68% (55, 79; 42 subjects) and for the placebo treatment arm was 59% (46, 71; 36 subjects). The unstratified odds ratio (95% CI) for rilotumumab was 1.45 (0.65, 3.26) relative to placebo, which favored rilotumumab.

Patient-reported Outcome Results

The primary analysis CSR summarizes the patient-reported outcomes data. No further analyses were conducted for this final report.

Pharmacokinetic Results

The majority of the PK data have been summarized in the primary analysis CSR. Since the primary analysis CSR, 3 additional samples (2 for ganitumab and 1 for rilotumumab) were collected at follow-up visits. The results of these samples are provided in a PK listing in this final analysis CSR. No additional PK analyses were performed.

Safety Results:

Gantiumab

At the time of the primary analysis CSR, only 1 subject was continuing to receive ganitumab therefore, there was no change from the primary analysis CSR in the total number of subjects who received ganitumab (N = 62). Furthermore, there were no changes in the mean or median number of infusions per subject or time on treatment. At the time of the primary analysis CSR, 7 subjects (11%) in the ganitumab treatment arm were continuing on study, all of which have discontinued from the study.

Since the primary analysis CSR, there were no additional treatment-emergent adverse events reported. Therefore, the results from part 2 of the study are identical to the primary CSR.

Rilotumumab

At the time of the primary analysis CSR, no subjects were continuing to receive rilotumumab, therefore, there was no change from the primary analysis CSR in the number of subjects who received rilotumumab (N = 62) or the extent of exposure. Thirteen subjects (21%) in the rilotumumab treatment arm were continuing on study at the time of the primary analysis CSR, all of which have discontinued from the study.

Since the primary analysis CSR, there were no additional treatment-emergent adverse events reported; therefore the results from part 2 of the study are identical to the primary CSR.

Conclusions:

For ganitumab, treatment at a dose of 18 mg/kg when combined with etoposide plus carboplatin or etoposide plus cisplatin resulted in a median Kaplan-Meier estimate for overall survival of 10.7 months compared to 10.8 months in the placebo treatment arm. The stratified hazard ratio (95% CI) controlled by baseline LDH was 1.01 (0.72, 1.60; p=0.787). Median Kaplan-Meier estimates for progression-free survival times were 5.5 and 5.4 months for ganitumab and placebo treatment arms, respectively. The progression-free survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was1.03 (0.70, 1.52). Objective response rates were 62.9% and 59.0% in the ganitumab and placebo treatment groups, respectively. The objective response unstratified odds ratio (95% CI) for ganitumab relative to placebo was 1.18 (0.54, 2.59). Overall, the efficacy profile of ganitumab remained unchanged from the primary analysis. The safety profile for the combination of ganitumab with etoposide plus carboplatin or cisplatin was consistent with the emerging safety profile of ganitumab and the

chemotherapy background in this population of subjects with extensive SCLC. The overall incidence of adverse events in the ganitumab group was similar to that in the placebo group and remained unchanged from the primary analysis.

For rilotumumab, treatment at a dose of 15 mg/kg when combined with etoposide plus carboplatin or cisplatin resulted in a median Kaplan-Meier estimate for overall survival of 12.2 months compared to 10.8 months in the placebo treatment group. The stratified hazard ratio (95% CI) controlled by baseline LDH was 0.91 (0.69, 1.20; p=0.384). Median Kaplan-Meier estimates for progression-free survival time was 5.4 months in both the rilotumumab and placebo treatment arms. The progression-free survival hazard ratio (95% CI) stratified by gender and chemotherapy and controlled by baseline LDH was 1.03 (0.69, 1.52). The objective response rate was 67.7% compared to 59.0% in the placebo treatment group. The objective response unstratified odds ratio (95% CI) for rilotumumab relative to placebo was 1.45 (0.65, 3.26). The safety profile for the combination of rilotumumab and etoposide plus carboplatin or cisplatin was consistent with the emerging safety profile of rilotumumab and the chemotherapy background in this population. The overall incidence of adverse events in the rilotumumab group was similar to that in the placebo group.

The PK conclusions have not changed from the primary analysis with the 3 additional samples.