2. SYNOPSIS

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

Name of Finished Product: To be determined

Name of Active Ingredient: Rilotumumab (AMG 102)

Title of Study: A Phase 1b/2 Study to Assess the Safety and Efficacy of AMG 102 in Combination with Mitoxantrone and Prednisone in Subjects with Previously Treated Castrate Resistant Prostate Cancer

Investigator(s) and Study Center(s): This study is being conducted at 39 centers in North America, European Union, and Australia. Names and investigators or sponsor's responsible medical officer are provided in Appendix 4.

Publication(s): None.

Study Period: 13 November 2008 (the first subject enrolled in part 1) through 26 August 2010 (the last subject to end investigational product administration). The data cutoff date for the primary analysis report was 14 January 2011. Twenty-five subjects remain in long-term follow-up and 3 subjects remain in the response follow-up.

Development Phase: 1b/2

Objectives:

Primary

Part 1 (Phase 1b, open-label):

- To identify a safe dose level of rilotumumab, up to 15 mg/kg every 3 weeks (Q3W), to combine with mitoxantrone and prednisone (MP)

Part 2 (Phase 2, double-blind):

- To estimate with adequate precision the effect of the addition of rilotumumab to MP, compared with placebo plus MP, as assessed by the hazard ratio for overall survival (OS) of previously treated subjects with castrate-resistant prostate cancer (CRPC)

Secondary

Part 1

- To evaluate the incidence of adverse events, abnormal laboratory values not defined as dose limiting toxicities (DLTs), and anti-rilotumumab antibody formation
- To evaluate the pharmacokinetics (PK) of rilotumumab maximum concentration (C_{max}) and minimum concentration (C_{min})

Part 2

To evaluate the following:

- Progression-free survival (PFS), objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), percentage changes in prostate specific antigen (PSA) level and response rates
- Patient reported outcomes, including pain
- The incidence of adverse events, laboratory abnormalities
- The incidence of anti- rilotumumab antibody formation
- To evaluate the PK (C_{max} and C_{min}) of rilotumumab, and to assess the impact of co-administration of rilotumumab on the PK of mitoxantrone

[redacted]

[redacted]

Methodology:

The study has 2 parts. Part 1 (phase 1b) was designed as an open-label, dose de-escalation study to determine the safety, tolerability, and PK of rilotumumab in combination with MP for subjects with CRPC. Data from part 1 were used to determine the appropriate dose of rilotumumab to study in part 2. Part 2 (Phase 2) was designed as a randomized, double-blind, placebo controlled study to evaluate the efficacy, safety, and PK of rilotumumab in combination with MP in subjects with CRPC.

In part 1, 6 subjects were enrolled to receive open-label rilotumumab 15 mg/kg + MP Q3W. Pending review of safety data from the first 6 subjects, additional cohorts of 6 subjects each could have been enrolled to receive rilotumumab at doses of 7.5 or 5 mg/kg with MP Q3W. The dose of rilotumumab was considered safe in combination with MP in the part 1 of the study if a DLT occurred in $\leq$ 2 of 6 evaluable subjects. If the 15 mg/kg rilotumumab dose was determined safe, then part 2 of the study would be a 3-arm design that evaluated rilotumumab at doses of 15 and 7.5 mg/kg. If the 7.5 or 5 mg/kg rilotumumab doses were considered safe, then part 2 of the study would be a 2-arm design that evaluated either the 7.5 or 5 mg/kg dose.

PSA and patient reported outcomes (PRO) were assessed every 3 weeks for the first 5 cycles, then at every other cycle thereafter. PRO assessments included Brief Pain Inventory-short Form (BPI-SF), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30), and Functional Assessment of Cancer Therapy-Prostate Cancer Subscale (FACT-P PCS). Tumor response was assessed according to modified RECIST, with complete response (CR) or partial response (PR) confirmed $\geq$ 28 days after the criteria for response were first met. Tumor response assessment was performed every 12 weeks (± 7 days) independent of treatment cycle until documented disease progression (radiological or clinical), intolerable adverse event, withdrawal of consent, or study discontinuation occurred. All subjects were to have been followed for survival, with data collected every 3 months after the last safety follow-up visit until 36 months after the date the last subject was randomized into the study.

To assess the impact of rilotumumab on the PK of mitoxantrone, approximately 12 subjects from each arm in part 2 (total of 36 subjects for 3-arm design) were to have been enrolled for PK assessment at selected sites outside of Europe.

Number of Subjects Planned:

Part 1: Up to 36 subjects

Part 2: Up to 135 subjects

Number of Subjects Enrolled: 148 subjects (6 subjects enrolled in part 1 and 142 subjects enrolled in part 2)

Diagnosis and Main Criteria for Eligibility:

- Men $\geq$ 18 years of age
- Pathologically confirmed adenocarcinoma of the prostate
- Progressive disease meeting $\geq$ 1 of the following criteria: a sequence of $\geq$ 2 rising PSA values measured at a minimum of 1 week apart with a 2 ng/mL minimum starting value; progression according to RECIST criteria for measurable lesions, or appearance of 2 or more new lesions on bone scan

- History of prior taxane-based chemotherapy for metastatic prostate cancer; no more than one prior chemotherapy regimen for CRPC was allowed (estramustine was considered a chemotherapy)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Rilotumumab was administered as a continuous intravenous (IV) infusion on day 1 of each 21-day cycle (± 3 days), prior to MP. The first dose rilotumumab was administered over 60 minutes (± 10 minutes). If the first dose was well-tolerated, a 30-minute (± 5 minutes) infusion duration could be used thereafter at the investigator's discretion. In part 1, subjects were to receive 15 mg/kg, 7.5 mg/kg, or 5 mg/kg of rilotumumab, depending of the incidence of DLTs. In part 2, rilotumumab doses of 15 and 7.5 mg/kg were administered. Lot numbers administered in the study were [redacted] for placebo.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Matched placebo was administered as a continuous IV infusion on day 1 of each 21-day cycle (+ 3 days) prior to MP infusions in part 2.

Duration of Treatment: Up to 12 cycles of treatment were to be given. Subjects who discontinued study treatment for reasons other than withdrawal of consent or death were requested to have 2 safety follow-up visits, 1 within 30 days of discontinuing treatment and 1 within 60 days of discontinuing treatment. All subjects were to have been followed for survival, with data collected every 3 months after the last safety follow-up visit until 36 months after the date the last subject was randomized into the study.

Study Endpoints:

Primary Endpoints

- Part 1: the incidence of adverse events defined as DLTs
- Part 2: OS

Secondary Endpoints

Part 1

- Incidence of adverse events, abnormal laboratory values not defined as DLTs, and anti-rilotumumab antibody
- C_{max} and C_{min} of rilotumumab concentration

Part 2

- PFS
- Maximum percentage of change in PSA concentration
- Percent change in PSA concentration from baseline to 12 weeks (or earlier for those subjects who discontinued from treatment)
- PSA response rate (≥ 50% reduction from baseline in PSA concentration)
- Objective response rate (CR and PR per modified RECIST)
- Patient Reported Outcomes (BPI-SF, FACT-P PCS, and EORTC QLQ-C30)
- Incidence of adverse events and significant changes from baseline for laboratory values
- Incidence of anti-rilotumumab antibody formation
- C_{max} and C_{min} for rilotumumab; C_{max} and AUC for mitoxantrone

[redacted]

Statistical Methods:

No formal hypothesis testing was planned; however, the effect of the addition of rilotumumab to MP on OS was estimated in part 2. Descriptive statistics, including confidence intervals were calculated for the study endpoints. For continuous variables, the mean, standard deviation, median, first and third quartiles, and minimum and maximum values were calculated. For categorical variables, the frequency and percentage in each category were calculated. For time-to-event variables, Kaplan-Meier (KM) estimates were calculated. All analyses were conducted separately for part 1 and part 2. A Tarone-ware Trend test was stratified by randomization factors and was performed to assess any increasing trend in OS or PFS among treatment arms.

Summary of Results:

Subject Disposition:

Six subjects were enrolled and received at least 1 dose of 15 mg/kg rilotumumab in part 1 of the study. [redacted]. Two subjects (33%) completed the 12 cycles of protocol-specified therapy and 4 subjects (67%) discontinued investigational product. As of the data cutoff date, 1 subject (17%) remains alive and progression-free, and 5 subjects (83%) died.

A total of 142 subjects were randomized into part 2 of the study and 138 subjects received at least 1 dose of investigational product at 39 investigative centers in Australia, Belgium, Canada, the Czech Republic, Finland, France, the Netherlands, Sweden, or the United States. Four subjects (2 from each rilotumumab arm) who were randomized did not receive investigational product. As of the 14 January 2011 data cutoff date, all subjects either completed or discontinued the investigational product. Overall, 12 subjects (8%) completed the 12 cycles of protocol-specified therapy and 126 subjects (89%) discontinued investigational product.

Baseline Demographics:

(Part 1: subjects enrolled; Part 2: subjects randomized)

Age:

Part 1: mean (standard deviation [SD]) = 66.8 (10.1) years

Part 2: mean (SD) = 67.9 (7.5) years

Ethnicity/Race:

Part 1: 6 [redacted]

Part 2: 129 white (91%), 6 black (4%), 4 Asian (3%), 2 Hispanic (1%), 1 Native Hawaiian or other Pacific Islander (1%)

Efficacy Results:

No efficacy analyses were performed for part 1. Based on the safety results of part 1 (phase 1b), the doses of 7.5 mg/kg and 15 mg/kg rilotumumab in combination with MP were selected for study in part 2 (phase 2). Efficacy results are presented for part 2 of the study only. The efficacy data are based on the primary analysis data cutoff date of 14 January 2011.

At the time of the data cutoff for the primary analysis, 88 subjects (62%) had died on the study. The incidence of death was similar between the combined rilotumumab arms (63%) and the placebo arm (59%). The median (80% confidence interval [CI]) KM estimates for OS were 12.2 months (11.1, 13.9) in the combined rilotumumab arms and 11.1 months (9.0, 12.7) in the

placebo arm. The adjusted hazard ratio (80% CI) for the combined rilotumumab arms compared with placebo was 1.102 (0.820, 1.482; p = 0.673). A Tarone's trend test adjusted for stratification factors of bone pain and response to prior taxane-based chemotherapy (as reported by interactive voice recognition system [IVRS]) indicated no significant dose trend in OS (p = 0.822).

A total of 125 subjects (88%) had a PFS event. The incidence of PFS was similar between the combined rilotumumab arms (87%) and the placebo arm (90%). The median (80% CI) KM estimates for PFS was 3.0 months (2.8, 3.6) in the combined rilotumumab arms, and 2.9 months (2.8, 3.6) in the placebo arm. The adjusted hazard ratio (80% CI) for the combined rilotumumab arm compared with placebo was 1.015 (0.787, 1.309; p = 0.940).

A total of 80 subjects (52 in the combined rilotumumab arms, 28 in the placebo arm) were evaluable for tumor response. No objective responses (CR + PR) were confirmed in this study; however, 3 subjects (2 in the 7.5 mg/kg arm and 1 in the 15 mg/kg arm) had unconfirmed PR. The incidence of stable disease was higher in the placebo group (42.9%) than in the combined rilotumumab arms (36.5%). A total of 142 subjects (93 in combined rilotumumab arms, 49 in the placebo arm) were evaluable for PSA response. Although the incidence of PSA response was also higher in the placebo group (14.3%) than in the combined rilotumumab arms (10.8%), this difference was not considered meaningful.

Pharmacokinetic Results:

The pharmacokinetics of rilotumumab was evaluated following 7.5 and 15 mg/kg Q3W intravenous (IV) infusions in combination with mitoxantrone and prednisone. The rilotumumab serum concentrations increased over time and reached the steady state approximately in cycle 5. Over the 30 minute to 1 hour intravenous infusion, the mean (SD) end-of-infusion concentration (C_{max}) was 179 (35.4) and 356 (90.9) µg/mL in cycle 1, and 297 (74.8) and 609 (126) µg/mL in cycle 5 for the 7.5 and 15 mg/kg arms, respectively. The mean concentrations of the 15 mg/kg dose increased approximately 2-fold over the 7.5 mg/kg dose, indicating that rilotumumab had linear kinetics over the tested doses. The accumulation of end of infusion concentration between cycle 1 and cycle 5 was approximately 1.7-fold in the 2 tested doses under the Q3W regimen. The median AUC (coefficient of variation [CV%]) of mitoxantrone was 218 ng•hr/mL (39.2%) in the placebo arm, which was similar to the median AUC (CV%) of 243 ng•hr/mL (48.8%) in combination rilotumumab arms, suggesting that the mitoxantrone PK was comparable in the absence and presence of rilotumumab. The PK of prednisone was not assessed in this study.

PRO Results:

The PRO analyses will be provided in the final report.

Antibody Results:

Antibody results showed 4 subjects in part 2 (2 subjects in the 7.5 mg/kg rilotumumab arm and 2 in the placebo arm) tested positive for anti-rilotumumab binding antibodies at any time during the study; 2 subjects (3% from part 2 overall or 2% from this study) of subjects treated with rilotumumab developed anti-rilotumumab binding antibodies. No neutralizing antibodies were detected in any of the subjects.

Safety Results:

Part 1: Six subjects received ≥ 1 dose of 15 mg/kg rilotumumab and were included in the Safety Analysis Set. All subjects had at least 1 treatment-emergent adverse event. The most frequent adverse events (≥ 50% of subjects) were nausea, constipation, back pain, and musculoskeletal pain, occurring in 4 subjects each (67%). Five subjects (83%) had adverse events related to investigational product. Overall, adverse events of Common Terminology Criteria for Adverse Events (CTCAE) worst grade ≥ 3 were reported for 4 subjects. Three subjects had serious adverse events and none of these subjects had investigational product-related serious adverse events. There were no treatment-emergent fatal adverse events in part 1 of the study; there were 4 deaths due to disease progression and one death attributed to a stroke that occurred > 30 days after the last dose of investigational product. One subject discontinued investigational product and withdrew from the study due to an adverse event.

In part 1, a total of 4 subjects (67%) had a prespecified adverse event of interest; 4 subjects were reported as having edema and 1 of these subjects also had neutropenia. One subject had a

serious adverse event of peripheral edema, which was considered by the investigator to be related to rilotumumab treatment.

Two subjects were reported as having grade ≥ 3 laboratory chemistry values (glucose, 14.4 mmol/L; albumin 17 and 18 g/L) and 3 subjects were reported as having grade ≥ 3 laboratory hematology values during part 1 of the study. None of the chemistry values was considered an adverse event and 1 subject had hematology laboratory values that were considered to be adverse events (anemia). Other safety data including vital signs and ECOG performance status showed no clear safety signals. Review of concomitant medications did not reveal any administered for additional adverse events not otherwise reported.

In part 1, no DLTs occurred in any subjects in cycle 1. Thus, rilotumumab target dose of 15 mg/kg was considered a tolerable dose to administer in combination with MP in part 2 of this study.

Part 2: In the second part of the study, 138 subjects received ≥ 1dose of investigational product (46 rilotumumab 7.5 mg/kg, 43 rilotumumab 15 mg/kg, and 49 placebo subjects) and were included in the Safety Analysis Set.

Overall, 137 subjects (99%) had ≥ 1 treatment-emergent adverse event during the study. The subject incidence of adverse events was similar across the 3 treatment arms: 100% for 7.5 mg/kg rilotumumab, 98% for 15 mg/kg/kg rilotumumab, and 100% for placebo. Adverse events with the greatest differences (≥ 10%) in subject incidence between combined rilotumumab and placebo arms were peripheral edema (24% rilotumumab and 8% placebo), constipation (20% rilotumumab and 35% placebo), and chest pain (10% rilotumumab and 0% placebo). Edema is an identified event of interest for rilotumumab. Upon medical review of the 9 subjects with treatment-emergent chest pain, it was concluded that chest pain was not a new safety signal associated with rilotumumab. The events of chest pain were reviewed and of the 9 subjects (10 events), all subjects had either a relevant medical history (n = 5), a concurrent adverse event (n = 7) such as events of pulmonary embolism or myocardial infarction, or both (n = 3).

Adverse events the investigators considered related to rilotumumab treatment were reported for 111 subjects (80%); the incidence in the rilotumumab arms and the placebo arm were similar (83% for 7.5 mg/kg rilotumumab, 77% for 15 mg/kg rilotumumab, and 82% for placebo).

The subject incidence of treatment-emergent adverse events worst CTCAE grade ≥ 3 was higher in the rilotumumab arms than placebo (63% rilotumumab and 47% placebo). Across all treatment arms, the most frequently reported worst grade ≥ 3 events were neutropenia (9% rilotumumab combined, 6% placebo), fatigue (7% rilotumumab combined, 10% placebo), pulmonary embolism (11% rilotumumab combined, 8% placebo), leukopenia (6% rilotumumab combined, 2%placebo), bone pain (3% rilotumumab combined, 10% placebo), and anemia (4% rilotumumab combined, 4% placebo).

A total of 34 subjects (25%) had an adverse event leading to study withdrawal or discontinuation from any study treatment component. The subject incidence of adverse events leading to discontinuation of investigational product was higher for the combined rilotumumab arms compared to the placebo arm (26% vs 14%). The most frequently reported adverse events leading to discontinuation of investigational product for the combined rilotumumab arms compared with the placebo arm were: pulmonary embolism (7%, 4%), fatigue (2%, 4%), and aspartate aminotransferase (AST) increased (2%, 0%).

The subject incidence of adverse events leading to discontinuation of MP was also higher for the combined rilotumumab arms compared to the placebo arm (26% vs 14%). The most frequently reported adverse events leading to discontinuation of MP for the combined rilotumumab arms compared with the placebo arm were pulmonary embolism (6%, 4%), AST increased (2%, 0%), bursitis (2%, 0%), deep vein thrombosis (2%, 0%), and fatigue (2%, 0%).

The subject incidence of treatment-emergent serious adverse events was higher for the combined rilotumumab arms compared to placebo (38% vs 33%). The most frequently reported serious adverse events for the combined rilotumumab arms compared with the placebo arm were pulmonary embolism (8%, 8%), nausea (3%, 0%), leukopenia (2%, 0%), and pyrexia (2%, 0%). None of the serious adverse events reported exhibited a ≥ 5% difference between the combined rilotumumab group and the placebo group.

The subject incidence of fatal adverse events was 3% combined rilotumumab arms and 0% placebo. Fatal adverse events reported were cardiac arrest (1 subject, 7.5 mg/kg rilotumumab), pulmonary embolism (1 subject, 7.5 mg/kg rilotumumab), and septic shock (1 subject, 7.5 mg/kg rilotumumab). The investigator considered the adverse events of cardiac arrest and pulmonary embolism as related to the investigational product.

Adverse events of interest were reported for 63% of subjects in the combined rilotumumab arms and 39% in the placebo arm. Overall, edema and neutropenia were the most commonly reported adverse event of interest, occurring in 29% and 17% of subjects, respectively. Edema and neutropenia were reported as $\geq$ 5% higher in the combined rilotumumab arms than in the placebo group. All other adverse events of interest occurred at lower frequencies ($\leq$ 15% of subjects) and were generally balanced between the combined rilotumumab and placebo groups. Overall, 14% of all subjects were reported as having serious adverse events of interest and the incidence of serious adverse events of interest were similar between the combined rilotumumab arms (16%) and the placebo arm (12%).

Analyses of laboratory data showed the overall incidence of shifts to grade 3 to 4 values for hematologic parameters such as lymphocytes (27%), absolute neutrophil count (ANC) (7%), total neutrophils (5%), white blood cells (WBC) (4%), hemoglobin (4%), platelets (1%), and segmented neutrophils (1%). The frequencies of these shifts to grade 3 and 4 values were similar between the combined rilotumumab and placebo groups. The overall incidence of grade 3 and 4 values for chemistry values were higher than 1% for the following parameters: increased alkaline phosphatase (7%); increased aspartate aminotransferase (AST) (6%); decreases sodium (4%); increased glucose (3%); and decrease albumin (3%). The incidence of grade 3 and 4 values was also similar between the combined rilotumumab and placebo groups.

Other safety data including vital signs and ECOG performance status showed no clear safety signals across the treatment groups. Review of concomitant medications did not reveal any administered for additional adverse events not otherwise reported.

Overall, the safety profile was similar between the 2 doses of rilotumumab.

Conclusions:

In summary, rilotumumab in combination with MP did not appear to show an improvement in OS or PFS in subjects with advanced stages of CRPC. In general, the safety profile in this study was similar to that observed in previous trials with rilotumumab with no new safety signals identified in this study. Rilotumumab exhibited linear pharmacokinetics at doses of 7.5 and 15 mg/kg in combination with mitoxantrone and prednisone in prostate cancer patients. The pharmacokinetics of mitoxantrone are comparable with and without rilotumumab co-administration.

2. SYNOPSIS

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

Name of Finished Product: To be determined

Name of Active Ingredient: Rilotumumab (AMG 102)

Title of Study: A Phase 1b/2 Study to Assess the Safety and Efficacy of AMG 102 in Combination with Mitoxantrone and Prednisone in Subjects with Previously Treated Castrate Resistant Prostate Cancer

Investigator(s) and Study Center(s): This study was conducted at 39 centers in North America, the European Union, and Australia. Names of centers and the principal investigator are provided in Appendix 2.

Publication(s): Ryan C, Rosenthal M, Ng S, Alumkal J, Picus J, et al. A multicenter, randomized phase II study of rilotumumab (R) (AMG 102) or placebo (Pbo) plus mitoxantrone (M) and prednisone (P) in patients (pts) with previously treated castrate-resistant prostate cancer (CRPC). *J Clin Oncol*. 2012:30(5) Abstract 115.

Study Period: 13 November 2008 (the first subject enrolled in part 1) through 30 April 2012 (last subject who completed long-term follow-up).

The last subject ended investigational product administration on 26 August 2010 and was included in the primary analysis report (data cutoff date 14 January 2011); at that time, 41 subjects in part 2 and 1 subject in part 1 who were continuing on study have since discontinued.

Development Phase: 1b/2

Introduction and Objectives:

Study 20070611 was a 2-part study consisting of an open-label, dose de-escalation, phase 1b portion followed by a randomized, double-blind, placebo-controlled phase 2 portion to assess the efficacy and safety of AMG 102 in combination with mitoxantrone and prednisone (MP) in subjects with previously treated castrate-resistant prostate cancer.

The primary analysis clinical study report (CSR) for this study was issued on 29 February 2012 and was based on a data cutoff of 14 January 2011. This final abbreviated CSR includes data through the last long-term follow-up visit with a final data cutoff of 30 April 2012. The numbers of subjects in the Safety Analysis Set (138) and Intent-to-Treat Analysis Set (142) in this final abbreviated CSR are consistent with the primary analysis; however, this final abbreviated CSR includes additional safety and efficacy data for the 42 subjects (1 subject from part 1 and 41 subjects from part 2) who remained in the follow-up period as of the data cutoff for the primary analysis (14 January 2011). The purpose of this final abbreviated CSR is to present the final cumulative subject disposition, safety (adverse events), and efficacy (overall survival [OS], progression-free survival [PFS], objective response rate [ORR], and prostate-specific antigen [PSA] response rate) from the study in addition to presenting the patient-reported outcomes data that were not previously summarized.

The primary and secondary objectives of the study are summarized below. Exploratory objectives are summarized in the primary analysis CSR.

Primary

Part 1 (Phase 1b, open-label):

- To identify a safe dose level of rilotumumab, up to 15 mg/kg every 3 weeks (Q3W), to combine with MP

Part 2 (Phase 2, double-blind):

- To estimate, with adequate precision, the effect of the addition of rilotumumab to MP compared with placebo plus MP as assessed by the hazard ratio for OS of previously treated subjects with castrate-resistant prostate cancer (CRPC)

Secondary

Part 1

- To evaluate the incidence of adverse events, abnormal laboratory values not defined as dose-limiting toxicities (DLTs), and anti-rilotumumab antibody formation
- To evaluate the pharmacokinetics (PK) of rilotumumab maximum concentration (C_{max}) and minimum concentration (C_{min})

Part 2

To evaluate the following:

- Progression-free survival, ORR as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), and percentage changes in PSA level and response rates
- Patient reported outcomes, including pain
- The incidence of adverse events or laboratory abnormalities
- The incidence of anti- rilotumumab antibody formation
- To evaluate the PK (C_{max} and C_{min}) of rilotumumab and to assess the impact of coadministration of rilotumumab on the PK of mitoxantrone

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Methodology:

The study had 2 parts. Part 1 (phase 1b) was designed as an open-label, dose de-escalation study to determine the safety, tolerability, and PK of rilotumumab in combination with MP for subjects with CRPC. Data from part 1 were used to determine the appropriate dose of rilotumumab to study in part 2. Part 2 (phase 2) was designed as a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and PK of rilotumumab in combination with MP in subjects with CRPC.

In part 1, 6 subjects were enrolled to receive open-label rilotumumab 15 mg/kg + MP Q3W. Pending review of safety data from the first 6 subjects, additional cohorts of 6 subjects each could have been enrolled to receive rilotumumab at doses of 7.5 or 5 mg/kg with MP Q3W. The dose of rilotumumab was considered safe in combination with MP in part 1 of the study if a DLT occurred in ≤ 2 of 6 evaluable subjects. If the 15 mg/kg rilotumumab dose was determined safe, then part 2 of the study would be a 3-arm design that evaluated rilotumumab at doses of 15 and 7.5 mg/kg. If the 7.5 or 5 mg/kg rilotumumab doses were considered safe, then part 2 of the study would be a 2-arm design that evaluated either the 7.5 or 5 mg/kg dose.

In part 2, PSA was assessed Q3W and patient-reported symptoms were assessed Q3W for the first 5 cycles and every other cycle thereafter. Patient reported outcomes assessments included Brief Pain Inventory-Short Form (BPI-SF), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30), and Functional Assessment of Cancer Therapy-Prostate Cancer Subscale (FACT-P PCS). Tumor response was assessed according to modified RECIST, with complete response (CR) or partial response (PR) confirmed ≥ 28 days after the criteria for response were first met. Tumor response assessment was performed every 12 weeks (± 7 days) independent of treatment cycle until documented disease progression (radiological or clinical, assessed according to Prostate Cancer Working Group consensus guidelines), intolerable adverse event, withdrawal of consent, or study discontinuation occurred. All subjects were to have been followed for survival, with data collected every 3 months after the last safety follow-up visit, until 36 months after the date the last subject was randomized into the study.

To assess the impact of rilotumumab on the PK of mitoxantrone, approximately 12 subjects from each arm in part 2 (total of 36 subjects for 3-arm design) were to have been enrolled for PK assessment at selected sites outside of Europe.

Number of Subjects Planned:

Part 1: Up to 36 subjects

Part 2: Up to 135 subjects

Number of Subjects Enrolled:

Part 1: 6 subjects

Part 2: 142 subjects

The primary analysis CSR (dated 29 February 2012) summarizes baseline demographic and disease characteristics. No further analyses were conducted for this final report.

Diagnosis and Main Criteria for Eligibility:

- Men ≥ 18 years of age
- Pathologically confirmed adenocarcinoma of the prostate
- Progressive disease meeting ≥ 1 of the following criteria: a sequence of ≥ 2 rising PSA values measured at a minimum of 1 week apart with a 2-ng/mL minimum starting value; progression according to RECIST criteria for measurable lesions, or appearance of 2 or more new lesions on bone scan
- History of prior taxane-based chemotherapy for metastatic prostate cancer; no more than 1 prior chemotherapy regimen for CRPC was allowed (estramustine was considered a chemotherapy)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number:
Rilotumumab was administered as a continuous intravenous (IV) infusion on day 1 of each 21-day cycle (± 3 days) prior to MP. The first dose rilotumumab was administered over 60 minutes (± 10 minutes). If the first dose was well-tolerated, a 30-minute (± 5 minutes) infusion duration could be used thereafter at the investigator's discretion. In part 1, subjects were to receive 15 mg/kg, 7.5 mg/kg, or 5 mg/kg of rilotumumab, depending of the incidence of DLTs. In part 2, rilotumumab doses of 15 and 7.5 mg/kg were administered. Lot numbers are provided in the primary analysis CSR (dated 29 February 2012).

Duration of Treatment: Up to 12 cycles of treatment were to be given. Subjects who discontinued study treatment for reasons other than withdrawal of consent or death were requested to have 2 safety follow-up visits, 1 within 30 days of discontinuing treatment and 1 within 60 days of discontinuing treatment. All subjects were to have been followed for survival, with data collected every 3 months after the last safety follow-up visit until 36 months after the date the last subject was randomized into the study.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: Matched placebo was administered as a continuous IV infusion on day 1 of each 21-day cycle (+ 3 days) prior to MP infusions in part 2.

Study Endpoints

Primary Endpoints

- Part 1: Incidence of adverse events defined as DLTs
- Part 2: Overall survival

Secondary Endpoints

Part 1

- Incidence of adverse events, abnormal laboratory values not defined as DLTs, and anti-rilotumumab antibody formation
- C_{max} and C_{min} of rilotumumab concentration

Part 2

- Progression-free survival
- Maximum percentage of change in PSA concentration
- Percent change in PSA concentration from baseline to 12 weeks (or earlier for those subjects who discontinued from treatment)
- Prostate-specific antigen response rate (≥ 50% reduction from baseline in PSA concentration)
- Objective response rate (CR and PR per modified RECIST)
- Patient reported outcomes (BPI-SF, FACT-P PCS, and EORTC QLQ-C30)
- Incidence of adverse events and significant changes from baseline for laboratory values
- Incidence of anti-rilotumumab antibody formation
- C_{max} and C_{min} for rilotumumab; C_{max} and area under the concentration-time curve (AUC) for mitoxantrone

Exploratory endpoints are summarized in the primary analysis CSR (dated 29 February 2012).

Statistical Methods:

No formal hypothesis testing was planned; however, the effect of the addition of rilotumumab to MP on OS was estimated in part 2. Descriptive statistics, including confidence intervals were calculated for the study endpoints. For continuous variables, the mean, standard deviation, median, first and third quartiles, and minimum and maximum values were calculated. For categorical variables, the frequency and percentage in each category were calculated. For time-to-event variables, Kaplan-Meier (KM) estimates were calculated. All analyses were

conducted separately for part 1 and part 2. A Tarone-ware Trend test was stratified by randomization factors and was performed to assess any increasing trend in OS or PFS among treatment arms.

Adverse events were summarized by system organ class and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v3.0). Subject incidences of adverse events were tabulated from first dose through 30 days after the last dose of protocol-specified treatment (excluding prednisone). Designated adverse events of interest for rilotumumab were edema, neutropenia, stroke, venous and arterial thrombotic events, drug-related hepatic disorders, thrombocytopenia, and infusion reaction; preferred terms included in the search strategies are provided in Appendix 10. The Medical Dictionary for Regulatory Affairs (MedDRA) version 13.1 was used for the primary analysis CSR and version 15.0 was used for the final analysis CSR. In the primary analysis CSR, the focus of the results was on the broad search strategies used for the prespecified events of interest; however, in this final analysis CSR, the focus of the results was on the narrow search strategies.

Summary of Results:

Subject Disposition:

No additional subjects were enrolled since the primary analysis CSR; therefore, a total of 6 subjects were enrolled and received at least 1 dose of 15-mg/kg rilotumumab in part 1 of the study. Two subjects (33%) completed the 12 cycles of protocol-specified therapy and 4 subjects (67%) discontinued investigational product. As of the primary analysis data cutoff date, 1 subject (17%) remained alive and progression-free and 5 subjects (83%) died. The 1 subject in part 1 of the study who was alive and progression-free at the time of the primary analysis CSR has died.

A total of 142 subjects were randomized into part 2 of the study and 138 subjects received at least 1 dose of investigational product. Four subjects (2 from each rilotumumab arm) who were randomized did not receive investigational product. Overall, 12 subjects (8%) completed the 12 cycles of protocol-specified therapy and 126 subjects (89%) discontinued investigational product. At the time of the primary analysis, 28 subjects were alive and progression free (17 subjects who received rilotumumab and 11 subjects who received placebo) and 26 subjects were alive with disease progression (17 subjects who received rilotumumab and 9 subjects who received placebo). Of these 54 subjects, 13 subjects withdrew consent or left the study for administrative reasons leaving 41 subjects (24 who received rilotumumab and 17 who received placebo) in part 2 who were continuing follow-up on the study and have since discontinued the study. Of the 41 subjects who were on study at the time of the primary analysis CSR, 29 subjects died, 11 subjects discontinued due to administrative decisions, and 1 subject was lost to follow-up.

Efficacy Results:

No efficacy analyses were performed for part 1; thus, efficacy results are presented for part 2 of the study only. The efficacy data are based on the final analysis data cutoff date of 30 April 2012.

At the time of the data cutoff for the primary analysis, 88 subjects (62%) in part 2 had died on the study. Since the primary analysis, 28 additional subjects in part 2 have died; therefore, a total of 116 subjects (82%) died and had a date of death available for the analysis and 26 subjects (18%) were censored in the final analysis. One subject in part 2 died, but a complete death date was not provided and, thus, the subject was censored in the final analysis. The incidence of death was identical between the combined rilotumumab arms (82%) and the placebo arm (82%). The median (80% confidence interval [CI]) KM estimates for OS in the final analysis were consistent with the primary analysis and were 12.2 months (11.1, 13.9) in the combined rilotumumab arms and 11.1 months (9.0, 12.7) in the placebo arm. The hazard ratio (80% CI) for the combined rilotumumab arms compared with placebo was 1.114 (0.864, 1.437; p = 0.583).

At the time of the primary data cutoff date, a total of 125 subjects (88%) had a PFS event. Since the primary analysis data cutoff date, 4 additional subjects had a PFS event; therefore, a total of 129 subjects (91%) had a PFS event. Similar to the primary analysis, the incidence of PFS was similar between the combined rilotumumab arms (90%) and the placebo arm (92%). The median (80% CI) KM estimates for PFS are 3.0 months (2.8, 3.5) in the combined rilotumumab arms and 2.9 months (2.8, 3.6) in the placebo arm. The adjusted hazard ratio (80% CI) for the combined rilotumumab arm compared with placebo was 1.004 (0.783, 1.288; p = 0.984).

Compared to the primary analysis, 2 fewer subjects (1 in the placebo arm and 1 in the 15-mg/kg rilotumumab arm) who were initially considered evaluable for tumor response in primary analysis were later determined to not have measurable disease at baseline; this resulted in a total of 78 subjects (51 in combined rilotumumab arms, 27 in the placebo arm) that were evaluable for tumor response in the final analysis. Consistent with the primary results, no objective responses (CR + PR) were confirmed in this study; however, 3 subjects (2 in the 7.5-mg/kg arm and 1 in the 15-mg/kg arm) had unconfirmed PR. The incidence of stable disease was numerically higher in the placebo group (40.7%) than in the combined rilotumumab arms (37.3%).

Patient reported outcome data showed there was little evidence of a treatment effect (rilotumumab compared with placebo) on BPI-SF, FACT-P PCS, and EORTC QLQ-C30, indicating that these treatments did not negatively impact quality of life in these subjects compared with placebo.

Safety Results:

At the time of the primary analysis CSR, all subjects in part 1 and part 2 had either completed or discontinued investigational product; however, additional prednisone exposure data was received after the primary analysis CSR for 1 subject (part 2) in the 15-mg/kg rilotumumab arm; the additional data did not affect the overall results.

No additional treatment-emergent fatal adverse events were reported since the primary analysis data cutoff date (14 January 2011) in part 1 or part 2; however, 3 additional serious adverse events (cardiac failure in 2 subjects) were reported in part 2. The additional cardiac failure events were reported in 1 subject receiving rilotumumab 15 mg/kg (grade 4 and grade 5) and 1 subject receiving placebo (grade 3). These events occurred 638 and 407 days after the last dose of rilotumumab and placebo, respectively, but were assessed by the investigator as treatment related. Two serious adverse events from the primary analysis (grade 3 pain and grade 3 pyrexia) were no longer considered serious adverse events in the final analysis. One grade 5 serious adverse event from the primary analysis (general physical health deterioration) was changed to a grade 4 serious adverse event in the final analysis and the cause of death was listed in the final analysis as disease progression.

No additional adverse events led to withdrawal or discontinuation of investigational product; however, 2 adverse events of pulmonary embolism (part 2) were no longer considered by the investigator as an adverse event that led to discontinuation of investigational product. Additional adverse events since the primary analysis CSR that demonstrated a ≥ 5% difference between rilotumumab and placebo were neutropenia (17%, 8%) and bone pain (12%, 18%); otherwise, the incidence of all other adverse events with a ≥ 5% difference between rilotumumab and placebo are consistent with the primary analysis. Grade ≥ 3 adverse events and treatment-related adverse events in part 1 and part 2 were consistent with the events reported in the primary analysis CSR.

Prespecified adverse events of interest included edema, neutropenia, stroke, embolic/thrombotic events (venous and arterial), drug-related hepatic dysfunction, thrombocytopenia, and infusion reaction. Gastric hemorrhage, which was considered an event of interest for the primary analysis, is no longer deemed a potential safety risk of rilotumumab and, thus, was no longer considered an adverse event of potential interest for the final analysis. In part 1, there were no changes in the frequencies of adverse events of interest; with 4 subjects (67%) having an

adverse event of interest and edema was the most common event. In part 2, the frequencies of adverse events of interest were similar to the primary analysis and occurred in 63% of subjects in the combined rilotumumab arm and 37% of subjects in the placebo arm (compared to 63% and 39% of subjects in the primary analysis). Similar to the primary analysis, edema and neutropenia were the most commonly reported adverse events of interest occurring in 26% and 16% of subjects, respectively, in the combined rilotumumab and placebo arms (compared to 29% and 17% of subjects in the primary analysis). All other adverse events of interest occurred at lower frequencies (≤ 15% of subjects), were reported at rates similar to the primary analysis, and showed a < 5% difference between the combined rilotumumab and placebo arms.

Conclusions:

This final abbreviated CSR updates the primary analysis CSR with additional data from the follow-up period of the study. The additional data do not change the conclusion of the primary analysis CSR: rilotumumab in combination with MP did not appear to show an improvement in OS or PFS in subjects with advanced stages of CRPC. The estimated hazard ratios (80% CI) from the final analysis were 1.114 (0.864, 1.437; p = 0.583) for OS and 1.004 (0.783, 1.288; p = 0.984) for PFS. In general, the safety profile was similar to that observed in previous trials with rilotumumab with no new safety signals identified in this study.