2. SYNOPSIS

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

Name of Finished Product: rilotumumab (AMG 102)

Name of Active Ingredient: rilotumumab (AMG 102)

Title of Study: A Multicenter, Double-Blind, 3-Arm, Phase 1b/2 Study in Subjects with Unresectable Locally Advanced or Metastatic Gastric or Esophagogastric Junction Adenocarcinoma to Evaluate the Safety and Efficacy of First-line Treatment with Epirubicin, Cisplatin, and Capecitabine (ECX) plus AMG 102

Investigators and Study Centers: This study was conducted at 42 centers in Asia, Australia, Europe, and North America. Principal investigators are listed in Appendix 4.

Publication(s): Iveson T, Donehower RC, Davidenko I, et al. Safety and Efficacy of Epirubicin, Cisplatin, and Capecitabine (ECX) Plus Rilotumumab as First-line Treatment for Unresectable Locally Advanced or Metastatic Gastric or Esophagogastric Junction (EGJ) Adenocarcinoma [abstract]. *Eur J Cancer*. 2011;47(suppl 1):S443. Abstract 6504.

Study Period: The first subject was enrolled on 05 February 2009. This study is ongoing; the primary analysis data cutoff date for this report was 30 November 2010. Two ad hoc updated analyses were conducted for the phase 2 portion of the study with data cutoff dates of 01 April 2011 and 16 January 2012, respectively.

Development Phase: 1b/2

Objectives:

Primary

Part 1 (phase 1b-open label):

- To identify safe dose levels of rilotumumab, up to 15 mg/kg Q3W, to combine with ECX

Part 2 (phase 2-double-blind):

- To estimate with pre-specified precision the effect of the addition of rilotumumab to ECX on the progression free survival (PFS) of previously untreated subjects with unresectable, locally advanced, or metastatic gastric or (EGJ) adenocarcinoma

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 and minimum concentrations [C_{max} and C_{min}]).

Part 2

- To evaluate the effect of the addition of rilotumumab to ECX on overall survival (OS), response rates, time to response, duration of response, disease control rates, incidence of adverse events, and laboratory abnormalities
- To evaluate the PK (C_{max} and C_{min}) of rilotumumab and estimate the impact of co-administration of rilotumumab to the PK of epirubicin and cisplatin in a subgroup of subjects at selected sites outside of Europe/Asia

[redacted]

Methodology: The study had 2 parts. Part 1 was designed as an open-label, dose de-escalation, phase 1b study to determine the safety and PK profile of rilotumumab administered in combination with the ECX regimen. Part 2 was designed as a randomized, double-blind, placebo-controlled, phase 2 study to assess the efficacy, safety, and PK of rilotumumab + ECX as first-line treatment of advance gastric or EGJ adenocarcinoma.

In part 1, approximately 6 subjects were to be enrolled initially to receive open-label rilotumumab 15 mg/kg + ECX 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 + ECX Q3W. The dose of rilotumumab was considered safe in combination with ECX in part 1 if a DLT occurred in ≤ 2 of 6 evaluable subjects. If the 15 mg/kg rilotumumab dose was determined to be 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. The 15 mg/kg rilotumumab dose was subsequently determined to be safe and well-tolerated; doses of 15 and 7.5 mg/kg were evaluated for safety and efficacy in part 2 of the study.

Tumor response was assessed according to modified Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0), 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 6 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 epirubicin, cisplatin, and capecitabine, approximately 12 subjects from each arm in part 2 (total of 36 subjects for 3-arm design or 24 subjects for 2-arm design) were to have been enrolled for PK assessment at selected sites outside of Europe and Asia.

Number of Subjects Planned: Up to approximately 18 subjects in part 1 and approximately 120 subjects in part 2

Number of Subjects Enrolled: 9 subjects were enrolled in part 1 and 121 subjects were randomized in part 2.

Diagnosis and Main Criteria for Eligibility:

- Men or women ≥ 18 years of age
- Previously untreated, pathologically confirmed, unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma including tumors of the distal esophagus within 5 cm of the EGJ
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate hematologic and organ function as specified in the protocol

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), before chemotherapy infusions. In part 1, subjects received 15 mg/kg of rilotumumab. In part 2, rilotumumab doses of 15 and 7.5 mg/kg were administered. Lot numbers were [redacted].

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 chemotherapy infusions in part 2. Lot numbers were [redacted].

Duration of Treatment: Up to 10 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: PFS

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

- OS, objective response rate (ORR) (defined as CR and PR per RECIST with modifications), disease control rate (CR, PR, and SD per RECIST with modifications), time to response (for responders only), duration of response (for responders only), and change in tumor burden (change in sum of the longest diameter [SLD] of target lesions)
- Incidence of adverse events, significant laboratory value changes from baseline and anti-rilotumumab antibody formation
- C_{max} and C_{min} for rilotumumab; C_{max} and AUC for epirubicin and cisplatin when used with or without rilotumumab in a subgroup of subjects at selected sites outside of Europe and Asia

[redacted]

Statistical Methods: No formal hypothesis testing was planned; however, the effect of the addition of rilotumumab to ECX on PFS was estimated in part 2. Descriptive statistics, including confidence intervals and p-values, if appropriate, 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.

Rilotumumab serum concentrations were tabulated and summary statistics were calculated for each sampling time point and summarized by dose group. Individual PK parameters were estimated and summarized by dose groups. Individual plasma ECX concentration data was determined in a PK substudy. The effect of ECX on rilotumumab PK was investigated by comparing the concentration exposures in the current study to those in the first-in-human study.

[redacted]

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received ≥ 1 dose of rilotumumab, epirubicin, cisplatin, or capecitabine (part 1), or ≥ 1 dose investigational product (part 2); subjects were analyzed according to the treatment received. Adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. The subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to

withdrawal of investigational product, and fatal adverse events was summarized. Adverse events of interest for rilotumumab were summarized (cerebrovascular disorders, edema, embolic/thrombotic events [venous and arterial], gastric hemorrhage, hepatic dysfunction, infusion reaction, neutropenia and thrombocytopenia). Clinical laboratory parameters and vital signs were summarized using descriptive statistics or shift tables. The incidence of subjects developing anti-rilotumumab antibodies was determined.

Summary of Results: The results for parts 1 and 2 are based on the planned primary analyses of the study with a data cutoff date of 30 November 2010. Two updated analyses that included more mature survival data were conducted with data cutoff dates of 01 April 2011 and 16 January 2012.

Subject Disposition: Part 1: Nine subjects were enrolled at centers in the United States and United Kingdom. Seven subjects received ≥ 1 dose of 15 mg/kg rilotumumab; 2 subjects did not receive rilotumumab because of study ineligibility or death. As of the primary analysis data cutoff date, 3 subjects had completed the 10 cycles of protocol-specified therapy and 4 subjects had discontinued rilotumumab due to adverse event (3 subjects) or partial consent withdrawn (1 subject). Four subjects (44%) remained on study; reasons for study discontinuation included death or other.

Part 2: A total of 121 subjects (42 [7.5 mg/kg rilotumumab], 40 [15 mg/kg rilotumumab], 39 [placebo]) were enrolled at 42 centers in Asia, Australia, Europe, and North America. A total of 120 subjects received ≥ 1 dose of investigational product; 1 subject did not receive investigational product due to an adverse event that occurred before the first dose. As of the primary analysis data cutoff date, 14 subjects (12%) have completed the 10 cycles of protocol-specified therapy (8 [7.5 mg/kg rilotumumab], 4 [15 mg/kg rilotumumab], and 2 [placebo]); common reasons for investigational product discontinuation included disease progression (22% combined rilotumumab arms vs 54% placebo) and adverse events (27% vs 8%). A total of 61 subjects (50%) (27 [7.5 mg/kg rilotumumab], 17 [15 mg/kg rilotumumab], 17 [placebo]) remained on study; the most common reason for study discontinuation was death (34% combined rilotumumab arms vs 41% placebo).

Baseline Demographics: (Part 1: 9 subjects enrolled; Part 2: 121 subjects randomized)

Sex: Part 1: [redacted]

Part 2: 88 men (73%), 33 women (27%)

Age (SD): Part 1: mean 60.1 (8.3%) years

Part 2: mean 58.9 (11.6%) years

Ethnicity/Race: Part 1: [redacted]

Part 2: 92 subjects white or Caucasian (76%), 22 Asian (18%), 5 Hispanic or Latino (4%), 1 Black or African American (1%), 1 other (1%)

Efficacy Results: Efficacy results are presented for part 2 of the study only. All efficacy endpoints were assessed in the primary analysis (data cutoff date 30 November 2010). In addition, PFS, OS, and ORR were assessed in an ad hoc updated analysis (01 April 2011) and PFS and OS in a second ad hoc analysis (16 January 2012).

In part 2, the primary objective was to estimate the effect of the addition of rilotumumab to ECX on PFS in gastric cancer. The primary analysis of PFS was conducted when 87 progression events occurred. The median PFS (80% CI) time was longer in the combined rilotumumab + ECX arms than in the placebo+ ECX arm (5.6 months [4.6, 6.8]) vs 4.2 months [3.7, 4.6]), with an absolute difference of 1.4 months. The HR (80% CI), adjusted for locally advanced vs metastatic disease and ECOG performance status at baseline, for the combined rilotumumab + ECX arms compared with placebo + ECX, was 0.59 (0.43, 0.79; stratified log-rank test: p = 0.02). PFS analysis showed a numerically longer PFS time in the 7.5 mg/kg rilotumumab + ECX arm compared with the 15 mg/kg rilotumumab + ECX arm (median PFS time [80% CI]: 6.3 months [4.5, 7.0] vs 5.3 months [4.1, 5.7]). The PFS results from the first updated analysis were consistent with the primary analysis; the median PFS (80% CI) was 5.6 months (4.9, 6.9) vs 4.2 (3.7, 4.6), respectively, for the combined rilotumumab + ECX arm and the placebo + ECX arm. The adjusted HR (80%) for PFS was 0.64 (0.48, 0.85; p = 0.05) in favor of the combined

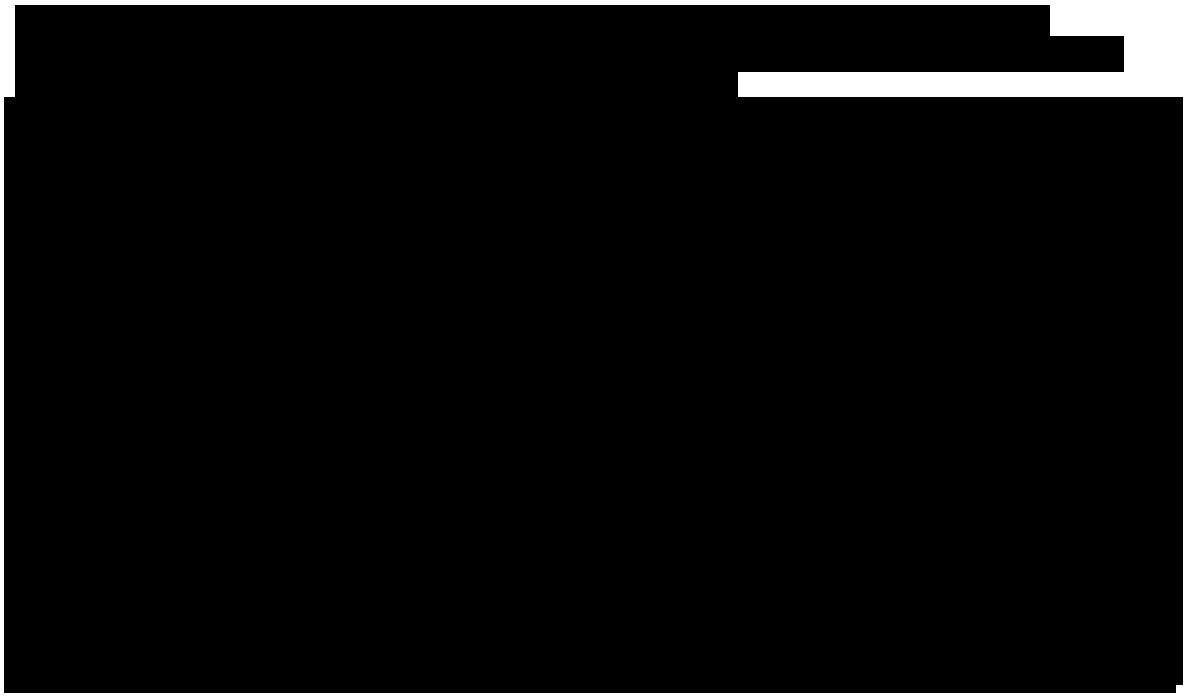
rilotumumab + ECX arms. The PFS results from the second updated analysis were consistent with both the primary and first updated analyses. The median PFS (80% CI) was 5.7 months (5.1, 6.9) vs 4.2 months (3.7, 4.6) in the combined rilotumumab arms vs placebo arms + ECX, respectively; the adjusted hazard ratio (80%) was 0.60 (0.45, 0.79) for the combined rilotumumab arms.

The OS data were immature at the time of the primary analysis (61% censoring). A total of 47 subjects (37% combined rilotumumab + ECX arms, 44% placebo +ECX arm) had died. The adjusted HR for combined rilotumumab arms compared with placebo was 0.71 (0.48, 1.07; p = 0.28). At the time of first updated analysis, 74 subjects had died (60% combined rilotumumab + ECX arms, 64% placebo + ECX arm), allowing for a more robust survival analysis. The median KM (80% CI) estimate for OS was longer in the combined rilotumumab arms than in the placebo arm (11.1 months [9.5, 12.1] vs 8.9 months [5.7, 10.6]), with an absolute increase of 2.2 months. The adjusted HR (80% CI) for combined rilotumumab arms compared with placebo was 0.73 (0.53, 1.01; p = 0.22). The OS results from the second updated analysis were consistent with those from the first updated analysis. The median KM (80% CI) estimate for OS was 11.1 months (9.5, 12.1) vs 8.9 months (5.7, 10.6) in the combined rilotumumab and placebo arms, respectively; the adjusted hazard ratio (80%) was 0.70 (0.53, 0.93) for the combined rilotumumab arms relative to placebo.

Among the 114 subjects with measurable disease at baseline, the ORR (CR + PR) at the primary analysis favored the combined rilotumumab + ECX arms over placebo + ECX (36.8% vs 23.7%). In rilotumumab arms, the confirmed ORR was higher in the 7.5 mg/kg than in the 15 mg/kg rilotumumab + ECX arm (45.0% vs 27.8%). One (2.5%) confirmed CR was observed in the 7.5 mg/kg rilotumumab + ECX arm. Comparisons of combined and individual rilotumumab treatment arms vs placebo using a logistic regression model for ORR yielded odds ratios > 1.0, indicating a favorable outcome for rilotumumab + ECX arms over placebo + ECX. The ORR in the first updated analysis was consistent with the primary analysis, favoring the combined rilotumumab + ECX arms over placebo + ECX (38% vs 21%). One additional subject (7.5 mg/kg rilotumumab) achieved a confirmed PR and 1 subject (placebo) no longer met the criterion for PR. The odds ratios were > 1.0 and improved over those at the primary analysis.

The median time to response was earlier in the placebo + ECX arm (47.2 days) than in the combined rilotumumab + ECX arms (65.1 days). The median duration of response was longer in the combined rilotumumab + ECX arms (5.6 months) than in the placebo + ECX arm (4.2 months).

Pharmacokinetics Results: Pharmacokinetics of rilotumumab was evaluated following 7.5 and 15 mg/kg Q3W IV infusions in combination with ECX. The rilotumumab serum concentrations increased over time and reached the steady state approximately in cycle 5. The mean (SD) end-of-infusion concentration (C_{max}) was 143 (45.1) and 275 (85.4) µg/mL in cycle 1 and 192 (89.7) and 424 (168) µg/mL in cycle 5 for the 7.5 and 15 mg/kg arms, respectively. The mean concentration 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 ≤ 1.5-fold in the 2 doses under the Q3W regimen in this study. Population PK analysis suggested that the rilotumumab concentration was not affected by co-administration of ECX. The PK of epirubicin, cisplatin, and capecitabine could not be assessed due to the limited number of samples collected. Exposure-efficacy analyses, conducted on the datasets for the first update (data cutoff date 01 April 2011) and second update (data cutoff date 16 January 2012) showed a consistent trend indicating that higher rilotumumab exposure was associated with longer survival, especially in subjects with high MET expression levels (MET^{High}, defined as > 50% of tumor cells expressing ≥ 1+ cytoplasmic MET by immunohistochemistry [IHC]). Exposure-safety analyses did not show apparent rilotumumab concentration-dependent adverse effects.



Safety Results: Safety was assessed for both parts 1 and 2 of the study, using data from the primary analysis, as planned. In addition, analyses of exposure, events of interest, neutropenia and thrombocytopenia, and DLTs were conducted using the first updated analysis data; safety in subjects with MET^{High} and MET^{Low} expression was analyzed with the first updated analysis data and compared to the primary analysis of the overall safety analysis set.

Part 1: Seven subjects received ≥ 1 dose of rilotumumab in the phase 1b portion of the study and were included in the Safety Analysis Set. At the time of the DLT safety review (16 July 2009), 7 subjects had received ≥ 1 dose of 15 mg/kg rilotumumab, and 6 subjects had completed the DLT window of ≥ 1 cycle of treatment. No adverse event met the definition for a DLT and a recommendation was made to move into the phase 2 portion of the study using 7.5- and 15-mg/kg rilotumumab doses. Subsequently, 2 adverse events (grade 4 cerebral ischemia and grade 3 deep vein thrombosis [DVT]) reported for 1 subject during the first treatment cycle, that the investigator initially considered not related to rilotumumab, were revised to possibly related and redefined as DLTs.

There were no treatment-emergent fatal adverse events. All subjects had ≥ 1 treatment-emergent adverse event. The most frequent adverse events (subject incidence ≥ 50%) were neutropenia (86%), alopecia and palmar-plantar erythrodysesthesia syndrome (PPES) (71% each), and nausea (57%). Six subjects (86%) had adverse events related to investigational product. Overall, adverse events of CTCAE worst grade ≥ 3 were reported for 7 subjects. Four subjects had serious adverse events and all 4 of these subjects had investigational product-related serious adverse events (cerebrovascular accident and cerebral ischemia: grade 4; nausea and vomiting: grade 2). Three subjects were discontinued from investigational product due to adverse events; there were no study withdrawals due to adverse events. Adverse events led to the discontinuation of ECX in 4 subjects (57%).

Part 2: In the phase 2 portion of the study, 120 subjects received ≥ 1dose of investigational product (42 rilotumumab 7.5 mg/kg, 39 rilotumumab 15 mg/kg, and 39 placebo subjects) and were included in the Safety Analysis Set. Most subjects (99%) had ≥ 1 treatment-emergent adverse event and the incidence was similar across treatment arms.

The subject incidence of treatment-emergent fatal (grade 5) adverse events was as follows: 3 (7%) 7.5 mg/kg rilotumumab, 6 (15%) 15 mg/kg rilotumumab, 9 (11%) combined rilotumumab arms, and 6 (15%) placebo subjects. Fatal adverse event preferred terms reported for > 1 subject were gastric cancer (1 subject combined rilotumumab arms and 1 subject placebo arm), hematemesis (2 subjects in combined rilotumumab arms), and neoplasm progression (2 subjects in the placebo arm).

Those adverse events with a higher subject incidence (≥ 5% difference) in the combined rilotumumab arms compared with placebo were, in order of greatest difference to least, neutropenia (54% rilotumumab, 33% placebo), peripheral edema (27%, 8%), alopecia (41%, 26%), decreased appetite (28%, 15%), anemia (40%, 28%), thrombocytopenia (11%, 0%), nausea (51%, 41%), abdominal pain (20%, 10%), constipation (32%, 23%), leukopenia (11%, 3%), dyspnea (16%, 8%), PPES (23%, 15%), DVT and rhinorrhea (7%, 0%, each), vomiting (35%, 28%), hypoalbuminemia (6%, 0%), stomatitis (9%, 3%), and diarrhea (28%, 23%).

The subject incidence of grade ≥ 3 adverse events was higher for the combined rilotumumab arms (86%) compared to the placebo arm (74%). The subject incidence was ≥ 5% higher for the combined rilotumumab arms compared with placebo for the following preferred terms: neutropenia (44% vs 28%), DVT (7% vs 0%), and thrombocytopenia (6% vs 0%).

More subjects in the combined rilotumumab arms than in the placebo arm had adverse events leading to discontinuation of investigational product (27% vs 13%, respectively). The most frequently reported preferred terms leading to discontinuation of investigational product in the combined rilotumumab arms were pulmonary embolism (5% combined rilotumumab vs 8% placebo), DVT and neutropenia (4% vs 0%, each), and thrombosis (2% vs 0%). Similarly, more subjects in the combined rilotumumab arms than in the placebo arm had adverse events leading to discontinuation of ECX (27% vs 13%, respectively). Of note, subjects who had CTCAE ≥ 3 thrombosis or vascular ischemic events were discontinued from investigational product as specified by the protocol. The most frequently reported preferred terms leading to discontinuation of ECX for the combined rilotumumab arms were vomiting (4% vs 3%), neutropenia (4% vs 0%), and PPES (4% vs 0%). Events leading to discontinuation of ECX that occurred at a higher incidence in the placebo arm than combined rilotumumab arms were fatigue (2% vs 3%), and abdominal pain and decreased creatinine renal clearance (1% vs 3%, each).

The subject incidence of treatment-emergent serious adverse events was higher in the combined rilotumumab arms compared with placebo (58% vs 49%). The most frequently reported serious adverse events (≥ 5% subject incidence) in the combined rilotumumab arms and occurring at a greater incidence than placebo were anemia (12% combined rilotumumab vs 0% placebo), diarrhea (7% vs 5%), neutropenia (7% vs 3%), pulmonary embolism (6% vs 3%), pyrexia (6%, 5%), and febrile neutropenia (each 5%) By system organ class, serious adverse events with ≥ 5% higher subject incidence in the combined rilotumumab arms compared with placebo were in the blood and lymphatic system disorders (22% vs 3%), general disorders and administration site conditions (15% vs 10%), and vascular disorders (7% vs 0%) systems.

Prespecified adverse events of interest were assessed and included edema, gastric hemorrhage, stroke, embolic/thrombotic events (venous and arterial), hepatic dysfunction, and infusion reaction. Recently, neutropenia and thrombocytopenia were added as known or possible risks of rilotumumab and were included in this assessment. Additionally, gastric hemorrhage was removed from the list of possible risks after the primary analysis for this study. Overall, the subject incidence of adverse events of interest, including gastric hemorrhage, was higher in the combined rilotumumab arms than in the placebo arm (77% vs 54%). Events of interest for which the subject incidence was ≥ 5% higher for the combined rilotumumab arms compared with placebo were neutropenia (58% vs 38%), edema (31% vs 8%, respectively), venous thromboembolic events (20% vs 13%), and thrombocytopenia (11% vs 0%).

No cases of confirmed drug-induced liver injury were identified using the parameters recommended in the FDA guidance. The subject incidence of left ventricular ejection fraction (LVEF) ≥ 50% (as measured at the 30-day safety follow-up visit) was 42% in the combined rilotumumab arms vs 41% in the placebo arm, and of LVEF < 50% was 1% vs 3%, and unavailable for 57% vs 56%.

Conclusions: In this study for combined treatment with rilotumumab at doses of 7.5 and 15 mg/kg and ECX compared with ECX alone in subjects with unresectable locally advanced or metastatic gastric or EGJ adenocarcinoma, the primary, the first-updated, and the second-updated analyses of PFS and OS yielded consistent results in favor of the combined rilotumumab + ECX arms. The estimated hazard ratios (80% CI) from the second updated analysis were 0.60 (0.45, 0.79) for PFS and 0.70 (0.53, 0.93) for OS. [redacted]

[redacted]. Rilotumumab exhibited linear pharmacokinetics at doses of 7.5 and 15 mg/kg in combination with ECX. The PK of rilotumumab did not appear to be affected by co-administration of ECX. In addition, higher rilotumumab exposure was associated with longer survival, especially in subjects with high MET expression levels. The safety findings for this study were generally consistent with those observed in earlier studies. Rilotumumab plus ECX may be associated with an increased incidence of neutropenia, alopecia, anemia, venous thromboembolic events, and thrombocytopenia; however, these events can be appropriately managed.

2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Rilotumumab (AMG 102)

Name of Active Ingredient: Rilotumumab (AMG 102)

Title of Study: A Multicenter, Double-blind, 3-Arm, Phase 1b/2 Study in Subjects With Unresectable Locally Advanced or Metastatic Gastric or Esophagogastric Junction Adenocarcinoma to Evaluate the Safety and Efficacy of First-line Treatment With Epirubicin, Cisplatin, and Capecitabine (ECX) Plus AMG 102.

Investigators and Study Centers: This study was conducted at 43 centers in Asia, Australia, Europe, and North America. Centers and principal investigators are listed in Section 16.1.4.

Publications: The publications based on this study are provided in Section 16.1.11.

Study Period: The first subject was enrolled on 05 February 2009 and the last subject completed long-term follow-up on 14 June 2013.

Development Phase: 1b/2

Objectives for Part 1:

Primary:

- to identify safe dose levels of rilotumumab, up to 15 mg/kg every 3 weeks (Q3W), to combine with ECX

Secondary:

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

Objectives for Part 2:

Primary:

- to estimate with pre-specified precision the effect of the addition of rilotumumab to ECX on the progression-free survival (PFS) of previously untreated subjects with unresectable locally advanced or metastatic gastric or esophagogastric junction (EGJ) adenocarcinoma

Secondary:

- to evaluate the effect of the addition of rilotumumab to ECX on overall survival (OS), response rates, time to response, duration of response, disease control rates, incidence of adverse events, and laboratory abnormalities
- to evaluate the PK (C_{max} and C_{min}) of rilotumumab and estimate the impact of co-administration of rilotumumab to the PK of epirubicin and cisplatin in a subgroup of subjects at selected sites outside of Europe/Asia

[redacted]

For additional objectives that are not included in this final analysis report, refer to the Protocol Section 1 (Section 16.1.1).

Methodology: This study had 2 parts.

Part 1 was an open-label, dose de-escalation, phase 1b study to determine the safety, tolerability, and PK profile of rilotumumab in combination with ECX therapy. Part 1 was performed to identify safe dose level of rilotumumab up to 15 mg/kg Q3W to be administered in combination with ECX in part 2. Results for part 1 of the study were previously presented in the primary Clinical Study Report (CSR) dated 20 September 2012. No additional results for part 1 are reported here.

Part 2 was a randomized, double-blind, placebo-controlled, phase 2 study to assess the efficacy, safety, and PK of rilotumumab in combination with ECX as first-line therapy in unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma. Randomization was stratified by the extent of disease (locally advanced vs metastatic disease) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). Part 2 was to commence upon identification of the appropriate dose of rilotumumab to be used in combination with ECX in part 1. Approximately 120 subjects were to be randomized in a 1:1:1 ratio to receive 1 of the following 3 treatments if rilotumumab 15 mg/kg Q3W was determined to be safe in combination with ECX in part 1: rilotumumab 15 mg/kg plus ECX (Arm A), rilotumumab 7.5 mg/kg plus ECX (Arm B), placebo plus ECX (Arm C). If rilotumumab 7.5 or 5 mg/kg Q3W was established as a maximum tolerated dose in combination with ECX in part 1, approximately 80 subjects were to be randomized in a 1:1 ratio to receive rilotumumab (at the maximum tolerated dose) plus ECX or placebo plus ECX.
Rilotumumab 15 mg/kg Q3W was subsequently determined able to be combined with ECX; therefore, doses of 15 and 7.5 mg/kg were evaluated for safety and efficacy in part 2.

Tumor response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.0). Imaging to evaluate tumor response was performed every 6 weeks (± 7days) from study day 1 independent of treatment cycle until documented disease progression (radiological or clinical), intolerable adverse event, withdrawal of consent, or study discontinuation.

Subjects continued to receive treatment until completing 10 cycles of therapy, documented disease progression, intolerable adverse event, withdrawal of consent or study termination by sponsor, whichever occurred first. All subjects were followed for survival unless full consent was withdrawn.

Number of Subjects Planned: Approximately 138 subjects were planned to be enrolled; 18 subjects in part 1 and 120 subjects in part 2.

Diagnosis and Main Criteria for Eligibility: Men or women ≥ 18 years of age; with previously untreated, pathologically confirmed, unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma including tumors of the distal esophagus within 5 cm of the EGJ; ECOG performance status of 0 or 1; life expectancy ≥ 3 months; and laboratory parameters as specified in the Protocol Section 4.1.4 (Section 16.1.1).

A detailed list of inclusion and exclusion criteria is provided in Protocol Section 4 (Section 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Rilotumumab was administered as an intravenous (IV) infusion before chemotherapy infusions: 15 mg/kg in part 1 and 15 and 7.5 mg/kg in part 2. Manufacturing batch numbers were [redacted]

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Matching placebo was administered as an IV infusion before chemotherapy infusions in part 2. Manufacturing batch numbers were [redacted]

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: The investigational product was administered on day 1 of each cycle (21 days [± 3 days]) for up to 10 cycles. The total study duration was approximately 48 months including treatment period, follow-up of subjects within 30 and 60 days of discontinuing treatment for reasons other than withdrawal of consent or death, and survival follow-up 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 for Part 1:

Study endpoints for part 1 were previously analyzed in the primary CSR dated 20 September 2012.

Study Endpoints for Part 2:

Primary Endpoints:

- PFS

Secondary Endpoints:

- OS, objective response rate (ORR) (defined as complete response [CR] and partial response [PR] per RECIST), time to response (for responders only), and duration of response (for responders only)
- incidence of adverse events, significant laboratory value changes from baseline, and anti-rilotumumab antibody formation
- C_{max} and C_{min} for rilotumumab

Additional endpoints for part 2 of this study are not included in this final analysis report (refer to the primary CSR dated 20 September 2012).

Statistical Methods: No formal hypotheses were tested in this study; however, the effect of the addition of rilotumumab to ECX on PFS was estimated. Descriptive statistics including confidence intervals (CI) if appropriate 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.

The final analysis was planned to occur 36 months after the last subject enrolled in part 2 was randomized. Hazard ratios (HR) and two-sided 80% CIs were estimated from Cox proportional hazards models stratified by the randomization factors for PFS and OS. Subjects were analyzed by randomized treatment for efficacy analyses and by actual treatment for safety analyses.

Adverse events were summarized for the first updated analysis (cutoff date of 01 April 2011) using the safety analysis set, which included all randomized subjects who received ≥ 1 dose of the investigational product, epirubicin, cisplatin, or capecitabine. The subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal

adverse events was summarized using the Medical Dictionary for Regulatory Activities (MedDRA) (version 13.1).

With the final analysis data, a subjects listing of new treatment-emergent adverse events occurring after the first updated analysis and treatment-emergent adverse events that were newly reported or updated after the first updated analysis (coded using MedDRA version 16.0) was provided. Clinical laboratory parameters were summarized using descriptive statistics or shift tables. The incidence of subjects developing anti-rilotumumab antibodies was summarized.

Additional information pertaining to the analysis of efficacy, safety, and PK data is provided in the Statistical Analysis Plan (Section 16.1.9).

Summary of Results: In the primary CSR dated 20 September 2012, data were presented for the primary analysis (cutoff date of 30 November 2010), the first updated analysis (cutoff date of 01 April 2011), and the second updated analysis of efficacy (cutoff date of 16 January 2012) conducted for this study. The results of the final analysis triggered by completion of 36 months from the date of randomization of the last subject enrolled in part 2 are presented in this report (final data lock date of 21 August 2013). Throughout the report, the 3 treatment arms in part 2 are referred to as the following: 7.5 mg/kg rilotumumab; 15 mg/kg rilotumumab; and placebo.

Subject Disposition: Part 1: At the time of the primary analysis, all subjects in part 1 were off treatment with 4 subjects remaining on study (follow-up). At the time of this final analysis, all subjects were off study. One subject had completed the phase 1b portion of the study and 8 subjects had discontinued the study (because of death [7 subjects] or other reason [1 subject]).

Part 2: A total of 121 subjects were enrolled and randomized in part 2 (42 [7.5 mg/kg rilotumumab], 40 [15 mg/kg rilotumumab], and 39 [placebo]). Of these, 120 subjects received ≥ 1 dose of the investigational product (rilotumumab or placebo). One subject (from 15 mg/kg rilotumumab) did not receive the investigational product due to an adverse event that occurred before the first dose. By the time of this final analysis, 17 subjects (14%) had completed 10 cycles of protocol-specified therapy (9 [7.5 mg/kg rilotumumab], 5 [15 mg/kg rilotumumab], and 3 [placebo]). A total of 103 subjects (85%) had discontinued the investigational product; 99 subjects (82%) had discontinued epirubicin; 101 subjects (83%) had discontinued cisplatin; and 103 subjects (85%) had discontinued capecitabine. Six subjects (5%) completed the study and 115 subjects (95%) discontinued the study. The most common reason for withdrawal from the study was death (83% [7.5 mg/kg rilotumumab], 80% [15 mg/kg rilotumumab], and 82% [placebo]).

Baseline Demographics: Baseline demographics and disease characteristics were not re-analyzed for this final analysis CSR and were previously summarized in the primary CSR dated 20 September 2012.

Efficacy Results: All efficacy endpoints assessed in the primary analysis (data cutoff date of 30 November 2010); PFS, OS, and ORR assessed in first updated analysis (cutoff date of 01 April 2011); and PFS and OS assessed in a second updated analysis (cutoff date of 16 January 2012) are presented in the primary CSR dated 20 September 2012. This report presents results of the final analysis triggered by completion of 36 months from the date of randomization of the last subject enrolled in part 2 (final data lock date of 21 August 2013).

At the time of this final analysis, 109 subjects (90%) in the intent-to-treat (ITT) set had a PFS event. The median KM (80% CI) estimate for PFS was longer in the combined rilotumumab arm than in the placebo arm (5.7 months [5.1, 6.9] vs 4.2 months [3.7, 4.6])

with an absolute difference of 1.5 months. Analysis of the treatment effect on PFS using a stratified Cox proportional hazard model to compare the combined rilotumumab arms vs placebo arm, resulted in a HR (80% CI) of 0.59 (0.44, 0.78; stratified log-rank test *P* = 0.01). The PFS analysis showed a numerically longer PFS in the 7.5 mg/kg rilotumumab arm compared with the 15 mg/kg rilotumumab arm (median [80% CI] PFS: 6.9 months [5.6, 7.5] vs 5.1 months [3.9, 5.7]). The results of the final analysis of PFS were consistent with all the previous analyses described in the primary CSR dated 20 September 2012.

At the time of this final analysis, 99 subjects (82%) in the ITT set had died (35 subjects [83%] in 7.5 mg/kg rilotumumab arm, 32 subjects [80%] in 15 mg/kg rilotumumab arm, and 32 subjects [82%] in placebo arm). The median KM (80% CI) estimate for OS was numerically longer in the combined rilotumumab arms than in the placebo arm (10.6 months [9.5, 12.0] vs 8.9 months [5.7, 10.6]) with an absolute difference of 1.7 months. The HR (80% CI), adjusted for stratification factors, for the combined rilotumumab arms compared with the placebo arm was 0.71 (0.53, 0.94; stratified log-rank test *P* = 0.12). The median (80% CI) for OS in the 7.5 mg/kg rilotumumab arm and 15 mg/kg rilotumumab arm was 11.1 months (9.5, 12.1) and 9.7 months (7.8, 12.5), respectively.

Among the 114 subjects with measurable disease at baseline, the ORR (CR plus PR) was numerically higher in the combined rilotumumab arms compared with the placebo arm (39.5% vs 21.1%, respectively). In the rilotumumab arms, the ORR was numerically higher in the 7.5 mg/kg arm than in the 15 mg/kg arm (47.5% vs 30.6%, respectively). Only 1 subject (7.5 mg/kg rilotumumab arm) had a confirmed CR.

The median time to response was earlier in the placebo arm (42.5 days) than in the combined rilotumumab arms (50.0 days). The median duration of response was numerically longer in the combined rilotumumab arms (5.7 months) than in the placebo arm (4.1 months).

Pharmacokinetic Results: Exposure-response analyses were performed using the second updated analysis. Data were divided into 2 groups according to the median steady state trough concentration (C_{minss}) value (94 μg/mL) (low exposure group: < median C_{minss}; high exposure group: ≥ median C_{minss}). The median PFS in the placebo, low exposure, and high exposure groups was 4.2, 4.9, and 6.9 months respectively; the median OS in these groups was, 8.9, 9.5, and 13.2 months, respectively, suggesting that higher rilotumumab exposure was associated with longer survival.

A similar exposure-response analysis was performed in subjects grouped according to MET status. In subjects with MET-positive tumors, higher rilotumumab exposure was associated with longer median PFS and OS compared with low exposure or placebo. Subjects with MET-negative tumors showed no beneficial treatment effect in median PFS or HR at either exposure level.

Safety Results: The safety analysis set was used to assess safety endpoints. In the primary CSR dated 20 September 2012, most safety analyses for part 2 were conducted using the primary analysis dataset (cutoff date of 30 November 2010), however, analyses of exposure and analysis of events of interest were conducted on the first updated analysis data (cutoff date of 01 April 2011). Safety in subjects with known MET expression was analyzed with the first updated analysis data and compared to the primary analysis of the overall safety analysis set. In this final analysis report, safety data from the first updated analysis are presented (cutoff date of 01 April 2011); including new treatment-emergent adverse events occurring after the first updated analysis; and treatment-emergent adverse events that were newly reported or had information updated after the first updated analysis.

A total of 80 subjects (99%) in the combined rilotumumab arms and all 39 subjects (100%) in the placebo arm had ≥ 1 treatment-emergent adverse events. Treatment-emergent adverse events with the highest subject incidence in the combined rilotumumab arms compared with the placebo arm (≥ 10% difference) included hematological toxicities (neutropenia [54% combined rilotumumab vs 33% placebo], anemia [42% vs 28%], and thrombocytopenia [11% vs 0%]), nausea (51% vs 41%), alopecia (41% vs 26%), decreased appetite (28% vs 15%), and peripheral edema (27% vs 8%). The subject incidence of grade ≥ 3 treatment-emergent adverse events was higher in the combined rilotumumab arms (88%) than in the placebo arm (74%). Most subjects (97%) had ≥ 1 treatment-emergent adverse event that was considered by the investigator to be related to the investigational product or ECX chemotherapy.

The subject incidence of treatment-emergent adverse events leading to discontinuation of investigational product was higher in the combined rilotumumab arms compared with the placebo arm (28% vs 13%). The most frequently reported preferred terms in the combined rilotumumab arms leading to discontinuation of investigational product were

pulmonary embolism (5% combined rilotumumab vs 8% placebo), deep vein thrombosis (DVT) (4% vs 0%), and neutropenia (4% vs 0%). The subject incidence of treatment-emergent adverse events leading to discontinuation of ECX was also higher in the combined rilotumumab arms compared with the placebo arm (30% vs 13%).

The subject incidences of grade ≥ 3 treatment-emergent adverse events (88% vs 74%) and serious treatment-emergent adverse events (58% vs 51%) were numerically higher in the combined rilotumumab arms compared with the placebo arm. The most frequently reported serious treatment-emergent adverse events in the combined rilotumumab arms (≥ 5% incidence), and occurring at a greater incidence than in the placebo arm, were anemia (12% combined rilotumumab vs 0% placebo), diarrhea (7% vs 5%), neutropenia (7% vs 3%), pulmonary embolism (6% vs 3%), pyrexia (6%vs 5%), febrile neutropenia (5% vs 3%), and hypomagnesemia (5% vs 0%).

No fatal treatment-emergent adverse events were reported in the study after the first updated analysis. The subject incidence of fatal treatment-emergent adverse events at the time of the first updated analysis was 9 subjects (11%) in the combined rilotumumab arms and 6 subjects (15%) in the placebo arm. Fatal treatment-emergent adverse event preferred terms reported for > 1 subject were gastric cancer (1 subject combined rilotumumab and 1 subject placebo), hematemesis (2 subjects combined rilotumumab), and neoplasm progression (2 subjects placebo). None of the fatal treatment-emergent adverse events reported were considered by the investigator to be related to the investigational product.

Fourteen subjects (29 events) in part 2 had treatment-emergent adverse events occurring after the first updated analysis and/or treatment-emergent adverse events that were newly reported or had information updated after the first updated analysis (12 subjects [27 events] combined rilotumumab and 2 subjects [2 events] placebo). Of these, only 1 subject in the placebo arm had treatment-emergent adverse event of anemia occurring after the cutoff date of first updated analysis and 3 subjects (4 events) had treatment-emergent adverse events that were reported after the cutoff date of first updated analysis (anemia [2 subjects] and injection site swelling [1 subject] in the 15 mg/kg rilotumumab arm). None of these events were serious. The remaining 10 subjects had updated information on the treatment-emergent adverse events (updated preferred term, added/updated end date, added relationship or action to the study drug, updated grade).

All subjects in the combined rilotumumab and placebo arms in the MET-positive and MET-negative groups (25% and 50% cutoffs) had ≥ 1 treatment-emergent adverse event. Similar to the overall population, the subject incidences of grade ≥ 3 treatment-emergent adverse events and serious treatment-emergent adverse events were numerically higher in the combined rilotumumab arms compared with the placebo arm for both the MET-positive and MET-negative groups defined by the 25% and 50% cutoffs. The subject incidence of fatal treatment-emergent adverse events in the MET-positive group was 10% rilotumumab vs 18% placebo (25% cutoff) and 4% vs 9% (50% cutoff). The subject incidence of fatal treatment-emergent adverse events in the MET-negative group was 18% rilotumumab vs 9% placebo (25% cutoff) and 18% vs 18% (50% cutoff).

Conclusions:

The results of this final analysis CSR are consistent with the primary CSR. Based on the final analyses conducted following completion of 36 months from the date of randomization of the last subject enrolled in part 2 (final data lock date of 21 August 2013), the following conclusions can be made:

- Treatment with rilotumumab at doses of 7.5 and15 mg/kg combined with ECX compared with ECX alone in subjects with unresectable locally advanced or metastatic gastric or EGJ adenocarcinoma, yielded consistent results in favor of the combined rilotumumab + ECX arms for the final analysis of the primary and secondary endpoints.
  - Final analysis of the primary endpoint, PFS, yielded results in favor of the combined rilotumumab + ECX arms compared with placebo (ECX alone). The adjusted HR (80% CI) was 0.59 (0.44, 0.78; stratified log-rank test *P* = 0.01).
  - Final analyses of the secondary endpoints, OS, ORR, and duration of response were similarly positive and in favor of the combined rilotumumab + ECX arms.
  - Substantial differences in median time to response were not observed across treatment arms; the median time to response was slightly longer in the combined rilotumumab +ECX arms compared with placebo.

[redacted]

- In general, the safety findings in this study were consistent with what has been observed to date for rilotumumab and with those expected from ECX chemotherapy. As noted in the primary CSR, rilotumumab in combination with ECX was associated with an increased incidence of peripheral edema, neutropenia, venous thromboembolism, and thrombocytopenia. In addition, increases in anemia, nausea, alopecia, decreased appetite, and abdominal pain were also noted in this final analysis. No dose-related toxicities were observed and no differences in safety were noted based on MET status (positive or negative at 25% and 50% cutoffs).
- The final analysis of this phase 2 rilotumumab with ECX chemotherapy study in MET-positive gastric cancer supports further development of rilotumumab in phase 3 gastric cancer studies.