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

AMG 479 and AMG 102
Amgen Protocol Number 20060534

Clinical Study Sponsor:	Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: 805.447.0000 Fax: 805.499.9495
Key Sponsor Contacts:	Ada Braun, MD PhD Clinical Research Medical Director Amgen Inc Phone: 805.447.4596 Fax: 805.480.4978 ada.braun@amgen.com Megan Ingram Clinical Research Study Manager - Primary Amgen SF LLC Phone: 650.244.2867 Fax: 650.837.9716 mingram@amgen.com Polly Rawlings Clinical Research Study Manager - Europe Amgen Limited Phone: +44 1895 525476 Fax: +44 1895 525101 prawling@amgen.com
Date:	07 June 2008
EudraCT Number:	2008-003292-42

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer dated 07 June 2008, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal <<*or Coordinating*>> Investigator | Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b/ 2

Indication: Previously Untreated Extensive Stage Small Cell Lung Cancer (SCLC)

Primary Objective:

Part 1: To identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin, and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: To estimate the relative treatment effect of AMG 479 (at the dose selected in Part 1) in combination with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1), and of AMG 102 (at the dose selected in Part 1) in combination with chemotherapy, compared with placebo plus chemotherapy, as measured by the respective hazard ratios (HR) for overall survival (OS).

Secondary Objectives:

Part 1:

- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and the minimum observed serum concentration (C_{min}) for AMG 479 and for AMG 102

Part 2:

- To evaluate clinical benefit as assessed by the objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), median OS (mOS), and OS rates at 10, 12, 24 and 36 months
- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate PK as assessed by C_{max} and C_{min} for AMG 479 and for AMG 102
- To estimate the effect of AMG 479 and of AMG 102 on subject's health related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Exploratory Objectives:

Part 1 and Part 2:

- To evaluate PK as assessed by area under the curve (AUC) and C_{max} for etoposide, cisplatin and carboplatin
- To investigate the relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- To investigate the biomarker profile at baseline, and the pharmacodynamic response, as assessed by biomarkers for AMG 479 (eg, serum IGF-1, IGF-BP3, GH, and other factors involved in regulating the IGF-1/IGF-1R pathway) and for AMG 102 (eg, HGF/SF:c-Met pathway markers, tumor apoptosis markers, angiogenic cytokines and other biomarkers), and correlate with treatment outcomes
- To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets, tumor somatic mutations in drug target, pathway, and cancer genes) by biochemical analysis of blood samples and tumor tissue (if available), and correlate with treatment outcomes
- To investigate the effect of genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlate with treatment outcomes (optional for subjects; requires separate informed consent)

Hypotheses:

Part 1 will identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that is safe and tolerated as determined by the incidence of DLT.

Part 2 will estimate the relative efficacy of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as measured by the respective OS HR. Given a hypothesized HR of 0.74 for each comparison, the target maximum half width of 0.22 for the OS HR 2-sided 80% CI will be achieved after 100 deaths.

Study Design:

This study has 2 parts.

Part 1 is a multi-center, open-label dose de-escalation phase 1b segment of AMG 479 in combination with etoposide plus cisplatin (Cohort 1) or carboplatin (Cohort 2), and of AMG 102 in combination with etoposide plus cisplatin (Cohort 3) or carboplatin (Cohort 4). Once respective doses of AMG 479 and of AMG 102 have been identified that are safe and tolerated based on the incidence of DLT, Part 2 will open for enrollment.

Part 2 is a randomized, double-blind, placebo-controlled phase 2 segment of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as first-line treatment for subjects with extensive stage SCLC. Subjects (n = 180) will be randomized in a 1:1:1 ratio to each treatment arm (n = 60 per arm). Randomization will be stratified according to gender (female; male) and chemotherapy (etoposide and cisplatin; etoposide and carboplatin).

In both parts of the study, chemotherapy (etoposide plus carboplatin or cisplatin) will be administered on day 1 of each 21-day (Q3W) cycle. Etoposide will also be administered on day 2 and 3 of each Q3W cycle. Premedication (see Section 6.2.2.3), vigorous hydration and diuresis (see Section 6.2.2.4) will be required for chemotherapy treatment. Investigational product (IP; AMG 479 [Part 1, Cohorts 1 and 2; Part 2, Arm A] or AMG 102 [Part 1, Cohorts 3 and 4; Part 2, Arm B] or placebo [Part 2, Arm C]) will be administered after the chemotherapy infusion on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter. Four cycles of chemotherapy will be given. Patients with best tumor response (maximum tumor regression, per RECIST) after the

second on-study treatment tumor assessment will receive an additional 2 cycles (a total of 6 cycles) of chemotherapy. Subjects who complete 4 to 6 cycles of chemotherapy or who discontinue chemotherapy early will continue to receive IP (AMG 479, or AMG 102, or placebo) single agent maintenance therapy on day 1 of each Q3W cycle for up to 24 months from the date of first study treatment administration (study day 1). Subjects who have completed 24 months of IP may be eligible for continued treatment with IP by extension protocol or as provided for by the local country's regulatory mechanism (see Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, unacceptable toxicity, withdraws consent, or due to an administrative decision (by the investigator or Amgen).

Radiological imaging to assess PD (per modified RECIST) will be performed every 6 weeks (± 7 days) during the first 6 months of the study, and every 9 weeks (± 7 days) thereafter, until subjects develop PD (per modified RECIST) or begin a new cancer treatment.

A follow-up visit will occur 30 days (+ 7 days) and 60 days (+ 14 days) after the last dose of protocol-specified treatment. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, for up to 36 months from the date of the last subject randomized, to assess survival. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints: See Section 10 for details

Primary Endpoints

Part 1: ▪ The incidence of adverse events and clinical laboratory abnormalities defined as DLT

Part 2: ▪ OS

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min} for AMG 479 and AMG 102)

Part 2:

- ORR, DOR, TTP, PFS, mOS, and OS rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min}) for AMG 479 and AMG 102
- EORTC QLQ-C30 and EORTC QLQ-LC13 scores

Exploratory Endpoints

Part 1 and Part 2:

- PK (AUC and C_{max}) for etoposide, cisplatin and carboplatin
- Relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- Baseline biomarker profile and pharmacodynamic response, as assessed by AMG 479 and AMG 102 biomarkers, and correlation with treatment outcomes
- Biochemical levels and abundance of drug targets and other biomarkers in blood samples and tumor tissue (if available), and correlation with treatment outcomes
- Genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes

Sample Size: Part 1: 24 to 108 subjects; Part 2: 180 subjects

Summary of Subject Eligibility Criteria: See Section 4 for details

Key Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Extensive disease, defined by at least one of the following criteria:
  - No limited disease (ie, no disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field)
  - Extrathoracic metastases
  - Malignant pericardial or pleural effusion
  - Contralateral hilar adenopathy
- Measurable or non-measurable disease, as defined by modified RECIST
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- ≥ 18 years old
- Life expectancy (with therapy) ≥ 3 months
- Adequate hematologic, hepatic, coagulation, renal, and metabolic function
- Diabetes, if present, must be controlled, with glycosylated hemoglobin (HgbA1c) ≤ 8% and fasting blood glucose level ≤ 160 mg/dL

Key Exclusion Criteria

- Prior chemotherapy, chemo-radiation, or investigational agent for SCLC
- Prior radiotherapy to > 25% of the bone marrow
- Symptomatic or untreated central nervous system (CNS) metastasis (with exceptions)
- Currently or previously treated with biological, immunological or other therapies for SCLC
- Current serious or non-healing wound or ulcer
- History of prior or concurrent other malignancy (with exceptions)
- Any clinically significant medical condition other than cancer (eg, cardiovascular disease or chronic obstructive pulmonary disease), which could interfere with the safe delivery of study treatment or increase risk of toxicity

Study Drug Dosage and Administration: See Section 6 for details.

Investigational Product:

Part 1: Cohorts 1a and 2a:
AMG 479 18 mg/kg intravenous (IV) on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 479 18 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Cohort 3a and 4a:
AMG 102 15 mg/kg IV on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 102 15 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Lower doses of AMG 479 and/or AMG 102 may be explored based on safety and PK data, to determine the maximum tolerated dose. Refer to Section 6.1.1.1 for details.

Part 2: AMG 479 (Arm A), AMG 102 (Arm B), at the respective doses selected in Part 1, or matching placebo (Arm C), IV Q3W:
day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

IP dose will be calculated based on the subject's actual body weight at baseline, and the dose is not required to be recalculated unless the actual body weight changes by > 10%. IP will be diluted in 0.9% normal saline.

IP will be administered Q3W, after completion of the chemotherapy infusion (if administered). IP will be administered over 60 minutes (min) (± 15 min). If a dose of IP is well tolerated (ie, without serious infusion-related reactions), then subsequent IV infusions may be given over 30 min (± 10 min). Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Chemotherapy (Part 1 and Part 2):

Etoposide 100 mg/m^2 will be administered IV over 90 min (± 15 min) on days 1, 2, and 3 of each Q3W cycle, per institutional guidelines.

Carboplatin (AUC = 5 mg/mL • min) will be administered IV over 30 min (+ 10 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 60 min for subjects deemed unable to tolerate the 30 min infusion.

Cisplatin 75 mg/m^2 will be administered IV over 60 min (± 15 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Subjects must receive adequate premedication (see Section 6.2.2.3), vigorous hydration and diuresis, and monitoring of fluid status (see Section 6.2.2.4).

Control Group:

Part 1: there is no control group

Part 2: Arm C: Placebo in combination with etoposide plus carboplatin or cisplatin Q3W

Key Study Procedures: See Section 7.1 and Schedule of Assessments (Appendix A) for details.

Screening Procedures

- Review of inclusion and exclusion criteria
- Medication and medical history, concomitant medications/treatment(s), adverse events
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including height and weight
- ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, coagulation, urinalysis, pregnancy test
- If available, submission of paraffin-embedded tumor tissue (paraffin tumor block, or slides) and all available pathology reports
- 12-lead electrocardiogram (ECG)
- Radiological imaging to assess disease extent (CT scan or MRI of the brain, chest, abdomen, and all other sites of disease; within 28 days prior to enrollment)

Treatment and Follow-Up Procedures

- Recording of adverse events and concomitant medications
- Patient completion of EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Part 2)
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, pregnancy test
- Samples for biomarkers and anti-AMG 479 or anti-AMG 102 antibodies
- Samples for AMG 479, AMG 102, carboplatin, cisplatin and etoposide PK (Part 1)
- ECG
- Radiological imaging to assess disease extent (CT scan or MRI [same modality throughout the study] of the chest, abdomen, and all other sites of disease [except: brain imaging only as clinically indicated] every 6 weeks [± 7 days] during the first 6 months of the study, and every 9 weeks [± 7 days] thereafter)

Statistical Considerations: See Section 10 for details.

Analyses will be presented separately for Part 1 and Part 2 of the study. The HR for OS will be estimated using a Cox regression model stratified by randomization stratification factors and controlled for the LDH level as an important covariate. A Wald chi-square test will provide a descriptive p-value for the HR. Overall survival between the respective pair of treatment arms (Arm A/Arm C and Arm B/Arm C) will use a stratified log-rank test for a descriptive comparison.

DRT Safety Reviews and Interim Analysis

For the protection of subjects, in Part 1 of the study, Safety Review Team (SRT) meetings will be held to review safety, laboratory, dosing information and PK data (when available) from each AMG 479 and AMG 102 dose cohort, to make recommendations regarding dose selection for Part 2, dose de-escalation, or dose stopping.

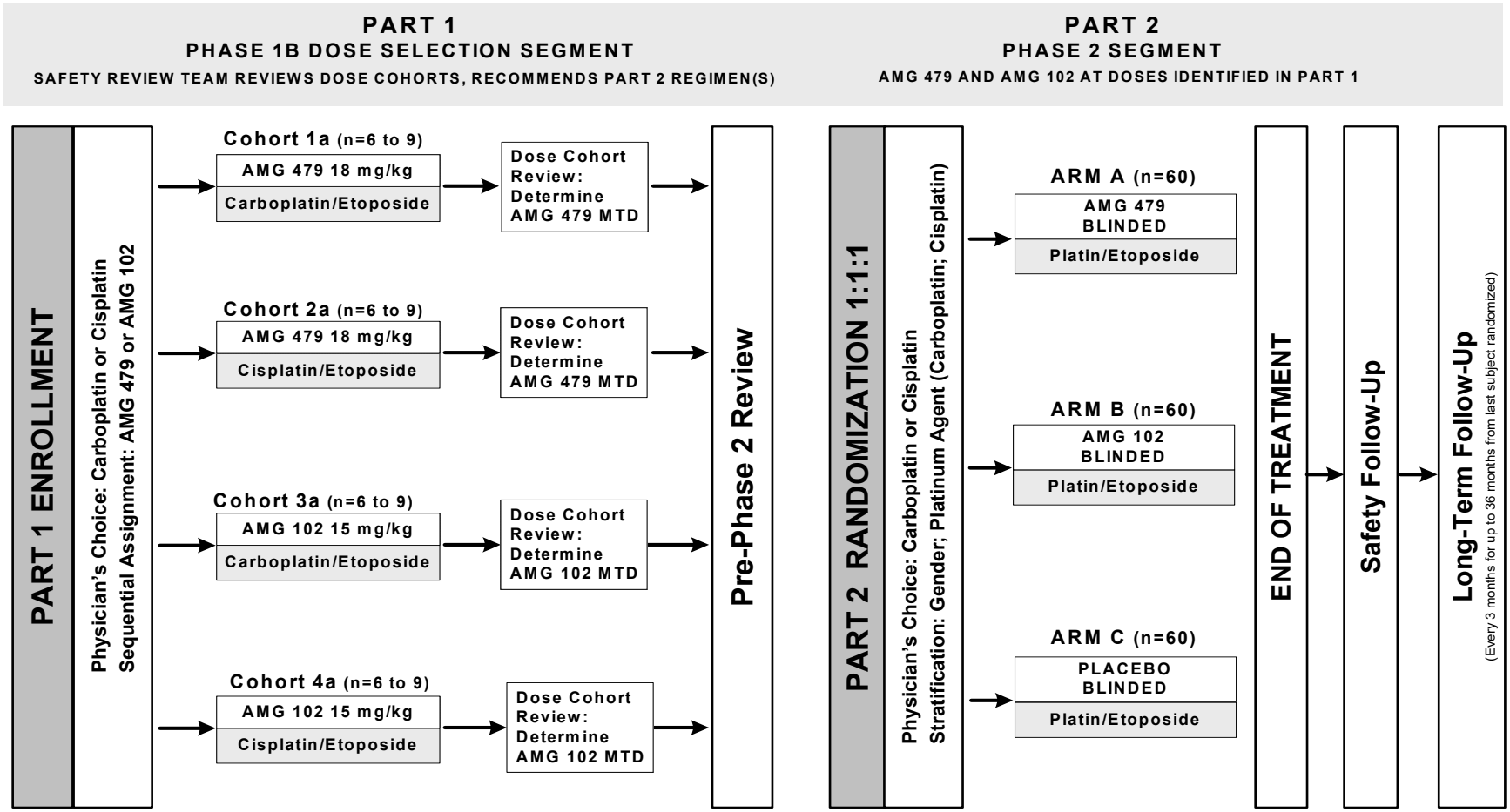
In Part 2, an Amgen Data Review Team (DRT) independent of the study team will perform two unblinded reviews of the safety data after at least 30 and 60 subjects have been randomized and had the opportunity to complete the first cycle of study treatment (safety interim analyses).

One interim efficacy analysis is planned to review both OS and PFS data 10 months after the last subject is randomized. Approximately 100 OS events are estimated (69 OS events per comparison: Arm A/Arm C and Arm B/Arm C) for the interim analysis assuming approximately half of the planned enrollment will occur at 15 months. Review of safety data will also occur during the interim efficacy analysis. The interim efficacy analysis will provide a preliminary assessment of the overall risk/benefit profile. Unless safety concerns arise, the study will not be discontinued or modified due to the results of the interim efficacy analysis.

The primary analysis of Part 2 will be event-driven and will occur after a total of approximately 130 deaths (89 deaths per planned comparison: Arm A/Arm C and Arm B/Arm C), which is anticipated to occur 18 months after end of enrollment. A final analysis is planned after a minimum expected follow-up of 36 months, at which time approximately 163 deaths are expected overall (110 per planned comparison).

Sponsor/Licensee: Amgen Inc

Study Design and Treatment Schema



STUDY TREATMENT (3 Week Cycles)

Chemotherapy: Etoposide (100 mg/m^2 Days 1, 2, 3) and Carboplatin (AUC = 5 mg/mL•min Day 1) or Cisplatin (75 mg/m^2 Day 1)
- **Chemotherapy for 4 Cycles (6 Cycles, if best tumor response [maximum tumor regression, per RECIST] after 2nd tumor assessment)**

Investigational Product: AMG 479 or AMG 102 or Placebo (Part 2 only)
- **Day 2 of initial Cycle**
- **Day 1 of Cycle = 2, up to 24 months from Study Day 1**

Prophylactic Cranial Irradiation (for responding subjects, if not previously administered) prior to IP maintenance treatment

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

AMG 479 and AMG 102

Amgen Protocol Number 20060534

Clinical Study Sponsor:	Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: 805.447.0000 Fax: 805.499.9495
Key Sponsor Contacts:	**Jesse McGreivy, MD** **Clinical Research Medical Director** **Amgen Inc** **Phone: 650.244.2634** **Fax: 650.837.9716** **jessem@amgen.com** Megan Ingram Clinical Research Study Manager - Primary Amgen SF LLC Phone: 650.244.2867 Fax: 650.837.9602 mingram@amgen.com **Jennifer Sampson** **Clinical Research Study Manager - Europe** **Amgen Limited** **Phone: +44 1895 525313** **Fax: +44 1895 525101** **Jennifer.Sampson@amgen.com**
Amendment 1 Date:	**01 April 2009**
Date:	07 June 2008
EudraCT Number:	2008-003292-42

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer dated **Amendment 1 01 April 2009**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal <<*or Coordinating*>> Investigator | Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b/ 2

Indication: Previously Untreated Extensive Stage Small Cell Lung Cancer (SCLC)

Primary Objective:

Part 1: To identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin, and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: To estimate the relative treatment effect of AMG 479 (at the dose selected in Part 1) in combination with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1), and of AMG 102 (at the dose selected in Part 1) in combination with chemotherapy, compared with placebo plus chemotherapy, as measured by the respective hazard ratios (HR) for overall survival (OS).

Secondary Objectives:

Part 1:

- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and the minimum observed serum concentration (C_{min}) for AMG 479 and for AMG 102

Part 2:

- To evaluate clinical benefit as assessed by the objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), median OS (mOS), and OS rates at 10, 12, 24 and 36 months
- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate PK as assessed by C_{max} and C_{min} for AMG 479 and for AMG 102
- To estimate the effect of AMG 479 and of AMG 102 on subject's health related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Exploratory Objectives:

Part 1 and Part 2:

- To evaluate PK as assessed by area under the curve (AUC) and C_{max} for etoposide, cisplatin and carboplatin
- To investigate the relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)

- To investigate the biomarker profile at baseline, and the pharmacodynamic response, as assessed by biomarkers for AMG 479 (eg, serum IGF-1, IGF-BP3, GH, and other factors involved in regulating the IGF-1/IGF-1R pathway) and for AMG 102 (eg, HGF/SF:c-Met pathway markers, tumor apoptosis markers, angiogenic cytokines and other biomarkers), and correlate with treatment outcomes
- To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets, tumor somatic mutations in drug target, pathway, and cancer genes) by biochemical analysis of blood samples and tumor tissue (if available), and correlate with treatment outcomes
- To investigate the effect of genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlate with treatment outcomes (optional for subjects; requires separate informed consent)

Hypotheses:

Part 1 will identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that is safe and tolerated as determined by the incidence of DLT.

Part 2 will estimate the relative efficacy of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as measured by the respective OS HR. Given a hypothesized HR of 0.74 for each comparison, the target maximum half width of 0.22 for the OS HR 2-sided 80% CI will be achieved **after 89 deaths are observed for a pairwise comparison.**

Study Design:

This study has 2 parts.

Part 1 is a multi-center, open-label dose de-escalation phase 1b segment of AMG 479 in combination with etoposide plus **carboplatin** (Cohort 1) or **cisplatin** (Cohort 2), and of AMG 102 in combination with etoposide plus **carboplatin** (Cohort 3) or **cisplatin** (Cohort 4). Once respective doses of AMG 479 and of AMG 102 have been identified that are safe and tolerated based on the incidence of DLT, Part 2 will open for enrollment.

Part 2 is a randomized, double-blind, placebo-controlled phase 2 segment of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as first-line treatment for subjects with extensive stage SCLC. Subjects (n = 180) will be randomized in a 1:1:1 ratio to each treatment arm (n = 60 per arm). Randomization will be stratified according to gender (female; male) and chemotherapy (etoposide and cisplatin; etoposide and carboplatin).

In both parts of the study, chemotherapy (etoposide plus carboplatin or cisplatin) will be administered on day 1 of each 21-day (Q3W) cycle. Etoposide will also be administered on day 2 and 3 of each Q3W cycle. Premedication (see Section 6.2.2.3), vigorous hydration and diuresis (see Section 6.2.2.4) will be required for chemotherapy treatment. Investigational product (IP; AMG 479 [Part 1, Cohorts 1 and 2; Part 2, Arm A] or AMG 102 [Part 1, Cohorts 3 and 4; Part 2, Arm B] or placebo [Part 2, Arm C]) will be administered after the chemotherapy infusion on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter. Four **to six** cycles of chemotherapy will be given. **Determination of the number of cycles of chemotherapy to be administered (between 4 to 6) will be left to the investigator's discretion.** Subjects who complete 4 to 6 cycles of chemotherapy or who discontinue chemotherapy early will continue to receive IP (AMG 479, or AMG 102, or placebo) single agent maintenance therapy on day 1 of each Q3W cycle for up to 24 months from the date of first study treatment administration (study day 1). Subjects who have completed 24 months of IP may be eligible for continued treatment with IP by extension protocol or as provided for by the local country's regulatory mechanism (see Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, unacceptable toxicity, withdraws consent, or due to an administrative decision (by the investigator or Amgen).

Radiological imaging to assess PD (per modified RECIST) will be performed every 6 weeks (± 7 days) during the first 6 months of the study, from Study Day 1 and every 9 weeks (± 7 days) thereafter, until subjects develop PD (per modified RECIST) or begin a new cancer treatment.

A follow-up visit will occur 30 days (+ 7 days) and 60 days (+ 14 days) after the last dose of protocol-specified treatment. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, for up to 36 months from the date of the last subject randomized, to assess survival. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints: See Section 10 for details

Primary Endpoints

Part 1: ▪ The incidence of adverse events and clinical laboratory abnormalities defined as DLT

Part 2: ▪ OS

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min} for AMG 479 and AMG 102)

Part 2:

- ORR, DOR, TTP, PFS, mOS, and OS rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min}) for AMG 479 and AMG 102
- EORTC QLQ-C30 and EORTC QLQ-LC13 scores

Exploratory Endpoints

Part 1 and Part 2:

- PK (AUC and C_{max}) for etoposide, cisplatin and carboplatin
- Relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- Baseline biomarker profile and pharmacodynamic response, as assessed by AMG 479 and AMG 102 biomarkers, and correlation with treatment outcomes
- Biochemical levels and abundance of drug targets and other biomarkers in blood samples and tumor tissue (if available), and correlation with treatment outcomes

- Genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes

Sample Size: Part 1: 24 to 108 subjects; Part 2: 180 subjects

Summary of Subject Eligibility Criteria: See Section 4 for details

Key Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Extensive disease, defined by at least one of the following criteria:
  - No limited disease (ie, no disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field)
  - Extrathoracic metastases
  - Malignant pericardial or pleural effusion
  - Contralateral hilar adenopathy
- Measurable or non-measurable disease, as defined by modified RECIST
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- ≥ 18 years old
- Life expectancy (with therapy) ≥ 3 months
- Adequate hematologic, hepatic, coagulation, renal, and metabolic function
- **Fasting blood glucose ≤ 160 mg/dL**

Key Exclusion Criteria

- Prior chemotherapy, chemo-radiation, or investigational agent for SCLC
- Prior radiotherapy to > 25% of the bone marrow
- Symptomatic or untreated central nervous system (CNS) metastasis (with exceptions)
- Currently or previously treated with biological, immunological or other therapies for SCLC
- Current serious or non-healing wound or ulcer
- History of prior or concurrent other malignancy (with exceptions)
- Any clinically significant medical condition other than cancer (eg, cardiovascular disease or chronic obstructive pulmonary disease), which could interfere with the safe delivery of study treatment or increase risk of toxicity

Study Drug Dosage and Administration: See Section 6 for details.

Investigational Product:

Part 1: Cohorts 1a and 2a:
AMG 479 18 mg/kg intravenous (IV) on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 479 18 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Cohort 3a and 4a:
AMG 102 15 mg/kg IV on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 102 15 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Lower doses of AMG 479 and/or AMG 102 may be explored based on safety and PK data, to determine the maximum tolerated dose. Refer to Section 6.1.1.1 for details.

Part 2: AMG 479 (Arm A), AMG 102 (Arm B), at the respective doses selected in Part 1, or matching placebo (Arm C), IV Q3W:
day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

IP dose will be calculated based on the subject's actual body weight at baseline, and the dose **must** be recalculated **if** the actual body weight changes by > 10%. IP will be diluted in 0.9% normal saline.

IP will be administered Q3W, after completion of the chemotherapy infusion (if administered). IP will be administered over 60 minutes (min) (± 1**0** min). If a dose of IP is well tolerated (ie, without serious infusion-related reactions), then subsequent IV infusions may be given over 30 min (± 10 min). Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Chemotherapy (Part 1 and Part 2):

Etoposide 100 mg/m^2 **to** be administered IV over 90 min (± **30** min) on days 1, 2, and 3 of each Q3W cycle, **or** per institutional guidelines.

Carboplatin (AUC = 5 mg/mL • min) will be administered IV over 30 min (+ 10 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 60 min for subjects deemed unable to tolerate the 30 min infusion.

Cisplatin 75 mg/m^2 will be administered IV over 60 min (± 15 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Subjects must receive adequate premedication (see Section 6.2.2.3), vigorous hydration and diuresis, and monitoring of fluid status (see Section 6.2.2.4).

Control Group:

Part 1: there is no control group

Part 2: Arm C: Placebo in combination with etoposide plus carboplatin or cisplatin Q3W

Key Study Procedures: See Section 7.1 and Schedule of Assessments (Appendix A) for details.

Screening Procedures

- Review of inclusion and exclusion criteria
- Medication and medical history, concomitant medications/treatment(s), adverse events
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including height and weight
- ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, coagulation, urinalysis, pregnancy test
- If available, submission of paraffin-embedded tumor tissue (paraffin tumor block, or slides) and all available pathology reports
- 12-lead electrocardiogram (ECG)
- Radiological imaging to assess disease extent (CT scan or MRI of the brain, chest, abdomen, and all other sites of disease; within 28 days prior to enrollment)

Treatment and Follow-Up Procedures

- Recording of adverse events and concomitant medications
- Patient completion of EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Part 2)
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, pregnancy test

- Samples for biomarkers and anti-AMG 479 or anti-AMG 102 antibodies
- Samples for AMG 479, AMG 102, carboplatin, cisplatin and etoposide PK (Part 1)
- ECG
- Radiological imaging to assess disease extent (CT scan or MRI [same modality throughout the study] of the chest, abdomen, and all other sites of disease [except: brain imaging only as clinically indicated] every 6 weeks [± 7 days] **from Study Day 1** during the first 6 months of the study, and every 9 weeks [± 7 days] thereafter)

Statistical Considerations: See Section 10 for details.

Analyses will be presented separately for Part 1 and Part 2 of the study. The HR for OS will be estimated using a Cox regression model stratified by randomization stratification factors and controlled for the LDH level as an important covariate. A Wald chi-square test will provide a descriptive p-value for the HR. Overall survival between the respective pair of treatment arms (Arm A/Arm C and Arm B/Arm C) will use a stratified log-rank test for a descriptive comparison.

DRT Safety Reviews and Interim Analysis

For the protection of subjects, in Part 1 of the study, Safety Review Team (SRT) meetings will be held to review safety, laboratory, dosing information and PK data (when available) from each AMG 479 and AMG 102 dose cohort, to make recommendations regarding dose selection for Part 2, dose de-escalation, or dose stopping.

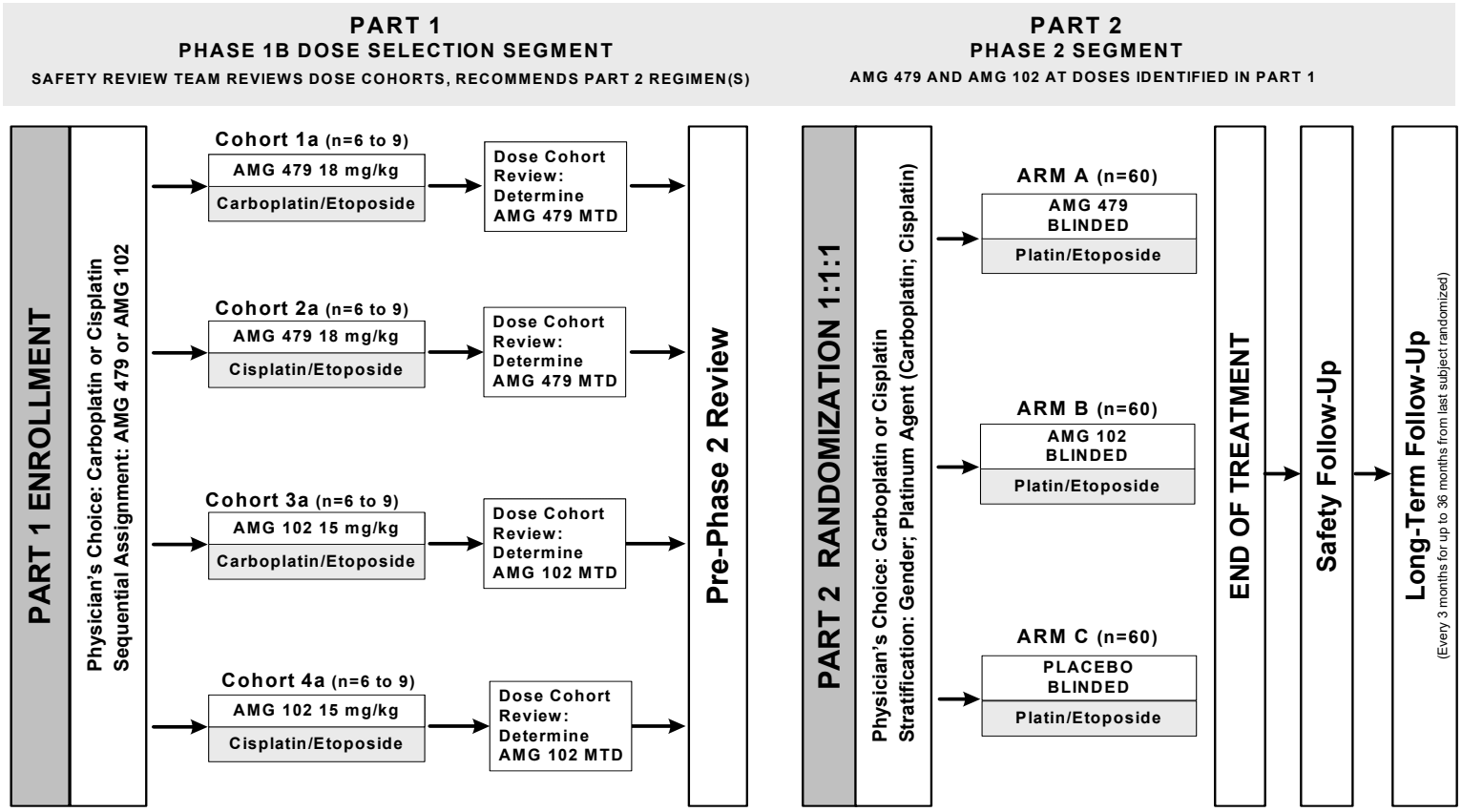
In Part 2, an Amgen Data Review Team (DRT) independent of the study team will perform two unblinded reviews of the safety data after at least 30 and 60 subjects have been randomized and had the opportunity to complete the first cycle of study treatment (safety interim analyses).

One interim efficacy analysis is planned to review both OS and PFS data 10 months after the last subject is randomized. Approximately 100 OS events are estimated (69 OS events per comparison: Arm A/Arm C and Arm B/Arm C) for the interim analysis assuming approximately half of the planned enrollment will occur at 15 months. Review of safety data will also occur during the interim efficacy analysis. The interim efficacy analysis will provide a preliminary assessment of the overall risk/benefit profile. Unless safety concerns arise, the study will not be discontinued or modified due to the results of the interim efficacy analysis.

The primary analysis of Part 2 will be event-driven and will occur after a total of approximately 130 deaths (89 deaths per planned comparison: Arm A/Arm C and Arm B/Arm C), which is anticipated to occur 18 months after end of enrollment. A final analysis is planned after a minimum expected follow-up of 36 months, at which time approximately 163 deaths are expected overall (110 per planned comparison).

Sponsor/Licensee: Amgen Inc

Study Design and Treatment Schema



STUDY TREATMENT (3 Week Cycles)

Chemotherapy: Etoposide (100 mg/m^2 Days 1, 2, 3) and Carboplatin (AUC = 5 mg/mL•min Day 1) or Cisplatin (75 mg/m^2 Day 1)
- Chemotherapy for 4 Cycles (6 Cycles, if best tumor response [maximum tumor regression, per RECIST])

Investigational Product: AMG 479 or AMG 102 or Placebo (Part 2 only)
- Day 2 of initial Cycle
- Day 1 of Cycle = 2, up to 24 months from Study Day 1

Prophylactic Cranial Irradiation (for responding subjects, if not previously administered) prior to IP maintenance treatment

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

AMG 479 and AMG 102

Amgen Protocol Number 20060534

Clinical Study Sponsor:	Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Phone: 805.447.0000 Fax: 805.499.9495
Key Sponsor Contacts:	Jesse McGreivy, MD Clinical Research Medical Director Amgen Inc Phone: 650.244.2634 Fax: 650.837.9716 jessem@amgen.com Megan Ingram Clinical Research Study Manager - Primary Amgen SF LLC Phone: 650.244.2867 Fax: 650.837.9602 mingram@amgen.com Jennifer Sampson Clinical Research Study Manager - Europe Amgen Limited Phone: +44 1895 525313 Fax: +44 1895 525101 Jennifer.Sampson@amgen.com

Amendment 2 Date:	**28 September 2009**
Amendment 1 Date:	01 April 2009
Date:	07 June 2008
EudraCT Number:	2008-003292-42

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer dated **Amendment 2, 28 September 2009**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal <<*or Coordinating*>> Investigator | Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b/ 2

Indication: Previously Untreated Extensive Stage Small Cell Lung Cancer (SCLC)

Primary Objective:

Part 1: To identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin, and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: To estimate the relative treatment effect of AMG 479 (at the dose selected in Part 1) in combination with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1), and of AMG 102 (at the dose selected in Part 1) in combination with chemotherapy, compared with placebo plus chemotherapy, as measured by the respective hazard ratios (HR) for overall survival (OS).

Secondary Objectives:

Part 1:

- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and the minimum observed serum concentration (C_{min}) for AMG 479 and for AMG 102

Part 2:

- To evaluate clinical benefit as assessed by the objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), median OS (mOS), and OS rates at 10, 12, 24 and 36 months
- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate PK as assessed by C_{max} and C_{min} for AMG 479 and for AMG 102
- To estimate the effect of AMG 479 and of AMG 102 on subject's health related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Exploratory Objectives:

Part 1 and Part 2:

- To evaluate PK as assessed by area under the curve (AUC) and C_{max} for etoposide, cisplatin and carboplatin
- To investigate the relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)

- To investigate the biomarker profile at baseline, and the pharmacodynamic response, as assessed by biomarkers for AMG 479 (eg, serum IGF-1, IGF-BP3, GH, and other factors involved in regulating the IGF-1/IGF-1R pathway) and for AMG 102 (eg, HGF/SF:c-Met pathway markers, tumor apoptosis markers, angiogenic cytokines and other biomarkers), and correlate with treatment outcomes
- To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets, tumor somatic mutations in drug target, pathway, and cancer genes) by biochemical analysis of blood samples and tumor tissue (if available), and correlate with treatment outcomes
- To investigate the effect of genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlate with treatment outcomes (optional for subjects; requires separate informed consent)

Hypotheses:

Part 1 will identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that is safe and tolerated as determined by the incidence of DLT.

Part 2 will estimate the relative efficacy of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as measured by the respective OS HR. Given a hypothesized HR of 0.74 for each comparison, the target maximum half width of 0.22 for the OS HR 2-sided 80% CI will be achieved after 89 deaths are observed for a pairwise comparison.

Study Design:

This study has 2 parts.

Part 1 is a multi-center, open-label dose de-escalation phase 1b segment of AMG 479 in combination with etoposide plus carboplatin (Cohort 1) or cisplatin (Cohort 2), and of AMG 102 in combination with etoposide plus carboplatin (Cohort 3) or cisplatin (Cohort 4). Once respective doses of AMG 479 and of AMG 102 have been identified that are safe and tolerated based on the incidence of DLT, Part 2 will open for enrollment.

Part 2 is a randomized, double-blind, placebo-controlled phase 2 segment of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as first-line treatment for subjects with extensive stage SCLC. Subjects (n = 180) will be randomized in a 1:1:1 ratio to each treatment arm (n = 60 per arm). Randomization will be stratified according to gender (female; male) and chemotherapy (etoposide and cisplatin; etoposide and carboplatin).

In both parts of the study, chemotherapy (etoposide plus carboplatin or cisplatin) will be administered on day 1 of each 21-day (Q3W) cycle. Etoposide will also be administered on day 2 and 3 of each Q3W cycle. Premedication (see Section 6.2.2.3), vigorous hydration and diuresis (see Section 6.2.2.4) will be required for chemotherapy treatment. Investigational product (IP; AMG 479 [Part 1, Cohorts 1 and 2; Part 2, Arm A] or AMG 102 [Part 1, Cohorts 3 and 4; Part 2, Arm B] or placebo [Part 2, Arm C]) will be administered after the chemotherapy infusion on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter. Four to six cycles of chemotherapy will be given. Determination of the number of cycles of chemotherapy to be administered (between 4 to 6) will be left to the investigator's discretion. Subjects who complete 4 to 6 cycles of chemotherapy or who discontinue chemotherapy early will continue to receive IP (AMG 479, or AMG 102, or placebo) single agent maintenance therapy on day 1 of each Q3W cycle for up to 24 months from the date of first study treatment administration (study day 1). Subjects who have completed 24 months of IP may be eligible for continued treatment with IP by extension protocol or as provided for by the local country's regulatory mechanism (see Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, unacceptable toxicity, withdraws consent, or due to an administrative decision (by the investigator or Amgen).

Radiological imaging to assess PD (per modified RECIST) will be performed every 6 weeks (± 7 days) during the first 6 months of the study, from Study Day 1 and every 9 weeks (± 7 days) thereafter, until subjects develop PD (per modified RECIST) or begin a new cancer treatment.

A follow-up visit will occur 30 days (+ 7 days) and 60 days (+ 14 days) after the last dose of protocol-specified treatment. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, for up to 36 months from the date of the last subject randomized, to assess survival. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints: See Section 10 for details

Primary Endpoints

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

Part 2:
- OS

Secondary Endpoints

Part 1:
- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min} for AMG 479 and AMG 102)

Part 2:
- ORR, DOR, TTP, PFS, mOS, and OS rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (C_{max} and C_{min}) for AMG 479 and AMG 102
- EORTC QLQ-C30 and EORTC QLQ-LC13 scores

Exploratory Endpoints

Part 1 and Part 2:
- PK (AUC and C_{max}) for etoposide, cisplatin and carboplatin
- Relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- Baseline biomarker profile and pharmacodynamic response, as assessed by AMG 479 and AMG 102 biomarkers, and correlation with treatment outcomes
- Biochemical levels and abundance of drug targets and other biomarkers in blood samples and tumor tissue (if available), and correlation with treatment outcomes
- Genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes

Sample Size: Part 1: 24 to 108 subjects; Part 2: 180 subjects

Summary of Subject Eligibility Criteria: See Section 4 for details

Key Inclusion Criteria
- Histologically or cytologically confirmed SCLC
- Extensive disease, defined by at least one of the following criteria:
  - No limited disease (ie, no disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field)
  - Extrathoracic metastases
  - Malignant pericardial or pleural effusion
  - Contralateral hilar adenopathy
- Measurable or non-measurable disease, as defined by modified RECIST
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

- ≥ 18 years old
- Life expectancy (with therapy) ≥ 3 months
- Adequate hematologic, hepatic, coagulation, renal, and metabolic function
- Fasting blood glucose ≤ 160 mg/dL

Key Exclusion Criteria

- Prior chemotherapy, chemo-radiation, or investigational agent for SCLC
- Prior radiotherapy to > 25% of the bone marrow
- Symptomatic or untreated central nervous system (CNS) metastasis (with exceptions)
- Currently or previously treated with biological, immunological or other therapies for SCLC
- Current serious or non-healing wound or ulcer
- History of prior or concurrent other malignancy (with exceptions)
- **Thrombosis or vascular ischemic events within the last twelve months, such as deep venous thrombosis, pulmonary embolism, transient ischemic attack, cerebral infarction, or myocardial infarction**
- Any clinically significant medical condition other than cancer (eg, cardiovascular disease or chronic obstructive pulmonary disease), which could interfere with the safe delivery of study treatment or increase risk of toxicity

Study Drug Dosage and Administration: See Section 6 for details.

Investigational Product:

Part 1: Cohorts 1a and 2a:
AMG 479 18 mg/kg intravenous (IV) on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 479 18 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Cohort 3a and 4a:
AMG 102 15 mg/kg IV on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter
AMG 102 15 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Lower doses of AMG 479 and/or AMG 102 may be explored based on safety and PK data, to determine the maximum tolerated dose. Refer to Section 6.1.1.1 for details.

Part 2: AMG 479 (Arm A), AMG 102 (Arm B), at the respective doses selected in Part 1, or matching placebo (Arm C), IV Q3W:
day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

IP dose will be calculated based on the subject's actual body weight at baseline, and the dose must be recalculated if the actual body weight changes by > 10%. IP will be diluted in 0.9% normal saline.

IP will be administered Q3W, after completion of the chemotherapy infusion (if administered). IP will be administered over 60 minutes (min) (± 10 min). If a dose of IP is well tolerated (ie, without serious infusion-related reactions), then subsequent IV infusions may be given over 30 min (± 10 min). Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Chemotherapy (Part 1 and Part 2):

Etoposide 100 mg/m^2 to be administered IV over 90 min (± 30 min) on days 1, 2, and 3 of each Q3W cycle, or per institutional guidelines.

Carboplatin (AUC = 5 mg/mL • min) will be administered IV over 30 min (+ 10 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 60 min for subjects deemed unable to tolerate the 30 min infusion.

Cisplatin 75 mg/m^2 will be administered IV over 60 min (± 15 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Subjects must receive adequate premedication (see Section 6.2.2.3), vigorous hydration and diuresis, and monitoring of fluid status (see Section 6.2.2.4).

Control Group:

Part 1: there is no control group

Part 2: Arm C: Placebo in combination with etoposide plus carboplatin or cisplatin Q3W

Key Study Procedures: See Section 7.1 and Schedule of Assessments (Appendix A) for details.

Screening Procedures

- Review of inclusion and exclusion criteria
- Medication and medical history, concomitant medications/treatment(s), adverse events
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including height and weight
- ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, coagulation, urinalysis, pregnancy test
- If available, submission of paraffin-embedded tumor tissue (paraffin tumor block, or slides) and all available pathology reports
- 12-lead electrocardiogram (ECG)
- Radiological imaging to assess disease extent (CT scan or MRI of the brain, chest, abdomen, and all other sites of disease; within 28 days prior to enrollment)

Treatment and Follow-Up Procedures

- Recording and reporting of adverse events and concomitant medications
- Patient completion of EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Part 2)
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, pregnancy test

- Samples for biomarkers and anti-AMG 479 or anti-AMG 102 antibodies
- Samples for AMG 479, AMG 102, carboplatin, cisplatin and etoposide PK (Part 1)
- ECG
- Radiological imaging to assess disease extent (CT scan or MRI [same modality throughout the study] of the chest, abdomen, and all other sites of disease [except: brain imaging only as clinically indicated] every 6 weeks [± 7 days] from Study Day 1 during the first 6 months of the study, and every 9 weeks [± 7 days] thereafter)

Statistical Considerations: See Section 10 for details.

Analyses will be presented separately for Part 1 and Part 2 of the study. The HR for OS will be estimated using a Cox regression model stratified by randomization stratification factors and controlled for the LDH level as an important covariate. A Wald chi-square test will provide a descriptive p-value for the HR. Overall survival between the respective pair of treatment arms (Arm A/Arm C and Arm B/Arm C) will use a stratified log-rank test for a descriptive comparison.

DRT Safety Reviews and Interim Analysis

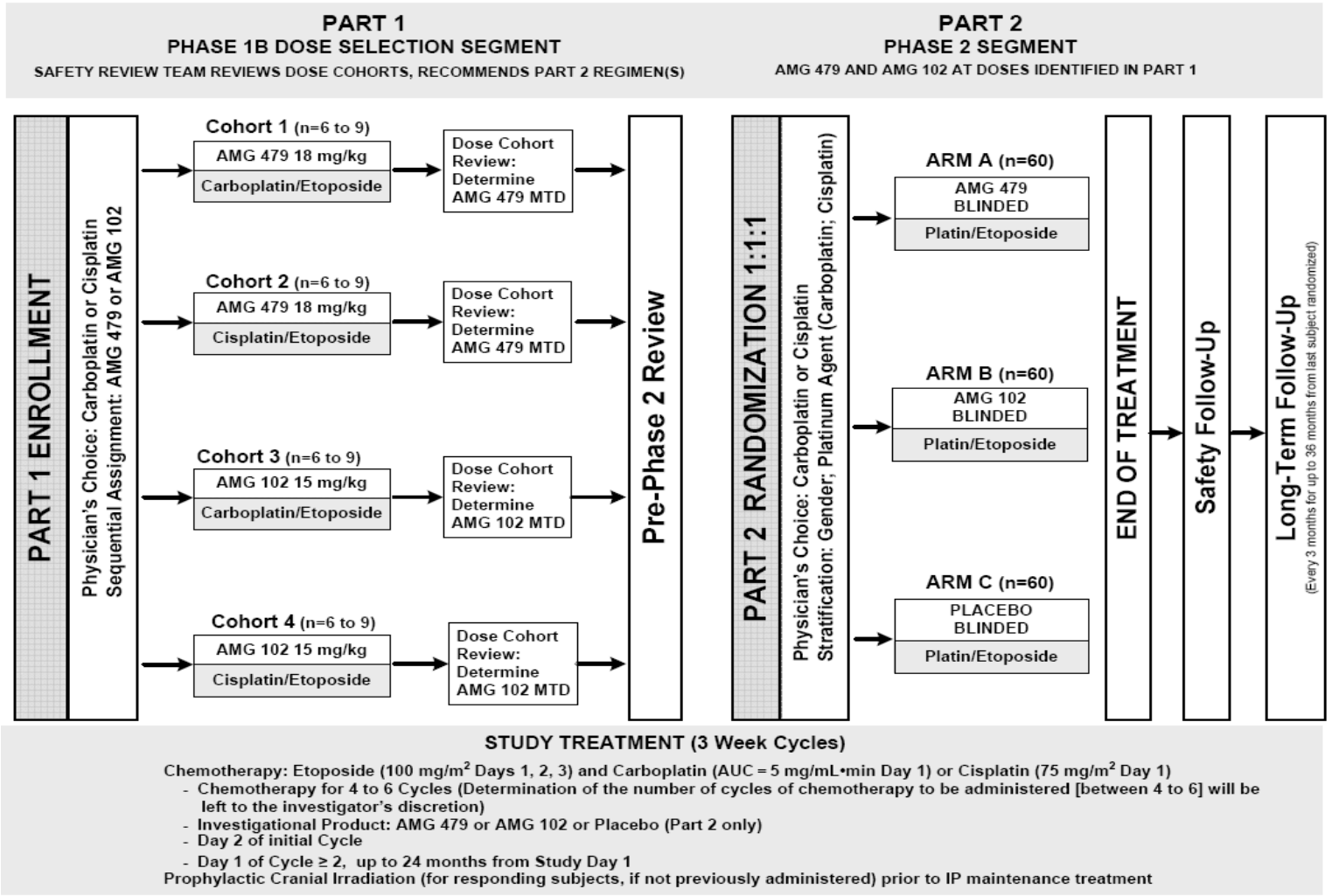
For the protection of subjects, in Part 1 of the study, Safety Review Team (SRT) meetings will be held to review safety, laboratory, dosing information and PK data (when available) from each AMG 479 and AMG 102 dose cohort, to make recommendations regarding dose selection for Part 2, dose de-escalation, or dose stopping.

In Part 2. and Amgen Data Review Team (DRT), independent of the study team will perform unblinded reviews of the safety data after at least 30 and 60 subjects have been randomized and had the opportunity to complete cycle 1 of the study treatment (safety interim analyses). **In addition, unblinded SAE information for thrombosis or vascular ischemic events will be made available to the DRT on an ongoing basis**

One interim efficacy analysis is planned to review both OS and PFS data 10 months after the last subject is randomized. Approximately 100 OS events are estimated (69 OS events per comparison: Arm A/Arm C and Arm B/Arm C) for the interim analysis assuming approximately half of the planned enrollment will occur at 15 months. Review of safety data will also occur during the interim efficacy analysis. The interim efficacy analysis will provide a preliminary assessment of the overall risk/benefit profile. Unless safety concerns arise, the study will not be discontinued or modified due to the results of the interim efficacy analysis

The primary analysis of Part 2 will be event-driven and will occur after a total of approximately 130 deaths (89 deaths per planned comparison: Arm A/Arm C and Arm B/Arm C), which is anticipated to occur 18 months after end of enrollment. A final analysis is planned after a minimum expected follow-up of 36 months, at which time approximately 163 deaths are expected overall (110 per planned comparison).

Study Design and Treatment Schema



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

AMG 479 and AMG 102

Amgen Protocol Number 20060534

Clinical Study Sponsor:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805.447.0000
Fax: 805.499.9495

Key Sponsor Contacts:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen Inc
Phone: 650.244.2634
Fax: 650.837.9716
jessem@amgen.com

Cat Goodall
Clinical Research Study Manager - Primary
Amgen Limited
Phone: +44 1895 525327
Fax: +44 1895 525101
cgoodall@amgen.com

Nancy Kenyon
Clinical Research Study Manager – U.S
Amgen Inc
Phone: 805.447.5737
Fax: 805.
nkenyon@amgen.com

Amendment 3 Date:	**01 February 2011**
Amendment 2 Date:	24 September 2010
Amendment 1 Date:	01 April 2009
Date:	07 June 2008
EudraCT Number:	2008-003292-42

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer dated **Amendment 3, 01 February 2011**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal <<*or Coordinating*>> Investigator | Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b/ 2

Indication: Previously Untreated Extensive Stage Small Cell Lung Cancer (SCLC)

Primary Objective:

Part 1: To identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin, and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: To estimate the relative treatment effect of AMG 479 (at the dose selected in Part 1) in combination with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1), and of AMG 102 (at the dose selected in Part 1) in combination with chemotherapy, compared with placebo plus chemotherapy, as measured by the respective hazard ratios (HR) for overall survival (OS).

Secondary Objectives:

Part 1:

- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and the minimum observed serum concentration (C_{min}) for AMG 479 and for AMG 102

Part 2:

- To evaluate clinical benefit as assessed by the objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), median OS (mOS), and OS rates at 10, 12, 24, and 36 months
- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate PK as assessed by C_{max} and C_{min} for AMG 479 and for AMG 102
- To estimate the effect of AMG 479 and of AMG 102 on subject's health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Exploratory Objectives:

Part 1 and Part 2:

- To evaluate PK as assessed by area under the curve (AUC) and Cmax for etoposide, cisplatin and carboplatin
- To investigate the relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)

- To investigate the biomarker profile at baseline, and the pharmacodynamic response, as assessed by biomarkers for AMG 479 (eg, serum IGF-1, IGF-BP3, GH, and other factors involved in regulating the IGF-1/IGF-1R pathway) and for AMG 102 (eg, HGF/SF:c-Met pathway markers, tumor apoptosis markers, angiogenic cytokines and other biomarkers), and correlate with treatment outcomes
- To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets, tumor somatic mutations in drug target, pathway, and cancer genes) by biochemical analysis of blood samples and tumor tissue (if available), and correlate with treatment outcomes
- To investigate the effect of genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlate with treatment outcomes (optional for subjects; requires separate informed consent)

Hypotheses:

- Part 1 will identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that is safe and tolerated as determined by the incidence of DLT.
- Part 2 will estimate the relative efficacy of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as measured by the respective OS HR. Given a hypothesized HR of 0.74 for each comparison, the target maximum half width of 0.22 for the OS HR 2-sided 80% CI will be achieved after 89 deaths are observed for a pairwise comparison.

Study Design:

This study has 2 parts.

Part 1 is a multi-center, open-label dose de-escalation phase 1b segment of AMG 479 in combination with etoposide plus carboplatin (Cohort 1) or cisplatin (Cohort 2), and of AMG 102 in combination with etoposide plus carboplatin (Cohort 3) or cisplatin (Cohort 4). Once respective doses of AMG 479 and of AMG 102 have been identified that are safe and tolerated based on the incidence of DLT, Part 2 will open for enrollment.

Part 2 is a randomized, double-blind, placebo-controlled phase 2 segment of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as first-line treatment for subjects with extensive stage SCLC. Subjects (n = 180) will be randomized in a 1:1:1 ratio to each treatment arm (n = 60 per arm). Randomization will be stratified according to gender (female; male) and chemotherapy (etoposide and cisplatin; etoposide and carboplatin).

In both parts of the study, chemotherapy (etoposide plus carboplatin or cisplatin) will be administered on day 1 of each 21-day (Q3W) cycle. Etoposide will also be administered on day 2 and 3 of each Q3W cycle. Premedication (see Section 6.2.2.3), vigorous hydration and diuresis (see Section 6.2.2.4) will be required for chemotherapy treatment. Investigational product (IP; AMG 479 [Part 1, Cohorts 1 and 2; Part 2, Arm A] or AMG 102 [Part 1, Cohorts 3 and 4; Part 2, Arm B] or placebo [Part 2, Arm C]) will be administered after the chemotherapy infusion on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter. Four to six cycles of chemotherapy will be given. Determination of the number of cycles of chemotherapy to be administered (between 4 to 6) will be left to the investigator's discretion. Subjects who complete 4 to 6 cycles of chemotherapy or who discontinue chemotherapy early will continue to receive IP (AMG 479, or AMG 102, or placebo) single agent maintenance therapy on day 1 of each Q3W cycle for up to 24 months from the date of first study treatment administration (study day 1). Subjects who have completed 24 months of IP may be eligible for continued treatment with IP by extension protocol

or as provided for by the local country's regulatory mechanism (see Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, unacceptable toxicity, withdraws consent, or due to an administrative decision (by the investigator or Amgen).

Radiological imaging to assess PD (per modified RECIST) will be performed every 6 weeks (± 7 days) during the first 6 months of the study, from Study Day 1 and every 9 weeks (± 7 days) thereafter, until subjects develop PD (per modified RECIST) or begin a new cancer treatment.

A follow-up visit will occur 30 days (+ 7 days) and 60 days (+ 14 days) after the last dose of protocol-specified treatment. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, for up to 36 months from the date of the last subject randomized, to assess survival. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints: See Section 10 for details

Primary Endpoints

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

Part 2:
- OS

Secondary Endpoints

Part 1:
- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (Cmax and Cmin for AMG 479 and AMG 102)

Part 2:
- ORR, DOR, TTP, PFS, mOS, and OS rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (Cmax and Cmin) for AMG 479 and AMG 102
- EORTC QLQ-C30 and EORTC QLQ-LC13 scores

Exploratory Endpoints

Part 1 and Part 2:
- PK (AUC and Cmax) for etoposide, cisplatin and carboplatin
- Relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- Baseline biomarker profile and pharmacodynamic response, as assessed by AMG 479 and AMG 102 biomarkers, and correlation with treatment outcomes
- Biochemical levels and abundance of drug targets and other biomarkers in blood samples and tumor tissue (if available), and correlation with treatment outcomes
- Genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes

Sample Size: Part 1: 24 to 108 subjects; Part 2: 180 subjects

Summary of Subject Eligibility Criteria: See Section 4 for details

Key Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Extensive disease, defined by at least one of the following criteria:
  - No limited disease (ie, no disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field)
  - Extrathoracic metastases
  - Malignant pericardial or pleural effusion
  - Contralateral hilar adenopathy
- Measurable or non-measurable disease, as defined by modified RECIST
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- ≥ 18 years old
- Life expectancy (with therapy) ≥ 3 months
- Adequate hematologic, hepatic, coagulation, renal, and metabolic function
- Fasting blood glucose ≤ 160 mg/dL

Key Exclusion Criteria

- Prior chemotherapy, chemo-radiation, or investigational agent for SCLC
- Prior radiotherapy to > 25% of the bone marrow
- Symptomatic or untreated central nervous system (CNS) metastasis (with exceptions)
- Currently or previously treated with biological, immunological or other therapies for SCLC
- Current serious or non-healing wound or ulcer
- History of prior or concurrent other malignancy (with exceptions)
- Thrombosis or vascular ischemic events within the last twelve months, such as deep venous thrombosis, pulmonary embolism, transient ischemic attack, cerebral infarction, or myocardial infarction
- Any clinically significant medical condition other than cancer (eg, cardiovascular disease or chronic obstructive pulmonary disease), which could interfere with the safe delivery of study treatment or increase risk of toxicity

Study Drug Dosage and Administration: See Section 6 for details.

Investigational Product:

Part 1: Cohorts 1a and 2a:
AMG 479 18 mg/kg intravenous (IV) on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

AMG 479 18 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Cohort 3a and 4a:

AMG 102 15 mg/kg IV on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

AMG 102 15 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Lower doses of AMG 479 and/or AMG 102 may be explored based on safety and PK data, to determine the maximum tolerated dose. Refer to Section 6.1.1.1 for details.

Part 2: AMG 479 (Arm A), AMG 102 (Arm B), at the respective doses selected in Part 1, or matching placebo (Arm C), IV Q3W:

day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

IP dose will be calculated based on the subject's actual body weight at baseline, and the dose must be recalculated if the actual body weight changes by > 10%. IP will be diluted in 0.9% normal saline.

IP will be administered Q3W, after completion of the chemotherapy infusion (if administered). IP will be administered over 60 minutes (min) (± 10 min). If a dose of IP is well tolerated (ie, without serious infusion-related reactions), then subsequent IV infusions may be given over 30 min (± 10 min). Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Chemotherapy (Part 1 and Part 2):

Etoposide 100 mg/m^2 to be administered IV over 90 min (± 30 min) on days 1, 2, and 3 of each Q3W cycle, or per institutional guidelines.

Carboplatin (AUC = 5 mg/mL • min) will be administered IV over 30 min (+ 10 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 60 min for subjects deemed unable to tolerate the 30 min infusion.

Cisplatin 75 mg/m^2 will be administered IV over 60 min (± 15 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Subjects must receive adequate premedication (see Section 6.2.2.3), vigorous hydration and diuresis, and monitoring of fluid status (see Section 6.2.2.4).

Control Group:

Part 1: there is no control group

Part 2: Arm C: Placebo in combination with etoposide plus carboplatin or cisplatin Q3W

Key Study Procedures: See Section 7.1 and Schedule of Assessments (Appendix A) for details.

Screening Procedures

- Review of inclusion and exclusion criteria
- Medication and medical history, concomitant medications/treatment(s), adverse events
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including height and weight
- ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, coagulation, urinalysis, pregnancy test
- If available, submission of paraffin-embedded tumor tissue (paraffin tumor block, or slides) and all available pathology reports
- 12-lead electrocardiogram (ECG)
- Radiological imaging to assess disease extent (CT scan or MRI of the brain, chest, abdomen, and all other sites of disease; within 28 days prior to enrollment)

Treatment and Follow-Up Procedures

- Recording and reporting of adverse events and concomitant medications
- Patient completion of EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Part 2)
- Vital signs: resting pulse, respiration, blood pressure, and temperature

- Physical examination, including weight, and ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, pregnancy test
- Samples for biomarkers and anti-AMG 479 or anti-AMG 102 antibodies
- Samples for AMG 479, AMG 102, carboplatin, cisplatin and etoposide PK (Part 1)
- ECG
- Radiological imaging to assess disease extent (CT scan or MRI [same modality throughout the study] of the chest, abdomen, and all other sites of disease [except: brain imaging only as clinically indicated] every 6 weeks [± 7 days] from Study Day 1 during the first 6 months of the study, and every 9 weeks [± 7 days] thereafter)

Statistical Considerations: See Section 10 for details.

Analyses will be presented separately for Part 1 and Part 2 of the study. The HR for OS will be estimated using a Cox regression model stratified by randomization stratification factors and controlled for the LDH level as an important covariate. A Wald chi-square test will provide a descriptive p-value for the HR. Overall survival between the respective pair of treatment arms (Arm A/Arm C and Arm B/Arm C) will use a stratified log-rank test for a descriptive comparison.

DRT Safety Reviews and Interim Analysis

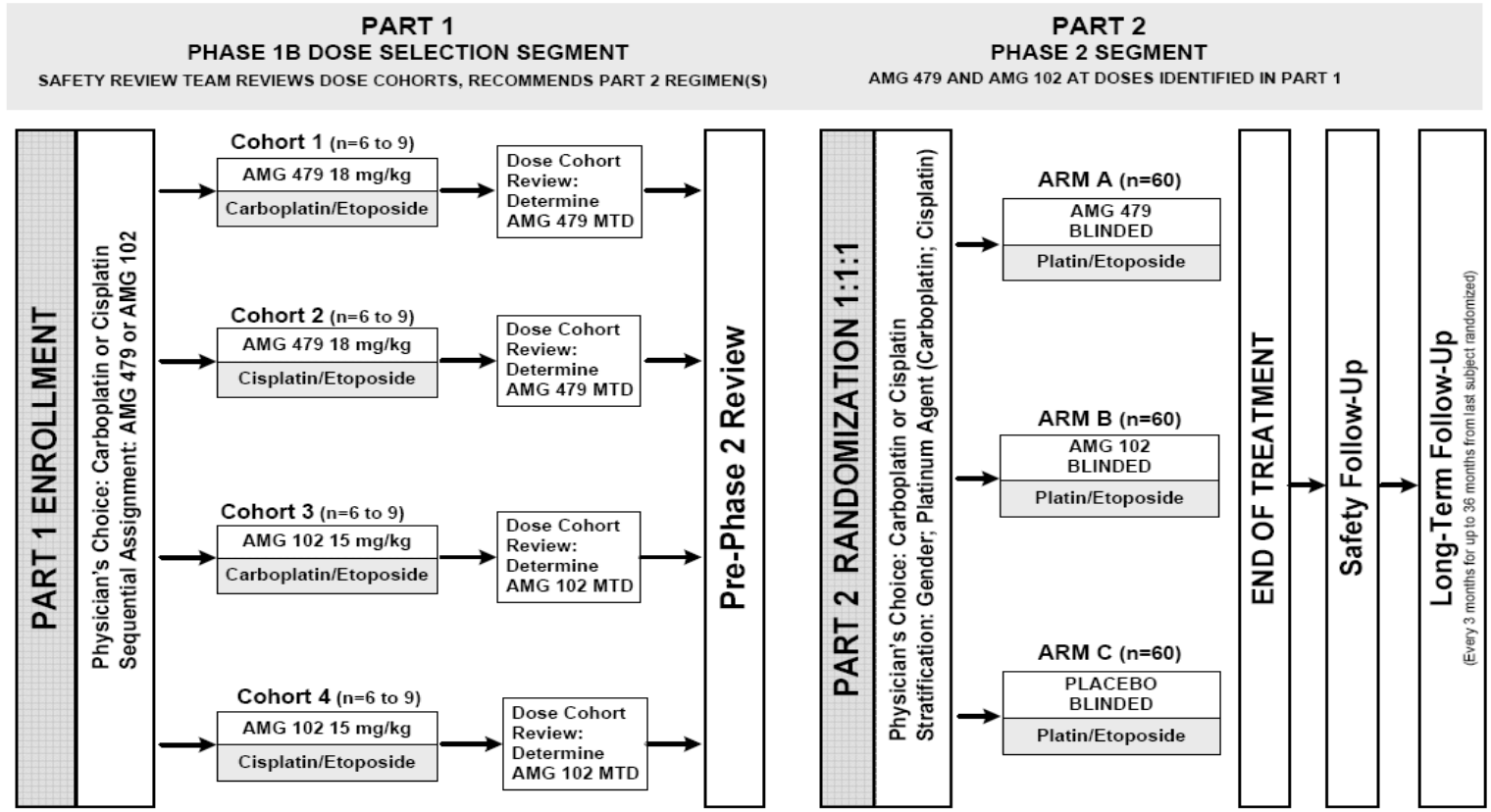
For the protection of subjects, in Part 1 of the study, Safety Review Team (SRT) meetings will be held to review safety, laboratory, dosing information and PK data (when available) from each AMG 479 and AMG 102 dose cohort, to make recommendations regarding dose selection for Part 2, dose de-escalation, or dose stopping.

In Part 2. and Amgen Data Review Team (DRT), independent of the study team will perform unblinded reviews of the safety data after at least 30 and 60 subjects have been randomized and had the opportunity to complete cycle 1 of the study treatment (safety interim analyses). In addition, unblinded SAE information for thrombosis or vascular ischemic events will be made available to the DRT on an ongoing basis

One interim efficacy analysis is planned to review both OS and PFS data 10 months after the last subject is randomized. Approximately 100 OS events are estimated (69 OS events per comparison: Arm A/Arm C and Arm B/Arm C) for the interim analysis assuming approximately half of the planned enrollment will occur at 15 months. Review of safety data will also occur during the interim efficacy analysis. The interim efficacy analysis will provide a preliminary assessment of the overall risk/benefit profile. Unless safety concerns arise, the study will not be discontinued or modified due to the results of the interim efficacy analysis

The primary analysis of Part 2 will be event-driven and will occur after a total of approximately 130 deaths (89 deaths per planned comparison: Arm A/Arm C and Arm B/Arm C), which is anticipated to occur 18 months after end of enrollment. A final analysis is planned after a minimum expected follow-up of 36 months, at which time approximately 163 deaths are expected overall (110 per planned comparison).

Study Design and Treatment Schema



STUDY TREATMENT (3 Week Cycles)

Chemotherapy: Etoposide (100 mg/m^2 Days 1, 2, 3) and Carboplatin (AUC = 5 mg/mL•min Day 1) or Cisplatin (75 mg/m^2 Day 1)
- Chemotherapy for 4 to 6 Cycles (Determination of the number of cycles of chemotherapy to be administered [between 4 to 6] will be left to the investigator's discretion)
- Investigational Product: AMG 479 or AMG 102 or Placebo (Part 2 only)
- Day 2 of initial Cycle
- Day 1 of Cycle ≥ 2, up to 24 months from Study Day 1

Prophylactic Cranial Irradiation (for responding subjects, if not previously administered) prior to IP maintenance treatment

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

AMG 479 and AMG 102

Amgen Protocol Number 20060534

Clinical Study Sponsor:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805.447.0000
Fax: 805.499.9495

Key Sponsor Contacts:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen Inc
Phone: 650.244.2634
Fax: 650.837.9716
jessem@amgen.com

Cat Goodall
Clinical Research Study Manager - Primary
Amgen Limited
Phone: +44 1895 525327
Fax: +44 1895 525101
cgoodall@amgen.com

Nancy Kenyon
Clinical Research Study Manager – U.S
Amgen Inc
Phone: 805.447.5737
Fax: 805.
nkenyon@amgen.com

Amendment 4 Date:	**05 April 2011**
Amendment 3 Date:	01 February 2011
Amendment 2 Date:	24 September 2010
Amendment 1 Date:	01 April 2009
Date:	07 June 2008
EudraCT Number:	2008-003292-42

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer dated **Amendment 4, 05 April 2011**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Principal <<*or Coordinating*>> Investigator

Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b/ 2

Indication: Previously Untreated Extensive Stage Small Cell Lung Cancer (SCLC)

Primary Objective:

Part 1: To identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin, and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT)

Part 2: To estimate the relative treatment effect of AMG 479 (at the dose selected in Part 1) in combination with chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1), and of AMG 102 (at the dose selected in Part 1) in combination with chemotherapy, compared with placebo plus chemotherapy, as measured by the respective hazard ratios (HR) for overall survival (OS).

Secondary Objectives:

Part 1:

- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities not defined as DLT
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate pharmacokinetics (PK) as assessed by the maximum observed serum concentration (C_{max}) and the minimum observed serum concentration (C_{min}) for AMG 479 and for AMG 102

Part 2:

- To evaluate clinical benefit as assessed by the objective response rate (ORR) as measured by modified Response Evaluation Criteria in Solid Tumors (RECIST), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), median OS (mOS), and OS rates at 10, 12, 24, and 36 months
- To evaluate safety as assessed by the incidence of adverse events and laboratory abnormalities
- To evaluate safety as assessed by the incidence of anti-AMG 479 antibody formation and anti-AMG 102 antibody formation
- To evaluate PK as assessed by C_{max} and C_{min} for AMG 479 and for AMG 102
- To estimate the effect of AMG 479 and of AMG 102 on subject's health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its lung cancer module (QLQ-LC13)

Exploratory Objectives:

Part 1 and Part 2:

- To evaluate PK as assessed by area under the curve (AUC) and Cmax for etoposide, cisplatin and carboplatin
- To investigate the relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)

- To investigate the biomarker profile at baseline, and the pharmacodynamic response, as assessed by biomarkers for AMG 479 (eg, serum IGF-1, IGF-BP3, GH, and other factors involved in regulating the IGF-1/IGF-1R pathway) and for AMG 102 (eg, HGF/SF:c-Met pathway markers, tumor apoptosis markers, angiogenic cytokines and other biomarkers), and correlate with treatment outcomes
- To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets, tumor somatic mutations in drug target, pathway, and cancer genes) by biochemical analysis of blood samples and tumor tissue (if available), and correlate with treatment outcomes
- To investigate the effect of genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlate with treatment outcomes (optional for subjects; requires separate informed consent)

Hypotheses:

- Part 1 will identify a dose of AMG 479 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin and of AMG 102 in combination with etoposide plus carboplatin and/or etoposide plus cisplatin that is safe and tolerated as determined by the incidence of DLT.
- Part 2 will estimate the relative efficacy of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as measured by the respective OS HR. Given a hypothesized HR of 0.74 for each comparison, the target maximum half width of 0.22 for the OS HR 2-sided 80% CI will be achieved after 89 deaths are observed for a pairwise comparison.

Study Design:

This study has 2 parts.

Part 1 is a multi-center, open-label dose de-escalation phase 1b segment of AMG 479 in combination with etoposide plus carboplatin (Cohort 1) or cisplatin (Cohort 2), and of AMG 102 in combination with etoposide plus carboplatin (Cohort 3) or cisplatin (Cohort 4). Once respective doses of AMG 479 and of AMG 102 have been identified that are safe and tolerated based on the incidence of DLT, Part 2 will open for enrollment.

Part 2 is a randomized, double-blind, placebo-controlled phase 2 segment of AMG 479 (at the dose selected in Part 1), and of AMG 102 (at the dose selected in Part 1), and of placebo plus platinum-based chemotherapy (etoposide plus carboplatin and/or etoposide plus cisplatin, as determined in part 1) as first-line treatment for subjects with extensive stage SCLC. Subjects (n = 180) will be randomized in a 1:1:1 ratio to each treatment arm (n = 60 per arm). Randomization will be stratified according to gender (female; male) and chemotherapy (etoposide and cisplatin; etoposide and carboplatin).

In both parts of the study, chemotherapy (etoposide plus carboplatin or cisplatin) will be administered on day 1 of each 21-day (Q3W) cycle. Etoposide will also be administered on day 2 and 3 of each Q3W cycle. Premedication (see Section 6.2.2.3), vigorous hydration and diuresis (see Section 6.2.2.4) will be required for chemotherapy treatment. Investigational product (IP; AMG 479 [Part 1, Cohorts 1 and 2; Part 2, Arm A] or AMG 102 [Part 1, Cohorts 3 and 4; Part 2, Arm B] or placebo [Part 2, Arm C]) will be administered after the chemotherapy infusion on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter. Four to six cycles of chemotherapy will be given. Determination of the number of cycles of chemotherapy to be administered (between 4 to 6) will be left to the investigator's discretion. Subjects who complete 4 to 6 cycles of chemotherapy or who discontinue chemotherapy early will continue to receive IP (AMG 479, or AMG 102, or placebo) single agent maintenance therapy on day 1 of each Q3W cycle for up to 24 months from the date of first study treatment administration (study day 1). Subjects who have completed 24 months of IP may be eligible for continued treatment with IP by extension protocol

or as provided for by the local country's regulatory mechanism (see Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, unacceptable toxicity, withdraws consent, or due to an administrative decision (by the investigator or Amgen).

Radiological imaging to assess PD (per modified RECIST) will be performed every 6 weeks (± 7 days) during the first 6 months of the study, from Study Day 1 and every 9 weeks (± 7 days) thereafter, until subjects develop PD (per modified RECIST) or begin a new cancer treatment.

A follow-up visit will occur 30 days (+ 7 days) and 60 days (+ 14 days) after the last dose of protocol-specified treatment. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, for up to 36 months from the date of the last subject randomized, to assess survival. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints: See Section 10 for details

Primary Endpoints

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

Part 2:
- OS

Secondary Endpoints

Part 1:
- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (Cmax and Cmin for AMG 479 and AMG 102)

Part 2:
- ORR, DOR, TTP, PFS, mOS, and OS rates at 10,12, 24, and 36 months
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 and anti-AMG 102 antibody formation
- PK (Cmax and Cmin) for AMG 479 and AMG 102
- EORTC QLQ-C30 and EORTC QLQ-LC13 scores

Exploratory Endpoints

Part 1 and Part 2:
- PK (AUC and Cmax) for etoposide, cisplatin and carboplatin
- Relationship between AMG 479 and AMG 102 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- Baseline biomarker profile and pharmacodynamic response, as assessed by AMG 479 and AMG 102 biomarkers, and correlation with treatment outcomes
- Biochemical levels and abundance of drug targets and other biomarkers in blood samples and tumor tissue (if available), and correlation with treatment outcomes
- Genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes

Sample Size: Part 1: 24 to 108 subjects; Part 2: 180 subjects

Summary of Subject Eligibility Criteria: See Section 4 for details

Key Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Extensive disease, defined by at least one of the following criteria:
  - No limited disease (ie, no disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field)
  - Extrathoracic metastases
  - Malignant pericardial or pleural effusion
  - Contralateral hilar adenopathy
- Measurable or non-measurable disease, as defined by modified RECIST
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- ≥ 18 years old
- Life expectancy (with therapy) ≥ 3 months
- Adequate hematologic, hepatic, coagulation, renal, and metabolic function
- Fasting blood glucose ≤ 160 mg/dL

Key Exclusion Criteria

- Prior chemotherapy, chemo-radiation, or investigational agent for SCLC
- Prior radiotherapy to > 25% of the bone marrow
- Symptomatic or untreated central nervous system (CNS) metastasis (with exceptions)
- Currently or previously treated with biological, immunological or other therapies for SCLC
- Current serious or non-healing wound or ulcer
- History of prior or concurrent other malignancy (with exceptions)
- Thrombosis or vascular ischemic events within the last twelve months, such as deep venous thrombosis, pulmonary embolism, transient ischemic attack, cerebral infarction, or myocardial infarction
- Any clinically significant medical condition other than cancer (eg, cardiovascular disease or chronic obstructive pulmonary disease), which could interfere with the safe delivery of study treatment or increase risk of toxicity

Study Drug Dosage and Administration: See Section 6 for details.

Investigational Product:

Part 1: Cohorts 1a and 2a:
AMG 479 18 mg/kg intravenous (IV) on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

AMG 479 18 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Cohort 3a and 4a:

AMG 102 15 mg/kg IV on day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

AMG 102 15 mg/kg IV on day 1 of each Q3W cycle during IP maintenance treatment

Lower doses of AMG 479 and/or AMG 102 may be explored based on safety and PK data, to determine the maximum tolerated dose. Refer to Section 6.1.1.1 for details.

Part 2: AMG 479 (Arm A), AMG 102 (Arm B), at the respective doses selected in Part 1, or matching placebo (Arm C), IV Q3W:

day 2 of the initial cycle, and day 1 of each Q3W cycle thereafter

IP dose will be calculated based on the subject's actual body weight at baseline, and the dose must be recalculated if the actual body weight changes by > 10%. IP will be diluted in 0.9% normal saline.

IP will be administered Q3W, after completion of the chemotherapy infusion (if administered). IP will be administered over 60 minutes (min) (± 10 min) **through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up.** If a dose of IP is well tolerated (ie, without serious infusion-related reactions), then subsequent IV infusions may be given over 30 min (± 10 min). Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Chemotherapy (Part 1 and Part 2):

Etoposide 100 mg/m^2 to be administered IV over 90 min (± 30 min) on days 1, 2, and 3 of each Q3W cycle, or per institutional guidelines.

Carboplatin (AUC = 5 mg/mL • min) will be administered IV over 30 min (+ 10 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 60 min for subjects deemed unable to tolerate the 30 min infusion.

Cisplatin 75 mg/m^2 will be administered IV over 60 min (± 15 min) on day 1 of each Q3W cycle after the etoposide infusion is complete, per institutional guidelines. Infusion time can be extended up to 120 min for subjects deemed unable to tolerate the 60 min infusion.

Subjects must receive adequate premedication (see Section 6.2.2.3), vigorous hydration and diuresis, and monitoring of fluid status (see Section 6.2.2.4).

Control Group:

Part 1: there is no control group

Part 2: Arm C: Placebo in combination with etoposide plus carboplatin or cisplatin Q3W

Key Study Procedures: See Section 7.1 and Schedule of Assessments (Appendix A) for details.

Screening Procedures

- Review of inclusion and exclusion criteria
- Medication and medical history, concomitant medications/treatment(s), adverse events
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including height and weight
- ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, coagulation, urinalysis, pregnancy test
- If available, submission of paraffin-embedded tumor tissue (paraffin tumor block, or slides) and all available pathology reports
- 12-lead electrocardiogram (ECG)
- Radiological imaging to assess disease extent (CT scan or MRI of the brain, chest, abdomen, and all other sites of disease; within 28 days prior to enrollment)

Treatment and Follow-Up Procedures

- Recording and reporting of adverse events and concomitant medications
- Patient completion of EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Part 2)

- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status assessment
- Laboratory tests; including hematology, chemistry, pregnancy test
- Samples for biomarkers and anti-AMG 479 or anti-AMG 102 antibodies
- Samples for AMG 479, AMG 102, carboplatin, cisplatin and etoposide PK (Part 1)
- ECG
- Radiological imaging to assess disease extent (CT scan or MRI [same modality throughout the study] of the chest, abdomen, and all other sites of disease [except: brain imaging only as clinically indicated] every 6 weeks [± 7 days] from Study Day 1 during the first 6 months of the study, and every 9 weeks [± 7 days] thereafter)

Statistical Considerations: See Section 10 for details.

Analyses will be presented separately for Part 1 and Part 2 of the study. The HR for OS will be estimated using a Cox regression model stratified by randomization stratification factors and controlled for the LDH level as an important covariate. A Wald chi-square test will provide a descriptive p-value for the HR. Overall survival between the respective pair of treatment arms (Arm A/Arm C and Arm B/Arm C) will use a stratified log-rank test for a descriptive comparison.

DRT Safety Reviews and Interim Analysis

For the protection of subjects, in Part 1 of the study, Safety Review Team (SRT) meetings will be held to review safety, laboratory, dosing information and PK data (when available) from each AMG 479 and AMG 102 dose cohort, to make recommendations regarding dose selection for Part 2, dose de-escalation, or dose stopping.

In Part 2. and Amgen Data Review Team (DRT), independent of the study team will perform unblinded reviews of the safety data after at least 30 and 60 subjects have been randomized and had the opportunity to complete cycle 1 of the study treatment (safety interim analyses). In addition, unblinded SAE information for thrombosis or vascular ischemic events will be made available to the DRT on an ongoing basis

One interim efficacy analysis is planned to review both OS and PFS data 10 months after the last subject is randomized. Approximately 100 OS events are estimated (69 OS events per comparison: Arm A/Arm C and Arm B/Arm C) for the interim analysis assuming approximately half of the planned enrollment will occur at 15 months. Review of safety data will also occur during the interim efficacy analysis. The interim efficacy analysis will provide a preliminary assessment of the overall risk/benefit profile. Unless safety concerns arise, the study will not be discontinued or modified due to the results of the interim efficacy analysis

The primary analysis of Part 2 will be event-driven and will occur after a total of approximately 130 deaths (89 deaths per planned comparison: Arm A/Arm C and Arm B/Arm C), which is anticipated to occur 18 months after end of enrollment. A final analysis is planned after a minimum expected follow-up of 36 months, at which time approximately 163 deaths are expected overall (110 per planned comparison).

Study Design and Treatment Schema