Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

AMG 479

Amgen Protocol Number 20080257

Clinical Study Sponsor:
Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: 805-447-1000

Key Sponsor Contact:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen, Inc.
1120 Veterans Blvd.
ASF B3-3
South San Francisco, CA 94080
Phone: 650-244-2634
Fax: 650-837-9716
Email: jessem@amgen.com

Nancy Kenyon
Clinical Research Study Manager-U.S.
Amgen, Inc.
Mail Stop 38-2-B
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-5737
Fax: 805-480-1291
Email: nkenyon@amgen.com

Polly Rawlings
Clinical Research Study Manager-Outside U.S.
Amgen, Inc.
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
UK
Tel: +44 (0)1895 525476
Fax: +44 (0)1895 525107
Email: prawling@amgen.com

Date: 02-September-2008

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer" dated 02-September-2008, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and local Ethic Committee 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 subinvestigators (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 Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

Study Phase: 1b/ 2

Indication: First-line advanced squamous Non-Small Cell Lung Cancer (NSCLC)

Primary Objective:

Part 1 (Phase 1b): To identify a dose of AMG 479 in combination with paclitaxel/carboplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT).

Part 2 (Phase 2): To estimate the efficacy of AMG 479 (at the final dose selected in Part 1) in combination with paclitaxel/carboplatin as measured by the objective response rate (ORR) as per modified RECIST by investigator review.

Secondary Objective(s):

Part 1:

To evaluate the safety and tolerability of de-escalating doses of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities not defined as dose-limiting toxicities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Subjects who received the final dose in Part 1 will be included in the Part 2 efficacy and safety analysis.

Part 2:

To estimate the efficacy of AMG 479 in combination with paclitaxel/carboplatin as measured by progression free survival (PFS), time to progression (TTP), duration of response (DOR), 1 and 2 year survival rates, and overall survival (including subjects who received the final dose in Part 1).

To evaluate the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Exploratory Objective(s):

Parts 1 and 2:

To evaluate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (optional; collect-and-hold approach).

To correlate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST with pharmacodynamic measures (serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway).

To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target genes and correlate with outcomes related to AMG 479 in combination with paclitaxel/carboplatin therapy (requires a separate informed consent, optional for subjects).

To investigate tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available).

To investigate mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens. This will include but will not be limited to analysis of PTEN expression by immunohistochemistry (if tissue is available).

Hypotheses:

In Part 1, AMG 479 can be given with paclitaxel/carboplatin at a safe and tolerated dose as determined by the incidence of DLTs.

In Part 2, the ORR of AMG 479 in combination with paclitaxel/carboplatin will exceed that for the historical control of paclitaxel/carboplatin alone (See 10.3.2 for the weighted historical average).

Study Design:

Part 1 is an open-label, single arm dose de-escalation phase 1b segment to determine the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin every 3 weeks (Q3W) for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 as first-line therapy in advanced squamous NSCLC.

Part 2 is a single arm open-label phase 2 segment in which AMG 479 in combination with paclitaxel/carboplatin Q3W for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 will be used to determine the efficacy and safety of this regimen. The dose of AMG 479 used in Part 2 will be based on the final dose of AMG 479 from Part 1.

In Part 1, approximately 6 to 9 subjects will be enrolled in Cohort 1 to receive AMG 479 at 18 mg/kg in combination with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) IV on day 1 every 3 week cycle for 4 to 6 cycles followed by AMG 479 at 18 mg/kg monotherapy for up to 24 months from study day 1. Pending review of dose limiting toxicities from Cohort 1 by the study team, in consultation with participating investigator(s), a lower dose of AMG 479 at 12 mg/kg in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at 12 mg/kg monotherapy for up to 24 months from study day 1 may be administered to an additional 6 to 9 subjects in Cohort 2 (please see Section 3.1 Study Design for further clarification here).

In Part 2, an additional 31 to 34 subjects will be treated with AMG 479 at the final dose from Part 1 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at the final dose from Part 1 monotherapy for up to 24 months from study day 1. Part 2 will be open following the review of the Part 1 data by the study team, in consultation with participating investigator(s) as outlined in Section 3.1.

In Part 1 and Part 2, AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter).

In Part 1 and Part 2, all subjects receive AMG 479 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 to be administered until progression of disease, intolerable adverse event, death, or withdrawal of consent.

Radiological imaging to assess progressive disease (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 (+ 7) days and 60 (+ 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 to assess disease and survival status for up to 36 months from the date of the last subject enrolled in the study. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities

Part 2:

- ORR as per modified RECIST criteria by investigator review

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as dose limiting toxicities
- The incidence of anti-AMG 479 antibody formation

Part 2:

- PFS, TTP, DOR, 1 and 2 year survival rates, and OS including subjects who received the final dose in Part 1
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 antibody formation

Part 1 and 2 (PK):

- Cmax and Cmin for AMG 479 for all subjects
- Cmax, C24 or AUC24 for paclitaxel and carboplatin in subjects with intensive sampling

Exploratory Endpoints

Part 1 and Part 2:

- ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (this analysis is optional and may be initiated by the sponsor; all radiographic images from the study will be sent to a central imaging vendor with a collect-and-hold approach)
- Pharmacodynamic response: serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway
- Analysis of genetic variation (optional separate informed consent required)
- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available)
- Analysis of mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens (if tissue is available). This will include but will not be limited to analysis of PTEN expression by immunohistochemistry.

Sample Size: Part 1: 6 to 18 subjects; Part 2: 31 to 34 subjects (see Section 10.3 Sample Size for rational)

Summary of Subject Eligibility Criteria: See Section 4 for further details

Key Inclusion Criteria

- Histologically or cytologically confirmed advanced squamous NSCLC defined as stage IIIB with malignant effusion or stage IV or recurrent disease (recurrent disease is defined as documented disease progression following complete surgical resection for stage I or II disease). Subjects with mixed tumors with squamous features are eligible unless small cell elements are present in which case the subject will be ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirates or biopsy. Confirmation must be prior to enrollment.
- Measurable disease as defined per modified RECIST criteria (see Appendix F)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix E)

- ≥18 years old
- Adequate glycemic function, for subjects with known diabetes (Type 1 or 2), as follows:
  - Must be controlled with a glycosylated hemoglobin (HgbA1c) of ≤ 8.0%
  - Documented fasting blood sugars ≤ 160 mg/dL

Key Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases
  - Subjects with a history of CNS metastases that are both definitively treated and stably controlled are eligible if all of the following apply: 1) definitive therapy has been administered (surgery and/or radiation therapy); 2) there is no additional treatment planned for brain metastases; 3) the subject is clinically stable; 4) the subject is off corticosteroids or on a stable dose of corticosteroids for at least 14 days prior to enrollment.
- Prior anti-cancer therapy as follows:
  - Any prior chemotherapy for advanced squamous NSCLC
  - Any prior adjuvant or neo-adjuvant chemotherapy for squamous NSCLC
  - Any prior chemoradiation for squamous NSCLC
  - Central (chest) radiation therapy ≤ 28 days prior to enrollment, radiation therapy for peripheral lesions ≤ 14 days prior to enrollment for squamous NSCLC
- Currently or previously treated with biological, immunological or other therapies for squamous NSCLC

Investigational Product Dosage (AMG 479) and Chemotherapy Administration:

Part 1 (dose de-escalation design):

- Cohort 1: AMG 479 18 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 18 mg/kg IV monotherapy for up to 24 months from study day 1
- Cohort 2: AMG 479 12 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 12 mg/kg IV monotherapy for up to 24 months from study day 1

Part 2:

- AMG 479 IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 IV monotherapy for up to 24 months from study day 1. The AMG 479 dose to be used in Part 2 will be the final AMG 479 dose explored from Part 1.

For Part 1 and Part 2: AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter). Moreover, for Part 1 and Part 2, AMG 479 will be given in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 until progression of disease, intolerable adverse event, death, or withdrawal of consent.

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

Key Screening Procedures (see Section 7.2 for a complete list):

- 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, weight, and 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, pelvis, and all other sites of disease; within 28 days prior to enrollment). To include bone scan if indicated by signs or symptoms

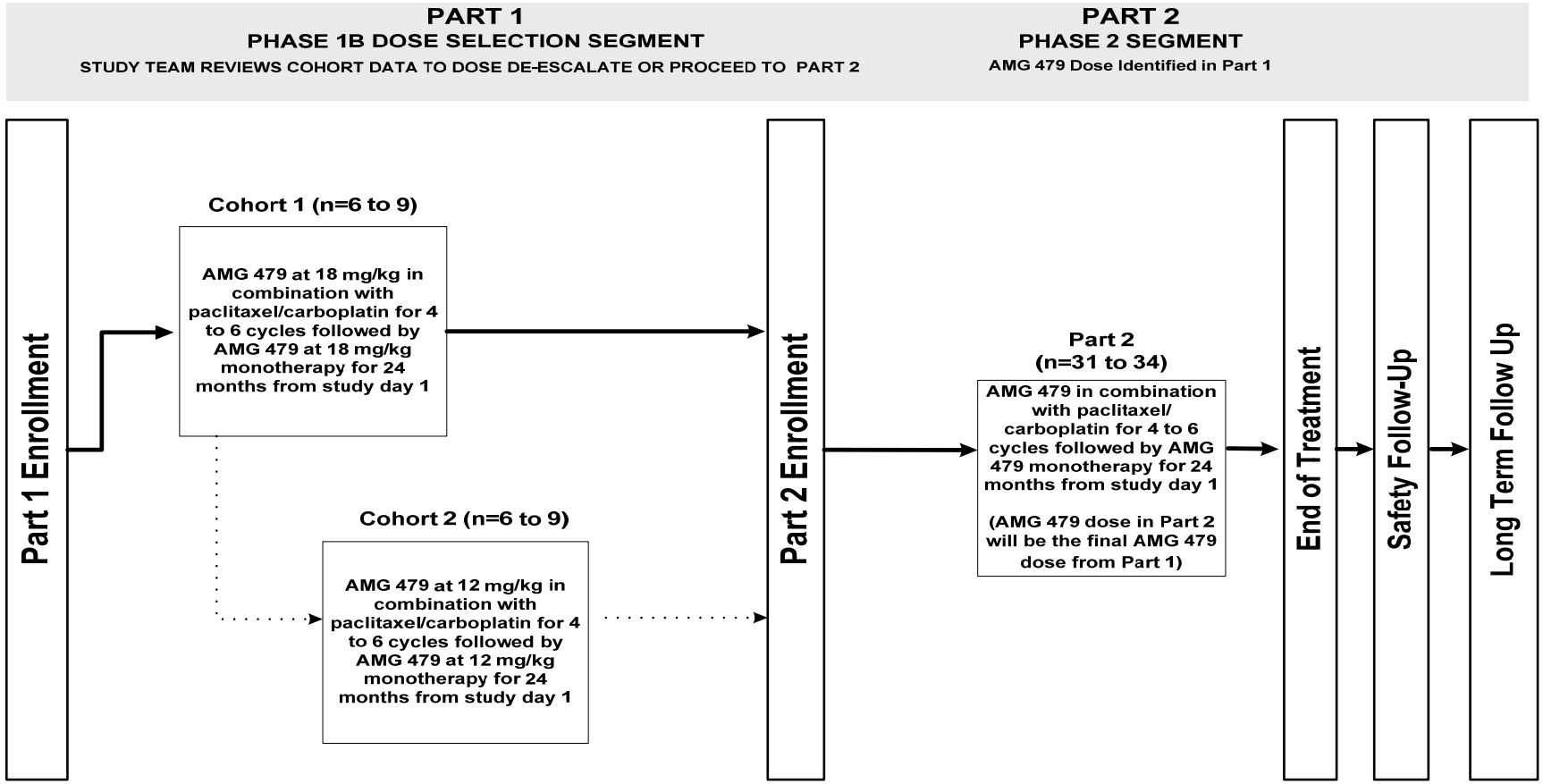
Key Treatment and Follow-Up Procedures (see Section 7.3, 7.4, and 7.5 for a complete list):

- Recording of adverse events and concomitant medications
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status
- Laboratory tests: including hematology, chemistry, coagulation, urinalysis, pregnancy test
- Samples for biomarkers and anti-AMG 479 antibodies
- Samples for AMG 479, paclitaxel and carboplatin PK
- Radiological imaging to assess disease extent will be performed every 6 weeks (±7 days) from study day 1 during the first 6 months of the study and then every 9 weeks (±7 days) thereafter, independent of the treatment cycle. Radiological assessment must include CT scan or MRI of the chest and abdomen. CT scan or MRI of the pelvis and all other site of disease will ONLY be assessed if positive at baseline and/or signs or symptoms suggestive of metastasis are present to confirm disease progression. The modality selected should be the same throughout the study.

Statistical Considerations: Overall safety will be evaluated for all subjects who received at least one dose of any study treatment component (AMG 479, paclitaxel, or carboplatin). The primary analysis of the ORR will include Part 1 subjects who receive the final dose of AMG 479 with paclitaxel/carboplatin and all Part 2 subjects in the full analysis set (10.2.4). The interim analysis is planned to evaluate first 20 subjects enrolled in Part 2 and will evaluate safety and efficacy of the study regimen. The study team, in consultation with participating investigator(s), may discontinue the study if the futility stopping rule is met.

The combination of AMG 479 with paclitaxel/carboplatin may warrant further study if the posterior probability is at least 90% that the observed ORR exceeds that expected for the historical control of paclitaxel/carboplatin alone. On the other hand, the study may suggest no further investigation of the combination is warranted if the posterior probability that the ORR is at least 20% higher than the historical ORR is less than 2.5%. An observed ORR not meeting these criteria may be considered inconclusive. All efficacy and safety outcomes will be considered in assessing the overall potential clinical benefit of the combination.

Study Design and Treatment Schema



STUDY TREATMENT (each cycle 3 weeks)

AMG 479 in combination paclitaxel 200 mg/m^2 / carboplatin (AUC 6) IV on day 1 of cycle 1 to 6 (for 4 to 6 cycles only). AMG 479 will be given IV on day 1 of each cycle except for intensive PK subjects who receive AMG 479 on day 2 of cycle 1 and then day 1 of each cycle thereafter. After completion or discontinuation of chemotherapy, continue AMG 479 monotherapy day 1 of each subsequent cycle for up to 24 months from study day 1

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

AMG 479

Amgen Protocol Number 20080257

Clinical Study Sponsor:
Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: 805-447-1000

Key Sponsor Contact:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen, Inc.
1120 Veterans Blvd.
ASF B3-3
South San Francisco, CA 94080
Phone: 650-244-2634
Fax: 650-837-9716
Email: jessem@amgen.com

Nancy Kenyon
Clinical Research Study Manager-U.S.
Amgen, Inc.
Mail Stop 38-2-B
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-5737
Fax: 805-480-1291
Email: nkenyon@amgen.com

Lutfat Rahaman
Clinical Research Study Manager-Outside U.S.
Amgen, Inc.
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
UK
Tel: +44 (0)1895 525496
Fax: +44 (0) 1223 228 134
Email:

Amendment 1 Date: **26-May-2009**

Date: 02-September-2008

Confidentiality Notice

This document contains confidential information of Amgen Inc..

This document must not be disclosed to anyone other than the study staff and members of the independent ethics committee/institutional review board.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number:

US sites: 1- 800-77-AMGEN

For all other countries: 1-805-447-5000

For all other study-related questions, continue to contact the Key Sponsor Contact.

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer" dated **Amendment 1 26 May 2009**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and local Ethic Committee 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 subinvestigators (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 Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

Study Phase: 1b/ 2

Indication: First-line advanced squamous Non-Small Cell Lung Cancer (NSCLC)

Primary Objective:

Part 1 (Phase 1b): To identify a dose of AMG 479 in combination with paclitaxel/carboplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT).

Part 2 (Phase 2): To estimate the efficacy of AMG 479 (at the final dose selected in Part 1) in combination with paclitaxel/carboplatin as measured by the objective response rate (ORR) as per modified RECIST by investigator review.

Secondary Objective(s):

Part 1:

To evaluate the safety and tolerability of de-escalating doses of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities not defined as dose-limiting toxicities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Subjects who received the final dose in Part 1 will be included in the Part 2 efficacy and safety analysis.

Part 2:

To estimate the efficacy of AMG 479 in combination with paclitaxel/carboplatin as measured by progression free survival (PFS), time to progression (TTP), duration of response (DOR), 1 and 2 year survival rates, and overall survival (including subjects who received the final dose in Part 1).

To evaluate the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Exploratory Objective(s):

Parts 1 and 2:

To evaluate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (optional; collect-and-hold approach).

To correlate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST with pharmacodynamic measures (serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway).

To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target genes and correlate with outcomes related to AMG 479 in combination with paclitaxel/carboplatin therapy (requires a separate informed consent, optional for subjects).

To investigate tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available).

To investigate mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens. This will include but will not be limited to analysis of PTEN expression by immunohistochemistry (if tissue is available).

Hypotheses:

In Part 1, AMG 479 can be given with paclitaxel/carboplatin at a safe and tolerated dose as determined by the incidence of DLTs.

In Part 2, the ORR of AMG 479 in combination with paclitaxel/carboplatin will exceed that for the historical control of paclitaxel/carboplatin alone (See Section 10.3.2 for the weighted historical average).

Study Design:

Part 1 is an open-label, single arm dose de-escalation phase 1b segment to determine the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin every 3 weeks (Q3W) for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 as first-line therapy in advanced squamous NSCLC.

Part 2 is a single arm open-label phase 2 segment in which AMG 479 in combination with paclitaxel/carboplatin Q3W for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 will be used to determine the efficacy and safety of this regimen. The dose of AMG 479 used in Part 2 will be based on the final dose of AMG 479 from Part 1.

In Part 1, approximately 6 to 9 subjects will be enrolled in Cohort 1 to receive AMG 479 at 18 mg/kg in combination with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) IV on day 1 every 3 week cycle for 4 to 6 cycles followed by AMG 479 at 18 mg/kg monotherapy for up to 24 months from study day 1. Pending review of dose limiting toxicities from Cohort 1 by the study team, in consultation with participating investigator(s), a lower dose of AMG 479 at 12 mg/kg in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at 12 mg/kg monotherapy for up to 24 months from study day 1 may be administered to an additional 6 to 9 subjects in Cohort 2 (please see Section 3.1 Study Design for further clarification here).

In Part 2, an additional 31 to 34 subjects will be treated with AMG 479 at the final dose from Part 1 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at the final dose from Part 1 monotherapy for up to 24 months from study day 1. Part 2 will be open following the review of the Part 1 data by the study team, in consultation with participating investigator(s) as outlined in Section 3.1.

In Part 1 and Part 2, AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter).

In Part 1 and Part 2, all subjects receive AMG 479 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 to be administered until progression of disease, intolerable adverse event, death, or withdrawal of consent.

Radiological imaging to assess progressive disease (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 (+ 7) days and 60 (+ 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 to assess disease and survival status for up to 36 months from the date of the last subject enrolled in the study. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities

Part 2:

- ORR as per modified RECIST criteria by investigator review

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as dose limiting toxicities
- The incidence of anti-AMG 479 antibody formation

Part 2:

- PFS, TTP, DOR, 1 and 2 year survival rates, and OS including subjects who received the final dose in Part 1
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 antibody formation

Part 1 and 2 (PK):

- Cmax and Cmin for AMG 479 for all subjects
- Cmax, C24 or AUC24 for paclitaxel and carboplatin in subjects with intensive sampling

Exploratory Endpoints

Part 1 and Part 2:

- ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (this analysis is optional and may be initiated by the sponsor; all radiographic images from the study will be sent to a central imaging vendor with a collect-and-hold approach)
- Pharmacodynamic response: serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway
- Analysis of genetic variation (optional separate informed consent required)
- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available)
- Analysis of mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens (if tissue is available). This will include but will not be limited to analysis of PTEN expression by immunohistochemistry.

Sample Size: Part 1: 6 to 18 subjects; Part 2: 31 to 34 subjects (see Section 9.3 Sample Size for rational)

Summary of Subject Eligibility Criteria: See Section 3 for further details

Key Inclusion Criteria

- Histologically or cytologically confirmed advanced squamous NSCLC defined as stage IIIB with malignant effusion or stage IV or recurrent disease (recurrent disease is defined as documented disease progression following complete surgical resection for stage I or II disease). Subjects with mixed tumors with squamous features are eligible unless small cell elements are present in which case the subject will be ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirates or biopsy. Confirmation must be prior to enrollment.
- Measurable disease as defined per modified RECIST criteria (see Appendix F)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix E)

- ≥18 years old
- **Glycosylated hemoglobin (HgbA1c) ≤ 8%**

Key Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases
  - Subjects with a history of CNS metastases that are both definitively treated and stably controlled are eligible if all of the following apply: 1) definitive therapy has been administered (surgery and/or radiation therapy); 2) there is no additional treatment planned for brain metastases; 3) the subject is clinically stable; 4) the subject is off corticosteroids or on a stable dose of corticosteroids for at least 14 days prior to enrollment.
- Prior anti-cancer therapy as follows:
  - Any prior chemotherapy for advanced squamous NSCLC
  - Any prior adjuvant or neo-adjuvant chemotherapy for squamous NSCLC
  - Any prior chemoradiation for squamous NSCLC
  - Central (chest) radiation therapy ≤ 28 days prior to enrollment, radiation therapy for peripheral lesions ≤ 14 days prior to enrollment for squamous NSCLC
- Currently or previously treated with biological, immunological or other therapies for squamous NSCLC

Investigational Product Dosage (AMG 479) and Chemotherapy Administration:

Part 1 (dose de-escalation design):

- Cohort 1: AMG 479 18 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 18 mg/kg IV monotherapy for up to 24 months from study day 1
- Cohort 2: AMG 479 12 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 12 mg/kg IV monotherapy for up to 24 months from study day 1

Part 2:

- AMG 479 IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 IV monotherapy for up to 24 months from study day 1. The AMG 479 dose to be used in Part 2 will be the final AMG 479 dose explored from Part 1.

For Part 1 and Part 2: AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter). Moreover, for Part 1 and Part 2, AMG 479 will be given in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 until progression of disease, intolerable adverse event, death, or withdrawal of consent.

Procedures: See Section 6.1 and Schedule of Assessments (Appendix A) for details.

Key Screening Procedures (see Section 6.2 for a complete list):

- 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, weight, and 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, pelvis, and all other sites of disease; within 28 days prior to enrollment). To include bone scan if indicated by signs or symptoms

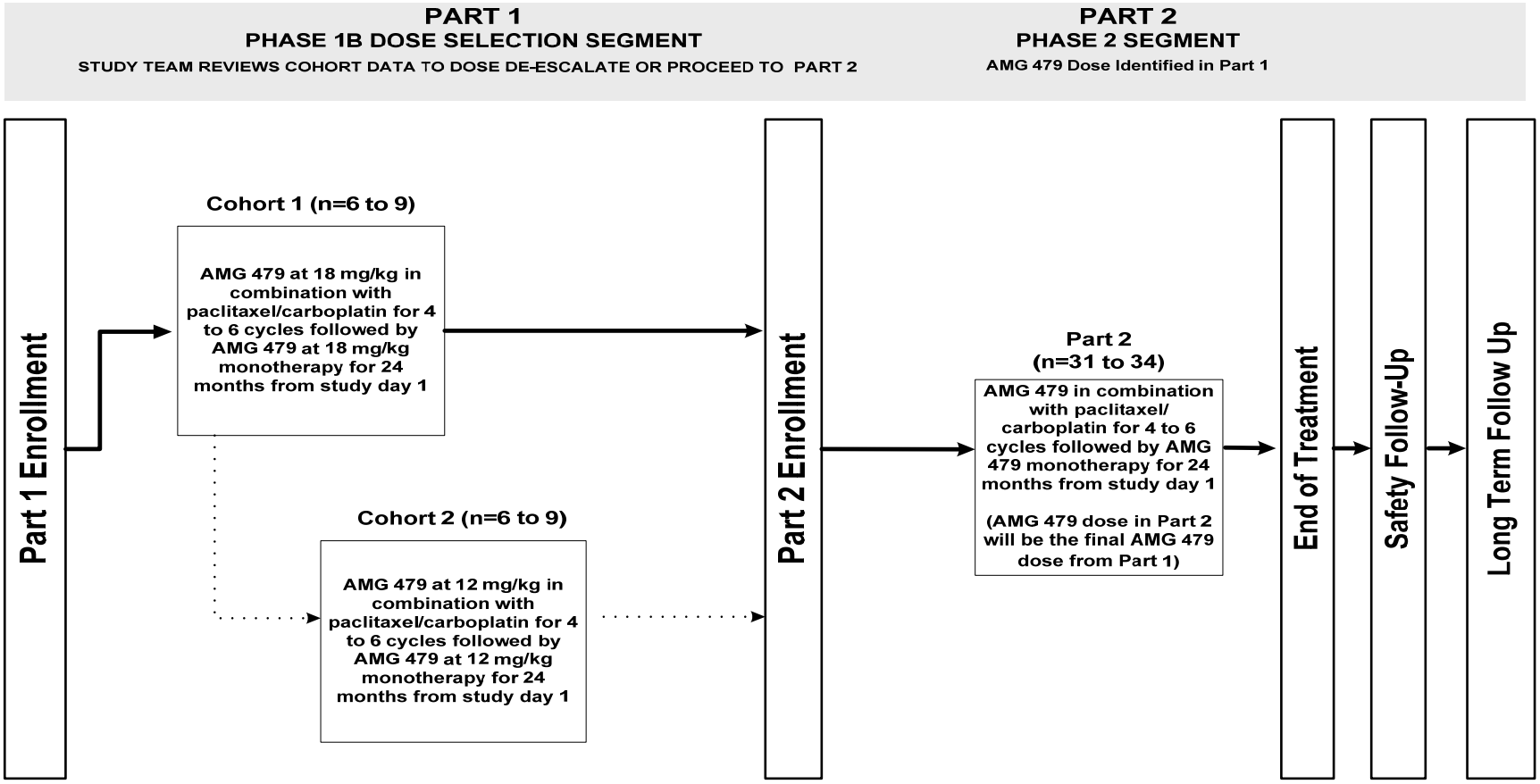
Key Treatment and Follow-Up Procedures (see Section 6.3, 6.4, and 6.5 for a complete list):

- Recording of adverse events and concomitant medications
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status
- Laboratory tests: including hematology, chemistry, coagulation, urinalysis, pregnancy test
- Samples for biomarkers and anti-AMG 479 antibodies
- Samples for AMG 479, paclitaxel and carboplatin PK
- Radiological imaging to assess disease extent will be performed every 6 weeks (± 7 days) from study day 1 during the first 6 months of the study and then every 9 weeks (± 7 days) thereafter, independent of the treatment cycle. Radiological assessment must include CT scan or MRI of the chest and abdomen. CT scan or MRI of the pelvis and all other site of disease will ONLY be assessed if positive at baseline and/or signs or symptoms suggestive of metastasis are present to confirm disease progression. The modality selected should be the same throughout the study.

Statistical Considerations: Overall safety will be evaluated for all subjects who received at least one dose of any study treatment component (AMG 479, paclitaxel, or carboplatin). The primary analysis of the ORR will include Part 1 subjects who receive the final dose of AMG 479 with paclitaxel/carboplatin and all Part 2 subjects in the full analysis set (Section 10.2.4). The interim analysis is planned to evaluate first 20 subjects enrolled in Part 2 and will evaluate safety and efficacy of the study regimen. The study team, in consultation with participating investigator(s), may discontinue the study if the futility stopping rule is met.

The combination of AMG 479 with paclitaxel/carboplatin may warrant further study if the posterior probability is at least 90% that the observed ORR exceeds that expected for the historical control of paclitaxel/carboplatin alone. On the other hand, the study may suggest no further investigation of the combination is warranted if the posterior probability that the ORR is at least 20% higher than the historical ORR is less than 2.5%. An observed ORR not meeting these criteria may be considered inconclusive. All efficacy and safety outcomes will be considered in assessing the overall potential clinical benefit of the combination.

Study Design and Treatment Schema



STUDY TREATMENT (each cycle 3 weeks)

AMG 479 in combination paclitaxel 200 mg/m^2 / carboplatin (AUC 6) IV on day 1 of cycle 1 to 6 (for 4 to 6 cycles only). AMG 479 will be given IV on day 1 of each cycle except for intensive PK subjects who receive AMG 479 on day 2 of cycle 1 and then day 1 of each cycle thereafter. After completion or discontinuation of chemotherapy, continue AMG 479 monotherapy day 1 of each subsequent cycle for up to 24 months from study day 1

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

AMG 479

Amgen Protocol Number 20080257

Clinical Study Sponsor:
Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: 805-447-1000

Key Sponsor Contact:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen, Inc.
1120 Veterans Blvd.
ASF B3-3
South San Francisco, CA 94080
Phone: 650-244-2634
Fax: 650-837-9716
Email: jessem@amgen.com

Nancy Kenyon
Clinical Research Study Manager-U.S.
Amgen, Inc.
Mail Stop 38-2-B
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-5737
Fax: 805-480-1291
Email: nkenyon@amgen.com

Lutfat Rahaman
Clinical Research Study Manager-Outside U.S.
Amgen, Inc.
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
UK
Tel: +44 (0)1895 525496
Fax: +44 (0) 1223 228 134
Email:

Superseding Date, Amendment 1 **18-June-2009**

Amendment 1 Date: **26-May-2009**

Original Protocol Date: 02-September-2008

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer", **Superseding Date 18-June-2009 Amendment 1**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and local Ethic Committee 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 subinvestigators (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 Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

Study Phase: 1b/ 2

Indication: First-line advanced squamous Non-Small Cell Lung Cancer (NSCLC)

Primary Objective:

Part 1 (Phase 1b): To identify a dose of AMG 479 in combination with paclitaxel/carboplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT).

Part 2 (Phase 2): To estimate the efficacy of AMG 479 (at the final dose selected in Part 1) in combination with paclitaxel/carboplatin as measured by the objective response rate (ORR) as per modified RECIST by investigator review.

Secondary Objective(s):

Part 1:

To evaluate the safety and tolerability of de-escalating doses of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities not defined as dose-limiting toxicities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Subjects who received the final dose in Part 1 will be included in the Part 2 efficacy and safety analysis.

Part 2:

To estimate the efficacy of AMG 479 in combination with paclitaxel/carboplatin as measured by progression free survival (PFS), time to progression (TTP), duration of response (DOR), 1 and 2 year survival rates, and overall survival (including subjects who received the final dose in Part 1).

To evaluate the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Exploratory Objective(s):

Parts 1 and 2:

To evaluate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (optional; collect-and-hold approach).

To correlate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST with pharmacodynamic measures (serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway).

To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target genes and correlate with outcomes related to AMG 479 in combination with paclitaxel/carboplatin therapy (requires a separate informed consent, optional for subjects).

To investigate tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available).

To investigate mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens. This will include but will not be limited to analysis of PTEN expression by immunohistochemistry (if tissue is available).

Hypotheses:

In Part 1, AMG 479 can be given with paclitaxel/carboplatin at a safe and tolerated dose as determined by the incidence of DLTs.

In Part 2, the ORR of AMG 479 in combination with paclitaxel/carboplatin will exceed that for the historical control of paclitaxel/carboplatin alone (See Section 10.3.2 for the weighted historical average).

Study Design:

Part 1 is an open-label, single arm dose de-escalation phase 1b segment to determine the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin every 3 weeks (Q3W) for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 as first-line therapy in advanced squamous NSCLC.

Part 2 is a single arm open-label phase 2 segment in which AMG 479 in combination with paclitaxel/carboplatin Q3W for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 will be used to determine the efficacy and safety of this regimen. The dose of AMG 479 used in Part 2 will be based on the final dose of AMG 479 from Part 1.

In Part 1, approximately 6 to 9 subjects will be enrolled in Cohort 1 to receive AMG 479 at 18 mg/kg in combination with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) IV on day 1 every 3 week cycle for 4 to 6 cycles followed by AMG 479 at 18 mg/kg monotherapy for up to 24 months from study day 1. Pending review of dose limiting toxicities from Cohort 1 by the study team, in consultation with participating investigator(s), a lower dose of AMG 479 at 12 mg/kg in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at 12 mg/kg monotherapy for up to 24 months from study day 1 may be administered to an additional 6 to 9 subjects in Cohort 2 (please see Section 3.1 Study Design for further clarification here).

In Part 2, an additional 31 to 34 subjects will be treated with AMG 479 at the final dose from Part 1 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at the final dose from Part 1 monotherapy for up to 24 months from study day 1. Part 2 will be open following the review of the Part 1 data by the study team, in consultation with participating investigator(s) as outlined in Section 3.1.

In Part 1 and Part 2, AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter).

In Part 1 and Part 2, all subjects receive AMG 479 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 to be administered until progression of disease, intolerable adverse event, death, or withdrawal of consent.

Radiological imaging to assess progressive disease (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 (+ 7) days and 60 (+ 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 to assess disease and survival status for up to 36 months from the date of the last subject enrolled in the study. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities

Part 2:

- ORR as per modified RECIST criteria by investigator review

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as dose limiting toxicities
- The incidence of anti-AMG 479 antibody formation

Part 2:

- PFS, TTP, DOR, 1 and 2 year survival rates, and OS including subjects who received the final dose in Part 1
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 antibody formation

Part 1 and 2 (PK):

- Cmax and Cmin for AMG 479 for all subjects
- Cmax, C24 or AUC24 for paclitaxel and carboplatin in subjects with intensive sampling

Exploratory Endpoints

Part 1 and Part 2:

- ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (this analysis is optional and may be initiated by the sponsor; all radiographic images from the study will be sent to a central imaging vendor with a collect-and-hold approach)
- Pharmacodynamic response: serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway
- Analysis of genetic variation (optional separate informed consent required)
- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available)
- Analysis of mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens (if tissue is available). This will include but will not be limited to analysis of PTEN expression by immunohistochemistry.

Sample Size: Part 1: 6 to 18 subjects; Part 2: 31 to 34 subjects (see Section10.3 Sample Size for rational)

Summary of Subject Eligibility Criteria: See Section 4 for further details

Key Inclusion Criteria

- Histologically or cytologically confirmed advanced squamous NSCLC defined as stage IIIB with malignant effusion or stage IV or recurrent disease (recurrent disease is defined as documented disease progression following complete surgical resection for stage I or II disease). Subjects with mixed tumors with squamous features are eligible unless small cell elements are present in which case the subject will be ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirates or biopsy. Confirmation must be prior to enrollment.
- Measurable disease as defined per modified RECIST criteria (see Appendix F)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix E)

- ≥18 years old
- **Glycosylated hemoglobin (HgbA1c) ≤ 8%**

Key Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases
  - Subjects with a history of CNS metastases that are both definitively treated and stably controlled are eligible if all of the following apply: 1) definitive therapy has been administered (surgery and/or radiation therapy); 2) there is no additional treatment planned for brain metastases; 3) the subject is clinically stable; 4) the subject is off corticosteroids or on a stable dose of corticosteroids for at least 14 days prior to enrollment.
- Prior anti-cancer therapy as follows:
  - Any prior chemotherapy for advanced squamous NSCLC
  - Any prior adjuvant or neo-adjuvant chemotherapy for squamous NSCLC
  - Any prior chemoradiation for squamous NSCLC
  - Central (chest) radiation therapy ≤ 28 days prior to enrollment, radiation therapy for peripheral lesions ≤ 14 days prior to enrollment for squamous NSCLC
- Currently or previously treated with biological, immunological or other therapies for squamous NSCLC

Investigational Product Dosage (AMG 479) and Chemotherapy Administration:

Part 1 (dose de-escalation design):

- Cohort 1: AMG 479 18 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 18 mg/kg IV monotherapy for up to 24 months from study day 1
- Cohort 2: AMG 479 12 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 12 mg/kg IV monotherapy for up to 24 months from study day 1

Part 2:

- AMG 479 IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 IV monotherapy for up to 24 months from study day 1. The AMG 479 dose to be used in Part 2 will be the final AMG 479 dose explored from Part 1.

For Part 1 and Part 2: AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter). Moreover, for Part 1 and Part 2, AMG 479 will be given in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 until progression of disease, intolerable adverse event, death, or withdrawal of consent.

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

Key Screening Procedures (see Section 7.2 for a complete list):

- 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, weight, and 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, pelvis, and all other sites of disease; within 28 days prior to enrollment). To include bone scan if indicated by signs or symptoms

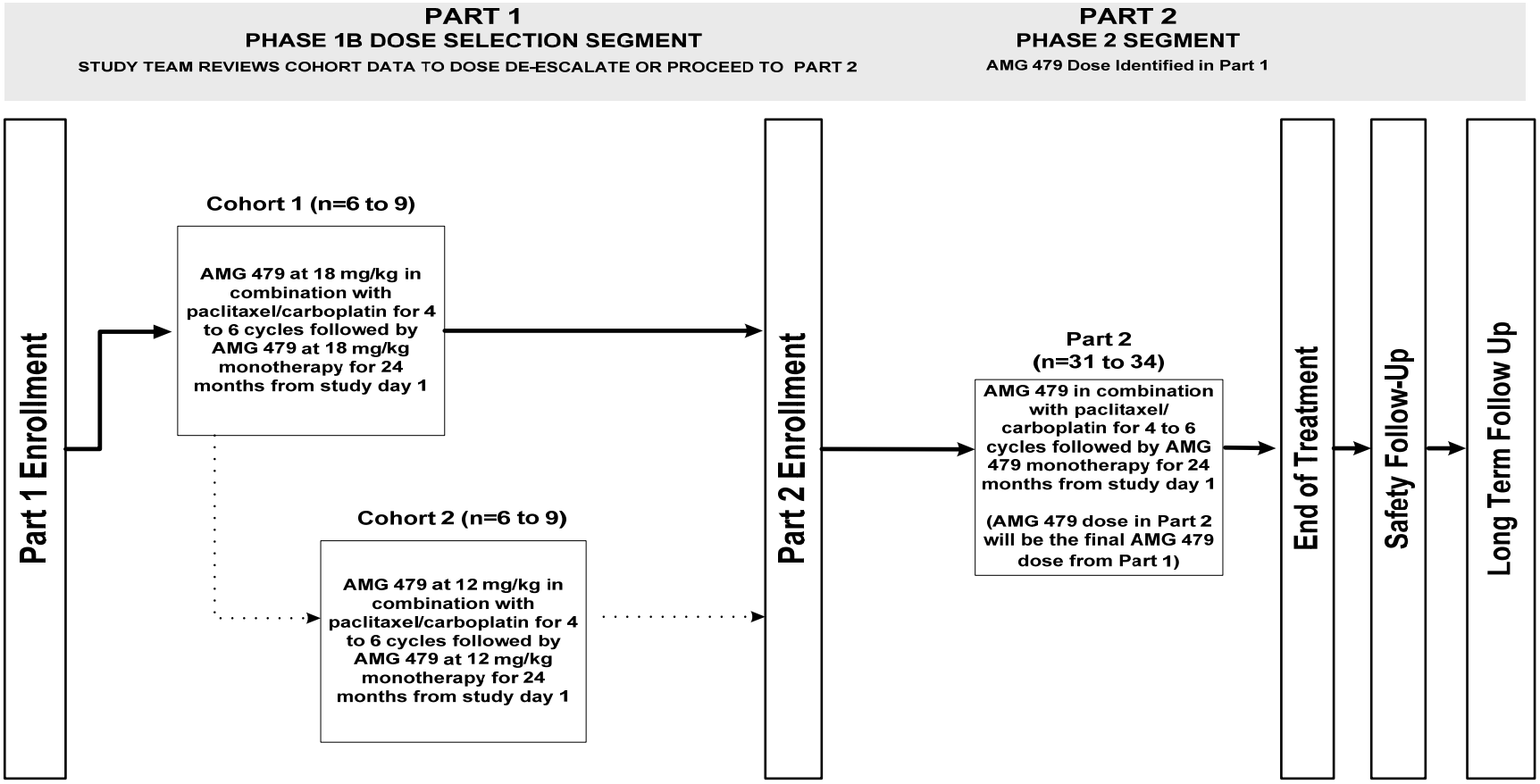
Key Treatment and Follow-Up Procedures (see Section 7.3, 7.4, and 7.5 for a complete list):

- Recording of adverse events and concomitant medications
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status
- Laboratory tests: including hematology, chemistry, coagulation, urinalysis, pregnancy test
- Samples for biomarkers and anti-AMG 479 antibodies
- Samples for AMG 479, paclitaxel and carboplatin PK
- Radiological imaging to assess disease extent will be performed every 6 weeks (± 7 days) from study day 1 during the first 6 months of the study and then every 9 weeks (± 7 days) thereafter, independent of the treatment cycle. Radiological assessment must include CT scan or MRI of the chest and abdomen. CT scan or MRI of the pelvis and all other site of disease will ONLY be assessed if positive at baseline and/or signs or symptoms suggestive of metastasis are present to confirm disease progression. The modality selected should be the same throughout the study.

Statistical Considerations: Overall safety will be evaluated for all subjects who received at least one dose of any study treatment component (AMG 479, paclitaxel, or carboplatin). The primary analysis of the ORR will include Part 1 subjects who receive the final dose of AMG 479 with paclitaxel/carboplatin and all Part 2 subjects in the full analysis set (Section 10.2.4). The interim analysis is planned to evaluate first 20 subjects enrolled in Part 2 and will evaluate safety and efficacy of the study regimen. The study team, in consultation with participating investigator(s), may discontinue the study if the futility stopping rule is met.

The combination of AMG 479 with paclitaxel/carboplatin may warrant further study if the posterior probability is at least 90% that the observed ORR exceeds that expected for the historical control of paclitaxel/carboplatin alone. On the other hand, the study may suggest no further investigation of the combination is warranted if the posterior probability that the ORR is at least 20% higher than the historical ORR is less than 2.5%. An observed ORR not meeting these criteria may be considered inconclusive. All efficacy and safety outcomes will be considered in assessing the overall potential clinical benefit of the combination.

Study Design and Treatment Schema



STUDY TREATMENT (each cycle 3 weeks)

AMG 479 in combination paclitaxel 200 mg/m^2 / carboplatin (AUC 6) IV on day 1 of cycle 1 to 6 (for 4 to 6 cycles only). AMG 479 will be given IV on day 1 of each cycle except for intensive PK subjects who receive AMG 479 on day 2 of cycle 1 and then day 1 of each cycle thereafter. After completion or discontinuation of chemotherapy, continue AMG 479 monotherapy day 1 of each subsequent cycle for up to 24 months from study day 1

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

AMG 479

Amgen Protocol Number 20080257

Clinical Study Sponsor:
Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: 805-447-1000

Key Sponsor Contact:
Jesse McGreivy, MD
Clinical Research Medical Director
Amgen, Inc.
1120 Veterans Blvd.
ASF B3-3
South San Francisco, CA 94080
Phone: 650-244-2634
Fax: 650-837-9716
Email: jessem@amgen.com

Nancy Kenyon
Clinical Research Study Manager-U.S.
Amgen, Inc.
Mail Stop 38-2-B
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-5737
Fax: 805-480-1291
Email: nkenyon@amgen.com

Kay Smith
Clinical Research Study Manager-Outside U.S.
Amgen, Inc.
240 Milton Road (Cambridge Science Park)
Cambridge
UK
Tel: +44 1223 420 305
Fax: +44 (0) 1223 423 049
Email:

Amendment 2	**06-August-2010**
Superseding Date, Amendment 1	18-June-2009
Amendment 1 Date:	26-May-2009
Original Protocol Date:	02-September-2008

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer", Amendment **2, Date 06 August 2010**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and local Ethic Committee 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 subinvestigators (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 Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer

Study Phase: 1b/ 2

Indication: First-line advanced squamous Non-Small Cell Lung Cancer (NSCLC)

Primary Objective:

Part 1 (Phase 1b): To identify a dose of AMG 479 in combination with paclitaxel/carboplatin that can be administered safely and is tolerated as determined by the incidence of dose-limiting toxicity (DLT).

Part 2 (Phase 2): To estimate the efficacy of AMG 479 (at the final dose selected in Part 1) in combination with paclitaxel/carboplatin as measured by the objective response rate (ORR) as per modified RECIST by investigator review.

Secondary Objective(s):

Part 1:

To evaluate the safety and tolerability of de-escalating doses of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities not defined as dose-limiting toxicities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Subjects who received the final dose in Part 1 will be included in the Part 2 efficacy and safety analysis.

Part 2:

To estimate the efficacy of AMG 479 in combination with paclitaxel/carboplatin as measured by progression free survival (PFS), time to progression (TTP), **and** duration of response (DOR), (including subjects who received the final dose in Part 1).

To evaluate the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin in terms of the incidence of adverse events and laboratory abnormalities.

To evaluate the pharmacokinetics of AMG 479 and paclitaxel/carboplatin and estimate the impact of co-administration of AMG 479 on the pharmacokinetics of paclitaxel/carboplatin.

To evaluate anti-AMG 479 antibody formation.

Exploratory Objective(s):

Parts 1 and 2:

To evaluate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (optional; collect-and-hold approach).

To correlate the ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST with pharmacodynamic measures (serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway).

To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target genes and correlate with outcomes related to AMG 479 in combination with paclitaxel/carboplatin therapy (requires a separate informed consent, optional for subjects).

To investigate tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available).

To investigate mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens. This will include but will not be limited to analysis of PTEN expression by immunohistochemistry (if tissue is available).

Hypotheses:

In Part 1, AMG 479 can be given with paclitaxel/carboplatin at a safe and tolerated dose as determined by the incidence of DLTs.

In Part 2, the ORR of AMG 479 in combination with paclitaxel/carboplatin will exceed that for the historical control of paclitaxel/carboplatin alone (See Section 10.3.2 for the weighted historical average).

Study Design:

Part 1 is an open-label, single arm dose de-escalation phase 1b segment to determine the safety and tolerability of AMG 479 in combination with paclitaxel/carboplatin every 3 weeks (Q3W) for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 as first-line therapy in advanced squamous NSCLC.

Part 2 is a single arm open-label phase 2 segment in which AMG 479 in combination with paclitaxel/carboplatin Q3W for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 will be used to determine the efficacy and safety of this regimen. The dose of AMG 479 used in Part 2 will be based on the final dose of AMG 479 from Part 1.

In Part 1, approximately 6 to 9 subjects will be enrolled in Cohort 1 to receive AMG 479 at 18 mg/kg in combination with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) IV on day 1 every 3 week cycle for 4 to 6 cycles followed by AMG 479 at 18 mg/kg monotherapy for up to 24 months from study day 1. Pending review of dose limiting toxicities from Cohort 1 by the study team, in consultation with participating investigator(s), a lower dose of AMG 479 at 12 mg/kg in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at 12 mg/kg monotherapy for up to 24 months from study day 1 may be administered to an additional 6 to 9 subjects in Cohort 2 (please see Section 3.1 Study Design for further clarification here).

In Part 2, an additional 31 to 34 subjects will be treated with AMG 479 at the final dose from Part 1 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 at the final dose from Part 1 monotherapy for up to 24 months from study day 1. Part 2 will be open following the review of the Part 1 data by the study team, in consultation with participating investigator(s) as outlined in Section 3.1.

In Part 1 and Part 2, AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter).

In Part 1 and Part 2, all subjects receive AMG 479 in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 to be administered until progression of disease, intolerable adverse event, death, or withdrawal of consent.

Radiological imaging to assess progressive disease (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 (+ 7) days and 60 (+ 14) days after the last dose of protocol-specified treatment. Please refer to the Study Schema for an overview of the 2-part study design.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1:

- The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities

Part 2:

- ORR as per modified RECIST criteria by investigator review

Secondary Endpoints

Part 1:

- The incidence of adverse events and laboratory abnormalities not defined as dose limiting toxicities
- The incidence of anti-AMG 479 antibody formation

Part 2:

- PFS, TTP **and** DOR, including subjects who received the final dose in Part 1
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 479 antibody formation

Part 1 and 2 (PK):

- Cmax and Cmin for AMG 479 for all subjects
- Cmax, C24 or AUC24 for paclitaxel and carboplatin in subjects with intensive sampling

Exploratory Endpoints

Part 1 and Part 2:

- ORR and other efficacy endpoints (DOR, PFS, TTP) as per modified RECIST by independent radiographic review (this analysis is optional and may be initiated by the sponsor; all radiographic images from the study will be sent to a central imaging vendor with a collect-and-hold approach)
- Pharmacodynamic response: serum IGF-1, IGF-BP3, growth hormone, and other factors that are involved in regulating the IGF-1/IGF-1R pathway
- Analysis of genetic variation (optional separate informed consent required)
- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R pathway and other genes that are known to be involved in the development and progression of solid tumors (if tissue is available)
- Analysis of mRNA and protein expression of genes that are known to regulate the IGF-1/IGF-1R pathway in archival tumor specimens (if tissue is available). This will include but will not be limited to analysis of PTEN expression by immunohistochemistry.

Sample Size: Fourteen total subjects received AMG 479 in combination with paclitaxel/carboplatin, 6 subjects in Part 1 and 8 subjects in Part 2.

Summary of Subject Eligibility Criteria: See Section 4 for further details

Key Inclusion Criteria

- Histologically or cytologically confirmed advanced squamous NSCLC defined as stage IIIB with malignant effusion or stage IV or recurrent disease (recurrent disease is defined as documented disease progression following complete surgical resection for stage I or II disease). Subjects with mixed tumors with squamous features are eligible unless small cell elements are present in which case the subject will be ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirates or biopsy. Confirmation must be prior to enrollment.
- Measurable disease as defined per modified RECIST criteria (see Appendix F)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix E)

- ≥18 years old
- Glycosylated hemoglobin (HgbA1c) ≤ 8%

Key Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases
  - Subjects with a history of CNS metastases that are both definitively treated and stably controlled are eligible if all of the following apply: 1) definitive therapy has been administered (surgery and/or radiation therapy); 2) there is no additional treatment planned for brain metastases; 3) the subject is clinically stable; 4) the subject is off corticosteroids or on a stable dose of corticosteroids for at least 14 days prior to enrollment.
- Prior anti-cancer therapy as follows:
  - Any prior chemotherapy for advanced squamous NSCLC
  - Any prior adjuvant or neo-adjuvant chemotherapy for squamous NSCLC
  - Any prior chemoradiation for squamous NSCLC
  - Central (chest) radiation therapy ≤ 28 days prior to enrollment, radiation therapy for peripheral lesions ≤ 14 days prior to enrollment for squamous NSCLC
- Currently or previously treated with biological, immunological or other therapies for squamous NSCLC

Investigational Product Dosage (AMG 479) and Chemotherapy Administration:

Part 1 (dose de-escalation design):

- Cohort 1: AMG 479 18 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 18 mg/kg IV monotherapy for up to 24 months from study day 1
- Cohort 2: AMG 479 12 mg/kg IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 at 12 mg/kg IV monotherapy for up to 24 months from study day 1

Part 2:

- AMG 479 IV in combination with paclitaxel 200 mg/m^2 and carboplatin (AUC 6) IV on day 1 of every 3 week cycle for 4 to 6 cycles, followed by AMG 479 IV monotherapy for up to 24 months from study day 1. The AMG 479 dose to be used in Part 2 will be the final AMG 479 dose explored from Part 1.

For Part 1 and Part 2: AMG 479 will be dosed on day 1 of every 3 week cycle (except for subjects being evaluated by intensive PK who will receive AMG 479 on day 2 of cycle 1 and then on day 1 of each cycle thereafter). Moreover, for Part 1 and Part 2, AMG 479 will be given in combination with paclitaxel/carboplatin for 4 to 6 cycles followed by AMG 479 monotherapy for up to 24 months from study day 1 until progression of disease, intolerable adverse event, death, or withdrawal of consent.

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

Key Screening Procedures (see Section 7.2 for a complete list):

- 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, weight, and 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, pelvis, and all other sites of disease; within 28 days prior to enrollment). To include bone scan if indicated by signs or symptoms

Key Treatment and Follow-Up Procedures (see Section 7.3, 7.4, and 7.5 for a complete list):

- Recording of adverse events and concomitant medications
- Vital signs: resting pulse, respiration, blood pressure, and temperature
- Physical examination, including weight, and ECOG performance status
- Laboratory tests: including hematology, chemistry, coagulation, urinalysis, pregnancy test
- Samples for biomarkers and anti-AMG 479 antibodies
- Samples for AMG 479, paclitaxel and carboplatin PK
- Radiological imaging to assess disease extent will be performed every 6 weeks (± 7 days) from study day 1 during the first 6 months of the study and then every 9 weeks (± 7 days) thereafter, independent of the treatment cycle. Radiological assessment must include CT scan or MRI of the chest and abdomen. CT scan or MRI of the pelvis and all other site of disease will ONLY be assessed if positive at baseline and/or signs or symptoms suggestive of metastasis are present to confirm disease progression. The modality selected should be the same throughout the study.

Statistical Considerations: Overall safety will be evaluated for all subjects who received at least one dose of any study treatment component (AMG 479, paclitaxel, or carboplatin). The primary analysis of the ORR will include Part 1 subjects who receive the final dose of AMG 479 with paclitaxel/carboplatin and all Part 2 subjects in the full analysis set (Section 10.2.4). **Given that enrollment was closed after 14 subjects were enrolled in both Part 1 and Part 2, neither the interim nor the primary analysis will occur. Only the final analysis will be performed at the end of study which will occur when all subjects have had the opportunity to complete the 60 day follow up visit, or all subjects have died, or 26 months after the date the last subject was randomized, whichever date is earlier.**

Study Design and Treatment Schema