A Phase 1b/2 Open Label, Dose Escalation Study of AMG 655 in Combination With AMG 479 in Subjects With Advanced, Refractory Solid Tumors

AMG 479 and AMG 655

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Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/2 Open Label, Dose Escalation Study of AMG 655 in Combination With AMG 479 in Subjects With Advanced, Refractory Solid Tumors, dated **25 May 2011**, 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 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 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 Open Label, Dose Escalation Study of AMG 655 in Combination With AMG 479 in Subjects With Advanced, Refractory Solid Tumors

Study Phase: 1b/2

Indications

Part 1: Advanced, treatment-refractory solid tumors

Part 2: Advanced non-small cell lung cancer (NSCLC), colorectal cancer (CRC), pancreatic cancer, ovarian cancer, or sarcoma

Primary Objectives (Section 1.1)

Part 1: To identify a dose of AMG 655 in combination with AMG 479 that is safe and tolerated as determined by the incidence of dose limiting toxicity (DLT).

Part 2: To estimate the efficacy, as measured by the objective response rate (ORR; confirmed complete response [CR] and partial response [PR] using modified Response Evaluation Criteria in Solid Tumors [RECIST]) of AMG 655 in combination with AMG 479.

Secondary Objectives (Section 1.2)

Part 1

- To evaluate the safety and tolerability of AMG 655 in combination with AMG 479
- To evaluate anti-AMG 655 antibody formation and anti-AMG 479 antibody formation
- To evaluate the pharmacokinetics (PK) of AMG 655 and of AMG 479

Part 2

- To estimate the efficacy of AMG 655 in combination with AMG 479, as measured by time to response, duration of response, and progression-free survival (PFS)
- To evaluate the safety and tolerability of AMG 655 in combination with AMG 479
- To evaluate anti-AMG 655 antibody formation and anti-AMG 479 antibody formation
- To evaluate the PK of AMG 655 and of AMG 479

Exploratory Objectives (Section 1.3)

Parts 1 and 2

- To investigate the relationship between AMG 655 PK and AMG 479 PK and treatment outcomes (including clinical and pharmacodynamic endpoints)
- To investigate the baseline biomarker profile and pharmacodynamic response, as assessed by AMG 655 and AMG 479 biomarkers, and correlation with treatment outcomes
- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1/IGF-1R and/or apoptosis pathways and other genes that are known to be involved in the development and progression of solid tumors (Required for subjects with CRC, ovarian cancer, and sarcoma; optional, if tissue is available, for subjects with NSCLC and pancreatic cancer).
- To investigate the genetic variations in cancer genes, drug target and pathway genes, and other biomarker genes, and correlation with treatment outcomes (optional for subjects; separate informed consent required).

Part 2

- To estimate the efficacy of AMG 655 in combination with AMG 479 using clinical benefit rate (CR, PR, and disease stabilization [SD] ≥ 12 weeks, as measured by modified RECIST)

Study Hypotheses

Part 1: AMG 655 in combination with AMG 479 is safe and tolerated as determined by the incidence of DLT when administered to subjects with advanced, treatment-refractory solid tumors.

Part 2: The combination of AMG 655 with AMG 479 will have an acceptable safety profile and will be associated with at least 3 objective responses out of 15 evaluable subjects in at least 1 cohort (advanced NSCLC [squamous and/or non-squamous histology], CRC, pancreatic cancer, ovarian cancer, and/or sarcoma).

Study Design (Section 3.1)

This is a multi-center, open-label, 2-part phase 1b/2 study of AMG 655 in combination with AMG 479.

Part 1 is a dose escalation segment to identify a dose of AMG 655 in combination with AMG 479 that is safe and tolerable as determined by the incidence of DLT. The maximum dose of AMG 655 planned is 15 mg/kg Q3W. There will be no intra-subject dose escalations in each of the planned dose cohorts.

Part 2 will open once a dose of AMG 655 has been identified that is safe and tolerated based on the incidence of DLT in Part 1 and evaluate the safety and estimate the efficacy (as measured by ORR) of AMG 655 at the dose selected in Part 1 in combination with AMG 479 for the treatment of patients with advanced NSCLC (Cohort 1: non-squamous histology; Cohort 2: squamous histology), CRC (Cohort 3), pancreatic cancer (Cohort 4), ovarian cancer (Cohort 5), and sarcoma (Cohort 6). Enrollment into the 6 cohorts will occur in parallel, independent of one another.

Parts 1 and 2

AMG 655 and AMG 479 treatment will be administered Q3W until disease progression, intolerable adverse event, death, withdrawal of consent, or administrative decision, for up to 24 months from the date of first study treatment (study day 1). Subjects who have completed 24 months of AMG 655 and/or AMG 479 treatment and who continue to benefit from treatment may be eligible for continued treatment with AMG 655 and/or AMG 479 by extension protocol or as provided for by the local country's regulatory mechanism (Section 13). Study treatment will cease if a subject experiences progressive disease (PD), death, intolerable adverse event(s), withdraws consent or due to an administrative decision (by the investigator or Amgen).

Radiological imaging (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. Safety follow-up visits 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, for up to 36 months from the date of the last subject enrolled, to assess survival.

To mitigate potential safety risks, the first 3 subjects in Part 1 will be enrolled at a rate of $\leq$ 1 subject per week. The study team will review Part 1 dose level cohort data to make recommendations on dose escalation, dose selection and dose stopping. During Part 2 of the study, the study team will review safety data after a total of at least 15 subjects (Interim Analysis [IA] 1) and 45 subjects (IA 2) have been enrolled and have completed 1 cycle of treatment, and additionally as warranted during the conduct of this clinical trial.

The Study Schema is provided at the end of the Protocol Synopsis section.

Primary and Secondary Endpoints (Section 10.2)

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

Part 2: ORR (confirmed CR and PR, by modified RECIST)

Secondary Endpoints

Part 1

- The incidence of adverse events and laboratory abnormalities not defined as DLT
- The incidence of anti-AMG 655 antibody formation and anti-AMG 479 antibody formation
- PK (C_{max} and C_{min} for AMG 655 and AMG 479)

Part 2

- Time to response
- Duration of response
- PFS
- The incidence of adverse events and laboratory abnormalities
- The incidence of anti-AMG 655 antibody formation and anti-AMG 479 antibody formation
- PK (C_{max} and C_{min} for AMG 655 and AMG 479)

Sample Size: Approximately 99 to 108 (Part 1: approximately 9 to 18 DLT-evaluable subjects; Part 2: approximately 90 response-evaluable subjects) (See Section 3.3 and Section 10.3)

Summary of Subject Eligibility Criteria: (See Section 4.1 and Section 4.2 for a complete list of eligibility criteria.)

Key Inclusion Criteria

- Locally advanced or metastatic, treatment-refractory solid tumors (Part 1)
- Locally advanced or metastatic NSCLC (up to 2 prior treatment regimens), CRC (up to 2 prior treatment regimens), pancreatic cancer (up to 1 prior treatment regimen), ovarian cancer (up to 2 prior treatment regimens), or sarcoma (up to 2 prior treatment regimens) (Part 2)
- Measurable disease (at least one measurable lesion) (Part 2)
- ≥ 16 years old
- Life expectancy ≥ 3 months
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate organ function (liver, kidneys, bone marrow, coagulation, heart, glycemic function)

Key Exclusion Criteria

- Presence of uncontrolled central nervous system (CNS) metastasis
- Prior treatment with death receptor agonists (eg, rhApo2L/TRAIL [AMG 951], apomab, mapatumumab, lexatumumab, CS-1008)
- Prior treatment with IGF receptor antagonists (eg, CP-751,871, MK0646, AVE1642 or IMC-A12)
- Systemic chemotherapy, hormonal therapy, immunotherapy, experimental or approved anticancer proteins/antibodies therapy ≤ 28 days before enrollment, except:
  - In Part 1, patients may continue approved hormonal therapy as medically indicated
- Any prior or synchronous malignancy (except for non-melanoma skin cancer or in situ cervical cancer) other than the study disease, unless treated with curative intent with no evidence of disease ≥ 3 years before enrollment (Part 2)
- Any clinically significant medical condition other than cancer, including cardiovascular disease or chronic obstructive pulmonary disease, which in the opinion of the investigator could interfere with the safe delivery of study treatment or increase risk of toxicity

Investigational Product Dosage and Administration: See Section 6, Treatment Procedures; Section 11, Investigational Products; Appendix C for AMG 655 and AMG 479 Pharmacy Guides.

Part 1

Cohort 1: AMG 479 18 mg/kg plus AMG 655 1 mg/kg IV on day 1 of each Q3W cycle

Cohort 2: AMG 479 18 mg/kg plus AMG 655 3 mg/kg IV on day 1 of each Q3W cycle

Cohort 3: AMG 479 18 mg/kg plus AMG 655 15 mg/kg IV on day 1 of each Q3W cycle

There will be no intra-subject dose escalations in each of the planned dose cohorts. Alternative AMG 655 doses (eg, 0.3 mg/kg IV) and/or AMG 479 doses may be explored based on safety and PK data.

Part 2: AMG 479 18 mg/kg plus AMG 655 at the dose selected in Part 1 (up to 15 mg/kg) IV on day 1 of each Q3W cycle

AMG 655 and AMG 479 will be administered 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.

Control Group: There is no control group.

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
- Submission of formalin-fixed, paraffin-embedded tumor tissue (paraffin tumor block, or slides) and associated pathology reports (Required for subjects with CRC, ovarian cancer, and sarcoma; optional, if tumor tissue is available, for subjects with NSCLC and pancreatic cancer).
- 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
- 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 655 and anti-AMG 479 antibodies
- Samples for AMG 655 and AMG 479 PK
- 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.

Part 1: A sample size of approximately 3 to 6 DLT-evaluable subjects per cohort was selected to identify a dosing regimen of AMG 655 in combination with AMG 479 that is safe and tolerated based on the incidence of DLT. A listing and summary of the incidence of DLT will be presented for each cohort. All other safety data collected in Part 1 of the study will be summarized using appropriate descriptive statistics. The study team will review Part 1 dose level cohort data after at least 3 subjects have completed the DLT window to make recommendations on dose escalation, dose selection and dose stopping.

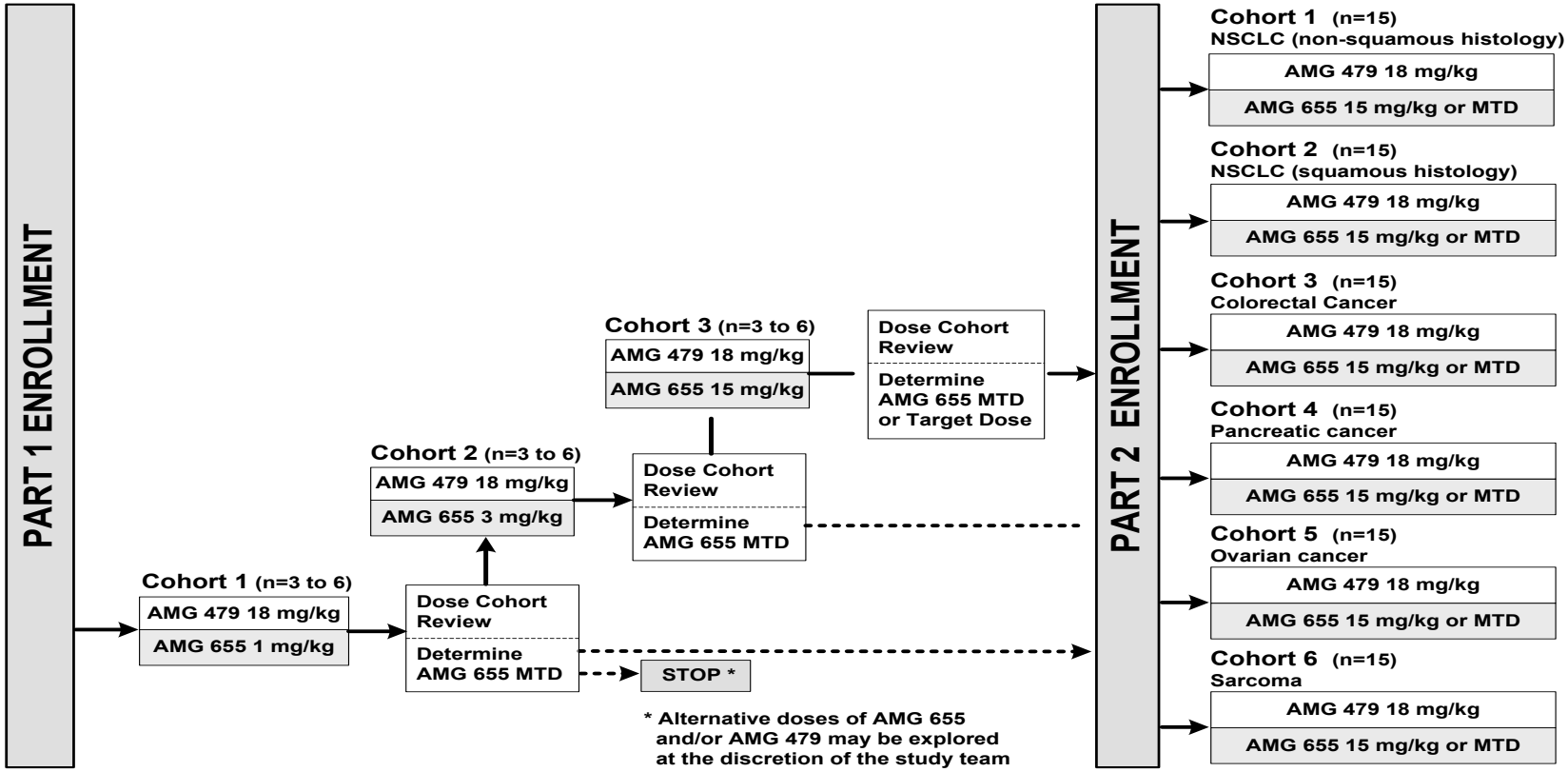
Part 2

Approximately 90 subjects (15 response-evaluable subjects per cohort [tumor type]) will be enrolled in Part 2. This part of the study will identify tumor types, in which further study of AMG 655 in combination with AMG 479 is warranted, using the following criterion: at least 3 out of 15 subjects have an objective response (an ORR of at least 20%). If 2 or less responders are observed in a given cohort, then all other parameters of clinical benefit (including clinical benefit rate and PFS, within others) and of patient safety will be evaluated to determine if further study is warranted of the AMG 655 and AMG 479 combination in that tumor type. The primary endpoint is ORR. The proportion of subjects with an objective response (confirmed CR or PR by modified RECIST) per local investigator assessment with corresponding 95% exact confidence intervals will be presented for each Part 2 cohort. All safety data collected in part 2 of the study will be summarized per cohort and in aggregate over all cohorts using appropriate descriptive statistics. During Part 2 of the study, the study team will review safety data after a total of at least 15 subjects (Interim Safety Analysis [IA] 1) and 45 subjects (IA 2) have been enrolled and have completed 1 cycle of treatment, and additionally as warranted during the conduct of this clinical trial. Unless safety concerns arise, enrollment will not be stopped during the Part 2 safety reviews.

The primary analysis of Part 2 will provide the proportion of subjects with an objective response and is planned to occur after all subjects have had the opportunity to complete 4 cycles of treatment. If the recruitment rate is not consistent across cohorts, a piecewise approach to the primary analysis may be taken with the analysis for the quickest recruiting cohorts occurring first.

The final analysis of this study will occur after all subjects have progressed, died, or terminated the study for other reasons.

Study Design and Treatment Schema



STUDY TREATMENT

Investigational Products (IP): AMG 479 and AMG 655 Administered on Day 1 of Each 21 Day Cycle (Q3W) (for up to 24 Months From Study Day 1). There will be no intra-subject dose escalations in each of the planned dose cohorts of the phase 1b portion (part 1) of the study.