Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Trial of AMG 479 or Placebo in Combination with Gemcitabine as First-line Therapy for Metastatic Adenocarcinoma of the Pancreas

GAMMA
(Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas)

Amgen Protocol Number (AMG 479) 20060540

EudraCT number 2010-020398-18

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

Kay Smith
Global Clinical Research Study Manager
Amgen Ltd
240 Cambridge Science Park
Milton Road
Cambridge, CB4 0WD, UK
Tel: +44 (0) 1223 436339
Fax: +44 (0) 1223 420319
Email: kay@amgen.com

Mandy Parson
Clinical Research Study Manager
Amgen Inc
One Amgen Center Drive, 38-3-C
Thousand Oaks, CA 91320-1799
Phone: 805- 313-4891
Fax: 805-375-9528
Email: mparson@amgen.com

Date: 20 September 2010

Investigator's Agreement

I have read the attached protocol entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Trial of AMG 479 or Placebo in Combination with Gemcitabine as First-line Therapy for Metastatic Adenocarcinoma of the Pancreas" dated 20 September 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 <<*or Coordinating*>> Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of AMG 479 or Placebo in Combination with Gemcitabine as First-line Therapy for Metastatic Adenocarcinoma of the Pancreas

Study Phase: 3

Indication: Metastatic adenocarcinoma of the pancreas

Primary Objective: To determine if the treatment of AMG 479 at 12 mg/kg and/or 20 mg/kg in combination with gemcitabine improves overall survival as compared with placebo in combination with gemcitabine in subjects with metastatic adenocarcinoma of the pancreas

Secondary Objective(s):

- To evaluate progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- To evaluate the survival rate at 12-months, and at the timepoints of 3, 6, 9, 18, and 24 months
- To evaluate objective response rate, time to disease progression, duration of response, and disease control rate (partial response [PR} + complete response [CR] + stable disease [SD]) as per RECIST version 1.1
- To evaluate subject incidence of adverse events, significant laboratory abnormalities, and immunogenicity
- To evaluate AMG 479 dose exposure, dose intensity, and pharmacokinetic (PK) parameters and to evaluate relationships between AMG 479 exposure measures and selected safety and efficacy measures
- To evaluate gemcitabine dose exposure, dose intensity in all subjects, and gemcitabine PK parameters in a subset of subjects
- To evaluate patient reported hepatobiliary symptoms measured by the Functional Assessment of Cancer Therapy – Hepatobiliary subscale questionnaire (FACT-Hep-HS)
- To evaluate the efficacy of AMG 479 versus (vs) placebo in combination with gemcitabine within an enriched sub-population defined by a single or composite biomarker (eg, high insulin growth factor binding protein-3 [IGFBP-3] and/or low IGFBP-2) with respect to OS

Hypotheses:

AMG 479 at 12 mg/kg and/or 20 mg/kg in combination with gemcitabine will improve OS compared with placebo in combination with gemcitabine in subjects with metastatic adenocarcinoma of the pancreas.

H0: The OS hazard ratio of AMG 479 + gemcitabine relative to gemcitabine alone = 1.00

H1: The OS hazard ratio of AMG 479 + gemcitabine relative to gemcitabine alone < 1.00

Study Design:

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled study. Subjects (n=825) will be randomized in a 2:2:1 ratio to first-line therapy in 1 of 3 arms:

- Arm 1: AMG 479-placebo plus gemcitabine
- Arm 2: AMG 479 at 12 mg/kg plus gemcitabine
- Arm 3: AMG 479 at 20 mg/kg plus gemcitabine

Randomization will be stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), the presence of liver metastases (Yes vs No), and by geographical region (Western Europe, United States, Canada, Australia vs rest of world).

AMG 479 at 12 mg/kg, AMG 479 at 20 mg/kg, and placebo will be double-blind; gemcitabine will be open label. Cycles of gemcitabine plus AMG 479 or gemcitabine plus placebo are planned to be administered every 28 days (± 3 days) by intravenous (IV) infusion. Gemcitabine at 1000 mg/m^2 will be administered on days 1, 8, and 15 of each 28 day cycle followed by the AMG 479 at 12 mg/kg, AMG 479 at 20 mg/kg, or placebo on days 1 and 15. Subjects will continue to receive protocol specified therapy until disease progression as per RECIST version 1.1, unacceptable toxicities, withdrawal of consent, or start of a new systemic anti-cancer therapy. Subjects who discontinue gemcitabine for toxicities or intolerance that are presumed related to gemcitabine can continue AMG 479 or placebo. Tumor response assessment will be performed by the investigator as per RECIST guidelines version 1.1. Subjects will be evaluated for tumor response every 8 weeks (± 7 days) independent of the treatment cycle until disease progression, withdrawal of consent, or initiation of new systemic anti-cancer therapy. Subjects with symptoms suggestive of disease progression will be evaluated radiologically for tumor progression at the time the symptoms occur.

All subjects will be assessed for non-intensive AMG 479 PK. Approximately thirteen evaluable subjects per arm will be assessed for intensive AMG 479 PK and gemcitabine PK and its metabolite (see Section 7.3 for additional details).

Subjects who discontinue all protocol specified therapy (ie, AMG 479 or AMG 479-placebo and gemcitabine) will be followed for safety, immunogenicity and PK at the 30 (+3) day follow-up visit, and for post-protocol therapy and survival every 12 weeks (± 14 days) until death, withdrawal of consent or the end of the study. The end of the study will be when a minimum of 90% of randomized subjects who have not withdrawn from the study have died.

Primary and Secondary Endpoints:

Primary Endpoint: Overall survival

Secondary Endpoints: Progression-free survival, survival rate at the timepoints of 3, 6, 9, 12, 18, and 24 months, objective response rate, time to disease progression, duration of response, disease control rate (PR+CR+SD); incidence of subject adverse events, laboratory abnormalities and immunogenicity; AMG 479 dose exposure, dose intensity and PK parameters; gemcitabine dose exposure, dose intensity and PK parameters; the change in hepatobiliary symptoms using the FACT-Hep HS.

Sample Size: 825 subjects

Summary of Subject Eligibility Criteria:

Key Inclusion criteria: Subjects must have histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas (American Joint Committee on Cancer Stage IV); ECOG score of 0 or 1; Men or women ≥ 18 years of age.

Key Exclusion Criteria: Islet cell, acinar cell carcinoma, non-adenocarcinoma, (eg, lymphoma, sarcoma, etc), adenocarcinoma originated from biliary tree or cystadenocarcinoma; currently treated or previously treated with biologic, small molecule, immunotherapy, chemotherapy (eg, gemcitabine), radiotherapy, chemoradiotherapy or other agents for pancreatic cancer.

Amgen Investigational Product Dosage and Administration:

Arm 1: AMG 479-placebo IV days 1 and 15 of a 28 day cycle

Arm 2: AMG 479 at 12 mg/kg IV days 1 and 15 of a 28 day cycle

Arm 3: AMG 479 at 20 mg/kg IV days 1 and 15 of a 28 day cycle

Refer to Section 6.1.1 for detailed dosage and administration guidance

Non Amgen Non-Investigational Product Dosage and Administration

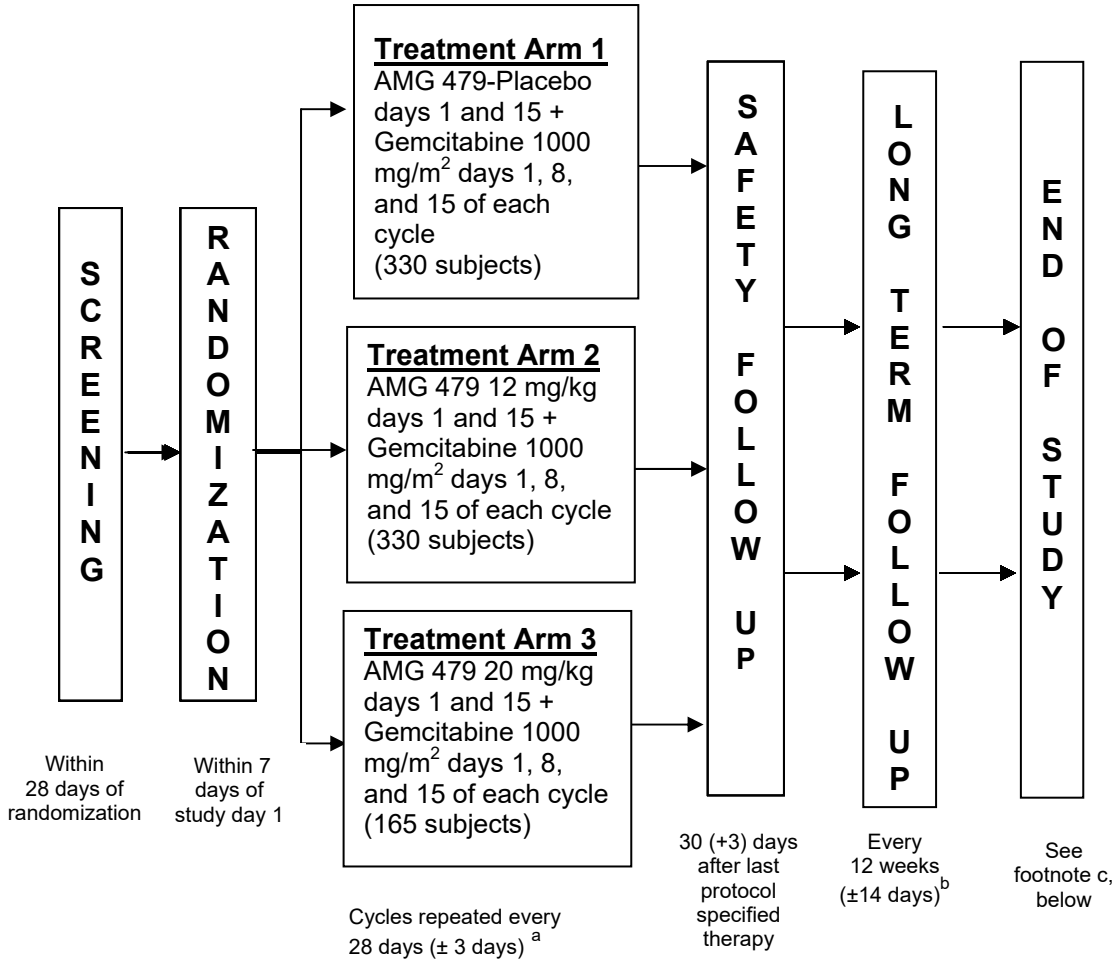
Gemcitabine at 1000 mg/m^2 IV over 30 (±10) minutes on days 1, 8, and 15 of each 28 day cycle in Arms 1, 2 and 3

Procedures: A complete schedule of assessments is provided in Appendix A.

Statistical Considerations: The primary goal of the statistical analysis is to determine if OS in Arm 2 and/or Arm 3 is statistically significantly improved compared to Arm 1. Eight hundred and twenty-five subjects will be randomized in a 2:2:1 ratio (330 in Arm 1 and 2, 165 in Arm 3) to attain a total of approximately 642 OS events. Randomization will be stratified by ECOG performance score (0 vs 1), and the presence of liver metastases (Yes vs No), and by geographical region (Western Europe, United States, Canada, Australia vs rest of world). A log-rank test stratified by the randomization factors will be used to compare OS and Hochberg's procedure will be used to achieve an overall one-sided 2.5% significance level for declaring superiority of Arm 2 vs 1 and/or Arm 3 vs 1. An independent Data Monitoring Committee (DMC) external to Amgen will be established to conduct two planned safety and one interim efficacy reviews. The two safety reviews will occur after 50 subjects (approximately 20, 20 and 10 per arm) and 150 subjects (approximately 60, 60 and 30 per arm) have been enrolled and had the opportunity to complete 1 cycle of protocol specified therapy. Thereafter the DMC safety reviews will occur approximately every 6 months until the primary analysis has been completed. This will occur without a hold in enrollment. The interim analysis of OS for lack of benefit for Arm 2 and/or Arm 3 vs Arm 1 will be performed at approximately 30% (188 events) of the primary analysis total event goal.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



[a] Subjects with evidence of disease progression (per RECIST v1.1) or unacceptable toxicities will discontinue protocol specified therapy and will be followed for survival every 12 weeks (± 14 days)

[b] Subjects in long term follow up who discontinue protocol specified therapy but have not progressed will continue to be evaluated by routine radiographic imaging every 8 weeks (± 7 days) until disease progression (per RECIST v1.1), withdrawal of consent or initiation of new systemic anti-cancer therapy

[c] The end of the study is defined per Section 3.4.2