A Phase 1b/2 Study to Evaluate the Safety and Efficacy of AMG 655 or AMG 479 in Combination With Gemcitabine as First-line Therapy for Metastatic Pancreatic Cancer

AMG 655 and AMG 479

Amgen Protocol Number 20060323

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Amendment 2 **20 NOVEMBER 2008**

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/2 Study to Evaluate the Safety and Efficacy of AMG 655 or AMG 479 in Combination With Gemcitabine as First-line Therapy for Metastatic Pancreatic Cancer", dated **20 November 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 applicable regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56 and 312.

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 to Evaluate the Safety and Efficacy of AMG 655 or AMG 479 in Combination With Gemcitabine as First-line Therapy for Metastatic Pancreatic Cancer

Study Phase: 1b/2

Indication: Metastatic adenocarcinoma of the pancreas

Primary Objective:

Part 1 (Phase 1b): To determine the maximum tolerated dose up to a target dose of 10 mg/kg of AMG 655 that can be administered in combination with gemcitabine

Part 2 (Phase 2): To estimate the efficacy as assessed by 6 month survival of AMG 655, AMG 479, or AMG 655-placebo in combination with gemcitabine

Secondary Objectives:

Part 1

- To evaluate the safety and tolerability of escalating doses of AMG 655 in combination with gemcitabine
- To evaluate parameters of clinical benefit as measured by response rate, progression-free survival (PFS), 6 month survival rate and overall survival
- To evaluate the pharmacokinetics (PK) of AMG 655 and gemcitabine
- To evaluate anti-AMG 655 antibody formation

Part 2

- To estimate the clinical benefit of AMG 655, AMG 479, or AMG 655-placebo in combination with gemcitabine as measured by response rate, PFS, and overall survival
- To evaluate the safety and tolerability of AMG 655, AMG 479, or AMG 655-placebo in combination with gemcitabine
- To evaluate the pharmacokinetics of AMG 655 or AMG 479
- To evaluate anti-AMG 655 or anti-AMG 479 antibody formation
- Dose intensity of gemcitabine when combined with AMG 655, AMG 655-placebo or AMG 479 (part 2 only)

Exploratory Objectives:

Parts 1 and 2

- To investigate pharmacodynamic response of AMG 655, AMG 479, or AMG 655-placebo in combination with gemcitabine as assessed by apoptosis biomarkers (eg, caspase 3/7; CK 18 epitopes M30/M65; and genomic DNA levels; part 1 and selected sites in part 2)
- To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target related genes and correlate with outcomes related to AMG 655, AMG 479 or AMG 655-placebo in combination with gemcitabine (participation in the investigation of heritable elements is optional and requires a separate informed consent)
- To investigate potential biomarker (other biomarkers) development by analysis of blood samples or other sample types (eg, tumor samples)
- To investigate the relationship between AMG 655 or AMG 479 PK, biomarkers, and treatment outcomes (including tumor response and pharmacodynamic endpoints)

Part 2

- To assess the impact of AMG 655 or AMG 479 in combination with gemcitabine on pancreatic cancer-related symptoms and health related quality of life.

Hypotheses:

In part 1, it is expected that a dose of AMG 655 in combination with gemcitabine will be identified that is safe and well tolerated as determined by the incidence of dose limiting toxicities.

In part 2, AMG 655 in combination with gemcitabine and/or AMG 479 in combination with gemcitabine will improve the 6 month overall survival rate compared to AMG 655-placebo with gemcitabine and have an acceptable safety profile when administered to subjects as first-line therapy for metastatic pancreatic cancer.

Study Design:

This study is a multi-center, 2-part study of AMG 655, AMG 479 or AMG 655-placebo plus gemcitabine as first-line treatment of subjects with metastatic pancreatic cancer.

Part 1 is an open-label, dose-escalation phase 1b segment to determine the safety, tolerability and maximum tolerated dose of AMG 655 (up to a target dose of 10 mg/kg) in combination with gemcitabine. Gemcitabine will be administered at a dose of 1000 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. Two doses of AMG 655 will be administered once every 2 weeks (on days 1 and 15 of every 28 day cycle) and tested sequentially in up to 6 subjects per AMG 655 dose level. Three mg/kg will be the starting dose of AMG 655. If this dose is safe (based upon the incidence of dose limiting toxicities), the next dose level that will be examined is 10 mg/kg once every 2 weeks. If the 3 mg/kg dose level is not safe lower doses of AMG 655 may be tested at the discretion of the Data Review Team (DRT). See Section 6 for details. AMG 479 will not be studied in part 1.

Part 2 is a randomized, placebo-controlled, phase 2 segment that will commence after dose selection in part 1. In part 2, subjects (n = 120) will be randomized 1:1:1 (stratified by ECOG performance status 0 or 1) to AMG 655, AMG 479, or AMG 655-placebo in combination with gemcitabine. The AMG 655 and AMG 655-placebo arms will be double-blind. The AMG 479 arm will be open-label. Part 2 will be conducted with similar eligibility criteria and schedule of assessments as in part 1.

In the event a subject experiences an unacceptable toxicity that in the investigator's opinion is possibly related to gemcitabine but not related to AMG 655, AMG 479, or AMG 655-placebo, the subject may continue to receive AMG 655, AMG 479 or AMG 655-placebo as monotherapy until disease progression (radiographic progression per RECIST with modifications or clinical progression), unacceptable toxicity, subject withdrawal of consent, or death.

In the event a subject experiences an unacceptable toxicity that is possibly related to AMG 655, AMG 479 or AMG 655-placebo or to the combination of gemcitabine and AMG 655, AMG 479 or AMG 655-placebo, the subject will be discontinued from study treatment.

Subjects will be discontinued from study treatment at any time for disease progression, subject withdrawal of consent, unacceptable toxicity, or death. Subjects alive at the time of discontinuation of all study specified therapy will be followed for up to 36 months from the date the last subject was randomized to determine overall survival.

In addition, any subject who discontinues treatment for unacceptable toxicity and who has not developed disease progression will continue to be followed for disease progression and overall survival during the long term follow-up.

Radiological imaging to evaluate tumor response will be performed every 8 weeks ± 7 days from study day 1 independent of the treatment cycle until disease progression.

A DRT, composed of Amgen study team members and at least one investigator will review all available safety data for each dose level in part 1. A second independent DRT will be formed for part 2 of the study to review all available safety data from all 3 arms after 6 and 18 subjects are randomized to the AMG 479 arm and have had the opportunity to complete one cycle (28 days) of protocol specified treatment in part 2.

Endpoints:

Primary Endpoints

Part 1: The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities

Part 2: Six month overall survival rate

Secondary Endpoints

Part 1 and Part 2:

- Objective response rate

- Duration of response
- Progression-free survival
- Overall survival (and 6 month overall survival rate for part 1)
- The incidence of adverse events and laboratory abnormalities
- The incidence of antibody formation of anti-AMG 655 (part 1 and 2) or anti-AMG 479 (part 2 only)
- AMG 655 (part1 and 2), AMG 479 (part 2 only), and gemcitabine (part 1 only) PK parameters
- Dose intensity of gemcitabine when combined with AMG 655, AMG 655-placebo or AMG 479 (part 2 only)

Exploratory Endpoints

Part 1 and Part 2:

- Pharmacodynamic response: caspase 3/7, CK 18 epitopes M30/M65 and genomic DNA levels (part 1 and selected sites in part 2)
- Levels of circulating IGF-1, IGFBP3 and growth hormone (AMG 479 arm only)
- Biochemical levels of drug, pathway, and cancer related targets in tumor tissue and blood samples and correlation with treatment outcomes
- Analysis of somatic genetic variations in drug, pathway, and cancer related genes and correlation with treatment outcomes
- Analysis of heritable genetic variations in drug metabolism, target genes or genes that regulate pathways related to the drug target (optional separate informed consent required for analysis of heritable elements)
- Pancreatic cancer related symptoms and health related quality of life measured by changes in FACT-Hep from baseline (part 2 only)

Sample Size:

Part 1, n = approximately 12 (6 subjects per AMG 655 dose level)

Part 2, n = approximately 120 subjects (randomized 1:1:1; AMG 655:AMG 479:AMG 655-placebo; all subjects will receive gemcitabine)

Summary of Subject Eligibility Criteria: (see Section 4 for complete eligibility criteria):

Inclusion Criteria

Disease Related

- Subjects must have histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas (AJCC Stage IV)
- Eastern Cooperative Oncology Group (ECOG) score of 0 or 1

Demographic

- Men or women ≥ 18 years of age

Laboratory

Adequate organ function as evidence by the following laboratory studies within 21 days before enrollment/randomization:

- Hematological function as follows:
  - Hemoglobin ≥ 9 g/dL
  - Absolute neutrophil count ≥ 1.5 x 10^9/L
  - Platelet count ≥ 100 x 10^9/L (without a transfusion within 14 days before enrollment/randomization)

- Partial thromboplastin (PTT) ≤ 1.3 x upper limit of normal (ULN) and INR ≤ 1.5, unless subject is on anti-coagulation therapy. Subjects on therapeutic anti-coagulation are eligible if there is no bleeding and they are on a stable dose of anticoagulation therapy (eg, coumadin with an INR of 2 to 3) for at least 7 days before randomization/enrollment
- Renal function, as follows:
  - Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 40 mL/minute
- Amylase ≤ 2.0 x ULN
- Lipase ≤ 2.0 x ULN
- Total bilirubin ≤ 2.0 x ULN
- **Fasting blood glucose level ≤ 160 mg/dL (part 2 only)**
- Hepatic Function, as follows:
  - Aspartate aminotransferase (AST) **and** alanine amino transferase (ALT) ≤ 2.5 x ULN OR AST **and** ALT ≤ 5.0 x ULN if clearly attributable to liver metastasis

General

- Able to tolerate infusions
- Plan to begin protocol specific therapy within 7 days after enrollment/randomization

Exclusion Criteria

Disease Related

- Islet cell, acinar cell carcinoma, non-adenocarcinoma, (eg, lymphoma, sarcoma, etc), adenocarcinoma originated from biliary tree or cystadenocarcinoma
- Known history of central nervous system metastases
- External biliary drain

Other Abnormal Medical Conditions

- Documented myocardial infarction or unstable/uncontrolled cardiac disease (eg, unstable angina, congestive heart failure [New York Heart Association > Class II]) within 6 months of enrollment/randomization
- History of any medical condition that in the opinion of the investigator, may increase the risks associated with study participation or study treatments or may interfere with the conduct of the study or interpretation of study results
- Major surgical procedure within 30 days before enrollment/randomization or not yet recovered from prior major surgery
- Minor surgical procedures within 7 days of enrollment/randomization or not yet recovered from prior minor surgery; although placement of central venous access device, fine needle aspiration, thoracentesis, endoscopic biliary stent or paracentesis ≥ 1 day before enrollment/randomization is acceptable
- Known positive test for human immunodeficiency virus, hepatitis C virus or acute or chronic hepatitis B infection

Medications

- Currently treated or previously treated with biologic, small molecule, immunotherapy, chemotherapy (eg, gemcitabine), radiotherapy or other agents for advanced pancreatic cancer
- Adjuvant chemotherapy or chemoradiotherapy
- Recent infection requiring a course of systemic anti-infectives that was completed within 7 days before enrollment/randomization (with the exception of uncomplicated urinary tract infection)

General

- Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or subject is receiving other investigational agent(s)
- Subject of child-bearing potential is evidently pregnant or is breast feeding
- Subject is not willing to use adequate contraceptive precautions
- Subject has known sensitivity to any of the products to be administered during the study
- Subject was previously enrolled or randomized in this study
- Subject will not be available for follow-up assessment
- Subject unwilling or unable to comply with study requirements
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures, unless informed consent is given by the subject's legally acceptable representative

Investigational Product Dosage and Administration:

AMG 655 and AMG 479 will be provided as a sterile, clear colorless liquid. Each glass vial will contain 3 mL of investigational product at a concentration of 30 mg/mL (90 mg/vial). AMG 655-placebo will be provided in identical vials to AMG 655 containing only vehicle and will only be administered in part 2 of the study.

In part 1, subjects are planned to be treated with one of 2 dose levels of AMG 655 (3 mg/kg and 10 mg/kg) with gemcitabine. In part 2, subjects are planned to be treated with the dose of AMG 655 selected in part 1, AMG 479 (12 mg/kg), or AMG 655-placebo in combination with gemcitabine. Gemcitabine (1000 mg/m^2) will be administered by intravenous infusion on days 1, 8 and 15 of each 28 day cycle followed by the AMG 655, AMG 479, or AMG 655-placebo infusion on days 1 and 15 after completion of the gemcitabine infusion. The actual dose of AMG 655, AMG 479 or AMG 655-placebo will be calculated based upon the subject's baseline weight, with recalculations required should weight change by 10%.

Control Group: gemcitabine plus AMG 655-placebo

Procedures:

Key Screening Procedures (key procedures, see Section 7.1 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, temperature and resting blood pressure
- Physical examination including height and weight
- ECOG performance status assessment
- Laboratory tests
- Collection of archival paraffin embedded tumor tissue, if available.
- 12-lead electrocardiogram
- Radiological imaging for disease assessments should be according to RECIST with modifications as in Appendix G (within 21 days before enrollment/randomization) and must include CT scan or magnetic resonance imaging of the chest, abdomen and pelvis and the modality selected must remain the same throughout the study.

Key Treatment Procedures (key procedures, see Section 7.2 for a complete list):

- Recording of adverse events and concomitant medications
- Physical examination including resting blood pressure, vital signs and weight
- ECOG performance status assessment
- Laboratory tests

- Baseline samples for apoptosis biomarkers and intensive PK samples pre- and post-dosing (part 1 and selected sites in part 2)
- Samples for immunogenicity and other biomarkers pre-and post-treatment
- Serum samples for PKs of AMG 655, AMG 479 (part 2) and gemcitabine (part 1)
- Radiological imaging to assess disease extent
- Completion of PRO questionnaires (part 2 only)

Statistical Considerations:

The primary objective of part 1 of this study is to determine the maximum tolerated dose of AMG 655 up to a target dose of 10 mg/kg that can be administered with gemcitabine. Approximately 12 subjects will be enrolled (6 subjects per AMG 655 dose level). Before starting part 1, a DRT will be formed and governed by a detailed charter. The DRT will be responsible for reviewing listings of the safety data, laboratory data, dosing information and PK data (when available) from each AMG 655 dose level and making recommendations regarding dose escalation and selection of the AMG 655 dose to be studied further in part 2. Part 2 will study an additional 120 subjects using the AMG 655 dose selected in part 1, AMG 479, or AMG 655-placebo in combination with gemcitabine. The primary objective of part 2 is to estimate the efficacy as assessed by the 6 month survival rate. Prior to starting part 2 a second DRT comprised of clinical safety and statistical members external to the study team but internal to Amgen will be formed. Two interim analyses of the safety data in all 3 arms will be conducted in part 2 by this DRT after 6 and 18 subjects are randomized to the AMG 479 arm and have had the opportunity to complete the first 28 days of the study treatment. The primary analysis of part 2 will occur when all subjects have completed 6 months of treatment or died.

The analysis will be presented separately for parts 1 and 2 of the study. For each part descriptive statistics will be provided by treatment arm for selected demographic, safety, PK, efficacy, antibody, and biomarker data. For part 1, the time-to-event endpoints will be listed only. For part 2, overall survival, progression-free survival and duration of response will be summarized using the Kaplan-Meier method to estimate the median time to event, 95% confidence interval (CI) for the median, 25th and 75th percentiles. Time-to-response will be summarized using descriptive statistics. In addition, the 6 month survival rates (with 80% and 95% CIs) will be estimated from the Kaplan-Meier analysis of overall survival. The proportion and corresponding exact 80% and 95% CIs of subjects with an objective response determined using RECIST with modifications will also be presented.

For part 2, the difference (AMG 655 minus AMG 655-placebo and AMG 479 minus AMG 655-placebo) in the proportion of subjects alive at 6 months and corresponding 80 and 95% CIs will be presented. For the primary analysis, the proportions will be estimated using the Kaplan-Meier method with the variance of the proportions estimated using Greenwood's formula. The overall survival, time-to-progression and duration of response endpoints will additionally be analyzed using stratified Cox's proportional hazards models to estimate the hazard ratio. The difference in objective response rate between treatment arms with corresponding exact 80% and 95% CIs will also be estimated firstly using the Newcombe-Wilson exact method and secondly using logistic regression. Where appropriate, based on sample size, the stratification variable ECOG and covariates age and sex will be used to examine selected efficacy and safety endpoints in subgroups or in multivariate analyses.

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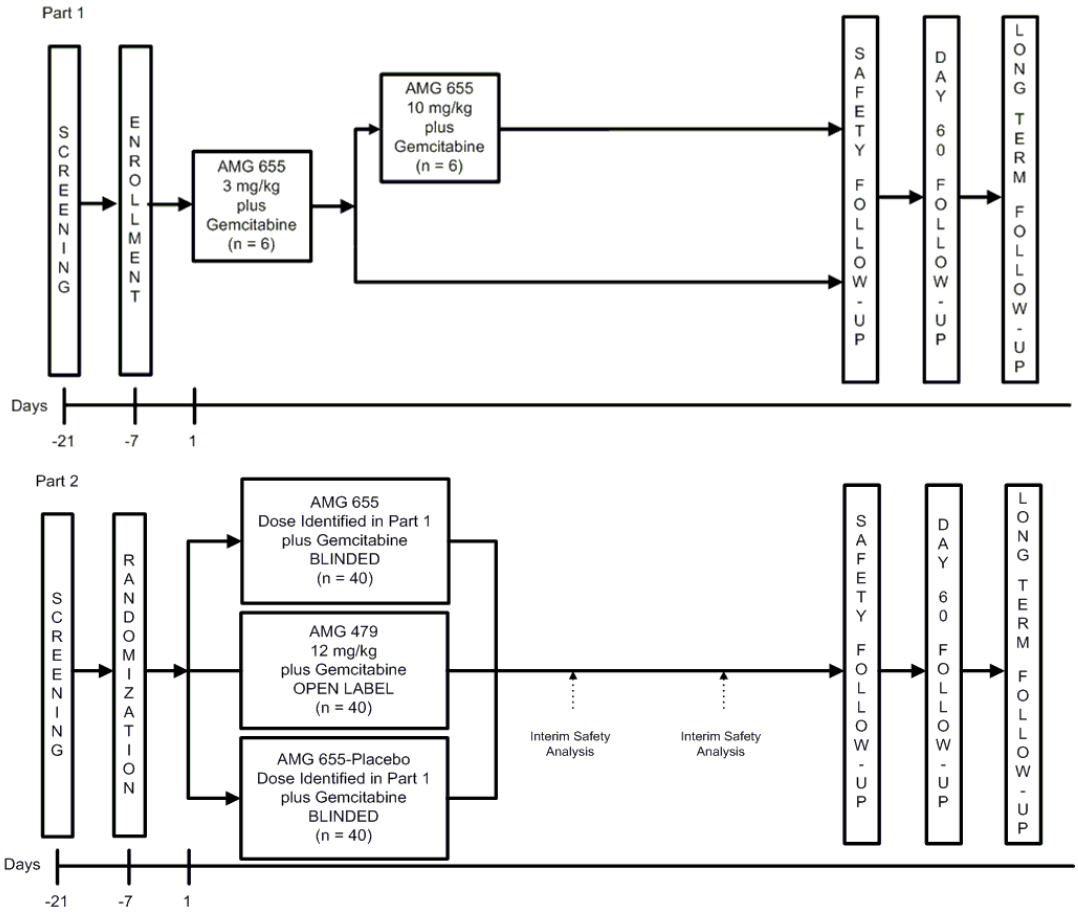
Study Design and Treatment Schema



Part 1 is an open label phase 1b segment to determine the safety and PK profiles of AMG 655 administered on days 1 and 15 of each cycle in combination with gemcitabine. Part 2 is a randomized, placebo-controlled segment that will commence upon identification of the maximum tolerated dose of AMG 655. In part 2, the AMG 655 and AMG 655-placebo arms will be double-blind. The AMG 479 arm will be open-label.

In part 1 and part 2 gemcitabine will be administered on days 1, 8 and 15 of each 28 day cycle. In part 1 AMG 655 will be administered after the completion of gemcitabine infusion on days 1 and 15 of each cycle. In part 2 AMG 655, AMG 479 or AMG 655-placebo will be administered after completion of the gemcitabine infusion on days 1 and 15 of each cycle.

Subjects may continue to receive treatment until documented disease progression, intolerable adverse event, subject withdrawal of consent or death.

The safety follow-up visit will occur 30 days (+ 3 days) after the last dose of protocol specified therapy. The day 60 follow-up visit will occur 60 days (+ 14 days) after the last dose of protocol specified therapy. Subjects will be contacted every 3 months (± 2 weeks) in the long-term follow-up, until 36 months after the last subject has been randomized, to assess survival.

15. APPENDICES

Appendix A. Schedule of Assessments

Screening to Week 20

	Screen	Treatment Period																			
Cycle		1				2				3				4				5			
Cycle days	-21	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Study weeks	-3	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
GENERAL AND SAFETY																					
Informed Consent	X																				
Medical History	X																				
Weight and vital signs[a]	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	
ECOG, physical exam[b]	X	X				X				X				X				X			
ECG[c]	X	X		X				X													
Tumor sample[d]	X																				
Concomitant Medication	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	
Adverse Events	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	
Survival status and PD																					
LABORATORY ASSESSMENTS AND DOSING																					
Pregnancy Test	X																				
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[f]	X	X		X		X		X		X		X		X		X		X		X	
Urinalysis, coagulation and PRO[g]	X	X				X				X				X				X			
CA 19-9, HgbA1c, LDH[h]	X	X								X								X			
IP PK[i]		X	X	X		X		X		X								X			
Gemcitabine PK[ij]		X	X																		
Anti-IP antibody[k]		X				X				X								X			
IP biomarkers[l]		X				X				X								X			
Apoptosis biomarkers[m]		X	X	X																	
Gemcitabine infusion[n]		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	
IP Infusion[o]		X		X		X		X		X		X		X		X		X		X	
RADIOLOGICAL ASSESSMENTS																					
CT, MRI Staging[p]	X									X								X			

Schedule of Assessments (cont'd) Week 21 through Long-Term Follow-up

	Treatment Period																		
Cycle	**6**				**7**				**8**				**9**						
Cycle days	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**SFU**	**DAY 60**	**LTFU**
Study week	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**			
GENERAL AND SAFETY																			
Informed Consent																			
Medical History, height																			
Weight and vital signs[a]	X	X	X		X	X	X		X	X	X		X	X	X		X		
ECOG, physical exam[b]	X				X				X				X				X		
ECG[c]																	X		
Tumor sample[d]																			
Concomitant Medication	X	X	X		X	X	X		X	X	X		X	X	X		X		
Adverse Events	X	X	X		X	X	X		X	X	X		X	X	X		X		
Survival status & DP																			X[q]
LABORATORY ASSESSMENTS AND DOSING																			
Pregnancy Test																	X		
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry[f]	X		X		X		X		X		X		X		X		X		
Urinalysis, coagulation and PRO[g]	X				X				X				X				X		
CA 19-9, HgbA1c, LDH[h]					X								X				X		
IP PK[i]					X								X				X	X	
Gemcitabine PK[ij]																			
Anti-IP antibody[jk]					X								X				X	X	
IP biomarkers[l]					X								X				X	X	
Apoptosis biomarkers[m]																			
Gemcitabine infusion[n]	X	X	X		X	X	X		X	X	X		X	X	X				
IP Infusion[o]	X		X		X		X		X		X		X		X				
RADIOLOGICAL ASSESSMENTS																			
CT, MRI Staging[p]					X								X					X	

ECG = electrocardiogram; DAY 60 = The study visit at 60 days (+ 14 days) after last dose of protocol specified therapy; MRI = magnetic resonance imaging;
CT = computed tomography; SFU = safety follow-up (The study visit at 30 days (+ 3 days) after last dose of protocol specified therapy; IP = investigational product;
PK = pharmacokinetics; Ab = antibody, PE = physical examination; DP = disease progression; PRO = patient reported outcomes

Subjects without documented disease progression, an intolerable adverse event, or withdrawal of consent will be allowed to continue receiving treatment (repeat assessment from cycles 6 through 9)

a Weight and pre-infusion vital signs includes resting blood pressure, resting respiration rate, resting pulse and temperature

b Includes brief physical examination and performance status

c A screening ECG will be performed within 7 days before enrollment/randomization (part 1 and 2). ECGs will be collected within 60 (+/- 10) minutes after the stop of the investigational product infusion in cycle 1 (days 1 and 15) and cycle 2 (day 15) (part 1). ECG will be performed at safety follow-up (part 1 and 2).

d Archived paraffin tissue on slides from the diagnostic biopsy will be submitted to a central laboratory during screening or within 6 weeks of enrollment/randomization

e The day 22 visit of each cycle is for a laboratory assessment (ie, hematology) only

f Fasting glucose at screening and on day 1 of cycles 2, 3 and 4, and every other cycle thereafter (AMG 479 arm only).

g The PRO questionnaires (part 2 only) should be completed before either gemcitabine, or investigational product infusion and before the subject obtains knowledge of their current disease status. PRO will not be collected at screening. **Coagulation: PTT and INR [for subjects on anticoagulation therapy (eg, coumadin) coagulation tests will be done weekly for the first cycle] and then as clinically indicated.** Coagulation will not be collected at the safety follow-up visit (SFU).

h LDH at screening and pre-dose on day 1 of every 2 cycles, and at safety follow up; CA 19-9 pre-dose on day 1 of every 2 cycles; HgbA1c at screening for all part 2 subjects, and pre-dose on day 1 of every 2 cycles for AMG 479 arm only.

i Investigational product PK (IP PK) samples (See Section 7.2 for all time points and Appendix B for detailed time points in cycle 1).

j Gemcitabine PK samples (in part 1 only) (See Section 7.2 for all time points and Appendix B for detailed time points in cycle 1).

k Anti-AMG 655 antibody or anti-AMG 479 antibody will be collected before investigational product infusion on day 1 of cycle 1, 2, 3 and every 2 cycles thereafter, at the safety follow-up and day 60 follow-up visit. Any subject positive for neutralizing antibodies at the last scheduled visit may be followed up every **12 (± 2)** weeks **beginning from the date the site is notified that a subject tested positive until neutralizing antibody level returns to baseline (or becomes negative) or up to 12 months from the date of the Day 60 Follow-up Visit, whichever occurs first.**

l For the analysis of IGF-1, IGFBP3, growth hormone for AMG 479 arm, and other potential biomarkers for the AMG 655 and AMG 655-placebo arms.

m Samples for apoptosis biomarkers (in part 1 and selected sites in part 2) will be collected before gemcitabine infusion and following the end of infustion of investigational product as follows: 3 hours ± 30 minutes and 24 hours ± 2 hours, on day 1 of cycle 1. Samples will also be collected before gemcitabine infusion on day 8, and 15 of cycle 1.

n Gemcitabine will be infused on days 1, 8 and 15 of each 28 day cycle

o Investigational product (part 2 only) will be administered IV on days 1 and 15 of each cycle after completion of the gemcitabine infusion until disease progression, unacceptable toxicity, subject withdrawal of consent, or death. In part 1, the AMG 655 infusion on study day 1 will not begin until the 2 hour gemcitabine PK sample is collected.

p Radiological assessments for tumor staging will be performed within 21 days before enrollment/randomization and every 8 weeks + 7 days from study day 1 independent of the timing of the treatment cycle. Responses must be confirmed no less than 28 days later. Anytime clinical progression is suspected an additional staging scan must be performed. Radiological assessment will be performed if not done in the previous 8 weeks.

q During the long term follow-up (LTFU) subjects will be followed for survival after the safety follow up visit, for once every 3 (± 2 weeks) months through 36 months from the date that the last subject is randomized. Subjects who discontinue treatment due to unacceptable toxicity will continue to be followed every 8 weeks for disease progression or until commencement of additional anti-cancer therapy.