Title: A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Panitumumab / AMG 102 / AMG 479

Amgen Protocol Number 20060447

Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 United States Tel: +1 805-447-1000 Fax: +1 805-480-0614
Key Sponsor Contact (US):	Shanna Stout Clinical Research Study Manager Tel: +1 805-447-8580 Fax: +1 805-480-1291
Key Sponsor Contact (US and Europe)	Dominic Smethurst Medical Director 1 Sanderson Road Uxbridge Business Park London UB81DH Tel: +44 1895 525364 Fax: +44 1895 525112
Date:	22 April 2008
EudraCT Number:	2008-001751-21

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer, dated 22 April 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 FDA regulations/guidelines set forth 21 CFR Parts 11, 50, 54, 56, and 312 and other applicable regulations/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 Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Study Phase: 1b/2

Indication: wild-type KRAS metastatic colorectal cancer

This protocol consists of 3 parts. Part 1 is the dose finding phase 1b portion of the study. Part 2 is the phase 2, randomized, three-cohort portion of the study. Part 3 is an extension of the phase 2 (part 2) in which select subjects from part 2 may continue treatment in one of two cohorts. Throughout this protocol synopsis, the various portions of the study will be referred to as part 1, 2, or 3.

Primary Objective:

Part 1: To identify a tolerable dose of AMG 102 in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs)

Part 2: To evaluate the efficacy as assessed by the overall objective response rate (ORR) of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone

Secondary Objective(s):

Part 1:

- To evaluate the safety of AMG 102 in combination with panitumumab
- Pharmacokinetics (PK) exposure of AMG 102 and panitumumab when given in combination

Part 2:

- To evaluate the safety and efficacy of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone
- PK exposure of AMG 102 and panitumumab when given in combination
- PK exposure of AMG 479 and panitumumab when given in combination
- PK exposure of panitumumab when given alone

Exploratory Objective(s):

The exploratory objectives will include, but will not be limited to the following:

- Part 1: To evaluate the efficacy of AMG 102 in combination with panitumumab
- Part 3: To evaluate the safety and efficacy of AMG 102 and AMG 479 monotherapy following treatment with panitumumab (cohort 3) in part 2
- Pharmacodynamic response of AMG 102 as assessed by hepatocyte growth factor/c-Met (HGF/c-Met), pathway markers, tumor apoptosis markers, angiogenic cytokines, and other biomarkers (Part 1, 2, and 3)
- Pharmacodynamic response of AMG 479 as assessed by insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and growth hormone (Part 2 and 3)
- Correlation between plasma HGF levels or tumor ribonucleic acid (RNA) expression, and tumor response (Parts 1, 2, and 3)

- Effects of tumor genetic variation in pathway genes, cancer genes, drug target genes, and other biomarker genes on subject response to investigational product (Parts 1, 2, and 3)
- Effect of genetic variation in cancer genes, drug target genes, drug metabolism genes, and other biomarker genes on subject response to investigational product on a subset of subjects. Separate pharmacogenetic informed consent required. (Parts 1, 2, and 3)

Hypotheses:

Part 1: Treatment with AMG 102 in combination with panitumumab will be safe and well tolerated.

Part 2: Treatment with AMG 102 or AMG 479 in combination with panitumumab will exhibit a greater ORR with acceptable safety than treatment with panitumumab alone.

Part 3: Hypothesis forming exploratory work will be undertaken to evaluate safety and efficacy among those subjects in part 2 that go on to receive AMG 102 or AMG 479 monotherapy in part 3.

Study Design: This is a global, multicenter, open-label phase 1b and randomized, double-blinded two-part phase 2 study designed to evaluate the safety and efficacy of AMG 102 or AMG 479 in combination with panitumumab versus panitumumab alone in mCRC subjects with wild-type KRAS tumor status.

Panitumumab will be open-label throughout the study (parts 1 and 2).

Investigational product will be administered every 2 weeks.

Part 1:

In part 1, approximately 6 to 18 subjects (6 to 9 subjects at each dose level of AMG 102 evaluated in combination with panitumumab) will be enrolled to receive open-label AMG 102 in combination with panitumumab with the purpose of identifying a tolerable dose of AMG 102 for the part 2 portion of the study.

AMG 102 10 mg/kg will be the starting dose evaluated in combination with panitumumab 6 mg/kg. Dose de-escalation of AMG 102 to 5 mg/kg will take place if determined necessary by the study team based on the interim safety analysis and incidence of DLTs. The dose of AMG 102 that is determined tolerable in combination with panitumumab in part 1 will be the selected dose used in part 2.

Subjects enrolled in part 1 will not be eligible for randomization in part 2.

Part 2:

Panitumumab will be open-label. AMG 102, AMG 479, and placebo will be blinded and will be referred to as blinded investigational product. In part 2, approximately 126 subjects will be randomized in a ratio of 1:1:1 to one of the following three double-blinded treatment groups. The randomization will be stratified for prior chemotherapy regimen: irinotecan or oxaliplatin vs both.

Cohort 1: panitumumab 6 mg/kg and AMG 102 (tolerable dose selected from part 1)

Cohort 2: panitumumab 6 mg/kg and AMG 479 12 mg/kg

Cohort 3: panitumumab 6 mg/kg

If a tolerable dose of AMG 102 is not identified in part 1, then part 2 will continue with cohorts 2 and 3 only. If this occurs, subjects will be randomized in part 2 in a ratio of 1:1 to one of the following two double-blinded treatment groups.

Cohort 2: panitumumab 6 mg/kg and AMG 479 12 mg/kg

Cohort 3: panitumumab 6 mg/kg

Subjects randomized to cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see below).

Part 3:

Upon radiographic disease progression per modified RECIST, clinical progression, or intolerability to all investigational products, subjects that meet the criteria outlined in protocol Section 4.3 may be unblinded via the IVRS by the investigator or designated study staff to determine treatment assignment. Subjects randomized to cohort 3 (ie, panitumumab) of part 2 may be further randomized in part 3 in a ratio of 1:1 to one of the following two double-blinded treatment groups. The randomization will be stratified for reason for panitumumab discontinuation in part 2: disease progression (radiographic or clinical) versus intolerability.

Cohort 3a: AMG 102 10 mg/kg

Cohort 3b: AMG 479 12 mg/kg

The dose of AMG 102 (ie, 10 mg/kg) in part 3 will not be affected by the outcome of the interim safety analysis in part 1.

Investigational product will be administered every 2 weeks (Q2W) until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team (see investigational product administration details below).

All subjects that permanently discontinue all investigational products will complete a safety follow-up visit 30 days (+3 day window) and a follow-up visit 60 days (+14 day window) after the last dose of investigational product.

Subjects will be followed for radiographic disease progression (if not documented previously) and survival in the long-term follow-up portion of the study every 3 months (± 28 day window) after the 30 day safety follow up visit for up to 2 years after the last subject is enrolled in part 2 or 3, whichever occurs last.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1: Subject incidence of DLTs

Part 2: Overall ORR

Secondary Endpoints:

Parts 2:

- Duration of response
- Time to response
- Disease control
- Progression-free survival
- Overall survival
- Incidence of all AEs and clinical laboratory abnormalities
- Incidence of antibody formation to panitumumab, AMG 102, and AMG 479
- C_{min}, C_{max}, and AUC for panitumumab and AMG 102 (Part 1)
- C_{min} and C_{max} for panitumumab, AMG 102, and AMG 479 (Part 2)

Sample Size:

Part 1: Approximately 6 to 18 subjects (n = 6 to 9 per dose level of AMG 102 evaluated in combination with panitumumab).

Part 2: Approximately 126 subjects (n = 42 per cohort)

Part 3: Subjects from cohort 3 of part 2 will cross over to part 3 (n = 42)

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria (Parts 1 and 2)

- Man or woman ≥ 18 years of age
- A life expectancy estimate of ≥ 3 months
- ECOG 0 or 1
- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- Subjects with wild-type KRAS tumor status confirmed by central laboratory assessment
- Radiographic evidence of disease progression during or following prior treatment with irinotecan and/or oxaliplatin based chemotherapy for mCRC
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm in one dimension per modified RECIST (CT or MRI)
- Adequate hematology, renal, and hepatic function (see Section 4.1.3)
- Magnesium ≥ lower limit of normal
- Subjects with known diabetes (Type 1 or 2) must have adequate glycemic function, as follows:
  - Must be controlled with a glycosylated hemoglobin (HgbA1c) of < 8.0%
  - Documented fasting blood sugars < 160 mg/dL

Key Exclusion Criteria (Parts 1 and 2)

- Participation in a phase 3 randomized study of panitumumab in combination with chemotherapy, regardless of treatment assignment
- Prior treatment with anti-EGFr inhibitors (eg, panitumumab, cetuximab, erlotinib, gefitinib), unless treatment was received in the adjuvant setting ≥ 6 months before enrollment
- Prior treatment with c-Met, IGF-IR, or IGF-IIR inhibitors
- Prior treatment with either AMG 102 or AMG 479
- Use of experimental or approved systemic chemotherapy or radiotherapy ≤ 21 days before enrollment
- Use of experimental or approved targeted therapies ≤ 30 days before enrollment
- History of prior or concurrent central nervous system (CNS) metastases
- History of other primary cancer, unless:
  - Curatively resected non-melanomatous skin cancer
  - Curatively treated cervical carcinoma in situ
  - Other primary solid tumor treated with curative intent and no known active disease present for ≥ 5 years before enrollment

- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrollment
- Active inflammatory bowel disease or other active bowel disease causing chronic diarrhea (defined as ≥ grade 2 per CTCAE version 3.0)
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)
- Serious or non-healing wound ≤ 35 days before enrollment
- Major surgical procedure ≤ 35 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Central venous catheter placement, fine needle aspiration, thoracentesis, or paracentesis is not considered a major or minor surgical procedure.

See protocol Section 4.3 for inclusion criteria for part 3.

Investigational Product Dosage and Administration:

Investigational product will be diluted in 0.9% sodium chloride. Investigational product will be administered by IV infusion beginning on week 1 and continuing Q2W until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team or DRT (see Sections 6.7 and 6.8). Note: Subjects in cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see Sections 4.3 and 7.2).

In part 1 and 2, panitumumab will be administered IV by infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding 0.2- or 0.22-micron pore size in-line filter (obtained by each center) infusion set up over 60 minutes ± 15 minutes. The infusion time should be extended to 90 minutes ± 15 minutes for doses higher than 1000 mg.

Following completion of the panitumumab infusion and proper flushing of the infusion line, AMG 102 (part 1) or blinded investigational product (part 2) will be administered IV over 60 minutes ± 15 minutes. Filtration of diluted AMG 102 and AMG 479 is not required.

If a dose of panitumumab and AMG 102 (part 1) or blinded investigational product (part 2) is well tolerated (ie, without any serious infusion-related reactions), then subsequent IV infusions may be administered over 30 minutes ± 10 minutes.

These infusion times also apply to blinded investigational product (ie, AMG 102 or AMG 479) in part 3.

AMG 102 (part 1) and blinded investigational product (part 2) must be stored frozen protected from light at a freezer set point of -30°C or -70°C. Panitumumab must be stored between 2-8°C and protected from direct sunlight.

Control Group: In part 2, panitumumab will serve as control group. There will be no control group in part 1 or 3.

Procedures:

Screening will occur within 35 days before enrollment/randomization.

During screening, archived paraffin-embedded tumor tissue block or unstained tumor slides will be submitted to the central laboratory along with the corresponding pathology report for evaluation of KRAS tumor status (wild-type or mutant). Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study (see Section 7.5.1.1). It is extremely important that adequate samples are sent to the central laboratory early in the 35 day screening period to allow the central laboratory time to process and analyze the samples, and report the results to the study center.

Screening and on-study assessments will be performed such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis.

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA, glycosylated hemoglobin (HgbA1c), thyroid stimulating hormone (TSH), and urine or serum pregnancy (for women of child-bearing potential).

During the study, blood samples will be collected for antibody formation, biomarker, and PK analyses and submitted to the central laboratory. Subjects enrolled in part 1 will undergo more frequent blood sample collection for PK during weeks 5 – 6. This will require 4 extra visits.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed at week 8 (+ 1 week window) and within ± 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another anti-cancer treatment.

Statistical Considerations: Tolerability of AMG 102 in combination of panitumumab will be assessed in part 1 based on the subject incidence of DLTs. A subject will be considered DLT evaluable if the subject has received at least 2 doses of panitumumab and AMG 102 as scheduled (ie, Week 1 and 3) and has a minimum 4 week (28 days) follow-up for safety or has received at lease 1 dose of panitumumab and AMG 102 and has a DLT within the first 4 weeks (28 days) on study.

Overall safety will be evaluated throughout the study including all enrolled subjects who receive at least 1 dose of investigational product (Safety Analysis Set). Efficacy will be evaluated on subjects with wild-type KRAS in the Safety Analysis Set. The primary analysis for the ORR will included all enrolled subjects in part 2 in the Safety Analysis set with measurable disease at baseline.

The primary analysis of efficacy in part 2 will include data 24 weeks after the last subject is enrolled in part 2. ORR will be analyzed based on Bayesian methodology. Historical ORRs from 4 previous panitumumab trials combined with the response outcome from cohort 3 of the study will provide a posterior distribution for the overall panitumumab monotherapy ORR. A combination regimen may be considered promising and possibly warrant further evaluation in a larger subsequent study if the posterior probability that the odds ratio (ie, combination versus panitumumab alone) is greater than 1 is ≥ 0.90. Likewise, a combination may not be considered promising if the posterior probability that the odds ratio is greater than 1 is ≤ 0.50.

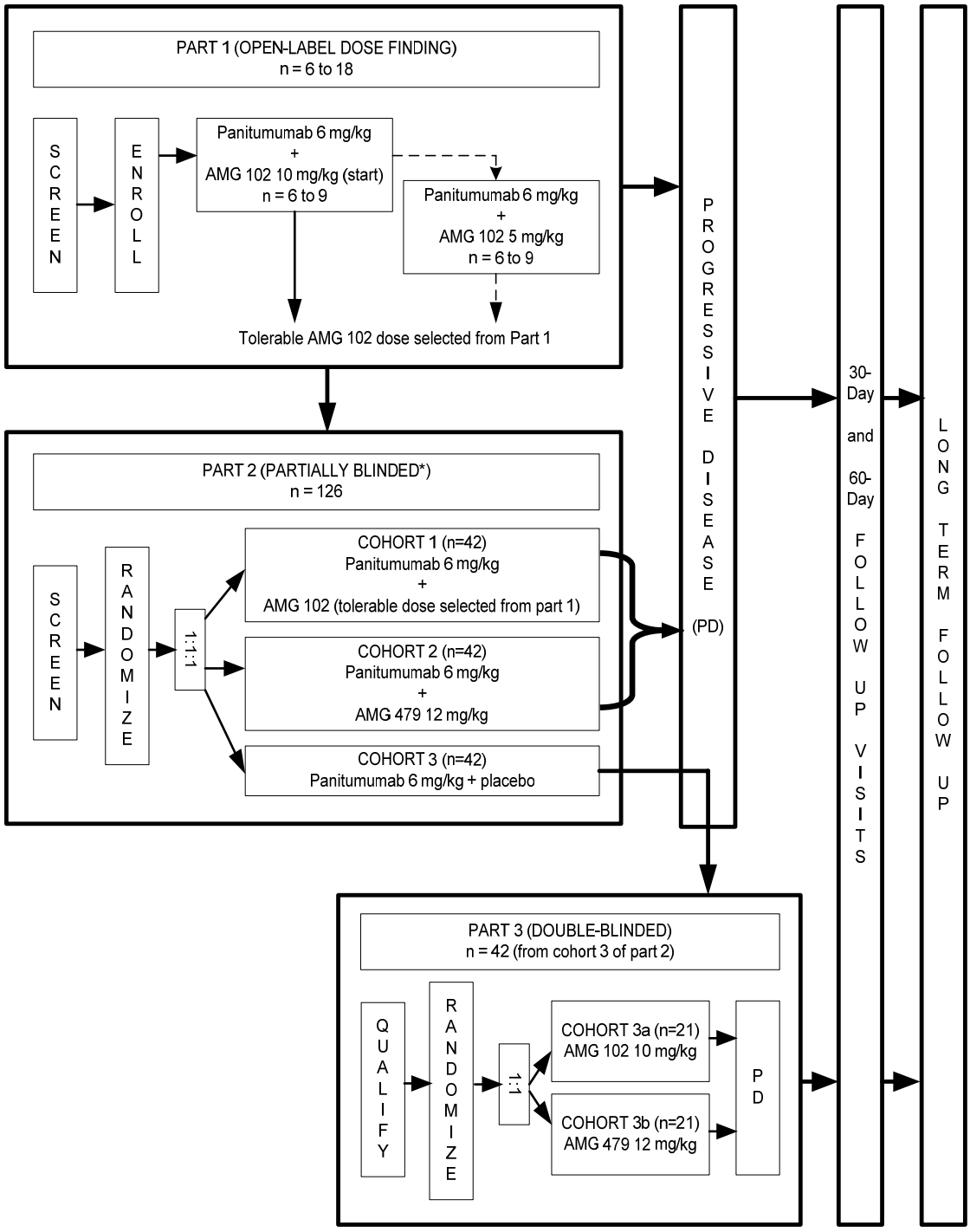
The primary analysis for part 3 will include data 24 weeks after the last subject is enrolled in part 3.

Final safety and efficacy analyses will include data 24 months after the last subject is enrolled in part 2 or in part 3, whichever occurs last.

Analyses will be separated by parts 1, 2 and 3.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



*In part 2, panitumumab will be open-label and AMG 102, AMG 479, and placebo will be double-blinded.

15. APPENDICES

Appendix A. Schedule of Assessments (Part 1 and Part 2)

	Screening		Week																					
Study Procedures[a]	**-35 days**	**-7 days**	**1**	**2**	**3**	**4**	**5**	**5**			**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Hour (D = day)							**D1**	**24 D2**	**48 D3**	**96 D5**															
PK Collection window[k]								**± 4 hrs**																	
General Assessments																									
Consent & eligibility review	X																								
Vital Signs[b]	X[e]		X		X		X					X		X		X		X		X		X		X	
PE, height, weight & ECOG[b]	X[e]		X				X							X				X				X			
ECG[c]		X																							
Review of AEs,SAEs,conmeds[d]	X		X		X		X					X		X		X		X		X		X		X	
Local Laboratory Tests[f]																									
Hematology		X[e]			X		X					X		X		X		X		X		X		X	
Chemistry[g]		X[e]			X		X					X		X		X		X		X		X		X	
HgbA1c		X	X				X							X				X				X			
TSH		X	X				X							X				X				X			
CEA		X[e]											X[f]				X				X				
Urine/Serum Pregnancy (-3 days)[f]		X[e]																							
Central Laboratory Sample Collection[h]																									
Tumor Tissue[i]	X[i]																								
PK (Part 1)[j]			X				X	X	X	X	X	X						X							
PK (Part 2)[k]			X		X		X					X						X							
Biomarker			X		X								X												
Antibodies[lp]			X									X													
Investigational Product Administration																									
Review dose adjustment criteria[m]					X		X					X		X		X		X		X		X		X	
Investigational product admin.[m]			X		X		X					X		X		X		X		X		X		X	
Radiological Assessments[n]																									
CT/MRI-Chest, Abdomen, & Pelvis	X[e]												X				X				X				
Investigator Assessment of Tumor Response													X				X				X				

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[a]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h]																												
PK (Part 1)[j]			X																								X	
PK (Part 2)[k]			X																								X	
Antibodies[lp]			X																								X	
Investigational Product Administration																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[a]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Review inclusion criteria for part 3 (see Section 4.3 & Appendix B)[o]													X[o]			
Local Laboratory Tests[f]																
Hematology	X		X		X		X		X		X		X			
Chemistry[g]	X		X		X		X		X		X		X			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[h]																
PK (Part 1)[j]												X	X	X		
PK (Part 2)[k]												X	X	X		
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n]																
CT or MRI of Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Appendix B. Schedule of Assessments (Part 3)

Study Procedures[a]	Qualification	Week																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
General Assessments																					
Review inclusion criteria for part 3 (see Section 4.3)	X[o]																				
Unblind in IVRS Note: only eligible subjects may be randomized in part 3 (see Section 7.2)	X[o]																				
Vital Signs[b]		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X	X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																					
Hematology	X	X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X	X		X		X		X		X		X		X		X		X		X	
HgbA1c	X	X				X				X				X				X			
TSH	X	X				X				X				X				X			
CEA	X								X[f]				X				X				
Central Laboratory Tests[h]																					
Biomarker		X							X												
Antibodies[ip]		X						X													
Investigational Product Administration																					
Review dose adjustment criteria[m]				X		X		X		X		X		X		X		X		X	
Investigational product administration[m]		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																					
CT/MRI - Chest, Abdomen, & Pelvis									X				X				X				
Investigator Assessment of Tumor Response									X				X				X				

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h]																												
Antibodies[lp]			X																								X	
Investigational Product Administration																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Local Laboratory Tests[f]																
Hematology	X		X		X		X		X		X		X			
Chemistry[g]	X		X		X		X		X		X		X			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[h]																
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n]																
CT/MRI - Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Appendix A & B. Schedule of Assessments Footnotes

a. **Study Procedures.** All treatment procedures must be performed within ± 3 days of the planned visit.

b. **Vital signs, PE, Height, Weight, ECOG.** Vital signs will include BP, resting pulse, respiration rate, and temp. Height will be collected at screening. See Appendix E for ECOG scale. For part 3, only ECOG is required at qualification.

c. **ECG.** A 12-lead ECG will be performed at screening and should include HR, QRS, QT, QTc, and PR intervals.

d. **AEs, SAEs, and Concomitant Medications.** AEs, SAEs, and con-meds should be reviewed at each study visit. Details including the start and stop dates of all AEs, SAEs, and con-meds will be recorded on the eCRF. All SAEs should be reported to Amgen within 24 hours. See Section 9 for details.

e. **Standard of Care.** Vitals, PE, ECOG, hematology, chemistry, CEA, pregnancy test, and CT or MRI scans of the chest, abdomen, and pelvis will be considered standard of care and may be performed before consent. However, for screening and baseline purposes, they must be performed within the timeframes specified (Section 7.1).

f. **Local Laboratory Analytes.** See Section 7, Table 7-1 for a complete list of laboratory analytes. The screening hematology and chemistry performed ≤ 7 days before enrollment will be used as baseline. Urine or serum pregnancy test must be completed ≤ 3 days before enrollment/randomization. Blood samples will be collected before each dose of investigational product. The blood samples may be collected up to 3 days before the dose of investigational product as long as they are collected no moare than 3 days before the planned visit.

g. **Chemistry.** Glucose (non-fasting) is included as part of the chemistry assessment. A fasting glucose will replace the glucose assessment at screening, weeks 3, 5, 11, 17, and 23.

h. **Central Laboratory Assessments.** Refer to the central laboratory manual(s) provided separately for instructions on the collection, processing, and shipment of samples.

i. **Tumor Tissue.** During screening, colorectal tumor tissue (paraffin-embedded block or unstained slides) collected prior to enrollment will be submitted to the central laboratory along with the associated pathology report(s) for eligibility determination of the subjects KRAS tumor status (ie, wild-type or mutant). Only subjects with wild-type KRAS tumor status will be eligible. These samples will also be used for exploratory biomarker development (see Section 7.5).

j. **PK Assessments (Part 1).** Subjects enrolled in part 1 will undergo more intensive PK blood sample collection during weeks 5 through 6. This will require 4 extra visits. For all subjects enrolled in part 1, PK samples will be collected pre-panitumumab infusion and post-AMG 102 infusion (± 5 min. after end of infusion) at weeks 1, 5, 6, 7, 13, 23, 47, and every 6 months thereafter during treatment. During week 5, PK samples will be collected at week 5, hours 24 (day 2), 48 (day 3), and 96 (day 5) post-AMG 102 infusion. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

k. **PK Assessments (Part 2).** PK samples will be collected pre-panitumumab infusion and post-AMG 102, AMG 479, or placebo infusion (± 5 min. after end of infusion) at weeks 1, 3, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

l. **Antibody Samples.** Antibody samples will be collected at weeks 1, 7, 23, 47, and every 6 months thereafter during treatment, and at the 30-day and 60-day follow-up visits. If the last antibody sample taken after the last dose of investigational product (ie, the 30-day safety follow-up or 60-day follow-up) is positive for HAPA or positive for neutralizing human anti-AMG 102 or anti-AMG 479 antibodies, then additional antibody samples will be collected at each 3 month LTFU visit (see Section 7.4). Note: subjects treated on cohort 3 in part 2 that go onto receive treatment in part 3, will be tested for HAPA at the 30-day safety follow-up for part 3.

m. **Investigational Product Administration.** Investigational product must be administered after all other study procedures (eg, laboratory sample collection), unless otherwise specified (eg, post-dose PK). After the first dose of investigational product, each subject will be assessed for dose adjustments (see Section 6). The Q2W schedule of all subsequent doses will be planned according to study day 1 or within ± 3 days of the planned dose.

n. **Radiological Assessments.** A CT or MRI of the chest, abdomen, pelvis, and all other sites of disease will be performed at weeks 8 (+1 week) and within +/- 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another treatment. Subjects with symptoms suggestive of disease progression will be evaluated for tumor response at the time symptoms occur. The same modality of imaging used at screening should be used throughout the study for direct comparison. Radiological images performed as standard of care ≤ 35 days before enrollment may be used for screening purposes. All assessments will be made by the investigator using modified RECIST (see Appendix F). Subjects with a complete response or partial response will have confirmatory radiological images performed no less than 4 weeks (28 days) after the criteria for response are first met. See footnote p below for LTFU imaging requirements.

o. **Inclusion Criteria for Part 3.** Subjects initially randomized in part 2 that meet the criteria outlined in Section 4.3 may be unblinded to determine their treatment assignment in part 2. Subjects assigned to Cohort 3 may be further randomized in part 3. The first dose of blinded investigational product (ie, AMG 102 or AMG 479) must be administered ≥ 2 weeks, but ≤ 5 weeks (2 to 5 weeks) after the last dose of panitumumab received in part 2. The first dose of part 3 investigational product must be received ≤ 3 days after randomization in part 3. See Sections 4.3 and 7.2, and Appendix B.

p. **LTFU.** After the 30-day safety follow-up visit, subjects will be followed for radiographic disease progression (if not documented previously) and survival every 3 months (± 28 day window) beginning after the 30-day safety follow-up and continuing for up to 2 years after the last subject is randomized in part 2 or 3, whichever occurs last (see Section 7.4 for details). See footnote l for additional information related to follow-up for positive antibodies to panitumumab, AMG 102, or AMG 479.

q. **End of Study.** The end of study will occur after the subject completes the LTFU[q], withdraws consent from the study, or death occurs.

Title: A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Panitumumab / AMG 102 / AMG 479

Amgen Protocol Number 20060447

Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 United States Tel: +1 805-447-1000 Fax: +1 805-480-0614
Key Sponsor Contact (US):	Shanna Stout Clinical Research Study Manager Tel: +1 805-447-8580 Fax: +1 805-480-1291
Key Sponsor Contact (US and Europe):	Dominic Smethurst Medical Director 1 Sanderson Road Uxbridge Business Park London UB81DH Tel: +44 1895 525364 Fax: +44 1895 525112
Date:	22 April 2008
Amendment 1 Date:	**09 February 2010**
EudraCT Number:	2008-001751-21

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer, dated **09 February 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 applicable FDA regulations/guidelines set forth 21 CFR Parts 11, 50, 54, 56, and 312 and other applicable regulations/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 Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Study Phase: 1b/2

Indication: wild-type KRAS metastatic colorectal cancer

This protocol consists of 3 parts. Part 1 is the dose finding phase 1b portion of the study**. Enrollment in part 1 was closed as of 04 May 2009.** Part 2 is the phase 2, randomized, 3-cohort portion of the study. **Enrollment in part 2 was closed as of 05 February 2010.** Part 3 is an extension of the phase 2 (part 2) in which select subjects from part 2 may continue treatment in 1 of 2 cohorts. Throughout this protocol synopsis, the various portions of the study will be referred to as part 1, 2, or 3.

Primary Objective:

Part 1: To identify a tolerable dose of AMG 102 in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs). **[Note: Enrollment in part 1 is now complete and a dose of AMG 102 (ie, 10 mg/kg) in combination with panitumumab has been identified for use in part 2. See Section 2.5.3 for additional information on dose selected. The information for part 1 remains throughout this protocol for reference only].**

Part 2: To evaluate the efficacy as assessed by the overall objective response rate (ORR) of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone

Secondary Objective(s):

Part 1:

- To evaluate the safety of AMG 102 in combination with panitumumab
- Pharmacokinetics (PK) exposure of AMG 102 and panitumumab when given in combination

Part 2:

- To evaluate the safety and efficacy of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone
- PK exposure of AMG 102 and panitumumab when given in combination
- PK exposure of AMG 479 and panitumumab when given in combination
- PK exposure of panitumumab when given alone

Exploratory Objective(s):

The exploratory objectives will include, but will not be limited to the following:

Part 1:

- To evaluate the efficacy of AMG 102 in combination with panitumumab

Part 3:

- To evaluate the safety and efficacy of AMG 102 and AMG 479 monotherapy following treatment with panitumumab (cohort 3) in part 2
- Pharmacodynamic response of AMG 102 as assessed by hepatocyte growth factor/c-Met (HGF/c-Met), pathway markers, tumor apoptosis markers, angiogenic cytokines, and other biomarkers (Part 1, 2, and 3)

- Pharmacodynamic response of AMG 479 as assessed by insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and growth hormone (Part 2 and 3)
- Correlation between plasma HGF levels or tumor ribonucleic acid (RNA) expression, and tumor response (Parts 1, 2, and 3)
- Effects of tumor genetic variation in pathway genes, cancer genes, drug target genes, and other biomarker genes on subject response to investigational product (Parts 1, 2, and 3)
- Effect of genetic variation in cancer genes, drug target genes, drug metabolism genes, and other biomarker genes on subject response to investigational product on a subset of subjects. Separate pharmacogenetic informed consent required. (Parts 1, 2, and 3)

Hypotheses:

Part 1: Treatment with AMG 102 in combination with panitumumab will be safe and well tolerated.

Part 2: Treatment with AMG 102 or AMG 479 in combination with panitumumab will exhibit a greater ORR with acceptable safety than treatment with panitumumab alone.

Part 3: Hypothesis forming exploratory work will be undertaken to evaluate safety and efficacy among those subjects in part 2 that go on to receive AMG 102 or AMG 479 monotherapy in part 3.

Study Design: This is a global, multicenter, open-label phase 1b and randomized, double-blinded 2-part phase 2 study designed to evaluate the safety and efficacy of AMG 102 or AMG 479 in combination with panitumumab versus panitumumab alone in mCRC subjects with wild-type KRAS tumor status.

Panitumumab will be open-label throughout the study (parts 1 and 2).

Investigational product will be administered every 2 weeks.

Part 1:

In part 1, approximately 6 to 18 subjects (6 to 9 subjects at each dose level of AMG 102 evaluated in combination with panitumumab) will be enrolled to receive open-label AMG 102 in combination with panitumumab with the purpose of identifying a tolerable dose of AMG 102 for the part 2 portion of the study.

AMG 102 10 mg/kg will be the starting dose evaluated in combination with panitumumab 6 mg/kg. Dose de-escalation of AMG 102 to 5 mg/kg will take place if determined necessary by the study team based on the interim safety analysis and incidence of DLTs. The dose of AMG 102 that is determined tolerable in combination with panitumumab in part 1 will be the selected dose used in part 2.

Subjects enrolled in part 1 will not be eligible for randomization in part 2.

Part 2:

Panitumumab will be open-label. AMG 102, AMG 479, and placebo will be blinded and will be referred to as blinded investigational product. In part 2, approximately 126 subjects will be randomized in a ratio of 1:1:1 to 1 of the following 3 double-blinded treatment groups. The randomization will be stratified for prior chemotherapy regimen received in the metastatic setting: irinotecan or oxaliplatin vs both.

Cohort 1: panitumumab 6 mg/kg and AMG 102 **10 mg/kg (the** tolerable dose selected from part 1 **was 10 mg/kg)**

Cohort 2: panitumumab 6 mg/kg and AMG 479 12 mg/kg

Cohort 3: panitumumab 6 mg/kg

Subjects randomized to cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see below).

Part 3:

Upon radiographic disease progression per modified RECIST **v1.0**, clinical progression, or intolerability to all investigational products, subjects that meet the criteria outlined in protocol Section 4.3 may be unblinded via the IVRS by the investigator or designated study staff to determine treatment assignment. Subjects randomized to cohort 3 (ie, panitumumab) of part 2 may be further randomized in part 3 in a ratio of 1:1 to 1 of the following 2 double-blinded treatment groups. The randomization will be stratified for reason for panitumumab discontinuation in part 2: disease progression (radiographic or clinical) versus intolerability.

Cohort 3a: AMG 102 10 mg/kg

Cohort 3b: AMG 479 12 mg/kg

The dose of AMG 102 (ie, 10 mg/kg) in part 3 will not be affected by the outcome of the interim safety analysis in part 1.

Investigational product will be administered every 2 weeks (Q2W) until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team (see investigational product administration details below).

All subjects that permanently discontinue all investigational products will complete a safety follow-up visit 30 days (+3 day window) and a follow-up visit 60 days (+14 day window) after the last dose of investigational product.

Subjects will be followed for radiographic disease progression (if not documented previously) and survival in the long-term follow-up portion of the study every 3 months (± 28 day window) after the 30 day safety follow up visit for up to 2 years after the last subject is enrolled in part 2.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1: Subject incidence of DLTs

Part 2: Overall ORR

Secondary Endpoints:

Part 2:

- Duration of response
- Time to response
- Disease control
- Progression-free survival
- **On-treatment progression-free-survival**
- Overall survival
- Incidence of all AEs and clinical laboratory abnormalities
- Incidence of antibody formation to panitumumab, AMG 102, and AMG 479
- C_{min}, C_{max}, and AUC for panitumumab and AMG 102 (Part 1)
- C_{min} and C_{max} for panitumumab, AMG 102, and AMG 479 (Part 2)

Sample Size:

Part 1: Approximately 6 to 18 subjects (n = 6 to 9 per dose level of AMG 102 evaluated in combination with panitumumab).

Part 2: Approximately 126 subjects (n = 42 per cohort)

Part 3: Subjects from cohort 3 of part 2 will cross over to part 3 (n = 42)

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria (Parts 1 and 2)

- Man or woman ≥ 18 years of age
- A life expectancy estimate of ≥ 3 months
- ECOG 0 or 1
- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- **Wild-type KRAS tumor status of archival tumor tissue confirmed by an Amgen approved central laboratory or an experienced laboratory (local laboratory) per local regulatory guidelines using a validated test method**
- Radiographic evidence of disease progression during or following prior treatment with irinotecan and/or oxaliplatin based chemotherapy for mCRC
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm **(CT or MRI) or ≥ 10 mm (spiral CT)** in 1 dimension per modified RECIST **v1.0**
- Adequate hematology, renal, and hepatic function (see Section 4.1.3)
- Magnesium ≥ lower limit of normal
- Subjects with known diabetes (Type 1 or 2) must have adequate glycemic function, as follows:
  - Must be controlled with a glycosylated hemoglobin (HgbA1c) of < 8.0%
  - Documented fasting blood sugars < 160 mg/dL

Key Exclusion Criteria (Parts 1 and 2)

- Prior treatment with anti-EGFr inhibitors (eg, panitumumab, cetuximab, erlotinib, gefitinib), unless treatment was received in the adjuvant setting ≥ 6 months before enrollment
- Prior treatment with c-Met, IGF-IR, or IGF-IIR inhibitors
- Prior treatment with either AMG 102 or AMG 479
- Use of experimental or approved systemic chemotherapy or radiotherapy ≤ 21 days before enrollment
- Use of experimental or approved targeted therapies ≤ 30 days before enrollment
- History of prior or concurrent central nervous system (CNS) metastases
- History of other primary cancer, unless:
  - Curatively resected non-melanomatous skin cancer
  - Curatively treated cervical carcinoma in situ
  - Other primary solid tumor treated with curative intent and no known active disease present for ≥ 5 years before enrollment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan

- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrollment
- Active inflammatory bowel disease or other active bowel disease causing chronic diarrhea (defined as ≥ grade 2 per CTCAE version 3.0)
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)
- Serious or non-healing wound ≤ 35 days before enrollment
- Major surgical procedure ≤ 35 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Central venous catheter placement, fine needle aspiration, thoracocentesis, or paracentesis is not considered a major or minor surgical procedure.

See protocol Section 4.3 for inclusion criteria for part 3.

Investigational Product Dosage and Administration:

Investigational product will be diluted in 0.9% sodium chloride. Investigational product will be administered by IV infusion beginning on week 1 and continuing Q2W until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team or DRT (see Sections 6.7 and 6.8). Note: Subjects in cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see Sections 4.3 and 7.2).

In part 1 and 2, panitumumab will be administered IV by infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding 0.2- or 0.22-micron pore size in-line filter (obtained by each center) infusion set up over 60 minutes ± 15 minutes. The infusion time should be extended to 90 minutes ± 15 minutes for doses higher than 1000 mg. **Administration of panitumumab by methods other than infusion pump must be discussed and approved by Amgen prior to administration**.

Following completion of the panitumumab infusion and proper flushing of the infusion line, AMG 102 (part 1) or blinded investigational product (part 2) will be administered IV over 60 minutes ± 15 minutes. Filtration of diluted AMG 102 **(part 1)** and **blinded investigational product (parts 2 and 3)** is not required.

If a dose of panitumumab and AMG 102 (part 1) or blinded investigational product (part 2) is well tolerated (ie, without any serious infusion-related reactions), then subsequent IV infusions may be administered over 30 minutes ± 10 minutes.

These infusion times also apply to blinded investigational product (ie, AMG 102 **or placebo, and** AMG 479 **or placebo**) in part 3.

AMG 102 (part 1) and blinded investigational product (part**s** 2 **and 3**) must be stored frozen protected from light at a freezer set point of -30°C or -70°C. Panitumumab must be stored between 2°C to 8°C and protected from direct sunlight.

Control Group: In part 2, panitumumab will serve as control group. There will be no control group in part 1 or 3.

Procedures:

Screening will occur within 35 days before enrollment/randomization **(date informed consent form is signed to date of enrollment/randomization)**.

Screening and on-study assessments will be performed such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis.

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study (see Section 4.1.1):

- **KRAS tumor status, for purposes of determining eligibility for this study, may be obtained through previously known KRAS tumor status, or local or central KRAS testing during study screening (see Section 7.1.1).**
- **Regardless of how KRAS tumor status is obtained, archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from the primary or metastatic site must be submitted to the central laboratory along with the associated pathology reports for other exploratory biomarker analyses and/or the evaluation of KRAS tumor status (if applicable) (see Section 7.2).**

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA), glycosylated hemoglobin (HgbA1c), thyroid stimulating hormone (TSH), **prothrombin time (PT)/international normalized ratio (INR),** and urine or serum pregnancy (for women of child-bearing potential).

During the study, blood samples will be collected for antibody formation, biomarker, and PK analyses and submitted to the central laboratory. Subjects enrolled in part 1 will undergo more frequent blood sample collection for PK during weeks 5 to 6. This will require 4 extra visits.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed at week 8 (+ 1 week window) and within ± 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another anti-cancer treatment.

Statistical Considerations: Tolerability of AMG 102 in combination of panitumumab will be assessed in part 1 based on the subject incidence of DLTs. A subject will be considered DLT evaluable if the subject has received at least 2 doses of panitumumab and AMG 102 as scheduled (ie, Week 1 and 3) and has a minimum 4 week (28 days) follow-up for safety or has received at lease 1 dose of panitumumab and AMG 102 and has a DLT within the first 4 weeks (28 days) on study. **See Section 2.5.3 for AMG 102 Dose Selected for Part 2.**

Overall safety will be evaluated throughout the study including all enrolled subjects who receive at least 1 dose of investigational product (Safety Analysis Set). Efficacy will be evaluated on subjects in the Safety Analysis Set. The primary analysis for the ORR will include all enrolled subjects in part 2 in the Safety Analysis set with measurable disease at baseline.

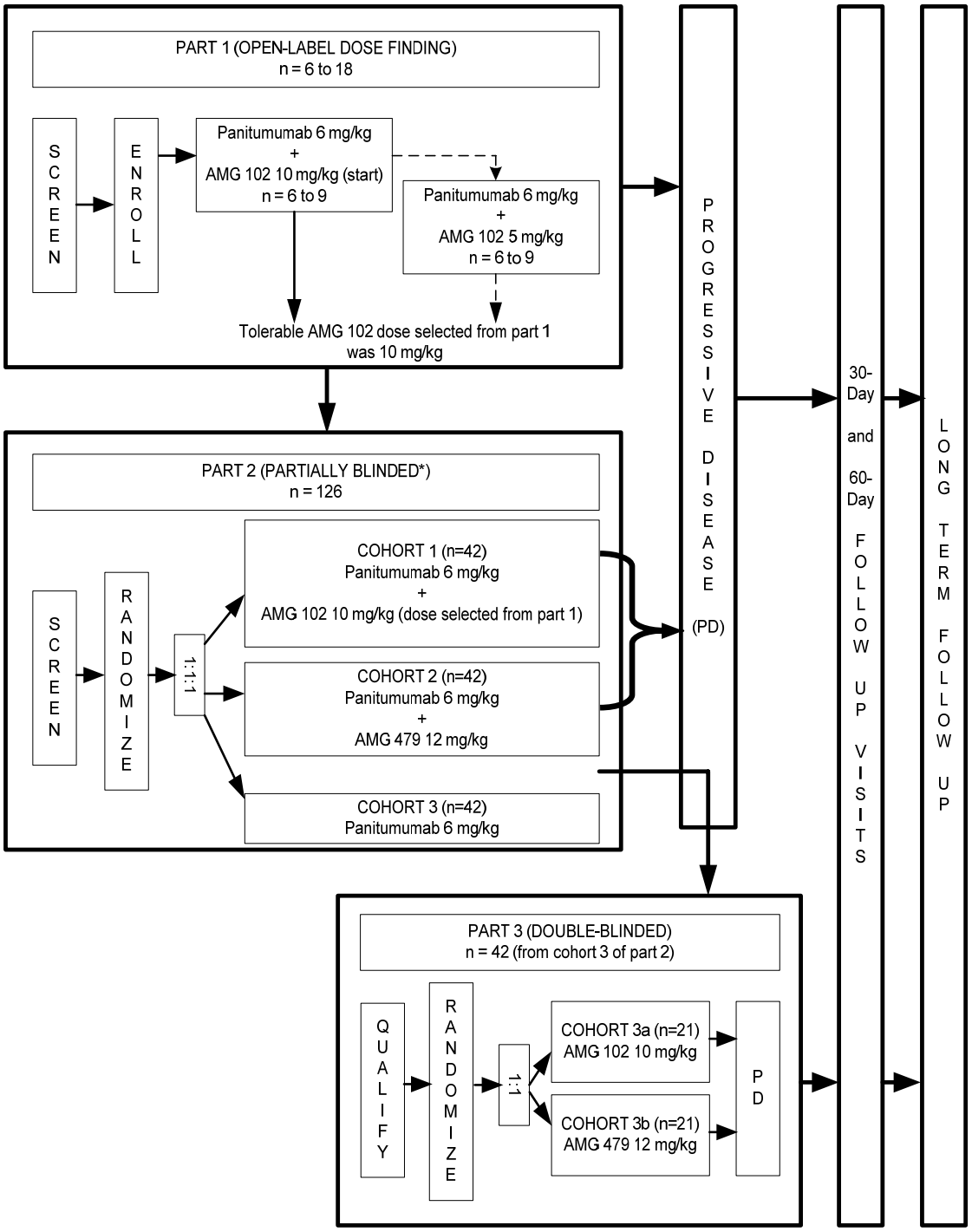
The primary analysis **for** part 2 will **occur after a minimum potential follow-up of** 24 weeks after the last subject is **randomized** in part 2. **All other available data will be summarized**. ORR will be analyzed based on Bayesian methodology. Historical ORRs from 4 previous panitumumab trials combined with the response outcome from cohort 3 of the study will provide a posterior distribution for the overall panitumumab monotherapy ORR. A combination regimen may be considered promising and possibly warrant further evaluation in a larger subsequent study if the posterior probability that the odds ratio (ie, combination versus panitumumab alone) is greater than 1 is ≥ 0.90. Likewise, a combination may not be considered promising if the posterior probability that the odds ratio is greater than 1 is ≤ 0.50.

Final analyses will include data 2 **years** after the last subject is **randomized** in part 2.

Analyses will be separated by parts 1, 2 and 3.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



*In part 2, panitumumab will be open-label and AMG 102, AMG 479, and placebo will be double-blinded.

15. APPENDICES

Appendix A. Schedule of Assessments (Part 1 and Part 2)

	Screening		Week																					
Study Procedures[ar]	**-35 days**	**-7 days**	**1**	**2**	**3**	**4**	**5**	**5**			**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Hour (D = day)							**D1**	**24 D2**	**48 D3**	**96 D5**															
PK Collection window[k]								**± 4 hrs**																	
General Assessments[r]																									
Consent & eligibility review	X																								
Vital Signs[b]	X[e]		X		X		X					X		X		X		X		X		X		X	
PE, height, weight & ECOG[b]	X[e]		X				X							X				X				X			
ECG[c]		X																							
Review of AEs, SAEs, conmeds[d]	X		X		X		X					X		X		X		X		X		X		X	
Local Laboratory Tests[fr]																									
Hematology		X[e]			X		X					X		X		X		X		X		X		X	
Chemistry[g]		X[eg]			X		X[g]					X		X[g]		X		X[g]		X		X[g]		X	
PT and INR (Part 2)							**X**									**X**						**X**			
HgbA1c		X					X							X				X				X			
TSH		X					X							X				X				X			
CEA		X[e]											X[f]				X				X				
Urine/Serum Pregnancy (-3 days)[f]		X[e]																							
Central Laboratory Sample Collection[hr]																									
Tumor Tissue[i]	X[i]																								
PK (Part 1)[jf]			X				X	X	X	X	X	X						X							
PK (Part 2)[kf]			X		X		X					X						X							
Biomarker			X		X								X												
Antibodies[lp]			X									X													
Investigational Product Administration[r]																									
Review dose adjustment criteria[m]					X		X					X		X		X		X		X		X		X	
Investigational product admin.[m]			X		X		X					X		X		X		X		X		X		X	
Radiological Assessments[nr]																									
CT/MRI-Chest, Abdomen, & Pelvis	X[e]												X				X				X				
Investigator Assessment of Tumor Response													X				X				X				

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[ar]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments[r]																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[fr]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR (Part 2)			**X**						**X**						**X**						**X**						**X**	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[hr]																												
PK (Part 1)[jf]			X																								X	
PK (Part 2)[kf]			X																								X	
Antibodies[lp]			X																								X	
Investigational Product Administration[r]																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[nr]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[ar]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments[r]																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Review inclusion criteria for part 3 (see Section 4.3 & Appendix B) [o]													X[o]			
Local Laboratory Tests[fr]																
Hematology	X		X		X		X		X		X		X			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
PT and INR (Part 2)	**X**						**X**						**X**			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[hr]																
PK (Part 1)[jf]												X[j]	X	X		
PK (Part 2)[kf]												X[k]	X	X		
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[nr]																
CT or MRI of Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Appendix B. Schedule of Assessments (Part 3)

Study Procedures[a]	**Qualification**	**Week**																			
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
General Assessments																					
Review inclusion criteria for part 3 (see Section 4.3)	X[o]																				
Unblind in IVRS Note: only eligible subjects may be randomized in part 3 (see Section 7.2)	X[o]																				
Vital Signs[b]		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X	X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																					
Hematology	X	X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR		**X**				**X**						**X**						**X**			
HgbA1c	X	X				X				X				X				X			
TSH	X	X				X				X				X				X			
CEA	X								X[f]				X				X				
Central Laboratory Tests[h]																					
Biomarker		X							X												
Antibodies[ip]		X						X													
Investigational Product Administration																					
Review dose adjustment criteria[m]				X		X		X		X		X		X		X		X		X	
Investigational product administration[m]		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																					
CT/MRI - Chest, Abdomen, & Pelvis									X				X				X				
Investigator Assessment of Tumor Response									X				X				X				

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR			**X**						**X**						**X**						**X**						**X**	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h]																												
Antibodies[lp]			X																								X	
Investigational Product Administration																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[ar]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Local Laboratory Tests[f]																
Hematology	X		X		X		X		X		X		X			
PT and INR	**X**						**X**						**X**			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[hr]																
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n]																
CT/MRI - Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Footnotes for Appendices A & B are on the following pages

Appendix A & B. Schedule of Assessments Footnotes

a. **Study Procedures.** All treatment procedures must be performed within ± 3 days of the planned visit.

b. **Vital signs, PE, Height, Weight, ECOG.** Vital signs will include BP, resting pulse, respiration rate, and temp. Height will be collected at screening. See Appendix E for ECOG scale. For part 3, only ECOG is required at qualification.

c. **ECG.** A 12-lead ECG will be performed at screening and should include HR, QRS, QT, QTc, and PR intervals.

d. **AEs, SAEs, and Concomitant Medications.** AEs, SAEs, and con-meds should be reviewed at each study visit **and recorded on the eCRF**. All SAEs should be reported to Amgen within 24 hours. See Section 9 for details.

e. **Standard of Care.** Vitals, PE, ECOG, hematology, chemistry, CEA, pregnancy test, and CT or MRI scans of the chest, abdomen, and pelvis will be considered standard of care and may be performed before consent. However, for screening and baseline purposes, they must be performed within the timeframes specified (Section 7.1).

f. **Local Laboratory Analytes.** See Section 7, Table 7-1 for a complete list of laboratory analytes. The screening hematology and chemistry performed ≤ 7 days before enrollment will be used as baseline. Urine or serum pregnancy test must be completed ≤ 3 days before enrollment/randomization. Blood samples will be collected before each dose of investigational product, **except for the post-infusion PK**. The blood samples may be collected **≤ 3** days before the dose of investigational product. **However, for PK, it is preferred that the pre-infusion blood samples are collected on the day of investigational product administration.**

g. **Chemistry.** Glucose (non-fasting) is included as part of the chemistry assessment **for all subjects**. **For subjects in part 2 and 3, a** fasting glucose will replace the glucose assessment at screening, weeks **5, 9, every 4 weeks thereafter, and at the 30-day safety follow-up visit.**

h. **Central Laboratory Assessments.** Refer to the central laboratory manual(s) provided separately for instructions on the collection, processing, and shipment of **tumor tissue, antibody, PK, and biomarker** samples.

i. **Tumor Tissue.** During screening, **archived formalin-fixed paraffin-embedded** colorectal tumor tissue (block or unstained slides) **from the primary or metastatic site** collected prior to the study will be submitted to the central laboratory along with the associated pathology report for **evaluation of** KRAS tumor status**, if applicable, EGFr membrane staining and/or other** exploratory biomarker **analyses** (see Section 7.5). **See KRAS testing in Section 7.1.1 for additional information on KRAS testing.**

j. **PK Assessments (Part 1).** Subjects enrolled in part 1 will undergo more intensive PK blood sample collection during weeks 5 through 6. This will require 4 extra visits. For all subjects enrolled in part 1, PK samples will be collected pre-panitumumab infusion[f] and post-AMG 102 infusion (± 5 min. after end of infusion) at weeks 1, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. During week 5, PK samples will be collected at week 5, hours 24 (day 2), 48 (day 3), 96 (day 5**), and 168 (day 8/week 6)** post-**end of** AMG 102 infusion. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

k. **PK Assessments (Part 2).** PK samples will be collected pre-panitumumab infusion[f] and post-**blinded investigational product** infusion (± 5 min. after end of infusion) at weeks 1, 3, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

l. **Antibody Samples.** Antibody samples will be collected at weeks 1, 7, 23, 47, and every 6 months thereafter during treatment, and at the 30-day and 60-day follow-up visits. **See Section 7.4 for additional antibody assessments in LTFU for subjects with a positive or neutralizing positive antibody result.** Note: subjects treated on cohort 3 in part 2 that go onto receive treatment in part 3, will be tested for HAPA at the 30-day safety follow-up for part 3.

m. **Investigational Product Administration.** Investigational product must be administered after all other study procedures (eg, laboratory sample collection), unless otherwise specified (eg, post-dose PK). After the first dose of investigational product, each subject will be assessed for dose adjustments (see Section 6). The Q2W schedule of all subsequent doses will be planned according to study day 1 or within ± 3 days of the planned dose.

n. **Radiological Assessments.** A CT or MRI of the chest, abdomen, pelvis, and all other sites of disease will be performed at weeks 8 (+1 week) and within +/- 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another treatment. Subjects with symptoms suggestive of disease progression will be evaluated for tumor response at the time symptoms occur. The same modality of imaging used at screening should be used throughout the study for direct comparison. Radiological images performed as standard of care ≤ 35 days before enrollment may be used for screening purposes. All assessments will be made by the investigator using modified RECIST **v1.0** (see Appendix F). Subjects with a complete response or partial response will have confirmatory radiological images performed no less than 4 weeks (28 days) after the criteria for response are first met. See footnote p below for LTFU imaging requirements**.**

o. **Inclusion Criteria for Part 3.** Subjects initially randomized in part 2 that meet the criteria outlined in Section 4.3 may be unblinded to determine their treatment assignment in part 2. Subjects assigned to Cohort 3 may be further randomized in part 3. The first dose of blinded investigational product must be administered ≥ 2 weeks, but **≤ 6** weeks (2 to **6** weeks) after the last dose of **investigational product** received in part 2. **Any exceptions to the first dose of blinded investigational product should be discussed with and approved by Amgen prior to implementation.** The first dose of part 3 investigational product must be received ≤ 3 days after randomization in part 3. See Sections 4.3 and 7.2, and Appendix B.

p. **LTFU.** After the 30-day safety follow-up visit, subjects will be followed for radiographic disease progression (if not documented previously) and survival every 3 months (± 28 day window) beginning after the 30-day safety follow-up and continuing for up to 2 years after the last subject is randomized in part 2 (see Section 7.4 for details). See footnote l for additional information related to follow-up for positive antibodies to panitumumab, AMG 102, or AMG 479.

q. **End of Study (subject).** The end of study **for each subject is defined** as the date the subject withdraws consent from study, completes the LTFU[p], or death.

Title: A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Panitumumab / AMG 102 / AMG 479

Amgen Protocol Number 20060447

Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 United States Tel: +1 805-447-1000 Fax: +1 805-480-0614
Key Sponsor Contact (US):	**Dawn Boisvert** Clinical Research Study Manager Tel: +1 805-**313-6416** Fax: +1 805-480-1291
Key Sponsor Contact (US and Europe):	Dominic Smethurst Medical Director 1 Sanderson Road Uxbridge Business Park London UB81DH Tel: +44 1895 525364 Fax: +44 1895 525112
Date:	22 April 2008
Amendment 1 Date:	09 February 2010
Amendment 2 Date:	**06 April 2011**
EudraCT Number:	2008-001751-21

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer, dated **06 April 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 applicable FDA regulations/guidelines set forth 21 CFR Parts 11, 50, 54, 56, and 312 and other applicable regulations/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 Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Study Phase: 1b/2

Indication: wild-type KRAS metastatic colorectal cancer

This protocol consists of 3 parts. Part 1 is the dose finding phase 1b portion of the study. Enrollment in part 1 was closed as of 04 May 2009. Part 2 is the phase 2, randomized, 3-cohort portion of the study. Enrollment in part 2 was closed as of 05 February 2010. Part 3 is an extension of the phase 2 (part 2) in which select subjects from part 2 may continue treatment in 1 of 2 cohorts. Throughout this protocol synopsis, the various portions of the study will be referred to as part 1, 2, or 3.

Primary Objective:

Part 1: To identify a tolerable dose of AMG 102 in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs). [Note: Enrollment in part 1 is now complete and a dose of AMG 102 (ie, 10 mg/kg) in combination with panitumumab has been identified for use in part 2. See Section 2.5.3 for additional information on dose selected. The information for part 1 remains throughout this protocol for reference only].

Part 2: To evaluate the efficacy as assessed by the overall objective response rate (ORR) of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone

Secondary Objective(s):

Part 1:

- To evaluate the safety of AMG 102 in combination with panitumumab
- Pharmacokinetics (PK) exposure of AMG 102 and panitumumab when given in combination

Part 2:

- To evaluate the safety and efficacy of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone
- PK exposure of AMG 102 and panitumumab when given in combination
- PK exposure of AMG 479 and panitumumab when given in combination
- PK exposure of panitumumab when given alone

Exploratory Objective(s):

The exploratory objectives will include, but will not be limited to the following:

Part 1:

- To evaluate the efficacy of AMG 102 in combination with panitumumab

Part 3:

- To evaluate the safety and efficacy of AMG 102 and AMG 479 monotherapy following treatment with panitumumab (cohort 3) in part 2
- Pharmacodynamic response of AMG 102 as assessed by hepatocyte growth factor/c-Met (HGF/c-Met), pathway markers, tumor apoptosis markers, angiogenic cytokines, and other biomarkers (Part 1, 2, and 3)

- Pharmacodynamic response of AMG 479 as assessed by insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and growth hormone (Part 2 and 3)
- Correlation between plasma HGF levels or tumor ribonucleic acid (RNA) expression, and tumor response (Parts 1, 2, and 3)
- Effects of tumor genetic variation in pathway genes, cancer genes, drug target genes, and other biomarker genes on subject response to investigational product (Parts 1, 2, and 3)
- Effect of genetic variation in cancer genes, drug target genes, drug metabolism genes, and other biomarker genes on subject response to investigational product on a subset of subjects. Separate pharmacogenetic informed consent required. (Parts 1, 2, and 3)

Hypotheses:

Part 1: Treatment with AMG 102 in combination with panitumumab will be safe and well tolerated.

Part 2: Treatment with AMG 102 or AMG 479 in combination with panitumumab will exhibit a greater ORR with acceptable safety than treatment with panitumumab alone.

Part 3: Hypothesis forming exploratory work will be undertaken to evaluate safety and efficacy among those subjects in part 2 that go on to receive AMG 102 or AMG 479 monotherapy in part 3.

Study Design: This is a global, multicenter, open-label phase 1b and randomized, double-blinded 2-part phase 2 study designed to evaluate the safety and efficacy of AMG 102 or AMG 479 in combination with panitumumab versus panitumumab alone in mCRC subjects with wild-type KRAS tumor status.

Panitumumab will be open-label throughout the study (parts 1 and 2).

Investigational product will be administered every 2 weeks.

Part 1:

In part 1, approximately 6 to 18 subjects (6 to 9 subjects at each dose level of AMG 102 evaluated in combination with panitumumab) will be enrolled to receive open-label AMG 102 in combination with panitumumab with the purpose of identifying a tolerable dose of AMG 102 for the part 2 portion of the study.

AMG 102 10 mg/kg will be the starting dose evaluated in combination with panitumumab 6 mg/kg. Dose de-escalation of AMG 102 to 5 mg/kg will take place if determined necessary by the study team based on the interim safety analysis and incidence of DLTs. The dose of AMG 102 that is determined tolerable in combination with panitumumab in part 1 will be the selected dose used in part 2.

Subjects enrolled in part 1 will not be eligible for randomization in part 2.

Part 2:

Panitumumab will be open-label. AMG 102, AMG 479, and placebo will be blinded and will be referred to as blinded investigational product. In part 2, approximately 126 subjects will be randomized in a ratio of 1:1:1 to 1 of the following 3 double-blinded treatment groups. The randomization will be stratified for prior chemotherapy regimen received in the metastatic setting: irinotecan or oxaliplatin vs both.

Cohort 1: panitumumab 6 mg/kg and AMG 102 10 mg/kg (the tolerable dose selected from part 1 was 10 mg/kg)

Cohort 2: panitumumab 6 mg/kg and AMG 479 12 mg/kg

Cohort 3: panitumumab 6 mg/kg

Subjects randomized to cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see below).

Part 3:

Upon radiographic disease progression per modified RECIST v1.0, clinical progression, or intolerability to all investigational products, subjects that meet the criteria outlined in protocol Section 4.3 may be unblinded via the IVRS by the investigator or designated study staff to determine treatment assignment. Subjects randomized to cohort 3 (ie, panitumumab) of part 2 may be further randomized in part 3 in a ratio of 1:1 to 1 of the following 2 double-blinded treatment groups. The randomization will be stratified for reason for panitumumab discontinuation in part 2: disease progression (radiographic or clinical) versus intolerability.

Cohort 3a: AMG 102 10 mg/kg

Cohort 3b: AMG 479 12 mg/kg

The dose of AMG 102 (ie, 10 mg/kg) in part 3 will not be affected by the outcome of the interim safety analysis in part 1.

Investigational product will be administered every 2 weeks (Q2W) until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team (see investigational product administration details below).

All subjects that permanently discontinue all investigational products will complete a safety follow-up visit 30 days (+3 day window) and a follow-up visit 60 days (+14 day window) after the last dose of investigational product.

Subjects will be followed for radiographic disease progression (if not documented previously) and survival in the long-term follow-up portion of the study every 3 months (± 28 day window) after the 30 day safety follow up visit for up to 2 years after the last subject is enrolled in part 2.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1: Subject incidence of DLTs

Part 2: Overall ORR

Secondary Endpoints:

Part 2:

- Duration of response
- Time to response
- Disease control
- Progression-free survival
- On-treatment progression-free-survival
- Overall survival
- Incidence of all AEs and clinical laboratory abnormalities
- Incidence of antibody formation to panitumumab, AMG 102, and AMG 479
- C_{min}, C_{max}, and AUC for panitumumab and AMG 102 (Part 1)
- C_{min} and C_{max} for panitumumab, AMG 102, and AMG 479 (Part 2)

Sample Size:

Part 1: Approximately 6 to 18 subjects (n = 6 to 9 per dose level of AMG 102 evaluated in combination with panitumumab).

Part 2: Approximately 126 subjects (n = 42 per cohort)

Part 3: Subjects from cohort 3 of part 2 will cross over to part 3 (n = 42)

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria (Parts 1 and 2)

- Man or woman ≥ 18 years of age
- A life expectancy estimate of ≥ 3 months
- ECOG 0 or 1
- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- Wild-type KRAS tumor status of archival tumor tissue confirmed by an Amgen approved central laboratory or an experienced laboratory (local laboratory) per local regulatory guidelines using a validated test method
- Radiographic evidence of disease progression during or following prior treatment with irinotecan and/or oxaliplatin based chemotherapy for mCRC
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm (CT or MRI) or ≥ 10 mm (spiral CT) in 1 dimension per modified RECIST v1.0
- Adequate hematology, renal, and hepatic function (see Section 4.1.3)
- Magnesium ≥ lower limit of normal
- Subjects with known diabetes (Type 1 or 2) must have adequate glycemic function, as follows:
  - Must be controlled with a glycosylated hemoglobin (HgbA1c) of < 8.0%
  - Documented fasting blood sugars < 160 mg/dL

Key Exclusion Criteria (Parts 1 and 2)

- Prior treatment with anti-EGFr inhibitors (eg, panitumumab, cetuximab, erlotinib, gefitinib), unless treatment was received in the adjuvant setting ≥ 6 months before enrollment
- Prior treatment with c-Met, IGF-IR, or IGF-IIR inhibitors
- Prior treatment with either AMG 102 or AMG 479
- Use of experimental or approved systemic chemotherapy or radiotherapy ≤ 21 days before enrollment
- Use of experimental or approved targeted therapies ≤ 30 days before enrollment
- History of prior or concurrent central nervous system (CNS) metastases
- History of other primary cancer, unless:
  - Curatively resected non-melanomatous skin cancer
  - Curatively treated cervical carcinoma in situ
  - Other primary solid tumor treated with curative intent and no known active disease present for ≥ 5 years before enrollment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan

- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrollment
- Active inflammatory bowel disease or other active bowel disease causing chronic diarrhea (defined as ≥ grade 2 per CTCAE version 3.0)
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)
- Serious or non-healing wound ≤ 35 days before enrollment
- Major surgical procedure ≤ 35 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Central venous catheter placement, fine needle aspiration, thoracocentesis, or paracentesis is not considered a major or minor surgical procedure.

See protocol Section 4.3 for inclusion criteria for part 3.

Investigational Product Dosage and Administration:

Investigational product will be diluted in 0.9% sodium chloride. Investigational product will be administered by IV infusion beginning on week 1 and continuing Q2W until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team or DRT (see Sections 6.7 and 6.8). Note: Subjects in cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see Sections 4.3 and 7.2).

In parts 1 and 2, panitumumab will be administered IV by infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding 0.2- or 0.22-micron pore size in-line filter (obtained by each center) infusion set up over 60 minutes ± 15 minutes. The infusion time should be extended to 90 minutes ± 15 minutes for doses higher than 1000 mg. Administration of panitumumab by methods other than infusion pump must be discussed and approved by Amgen prior to administration.

In parts 2 and 3, the blinded investigational product (AMG 102, AMG 479, and placebo) will be administered IV 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 (obtained by each center) infusion set-up.

Following completion of the panitumumab infusion and proper flushing of the infusion line, AMG 102 (part 1) or blinded investigational product (part 2) will be administered IV over 60 minutes ± 15 minutes.

If a dose of panitumumab and AMG 102 (part 1) or blinded investigational product (part 2) is well tolerated (ie, without any serious infusion-related reactions), then subsequent IV infusions may be administered over 30 minutes ± 10 minutes.

These infusion times also apply to blinded investigational product (ie, AMG 102 or placebo, and AMG 479 or placebo) in part 3.

AMG 102 (part 1) and blinded investigational product (part**s** 2 and 3) must be stored frozen protected from light at a freezer set point of -30°C or -70°C. Panitumumab must be stored between 2°C to 8°C and protected from direct sunlight.

Control Group: In part 2, panitumumab will serve as control group. There will be no control group in part 1 or 3.

Procedures:

Screening will occur within 35 days before enrollment/randomization (date informed consent form is signed to date of enrollment/randomization).

Screening and on-study assessments will be performed such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis.

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study (see Section 4.1.1):

- KRAS tumor status, for purposes of determining eligibility for this study, may be obtained through previously known KRAS tumor status, or local or central KRAS testing during study screening (see Section 7.1.1).
- Regardless of how KRAS tumor status is obtained, archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from the primary or metastatic site must be submitted to the central laboratory along with the associated pathology reports for other exploratory biomarker analyses and/or the evaluation of KRAS tumor status (if applicable) (see Section 7.2).

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA), glycosylated hemoglobin (HgbA1c), thyroid stimulating hormone (TSH), prothrombin time (PT)/international normalized ratio (INR), and urine or serum pregnancy (for women of child-bearing potential).

During the study, blood samples will be collected for antibody formation, biomarker, and PK analyses and submitted to the central laboratory. Subjects enrolled in part 1 will undergo more frequent blood sample collection for PK during weeks 5 to 6. This will require 4 extra visits.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed at week 8 (+ 1 week window) and within ± 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another anti-cancer treatment.

Statistical Considerations: Tolerability of AMG 102 in combination of panitumumab will be assessed in part 1 based on the subject incidence of DLTs. A subject will be considered DLT evaluable if the subject has received at least 2 doses of panitumumab and AMG 102 as scheduled (ie, Week 1 and 3) and has a minimum 4 week (28 days) follow-up for safety or has received at lease 1 dose of panitumumab and AMG 102 and has a DLT within the first 4 weeks (28 days) on study. See Section 2.5.3 for AMG 102 Dose Selected for Part 2.

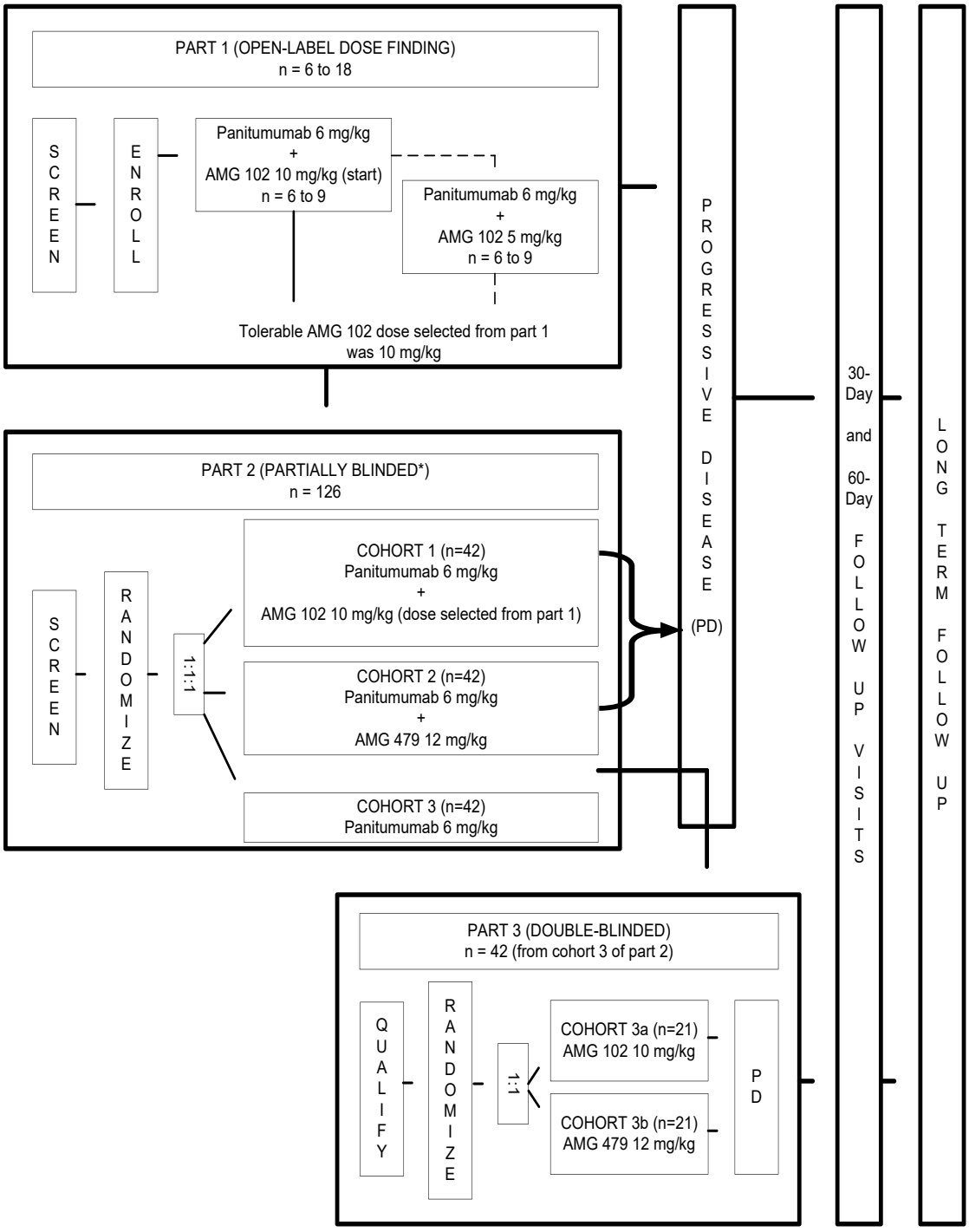
Overall safety will be evaluated throughout the study including all enrolled subjects who receive at least 1 dose of investigational product (Safety Analysis Set). Efficacy will be evaluated on subjects in the Safety Analysis Set. The primary analysis for the ORR will include all enrolled subjects in part 2 in the Safety Analysis set with measurable disease at baseline.

The primary analysis for part 2 will occur after a minimum potential follow-up of 24 weeks after the last subject is randomized in part 2. All other available data will be summarized. ORR will be analyzed based on Bayesian methodology. Historical ORRs from 4 previous panitumumab trials combined with the response outcome from cohort 3 of the study will provide a posterior distribution for the overall panitumumab monotherapy ORR. A combination regimen may be considered promising and possibly warrant further evaluation in a larger subsequent study if the posterior probability that the odds ratio (ie, combination versus panitumumab alone) is greater than 1 is ≥ 0.90. Likewise, a combination may not be considered promising if the posterior probability that the odds ratio is greater than 1 is ≤ 0.50.

Final analyses will include data 2 years after the last subject is randomized in part 2.

Analyses will be separated by parts 1, 2 and 3.

Study Design and Treatment Schema



*In part 2, panitumumab will be open-label and AMG 102, AMG 479, and placebo will be double-blinded.

15. APPENDICES

Appendix A. Schedule of Assessments (Part 1 and Part 2)

	Screening		Week																					
Study Procedures[ar]	**-35 days**	**-7 days**	**1**	**2**	**3**	**4**	**5**	**5**			**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Hour (D = day)							**D1**	**24 D2**	**48 D3**	**96 D5**															
PK Collection window[k]								**± 4 hrs**																	
General Assessments[r]																									
Consent & eligibility review	X																								
Vital Signs[b]	X[e]		X		X		X					X		X		X		X		X		X		X	
PE, height, weight & ECOG[b]	X[e]		X				X							X				X				X			
ECG[c]		X																							
Review of AEs, SAEs, conmeds[d]	X		X		X		X					X		X		X		X		X		X		X	
Local Laboratory Tests[fr]																									
Hematology		X[e]			X		X					X		X		X		X		X		X		X	
Chemistry[g]		X[eg]			X		X[g]					X		X[g]		X		X[g]		X		X[g]		X	
PT and INR (Part 2)							X									X						X			
HgbA1c		X					X							X				X				X			
TSH		X					X							X				X				X			
CEA		X[e]											X[f]				X				X				
Urine/Serum Pregnancy (-3 days)[f]		X[e]																							
Central Laboratory Sample Collection[hr]																									
Tumor Tissue[i]	X[i]																								
PK (Part 1)[jf]			X				X	X	X	X	X	X						X							
PK (Part 2)[kf]			X		X		X					X						X							
Biomarker			X		X								X												
Antibodies[lp]			X									X													
Investigational Product Administration[r]																									
Review dose adjustment criteria[m]					X		X					X		X		X		X		X		X		X	
Investigational product admin.[m]			X		X		X					X		X		X		X		X		X		X	
Radiological Assessments[nr]																									
CT/MRI-Chest, Abdomen, & Pelvis	X[e]												X				X				X				
Investigator Assessment of Tumor Response													X				X				X				

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[ar]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments[r]																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[fr]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR (Part 2)			X						X						X						X						X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[hr]																												
PK (Part 1)[jf]			X																								X	
PK (Part 2)[kf]			X																								X	
Antibodies[lp]			X																								X	
Investigational Product Administration[r]																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[nr]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[ar]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments[r]																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Review inclusion criteria for part 3 (see Section 4.3 & Appendix B)[o]													X[o]			
Local Laboratory Tests[fr]																
Hematology	X		X		X		X		X		X		X			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
PT and INR (Part 2)	X						X						X			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[hr]																
PK (Part 1)[jt]												X[j]	X	X		
PK (Part 2)[kt]												X[k]	X	X		
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[nr]																
CT or MRI of Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Appendix B. Schedule of Assessments (Part 3)

Study Procedures[a]	Qualification	Week																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
General Assessments																					
Review inclusion criteria for part 3 (see Section 4.3)	X[o]																				
Unblind in IVRS Note: only eligible subjects may be randomized in part 3 (see Section 7.2)	X[o]																				
Vital Signs[b]		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X	X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																					
Hematology	X	X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR		X				X						X						X			
HgbA1c	X	X				X				X				X				X			
TSH	X	X				X				X				X				X			
CEA	X								X[f]				X				X				
Central Laboratory Tests[h]																					
Biomarker		X							X												
Antibodies[ip]		X						X													
Investigational Product Administration																					
Review dose adjustment criteria[m]				X		X		X		X		X		X		X		X		X	
Investigational product administration[m]		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																					
CT/MRI - Chest, Abdomen, & Pelvis									X				X				X				
Investigator Assessment of Tumor Response									X				X				X				

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR			X						X						X						X						X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h]																												
Antibodies[lp]			X																								X	
Investigational Product Administration																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[ar]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Local Laboratory Tests[r]																
Hematology	X		X		X		X		X		X		X			
PT and INR	X						X						X			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[hr]																
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n]																
CT/MRI - Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Footnotes for Appendices A & B are on the following pages

Appendix A & B. Schedule of Assessments Footnotes

a. **Study Procedures.** All treatment procedures must be performed within ± 3 days of the planned visit.

b. **Vital signs, PE, Height, Weight, ECOG.** Vital signs will include BP, resting pulse, respiration rate, and temp. Height will be collected at screening. See Appendix E for ECOG scale. For part 3, only ECOG is required at qualification.

c. **ECG.** A 12-lead ECG will be performed at screening and should include HR, QRS, QT, QTc, and PR intervals.

d. **AEs, SAEs, and Concomitant Medications.** AEs, SAEs, and con-meds should be reviewed at each study visit and recorded on the eCRF. All SAEs should be reported to Amgen within 24 hours. See Section 9 for details.

e. **Standard of Care.** Vitals, PE, ECOG, hematology, chemistry, CEA, pregnancy test, and CT or MRI scans of the chest, abdomen, and pelvis will be considered standard of care and may be performed before consent. However, for screening and baseline purposes, they must be performed within the timeframes specified (Section 7.1).

f. **Local Laboratory Analytes.** See Section 7, Table 7-1 for a complete list of laboratory analytes. The screening hematology and chemistry performed ≤ 7 days before enrollment will be used as baseline. Urine or serum pregnancy test must be completed ≤ 3 days before enrollment/randomization. Blood samples will be collected before each dose of investigational product, except for the post-infusion PK. The blood samples may be collected ≤ 3 days before the dose of investigational product. However, for PK, it is preferred that the pre-infusion blood samples are collected on the day of investigational product administration.

g. **Chemistry.** Glucose (non-fasting) is included as part of the chemistry assessment for all subjects. For subjects in part 2 and 3, a fasting glucose will replace the glucose assessment at screening, weeks 5, 9, every 4 weeks thereafter, and at the 30-day safety follow-up visit.

h. **Central Laboratory Assessments.** Refer to the central laboratory manual(s) provided separately for instructions on the collection, processing, and shipment of tumor tissue, antibody, PK, and biomarker samples.

i. **Tumor Tissue.** During screening, archived formalin-fixed paraffin-embedded colorectal tumor tissue (block or unstained slides) from the primary or metastatic site collected prior to the study will be submitted to the central laboratory along with the associated pathology report for evaluation of KRAS tumor status, if applicable, EGFr membrane staining and/or other exploratory biomarker analyses (see Section 7.5). See KRAS testing in Section 7.1.1 for additional information on KRAS testing.

j. **PK Assessments (Part 1).** Subjects enrolled in part 1 will undergo more intensive PK blood sample collection during weeks 5 through 6. This will require 4 extra visits. For all subjects enrolled in part 1, PK samples will be collected pre-panitumumab infusion[f] and post-AMG 102 infusion (± 5 min. after end of infusion) at weeks 1, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. During week 5, PK samples will be collected at week 5, hours 24 (day 2), 48 (day 3), 96 (day 5), and 168 (day 8/week 6) post-end of AMG 102 infusion. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

k. **PK Assessments (Part 2).** PK samples will be collected pre-panitumumab infusion[f] and post-blinded investigational product infusion (± 5 min. after end of infusion) at weeks 1, 3, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

l. **Antibody Samples.** Antibody samples will be collected at weeks 1, 7, 23, 47, and every 6 months thereafter during treatment, and at the 30-day and 60-day follow-up visits. See Section 7.4 for additional antibody assessments in LTFU for subjects with a positive or neutralizing positive antibody result. Note: subjects treated on cohort 3 in part 2 that go onto receive treatment in part 3, will be tested for HAPA at the 30-day safety follow-up for part 3.

m. **Investigational Product Administration.** Investigational product must be administered after all other study procedures (eg, laboratory sample collection), unless otherwise specified (eg, post-dose PK). After the first dose of investigational product, each subject will be assessed for dose adjustments (see Section 6). The Q2W schedule of all subsequent doses will be planned according to study day 1 or within ± 3 days of the planned dose.

n. **Radiological Assessments.** A CT or MRI of the chest, abdomen, pelvis, and all other sites of disease will be performed at weeks 8 (+1 week) and within +/- 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another treatment. Subjects with symptoms suggestive of disease progression will be evaluated for tumor response at the time symptoms occur. The same modality of imaging used at screening should be used throughout the study for direct comparison. Radiological images performed as standard of care ≤ 35 days before enrollment may be used for screening purposes. All assessments will be made by the investigator using modified RECIST v1.0 (see Appendix F). Subjects with a complete response or partial response will have confirmatory radiological images performed no less than 4 weeks (28 days) after the criteria for response are first met. See footnote p below for LTFU imaging requirements**.**

o. **Inclusion Criteria for Part 3.** Subjects initially randomized in part 2 that meet the criteria outlined in Section 4.3 may be unblinded to determine their treatment assignment in part 2. Subjects assigned to Cohort 3 may be further randomized in part 3. The first dose of blinded investigational product must be administered ≥ 2 weeks, but ≤ 6 weeks (2 to 6 weeks) after the last dose of investigational product received in part 2. Any exceptions to the first dose of blinded investigational product should be discussed with and approved by Amgen prior to implementation. The first dose of part 3 investigational product must be received ≤ 3 days after randomization in part 3. See Sections 4.3 and 7.2, and Appendix B.

p. **LTFU.** After the 30-day safety follow-up visit, subjects will be followed for radiographic disease progression (if not documented previously) and survival every 3 months (± 28 day window) beginning after the 30-day safety follow-up and continuing for up to 2 years after the last subject is randomized in part 2 (see Section 7.4 for details). See footnote l for additional information related to follow-up for positive antibodies to panitumumab, AMG 102, or AMG 479.

q. **End of Study (subject).** The end of study for each subject is defined as the date the subject withdraws consent from study, completes the LTFU[p], or death.

Title: A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination With Panitumumab Versus Panitumumab Alone in Subjects With Wild-Type KRAS Metastatic Colorectal Cancer

Panitumumab / AMG 102 / AMG 479

Amgen Protocol Number 20060447

Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 United States Tel: +1 805-447-1000 Fax: +1 805-480-0614
Key Sponsor Contact (US **and Europe**):	**Gosia Orywal-Sykes** Clinical Research **Senior** Manager Tel: **+44 1895 525472** Fax: **+44 1895 525101**
Key Sponsor Contact (US and Europe):	Stephan Braun, MD, PhD Medical Director Dammstrasse 23, Opus 105 6301 Zug Switzerland Tel: +41 41 2692 549 Fax: +41 41 3690 405
Date:	22 April 2008
Amendment 1 Date:	09 February 2010
Amendment 2 Date:	06 April 2011
Superseding Amendment 2 Date:	12 December 2012
Amendment 3 Date:	**17 June 2013**
EudraCT Number:	2008-001751-21

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer, dated **17 June 2013**, 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 FDA regulations/guidelines set forth 21 CFR Parts 11, 50, 54, 56, and 312 and other applicable regulations/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 Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer

Study Phase: 1b/2

Indication: wild-type KRAS metastatic colorectal cancer

This protocol consists of 3 parts. Part 1 is the dose finding phase 1b portion of the study. Enrollment in part 1 was closed as of 04 May 2009. Part 2 is the phase 2, randomized, 3-cohort portion of the study. Enrollment in part 2 was closed as of 05 February 2010. Part 3 is an extension of the phase 2 (part 2) in which select subjects from part 2 may continue treatment in 1 of 2 cohorts. Throughout this protocol synopsis, the various portions of the study will be referred to as part 1, 2, or 3.

Primary Objective:

Part 1: To identify a tolerable dose of AMG 102 in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs). [Note: Enrollment in part 1 is now complete and a dose of AMG 102 (ie, 10 mg/kg) in combination with panitumumab has been identified for use in part 2. See Section 2.5.3 for additional information on dose selected. The information for part 1 remains throughout this protocol for reference only].

Part 2: To evaluate the efficacy as assessed by the overall objective response rate (ORR) of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone

Secondary Objective(s):

Part 1:

- To evaluate the safety of AMG 102 in combination with panitumumab
- Pharmacokinetics (PK) exposure of AMG 102 and panitumumab when given in combination

Part 2:

- To evaluate the safety and efficacy of AMG 102 (tolerable dose selected from part 1) in combination with panitumumab and AMG 479 in combination with panitumumab versus panitumumab alone
- PK exposure of AMG 102 and panitumumab when given in combination
- PK exposure of AMG 479 and panitumumab when given in combination
- PK exposure of panitumumab when given alone

Exploratory Objective(s):

The exploratory objectives will include, but will not be limited to the following:

Part 1:

- To evaluate the efficacy of AMG 102 in combination with panitumumab

Part 3:

- To evaluate the safety and efficacy of AMG 102 and AMG 479 monotherapy following treatment with panitumumab (cohort 3) in part 2
- Pharmacodynamic response of AMG 102 as assessed by hepatocyte growth factor/c-Met (HGF/c-Met), pathway markers, tumor apoptosis markers, angiogenic cytokines, and other biomarkers (Part 1, 2, and 3)

- Pharmacodynamic response of AMG 479 as assessed by insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and growth hormone (Part 2 and 3)
- Correlation between plasma HGF levels or tumor ribonucleic acid (RNA) expression, and tumor response (Parts 1, 2, and 3)
- Effects of tumor genetic variation in pathway genes, cancer genes, drug target genes, and other biomarker genes on subject response to investigational product (Parts 1, 2, and 3)
- Effect of genetic variation in cancer genes, drug target genes, drug metabolism genes, and other biomarker genes on subject response to investigational product on a subset of subjects. Separate pharmacogenetic informed consent required. (Parts 1, 2, and 3)

Hypotheses:

Part 1: Treatment with AMG 102 in combination with panitumumab will be safe and well tolerated.

Part 2: Treatment with AMG 102 or AMG 479 in combination with panitumumab will exhibit a greater ORR with acceptable safety than treatment with panitumumab alone.

Part 3: Hypothesis forming exploratory work will be undertaken to evaluate safety and efficacy among those subjects in part 2 that go on to receive AMG 102 or AMG 479 monotherapy in part 3.

Study Design: This is a global, multicenter, open-label phase 1b and randomized, double-blinded 2-part phase 2 study designed to evaluate the safety and efficacy of AMG 102 or AMG 479 in combination with panitumumab versus panitumumab alone in mCRC subjects with wild-type KRAS tumor status.

Panitumumab will be open-label throughout the study (parts 1 and 2).

Investigational product will be administered every 2 weeks.

Part 1:

In part 1, approximately 6 to 18 subjects (6 to 9 subjects at each dose level of AMG 102 evaluated in combination with panitumumab) will be enrolled to receive open-label AMG 102 in combination with panitumumab with the purpose of identifying a tolerable dose of AMG 102 for the part 2 portion of the study.

AMG 102 10 mg/kg will be the starting dose evaluated in combination with panitumumab 6 mg/kg. Dose de-escalation of AMG 102 to 5 mg/kg will take place if determined necessary by the study team based on the interim safety analysis and incidence of DLTs. The dose of AMG 102 that is determined tolerable in combination with panitumumab in part 1 will be the selected dose used in part 2.

Subjects enrolled in part 1 will not be eligible for randomization in part 2.

Part 2:

Panitumumab will be open-label. AMG 102, AMG 479, and placebo will be blinded and will be referred to as blinded investigational product. In part 2, approximately 126 subjects will be randomized in a ratio of 1:1:1 to 1 of the following 3 double-blinded treatment groups. The randomization will be stratified for prior chemotherapy regimen received in the metastatic setting: irinotecan or oxaliplatin vs both.

Cohort 1: panitumumab 6 mg/kg and AMG 102 10 mg/kg (the tolerable dose selected from part 1 was 10 mg/kg)

Cohort 2: panitumumab 6 mg/kg and AMG 479 12 mg/kg

Cohort 3: panitumumab 6 mg/kg

Subjects randomized to cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see below).

Part 3:

Upon radiographic disease progression per modified RECIST v1.0, clinical progression, or intolerability to all investigational products, subjects that meet the criteria outlined in protocol Section 4.3 may be unblinded via the IVRS by the investigator or designated study staff to determine treatment assignment. Subjects randomized to cohort 3 (ie, panitumumab) of part 2 may be further randomized in part 3 in a ratio of 1:1 to 1 of the following 2 double-blinded treatment groups. The randomization will be stratified for reason for panitumumab discontinuation in part 2: disease progression (radiographic or clinical) versus intolerability.

Cohort 3a: AMG 102 10 mg/kg

Cohort 3b: AMG 479 12 mg/kg

The dose of AMG 102 (ie, 10 mg/kg) in part 3 will not be affected by the outcome of the interim safety analysis in part 1.

Investigational product will be administered every 2 weeks (Q2W) until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team (see investigational product administration details below).

All subjects that permanently discontinue all investigational products will complete a safety follow-up visit 30 days (+3 day window) and a follow-up visit 60 days (+14 day window) after the last dose of investigational product.

Subjects will be followed for radiographic disease progression (if not documented previously) and survival in the long-term follow-up portion of the study every 3 months (± 28 day window) after the 30 day safety follow up visit for up to 2 years after the last subject is enrolled in part 2.

The subject treatment assignments in parts 2 and 3 will be unblinded after the planned data snapshot of the final analysis has been completed. Subjects receiving placebo will discontinue placebo administration and, in the absence of disease progression or unacceptable toxicities, may continue to receive investigational product (panitumumab AMG 102, or AMG 479, if applicable), Q2W at the investigator's discretion until disease progression, withdrawal of consent, death, or unless otherwise indicated by the study team. Data collection during this period will be limited to investigational product administration and serious adverse event reporting (see Section 9.3). Other protocol-specified procedures and observations outlined in the Sections 7.1 through 7.6 and Schedule of Assessments (Appendices A and B), including blood samples and radiographic tumor imaging, will not be collected. However, the investigator, at his or her discretion, may continue to perform the procedures and observations outlined in the Section 7 and Schedule of Assessments per local institution standard of care.

Primary and Secondary Endpoints:

Primary Endpoints:

Part 1: Subject incidence of DLTs

Part 2: Overall ORR

Secondary Endpoints:

Part 2:

- Duration of response
- Time to response
- Disease control

- Progression-free survival
- On-treatment progression-free-survival
- Overall survival
- Incidence of all AEs and clinical laboratory abnormalities
- Incidence of antibody formation to panitumumab, AMG 102, and AMG 479
- C_{min}, C_{max}, and AUC for panitumumab and AMG 102 (Part 1)
- C_{min} and C_{max} for panitumumab, AMG 102, and AMG 479 (Part 2)

Sample Size:

Part 1: Approximately 6 to 18 subjects (n = 6 to 9 per dose level of AMG 102 evaluated in combination with panitumumab).

Part 2: Approximately 126 subjects (n = 42 per cohort)

Part 3: Subjects from cohort 3 of part 2 will cross over to part 3 (n = 42)

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria (Parts 1 and 2)

- Man or woman ≥ 18 years of age
- A life expectancy estimate of ≥ 3 months
- ECOG 0 or 1
- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- Wild-type KRAS tumor status of archival tumor tissue confirmed by an Amgen approved central laboratory or an experienced laboratory (local laboratory) per local regulatory guidelines using a validated test method
- Radiographic evidence of disease progression during or following prior treatment with irinotecan and/or oxaliplatin based chemotherapy for mCRC
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm (CT or MRI) or ≥ 10 mm (spiral CT) in 1 dimension per modified RECIST v1.0
- Adequate hematology, renal, and hepatic function (see Section 4.1.3)
- Magnesium ≥ lower limit of normal
- Subjects with known diabetes (Type 1 or 2) must have adequate glycemic function, as follows:
  - Must be controlled with a glycosylated hemoglobin (HgbA1c) of < 8.0%
  - Documented fasting blood sugars < 160 mg/dL

Key Exclusion Criteria (Parts 1 and 2)

- Prior treatment with anti-EGFr inhibitors (eg, panitumumab, cetuximab, erlotinib, gefitinib), unless treatment was received in the adjuvant setting ≥ 6 months before enrollment
- Prior treatment with c-Met, IGF-IR, or IGF-IIR inhibitors
- Prior treatment with either AMG 102 or AMG 479
- Use of experimental or approved systemic chemotherapy or radiotherapy ≤ 21 days before enrollment
- Use of experimental or approved targeted therapies ≤ 30 days before enrollment
- History of prior or concurrent central nervous system (CNS) metastases
- History of other primary cancer, unless:
  - Curatively resected non-melanomatous skin cancer

  - Curatively treated cervical carcinoma in situ
  - Other primary solid tumor treated with curative intent and no known active disease present for ≥ 5 years before enrollment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrollment
- Active inflammatory bowel disease or other active bowel disease causing chronic diarrhea (defined as ≥ grade 2 per CTCAE version 3.0)
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)
- Serious or non-healing wound ≤ 35 days before enrollment
- Major surgical procedure ≤ 35 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Central venous catheter placement, fine needle aspiration, thoracocentesis, or paracentesis is not considered a major or minor surgical procedure.

See protocol Section 4.3 for inclusion criteria for part 3.

Investigational Product Dosage and Administration:

Investigational product will be diluted in 0.9% sodium chloride. Investigational product will be administered by IV infusion beginning on week 1 and continuing Q2W until disease progression, intolerability, withdrawal, death, or unless otherwise indicated by the study team or DRT (see Sections 6.7 and 6.8). Note: Subjects in cohort 3 of part 2 may be eligible to receive treatment with blinded investigational product in part 3 (see Sections 4.3 and 7.2).

In parts 1 and 2, panitumumab will be administered IV by infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding 0.2- or 0.22-micron pore size in-line filter (obtained by each center) infusion set up over 60 minutes ± 15 minutes. The infusion time should be extended to 90 minutes ± 15 minutes for doses higher than 1000 mg. Administration of panitumumab by methods other than infusion pump must be discussed and approved by Amgen prior to administration.

In parts 2 and 3, the blinded investigational product (AMG 102, AMG 479, and placebo) will be administered IV 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 (obtained by each center) infusion set-up.

Following completion of the panitumumab infusion and proper flushing of the infusion line, AMG 102 (part 1) or blinded investigational product (part 2) will be administered IV over 60 minutes ± 15 minutes.

If a dose of panitumumab and AMG 102 (part 1) or blinded investigational product (part 2) is well tolerated (ie, without any serious infusion-related reactions), then subsequent IV infusions may be administered over 30 minutes ± 10 minutes.

These infusion times also apply to blinded investigational product (ie, AMG 102 or placebo, and AMG 479 or placebo) in part 3.

AMG 102 (part 1) and blinded investigational product (part**s** 2 and 3) must be stored frozen protected from light at a freezer set point of -30°C or -70°C. Panitumumab must be stored between 2°C to 8°C and protected from direct sunlight.

Control Group: In part 2, panitumumab will serve as control group. There will be no control group in part 1 or 3.

Procedures:

Screening will occur within 35 days before enrollment/randomization (date informed consent form is signed to date of enrollment/randomization).

Screening and on-study assessments will be performed such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis.

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study (see Section 4.1.1):

- KRAS tumor status, for purposes of determining eligibility for this study, may be obtained through previously known KRAS tumor status, or local or central KRAS testing during study screening (see Section 7.1.1).
- Regardless of how KRAS tumor status is obtained, archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from the primary or metastatic site must be submitted to the central laboratory along with the associated pathology reports for other exploratory biomarker analyses and/or the evaluation of KRAS tumor status (if applicable) (see Section 7.2).

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA), glycosylated hemoglobin (HgbA1c), thyroid stimulating hormone (TSH), prothrombin time (PT)/international normalized ratio (INR), and urine or serum pregnancy (for women of child-bearing potential).

During the study, blood samples will be collected for antibody formation, biomarker, and PK analyses and submitted to the central laboratory. Subjects enrolled in part 1 will undergo more frequent blood sample collection for PK during weeks 5 to 6. This will require 4 extra visits.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed at week 8 (+ 1 week window) and within ± 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another anti-cancer treatment.

Data collection for subjects who remain on study treatment after the planned data snapshot of the final analysis has been completed will be limited to investigational product administration and serious adverse event reporting (see Section 7.7 and Section 9.3).

Statistical Considerations: Tolerability of AMG 102 in combination of panitumumab will be assessed in part 1 based on the subject incidence of DLTs. A subject will be considered DLT evaluable if the subject has received at least 2 doses of panitumumab and AMG 102 as scheduled (ie, Week 1 and 3) and has a minimum 4 week (28 days) follow-up for safety or has received at least 1 dose of panitumumab and AMG 102 and has a DLT within the first 4 weeks (28 days) on study. See Section 2.5.3 for AMG 102 Dose Selected for Part 2.

Overall safety will be evaluated throughout the study including all enrolled subjects who receive at least 1 dose of investigational product (Safety Analysis Set). Efficacy will be evaluated on subjects in the Safety Analysis Set. The primary analysis for the ORR will include all enrolled subjects in part 2 in the Safety Analysis set with measurable disease at baseline.

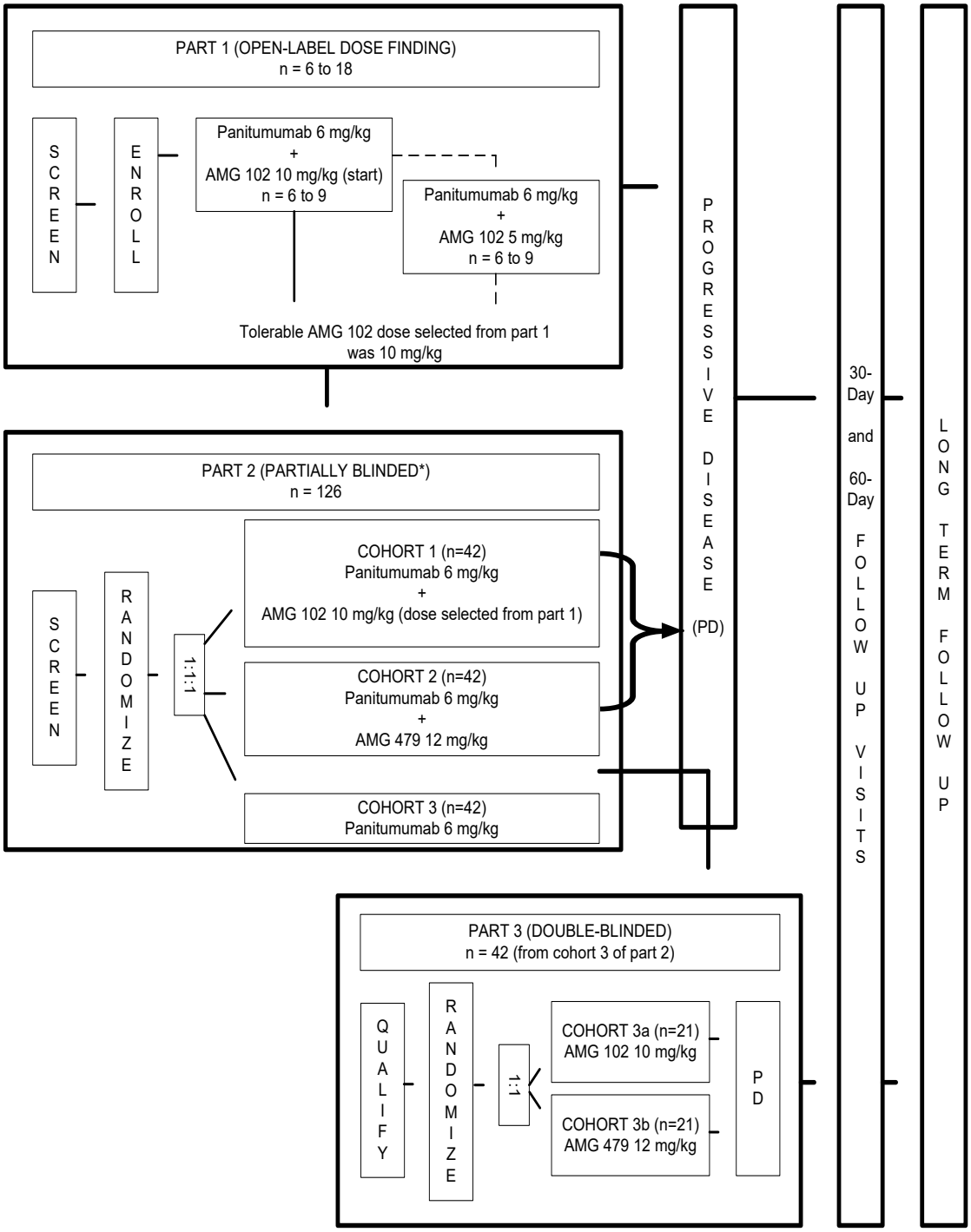
The primary analysis for part 2 will occur after a minimum potential follow-up of 24 weeks after the last subject is randomized in part 2. All other available data will be summarized. ORR will be analyzed based on Bayesian methodology. Historical ORRs from 4 previous panitumumab trials combined with the response outcome from cohort 3 of the study will provide a posterior distribution for the overall panitumumab monotherapy ORR. A combination regimen may be considered promising and possibly warrant further evaluation in a larger subsequent study if the posterior probability that the odds ratio (ie, combination versus panitumumab alone) is greater than 1 is ≥ 0.90. Likewise, a combination may not be considered promising if the posterior probability that the odds ratio is greater than 1 is ≤ 0.50.

Final analyses will include data 2 years after the last subject is randomized in part 2.

Analyses will be separated by parts 1, 2 and 3.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



*In part 2, panitumumab will be open-label and AMG 102, AMG 479, and placebo will be double-blinded.

Appendix A. Schedule of Assessments (Part 1 and Part 2)

	Screening		Week																						
Study Procedures[a,r]	**-35 days**	**-7 days**	**1**	**2**	**3**	**4**	**5**	**5**			**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Hour (D = day)							**D1**	**24 D2**	**48 D3**	**96 D5**															
PK Collection window[k]								**± 4 hrs**																	
General Assessments[r]																									
Consent & eligibility review	X																								
Vital Signs[b]	X[e]		X		X		X					X		X		X		X		X	X			X	
PE, height, weight & ECOG[b]	X[e]		X				X							X				X				X			
ECG[c]		X																							
Review of AEs, SAEs, conmeds[d]	X		X		X		X					X		X		X		X		X	X			X	
Local Laboratory Tests[f,r]																									
Hematology		X[e]			X		X					X		X		X		X		X	X			X	
Chemistry[g]		X[eg]			X		X[g]					X		X[g]		X		X g		X		X g		X	
PT and INR (Part 2)							X									X						X			
HgbA1c		X					X							X				X				X			
TSH		X					X							X				X				X			
CEA		X[e]											X f				X				X				
Urine/Serum Pregnancy (-3 days)[f]		X[e]																							
Central Laboratory Sample Collection[h,r]																									
Tumor Tissue[i]	X[i]																								
PK (Part 1)[jf]			X				X	X	X		X	X						X							
PK (Part 2)[kf]			X		X		X					X						X							
Biomarker			X		X								X												
Antibodies[lp]			X									X													
Investigational Product Administration[r]																									
Review dose adjustment criteria[m]					X		X					X		X		X		X		X	X			X	
Investigational product admin.[m]			X		X		X					X		X		X		X		X	X			X	
Radiological Assessments[n,r]																									
CT/MRI-Chest, Abdomen, & Pelvis	X[e]												X				X				X				
Investigator Assessment of Tumor Response													X				X				X				

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[a,r]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments[r]																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f,r]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR (Part 2)			X						X						X						X						X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h,r]																												
PK (Part 1)[jf]			X																								X	
PK (Part 2)[kf]			X																								X	
Antibodies[lp]			X																								X	
Investigational Product Administration[r]																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n,r]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix A. Schedule of Assessments (continued)

(Part 1 and Part 2)

Study Procedures[a,r]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments[r]																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Review inclusion criteria for part 3 (see Section 4.3 & Appendix B)[o]													X[o]			
Local Laboratory Tests[f,r]																
Hematology	X		X		X		X		X		X		X			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
PT and INR (Part 2)	X						X						X			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[h,r]																
PK (Part 1)[if]												X[j]	X	X		
PK (Part 2)[kf]												X[k]	X	X		
Biomarker													X	X		
Antibodies[lp]												X	X[l]	X[l]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n,r]																
CT or MRI of Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Appendix B. Schedule of Assessments (Part 3)

Study Procedures[a,r]	**Qualification**	**Week**																			
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
General Assessments																					
Review inclusion criteria for part 3 (see Section 4.3)	X[o]																				
Unblind in IVRS Note: only eligible subjects may be randomized in part 3 (see Section 7.2)	X[o]																				
Vital Signs[b]		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X	X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f,r]																					
Hematology	X	X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR		X				X						X						X			
HgbA1c	X	X				X				X				X				X			
TSH	X	X				X				X				X				X			
CEA	X								X[f]				X				X				
Central Laboratory Tests[h,r]																					
Biomarker		X							X												
Antibodies[ip]		X						X													
Investigational Product Administration[r]																					
Review dose adjustment criteria[m]				X		X		X		X		X		X		X		X		X	
Investigational product administration[m]		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n,r]																					
CT/MRI - Chest, Abdomen, & Pelvis									X				X				X				
Investigator Assessment of Tumor Response									X				X				X				

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a,r]	Week																											
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
General Assessments[r]																												
Vital Signs[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
PE, weight & ECOG[b]	X				X				X				X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Local Laboratory Tests[f,r]																												
Hematology	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X		X[g]		X	
PT and INR			X						X						X						X						X	
HgbA1c	X				X				X				X				X				X				X			
TSH	X				X				X				X				X				X				X			
CEA				X								X								X								X
Central Laboratory Sample Collection[h,r]																												
Antibodies[l,p]			X																								X	
Investigational Product Administration[r]																												
Review dose adjustment criteria[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Investigational product administration[m]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Radiological Assessments[n,r]																												
CT/MRI - Chest, Abdomen, & Pelvis				X								X								X								X
Investigator Assessment of Tumor Response				X								X								X								X

Appendix B. Schedule of Assessments (continued)

(Part 3)

Study Procedures[a,r]	Week 49 until Radiographic Disease Progression Visits repeated every 12 weeks (unless otherwise indicated)												30-Day Safety Follow-up Visit (+3 day window)	60-Day Follow-up Visit (+14 day window)	LTFU (± 28 day window)	End of Study[q]
	1	2	3	4	5	6	7	8	9	10	11	12				
General Assessments[r]																
Vital Signs[b]	X		X		X		X		X		X		X			
PE, weight & ECOG[b]	X				X				X				X			
Review of AEs, SAEs, & conmeds[d]	X		X		X		X		X		X		X			
Local Laboratory Tests[f,r]																
Hematology	X		X		X		X		X		X		X			
PT and INR	X						X						X			
Chemistry[g]	X[g]		X		X[g]		X		X[g]		X		X[g]			
HgbA1c	X				X				X				X			
TSH	X				X				X				X			
CEA												X	X			
Central Laboratory Samples[h,r]																
Biomarker													X	X		
Antibodies[i,p]												X	X[i]	X[i]	X[p]	
Investigational Product Administration[r]																
Review dose adjustment criteria[m]	X		X		X		X		X		X					
Investigational product administration[m]	X		X		X		X		X		X					
Radiological Assessments[n,r]																
CT/MRI - Chest, Abdomen, & Pelvis												X	X[np]		X[np]	
Investigator Assessment of Tumor Response												X	X[np]		X[np]	

Footnotes for Appendices A & B are on the following pages

Appendix A & B. Schedule of Assessments Footnotes

a. **Study Procedures.** All treatment procedures must be performed within ± 3 days of the planned visit.

b. **Vital signs, PE, Height, Weight, ECOG.** Vital signs will include BP, resting pulse, respiration rate, and temp. Height will be collected at screening. See Appendix E for ECOG scale. For part 3, only ECOG is required at qualification.

c. **ECG.** A 12-lead ECG will be performed at screening and should include HR, QRS, QT, QTc, and PR intervals.

d. **AEs, SAEs, and Concomitant Medications.** AEs, SAEs, and con-meds should be reviewed at each study visit and recorded on the eCRF. All SAEs should be reported to Amgen within 24 hours. See Section 9 for details.

e. **Standard of Care.** Vitals, PE, ECOG, hematology, chemistry, CEA, pregnancy test, and CT or MRI scans of the chest, abdomen, and pelvis will be considered standard of care and may be performed before consent. However, for screening and baseline purposes, they must be performed within the timeframes specified (Section 7.1).

f. **Local Laboratory Analytes.** See Section 7, Table 6 for a complete list of laboratory analytes. The screening hematology and chemistry performed ≤ 7 days before enrollment will be used as baseline. Urine or serum pregnancy test must be completed ≤ 3 days before enrollment/randomization. Blood samples will be collected before each dose of investigational product, except for the post-infusion PK. The blood samples may be collected ≤ 3 days before the dose of investigational product. However, for PK, it is preferred that the pre-infusion blood samples are collected on the day of investigational product administration.

g. **Chemistry.** Glucose (non-fasting) is included as part of the chemistry assessment for all subjects. For subjects in part 2 and 3, a fasting glucose will replace the glucose assessment at screening, weeks 5, 9, every 4 weeks thereafter, and at the 30-day safety follow-up visit.

h. **Central Laboratory Assessments.** Refer to the central laboratory manual(s) provided separately for instructions on the collection, processing, and shipment of tumor tissue, antibody, PK, and biomarker samples.

i. **Tumor Tissue.** During screening, archived formalin-fixed paraffin-embedded colorectal tumor tissue (block or unstained slides) from the primary or metastatic site collected prior to the study will be submitted to the central laboratory along with the associated pathology report for evaluation of KRAS tumor status, if applicable, EGFr membrane staining and/or other exploratory biomarker analyses (see Section 7.5). See KRAS testing in Section 7.1.1 for additional information on KRAS testing.

j. **PK Assessments (Part 1).** Subjects enrolled in part 1 will undergo more intensive PK blood sample collection during weeks 5 through 6. This will require 4 extra visits. For all subjects enrolled in part 1, PK samples will be collected pre-panitumumab infusion[f] and post-AMG 102 infusion (± 5 min. after end of infusion) at weeks 1, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. During week 5, PK samples will be collected at week 5, hours 24 (day 2), 48 (day 3), 96 (day 5), and 168 (day 8/week 6) post-end of AMG 102 infusion. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

k. **PK Assessments (Part 2).** PK samples will be collected pre-panitumumab infusion[f] and post-blinded investigational product infusion (± 5 min. after end of infusion) at weeks 1, 3, 5, 7, 13, 23, 47, and every 6 months thereafter during treatment. A PK sample will also be collected at the 30-day and 60-day follow-up visit(s). Note: If a subject is receiving only one of the two investigational products on a day PK is collected, then a pre-and post-infusion blood sample will be collected.

l. **Antibody Samples.** Antibody samples will be collected at weeks 1, 7, 23, 47, and every 6 months thereafter during treatment, and at the 30-day and 60-day follow-up visits. See Section 7.4 for additional antibody assessments in LTFU for subjects with a positive or neutralizing positive antibody result. Note: subjects treated on cohort 3 in part 2 that go onto receive treatment in part 3, will be tested for HAPA at the 30-day safety follow-up for part 3.

m. **Investigational Product Administration.** Investigational product must be administered after all other study procedures (eg, laboratory sample collection), unless otherwise specified (eg, post-dose PK). After the first dose of investigational product, each subject will be assessed for dose adjustments (see Section 6). The Q2W schedule of all subsequent doses will be planned according to study day 1 or within ± 3 days of the planned dose.

n. **Radiological Assessments.** A CT or MRI of the chest, abdomen, pelvis, and all other sites of disease will be performed at weeks 8 (+1 week) and within +/- 1 week at weeks 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter until radiographic disease progression or the subject begins another treatment. Subjects with symptoms suggestive of disease progression will be evaluated for tumor response at the time symptoms occur. The same modality of imaging used at screening should be used throughout the study for direct comparison. Radiological images performed as standard of care ≤ 35 days before enrollment may be used for screening purposes. All assessments will be made by the investigator using modified RECIST v1.0 (see Appendix F). Subjects with a complete response or partial response will have confirmatory radiological images performed no less than 4 weeks (28 days) after the criteria for response are first met. See footnote p below for LTFU imaging requirements**.**

o. **Inclusion Criteria for Part 3.** Subjects initially randomized in part 2 that meet the criteria outlined in Section 4.3 may be unblinded to determine their treatment assignment in part 2. Subjects assigned to Cohort 3 may be further randomized in part 3. The first dose of blinded investigational product must be administered ≥ 2 weeks, but ≤ 6 weeks (2 to 6 weeks) after the last dose of investigational product received in part 2. Any exceptions to the first dose of blinded investigational product should be discussed with and approved by Amgen prior to implementation. The first dose of part 3 investigational product must be received ≤ 3 days after randomization in part 3. See Sections 4.3 and 7.2, and Appendix B.

p. **LTFU.** After the 30-day safety follow-up visit, subjects will be followed for radiographic disease progression (if not documented previously) and survival every 3 months (± 28 day window) beginning after the 30-day safety follow-up and continuing for up to 2 years after the last subject is randomized in part 2 (see Section 7.4 for details). See footnote l for additional information related to follow-up for positive antibodies to panitumumab, AMG 102, or AMG 479.

q. **End of Study (subject).** The end of study for each subject is defined as the date the subject withdraws consent from study, completes the LTFU[p], or death. **The end of study for each subject who remains on study after the planned data snapshot of the final analysis is defined as date the subject withdrew consent from the study, completes the 30-day safety follow-up visit, or death.**

r. **Study Procedures Following Completion of Data Snapshot of Final Analysis: Data collection for subjects who remain on study treatment after the planned data snapshot of the final analysis has been completed will be limited to investigational product administration and serious adverse event reporting (see Section 7.7 and Section 9.3). Other protocol-specified procedures and observations outlined in the Schedule of Assessments and in Sections 7.1 through 7.6 of the protocol, including blood samples and radiographic imaging, will not be collected. However, the investigator, at his or her discretion, may continue to perform the procedures and observations outlined in Section 7 and Schedule of Assessments per local institution standard of care.**