Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Panitumumab / AMG 479

Amgen Protocol Number 20070820

EudraCT Number: 2008-004752-77

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Date:	28 August 2008

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab, dated 28 August 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 9 May 1997 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 Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Study Phase: 2

Indication: Metastatic colorectal cancer expressing wild type (wt) KRAS and refractory to irinotecan- and oxaliplatin-containing regimens, or refractory to oxaliplatin-containing regimens.

OBJECTIVES

Primary

Part 1:

To determine if acquired resistance to panitumumab therapy in subjects with KRAS wild-type mCRC correlates with emergence of mutant KRAS tumors. (Acquired resistance is defined as disease progression on panitumumab and irinotecan that occurs after a period of disease response or stable disease on treatment with this regimen is observed and radiographically-confirmed.)

Part 2:

To determine if inhibition of the IGF-1R pathway with AMG 479 can overcome resistance to panitumumab therapy, as demonstrated by the objective response rate (ORR) to panitumumab and AMG 479 following disease progression on panitumumab and irinotecan.

Secondary

Part 1:

- To determine ORR and other measures of efficacy (ie, TTR, DOR, PFS, OS) to panitumumab plus irinotecan
- To evaluate the safety of panitumumab and irinotecan

Part 2:

- To determine measures of efficacy (ie, TTR, DOR, PFS, OS) of panitumumab plus AMG 479
- To evaluate the safety of panitumumab and AMG 479

Exploratory

- To evaluate whether mutations of any other tumor genes, including but not limited to Raf and PI3K, predict disease response to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To evaluate whether any baseline subject characteristics, including but not limited to prior treatment history, predict responses to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To determine whether the status of potential tumor biomarkers (eg Raf, PI3K) evolve during tumor progression by comparing the status of biomarkers of the archival primary tumor tissue with that of the tumors biopsied on study

Hypotheses:

The KRAS mutation rate is higher in subjects with acquired resistance to panitumumab therapy than other subjects in mCRC with wt KRAS receiving panitumumab and irinotecan

Study Design:

This is a global, multicenter, open-label phase 2 study designed to evaluate the mechanism(s) of resistance to the anti-EGFR antibody panitumumab given in combination with irinotecan in mCRC subjects with wild-type KRAS tumor status at the time of initial diagnosis.

In Part 1, all subjects will undergo a baseline tumor biopsy and will receive panitumumab with irinotecan. Subjects that respond (complete or partial response ± confirmation) or have stable disease (based on modified RECIST criteria, Appendix F) will continue to receive treatment until radiographically-confirmed disease progression. These subjects will then undergo a second tumor biopsy and blood sampling and then proceed to Part 2 of the study.

Subjects that experience radiographically-confirmed disease progression at the time of first tumor measurement will undergo blood sampling then proceed directly on to Part 2 of the study; tumor biopsy will not be required in these subjects.

In Part 2, all subjects will receive panitumumab with AMG 479.

In both parts of the study, panitumumab and irinotecan (Part 1) and panitumumab and AMG 479 (Part 2) will be administered Q2W until disease progression, intolerability, withdrawal of consent, death, or unless otherwise indicated by the study team.

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

Subjects that end the treatment prior to radiographically-confirmed disease progression will be followed for radiographically-confirmed disease progression at the 30 day safety follow-up visit and then every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Subjects who have discontinued study treatment for any reason but have not withdrawn full consent to participate in the study, will be contacted by telephone or clinical visit every 3 months for overall survival and disease status assessments up to 2 years after the last subject is enrolled in Part 1.

Primary and Secondary Endpoints:

Primary Endpoints:

- Emergence of Mutant KRAS: KRAS mutation status changed from wild-type at baseline to mutant at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab plus irinotecan (Part 1).
- Objective Response Rate (ORR): Confirmed complete or partial response (per modified RECIST) to panitumumab and AMG 479 (Part 2)

Secondary Endpoints:

- Efficacy: ORR (Part 1), Time to Response (TTR), Duration of Response (DOR), Progression-free Survival (PFS), and Overall Survival (OS) (both Part 1 and Part 2)
- Safety: Incidence and severity of adverse events, significant changes in laboratory values, incidence of anti-antibody formation (both Part 1 and Part 2)

Sample Size: Approximately 75 subjects

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

- 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 while on or ≤ 6 months after treatment with irinotecan- and oxaliplatin- or oxaliplatin-based chemotherapy for mCRC
- Radiographic measurement of tumor burden done within 28 days prior to Day 1 (start of treatment with investigational product)
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm using conventional CT or MRI or ≥ 10 mm by spiral CT per modified RECIST. Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to enrollment. All sites of disease must be evaluated
- At least 1 tumor (metastatic lesion or unresected primary tumor) that is amenable to core needle biopsy, as determined by the clinician who will perform the biopsy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E)
- Male or female ≥ 18 years of age at the time of informed consent
- Willing to undergo two core biopsy procedures of tumors (metastasis or unresected primary)

Key Exclusion Criteria

- History of prior or concurrent central nervous system (CNS) metastases
- *Prior treatment with anti-EGFR antibodies (eg, panitumumab, cetuximab) or EGFR small molecule inhibitors (eg, erlotinib, gefitinib)*
- Prior treatment with monoclonal antibodies directed against IGF-1R
- Use of systemic chemotherapy and radiotherapy ≤ 21 days before enrollment
- Use of any antibody therapy (eg, bevacizumab) ≤ 42 days before enrollment
- Use of anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules ≤ 30 days before enrollment
- Known UGT1A1 polymorphisms predisposing to increased irinotecan toxicity
- History of irinotecan intolerance that may interfere with planned treatment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Known positive test(s) for human immunodeficiency virus (HIV) infection, hepatitis C virus, acute or chronic active hepatitis B infection
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)
- Any uncontrolled concurrent illness (eg, infection, bleeding diathesis) or history of any medical condition that may interfere with the interpretation of the study results
- Major surgical procedure ≤ 28 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities.

Investigational Product Dosage and Administration:

Panitumumab (6 mg/kg starting dose) and AMG 479 (12 mg/kg starting dose) will be open-label throughout the study. The total dose of panitumumab and AMG 479 may be rounded up or down by no greater than 10 mg.

The first dose of investigational products will be referred to as study day 1 of week 1. Investigational products will be administered on the same day Q2W (eg, week 1, 3, 5, 7) until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated. The Q2W schedule of all subsequent doses of investigational product will be planned according to study day 1 or within ± 3 days of the planned dose.

In Part 1, the first dose of investigational product (panitumumab) must be administered ≥ 7 days after the first biopsy and ≤ 28 days after the last radiographic measurement of disease burden.

In Part 2, for subjects that undergo the second core biopsy, the first dose of investigational product (panitumumab and AMG 479) must be administered ≥ 7 days after the second biopsy procedure and < 28 days after radiographically-confirmed disease progression. For subjects who do not undergo the second core biopsy procedure, the first dose of investigational product (panitumumab and AMG 479) must be administered ≤ 28 days after radiographically-confirmed disease progression. If the investigational product dosing cannot be done within the time windows specified above, permission to start treatment must be sought from Amgen.

In Part 1, the first infusion of panitumumab will be given over 60 ± 15 minutes. If the first infusion of panitumumab is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions (including all infusions given in Part 2) may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Doses higher than 1000 mg should be diluted to 150 ml in 0.9% sodium chloride solution, USP (saline solution) and infused over 60 to 90 ± 15 minutes.

AMG 479 will be administered by an IV infusion over a 60 ± 15 minute period during the initial dose administration. If the dose administration is well tolerated, subsequent administrations may be made over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, AMG 479 will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Infusion times can be extended to a maximum of 120 min for subjects deemed unable to tolerate the 90 min infusion.

Filtration of diluted AMG 479 is not required.

All subjects should be observed for any adverse reactions during infusions of panitumumab (Part 1) and during panitumumab and AMG 479 infusions and for at least 60 minutes following completion of the first administration of AMG 479 (Part 2). The observation period for subsequent infusions may be reduced at the discretion of the investigator.

Control Group: N/A

Procedures:

Screening for Part 1 will occur within 35 days before enrollment.

Screening for Part 2 will begin on the date of radiographically confirmed disease progression and must be completed within 28 days.

During initial 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) and other biomarker analysis. Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study. 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 such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis will be performed.

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

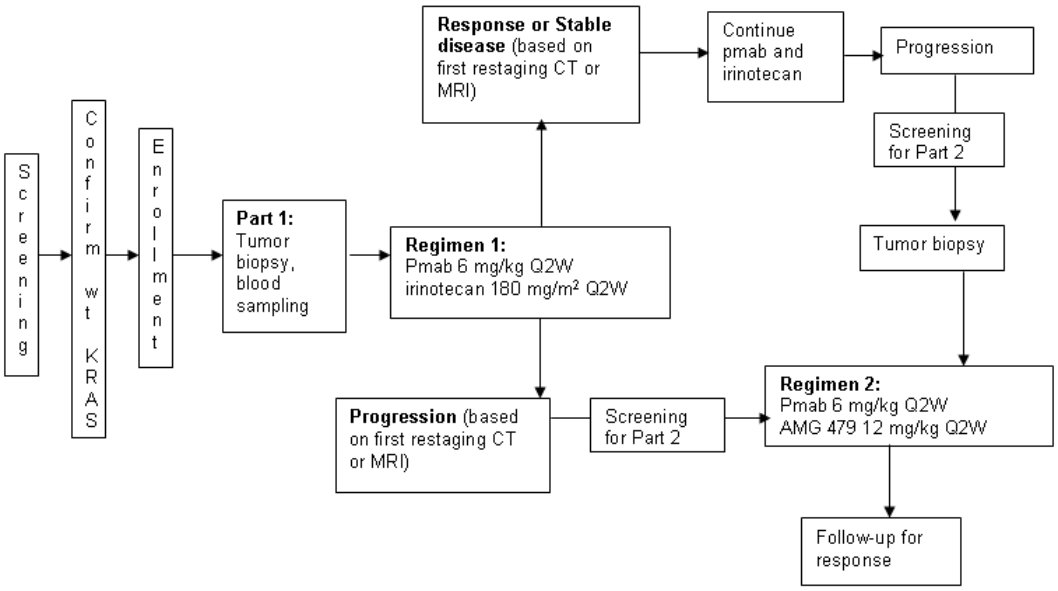
During the study, blood samples will be collected for antibody formation and biomarkers and submitted to the central laboratory. Tumor tissue sampling by core biopsy of a locally advanced or metastatic lesion will also be collected prior to the start of study treatment in Part 1 and in addition, for subjects who initially respond to panitumumab plus irinotecan or have stable disease and subsequently have radiographically-confirmed disease progression, there will be a second biopsy collection prior to start of study treatment in Part 2. These samples will be submitted to the central laboratory.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed every 8 weeks (± 1 week window) until radiographically-confirmed disease progression.

Statistical Considerations:

The primary goal of the statistical analysis is to test whether acquired resistance to panitumumab therapy in mCRC with wt KRAS tumors correlates with emergence of mutant KRAS tumors and to evaluate the efficacy and safety of both panitumumab plus irinotecan and panitumumab plus AMG 479. Summary statistics including confidence intervals will be generated for all efficacy endpoints. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics. One interim analysis is planned for this study. The study is not anticipated to stop early unless a major unexpected safety signal is detected.

Study Design and Treatment Schema



Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Panitumumab / AMG 479

Amgen Protocol Number 20070820

EudraCT Number: 2008-004752-77

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 (EU):	Ines Barbosa Clinical Research Study Manager 1, Sanderson Road Uxbridge Business Park London UB8 1DH Tel: + 44 1895 525516 Fax: + 44 1895 525112
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Date:	28 August 2008
Amendment 1	**01 October 2009**

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab, dated **01 October** 200**9**, 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 9 May 1997 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 Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Study Phase: 2

Indication: Metastatic colorectal cancer expressing wild type (wt) KRAS and refractory to irinotecan- and oxaliplatin-containing regimens, or refractory to oxaliplatin-containing regimens.

OBJECTIVES

Primary

Part 1:

To determine if acquired resistance to panitumumab therapy in subjects with KRAS wild-type mCRC correlates with emergence of mutant KRAS tumors. (Acquired resistance is defined as disease progression on panitumumab and irinotecan that occurs after a period of disease response or stable disease on treatment with this regimen is observed and radiographically-confirmed.)

Part 2:

To determine if inhibition of the IGF-1R pathway with AMG 479 can overcome resistance to panitumumab therapy, as demonstrated by the objective response rate (ORR) to panitumumab and AMG 479 following disease progression on panitumumab and irinotecan.

Secondary

Part 1:

- To determine ORR and other measures of efficacy (ie, TTR, DOR, PFS, OS) to panitumumab plus irinotecan
- To evaluate the safety of panitumumab and irinotecan

Part 2:

- To determine measures of efficacy (ie, TTR, DOR, PFS, OS) of panitumumab plus AMG 479
- To evaluate the safety of panitumumab and AMG 479

Exploratory

- To evaluate whether mutations of any other tumor genes, including but not limited to Raf and PI3K, predict disease response to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To evaluate whether any baseline subject characteristics, including but not limited to prior treatment history, predict responses to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To determine whether the status of potential tumor biomarkers (eg Raf, PI3K) evolve during tumor progression by comparing the status of biomarkers of the archival primary tumor tissue with that of the tumors biopsied on study

Hypotheses:

The KRAS mutation rate is higher in subjects with acquired resistance to panitumumab therapy than other subjects in mCRC with wt KRAS receiving panitumumab and irinotecan.

Study Design:

This is a global, multicenter, open-label phase 2 study designed to evaluate the mechanism(s) of resistance to the anti-EGFR antibody panitumumab given in combination with irinotecan in mCRC subjects **with** wild-type KRAS tumor status.

In Part 1, all subjects will undergo a baseline tumor biopsy and will receive panitumumab with irinotecan. Subjects that respond (complete or partial response ± confirmation) or have stable disease (based on modified RECIST **v1.0** criteria, Appendix F) will continue to receive treatment until radiographically-confirmed disease progression. These subjects will then undergo a second tumor biopsy and blood sampling and then proceed to Part 2 of the study.

Subjects that experience radiographically-confirmed disease progression at the time of first tumor measurement will undergo blood sampling then proceed directly on to Part 2 of the study; tumor biopsy will not be required in these subjects.

In Part 2, all subjects will receive panitumumab with AMG 479.

In both parts of the study, panitumumab and irinotecan (Part 1) and panitumumab and AMG 479 (Part 2) will be administered Q2W until disease progression, intolerability, withdrawal of consent, death, or unless otherwise indicated by the study team.

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

Subjects that end the treatment prior to radiographically-confirmed disease progression will be followed for radiographically-confirmed disease progression at the 30 day safety follow-up visit and then every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Subjects who have discontinued study treatment for any reason but have not withdrawn full consent to participate in the study, will be contacted by telephone or clinical visit every 3 months for overall survival and disease status assessments up to 2 years after the last subject is enrolled in Part **2**.

Primary and Secondary Endpoints:

Primary Endpoints:

- Emergence of Mutant KRAS: KRAS mutation status changed from wild-type at baseline to mutant at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab plus irinotecan (Part 1).
- Objective Response Rate (ORR): Confirmed complete or partial response (per modified RECIST **v1.0**) to panitumumab and AMG 479 (Part 2)

Secondary Endpoints:

- Efficacy: ORR (Part 1), Time to Response (TTR), Duration of Response (DOR), Progression-free Survival (PFS), **On-treatment PFS,** and Overall Survival (OS) (both Part 1 and Part 2)
- Safety: Incidence and severity of adverse events, significant changes in laboratory values, incidence of anti-antibody formation (both Part 1 and Part 2)

Sample Size: Approximately 75 subjects

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- **W**ild-type KRAS tumor status **of archival tumor tissue (preferably from the primary tumor)** 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 while on or ≤ 6 months after treatment with irinotecan- and oxaliplatin- or oxaliplatin-based chemotherapy for mCRC
  - Subjects in whom relapse is diagnosed within 6 months after completing adjuvant chemotherapy (with oxaliplatin containing regimen) will be considered as having failed a prior regimen for metastatic disease
- Radiographic measurement of tumor burden done within 28 days prior to Day 1 (start of treatment with investigational product)
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm using conventional CT or MRI or ≥ 10 mm by spiral CT per modified RECIST **v1.0**. Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to enrollment. All sites of disease must be evaluated
- At least 1 tumor (metastatic lesion or unresected primary tumor) that is amenable to core needle biopsy, as determined by the clinician who will perform the biopsy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E)
- Male or female ≥ 18 years of age at the time of informed consent
- Willing to undergo 2 **serial** core biopsy procedures of tumors (metastasis or unresected primary)

Key Exclusion Criteria

- History of prior or concurrent central nervous system (CNS) metastases
- Prior treatment with anti-EGFR antibodies (eg, panitumumab, cetuximab) or EGFR small molecule inhibitors (eg, erlotinib, gefitinib)
- Prior treatment with monoclonal antibodies directed against IGF-1R **or small molecule inhibitors directed against IGF-1R**
- Use of systemic chemotherapy and radiotherapy ≤ 21 days before enrollment**. Subject must have recovered from acute toxicities related to radiotherapy.**
- Use of any antibody therapy (eg, bevacizumab) ≤ 42 days before enrollment
- Use of anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules ≤ 30 days before enrollment
- Known UGT1A1 polymorphisms predisposing to increased irinotecan toxicity
- History of irinotecan intolerance that may interfere with planned treatment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Known positive test(s) for human immunodeficiency virus (HIV) infection, hepatitis C virus, acute or chronic active hepatitis B infection
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)

- Any uncontrolled concurrent illness (eg, infection, bleeding diathesis) or history of any medical condition that may interfere with the interpretation of the study results
- Major surgical procedure ≤ 28 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. **Core biopsy, central venous catheter placement, fine needle aspiration, thoracentesis, or paracentesis is not considered a major or minor surgical procedure.**

Investigational Product Dosage and Administration:

Panitumumab (6 mg/kg starting dose) and AMG 479 (12 mg/kg starting dose) will be open-label throughout the study. The total dose of panitumumab and AMG 479 may be rounded up or down by no greater than 10 mg.

The first dose of investigational products will be referred to as study day 1 of week 1. Investigational products will be administered on the same day Q2W (eg, week 1, 3, 5, 7) until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated. The Q2W schedule of all subsequent doses of investigational product will be planned according to study day 1 or within ± 3 days of the planned dose.

In Part 1 the subjects will receive panitumumab 6 mg/kg Q2W plus irinotecan 180 mg/m^2 Q2W. The first dose of investigational product (panitumumab) must be administered ≥ 7 days after the first biopsy and ≤ 28 days after enrollment and the most recent radiographic measurement of disease burden. Upon radiographically-confirmed disease progression per modified RECIST v1.0 or clinical progression, subjects will go on to receive panitumumab 6 mg/kg Q2W plus AMG 479 12 mg/kg Q2W (Part 2). Subjects that experience disease control (CR, PR, or SD) followed by the development of acquired resistance and subsequent disease progression during Part 1 of the study will undergo a second core biopsy prior to starting treatment on Part 2. Subjects with primary resistance to panitumumab and irinotecan demonstrating disease progression on the first restaging radiographic scans done on study will proceed directly to Part 2 of the study without undergoing a second core biopsy.

In Part 2, for subjects that undergo the second core biopsy, the first dose of investigational product (panitumumab **6 mg/kg Q2W** and AMG 479 **12 mg/kg Q2W**) must be administered ≥ 7 days after the second biopsy procedure and ≤ 28 days after radiographically-confirmed disease progression. For subjects who do not undergo the second core biopsy procedure, the first dose of investigational product (panitumumab and AMG 479) must be administered ≤ 28 days after radiographically-confirmed disease progression. If the investigational product dosing cannot be done within the time windows specified above, permission to start treatment must be sought from Amgen.

In Part 1, **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**. If the first infusion of panitumumab is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions (including all infusions given in Part 2) may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Doses higher than 1000 mg should be diluted to 150 mL in 0.9% sodium chloride solution, USP (saline solution) and infused over 60 to 90 ± 15 minutes.

AMG 479 will be administered by an IV infusion over a 60 ± 15 minute period during the initial dose administration. If the dose administration is well tolerated, subsequent administrations may be made over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, AMG 479 will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Infusion times can be extended to a maximum of 120 min for subjects deemed unable to tolerate the 90 min infusion.

Filtration of diluted AMG 479 is not required.

All subjects should be observed for any adverse reactions during infusions of panitumumab (Part 1) and during panitumumab and AMG 479 infusions and for at least 60 minutes following completion of the first administration of AMG 479 (Part 2). The observation period for subsequent infusions may be reduced at the discretion of the investigator.

Control Group: N/A

Procedures:

Screening for Part 1 will occur within 35 days before enrollment **(date main informed consent form is signed to date of enrollment)**.

Screening for Part 2 will begin on the date of radiographically confirmed disease progression and must be completed within 28 days.

- **If the KRAS status of tumor tissue from the primary tumor or metastasis for a subject has not previously been determined by an Amgen approved central laboratory or by an experienced laboratory (per local regulatory guidelines) using a validated test method** during initial screening, archived **formalin-fixed** paraffin-embedded tumor tissue block or unstained tumor slides **along with the corresponding pathology report** will be submitted to the central laboratory or **local laboratory** for evaluation of KRAS tumor status (wild-type or mutant).

Regardless of how the 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 report for evaluation of *KRAS* (if applicable), EGFR membrane staining, and other exploratory biomarker analyses (see Section 7.7).

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study. 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 such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis will be performed.

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

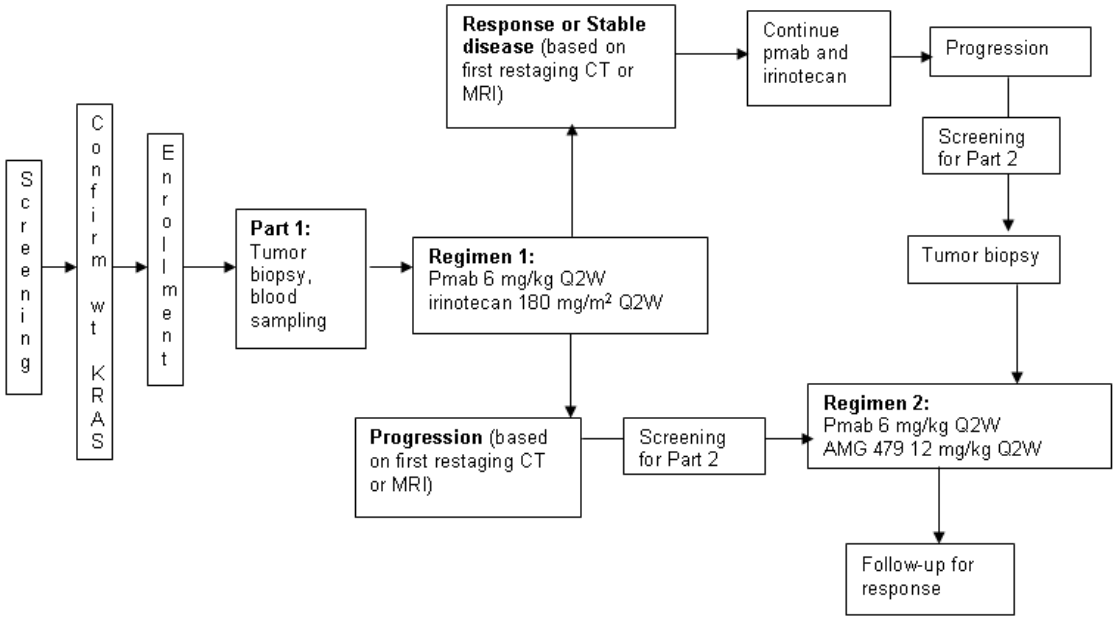
During the study, blood samples will be collected for antibody formation and biomarkers and submitted to the central laboratory. Tumor tissue sampling by core biopsy of a locally advanced or metastatic lesion will be collected prior to the start of study treatment in Part 1. **I**n addition, for subjects who initially respond to panitumumab plus irinotecan or have stable disease and subsequently have radiographically-confirmed disease progression, a second biopsy **will be collected** prior to start of study treatment in Part 2. These samples will be submitted to the central laboratory.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed every 8 weeks (± 1 week window) until radiographically-confirmed disease progression**, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier**.

Statistical Considerations:

The primary goal of the statistical analysis is to test whether acquired resistance to panitumumab therapy in mCRC with wt KRAS tumors correlates with emergence of mutant KRAS tumors and to evaluate the efficacy and safety of both panitumumab plus irinotecan and panitumumab plus AMG 479. Summary statistics including confidence intervals will be generated for all efficacy endpoints. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics. One interim analysis is planned for this study. The study is not anticipated to stop early unless a major unexpected safety signal is detected.

Study Design and Treatment Schema



Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Panitumumab / AMG 479

Amgen Protocol Number 20070820

EudraCT Number: 2008-004752-77

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
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Date:	28 August 2008
Amendment 1	01 October 2009
Amendment 2	**27 May 2011**

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab, dated **27 May 2011**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice 9 May 1997 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 Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Study Phase: 2

Indication: Metastatic colorectal cancer expressing wild type (wt) KRAS and refractory to irinotecan- and oxaliplatin-containing regimens, or refractory to oxaliplatin-containing regimens.

OBJECTIVES

Primary

Part 1:

To determine if acquired resistance to panitumumab therapy in subjects with KRAS wild-type mCRC correlates with emergence of mutant KRAS tumors. (Acquired resistance is defined as disease progression on panitumumab and irinotecan that occurs after a period of disease response or stable disease on treatment with this regimen is observed and radiographically-confirmed.)

Part 2:

To determine if inhibition of the IGF-1R pathway with AMG 479 can overcome resistance to panitumumab therapy, as demonstrated by the objective response rate (ORR) to panitumumab and AMG 479 following disease progression on panitumumab and irinotecan.

Secondary

Part 1:

- To determine ORR and other measures of efficacy (ie, TTR, DOR, PFS, OS) to panitumumab plus irinotecan
- To evaluate the safety of panitumumab and irinotecan

Part 2:

- To determine measures of efficacy (ie, TTR, DOR, PFS, OS) of panitumumab plus AMG 479
- To evaluate the safety of panitumumab and AMG 479

Exploratory

- To evaluate whether mutations of any other tumor genes, including but not limited to Raf and PI3K, predict disease response to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To evaluate whether any baseline subject characteristics, including but not limited to prior treatment history, predict responses to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To determine whether the status of potential tumor biomarkers (eg Raf, PI3K) evolve during tumor progression by comparing the status of biomarkers of the archival primary tumor tissue with that of the tumors biopsied on study

Hypotheses:

The KRAS mutation rate is higher in subjects with acquired resistance to panitumumab therapy than other subjects in mCRC with wt KRAS receiving panitumumab and irinotecan.

Study Design:

This is a global, multicenter, open-label phase 2 study designed to evaluate the mechanism(s) of resistance to the anti-EGFR antibody panitumumab given in combination with irinotecan in mCRC subjects with wild-type KRAS tumor status.

In Part 1, all subjects will undergo a baseline tumor biopsy and will receive panitumumab with irinotecan. Subjects that respond (complete or partial response ± confirmation) or have stable disease (based on modified RECIST v1.0 criteria, Appendix F) will continue to receive treatment until radiographically-confirmed disease progression. These subjects will then undergo a second tumor biopsy and blood sampling and then proceed to Part 2 of the study.

Subjects that experience radiographically-confirmed disease progression at the time of first tumor measurement will undergo blood sampling then proceed directly on to Part 2 of the study; tumor biopsy will not be required in these subjects.

In Part 2, all subjects will receive panitumumab with AMG 479.

In both parts of the study, panitumumab and irinotecan (Part 1) and panitumumab and AMG 479 (Part 2) will be administered Q2W until disease progression, intolerability, withdrawal of consent, death, or unless otherwise indicated by the study team.

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

Subjects that end the treatment prior to radiographically-confirmed disease progression will be followed for radiographically-confirmed disease progression at the 30 day safety follow-up visit and then every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Subjects who have discontinued study treatment for any reason but have not withdrawn full consent to participate in the study, will be contacted by telephone or clinical visit every 3 months **(± 28 days)** for overall survival and disease status assessments up to 2 years after the last subject is enrolled in Part 2.

Primary and Secondary Endpoints:

Primary Endpoints:

- Emergence of Mutant KRAS: KRAS mutation status changed from wild-type at baseline to mutant at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab plus irinotecan (Part 1).
- Objective Response Rate (ORR): Confirmed complete or partial response (per modified RECIST v1.0) to panitumumab and AMG 479 (Part 2)

Secondary Endpoints:

- Efficacy: ORR (Part 1), Time to Response (TTR), Duration of Response (DOR), Progression-free Survival (PFS), and Overall Survival (OS) (both Part 1 and Part 2)
- Safety: Incidence and severity of adverse events, significant changes in laboratory values, incidence of anti-antibody formation (both Part 1 and Part 2)

Sample Size: Approximately 75 subjects

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- Wild-type KRAS tumor status of archival tumor tissue (preferably from the primary tumor) 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 while on or ≤ 6 months after treatment with irinotecan- and oxaliplatin- or oxaliplatin-based chemotherapy for mCRC
    - Subjects in whom relapse is diagnosed within 6 months after completing adjuvant chemotherapy (with oxaliplatin containing regimen) will be considered as having failed a prior regimen for metastatic disease
- Radiographic measurement of tumor burden done within 28 days prior to Day 1 (start of treatment with investigational product)
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm using conventional CT or MRI or ≥ 10 mm by spiral CT per modified RECIST v1.0. Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to enrollment. All sites of disease must be evaluated
- At least 1 tumor (metastatic lesion or unresected primary tumor) that is amenable to core needle biopsy, as determined by the clinician who will perform the biopsy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E)
- Male or female ≥ 18 years of age at the time of informed consent
- Willing to undergo two serial core biopsy procedures of tumors (metastasis or unresected primary)

Key Exclusion Criteria

- History of prior or concurrent central nervous system (CNS) metastases
- Prior treatment with anti-EGFR antibodies (eg, panitumumab, cetuximab) or EGFR small molecule inhibitors (eg, erlotinib, gefitinib)
- Prior treatment with monoclonal antibodies directed against IGF-1R or small molecule inhibitors directed against IGF-1R
- Use of systemic chemotherapy and radiotherapy ≤ 21 days before enrollment. Subject must have recovered from acute toxicities related to radiotherapy.
- Use of any antibody therapy (eg, bevacizumab) ≤ 42 days before enrollment
- Use of anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules ≤ 30 days before enrollment
- Known UGT1A1 polymorphisms predisposing to increased irinotecan toxicity
- History of irinotecan intolerance that may interfere with planned treatment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Known positive test(s) for human immunodeficiency virus (HIV) infection, hepatitis C virus, acute or chronic active hepatitis B infection
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)

- Any uncontrolled concurrent illness (eg, infection, bleeding diathesis) or history of any medical condition that may interfere with the interpretation of the study results
- Major surgical procedure ≤ 28 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Core biopsy, central venous catheter placement, fine needle aspiration, thoracentesis, or paracentesis is not considered a major or minor surgical procedure.

Investigational Product Dosage and Administration:

Panitumumab (6 mg/kg starting dose) and AMG 479 (12 mg/kg starting dose) will be open-label throughout the study. The total dose of panitumumab and AMG 479 may be rounded up or down by no greater than 10 mg.

The first dose of investigational products will be referred to as study day 1 of week 1. Investigational products will be administered on the same day Q2W (eg, week 1, 3, 5, 7) until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated. The Q2W schedule of all subsequent doses of investigational product will be planned according to study day 1 or within ± 3 days of the planned dose.

In Part 1 the subjects will receive panitumumab 6 mg/kg Q2W plus irinotecan 180 mg/m^2 Q2W. The first dose of investigational product (panitumumab) must be administered ≥ 7 days after the first biopsy and ≤ 28 days after enrollment and the most recent radiographic measurement of disease burden. Upon radiographically-confirmed disease progression per modified RECIST v1.0 or clinical progression, subjects will go on to receive panitumumab 6 mg/kg Q2W plus AMG 479 12 mg/kg Q2W (Part 2). Subjects that experience disease control (CR, PR, or SD) followed by the development of acquired resistance and subsequent disease progression during Part 1 of the study will undergo a second core biopsy prior to starting treatment on Part 2. Subjects with primary resistance to panitumumab and irinotecan demonstrating disease progression on the first restaging radiographic scans done on study will proceed directly to Part 2 of the study without undergoing a second core biopsy.

In Part 2, for subjects that undergo the second core biopsy, the first dose of investigational product (panitumumab 6 mg/kg Q2W and AMG 479 12 mg/kg Q2W) must be administered ≥ 7 days after the second biopsy procedure and ≤ 28 days after radiographically-confirmed disease progression. For subjects who do not undergo the second core biopsy procedure, the first dose of investigational product (panitumumab and AMG 479) must be administered ≤ 28 days after radiographically-confirmed disease progression. If the investigational product dosing cannot be done within the time windows specified above, permission to start treatment must be sought from Amgen.

In Part 1, 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. If the first infusion of panitumumab is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions (including all infusions given in Part 2) may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Doses higher than 1000 mg should be diluted to 150 mL in 0.9% sodium chloride solution, USP (saline solution) and infused over 60 to 90 ± 15 minutes.

AMG 479 will be administered by an IV infusion **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** over a 60 ± 15 minute period during the initial dose administration. If the dose administration is well tolerated, subsequent administrations may be made over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, AMG 479 will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Infusion times can be extended to a maximum of 120 minutes for subjects deemed unable to tolerate the 90 minutes infusion.

All subjects should be observed for any adverse reactions during infusions of panitumumab (Part 1) and during panitumumab and AMG 479 infusions and for at least 60 minutes following completion of the first administration of AMG 479 (Part 2). The observation period for subsequent infusions may be reduced at the discretion of the investigator.

Control Group: N/A

Procedures:

Screening for Part 1 will occur within 35 days before enrollment (date main informed consent form is signed to date of enrollment).

Screening for Part 2 will begin on the date of radiographically confirmed disease progression and must be completed within 28 days.

- If the KRAS status of tumor tissue from the primary tumor or metastasis for a subject has not previously been determined by an Amgen approved central laboratory or by an experienced laboratory (per local regulatory guidelines) using a validated test method during initial screening, archived formalin-fixed paraffin-embedded tumor tissue block or unstained tumor slides along with the corresponding pathology report will be submitted to the central laboratory or local laboratory for evaluation of KRAS tumor status (wild-type or mutant).

Regardless of how the 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 report for evaluation of *KRAS* (if applicable), EGFR membrane staining, and other exploratory biomarker analyses (see Section 7.7).

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study. 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 such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis will be performed.

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA), glycosylated hemoglobin (HgbA1c), 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 and biomarkers and submitted to the central laboratory. Tumor tissue sampling by core biopsy of a locally advanced or metastatic lesion will be collected prior to the start of study treatment in Part 1. In addition, for subjects who initially respond to panitumumab plus irinotecan or have stable disease and subsequently have radiographically-confirmed disease progression, a second biopsy will be collected prior to start of study treatment in Part 2. These samples will be submitted to the central laboratory.

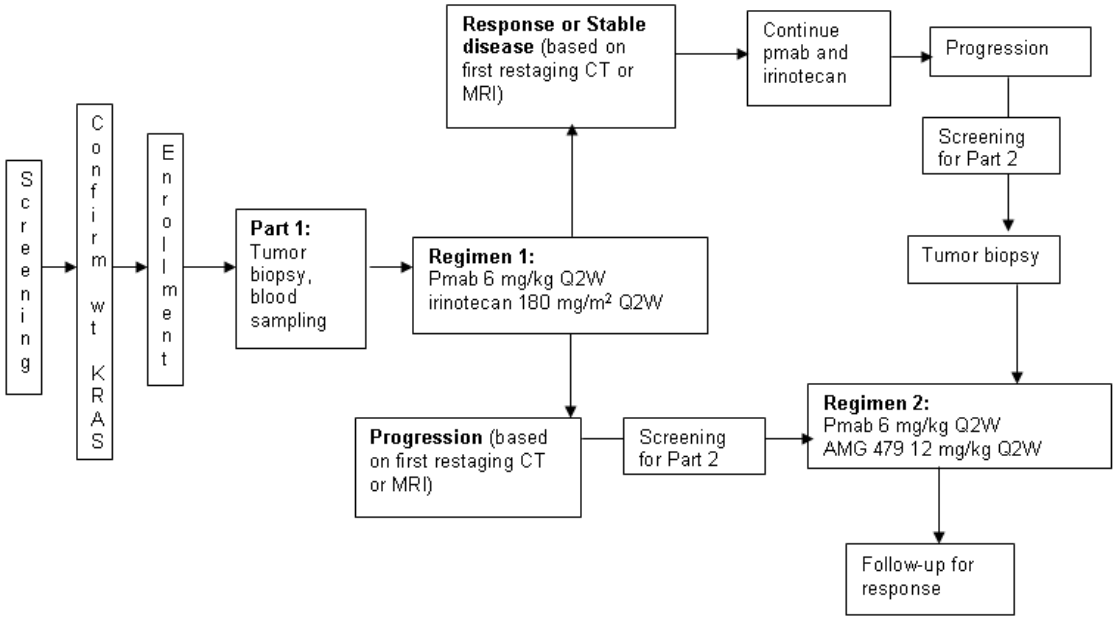
During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Statistical Considerations:

The primary goal of the statistical analysis is to test whether acquired resistance to panitumumab therapy in mCRC with wt KRAS tumors correlates with emergence of mutant KRAS tumors and to evaluate the efficacy and safety of both panitumumab plus irinotecan and panitumumab plus AMG 479. Summary statistics including confidence intervals will be generated for all efficacy endpoints. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics. One interim analysis is planned for this study. The study is not anticipated to stop early unless a major unexpected safety signal is detected.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



Title: A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Panitumumab / AMG 479

Amgen Protocol Number 20070820

EudraCT Number: 2008-004752-77

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 (EU):	**Lis Mable** Clinical Research Study Manager **240 Cambridge Science Park** **Milton Road** **Cambridge, CB4 0WD** **United Kingdom** Tel: **+ 44 1223 436719** Fax: **+ 44 1223 420319**
Key Sponsor Contact (US & EU):	**Roger Sidhu, MD, FRCPC** **Clinical Research Medical Director** 1 Amgen Center Dr. Mailstop **38-2-A** Thousand Oaks, CA 91320 Tel: + 1 805-447-**5857** Fax: +1 805-**480-4978**
Date:	28 August 2008
Amendment 1	01 October 2009
Amendment 2	27 May 2011
Amendment 3	**14 November 2012**

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab, dated **14 November 2012**, and agree to abide by all provisions set forth therein.

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- me (including, if applicable, my spouse [or legal partner] and dependent children)
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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 Date (DD Month YYYY)

Protocol Synopsis

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Study Phase: 2

Indication: Metastatic colorectal cancer expressing wild type (wt) KRAS and refractory to irinotecan- and oxaliplatin-containing regimens, or refractory to oxaliplatin-containing regimens.

OBJECTIVES

Primary

Part 1:

To determine if acquired resistance to panitumumab therapy in subjects with KRAS wild-type mCRC correlates with emergence of mutant KRAS tumors. (Acquired resistance is defined as disease progression on panitumumab and irinotecan that occurs after a period of disease response or stable disease on treatment with this regimen is observed and radiographically-confirmed.)

Part 2:

To determine if inhibition of the IGF-1R pathway with AMG 479 can overcome resistance to panitumumab therapy, as demonstrated by the objective response rate (ORR) to panitumumab and AMG 479 following disease progression on panitumumab and irinotecan.

Secondary

Part 1:

- To determine ORR and other measures of efficacy (ie, TTR, DOR, PFS, OS) to panitumumab plus irinotecan
- To evaluate the safety of panitumumab and irinotecan

Part 2:

- To determine measures of efficacy (ie, TTR, DOR, PFS, OS) of panitumumab plus AMG 479
- To evaluate the safety of panitumumab and AMG 479

Exploratory

- To evaluate whether mutations of any other tumor genes, including but not limited to Raf and PI3K, predict disease response to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To evaluate whether any baseline subject characteristics, including but not limited to prior treatment history, predict responses to panitumumab and irinotecan (Part 1) or panitumumab and AMG 479 (Part 2)
- To determine whether the status of potential tumor biomarkers (eg Raf, PI3K) evolve during tumor progression by comparing the status of biomarkers of the archival primary tumor tissue with that of the tumors biopsied on study

Hypotheses:

The KRAS mutation rate is higher in subjects with acquired resistance to panitumumab therapy than other subjects in mCRC with wt KRAS receiving panitumumab and irinotecan.

Study Design:

This is a global, multicenter, open-label phase 2 study designed to evaluate the mechanism(s) of resistance to the anti-EGFR antibody panitumumab given in combination with irinotecan in mCRC subjects with wild-type KRAS tumor status.

In Part 1, all subjects will undergo a baseline tumor biopsy and will receive panitumumab with irinotecan. Subjects that respond (complete or partial response ± confirmation) or have stable disease (based on modified RECIST v1.0 criteria, Appendix F) will continue to receive treatment until radiographically-confirmed disease progression. These subjects will then undergo a second tumor biopsy and blood sampling and then proceed to Part 2 of the study.

Subjects that experience radiographically-confirmed disease progression at the time of first tumor measurement will undergo blood sampling then proceed directly on to Part 2 of the study; tumor biopsy will not be required in these subjects.

In Part 2, all subjects will receive panitumumab with AMG 479.

In both parts of the study, panitumumab and irinotecan (Part 1) and panitumumab and AMG 479 (Part 2) will be administered Q2W until disease progression, intolerability, withdrawal of consent, death, or unless otherwise indicated by the study team.

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

Subjects that end the treatment prior to radiographically-confirmed disease progression will be followed for radiographically-confirmed disease progression at the 30 day safety follow-up visit and then every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Subjects who have discontinued study treatment for any reason but have not withdrawn full consent to participate in the study, will be contacted by telephone or clinical visit every 3 months (± 28 days) for overall survival and disease status assessments up to 2 years **(± 2 months)** after the last subject is enrolled in **Part 1**.

Primary and Secondary Endpoints:

Primary Endpoints:

- Emergence of Mutant KRAS: KRAS mutation status changed from wild-type at baseline to mutant at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab plus irinotecan (Part 1).
- Objective Response Rate (ORR): Confirmed complete or partial response (per modified RECIST v1.0) to panitumumab and AMG 479 (Part 2)

Secondary Endpoints:

- Efficacy: ORR (Part 1), Time to Response (TTR), Duration of Response (DOR), Progression-free Survival (PFS), and Overall Survival (OS) (both Part 1 and Part 2)
- Safety: Incidence and severity of adverse events, significant changes in laboratory values, incidence of anti-antibody formation (both Part 1 and Part 2)

Sample Size: Approximately 75 subjects

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum
- Wild-type KRAS tumor status of archival tumor tissue (preferably from the primary tumor) 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 while on or ≤ 6 months after treatment with irinotecan- and oxaliplatin- or oxaliplatin-based chemotherapy for mCRC
  - Subjects in whom relapse is diagnosed within 6 months after completing adjuvant chemotherapy (with oxaliplatin containing regimen) will be considered as having failed a prior regimen for metastatic disease
- Radiographic measurement of tumor burden done within 28 days prior to Day 1 (start of treatment with investigational product)
- At least 1 uni-dimensionally measurable lesion ≥ 20 mm using conventional CT or MRI or ≥ 10 mm by spiral CT per modified RECIST v1.0. Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to enrollment. All sites of disease must be evaluated
- At least 1 tumor (metastatic lesion or unresected primary tumor) that is amenable to core needle biopsy, as determined by the clinician who will perform the biopsy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E)
- Male or female ≥ 18 years of age at the time of informed consent
- Willing to undergo two serial core biopsy procedures of tumors (metastasis or unresected primary)

Key Exclusion Criteria

- History of prior or concurrent central nervous system (CNS) metastases
- Prior treatment with anti-EGFR antibodies (eg, panitumumab, cetuximab) or EGFR small molecule inhibitors (eg, erlotinib, gefitinib)
- Prior treatment with monoclonal antibodies directed against IGF-1R or small molecule inhibitors directed against IGF-1R
- Use of systemic chemotherapy and radiotherapy ≤ 21 days before enrollment. Subject must have recovered from acute toxicities related to radiotherapy.
- Use of any antibody therapy (eg, bevacizumab) ≤ 42 days before enrollment
- Use of anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules ≤ 30 days before enrollment
- Known UGT1A1 polymorphisms predisposing to increased irinotecan toxicity
- History of irinotecan intolerance that may interfere with planned treatment
- History of interstitial lung disease (eg, pneumonitis, pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest computerized tomography (CT) scan
- Known positive test(s) for human immunodeficiency virus (HIV) infection, hepatitis C virus, acute or chronic active hepatitis B infection
- Any co-morbid disease or condition that could increase the risk of toxicity (eg, significant ascites, significant pleural effusion)

- Any uncontrolled concurrent illness (eg, infection, bleeding diathesis) or history of any medical condition that may interfere with the interpretation of the study results
- Major surgical procedure ≤ 28 days before enrollment or minor surgical procedure ≤ 14 days before enrollment. Subjects must have recovered from surgery related toxicities. Core biopsy, central venous catheter placement, fine needle aspiration, thoracentesis, or paracentesis is not considered a major or minor surgical procedure.

Investigational Product Dosage and Administration:

Panitumumab (6 mg/kg starting dose) and AMG 479 (12 mg/kg starting dose) will be open-label throughout the study. The total dose of panitumumab and AMG 479 may be rounded up or down by no greater than 10 mg.

The first dose of investigational products will be referred to as study day 1 of week 1. Investigational products will be administered on the same day Q2W (eg, week 1, 3, 5, 7) until progressive disease, intolerability, withdrawal, death, or unless otherwise indicated. The Q2W schedule of all subsequent doses of investigational product will be planned according to study day 1 or within ± 3 days of the planned dose.

In Part 1 the subjects will receive panitumumab 6 mg/kg Q2W plus irinotecan 180 mg/m^2 Q2W. The first dose of investigational product (panitumumab) must be administered ≥ 7 days after the first biopsy and ≤ 28 days after enrollment and the most recent radiographic measurement of disease burden. Upon radiographically-confirmed disease progression per modified RECIST v1.0 or clinical progression, subjects will go on to receive panitumumab 6 mg/kg Q2W plus AMG 479 12 mg/kg Q2W (Part 2). Subjects that experience disease control (CR, PR, or SD) followed by the development of acquired resistance and subsequent disease progression during Part 1 of the study will undergo a second core biopsy prior to starting treatment on Part 2. Subjects with primary resistance to panitumumab and irinotecan demonstrating disease progression on the first restaging radiographic scans done on study will proceed directly to Part 2 of the study without undergoing a second core biopsy.

In Part 2, for subjects that undergo the second core biopsy, the first dose of investigational product (panitumumab 6 mg/kg Q2W and AMG 479 12 mg/kg Q2W) must be administered ≥ 7 days after the second biopsy procedure and ≤ 28 days after radiographically-confirmed disease progression. For subjects who do not undergo the second core biopsy procedure, the first dose of investigational product (panitumumab and AMG 479) must be administered ≤ 28 days after radiographically-confirmed disease progression. If the investigational product dosing cannot be done within the time windows specified above, permission to start treatment must be sought from Amgen.

In Part 1, 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. If the first infusion of panitumumab is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions (including all infusions given in Part 2) may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Doses higher than 1000 mg should be diluted to 150 mL in 0.9% sodium chloride solution, USP (saline solution) and infused over 60 to 90 ± 15 minutes.

AMG 479 will be administered by an IV infusion 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 over a 60 ± 15 minute period during the initial dose administration. If the dose administration is well tolerated, subsequent administrations may be made over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, AMG 479 will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. Infusion times can be extended to a maximum of 120 minutes for subjects deemed unable to tolerate the 90 minutes infusion.

All subjects should be observed for any adverse reactions during infusions of panitumumab (Part 1) and during panitumumab and AMG 479 infusions and for at least 60 minutes following completion of the first administration of AMG 479 (Part 2). The observation period for subsequent infusions may be reduced at the discretion of the investigator.

Control Group: N/A

Procedures:

Screening for Part 1 will occur within 35 days before enrollment (date main informed consent form is signed to date of enrollment).

Screening for Part 2 will begin on the date of radiographically confirmed disease progression and must be completed within 28 days.

- If the KRAS status of tumor tissue from the primary tumor or metastasis for a subject has not previously been determined by an Amgen approved central laboratory or by an experienced laboratory (per local regulatory guidelines) using a validated test method during initial screening, archived formalin-fixed paraffin-embedded tumor tissue block or unstained tumor slides along with the corresponding pathology report will be submitted to the central laboratory or local laboratory for evaluation of KRAS tumor status (wild-type or mutant).

Regardless of how the 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 report for evaluation of *KRAS* (if applicable), EGFR membrane staining, and other exploratory biomarker analyses (see Section 7.7).

Only subjects with confirmed wild-type KRAS tumor status will be eligible for this study. 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 such as physical exam, vital signs, ECOG, ECG (screening only), and CT or MRI scans of the chest, abdomen, and pelvis will be performed.

Screening and on-study local laboratory tests will be performed including hematology, chemistry, carcinoembryonic antigen (CEA), glycosylated hemoglobin (HgbA1c), 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 and biomarkers and submitted to the central laboratory. Tumor tissue sampling by core biopsy of a locally advanced or metastatic lesion will be collected prior to the start of study treatment in Part 1. In addition, for subjects who initially respond to panitumumab plus irinotecan or have stable disease and subsequently have radiographically-confirmed disease progression, a second biopsy will be collected prior to start of study treatment in Part 2. These samples will be submitted to the central laboratory.

During the study, CT or MRI scans of the chest, abdomen, pelvis and all other sites of disease will be performed every 8 weeks (± 1 week window) until radiographically-confirmed disease progression, start of new cancer treatment, death, withdrawal of consent or at the end of the study, whichever is earlier.

Refer to Sections 7.4 and 7.5 for study procedures during the 30-day safety follow-up visit and the long-term follow-up visit, respectively. Refer to Section 7.8 for study procedures following the completion of all planned study analyses.

Statistical Considerations:

The primary goal of the statistical analysis is to test whether acquired resistance to panitumumab therapy in mCRC with wt KRAS tumors correlates with emergence of mutant KRAS tumors and to evaluate the efficacy and safety of both panitumumab plus irinotecan and panitumumab plus AMG 479. Summary statistics including confidence intervals will be generated for all efficacy endpoints. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics. One interim analysis is planned for this study. The study is not anticipated to stop early unless a major unexpected safety signal is detected.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema