



Protocol Abstract Page

Phase II Study of Panitumumab in KRAS Wild-type Locally Advanced or Metastatic Adenocarcinoma of the Small Bowel or Ampulla of Vater. 2009-0458

Core Protocol Information

Study Chairman:	Michael Overman
Department:	Gastrointestinal Medical Oncology
Phone:	713-745-4317
Unit:	0426
Full Title:	Phase II Study of Panitumumab in KRAS Wild-type Locally Advanced or Metastatic Adenocarcinoma of the Small Bowel or Ampulla of Vater.
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 04/26/2016
Version:	16
Document Status:	Final

Abstract

Objectives:

Primary

To determine the response rate (RR) for patients with Kirsten rat sarcoma (KRAS) wild-type locally advanced or metastatic adenocarcinoma of the small bowel or ampulla of Vater treated with panitumumab.

Secondary

- 1) To determine the overall progression-free survival (PFS) for panitumumab.
- 2) To determine overall PFS for panitumumab in the subset of patients with metastatic disease only.
- 3) To determine the overall survival (OS) panitumumab.
- 4) To determine the OS for panitumumab in the subset of patients with metastatic disease only.
- 5) To determine the toxicity of panitumumab.

Rationale: (Be as concise as possible)

Adenocarcinoma of the small bowel is a rare cancer that has many molecular, genetic, and epidemiological similarities with adenocarcinoma of the large bowel. In particular both cancers demonstrate an identical frequency and pattern of mutations in the KRAS oncogene. The use of anti-epidermal growth factor receptor (anti-EGFR) antibodies, such as panitumumab, has demonstrated clear anti-cancer activity in the treatment of

adenocarcinoma of the colorectum. Recently, the benefit with anti-EGFR therapy in the treatment of colorectal adenocarcinoma has been shown to be limited to the subset of patients who have a wild-type KRAS gene. Given the similarities between adenocarcinoma of the small and large bowel, we feel that the lack of activity of panitumumab in mutant KRAS colorectal cancer patients, supports the selection of only small bowel adenocarcinoma patients with a wild-type KRAS oncogene for treatment with CAPOX and panitumumab. Thus, the selection of only wild-type KRAS patients will serve as a molecular enrichment of patients who have the greatest chance of benefit from the addition of panitumumab to CAPOX chemotherapy.

Based upon retrospective studies and two prospective studies that have been conducted in this tumor type, the general combination of a fluorinated pyrimidine and a platinum compound such as CAPOX or FOLFOX represents the current standard of care approach for adenocarcinoma of the small bowel and ampulla of Vater.

We have recently completed a phase II study of capecitabine combined with oxaliplatin, CAPOX, in the treatment of SBA and AAC. This single institution study conducted at M.D. Anderson Cancer Center enrolled 31 patients with metastatic or unresectable disease. The overall response rate was 52%.

The combination of CAPOX chemotherapy with the anti-EGFR antibody cetuximab has been explored in two phase II studies. Panitumumab is an anti-EGFR monoclonal antibody of the IgG2 isotype that was approved by the US Food and Drug Administration (FDA) in September of 2006 for the treatment of EGFR-expressing colorectal cancers with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Thus, given these known facts, we hypothesize that the addition of panitumumab to CAPOX chemotherapy in KRAS wild-type patients will result in improved anti-cancer activity and improved outcomes for patients with unresectable or metastatic adenocarcinoma of the small bowel and ampulla of Vater. We now propose a study to test this hypothesis by evaluating the addition of panitumumab to the standard of care chemotherapy treatment, CAPOX, for locally advanced or metastatic Small bowel adenocarcinoma (SBA) and ampullary adenocarcinoma (AAC).

Updated Background Data on Anti-EGFR Therapy Combined with Oxaliplatin and Rationale for Study Design Change as of October 1, 2012.

Since the initiation of this study further results regarding the combination of oxaliplatin and capecitabine therapy and anti-EGFR therapy have been presented and published in both metastatic colorectal cancer and metastatic esophagogastric cancer. The overall summation of this data is that anti-EGFR therapy when combined with capecitabine and oxaliplatin has not provided any added benefit. Anti-EGFR in combination with other chemotherapy and as a single-agent has shown marked activity in colorectal cancer and thus it appears that an antagonistic interaction between oxaliplatin and capecitabine and anti-EGFR therapy may be occurring. We are thus providing an amendment to alter this study in the interest of both the outcome for patients and patient safety. As a single agent panitumumab continues to represent a scientifically sound and interesting anti-cancer agent to explore in small bowel adenocarcinoma and ampullary adenocarcinoma, and thus this study will no longer explore combination therapy but will explore panitumumab as a single-agent in refractory disease.

Eligibility: (List All Criteria)

Inclusion:

- 1) Patients must have histologically confirmed adenocarcinoma of the small bowel or ampulla of Vater that is either unresectable or metastatic.
- 2) Adequate tumor tissue available for KRAS mutational analysis or known KRAS wild-type status.
- 3) Prior progression on or intolerance to treatment with a fluoropyrimidine and oxaliplatin. Recurrence of disease within 6 months from the completion of adjuvant therapy with both a fluoropyrimidine and oxaliplatin is considered progression.
- 4) Patients must have measurable disease as per the revised Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Version 1.1).
- 5) If radiation was previously received, the measurable disease must be outside the previous radiation field, unless this area has demonstrated evidence of radiographic growth.
- 6) A minimum of 2 weeks must have elapsed from completion of any prior chemotherapy or radiotherapy or surgery and the start date of study therapy.
- 7) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 - 2.
- 8) Adequate organ function including: a) Absolute neutrophil count (ANC) $\geq 1,000/\mu\text{L}$; b) Platelets $\geq 75,000/\mu\text{L}$; c) Total bilirubin $\leq 1.5 \times \text{ULN}$; in patients with known Gilbert's syndrome direct bilirubin $\leq 1.5 \times \text{ULN}$ will be used as organ function criteria, instead of total bilirubin; d) AST (SGOT)/ALT (SGPT) $< 3 \times \text{ULN}$; e) Creatinine $< 2 \times \text{ULN}$.
- 9) Negative urine or serum pregnancy test in women with childbearing potential (defined as not post-menopausal for 12 months or no previous surgical sterilization), within one week prior to initiation of treatment.
- 10) The effects of panitumumab on the developing fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of

birth control) prior to study entry, for the duration of study participation, and for six months following the completion of therapy. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately.

11) Patients must sign an Informed Consent and Authorization indicating that they are aware of the investigational nature of this study and the known risks involved.

12) Magnesium level \geq lower limit of normal.

Exclusion:

1) Prior anti-epidermal growth factor receptor antibody therapy (eg. panitumumab or cetuximab) or prior small molecule anti-epidermal growth factor receptor therapy (eg. erlotinib) for adenocarcinoma of the small bowel or ampulla of Vater.

2) Patients may not be receiving any other investigational agents nor have received any investigational drug 30 days prior to enrollment.

3) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit adherence with study requirements.

4) Interstitial pneumonia or extensive and symptomatic interstitial fibrosis of the lung.

5) Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with panitumumab, breast feeding must be discontinued.

6) Age <18 years. Because no dosing or adverse event data are currently available on the use of panitumumab in patients <18 years of age, children are excluded from this study.

Is there an age limit? Yes

Why? Provide scientific justification:

18 years or older. Because no dosing or adverse event data are currently available on the use of CAPOX and panitumumab in the pediatric age group.

Disease Group:

Gastrointestinal

Treatment Agents/Devices/Interventions:

Capecitabine, Oxaliplatin, Panitumumab

Proposed Treatment/Study Plan:

This is a single-center, open-label, single-arm phase II study. Patients who enroll will have tumors tested for the presence of activating mutations in codons 12 or 13, or at codon 61 (if tested) of the KRAS oncogene. Only patients who have wild-type KRAS gene sequences at these codons will be eligible to undergo study treatment with panitumumab.

Panitumumab will be administered at 9 mg/kg given over approximately a 60-minute

infusion through a peripheral or central catheter on Day 1 of a two-week cycle. For doses >1000 mg the infusion time should be increased to 90 minutes. The panitumumab being administered in this study is not a commercially marketed product. Although it is expected to be very similar in safety and activity to the commercially marketed drug, it is possible that some differences may exist. Because this is not a commercially marketed drug, panitumumab can only be administered to patients enrolled in this clinical trial and may only be administered under the direction of physicians who are investigators in this clinical trial.

Study Calendar

Evaluation or Procedure	Screening		Study Treatment	End of Treatment Evaluation ¹²	30-day Post-Treatment Evaluation ¹³ /Long Term Follow-up
	KRAS Testing	Additional Evaluations/ Testing ²			
			On or before Day 1 of each cycle		
Informed consent	X ¹				
Medical History		X			
Physical Examination		X	X ^{3,4}	X	
Inclusion/Exclusion criteria		X			
Weight		X	X ⁴	X	
ECOG Performance Status		X	X ^{3,4}	X	
Hematology ¹¹		X	X ^{3,4}	X	
Biochemistry ¹¹		X	X ^{3,4}	X	
Urine or serum pregnancy test (for females of child-bearing potential)		X			
ECG		X			
Archival Tumor Tissue for KRAS mutational testing or known KRAS wildtype	X ²				
Optional Collection of Additional Archival Tumor Tissue for Future Research	X ²				
Toxicity assessment		X	X ^{3,5}	X	X ⁹
Concomitant Medications		X	X		
Diagnostic Imaging for Tumor Assessment ⁸		X	Restaging every 4 cycles ⁶	X ^{6,7}	
Survival					X ¹⁰

1 Informed consent must be obtained before any evaluations on this study to occur.

2 Only patients who have wild-type KRAS gene sequences at codons 12 or 13, or at codon 61 if it is tested, will be eligible. Testing may be performed at MD Anderson Cancer Center or an outside CLIA-certified laboratory. For testing at MD Anderson Cancer Center five unstained slides or a paraffin embedded tumor block are required. Tissue may be requested up to 6 weeks prior to first day of study treatment. In consenting patients, additional archival tissue may be collected at the same time for use in future research. Diagnostic imaging studies must be completed within 28 days prior to first day of study treatment. Hematologic, biochemistry, and serum pregnancy (if applicable) testing must be performed within 7 days prior to first dose of study drug. All other baseline evaluations must be completed within 10 days prior to first dose of study drug.

- 3 For Cycle 1, baseline evaluations will suffice if performed within 7 days prior to first dose of study drug.
- 4 Within 72 hours prior to start of the cycle (except for Cycle 1 as noted above).
- 5 Patient will be instructed to report any adverse events to the research nurse at least once weekly (+/- 1 day).
- 6 Imaging should be obtained every 4 cycles (+/- 1 week allowance is made for scheduling). After a tumor evaluation is performed which demonstrates a tumor response (partial or complete), confirmation of the response may be obtained by a second evaluation to be performed 3 cycles later.
- 7 For patients taken off study treatment for reasons other than progression, perform every 12 weeks (+/- 2 week allowance is made for scheduling) after the End of Treatment Evaluation visit until documentation of progression if no other anti-cancer treatment is given.
- 8 CT scans or other imaging modality. MRI may be used in cases where it is felt to be unsafe to perform CT secondary to patient's history of dye allergy, or if the tumor is not adequately seen on CT for the purposes of this study.
- 9 Treatment-related adverse events occurring during study treatment or within 30 days after the last administration of study drug(s) will be followed until resolution or stabilization. If the patient is unable or unwilling to return to M. D. Anderson for this assessment, the patient will be contacted by phone for this assessment.
- 10 Every 3 months (+/- 2 weeks) from Post-Treatment Evaluation.
- 11 Hematology: hemoglobin, platelets, and absolute neutrophil count. Chemistry: creatinine, total bilirubin, AST, ALT, Magnesium, Potassium, Calcium. In patients with known Gilbert's syndrome direct bilirubin will also be performed
- 12 At time of or up to 10 days after decision to discontinue study treatment.
13. Up to 35 days from last dose of study medication.

Statistical Considerations:

Study design and Sample Size:

Amended Study Design, Sample Size, Efficacy and Toxicity Monitoring as of October 1, 2012:

The primary endpoint of this phase II, single arm study is response rate (RR) for patients treated with single-agent Panitumumab. Patients will be evaluated for up to 8 cycles from their first dose, and a patient will be considered as a non-responder if no PR or CR has been documented after 8 cycles of treatment. Patients who withdraw early will be included in the ITT analysis. Based on our current data with a null hypothesis of $\leq 1\%$ RR to an inactive drug for refractory patients, a sample size of 17 patients with Panitumumab would be required to demonstrate a response rate of 17% using a binomial one-sample test with a two-sided alpha of 0.05 and power of 90%.

The primary adverse event to be monitored will be the toxicity rate. Toxicities to be included in toxicity monitoring include definite or probably treatment-related grade 3 or 4 non-hematological toxicities, excluding grade 3 rash and grade 3 hypomagnesemia, which are both expected and manageable toxicities. Only toxicities during the first 4 cycles of therapy will be used in toxicity monitoring. Accrual is estimated at 1 to 2 patients per month.

Sample Size and Endpoint Monitoring

Response and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998). Data from a previous study of single agent Panitumumab in Kras wildtype colorectal cancer demonstrated a response rate for Panitumumab is approximately 17%. The toxicity rate of Panitumumab will estimate it will be approximately 25%. For the prior distribution of standard Panitumumab, we assumed a simple Dirichlet distribution and independence between OR and toxicity in 124 patients. The parameters for this prior distribution are as follows:

Dirichlet parameters for the joint prior distribution of objective response and toxicity rate assuming information on 124 patients and independence among response and toxicity for Panitumumab.

	No Response	Response
No Toxicity	77	16
Toxicity	26	5

A flat Dirichlet prior distribution for experimental Panitumumab was chosen reflective of information from the equivalent of 4 patients with the same marginal distributions as for Panitumumab (e.g., RR rate of 17% and toxicity rate of 25%).

This regimen of Panitumumab will be considered worthy of further investigation if it elicits an increase in RR to 25% with acceptable toxicity. A 25% toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed that meet the following two conditions,

- 1) $\Pr(\emptyset_S, \text{Toxicity} < \emptyset_E, \text{Toxicity} \mid \text{data}) > 0.95$ and,
- 2) $\Pr(\emptyset_S, \text{Response} < \emptyset_E, \text{Response} \mid \text{data}) < 0.05$

Where $\emptyset_{E, \text{Toxicity}}$ and $\emptyset_{E, \text{Response}}$ are the true toxicity and response rates for Panitumumab, respectively. The first rule provides for stopping the study if excessive toxicity is highly probable (i.e., probability $> 95\%$) for Panitumumab. The second condition will stop the study early if the data suggest that it is unlikely (i.e., probability $< 5\%$) that response rate

of the drug is 17%. Assuming the minimum number of patients is 1, the maximum number of patients is 17 and the cohort size is 1.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in the following table. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients treated or if 6 or more patients experience toxicities among the first 10 patients.

Stop accrual if the number of toxicities is equal to or greater than indicated (i.e., # toxicities) among the number of patients evaluated (i.e., # patients)						
# Toxicities	3-4	4-6	5-9	6-11	17-14	8-16
# Patients	3-4	5-6	7-9	10-11	12-14	15-16

Monitoring the response rate, based on the above assumptions and monitoring will begin after 1 patient is treated (on an intent-to-treat basis). Following this rule, the trial will be terminated if $[\# \text{ Response}]/[\# \text{ patients evaluated}] \leq 0/8$. For example, accrual will cease if 0 or fewer patients experience a response in the first 8 patients treated.

Multic Lean Desktop (version 2.0.0) was used to generate the toxicity and futility stopping boundaries and the OC table. In order to utilize the software for the design, a beta (21, 103) prior was assumed for the historical control response rate and a beta (31, 93) prior was assumed for the historical control toxicity rate.

The probability of stopping the study early if the true response rate of the Panitumumab was not better than 17% was 35%. Probabilities of stopping early for high true toxicity rates (i.e., 37%) were 57% when the true RR rate was 17% and 48% when true RR was 25%.

Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with Panitumumab.				
True RR	True Toxicity Rate	True Probability Vector (RR/TX, RR/NTX, NRR/TX, NRR/NTX)	Probability of Stopping	Average number of patients treated
8%	12%	(0.010,0.070,0.110,0.810)	0.5174	12
8%	25%	(0.020,0.060,0.230,0.690)	0.5637	12
8%	37%	(0.030,0.050,0.340,0.580)	0.6885	10
17%	12%	(0.020,0.150,0.099,0.730)	0.2319	15
17%	25%	(0.042,0.127,0.207,0.622)	0.3055	14
17%	37%	(0.062,0.107,0.307,0.523)	0.5042	12
25%	12%	(0.030,0.220,0.090,0.660)	0.1078	16
25%	25%	(0.062,0.187,0.187,0.562)	0.1934	15
25%	37%	(0.092,0.157,0.277,0.472)	0.4241	13

Where Will Participants Be Enrolled:

Only at MDACC

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC: 27

Estimated monthly accrual at MDACC: 1-2

Accrual Comments:

The total accrual for this study is 27. There are 10 patients already enrolled and 3 have been treated with combination therapy, and 17 patients are to be enrolled for the single agent treatment.

Do you expect your target population to include non-english speaking participants? No

Location of Treatment:

This protocol is performed on an Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

NA

Return Visits: How often must participants come to MDACC?

Every 2 weeks

Home Care: Specify what, if any, treatment may be given at home.

NA

Name of Person at MDACC Responsible for Data Management: [Mary E. Brimer](#)

Prior protocol at M. D. Anderson:

Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
Yes

Data Monitoring Committee:

Is treatment assignment randomized? No

Is this a blinded or double-blinded study? No

Does this protocol have a schedule for interim and final analysis? Yes

Please describe:

Amended Study Design, Sample Size, Efficacy and Toxicity Monitoring as of October 1, 2012:

Response and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998). Bayesian interim futility and toxicity rules will be used. Complete details are included in the Statistical Considerations section. Data from a previous study of single agent Panitumumab in Kras wildtype colorectal cancer demonstrated a response rate for Panitumumab is approximately 17%. The toxicity rate of Panitumumab will estimate it will be approximately 25%. For the prior distribution of standard Panitumumab, we assumed a simple Dirichlet distribution and independence between OR and toxicity in 124 patients. The parameters for this prior distribution are as follows:

Dirichlet parameters for the joint prior distribution of objective response and toxicity rate assuming information on 124 patients and independence among response and toxicity for Panitumumab.

	No Response	Response
No Toxicity	77	16
Toxicity	26	5

A flat Dirichlet prior distribution for experimental Panitumumab was chosen reflective of information from the equivalent of 4 patients with the same marginal distributions as for Panitumumab (e.g., RR rate of 17% and toxicity rate of 25%).

This regimen of Panitumumab will be considered worthy of further investigation if it elicits an increase in RR to 25% with acceptable toxicity. A 25% toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed that meet the following two conditions,

- 1) $\Pr(\emptyset S, \text{Toxicity} < \emptyset E, \text{Toxicity} \mid \text{data}) > 0.95$ and,
- 2) $\Pr(\emptyset S, \text{Response} < \emptyset E, \text{Response} \mid \text{data}) < 0.05$

Where $\emptyset E$, Toxicity and $\emptyset E$, Response are the true toxicity and response rates for Panitumumab, respectively. The first rule provides for stopping the study if excessive toxicity is highly probable (i.e., probability >95%) for Panitumumab. The second condition will stop the study early if the data suggest that it is unlikely (i.e., probability < 5%) that response rate of the drug is 17%. Assuming the minimum number of patients is 1, the maximum number of patients is 17 and the cohort size is 1.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in the following table. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients treated or if 6 or more patients experience toxicities among the first 10 patients.

Stop accrual if the number of toxicities is equal to or greater than indicated
(i.e., # toxicities) among the number of patients evaluated (i.e., # patients)

# Toxicities	3-4	4-6	5-9	6-11	17-14	8-16
# Patients	3-4	5-6	7-9	10-11	12-14	15-16

Monitoring the response rate, based on the above assumptions and monitoring will begin after 1 patient is treated (on an intent-to-treat basis). Following this rule, the trial will be terminated if $[\# \text{ Response}] / [\# \text{ patients evaluated}] \leq 0/8$. For example, accrual will cease if 0 or fewer patients experience a response in the first 8 patients treated.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
----------------------------------------------------------------------------------------------	----

Is the radioactive compound (or drug) FDA approved and/or commercially available?

No

Investigational New Drugs:

Does this protocol require an IND? Yes

Please list the IND holder and provide the IND number:

IND Holder: MDACC

IND Number: 109220

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA? N/A

Has the Investigational Device been modified in a manner not approved by the FDA? N/A

Name of Device: NA

Manufacturer: NA

What is the FDA Status of the Investigational Device? Not Marketed.

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder: NA

IDE Number: NA

Risk Assessment:

Please answer the following questions regarding the Investigational Device.

Intended as an implant? No

Purported or represented to be for use supporting or sustaining human life? No

For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health? No

You may attach sponsor documentation of the risk assessment:

NA

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: Amgen
Type(s) of Support: Funds
Agent

Monitored by Sponsor or Sponsor Representative (CRO)? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve stem cells? No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No