A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

AMG 954
Amgen Protocol Number 20050203

Clinical Study Sponsor:
Amgen Inc
One Amgen Center Drive
Thousand Oaks CA 91320-1799
United States
Telephone: +1 805 447 1000
Fax: +1 805 480 0614

Key Sponsor Contact:
Pam Dixon
Clinical Research Study Manager
Amgen Ltd
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom
Telephone: **+44 1895 525491**
Fax: **+44 1223 228164**

Date:	06 March 2006
Superseding Date:	09 March 2006
Amendment 1	10 October 2007
Amendment 2	**21 January 2009**
EudraCT Number:	2006-000170-70

Investigator's Agreement

I have read the attached protocol entitled "A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer", dated 09 March 2006, amended 10 October 2007**, and further amended 21 January 2009** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines and set forth in 21 CFR Parts 11,50, 54, 56 and 312.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Principal Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

Study Phase: Phase 3

Indication: 1st line metastatic colorectal cancer in combination with chemotherapy

---

Primary Objective: To assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) among **subjects with wild-type KRAS tumors (subjects whose tumors contain non-mutated KRAS) and subjects with mutant KRAS tumors.**

Secondary Objectives: To evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Tertiary Objectives: To evaluate time to response and patient reported outcomes (PRO) among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Exploratory Objectives: To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of study drug among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Hypothesis:

> **Primary:** The addition of panitumumab to chemotherapy (FOLFOX) will increase progression-free survival (PFS) compared to chemotherapy (FOLFOX) alone as first-line treatment of mCRC among **subjects with wild-type KRAS tumors.**
>
> **Secondary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression-free survival (PFS) compared to chemotherapy (FOLFOX) alone as first-line treatment of mCRC among subjects with mutant KRAS tumors.**

Study Design: This is a phase 3, open-label, randomized, multicenter study. Eligible subjects will be randomized in a 1:1 ratio to first-line therapy consisting of either:

- Arm 1: FOLFOX with panitumumab or
- Arm 2: FOLFOX alone

Randomization will be stratified by geographic region and ECOG performance status

One cycle of chemotherapy +/- panitumumab is 14 days (± 3 days). Subjects will be permitted to receive chemotherapy +/-panitumumab until disease progression (per modified RECIST [Response Evaluation Criteria in Solid Tumors] guidelines) or until unacceptable toxicity.

Response Evaluation:

Tumor response assessment will be performed by the investigator and blinded central radiology review per modification of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Subjects will be evaluated for tumor response every 8 weeks (±1 week) until disease progression. Responses will be confirmed no less than 4 weeks after the criteria for response are first met. Subjects with symptoms suggestive of disease progression should be evaluated for tumor progression at the time the symptoms occur. If withdrawal from study treatment occurs prior to disease progression eg, due to unacceptable toxicities, tumor response assessments should continue as above until disease progression or the end of the study whichever is earlier.

Patient Reported Outcome Measures:

Subjects will complete an EQ-5D every 4 weeks ± 1 week, starting at baseline and continuing while receiving assigned study treatment until disease progression and once at the safety follow-up visit. If withdrawal from assigned study treatment occurs prior to disease progression (eg due to unacceptable toxicities) subjects should continue to complete the EQ-5D every 8 weeks ± 1 week until disease progression.

Endpoints:

Primary Endpoint:

- Progression-free survival (PFS)

Secondary Endpoints:

- Efficacy: Overall Survival (OS), Objective Response Rate (ORR); Time to progression (TTP); Duration of response (DOR);
- Safety: Incidence of AEs and significant laboratory changes

Tertiary Endpoints:

- Time to response
- Patient-reported outcomes: EuroQoL (EQ-5D)

Exploratory Endpoints:

- Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of the study drug

---

Sample Size: Approximately 1150 subjects (approximately 575 per treatment arm)

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

- Histologically or cytologically-confirmed adenocarcinoma of the colon or rectum in subjects who are presenting with metastatic disease
- At least 1 uni-dimensionally measurable lesion of at least 20mm per modified RECIST guidelines (all sites of disease must be evaluated ≤ 28 days prior to randomization)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Paraffin-embedded tumor tissue from the primary tumor or metastasis available for central analyses of EGFr and biomarker testing
- Man or woman ≥ 18 years of age
- Hematologic function, as follows (≤ 7 days prior to randomization):
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Platelet count ≥ 100 x 10^9/L
  - Hemoglobin ≥ 9 g/dL
- Renal function, as follows (≤7 days prior to randomization):
  - Estimated creatinine clearance ≥ 50 ml/min
- Hepatic function, as follows (≤7 days prior to randomization):
  - Aspartate aminotransferase (AST) ≤ 3 x ULN (if liver metastases ≤ 5 x ULN)
  - Alanine aminotransferase (ALT) ≤ 3 x ULN (if liver metastases ≤ 5 x ULN)

  - Total bilirubin ≤ 1.5 x ULN
- Metabolic function, as follows (≤7 days prior to randomization):
  - Magnesium ≥ lower limit of normal
- Negative pregnancy test ≤ 72 hours prior to randomization (females of childbearing potential only)
- Competent to comprehend, sign, and date an IEC/IRB-approved informed consent form
- Life expectancy ≥ 3 months

Key Exclusion Criteria:

- History or known presence of central nervous system (CNS) metastases
- History of another primary cancer, except:
  - Curatively treated in situ cervical cancer, or
  - Curatively resected non-melanoma skin cancer, or
  - Other primary solid tumor curatively treated with no known active disease present and no treatment administered for ≥ 5 years before randomization
- Prior chemotherapy or systemic therapy for the treatment of metastatic colorectal carcinoma with the following exceptions:
  - Subject may have received adjuvant fluoropyrimidine-based chemotherapy if disease progression is documented at least 6 months after completion of chemotherapy
  - Subjects may have received prior fluoropyrimidine therapy if administered solely for the purpose of radiosensitization
- Prior oxaliplatin therapy
- Prior anti-EGFr antibody therapy (eg, cetuximab) or treatment with small molecule EGFr inhibitors (eg, erlotinib)
- Any investigational agent or therapy ≤ 30 days prior to randomization
- Radiotherapy ≤ 14 days prior to randomization. Subjects must have recovered from all radiotherapy related toxicities
- Known allergy or hypersensitivity to platinum-containing medications, 5-FU or leucovorin
- Active infection requiring systemic treatment or any uncontrolled infection ≤ 14 days prior to randomization
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year prior to randomization
- History of interstitial lung disease (eg, pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest CT scan
- Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as ≥ CTC grade 2 [CTCAE version 3.0])
- Known positive tests 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, dihydropyrimidine deficiency, significant ascites or pleural effusion
- Peripheral sensory neuropathy with functional impairment (≥ CTC grade 3 [CTCAE version 3.0] neuropathy, regardless of causality)

- Any uncontrolled concurrent illness or history of any medical condition that may interfere with the interpretation of the study results
- Major surgical procedure (requiring general anesthesia) ≤ 28 days or minor surgical procedure (excluding central venous catheter placement) ≤ 14 days prior to randomization. Subjects must have recovered from surgery related toxicities.
- Subject who is pregnant or breast feeding
- Woman or man of child-bearing potential not consenting to use adequate contraceptive precautions ie. double barrier contraceptive methods (eg, diaphragm plus condom), or abstinence during the course of the study and for 6 months after the last study drug administration for women, and 1 month for men
- Subject unwilling or unable to comply with study requirements
- Previously randomized into this study protocol

Investigational Product Dosage and Administration: Panitumumab is a fully human monoclonal antibody directed against human epidermal growth factor receptor (EGFr).

Panitumumab will be supplied at a concentration of 20 mg/mL in 10 mL vials. The panitumumab starting dose is 6 mg/kg. The total dose may be rounded up or down by no greater than 10 mg. The panitumumab dose will be calculated based on the subject's actual body weight at baseline and will not be re-calculated unless the actual body weight changes by at least 10%. Panitumumab will be diluted in a minimum volume of 100 mL pyrogen-free 0.9% sodium chloride solution, USP (saline solution). Panitumumab will be administered intravenously (IV) by an infusion pump through a peripheral line or indwelling catheter using a 0.22-micron in-line filter over 1 hour ±15 minutes. If the first infusion is well tolerated, then all subsequent infusions may be administered over 30 minutes ± 10 minutes.

Background Chemotherapy Regimen:

Chemotherapy: The FOLFOX4 regimen will be administered every 2 weeks as follows:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL **D5W** and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in **D5W** both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour continuous infusion

Procedures:

Refer to Section 7 and Schedule of Assessments (appendices A and B) for detailed procedures required at each visit.

A signed and dated informed consent must be obtained before any study-specific procedures are performed.

Statistical Considerations:

Primary Analysis

The primary goal of the statistical analysis is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS) among **subjects with wild-type KRAS tumors (the Wild-type KRAS Efficacy Analysis Set) as well as subjects with mutant KRAS tumors (the Mutant KRAS Efficacy Analysis Set)** and to characterize and compare overall survival (OS). The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each

endpoint. The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors. Significance levels described will be 2-sided unless stated otherwise. PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.

Safety Interim Analyses

An independent Data Monitoring Committee (DMC) will compare study AE and SAE information on a regular basis throughout the entire treatment phase. If warranted from these reviews, the DMC may request additional specific safety data. Audited and unaudited data will be provided to the DMC.

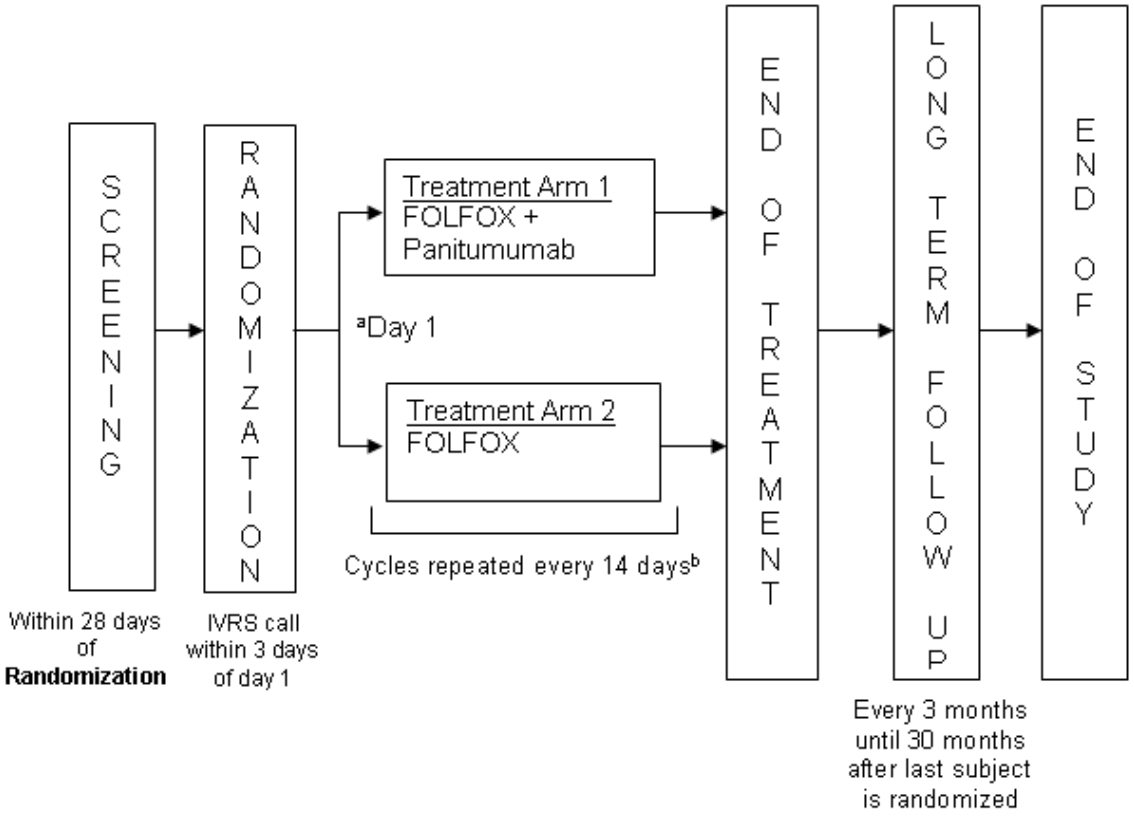
Efficacy Interim Analyses

When 258 PFS events are collected in the ITT Efficacy Analysis Set, an interim analysis will be performed to allow the DMC to obtain an overall assessment of benefit-risk in the all randomized study population by an examination of overall PFS and safety by treatment. If warranted from this analysis, the DMC may subsequently recommend that they also obtain an overall assessment of benefit-risk separately within the wild-type KRAS and mutant KRAS sub-populations. Prospective guidelines for DMC actions will be pre-specified in an amended DMC charter for the revised interim PFS analysis and potential subsequent KRAS-stratified PFS analysis.

The projected time for this planned efficacy interim analysis is at 258 PFS events (approximately 18 months after the first subject is randomized). No significance level adjustment is required for the primary hypothesis testing of PFS and OS due to the revised non-inferential interim analysis plan.

Two interim analyses of OS are planned in this study. The first OS interim analysis will be synchronized with the primary PFS analysis. The second OS interim analysis will be conducted with a data cutoff of approximately 9 months later. The second OS interim analysis may be omitted if the data cutoff date of the primary OS analysis is expected to be within 12 months of data cutoff date of the primary PFS analysis.

Study Design and Treatment Schema



[a] Day 1 = day of 1st treatment administration
[b] Subsequent cycles may be delayed due to panitumumab or chemotherapy associated toxicity

Study Glossary

Abbreviation/Acronym	Definition
5-FU	5-fluorouracil
AE	Adverse event
ANC	Absolute neutrophil count
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BP	Biomarker predictive
BSA	Body surface area
BUN	Blood urea nitrogen
CEA	Carcinoembryonic antigen
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CXR	Chest x-ray
D5W	**Dextrose 5% in water**
DMC	Data monitoring committee
DOR	Duration of response
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFr	Epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
End of Study	Defined as the point of conclusion of all aspects of the study including post treatment follow-up for survival
End of Treatment	Defined as the point of stopping all components of the protocol assigned treatment (FOLFOX and/or panitumumab)
Enrollment	Defined as randomization into the study via the IVRS
EQ-5D	EuroQOL instrument for measuring health outcomes in 5 dimensions including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression
FDA	Food and Drug Administration (U.S.A.)
FOLFIRI	A chemotherapy regimen consisting of infusional irinotecan and 5-FU/leucovorin
FOLFOX (4)	Oxaliplatin 85mg/m^2 IV over 2 hours day 1; racemic leucovorin 200mg/m^2 (or 100 mg/m^2 *l*-leucovorin) IV over 2 hours days 1 and 2; 5-FU 400mg/m^2 IV bolus, then 600mg/m^2 IV over 22 hours days 1 and 2

G-CSF	Granulocyte colony stimulating factor
HIV	Human immunodeficiency virus
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IEC	Independent ethics committee
IFL	A chemotherapy regimen consisting of infusional irinotecan and bolus 5-FU/leucovorin
IMP	Investigational medicinal product (panitumumab)
IRB	Institutional review board
IR	Incomplete response
ITD	**Intent-to-Diagnosis**
ITT	Intent to treat ie, all subjects randomized via the IVRS
IV	Intravenous
IVRS	Interactive voice response system
KRAS	Kirsten rat Sarcoma-2 virus
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LV	Leucovorin
mAb	Monoclonal antibody
MAHA	Monkey anti-human antibody
mCRC	Metastatic colorectal cancer
MRI	Magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PRO	Patient reported outcome
QoL	Quality of life
Randomization	Defined as the point when the randomization call is made using the study IVR system
RECIST	Response evaluation criteria in solid tumors
SD	Stable disease
RBC	Red blood cell
SAE	Serious adverse event
SAP	**Statistical Analysis Plan**
Screening period	Defined as the period from signing of the informed consent until randomization via the IVRS
SLD	Sum of the longest diameters
Study day 1	Defined as the first day investigational product and/or chemotherapy is administered to the subject
Study Treatment	FOLFOX +/- panitumumab

TGF-α	Transforming growth factor-alpha
TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell

Table of Contents

Page

List of Appendices

1. OBJECTIVES

1.1 Primary

The primary objective of this study is to assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) among **subjects with wild-type KRAS tumors (subjects whose tumors contain non-mutated KRAS) and subjects with mutant KRAS tumors.**

1.2 Secondary

The secondary objectives are to evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

1.3 Tertiary

Tertiary objectives are to evaluate time to response and patient reported outcomes (PRO) among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

1.4 Exploratory

To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of the study drug among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

2. BACKGROUND AND RATIONALE

2.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in both men and women, comprising approximately 10% of the 710,040 new cancers in men and 11% of the 662,870 new cancers in women worldwide (Jemal et al, 2005). Despite improvement in the diagnosis and treatment of CRC, in 2005 CRC is expected to result in 54,290 cancer deaths in the US (Jemal et al, 2005) and over 203,700 in Europe (Boyle & Ferlay, 2005). Of newly diagnosed patients, 15-25% have metastatic disease at diagnosis (Kindler and Shulman, 2001) and up to 50% of all patients eventually develop metastatic

disease (McLeod et al, 2000; Kindler and Shulman, 2001). If diagnosis is made early and is localized to the bowel mucosa, CRC is generally curable, with a 93% 5-year survival rate (Pazdur et al, 1999). However, the 5-year survival rate decreases to 67% upon involvement of adjacent organs and lymph nodes and is only 8% in patients with widespread metastatic disease (Pazdur et al, 1999; Kindler and Shulman, 2001).

2.1.1 Treatment of Colorectal Cancer

For years, effective treatment for CRC was limited to 5-fluorouracil (5-FU), which inhibits either ribonucleic acid synthesis or deoxyribonucleic acid synthesis through inhibition of thymidylate synthetase, depending on the schedule of administration. Although it was used initially as a single agent, combination with leucovorin (LV) has demonstrated improved outcomes resulting in a response rate of 23% and median survival time of approximately 10 to 12 months (Advanced Colorectal Cancer Meta-Analysis Project, 1992).

Two other chemotherapy agents, irinotecan and oxaliplatin, have also been shown to have activity in the treatment of metastatic colorectal cancer (mCRC). Irinotecan, a specific inhibitor of DNA topoisomerase I, demonstrated a significant single-agent activity in the treatment of patients with 5-FU refractory CRC (Rougier et al, 1998; Cunningham et al, 1998). Furthermore, the addition of irinotecan to 5-FU/LV combination therapy (FOLFIRI regimen) produced a significant improvement over 5-FU/LV alone in overall survival (17.4 vs 14.1 months, respectively; $p=0.031$), response rate (35% vs 22%, respectively; $p<0.005$), and time to progression (6.7 vs 4.4 months, respectively; $p<0.001$) in the treatment of patients with previously untreated mCRC (Douillard et al, 2000).

Oxaliplatin, a platinum analog, forms cross-linking adducts and blocks deoxyribonucleic acid replication. Oxaliplatin has been shown to be effective and well-tolerated when administered with bolus and infusional 5-FU (FOLFOX regimen), with neutropenia and sensory neuropathies occurring more frequently than when 5-FU and LV are given alone (Maindrault-Goebel et al, 1999; de Gramont et al, 2000; Rothenberg et al, 2003). In first-line advanced colorectal cancer therapy, the FOLFOX4 regimen was shown to be superior to irinotecan, bolus 5-FU, leucovorin (IFL regimen) and to irinotecan and oxaliplatin (IROX regimen), with median overall survival times of 19.5 months, 15.0 months, and 17.4 months, respectively. The response rates and median times to progression were 45%, 8.7 months; 31%, 6.9 months; and 35%, 6.5 months,

respectively (Goldberg et al, 2004). Tournigand et al (2004), compared the efficacy of FOLFIRI followed by FOLFOX6 at progression to that of FOLFOX6 followed by FOLFIRI at progression in patients with previously untreated mCRC, and found a similar median survival (21.5 vs 20.6 months, respectively; p=0.99). In this study NCI CTC grade ¾ mucositis, nausea, and vomiting, and grade 2 alopecia were more frequent with FOLFIRI, while grade 3/4 neutropenia and neurosensory toxicity were more frequent with FOLFOX6.

Targeted biologic agents designed specifically to inhibit the biochemical processes of carcinogenesis have been shown to be effective in the treatment of mCRC. Cetuximab (Erbitux®), a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFr), has activity as a single agent in irinotecan-refractory CRC (Saltz et al, 2004) and improves both response rate and time to tumor progression when given concurrently with irinotecan after irinotecan failure (Cunningham et al, 2004). Cetuximab is licensed by the FDA for use in combination with irinotecan for the treatment of patients with mCRC who have EGFr-expressing tumors that are refractory to irinotecan-based therapy or as monotherapy in irinotecan-intolerant patients who have EGFR-expressing tumors. In addition, cetuximab has also received licensing authorization in the European Union, Switzerland, Norway and Iceland for administration in combination with irinotecan for the treatment of patients with mCRC who no longer respond to standard chemotherapy with irinotecan.

Another targeted agent is bevacizumab (Avastin™), which binds and inhibits vascular endothelial growth factor A (VEGF-A), a protein that plays a critical role in tumor angiogenesis. The addition of bevacizumab to IFL (a regimen consisting of infusional irinotecan and bolus 5-FU/leucovorin), compared to IFL alone, significantly improved survival (20.3 months vs 15.6 months, respectively; p<0.0001) in a randomized study (Hurwitz et al, 2004). Bevacizumab is used in combination with intravenous 5-fluorouracil-based chemotherapy and is licensed for first-line treatment of patients with mCRC.

2.1.2 Role of Epidermal Growth Factor Receptor in Cancer

EGFr is a 170,000-Dalton transmembrane glycoprotein that functions to promote cell growth, development and differentiation in a variety of normal and transformed tissues. EGFr is activated by numerous ligands, including EGF and transforming growth factor α (TGFα) (Salomon et al, 1995). Expression of EGFr is frequently associated with

malignant transformation in carcinomas of the prostate, breast, ovary, lung, kidney, and colon, among others (Gullick, 1991; Herbst and Shin, 2002). In mouse xenograft models with human tumors, anti-EGFr antibodies were shown to both inhibit tumor growth and eradicate established tumors (Baselga and Mendelsohn, 1994; Yang et al, 1999).

Colorectal cancer cells have been shown to express EGF and EGFr mRNA (Shirai et al, 1995; Porebska, 2000). Colorectal cancer cells secrete EGF in an autocrine fashion and respond to it through the cell-surface receptor thus sustaining their malignant phenotype (De Jong et al, 1998; Saeki et al, 1995; Wang et al, 1998). Furthermore, studies show that EGFr expression is greatly increased during tumor progression (Tong et al, 1998).

Blocking the EGFr by using an anti-EGFr monoclonal antibody can provide a therapeutic strategy in colorectal cancer. Cetuximab (Erbitux®) has both single-agent activity and activity in combination with irinotecan in patients with EGFr-positive, irinotecan-refractory mCRC. The overall response rate was 22.9%, and median time to progression was 4.1 months in the combination-therapy group, while in the monotherapy group, the overall response rate was 10.8%, and median time to progression was 1.5 months.

2.2 Panitumumab Background

Panitumumab, previously known as ABX-EGF, is a high affinity (K_d = 5 x 10^{-11} M) fully human IgG_2 monoclonal antibody directed against human EGFr. Panitumumab blocks the ligands EGF and TGFα binding to EGFr, inhibits tumor growth, and elicits both tumor regression and eradication of established tumors in murine xenograft tumor models (Yang et al, 1999).

2.2.1 Panitumumab Preclinical Pharmacology

The antineoplastic effects of panitumumab *in vivo* have been demonstrated using human xenograft mouse models. Panitumumab has been shown to inhibit the growth of human epidermoid carcinoma A431 xenografts in athymic mice resulting in the complete regression of large (up to 1.2 cm^3) established A431 tumors, regardless of initial tumor size. Lower doses of panitumumab administered twice weekly for 3 weeks inhibited growth of preexisting solid tumors. Furthermore, a single injection of 1 mg of panitumumab resulted in significant and prolonged tumor inhibition.

Please refer to the current Panitumumab Investigator's Brochure for further details.

2.2.2 Panitumumab Preclinical Toxicology and Pharmacokinetics

Results of panitumumab toxicology studies (1- and 3-month duration) have identified diarrhea and skin rash as the principal toxicities, which were considered related to the pharmacological action of panitumumab.

Pharmacokinetics were shown to be nonlinear, and the production of monkey anti-human antibodies (MAHA) against panitumumab in animals caused a significant decrease in exposure over the course of the 3-month study.

In a 6-month toxicology study where panitumumab was administered IV at weekly doses of 7.5, 15, and 30 mg/kg to cynomolgus monkeys, skin rash and diarrhea were observed in several animals in all dose groups; both of these toxicities were considered to be related to the pharmacological action of panitumumab. Additionally, several animals showed decreased food consumption and body weight loss (Panitumumab Toxicology Study 103419).

Please refer to the current Panitumumab Investigator's Brochure for further details.

2.2.3 Panitumumab Clinical Experience

Since the commencement of clinical studies 1700 subjects with cancer have been enrolled in panitumumab phase 1, 2, and 3 clinical studies, receiving panitumumab doses ranging from 0.01 mg/kg to 5 mg/kg given once every week, 6 mg/kg given once every 2 weeks, and 9 mg/kg given once every 3 weeks. Panitumumab has been studied as monotherapy in multiple studies of mCRC and solid tumors (renal, prostate, pancreatic, non small-cell lung, esophageal and head and neck). Panitumumab has also been studied in combination with chemotherapy for non-small cell lung cancer and with chemotherapy and bevacizumab for mCRC.

Please refer to the current Panitumumab Investigator's Brochure for further details.

2.2.4 Panitumumab Clinical Safety Experience

The below referenced studies reflect the reported serious adverse events at the time of the last Panitumumab Investigators Brochure (Version 5.0, 17 September 2004) and the Panitumumab Clinical Trial Directive Annual Safety Report (August 2005). Please review the updated safety information contained in the Investigational New Drug safety letters for further updates.

Panitumumab has generally been well tolerated in each of the studies to date. As with other EGFr inhibitors, the most commonly reported side effects of panitumumab are dermatological in nature. The most common adverse event attributed to panitumumab is a dose-related, reversible, acneiform, or maculopapular skin rash. In a recent phase 2 trial in subjects with mCRC, skin toxicity was reported by 95% of subjects (Malik et al, 2005). Most treatment-related rashes were mild to moderate in severity, with severe rash reported infrequently. The rash often involved the face, upper chest and back, but can affect any part of the body. Less commonly reported skin effects were vesicular or exfoliative rash, skin erythema, and dry skin. Some skin-related toxicities have been associated with pain or pruritus. Other skin effects that have been infrequently reported include fissures of the fingers or toes, and fingertip infection or inflammation.

2.2.4.1 Panitumumab Monotherapy Studies

In clinical studies with panitumumab as monotherapy, mild to moderate diarrhea has been reported. Hypomagnesemia has been also been reported, with the majority of events grade 1 or 2 in severity. As of the most recent annual safety report, a total of 4 panitumumab-related serious adverse events of low magnesium levels have been reported, and in 2 instances this was associated with hypocalcaemia. Other non-dermatological manifestations reported during monotherapy studies include asthenia, pain, constipation, nausea, fever, back pain, abdominal pain, anorexia, diarrhea, arthralgia, dizziness, increased cough, dyspnea, vomiting, and upper respiratory infection.

In the monotherapy studies, 32 cases of panitumumab-related serious adverse events have been reported by investigators. These include: hypersensitivity (4), rectal hemorrhage/hyperglycemia (1), hypocalcemia (1), pulmonary embolism (2), intestinal obstruction (1), renal failure/dehydration (1), skin toxicity (1), pyrexia (1), catheter-related infection (1), petechia/abdominal pain (1), hypomagnesemia (3), deep vein thrombosis (1), dehydration (2), asthma/dyspnea (1), asthenia (1), hematuria/dehydration (1), paronychia (1), infusion reaction (1), myocardial infarct (1), myocardial infarct/cerebrovascular accident (1), hypomagnesemia/hypocalcemia (1), convulsions (1), hypoxia/lung infiltration (1), fluid retention (1), diarrhea/nausea/vomiting (1).

2.2.4.2 Panitumumab Combination Therapy Studies

Panitumumab is currently being studied in combination with chemotherapy in subjects with CRC and non small-cell lung cancer. In these studies, skin-toxicities were reported to be similar in nature and severity to those reported in the monotherapy studies.

In the CRC studies involving administration of panitumumab in combination with IFL, diarrhea was more frequently reported than when compared to the monotherapy studies. Other frequent adverse events when panitumumab was used in combination with IFL were skin toxicity, asthenia and nausea. As the IFL chemotherapy regimen caused significant diarrhea, this study was amended to switch the chemotherapy to the infusional 5-fluorouracil based regimen, FOLFIRI. The AEs of diarrhea, asthenia, and nausea were less frequent with FOLFIRI.

In a phase 2 non small-cell lung cancer study in which panitumumab was administered in combination with paclitaxel and carboplatin, approximately 80% of subjects have been reported to have a dose-related, reversible, acneiform, or maculopapular skin rash similar to that seen in the monotherapy studies. Reported less frequently were fingertip or nail bed infection and inflammation. Beyond these skin effects, the most frequent AEs reported as related to panitumumab were asthenia, diarrhea, nausea, and throat irritation. Examining AEs overall, regardless of relationship, the most frequently reported AEs other than skin rash were nausea, asthenia, alopecia, myalgia, arthralgia, constipation, diarrhea, vomiting, and throat irritation.

In the studies involving administration of panitumumab in combination with chemotherapy, 10 cases of panitumumab-related serious adverse events were reported by investigators. These include: pulmonary embolism/neutropenia (1), pulmonary embolism (2), atrial fibrillation (1), dehydration/hypotension (1), deep vein thrombosis/dehydration (1), thrombosis (1), diarrhea (1), hypoxia (1), dehydration/vomiting/nausea (1).

2.2.4.3 Panitumumab in All Studies

Infusion-associated reactions may occur during or after panitumumab administration. To date there have been 4 subjects that were identified as having a possible infusion reaction (3 reported as hypersensitivity, and 1 as an infusion reaction). In these 4 subjects the investigator attributed these reactions to panitumumab. The reactions were reported as chills, feeling of coldness, tachycardia, chest pressure and dyspnea.

In some instances medication was given, but often no action was taken. All reactions were mild to moderate in severity. Due to the fact that infusions reactions are expected to be uncommon, it is recommended that panitumumab infusions should be administered without specific panitumumab pre-medication (see Section 6.1.1).

A potential risk of administering panitumumab is the development of anti-panitumumab antibodies. To date, using a very sensitive methodology for antibody detection, the immunogenicity of panitumumab has been very low. The development of anti-panitumumab antibodies has not been associated with pharmacokinetic or clinical consequences. Pre-existing anti-panitumumab antibodies have been detected in 11 subjects, of which 2 showed increased anti-panitumumab antibody titers after receiving panitumumab. In one subject the antibody was able to neutralize the biological activity of panitumumab as measured on a cell based assay. If subjects receiving panitumumab develop an anti-panitumumab antibody response, they may not be able to receive further treatment with panitumumab.

Based upon early findings in toxicology studies, cardiac monitoring was included in clinical studies. After review of interim data on more than 300 subjects, there were no indications of cardiac toxicity resulting from panitumumab treatment. As a result cardiac monitoring is no longer part of the routine safety monitoring of subjects on panitumumab studies.

Similar to recent findings with cetuximab (Erbitux®), in clinical studies of panitumumab given as a single agent or in combination with various chemotherapy regimens, several hypomagnesemia AEs and SAEs (with or without concomitant hypocalcemia) have been reported. Therefore, routine magnesium monitoring is recommended for subjects receiving panitumumab.

2.2.5 Panitumumab Clinical Efficacy Experience

Panitumumab is being studied as a monotherapy and in combination with chemotherapy in several clinical studies. Efficacy has been observed in various tumor types when given as both monotherapy and in combination with chemotherapy.

In a phase 1 clinical trial being conducted with panitumumab in subjects with advanced carcinoma at doses ranging from 0.01 mg/kg to 5.0 mg/kg given once every week, and 6.0 mg/kg given once every 2 weeks to 9.0 mg/kg given once every 3 weeks, fifty-six

subjects, including subjects with colorectal, renal cell, prostate, pancreatic, esophageal and non small-cell lung cancer, have received panitumumab by IV infusion weekly for 4 weeks in the initial study.

Of these 56 subjects, a partial response with regression of liver metastases was observed in 1 subject with CRC who received panitumumab 2.5 mg/kg administered weekly. This subject received 10 months of therapy before progressing. A second subject with CRC treated at the 1.5 mg/kg dose had stable disease and received 4 months of therapy before progressing. In addition, stable disease was observed in 4 other subjects: 1 subject with esophageal carcinoma who received panitumumab 0.1 mg/kg after a loading dose of 0.2 mg/kg, 1 subject with prostate cancer who received 0.75 mg/kg after a loading dose of 1.5 mg/kg, and 2 subjects with non small-cell lung cancer who received 3.5 mg/kg. All 4 subjects went on to receive further drug in the phase 1 maintenance therapy study; the subject with esophageal cancer progressed after 7 months of panitumumab therapy, while the subject with prostate cancer achieved a minor response but progressed after a total of 8 months of therapy. One subject with non small-cell lung cancer progressed after 4 months, whereas the other subject with non small-cell lung cancer progressed after 7 months of therapy.

In a multicenter, open label, 2-part, phase 2 clinical trial evaluating the safety and efficacy of panitumumab in subjects with renal cell carcinoma, the first part of the study involved open-label, sequential enrollment of 88 subjects to 1 of 4 escalating weekly dose levels of panitumumab (1.0, 1.5, 2.0, and 2.5 mg/kg). Of the 88 subjects enrolled in part 1, major tumor responses were seen in 3 subjects and minor responses in 2 subjects, while 44 subjects (50%) had stable disease (Rowinsky et al, 2004).

In a recent large phase 2 trial, 148 patients with CRC resistant to 2 or more chemotherapy drugs, and with at least weak tumor EGFr expression by immuno-histochemistry, received single-agent panitumumab at 2.5 mg/kg weekly. Partial responses were seen in 7% of subjects, with stable disease in a further 28%, which compares favorably with results seen with single-agent cetuximab (Saltz et al, 2004). The median duration of response was 18 weeks, median progression free survival was 14 weeks, and median overall survival was 9 months. In this study, no clear relationship was found between the intensity of EGFr staining and response to panitumumab.

In a multi-center, open-label, controlled Phase 3 study conducted in Europe, Australia and Canada, 463 patients with metastatic colorectal cancer who had failed standard chemotherapy, including oxaliplatin and irinotecan were enrolled. Patients were randomized to receive panitumumab plus best supportive care (n=231) or best supportive care alone (n=232). Panitumumab was administered at a dose of 6 mg/kg once every two weeks. Best supportive care was defined as the best palliative care available, as judged appropriate by the investigator, and could not include palliative chemotherapy. Patients who received panitumumab every two weeks showed a 46 percent decrease in tumor progression rate (primary endpoint) versus those who received best supportive care alone ($p < 0.0001$).

Based on the Phase 3 data above, on 27 September 2006, the United States Food and Drug Administration (FDA) approved panitumumab (Vectibix™) for the treatment of EGFR-expressing mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

On 03 December 2007, the European Commission granted the conditional approval for the use of panitumumab as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Health Canada issued a Notice of Compliance with Conditions for Vectibix® on 3 April 2008. For this approval, Vectibix® is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens.

Australian Therapeutic Goods Administration (TGA) issued an Approval for Registration for Vectibix® on 30 April 2008. For this approval, Vectibix® is indicated for treatment of EGFR expressing, metastatic colorectal carcinoma in patients who have disease progression following treatment with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy.

Information **that** contributed to the **approvals** in Europe **and Canada** included analyses of the KRAS status of patients in the above phase 3 clinical study, which provided

evidence that KRAS status is a biomarker in this setting that may predict which patients are more likely to respond to panitumumab monotherapy (Amado et al., 2007).

In the phase 3 clinical study, KRAS status was assessed in 427/463 (92%) patients. KRAS mutations were found in 43% of patients. The treatment effect on progression-free survival (PFS) in the wild-type KRAS (patients whose tumors contain non-mutated KRAS) group was significantly greater ($p < 0.0001$) with a hazard ratio=0.45 (95%CI: 0.34-0.59) than in the mutant KRAS group with a hazard ratio=0.99 (95%CI: 0.73-1.36), which means that patients in the wild-type KRAS group who received panitumumab every two weeks showed a 55 percent risk reduction in tumor progression or death rate versus those who received best supportive care alone. Median PFS in the wild-type KRAS group was 12.3 weeks for patients who received panitumumab and 7.3 weeks for patients who received best supportive care alone. No significant differences in toxicity were observed between the wild-type KRAS group and the overall population (Amado et al., 2007).

Amgen study 20040249 (PACCE) is an open-label, controlled study of bevacizumab and chemotherapy administered with and without panitumumab as first-line treatment of subjects with mCRC. Chemotherapy included oxaliplatin-or irinotecan-based regimens. Based on the results of a planned interim analysis of ~231 PFS events in the oxaliplatin -based cohort, adding panitumumab to bevacizumab and chemotherapy did not prolong progression-free survival and contributed increased toxicity to the multi-agent regimens. Hence, panitumumab was discontinued from the PACCE study.

Previous clinical experience with panitumumab indicates a median time to response within a range of 7 to 15 weeks when given as a monotherapy in 3rd/4th line mCRC and within a range 5 to 13 weeks when given in combination with chemotherapy 1st-line mCRC.

2.3 Rationale

Aside from limited cases of resectable metastatic disease, metastatic colorectal cancer cannot be cured with the currently available chemotherapy regimens, and there is a continued need to improve the current treatment. The epidermal growth factor receptor pathway has been shown to play an important role in carcinogenesis, and inhibiting EGFr with anti-EGFr antibodies has been shown to have clinical efficacy in the treatment of metastatic colorectal cancer (Saltz et al, 2004).

Panitumumab has demonstrated objective tumor response, increase in progression free survival and has an acceptable safety profile in clinical studies in patients with metastatic colorectal cancer when used as a monotherapy or in combination with irinotecan (Meropol et al, 2003; Berlin et al, 2004; Hecht et al, 2004; Malik et al, 2005). The addition of panitumumab to chemotherapy is expected to enhance the treatment effect of chemotherapy.

Based on new information about KRAS status as a biomarker for panitumumab monotherapy, and as part of the conditions for the European approval of panitumumab, which require KRAS status to be investigated in ongoing and future clinical studies with panitumumab in mCRC, Study 20050203 will ensure adequate statistical power for analysis by KRAS status within this clinical study.

2.4 Hypothesis

Primary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression free survival (PFS) compared to chemotherapy alone as first-line treatment of mCRC among **subjects with wild-type KRAS tumors.**

Secondary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression free survival (PFS) compared to chemotherapy alone as first-line treatment of mCRC among subjects with mutant KRAS tumors.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3, open-label, randomized, multicenter study. Eligible subjects will be randomized in a 1:1 ratio to first-line therapy consisting of either:

- Arm 1: FOLFOX with panitumumab or
- Arm 2: FOLFOX alone

Randomization will be stratified by geographic region (Western Europe, Canada and Australia vs Rest of World) and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2; see Appendix C).

One cycle of chemotherapy +/- panitumumab is 14 days. Subjects will be permitted to receive chemotherapy +/- panitumumab until disease progression (per modified RECIST

[Response Evaluation Criteria in Solid Tumors] guidelines, Appendix I) or until unacceptable toxicity.

Response Evaluation:

Tumor response assessment will be performed by the investigator and blinded central radiology review per modification of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse et al, 2000). Subjects will be evaluated for tumor response every 8 weeks (±1 week) until disease progression. Any complete or partial response observed will be confirmed by repeating the imaging studies no less than 28 days after the criteria for response are first met. Subjects with symptoms suggestive of disease progression should be evaluated for tumor progression at the time the symptoms occur.

Subjects with evidence of complete response (CR), partial response (PR), or stable disease (SD) will continue to receive panitumumab and chemotherapy or chemotherapy alone every 2 weeks until disease progression or unacceptable toxicities; subjects in Arm 1 who demonstrate objective response (CR or PR) or who have stable disease but become intolerant to chemotherapy or panitumumab may continue panitumumab or chemotherapy, respectively, until disease progression or intolerance of study treatment. If withdrawal from study treatment occurs prior to disease progression eg, due to unacceptable toxicities, tumor response assessments should continue as above until disease progression or the end of the study whichever is earlier. Imaging data should be sent to central radiology for modified RECIST assessments, up to and including the subject's disease progression. Subjects with evidence of disease progression will be discontinued from treatment dosing and will be followed for safety (30 days ± 3 days) after the last study treatment administration and survival (every 3 months ± 28 days) until 30 months after the last subject is randomized.

For subjects who discontinue the study due to an assessment of disease progression by the investigator, which was subsequently not confirmed by the central radiology review committee, any available additional imaging data, subsequent to the safety follow-up visit, will be requested to be submitted to the central radiology review committee in order to confirm disease progression by central review.

Patient Reported Outcome Measures:

Subjects will complete the EQ-5D every 4 weeks (±1 week), starting at baseline and continuing while receiving assigned study treatment until disease progression, and once at the safety follow-up visit. If withdrawal from study treatment occurs prior to disease progression eg, due to unacceptable toxicities, subjects should continue to complete the EQ-5D every 8 weeks (±1 week) until disease progression or the end of the study whichever is earlier.

The EQ-5D is a standardized instrument developed by the EuroQOL Group for use as a generic, preference-based measure of health outcome. It is applicable to a wide range of health conditions and treatments and is available in numerous languages. The EQ-5D questionnaire captures two basic types of information, a descriptive "profile," or "health state," and an overall health rating using a visual analog scale (VAS). The health states include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which can be combined to produce a single weighted index score by applying coefficients from a validated value set. The VAS is a linear, thermometer like scale that respondents can use to rate their health status, with zero representing the worst imaginable health status and 100 the best (EuroQol Group, 1990; Appendix D).

The EQ-5D is recommended for use in cost-effectiveness analyses commonly employed in health technology assessments (HTA) by the Washington Panel on Cost Effectiveness in Health and Medicine (Gold, 1996). The health state index score is used in both clinical and economic evaluations of health care.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.2.

3.2 Number of Centers

Approximately 200 sites will be participating globally in this study including Western, Central and Eastern Europe, **Canada**, Australia, and South America.

Sites that do not enroll subjects within 3 months of site initiation may be terminated.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

The planned sample size is approximately 1150 subjects randomized in a 1:1 ratio to receive chemotherapy plus panitumumab or chemotherapy alone. Please refer to Section 10.3 for a justification of the sample size.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The subject accrual period is planned for approximately 19 months. Subjects will remain on treatment until they develop disease progression or are unable to tolerate panitumumab and/or FOLFOX (Arm 1), or FOLFOX (Arm 2). To assess overall survival, all subjects will be followed up by clinic visit or by telephone contact every 3 months (±28 days) from the safety follow up visit until up to 30 months after the last subject is randomized. As such, the maximum estimated study duration is approximately 49 months.

3.4.2 End of Study

All subjects will be followed up either by clinic visit or telephone contact approximately every 3 months (± 28 days) until 30 months after the last subject is randomized.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (age, sex, race), date, and outcome of the screening process (eg, randomized into study, reason for ineligibility, or refused to participate). This log will be completed and updated by telephoning an Interactive Voice Response System (IVRS).

4.1 Inclusion Criteria

4.1.1 Disease related

101) Histologically or cytologically-confirmed adenocarcinoma of the colon or rectum in subjects who are presenting with metastatic disease

102) At least 1 uni-dimensionally measurable lesion of at least 20mm per modified RECIST guidelines (all sites of disease must be evaluated ≤ 28 days prior to randomization)

103) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

104) Paraffin-embedded tumor tissue from the primary tumor or metastasis available for central analyses of EGFr and biomarker testing

4.1.2 Demographic

105) Man or woman ≥ 18 years of age

4.1.3 Laboratory

Hematologic function, as follows (≤ 7 days prior to randomization):

106) Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

107).Platelet count ≥ 100 x 10^9/L

108) Hemoglobin ≥ 9 g/dL

Renal function, as follows (≤ 7 days prior to randomization):

109) Creatinine clearance, estimated with Cockcroft-Gault* ≥ 50 ml/min

*Cockcroft-Gault:

$$\text{CrCl, estimated [ml/min]} = \left\{ \frac{(140 - \text{age[years]}) \times (\text{Lean body mass [kg]})}{(\text{Serum Creatinine [mg/dL]} \times 72)} \right\} \times 0.85 \text{ [for women]}$$

Hepatic function, as follows (≤ 7 days prior to randomization):

110) Aspartate aminotransferase (AST) ≤ 3 x ULN (if liver metastases ≤ 5 x ULN)

111) Alanine aminotransferase (ALT) ≤ 3 x ULN (if liver metastases ≤ 5 x ULN)

112) Total bilirubin ≤ 1.5 x ULN

Metabolic function, as follows (≤ 7 days prior to randomization):

113) Magnesium ≥ lower limit of normal

114) Negative pregnancy test ≤ 72 hours prior to randomization (females of childbearing potential only)

4.1.4 Ethical

115) Competent to comprehend, sign, and date an IEC/IRB-approved informed consent form

116) Life expectancy ≥ 3 months

4.2 Exclusion Criteria

4.2.1 Disease Related

201) History or known presence of central nervous system (CNS) metastases

202) History of another primary cancer, except:

- Curatively treated in situ cervical cancer, or
- Curatively resected non-melanoma skin cancer, or
- Other primary solid tumor curatively treated with no known active disease present and no treatment administered for ≥ 5 years prior to randomization

4.2.2 Therapies

203) Prior chemotherapy or systemic therapy for the treatment of metastatic colorectal carcinoma with the following exceptions:

- Subject may have received adjuvant fluoropyrimidine-based chemotherapy if disease progression is documented at least 6 months after completion of chemotherapy
- Subjects may have received prior fluoropyrimidine therapy if administered solely for the purpose of radiosensitization

204) Prior oxaliplatin therapy

205) Prior anti-EGFr antibody therapy (eg, cetuximab) or treatment with small molecule EGFr inhibitors (eg, erlotinib)

206) Any investigational agent or therapy ≤ 30 days prior to randomization

207) Radiotherapy ≤ 14 days prior to randomization (subjects must have recovered from all radiotherapy related toxicities)

208) Known allergy or hypersensitivity to platinum-containing medications, 5-FU or leucovorin

4.2.3 General

209) Active infection requiring systemic treatment or any uncontrolled infection ≤ 14 days prior to randomization

210) Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, cardiac arrhythmia) ≤ 1 year prior to randomization

211) History of interstitial lung disease (eg, pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest CT scan

212) Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as ≥ CTC grade 2, [CTCAE version 3.0])

213) Known positive tests for human immunodeficiency virus (HIV) infection, hepatitis C virus, acute or chronic active hepatitis B infection

214) Any co-morbid disease or condition that could increase the risk of toxicity, eg, dihydropyrimidine deficiency, significant ascites or pleural effusion

215) Peripheral sensory neuropathy with functional impairment (≥ CTC grade 3 [CTCAE version 3.0] neuropathy, regardless of causality)

216) Any uncontrolled concurrent illness or history of any medical condition that may interfere with the interpretation of the study results

217) Major surgical procedure (requiring general anesthesia) ≤ 28 days or minor surgical procedure (excluding central venous catheter placement) ≤ 14 days prior to randomization. Subjects must have recovered from surgery related toxicities.

218) Subject who is pregnant or breast feeding

219) Woman or man of child-bearing potential not consenting to use adequate contraceptive precautions ie, double barrier contraceptive methods (eg, diaphragm plus condom), or abstinence during the course of the study and for

6 months after the last study drug administration for women, and 1 month for men

220) Subject unwilling or unable to comply with study requirements

221) Previously randomized into this study protocol

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3). A subject is considered enrolled when he or she has been randomized into the study via the IVRS.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of re-screening or randomization. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects who do not meet eligibility may be re-screened at the discretion of the Investigator. Subjects who will not be re-screened or are determined not eligible after re-screen must be screen failed through the IVRS. Subjects may only be randomized once into this protocol.

5.1 Treatment Assignment

Upon confirmation of eligibility, the site staff will telephone IVRS to randomize a subject to one of two treatment arms:

Arm 1: FOLFOX with panitumumab or,

Arm 2: FOLFOX alone

5.2 Randomization

Subjects will be randomized through the IVRS. The randomization will be stratified by geographic region (Western Europe, Canada and Australia vs Rest of World) and ECOG performance status (0 or 1 vs 2; see Appendix C).

Following randomization via the IVRS, study treatment should commence within 3 days.

6. TREATMENT PROCEDURES

Panitumumab will be the only investigational product administered in this study (see Section 11 for a complete description of panitumumab).

6.1 Investigational Product Dosage, Administration, and Schedule

For subjects randomized to receive FOLFOX with panitumumab, panitumumab will be administered by IV infusion on day 1 of each cycle just prior to the administration of chemotherapy (see Section 6.6.2). One treatment cycle is defined as the 14 day period following the commencement of treatment with FOLFOX + panitumumab or FOLFOX alone plus additional time, as needed, for the resolution of FOLFOX-related toxicities. In the event a cycle is delayed beyond 14 days due to chemotherapy-related toxicity, administration of panitumumab should also be delayed. For subjects randomized to receive FOLFOX with panitumumab but subsequently switched to panitumumab monotherapy due to FOLFOX intolerance (see Section 6.6.3.2), panitumumab should be administered every 14 days ± 3 days.

The starting panitumumab dose is 6 mg/kg. The total dose may be rounded up or down by no greater than 10 mg. The panitumumab dose will be calculated based on the subject's actual body weight at baseline (ie, cycle 1, day 1) and will not be re-calculated unless the actual body weight changes by at least 10%. Panitumumab will be diluted in a minimum of 100 mL of pyrogen-free 0.9% sodium chloride solution USP/PhEur (normal saline solution, supplied by the site). The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL; if necessary, the volume of normal saline should be increased.

Panitumumab will be administered intravenously (IV) by an infusion pump through a peripheral line or indwelling catheter using a 0.22-micron in-line filter infusion set-up (which will be provided by the sponsor) over 1 hour ± 15 minutes by a trained healthcare professional. If the first infusion is well tolerated (ie, without any

serious infusion-related reactions) then all subsequent infusions may be administered over 30 minutes ± 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.

If the filter extension set is not compatible with the infusion set-up at the study center, the sponsor should be contacted immediately. Strict adherence to aseptic technique should be used during panitumumab preparation and administration. The bag should be labeled per site pharmacy Standard Operating Procedures and promptly forwarded to the clinical research center for infusion.

The effects of overdose of panitumumab are not known.

See Appendix J Pharmacy Guide for information on panitumumab packaging and formulation, labeling, storage, preparation, supply/return, and accountability.

6.1.1 Pre-medication for Panitumumab

Panitumumab specific pre-medication is not required for routine panitumumab infusions. If, during or after any infusion, a reaction occurs, pre-medication may be used for subsequent panitumumab infusions (eg, acetaminophen/paracetamol and/or an H1 blocker eg, diphenhydramine).

6.1.2 Interruption of Panitumumab Infusion

Subjects who experience any serious infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

6.2 Toxicity Assessment

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using the National Cancer Institute's Common Toxicity Criteria (CTC) version 3.0 (Appendix E), with the exception of skin- or nail-related toxicities, which must be graded using CTC version 3.0 with modifications (see Appendix F).

6.3 Panitumumab Dosage Adjustments

For subjects who experience toxicities while on study, one or more doses of panitumumab may need to be withheld, reduced, or delayed (administered at > 14 day intervals). On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed (outlined in Figure 1). Dose escalations above 6.0 mg/kg starting dose are not allowed. Panitumumab dose reductions are listed in Table 1.

Table 1. Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

6.3.1 Criteria for Withholding a Dose of Panitumumab

Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment
- Need for surgical debridement
- Any skin- or nail-related serious adverse event (see Section 9.1.2)

Non-skin- or nail-related toxicities:

- Any grade 3 or 4 toxicity with the following exceptions:
  - Panitumumab will be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement
  - Panitumumab will be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care
  - Panitumumab will be withheld for grade ≥ 3 anemia or grade 4 thrombocytopenia that can not be managed by transfusion(s) or cytokine therapy

6.3.2 Criteria for Re-treatment with Panitumumab

Skin- or nail-related toxicities:

Panitumumab administration may be restarted once:

- The adverse event has improved to ≤ Grade 2 (Appendix F) or returned to baseline, or;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
- Systemic steroids are no longer required, or
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

Panitumumab administration may be restarted once the adverse event has improved to ≤ Grade 1 or returned to baseline.

6.3.3 Dose Modification Schedule

Subjects should be assessed for toxicity before each treatment cycle. For subjects randomized to receive panitumumab, dose modification should be performed according to the schedule described below and outlined in Figure 1.

Subjects who develop a toxicity that does not meet the criteria for withholding a dose of panitumumab (Section 6.3.1) should continue to receive panitumumab and their symptoms should be treated.

Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with panitumumab (Section 6.3.2).

For subjects who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

- Subjects receiving either 100% or 80% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.
- Subjects treated at the 100% dose level, whose toxicity resolves after 1 dose of panitumumab is withheld, should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab.
- Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of panitumumab are withheld should be re-started at the 80% dose level.

- Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of panitumumab should be re-started at the 60% dose level.
- Subjects who experience toxicity at the 60% dose level will not be re-treated with panitumumab.

It is recommended that panitumumab doses will be escalated in subjects whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab (Section 6.3.2). Dose escalations are recommended but not required. Dose escalations should occur in the following manner:

- Subjects treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next cycle unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).
- Subjects treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next cycle unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

Subjects, who must have a delay of panitumumab administration beyond 6 weeks from the previous dose of panitumumab (ie, 3 or more consecutively missed doses) due to toxicity, will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.

If a subject demonstrates a clinical benefit with a documented response of stable disease, partial response or complete response and there are reasons that the above dose modification rules can not be implemented, the investigator should contact and discuss these reasons with Amgen. The investigator must obtain written agreement from Amgen before any changes in the dose modification rules can be implemented.

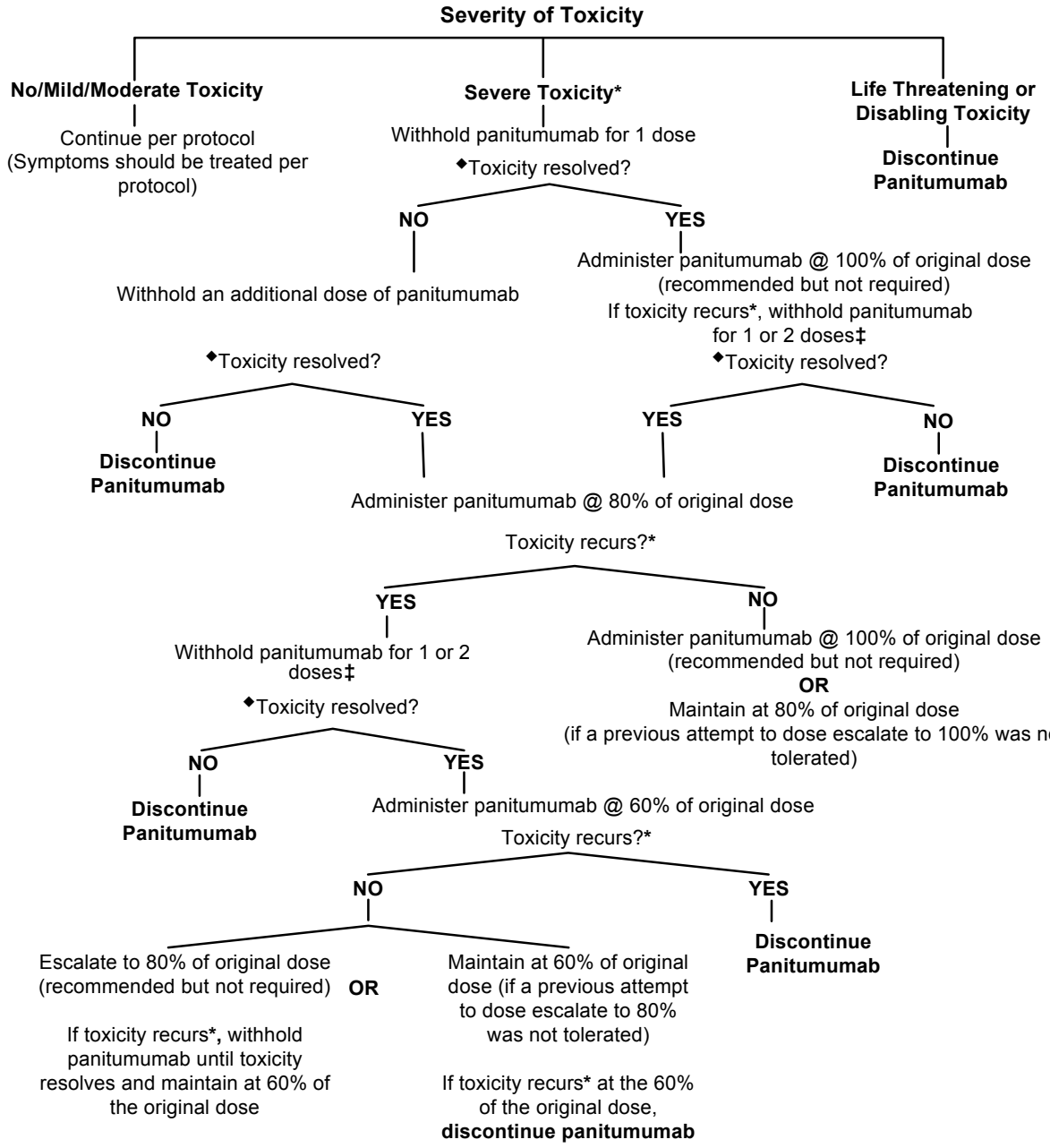
6.4 Panitumumab Delayed- or Missed-Doses

Panitumumab should be given on the first day of each chemotherapy cycle. If a cycle of chemotherapy is delayed, panitumumab administration should also be delayed. If the subsequent cycle of chemotherapy is also delayed, with greater than 4 weeks from the previous dose of chemotherapy, and the subject has not had disease progression, panitumumab monotherapy should be administered as soon as possible. Delays of panitumumab administration greater than 6 weeks from the previous dose of panitumumab are not allowed.

Reasons to withhold a dose of panitumumab are described in Section 6.3.1. If a subject is able to receive a cycle of FOLFOX but panitumumab must be withheld due to toxicity,

FOLFOX should be administered, and this dose of panitumumab will be considered missed. For all subjects, delays of panitumumab administration beyond 6 weeks from the previous dose of panitumumab (ie, 3 or more consecutively missed doses) are not allowed and panitumumab therapy will be permanently discontinued. Missed panitumumab doses will not be made up.

Figure 1. Panitumumab Dose Modification Algorithm for Toxicity



* Assess toxicity before each cycle. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study (See Section 6.3.1).

◆ Assess toxicity before each cycle. Toxicity resolved = meets the criteria for restarting panitumumab (see section 6.3.2). Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

‡ Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 6 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

6.5 Discontinuation of Panitumumab

Panitumumab will be administered until subjects develop disease progression or are unable to tolerate panitumumab. Any subject permanently discontinued from receiving panitumumab will be allowed to continue to receive FOLFOX until disease progression or intolerance to FOLFOX.

6.6 Other Protocol-Required Drugs

FOLFOX chemotherapy agents should be obtained by each site as per routine institutional practice. For preparation and complete prescribing information, please refer to the most current package inserts in the region.

Prior to FOLFOX chemotherapy administration the investigator or designee will review the subject's hematology and chemistry panels, liver function tests, and incidence of hematologic and non-hematologic toxicities and will follow the parameters in Section 6.6.2 and 6.6.3 to determine treatment suitability.

6.6.1 FOLFOX Regimen Pre-medication

Antiemetics may be used, where clinically indicated, at the discretion of the investigator or according to standard institutional or regional practice. See Section 6.9 for further supportive therapy recommendations.

6.6.2 FOLFOX Regimen Schedule

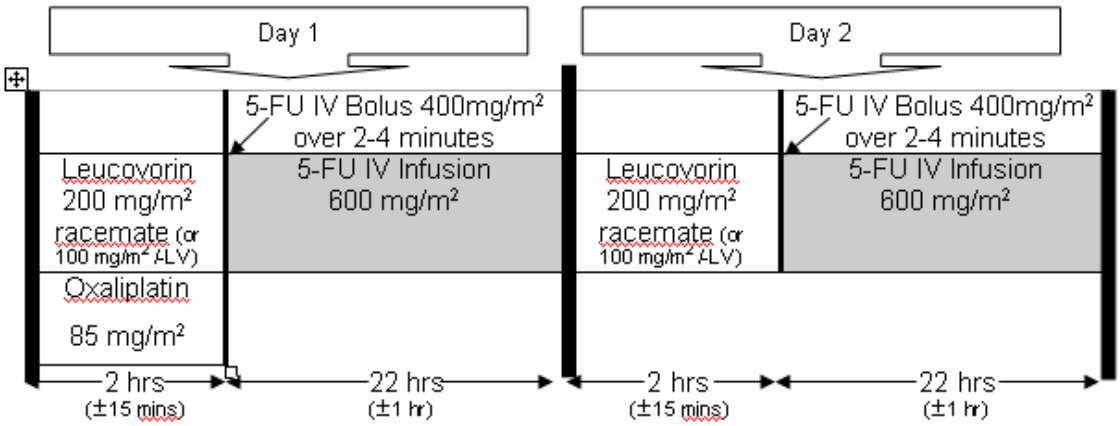
Administration of FOLFOX4 chemotherapy will commence on day 1 of each treatment cycle. In those subjects randomized to receive FOLFOX4 plus panitumumab, FOLFOX4 chemotherapy agents will be administered after the administration of panitumumab.

The FOLFOX4 regimen will be administered every 2 weeks (± 3 days) as follows:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL **D5W** and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in **D5W** both given over 120 minutes (± 15 minutes) at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour (± 1 hour) continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes (± 15 minutes), followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour (± 1 hour) continuous infusion

Figure 2. Chemotherapy Administration Schedule



A new cycle of FOLFOX4 treatment will be repeated every 2 weeks but may not be administered to the subject if the ANC <1.5 x 10^9 cells/L; or if the platelet count is < 75 x 10^9/L; or if skin toxicity (non-panitumumab related), stomatitis, or diarrhea have not recovered to ≤ grade 1; or if fatigue has not recovered to ≤ grade 2. Up to a 4 week delay is allowed in the initiation of a new cycle of treatment for resolution of toxicities. A treatment delay of one component of the FOLFOX4 regimen (ie, 5-FU/leucovorin or oxaliplatin) results in a similar delay of the other component to allow both therapies to be given together on day 1 of each 2-week cycle.

In the event that FOLFOX4 chemotherapy administration is discontinued for any reason prior to disease progression, panitumumab may continue as monotherapy in subjects who have been randomized to study arm 1. Panitumumab infusions should remain on a once every 14 days (± 3 days) schedule until the subject develops disease progression or is unable to tolerate panitumumab monotherapy.

In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy and panitumumab **(for subject randomized to study arm 1) or 5-FU/leucovorin therapy (for subject randomized to study arm 2)** may continue on a once every 14 days (±3 days) schedule until disease progression or intolerance to the study therapy.

If FOLFOX4 chemotherapy interruption is ≤ 6 weeks from the previous cycle, and the subject has recovered from toxicity, as specified above, and the subject's disease has not progressed, FOLFOX4 chemotherapy with/without panitumumab should be restarted at doses according to Tables 2, 3, and 4. If FOLFOX4 chemotherapy interruption is > 6 weeks, but the subject has recovered from toxicity and the subject's disease has not

progressed, the case should be reviewed by the sponsor study team in conjunction with the investigator to determine the appropriateness of treatment resumption.

6.6.3 FOLFOX Regimen Dose Levels and Modifications Guidelines

6.6.3.1 FOLFOX4 Dose Levels

Subjects should be closely monitored for FOLFOX4 toxicity. Doses of 5-FU and oxaliplatin may be adjusted depending on an individual subject's tolerance. The dose of leucovorin will remain fixed at 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV). Tables 2 to 4 indicate recommended dose levels and modification guidelines for oxaliplatin and 5-FU for non-neurological and neurological toxicity.

6.6.3.2 FOLFOX4 Dose Modification

Table 2 describes the recommended dose reductions for non-neurological toxicity.

Table 2. FOLFOX4 Dose Reductions – Non-Neurological Toxicity

	Starting Dose	Dose Level –1	Dose Level –2
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-FU Bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2
5-FU Infusion	600 mg/m^2	500 mg/m^2	400 mg/m^2

Table 3 describes the recommended dose modifications at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding toxicity.

Table 3. FOLFOX4 Dose Modification Guidelines

Toxicity NCI Grade* (Value)	Dose Level for Subsequent Cycles Based on Interval Toxicity**	At Time of Retreatment
No toxicity	Maintain dose level	Maintain dose level
Neutropenia (ANC)		
Grade 1 (ANC <LLN - 1.5 x 10^9/L)	Maintain dose level	If ANC < 1.5 x 10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity.
Grade 2 (ANC 1.5 x 10^9/L - 1.0 x 10^9/L)	Maintain dose level	
Grade 3 (ANC 1.0 x 10^9/L – 0.5 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	
Grade 4 (ANC < 0.5 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	If ANC < 1.5 x 10^9/L after 4 weeks, discontinue therapy.
Thrombocytopenia		
Grade 1 (PLT < LLN - 75.0 x 10^9/L)	Maintain dose level	If PLT < 75.0 x 10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity.
Grade 2 (PLT 75.0 x 10^9/L - 50.0 x 10^9/L)	Maintain dose level	
Grade 3 (PLT 50.0 x 10^9/L - 25.0 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	
Grade 4 (PLT < 25.0 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	If PLT < 75.0 x 10^9/L after 4 weeks, discontinue therapy.
Neutropenic fever		
ANC <1.0 x 10^9/L (i.e. Grade 3 or 4 neutropenia) & fever $\geq$ 38.5°C	Decrease both 5-FU & OXAL 1 dose level	
Other hematologic toxicities	Dose modifications for leukopenia at the start of subsequent courses of therapy and at time of retreatment are also based on NCI toxicity criteria (CTC Version 3.0) and are the same as recommended for neutropenia above.	
Diarrhea		
Grade 1	Maintain dose level	If Grade 2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity.
Grade 2	Maintain dose level	
Grade 3	Decrease both 5-FU & OXAL 1 dose level	
Grade 4	Decrease both 5-FU & OXAL 1 dose level	If Grade 2 diarrhea after 4 weeks, discontinue therapy.

Page 1 of 2

* National Cancer Institute Common Toxicity Criteria (CTC Version 3.0).
** Refers to initial dose used in previous course.
1 For mucositis/stomatitis decrease only 5-FU, not Oxaliplatin.
2 Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

Table 3. FOLFOX4 Dose Modification Guidelines

Toxicity NCI Grade* (Value)	Dose Level for Subsequent Cycles Based on Interval Toxicity**	At Time of Retreatment
Other nonhematologic toxicities[1,2]	Dose modifications for other nonhematologic toxicities at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC version 3.0) and are the same as recommended for diarrhea above.	
The dose of LV will not be adjusted due to toxicity. It should remain at 200 mg/m² racemate (or 100 mg/m² *l*-LV) for all courses. LV will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, LV will be delayed.		

Page 2 of 2

* National Cancer Institute Common Toxicity Criteria (CTC Version 3.0).
** Refers to initial dose used in previous course.
1 For mucositis/stomatitis decrease only 5-FU, not Oxaliplatin.
2 Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

Table 4 describes the recommended dose modifications of oxaliplatin based on the duration of oxaliplatin-associated neurotoxicity.

Table 4. Dose Modification Guidelines Oxaliplatin-Associated Neurotoxicity

Toxicity (Grade)	Duration of Toxicity		Persistent (Not Resolved Between Cycles)
	1 - 7 Days	> 7 Days	
Paresthesias/dysesthesias[1] of short duration that resolve and do not interfere with function (Grade 1)	No Change	No Change	No Change
Paresthesias/dysesthesias[1] interfering with function, but not activities of daily living (ADL) (Grade 2)	No Change	No Change	Decrease to 65 mg/m²
Paresthesias/dysesthesias[1] with pain or with functional impairment that also interfere with ADL (Grade 3)	1st time: Decrease to 65 mg/m² 2nd time: Decrease to 40 mg/m²	STOP	STOP
Persistent paresthesias /dysesthesias that are disabling or life-threatening (Grade 4)	STOP	STOP	STOP
Pharyngo-laryngeal dysesthesias	No Change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

[1] May be cold-induced

A new cycle of FOLFOX4 treatment will be repeated every 2 weeks but may not be administered to the subject if the ANC <1.5 x 10^9 cells/L; or if the platelet count is < 75 x 10^9/L; or if skin toxicity (non-panitumumab related), stomatitis, or diarrhea have not recovered to ≤ grade 1; or if fatigue has not recovered to ≤ grade 2. Up to a 4 week delay is allowed in the initiation of a new cycle of treatment for resolution of toxicities. A treatment delay of one component of the FOLFOX4 regimen (ie, 5-FU/leucovorin or oxaliplatin) results in a similar delay of the other component to allow both therapies to be given together on day 1 of each 2-week cycle.

In the event that FOLFOX4 chemotherapy administration is discontinued for any reason prior to disease progression, panitumumab may continue as monotherapy in subjects who have been randomized to study arm 1. Panitumumab infusions should remain on a once every 14 days (± 3 days) schedule until the subject develops disease progression or is unable to tolerate panitumumab monotherapy.

In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy and panitumumab **(for subjects randomized to study arm 1) or 5-FU/leucovorin therapy (for subjects randomized to study arm 2)** may continue on a once every 14 days (±3 days) schedule until disease progression or intolerance to the study therapy.

If FOLFOX4 chemotherapy interruption is ≤ 6 weeks from the previous cycle, and the subject has recovered from toxicity, as specified above, and the subject's disease has not progressed, FOLFOX4 chemotherapy with/without panitumumab should be restarted at doses according to Tables 2, 3, and 4. If FOLFOX4 chemotherapy interruption is > 6 weeks, but the subject has recovered from toxicity and the subject's disease has not progressed, the case should be reviewed by the sponsor study team in conjunction with the investigator to determine the appropriateness of treatment resumption.

6.6.4 Discontinuation of FOLFOX

Oxaliplatin / 5-FU / Leucovorin will be administered until subjects develop disease progression or are discontinued due to intolerance. Upon disease progression oxaliplatin / 5-FU / Leucovorin will be permanently discontinued.

6.7 Electrolyte Management

Subjects should be evaluated as outlined in Section 7 and managed as per local medical practice. If hypomagnesemia is present, replacement should be managed with either oral or parental replacement, or both, according to institutional practice and to the degree of hypomagnesemia present. It is recommended that the subject's serum magnesium level should be maintained within the normal range during study treatment.

It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesemia. Subjects' serum potassium and calcium parameters are recommended to be maintained, as per local medical practice, within the normal ranges during study treatment.

6.8 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.10.

All prescribed and non-prescription concomitant medications that are ingested, applied, or injected on an ongoing basis from signing of the informed consent, as well as changes in such concomitant medications, and any new concomitant medication taken while the subject is on study, should be recorded on the appropriate case report form. Concomitant medications should be recorded until 30 days after the last dose of study treatment. Concomitant medications for medically significant adverse events which are ongoing at the end of study treatment and considered related to study treatment, should be followed until the adverse event is resolved or considered stable.

The use of topical, oral or IV antibiotics to treat skin- or nail-related toxicities is allowed at the investigator's discretion; such use should be recorded on the appropriate case report form.

For subjects on anticoagulant therapy, close monitoring of coagulation parameters is recommended during the study treatment period.

6.9 Supportive Therapy for FOLFOX Chemotherapy

6.9.1 Antiemetics

5-FU and oxaliplatin may be emetogenic. Prior to the administration of FOLFOX, pre-medication with antiemetics, such as serotonin ($5HT_3$) antagonists (ie, ondansetron, or granisetron) with or without dexamethasone may be used at the investigator's discretion or according to institutional standards. Variances by regional practice are acceptable.

6.9.2 Growth Factors

For low white blood cell counts, granulocyte-colony-stimulating factor (G-CSF) should be used in subjects with serious neutropenic complications such as febrile neutropenia, tissue infections, sepsis syndrome, fungal infection, etc. It is recommended that G-CSF be used and administered according to the product label or applicable guidelines. For chemotherapy-induced anemia, epoetins should also be used and administered according to the product label or applicable guidelines.

6.9.3 Oral Cryotherapy

Subjects receiving oxaliplatin should not receive oral cryotherapy (ie. ice for mucositis prophylaxis) on Day 1 of each treatment cycle as this may exacerbate laryngopharyngeal dysesthesia caused by oxaliplatin.

6.9.4 Hypersensitivity

Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment may include supplemental oxygen, standard epinephrine, corticosteroid, antihistamine therapy, bronchodilators or vasopressors. Platinum hypersensitivity is a rare event and should be treated promptly.

6.9.5 Pharyngolaryngeal Dysesthesias

Oxaliplatin may cause discomfort in the larynx or pharynx associated with dyspnea, anxiety and difficulty swallowing. This discomfort is exacerbated by cold. Appropriate therapy may include the use of antihistamine therapy, bronchodilators, cold avoidance or monitoring.

6.10 Proscribed Therapy During Study Period

Subjects must be withdrawn from study treatment if they receive any other:

- investigational agents,
- anti-EGFr targeting agents other than panitumumab,
- experimental or approved anti-tumor therapies (eg, bevacizumab),
- chemotherapy other than FOLFOX4,
- radiotherapy (with the exception of use for pain control),
- systemic steroids (with the exception of those used for symptomatic skin- or nail-related toxicities requiring withholding of the panitumumab dose (see Section 6.3.1), those used as chemotherapy pre-medication or post chemotherapy to delay chemotherapy related toxicities, or those used for an infusion reaction).

Subjects should not schedule any elective surgeries (excluding central venous catheter placement) during their participation in the study treatment period, or until 7 days after their last administration of study treatment (chemotherapy and/or panitumumab, whichever is the last administration). If a subject undergoes any unexpected surgery during the course of the study, that subject must discontinue all study treatment immediately, and the sponsor should be notified as soon as possible. A subject may be allowed to resume study treatment (chemotherapy and/or panitumumab) after each surgical case is reviewed by the sponsor study team in conjunction with the investigator to determine the appropriateness of treatment resumption.

For any subjects who undergo metastases resection during the study, refer to Section 6.11.

6.11 Metastases Interventional Therapy

During the study, subjects who undergo interventional therapy for metastases eg, surgical resection, radiofrequency ablation or cryotherapy, will do so according to standard institutional practice. Study treatment (chemotherapy and/or panitumumab) should be withheld for ≥7 days prior to the interventional therapy. Protocol scheduled tumor assessments or an assessment to confirm objective response must be done prior to intervention.

After the intervention, subjects will undergo radiological imaging of the chest, abdomen, pelvis and all other sites of disease by either CT or MRI (see Section 7.6 for further details). The first post-intervention radiological imaging will provide the “new baseline” tumor measurements, from which progression will be assessed and/or the “new nadir”

from which progression will be assessed for the post-intervention modified RECIST tumor response assessments (according to Appendix I). Any remaining sites of disease must continue to be followed as target or non-target disease as designated at study screening. Post-intervention radiological imaging will be performed until disease progression, according to the treatment phase schedule of the study protocol.

When appropriate, within 6 weeks post-intervention and if intervention-related toxicities are resolved, subjects may resume pre-surgery study treatment (chemotherapy and/or panitumumab) and treatment phase study protocol assessments until disease progression or intolerance to the study treatment. All subjects who discontinue study treatment prior to disease progression should continue to be followed every 8 weeks ±1 week for disease progression (per modified RECIST) or disease recurrence (as applicable) and patient reported outcomes until disease progression or the end of the study, whichever is earlier.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Appendices A and B) for an outline of procedures required at each visit.

Serious adverse events will be collected as described in Section 9.

7.1 Screening

A signed and dated IEC/IRB approved informed consent (see Appendix G) must be obtained before any study specific procedures are performed. All hematology and chemistry panels, pregnancy test, and carcinoembryonic antigen (CEA) will be analyzed at a local laboratory. Procedures that are part of routine care are not considered study specific procedures. Procedures that are part of routine care may be used as screening procedures to determine eligibility. All subjects will be screened for eligibility before randomization into the study. The screening process begins on the date the subject signs the IEC/IRB approved informed consent form and continues until study randomization via the study IVRS. Only eligible subjects will be randomized into the study.

All subjects must have the following procedures completed ≤ 28 days (unless otherwise noted) before randomization (and starting treatment if the subject is eligible):

- Review of inclusion and exclusion criteria

- Recording of concomitant medication
- Medical and medication history
- Resting pulse, blood pressure, respiration, and temperature measurements
- Weight
- ECOG performance status assessment (≤ 7 days prior to randomization)
- Physical examination including height
- Laboratory Tests (≤7 days prior to study randomization unless otherwise noted):
    - Hematology panel: hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular volume, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
    - Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice),** blood urea nitrogen (BUN) or urea (depending on local institutional practice), lactate dehydrogenase (LDH), magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, phosphorous, and uric acid
- Serum CEA
- Urine or serum pregnancy test for female subjects with childbearing potential (≤ 72 hours prior to study randomization)
- ECG (All ECG reports must include HR, QRS, QT, QTc, and PR intervals)
- Radiological imaging of the chest, abdomen, pelvis and all other sites of disease by CT (or MRI if clinically indicated) - see Section 7.6 for more details
- Obtain archived paraffin-embedded tumor tissue sample;

or

- Obtain paraffin-embedded tumor tissue sample from a routine biopsy performed during the screening period, for EGFr testing and biomarker analyses. See Section 7.8.1 for full details of requirements
- Completion of Patient Reported Outcome (PRO) questionnaire by the subject (≤ 7 days prior to randomization):
    - EQ-5D: A five-item scale assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which can be scored to produce a single index value. The questionnaire also contains a

0-100 visual analogue scale that respondents can use to rate their health status (EuroQol Group, 1990).

[Note: Only subjects who provide their own informed consent for the study will contribute to the EQ-5D data.]

7.2 Enrollment and Randomization

Upon confirmation of eligibility, subjects will be randomized through the IVRS. The randomization will be stratified by geographic region (Western Europe, Canada and Australia vs Rest of World) and ECOG performance status (0 or 1 vs 2). Subjects will be randomized in a 1:1 ratio to receive FOLFOX with panitumumab or FOLFOX alone.

7.3 Treatment Phase

Study treatment should be started as soon as possible after the IVRS randomization call is made, and no later than 3 days post randomization.

Study day 1 is defined as the 1st day that study treatment is administered to the subject.

The 2-week (14 day) FOLFOX regimen (plus the time required to recover from toxicity, if encountered) is defined as a cycle.

Panitumumab will be administered at a dose of 6 mg/kg every 2 weeks on day 1 of each cycle. A subject may continue to receive panitumumab until he or she develops disease progression as defined by the modified RECIST criteria, or is unable to tolerate panitumumab.

The following procedures will be completed:

- Recording of concomitant medication (day 1 of each cycle)
- Recording of adverse events: including skin- or nail-related toxicities (day 1 of each cycle)
- ECOG performance status assessment (day 1 of every second cycle)
- Physical examination (day 1 of each cycle)
- Resting pulse, respiration, temperature and blood pressure measurements (day 1 of each cycle)
- Weight (day 1 of each cycle)
- Body Surface Area (BSA): To be calculated at day 1 of cycle 1 and at the beginning of any cycle during which the subject's weight has changed by 10% from baseline (ie, cycle 1)

- Laboratory Tests (≤ 48 hours prior to commencement of each cycle). Whenever possible the same local laboratory should be used throughout the study:
    - Hematology panel: hemoglobin, hematocrit, RBC count, mean corpuscular volume, platelets, WBC count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
    - Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice)**, BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid
- Serum CEA (every 8 weeks ± 1 week until disease progression [per the modified RECIST criteria])
- Blood (serum sample, EDTA blood [plasma and cell pellet], PAXgene blood [RNA]) sample collection for exploratory biomarker development (prior to panitumumab administration on day 1 of cycles 1 and 2 and ± 7 days of each radiological tumor assessment)
- Serum sample collection for anti-panitumumab antibody analyses (prior to study treatment administration on day 1 of cycle 1). To be collected for all randomized study subjects
- Radiological imaging of the chest, abdomen, pelvis and all other sites of disease by either CT or MRI - see Section 7.6 for more details. Disease assessment should be performed every 8 weeks ± 1 week until disease progression (per the modified RECIST criteria):
    - Any complete or partial response observed will be confirmed by repeating the imaging studies no less than 28 days after the initial complete or partial response is observed
- Completion of PRO questionnaire (every 4 weeks ± 1 week while on study treatment):
    - EQ-5D

7.4 Safety Follow-Up Visit

When any subject discontinues dosing of all study treatment (ie, they are no longer receiving either panitumumab or FOLFOX), he or she will undergo a safety follow-up assessment 30 days ± 3 days after the last dosing of study treatment.

The following assessments will be obtained:

- Recording of concomitant medications
- Recording of adverse events: including skin- or nail-related toxicities
- ECOG performance status
- Physical examination
- Resting pulse, respiration, temperature and blood pressure
- Weight
- Laboratory Tests (whenever possible the same local laboratory should be used throughout the study):
    - Hematology panel: hemoglobin, hematocrit, RBC count, mean corpuscular volume, platelets, WBC count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
    - Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice)** , BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid
- Serum CEA [Note: Serum CEA will only be analyzed for subjects who have withdrawn from the study for reasons other than progressive disease and have not had a serum CEA analysis within the previous 8 weeks $\pm$ 1 week]
- Urine or serum pregnancy test for female subjects of childbearing potential
- Blood (serum sample, EDTA blood [plasma and cell pellet], PAXgene blood [RNA]) and sample collection for exploratory biomarker development studies
- Serum sample collection for anti-panitumumab antibody analyses
- Radiological imaging of the chest, abdomen, pelvis and all other sites of disease. Disease assessment should be performed according to the modified RECIST guidelines. [Note: Tumor imaging and assessment will only be performed for subjects who have withdrawn from the study for reasons other than progressive disease and have not had a specified tumor evaluation completed within the previous 8 weeks $\pm$ 1 week]
- Completion of PRO questionnaire:
    - EQ-5D

All subjects with serious adverse event(s) ongoing at the time of the safety follow-up visit will continue to be followed until resolution of the serious adverse event(s).

All subjects who discontinue study treatment prior to disease progression eg, due to unacceptable toxicities, should continue to be followed for disease progression (per

modified RECIST) and patient reported outcomes every 8 weeks ± 1 week until disease progression or the end of the study.

For subjects who discontinue the study due to an assessment of disease progression by the investigator, which was subsequently not confirmed by the central radiology review committee, any available additional imaging data, subsequent to the safety follow up visit, will be requested to be submitted to the central radiology review committee in order to confirm disease progression by central review.

7.5 Long-Term Follow-Up Clinic Visit or Telephone Contact

All subjects will be contacted via clinic visit or telephone (by a member of the site staff) to assess disease status, subsequent cancer therapy, and survival following their last study drug administration. Contact will be made every 3 months ± 28 days from the safety follow-up visit until 30 months after the last subject is randomized.

7.6 Tumor Response Assessment

Baseline tumor measurements will be determined during screening. Tumor response assessments will be performed using a modified version of RECIST (Appendix I). For subjects who undergo curative intervention during the treatment phase, only pre-intervention tumor assessments will be used for ascertainment of a best overall response of CR, PR, or SD. Their post-intervention tumor assessments will be used to determine the time when PD occurs (eg, when a new lesion appears). In the event there is remnant disease after intervention, the first post-intervention radiological exam will serve as baseline or nadir for PD assessment.

Subjects will be evaluated for tumor response after every 8 weeks ± 1 week until documentation of disease progression (per the modified RECIST criteria). Subjects with symptoms suggestive of disease progression should be evaluated for tumor progression at the time symptoms occur. Subjects determined to have progressive disease will be discontinued from the treatment phase of the study and will undergo safety follow-up assessments 30 days ± 3 days after the last study treatment. Imaging data should be sent to central radiology for modified RECIST assessments, up to and including the subject's disease progression.

At baseline, CT scans of the chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Magnetic resonance imaging (MRI) is

acceptable to assess disease if it is clinically indicated and if used throughout the study. If the chest CT scan is normal at baseline, a chest X-ray (CXR) will be performed at each subsequent tumor imaging during the treatment phase. In the event the chest X-ray is found to be abnormal during the treatment phase, a chest CT scan will be obtained, and this modality should be used for subsequent tumor imaging. If the baseline chest CT scan is found to be abnormal, a chest CT scan will be performed throughout the treatment phase, even if no target lesions are located within that scan. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. At all imaging assessment points, all sites of disease identified at baseline should be scanned, even if they were chosen by the Investigator as non-target lesions.

A switch from CT to MRI (or visa versa) of the liver is considered the only acceptable change in modality and should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to IV contrast for CT scan while on trial. This change would require the pre-approval of the sponsor. CT and MRI are the best currently available and most reproducible methods of measuring index lesions selected for response assessment.

Ultrasound should not be used for assessment of visceral lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules or to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

In addition to the investigator's assessment, scans of all subjects evaluated for disease response will be reviewed centrally by a panel of at least 2 blinded independent radiologists unaffiliated with the sponsor and the conduct of the study. Blinded reviews will not be accessible to the study site nor to the subject.

7.7 Disease Progression

Disease progression will be defined per the modified RECIST criteria (Appendix I).

Subjects with evidence of disease progression will be discontinued from study treatment (FOLFOX with or without panitumumab) and will be followed up for safety (30 ± 3 days

after the last study drug administration) and survival (every 3 months ± 28 days until up to 30 months after the last subject is randomized).

For subjects who discontinue the study due to an assessment of disease progression by the investigator, which was subsequently not confirmed by the central radiology review committee, any available additional imaging data, subsequent to the safety follow up visit, will be requested to be submitted to the central radiology review committee in order to confirm disease progression by central review.

7.8 Biomarker Development and Pharmacogenetic Studies

7.8.1 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and response to panitumumab. These investigations may be useful in developing markers to identify disease subtypes, guide therapy and/or predict disease progression.

In addition to studying the safety of panitumumab in combination with FOLFOX, Amgen may attempt to develop blood and/or tumor test(s) designed to identify subjects most likely to benefit from panitumumab. A 20 mL blood sample will be drawn prior to panitumumab administration on day 1 of cycles 1 and 2, within 7 days of every radiological assessment(s) of tumor and at the safety follow-up visit. The study centers will be responsible for sending paraffin blocks collected before the study to Amgen. If paraffin blocks cannot be shipped, a minimum of 10 charged and 10 uncharged slides, and a core punch biopsy are requested from paraffin-embedded tumor samples collected either before the study (ie, archived tissue) or from a routine investigational biopsy performed during screening.

No additional invasive procedure for collection of tumor samples is intended as a part of this study. If a biopsy is performed during the course of the study as part of the routine investigations of the subject's disease, a paraffin embedded tumor sample may be collected for biomarker development purposes. A copy of the corresponding pathology report and the specimen report for each block/set of slides should be sent with the

samples. Biomarker development may be pursued by use of advanced biochemical analyses, such as ribonucleic acid transcript profiling and/or proteomic methods.

Please refer to the central laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.8.2 Pharmacogenetic Studies

Additionally, **and only if the subject signs a separate informed consent form (Appendix H)**, DNA may be utilized for exploratory pharmacogenetic analysis. These pharmacogenetic analyses are different from the blood analyses described above because they are focused on evaluating the different inherited gene forms in DNA that may influence the different responses subjects have to the same drug. The goals of these exploratory studies are to identify potential genetic markers that may help in the investigation of cancer and/or subjects who may have the best possible response to the investigational product.

To study the effects of human genetic variation on drug response, we plan to conduct exploratory pharmacogenetic studies as an **optional** part of this study. No additional blood will be collected for this part of the study, however for those subjects that consent to participate in these pharmacogenetic studies, DNA will be extracted from the samples collected for the biomarker development studies.

7.8.3 Sample Storage and Destruction

Blood and tumor samples, and any other components from the cells may be stored for up to 20 years to address research scientific questions related to colorectal cancer and/or panitumumab. The subject will continue to retain the right to have the sample material destroyed at any time by contacting the investigator. The sponsor will be the exclusive owner of any data, discoveries or derivative materials from the sample materials and is responsible for the destruction of the samples at the request of the subject through the investigator or at the end of the storage period. The investigator will provide the sponsor with the required study and subject numbers, so that any remaining blood, tumor, and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product, and the subject will have no commercial rights to such a product and will have no commercial rights to the data, information, discoveries, or derivative

materials gained or produced from the sample (see Sections 12.4 and 12.5 regarding subject confidentiality).

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health. Any subject who withdraws full consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request.

Withdrawal of partial consent means that the subject does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures). Subjects may decline to continue receiving investigational product at any time during the study. These subjects, as well as those who have stopped receiving investigational product for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations.

Reasons for removal from investigational product or observation might include:

- withdrawal of consent
- administrative decision by the investigator or Amgen
- pregnancy (report on Pregnancy Notification Worksheet, see Appendix K)
- ineligibility
- significant protocol deviation
- patient noncompliance
- adverse event (report on adverse event CRF)

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as

thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable case report forms.

8.2 Replacement of Subjects

Subjects who are removed or withdrawn from study following randomization will not be replaced. This study will enroll approximately **1150** subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment." (ICH E6:1.2)

This definition of adverse events is broadened in this study to include any such occurrence (eg, sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject has signed informed consent to the time of initiation of study treatment.

Worsening of a pre-existing medical condition (eg, cancer, diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events. Please refer to Sections 6.10 and 6.11 for further information around timing of surgery.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for the performing of protocol-required procedures or administration of study treatment **or for subjects undergoing hospitalization for planned metastasis interventional therapy** is not classified as an SAE.

9.2 Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1) observed by the investigator or reported by subjects are properly captured in the subjects' medical records, with 1 exclusion: those that both occur before randomization and are deemed by the investigator to be unrelated to study screening.

In addition, the investigator is responsible for ensuring that, for those subjects randomized to study treatment, all adverse events captured on the subjects' medical records (as specified above) are reported on the CRF.

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study treatment; and action taken. The investigator may

be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs.

If applicable, the relationship of the adverse event to the study treatment will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study treatment?" The investigator should respond to this question with either Yes or No.

If the adverse event occurred after informed consent but before initiation of study treatment, the relationship of the adverse event to study screening is to be assessed by means of the question: "Is there a reasonable possibility that the event may have occurred because of study screening?" The investigator should respond to this question with either Yes or No. If the answer is Yes, record what part of the study screening is suspected.

The severity grading scale used in this study is described in Appendix E.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Serious Adverse Event Reporting Procedures

With 1 exception, serious adverse events will be collected and recorded throughout the study period, beginning with the signing of the informed consent through **to the Safety Follow-Up Visit or** 30 **(+ 3)** days after the last dose of **protocol specified therapy**, whichever is longer. The only exception to this rule is the collection and recording of serious adverse events that both occur before randomization and are deemed by the investigator to be unrelated to study screening.

All serious adverse events that are recorded in subjects' medical records (as specified above) must be reported to Amgen within 1 working day of discovery or notification of

the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and faxed to Amgen Global Safety.

Serious adverse events also will be collected and reported within 1 working day of discovery or notification of the event if it occurs > 30 days after the last dose of investigational product or after the end of the study AND is thought to be possibly related to investigational product.

For all deaths, available autopsy reports and relevant medical reports should be faxed to Amgen Global Safety. For this reporting process, subject assessments must be made 30 days or longer after administration of the last dose of investigational product.

To comply with worldwide serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events will be unblinded before submission to regulatory authorities. Determination of expectedness will be based on the contents of Appendix A **and B** in the investigator's brochure for preapproval products and the regional prescribing information for marketed products.

Amgen will report serious adverse events (SAEs) and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/institutions and ethics committees in compliance with all applicable regulatory requirements and ICH GCP guidelines.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study Case Report Form.

The investigator should notify the appropriate IRB or ethics committee of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is an open-label, randomized, multicenter, phase 3 study to compare the efficacy of panitumumab in combination with chemotherapy to the efficacy of chemotherapy alone

for first-line treatment of mCRC among **subjects with** wild-type KRAS **tumors** (the Wild-Type KRAS Efficacy Analysis Set) and **subjects with mutant KRAS tumors** (**the Mutant KRAS** Efficacy Analysis Set). Subjects will be randomized at a 1:1 ratio to the experimental arm of panitumumab plus FOLFOX and the control arm of FOLFOX alone, stratified by geographic region and baseline ECOG performance status (See Section 3.1). KRAS status will be retrospectively measured prior to any unblinded efficacy comparisons by KRAS status.

For each of the two patient populations, the Wild-Type KRAS and the **Mutant KRAS** Efficacy Analysis Set (section 10.2.2), the goal of the primary statistical analysis of the study is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS), and to characterize and compare overall survival. The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each endpoint within each analysis set (see Section 10.3). The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors. Significance levels described will be 2-sided unless stated otherwise. PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Endpoints

10.2.1.1 Primary

- Progression-free survival (PFS): time from randomization date to date of disease progression per the modified RECIST criteria or death. Subjects not meeting criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

10.2.1.2 Secondary

- Overall survival (OS): time from randomization date to date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.
- Objective Response Rate (ORR): The incidence of either a confirmed complete response (CR) or partial response (PR) per modified RECIST criteria (responder) while on first-line treatment. A confirmed CR requires two assessments of CR at least 28 days apart. A confirmed PR requires two assessments at least 28 days apart of PR or CR. All subjects that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.
- Time to progression (TTP): time from randomization date to date of disease progression per the modified RECIST criteria. Subjects not meeting criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.
- Duration of response (DOR): (calculated only for those subjects with an objective response) time from first confirmed objective response to disease progression per the modified RECIST criteria. Subjects not meeting criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.
- Incidence of AEs and significant laboratory changes.

10.2.1.3 Tertiary

- Time to response: time from randomization date to date of first confirmed objective response. Non-responders by the analysis data cutoff date with a best response of SD will be censored at their last assessment of SD, and subjects with a best response of PD will be censored at the maximum observed time to a first confirmed response among all responders.
- Patient-reported outcomes:
  - EQ-5D health state index score
  - EQ-5D overall health rating

10.2.1.4 Exploratory

- Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of the study drug
- Investigation of the effects of genetic variation in drug metabolism genes, cancer genes, and drug target genes on subject response to investigational products (separate informed consent required)

10.2.2 Analysis Subsets

The ITT Efficacy Analysis Set includes all randomized subjects. Subjects will be analyzed according to treatment randomized regardless of treatment received. This analysis set is further broken down into the KRAS Evaluable Efficacy Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set whose **tumor** KRAS

status can be assessed), the Wild-Type KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose **tumor** KRAS status is tested as Wild-Type), the Mutant KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose **tumor** KRAS status is tested as Mutant), the KRAS Unevaluable Efficacy Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set who have no measurement of **tumor** KRAS status), **and the Wild-type Intent-to-Diagnosis (ITD) KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Efficacy Analysis Set whose tumor KRAS status is tested as wild-type plus subjects who have no measurement of tumor KRAS status, i.e., the union of the Wild-type and the Unevaluable KRAS Efficacy Analysis Sets)**. The **Wild-type KRAS Efficacy Analysis Set and the Mutant KRAS Efficacy Analysis Set** will be the primary analysis sets for analyses of PFS and OS.

The Central Tumor Response Evaluable Analysis set is defined as the subset of subjects in the ITT Efficacy Analysis Set with at least one uni-dimensionally measurable lesion per the modified RECIST criteria per blinded central radiology review (see Appendix I). This analysis set is further broken down into the KRAS Central Tumor Response Evaluable Analysis Set, and the Wild-Type **KRAS**, Mutant **KRAS**, Unevaluable KRAS **and Wild-type ITD KRAS** Central Tumor Response Evaluable Analysis Sets. The **Wild-type and the Mutant KRAS Central Tumor Response Analysis Sets** will be the primary analysis sets for the analyses of objective response rate, duration of response, and time to response. The **other** analysis sets will also be used for sensitivity analyses of **objective response rate, duration of response, and time to response to estimate treatment effects**. The Local Tumor Response **Evaluable An**alysis **S**et is defined as the subset of subjects in the ITT Efficacy Analysis Set with at least one uni-dimensionally measurable lesion per the local investigator. This analysis set will be used in a comparable manner for analyses based on local tumor assessments. Breakdown of this analysis set by KRAS status is similar to that of the Central Tumor Response Evaluable Analysis Set.

A sensitivity analysis may be performed on selected efficacy endpoints to assess the impact of protocol deviations using the Per Protocol (PP) Analysis Set, defined as the subjects in the ITT Analysis Set without pre-specified, selected important protocol deviations thought to impact on efficacy analyses. Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.

The primary PRO analyses will be conducted on the subset of subjects in the ITT Analysis Set who have at least 1 post-baseline PRO assessment (PRO All Randomized Analysis Set). Secondary analyses for the PRO endpoints may be performed for subjects in the PP Analysis Set (PRO Per Protocol Analysis Set) who have at least 1 post-baseline PRO assessment. Breakdown of these two analysis sets by KRAS status is similar to that of the ITT Efficacy Analysis Set.

The safety analyses will be conducted on all randomized subjects that received at least one dose of panitumumab or chemotherapy (the Safety Analysis Set) analyzed according to treatment received. Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.

10.2.3 Covariates

The primary efficacy treatment analyses will be stratified by the randomization factors for geographic region (Western Europe, Canada and Australia vs Rest of World), and ECOG performance status (0 or 1 vs 2).

The following covariates may be used to examine efficacy in subgroups or in multivariate analyses:

Geographic region: Western Europe, Canada and Australia vs Rest of World

ECOG performance status: 0 or 1 vs 2

KRAS status: mutant vs. wild-type vs. unknown

Location of primary tumor: colon vs rectum

Number of sites of metastatic disease: 1 vs 2 vs $\geq$ 3

Location of sites of metastatic disease: liver only vs other sites $\pm$ liver

Baseline LDH concentration: LDH < 1.5x ULN vs LDH $\geq$ 1.5x ULN and LDH < 2.0x ULN vs LDH $\geq$ 2.0x ULN

Age: < 65, ≥ 65, < 75 and ≥ 75 years

Sex: male and female

Race: white and other categories depending on frequency observed

Tumor tissue samples obtained will be analyzed to evaluate EGFr expression (eg, by immunohistochemistry). **The following parameters will be obtained using the Dako EGFR pharmDx Kit:**

- **Percent of tumor cells with membrane EGFr staining at each of the following intensities: 0, 1+, 2+, 3+**
- **Percent of tumor cells with cytoplasmic EGFr staining at each of the following staining intensities: 0, 1+, 2+, 3+**
- **Overall EGFr results: negative vs. positive**

Additional EGFr pharmDx variables may be derived from the above parameters. Analyses of EGFr in relation to treatment effects and prognostic value will be reported in the primary analysis. Detailed plans will be documented in a Biomarker SAP addendum, which will be finalized after the interim efficacy analysis, but prior to the primary PFS efficacy analysis.

Tumor tissue samples obtained may be analyzed to evaluate the level and expression of other proteins involved in EGFr signaling. This exploratory work may investigate the potential role of tumor biomarkers such as:

- Tumor tissue expression of HER 1 (EGFr), HER 2, and HER 3 homo- and heterodimer protein assessment
- Tumor tissue total HER 2 protein
- Tumor tissue EGFr gene amplification
- Tumor tissue RNA signaling pathway analysis to determine tumor gene profile

Additional tumor biomarkers other than KRAS may also be explored, as well as additional analysis incorporating efficacy information on subject outcome. The analyses of these data may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

10.3 Sample Size Considerations

For the purpose of sample size and study duration estimation, all time to event endpoints are assumed to be exponentially distributed. **PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS**

Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.

Submission of paraffin-embedded tumor tissue obtained prior to randomization from the primary tumor or metastasis for central analyses of EGFr and biomarker testing is mandatory in this study. However, it is not expected that all subjects will have known KRAS status. It is assumed that 90% of subjects will be evaluable for KRAS status (ie., 10% of randomized subjects will have unknown KRAS status either due to lack of tumor tissue sample availability or due to test failures) in the sample size calculation for the KRAS analysis sets.

10.3.1 Sample Size Revision

The study was initially estimated to require 900 subjects to demonstrate a treatment effect on PFS in the all randomized analysis set alone. However, in September 2007 a retrospective analysis of the phase 3 pivotal study in the 3rd line monotherapy mCRC setting provided evidence that clinical benefit of panitumumab was isolated to patients with non-mutant (wild-type) KRAS status. These results are specific to monotherapy use of panitumumab in a 3rd–line setting, and prospective confirmation of the clinical utility of KRAS for patient selection is required in a 1st-line mCRC setting in combination with chemotherapy. Therefore, the current study was amended, prior to any efficacy analysis, to ensure that sufficient subjects would be enrolled to enable adequate statistical power for analysis within the wild-type KRAS and the population, within this 1st line mCRC clinical study. Achievement of this goal requires an enrollment extension. Although the original accrual had been met at the time of amendment **1**, enrollment **was continued** without disruption to maintain continuity for trial integrity. All other aspects of study conduct, ie. protocol eligibility criteria, study treatments, etc., remain**ed** unchanged as per the original protocol; thus, the amendment for **the** evaluation of KRAS **did** not alter the study population enrolled or the risk-benefit of subject participation in the study.

10.3.2 Sample Size and PFS Event Goals

The primary goal of the statistical analysis of the study is to demonstrate whether there is an increase in PFS in subjects treated with panitumumab plus FOLFOX versus FOLFOX alone in the Wild-type KRAS Efficacy Analysis Set. Therefore sample size considerations were focused on ensuring sufficient power in the wild-type KRAS stratum alone.

For the Wild-Type KRAS sub-population, a PFS hazard ratio (FOLFOX plus panitumumab to FOLFOX) of 0.714 is hypothesized. Assuming the prevalence of Wild-Type KRAS in the ITT Efficacy Analysis Set is 55%, it is estimated that the median PFS for Wild-Type KRAS FOLFOX is approximately 1**0**.0 months. Hence this hypothesized hazard ratio translates into a median of **14.0** months for the FOLFOX plus panitumumab arm (i.e., **10.0** vs. **14.0** months) for the Wild-Type KRAS sub-population. To achieve 90% power to reject the null hypothesis at a 5% significance level in the Wild-Type KRAS Efficacy Analysis Set, a total of 380 PFS events are required (Lachin and Foulkes, 1986).

In the original protocol dated 09 March 2006, the enrollment rate was projected at 65 subjects per month with a concave pattern of enrollment of 50% subjects after 2/3 of accrual time had elapsed, and a yearly 5% exponentially distributed lost-to-follow-up. These assumptions turn out to be very close to the real enrollment pattern for those 970 subjects that have been randomized up to protocol amendment **1**. Hence for the period of enrollment extension, similar assumptions are used with the average accrual rate set at 50 subjects per month.

Based on the above assumptions, it is estimated that 1150 subjects (575 per arm) will need to be randomized (with about 900 from the original protocol and about 250 from the enrollment extension) and accrued over a 19 months (with 14 months under the original protocol and 5 months for the enrollment extension) with a minimum follow-up of approximately **12** months to achieve 380 events for PFS **in the** Wild-Type KRAS Efficacy Analysis Set. With Wild-Type KRAS prevalence of 55% and a KRAS Evaluability rate of 90%, 1150 randomized subjects will produce about 570 subjects that will be tested as Wild-Type KRAS and about 466 subjects that will be tested as Mutant KRAS. **The study completed enrollment on 1 February 2008 with 1183 subjects accrued, with 586 expected to have wild-type KRAS, 479 to have mutant KRAS, and 118 to have unevaluable KRAS status.**

10.3.3 OS Event Goals

To allow estimation of the median survival time in both treatment groups for both the Wild-Type KRAS **and the Mutant KRAS** sub-population, the primary overall survival analysis will occur when **at least 50% of subjects in both randomized treatment groups have an event** in the Wild-Type KRAS Efficacy Analysis Set. The study will end

when th**is** event goal **is** achieved (approximately 49 months after first subject is randomized).

10.4 Access to Individual Subject Treatment Assignments

As this is an open-label study, the investigators and the trial participating subjects will know the treatment assignments. To guard against actual or perceived bias due to subjective decisions made by subjects, investigators or Amgen in light of the treatment knowledge and data captured during the study, Amgen will implement study-specific guidelines to blind access to subject-level randomized or received treatment and all post-baseline data for persons not directly involved in subject treatment management, including all sponsor personnel or agents whenever feasible. Exceptions will be pre-specified, justified and documented in order to maintain study integrity, eg, personnel involved in safety due diligence, data management, or analysis preparation where access to unblinded data is required or unavoidable.

10.5 Interim Analysis and Early Stopping Guidelines

An external Data Monitoring Committee (DMC) will be formed to review accumulating data periodically throughout the study and to make recommendations to Amgen regarding the conduct of the study in order to safeguard the interests of trial participants while preserving the integrity and credibility of the study. The sponsor will implement guidelines to provide internal access of unblinded data on a strictly as required basis for the purpose of data capture, cleaning and analysis of this study. A biostatistician external to Amgen will prepare interim safety analyses for the DMC and key analyses associated with the planned interim analysis of progression-free survival (PFS). Amgen biostatistics will prepare all subsequent analyses.

10.5.1 Safety Interim Analyses

The DMC will review study AE and SAE information on a regular basis throughout the entire treatment phase. If warranted from these reviews, the DMC may request additional specific safety data or recommend modifying the study conduct. The sponsor may request additional reviews by the DMC on the basis of safety concerns from this or other studies. These requests may be fulfilled by summary and listings based on unaudited data from the Amgen clinical database to facilitate the review by the DMC. Audited and unaudited data will be provided to the DMC.

10.5.2 Efficacy Interim Analyses

10.5.2.1 Progression-free Survival

In the original protocol dated 09 March 2006, one interim analysis of PFS was planned when approximately 258 centrally reviewed PFS events in the ITT Efficacy Analysis Set have occurred (i.e. 50% of the original primary analysis event goal of 516), with a nominal 0.01 significance level to declare PFS superiority. If superiority was not declared, there was also a provision to allow adaptive resizing to adjust the PFS primary analysis target event goal to preserve power.

In protocol amendment 1, the interim analysis **was** conducted by the DMC at approximately 258 PFS events to obtain an overall assessment of benefit-risk in the all randomized study population by an examination of overall PFS and safety by treatment; however, the interim analysis will not formally compare PFS, so that a 5% significance level will be preserved for the primary PFS analysis. Prospective guidelines for DMC actions **were** pre-specified in an amended DMC charter.

The projected time for this planned efficacy interim analysis is at 258 PFS events (approximately 18 months after the first subject is randomized). A test for a treatment difference in PFS and/or OS will not be performed at the interim analysis in any analysis set. No significance level adjustment is therefore required for the primary hypothesis testing of PFS and OS due to the revised non-inferential interim analysis plan.

10.5.2.2. Overall Survival

Two interim analyses of OS are planned in this study. The first OS interim analysis will be synchronized with the primary PFS analysis. The second OS interim analysis will be conducted with a data cutoff of approximately 9 months later. The second OS interim analysis may be omitted if the data cutoff date of the primary OS analysis is expected to be within 12 months of data cutoff date of the primary PFS analysis. The Haybittle-Peto boundaries of 0.001 will be used as the nominal significance levels for the interim OS analyses. The primary OS in Wild-type KRAS and Mutant KRAS Efficacy Analysis Sets will be compared at a significance level of 5% conditional on a superior result of PFS in the Wild-type KRAS and Mutant KRAS Efficacy Analysis Sets, respectively.

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

The analysis objectives and testing strategy are described in Section 10.1, and the estimated timing of event goals in Section 10.3.

Prior to each efficacy analysis, blinded monitoring and modeling of cumulative events in the Wild-Type KRAS Efficacy Analysis Set will be employed to determine an initial data cutoff date to achieve the planned analysis target total event goal**.** A prospective lower limit for th**is** target goal will be set. Subsequent to data collection for the data cutoff date, the observed total events will be determined. If this is below the lower limit, then a sufficiently later data cutoff date will be utilized for which the observed total events are at or above the limit. The limits will be prospectively defined in the Statistical Analysis Plan.

Primary efficacy analysis on PFS and OS will use the Wild-Type KRAS Efficacy Analysis Set **and the Mutant KRAS Efficacy Analysis Set**. The primary analysis of all tumor measurement related endpoints will be based on the **Wild-type KRAS** and the **Mutant** KRAS Central Tumor Response Evaluable Analysis Set**s**. Sensitivity analysis using investigator assessed tumor response or disease progression may be performed, using similar analysis sets of local review. **Primary safety analyses will use the Wild-type KRAS and the Mutant KRAS Safety Analysis Sets.** Additional descriptive efficacy and safety analyses may be performed on other analysis sets described in section 10.2.2 to provide a robust assessment of the overall risk-benefit profile of panitumumab.

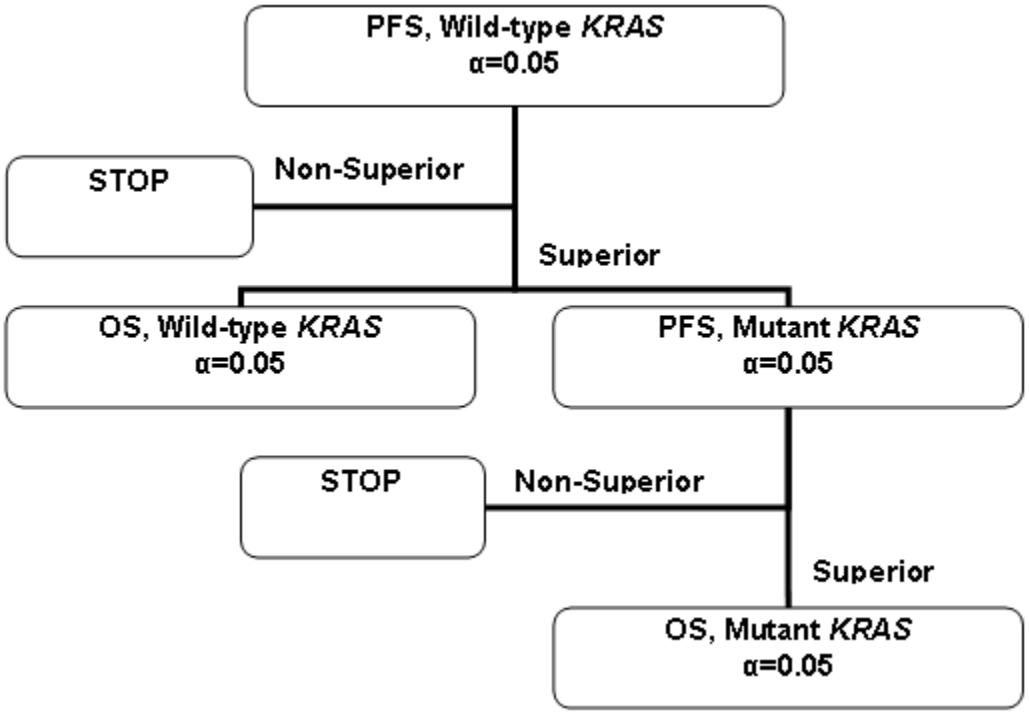
10.6.2 Analysis of Key Study Endpoints

10.6.2.1 Progression-Free and Overall Survival

PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the Mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%. The PFS and OS efficacy analyses schema is shown

in Figure 3. A log-rank test will be used to compare treatments with respect to both OS and PFS stratified by the randomization factors.

Figure 3. Efficacy Analyses Schema



A hazard ratio of test to control and associated 95% CI will be estimated from a Cox model stratified by the randomization factors as captured via IVRS. A piecewise Cox model with pre-defined intervals will be considered given evidence of non-proportional hazards.

Kaplan-Meier (KM) time to event curves will be presented by randomized treatment and actual received treatment for PFS and OS, respectively. KM estimates and 95% CIs will be calculated by randomized treatment for event time quartiles, event-free rates at selected times, and for the difference in event-free rates between treatments at selected times.

Since the Wild-Type KRAS **and the Mutant KRAS** Efficacy Analysis Set**s are** subgroup**s** of all randomized subjects, sensitivity analys**e**s of the PFS treatment effect will be conducted to evaluate the impact of baseline treatment arm prognostic factor imbalances. For OS, the impact of second-line treatment will also be assessed. Details will be provided in the amended Statistical Analysis Plan.

10.6.2.2 Time to Progression

Time to progression will be descriptively analyzed as per PFS (see Section 10.6.2.1).

10.6.2.3 Objective response rate

An exact 95% confidence interval will be calculated for the common odds ratio for objective response across randomization strata for Arm 1 (panitumumab) relative to Arm 2 (no panitumumab). Wilson's score method with continuity correction will be used to calculate a 95% confidence interval for the difference in rates (Newcombe 1998).

10.6.2.4 Duration of Response

For subjects with an objective response, Kaplan-Meier (KM) time to event curves will be presented by randomized treatment. KM estimates and 95% CIs will be calculated by randomized treatment for event time quartiles, and event-free rates at selected times.

10.6.2.5 Time to Response

Time to response will be descriptively analyzed as per overall survival (see Section 10.6.2.1). In addition, for subjects with an objective response, summary statistics of the number, percentage, cumulative number and cumulative percentage of subjects responding over time will be reported by randomized treatment.

10.6.2.6 Patient-Reported Outcomes

The PRO endpoints include the EQ-5D health state index score and overall health rating. Descriptive statistics by treatment group (including mean, median, standard deviation, and range) will be provided for each pre-specified time of assessment (at baseline, every 4 weeks while receiving *assigned* study treatment, every 8 weeks after withdrawal from *assigned* study treatment but prior to disease progression, and at the 4 week safety follow-up visit).

More detailed methods for PRO analysis including treatment of missing data and derivation of scores will be provided in the Statistical Analysis Plan.

10.6.2.7 Safety

Safety will be analyzed according to treatment received. The primary analysis of safety will summarize all adverse events during the treatment phase (including those from the 30-day safety follow-up). T**he following safety analyses will be performed on all five KRAS Safety Analysis Sets (i.e., KRAS Safety Analysis Set, Wild-type KRAS Safety**

Analysis Set, Mutant KRAS Safety Analysis Set, Wild-type ITD KRAS Safety Analysis Set, and Unevaluable KRAS Safety Analysis Set) as well as the Safety Analysis Set.

Subject incidence rates of adverse events (including all, serious, fatal, grade 3 or higher, and treatment related) will be tabulated by treatment received using the NCI common toxicity criteria version 3.0 with the exception of skin toxicity per Section 6.2. Changes in laboratory values and vital signs will be summarized with descriptive statistics. Concomitant medications, dose adjustments and changes in ECOG performance status will be evaluated.

Tables and/or narratives of deaths through the post-treatment safety follow-up, and treatment-related SAEs will be provided.

10.6.2.8 Long-term Data Analyses

All subjects will be followed for survival for up to approximately 30 months after the last subject is randomized. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary OS analysis. Descriptive estimates of key comparative efficacy and safety analyses may be updated to assess the overall relative treatment profile.

11. INVESTIGATIONAL PRODUCT

Investigational Product Details including labeling, storage, preparation, etc. are provided in the Pharmacy Guide (Appendix J).

11.1 Panitumumab

Panitumumab will be packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20 mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Amgen's Clinical Supply Chain will conduct initial shipments of drug and 0.22-micron in-line filters and ongoing re-supply. Panitumumab will be diluted in a minimum volume of 100 mL pyrogen-free 0.9% sodium chloride solution, USP (saline solution) and **must be administered IV by an infusion pump through a peripheral line or indwelling catheter using a 0.22-micron in-line filter infusion set-up over 1 hour ± 15 minutes by a trained healthcare professional.**

The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. In the event a subject's actual body weight requires greater than a 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. The volume of saline should be increased as needed to ensure that maximum concentration of the diluted solution does not exceed 10 mg/mL.

The manufacturing batch (or lot number) of panitumumab (investigational product) is to be recorded on each subject's Drug Administration case report form.

11.2 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the subject during a study, the investigator or responsible person will determine the level of compliance with the administration of the investigational product. The subject's investigational product compliance (eg, amount used) will be recorded on the drug administration case report form.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent form is provided in Appendix G for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the clinical study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Only those subjects who provide their own informed consent will contribute to the EQ-5D patient reported outcomes data.

12.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB's continuance of approval must be sent to Amgen.

12.3 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to Amgen for review before study initiation from Amgen can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet, if applicable
- Copy of the IEC/IRB approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all co/subinvestigators
- IEC/IRB composition and/or written statement that IEC/IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Current subject/investigator indemnity insurance
- Signed study contract
- Completed FDA form 1572 (or equivalent)
- Completed Financial Disclosure statements for the principal investigator, all subinvestigators, and their spouses (legal partners) and dependent children

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to Amgen subjects should be identified by their subject study number only. Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12.5 Pharmacogenetics Confidentiality (for subjects who sign a separate consent only)

All pharmacogenetic samples and the information associated with the samples will be double-coded and stored in independent, secure databases to ensure confidentiality of the subject's information and to enable destruction of the samples when requested. Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results will not be placed in the subject's medical record and will not be made available to members of the family, the personal physician, or other third parties, except as specified in the informed consent.

12.6 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IEC/IRB to Amgen.

Both Amgen and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply the investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

13.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the case report form is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation (see Section 12.3), and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Amgen and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Amgen in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The Amgen representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the case report forms at regular intervals (approximately every 4-6 weeks) throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Clinical Quality Assurance Department (or designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

All paper case report forms should be typed or filled out with a black ballpoint pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Amgen Delegation of Authority Form. No erasures, correction fluid, or tape may be used. Corrections to electronic forms will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and returned to Amgen.
- The principal investigator will sign and date the indicated places on the case report form. These signatures will indicate that the principal investigator

inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.

- Amgen's clinical data management department will correct the database for the following CRF issues **without notification** to site staff:
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect CRF (eg, moving lab data from general comments to the appropriate lab table)
  - date errors that occur into the new year
  - standard time to 24-hour clock
  - temperature unit errors (Fahrenheit vs Centigrade)
  - weight unit errors (pounds vs kilograms) if a baseline weight has been established
  - height unit errors (in. vs cm)
  - administrative data (eg, event names for unscheduled visits or retests)
  - clarifying "other, specify" if data are provided (eg, race, physical exam)
  - correct or enter either "Absolute (A)/Percentage (P)" on hematologies if blank; can be determined from differential data
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - deletion of obvious duplicate data (eg, same results sent twice with the same date but different clinical planned events—week 4 and early termination)
  - for adverse events that record action taken code = 01 (none) and any other action code, 01 (none) may be deleted as it is superseded by other existing data
  - if equivalent units or terms are recorded instead of the acceptable Amgen standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen units or terms will be used
  - if the answer to a YES or NO question is blank or obviously incorrect (eg, Answers to the following questions do not reflect the data that are recorded or missing: Were there any adverse events? Concomitant medications? Hospitalizations?)
  - correct CRF page numbers

13.4 Language

Case report forms **must** be completed in English. TRADENAMES® for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

13.5 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal investigators and appropriate Amgen staff. The committee is expected to solicit input and assistance from other investigators and Amgen staff as appropriate. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2004), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13.6 Compensation

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent (Appendix G).

14. REFERENCES

Advanced Colorectal Cancer Meta-Analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol.* 10(6): 896–903, 1992.

Amado R, Wolf M, Freeman D, Peeters M, Van Cutsem E, Siena S, Suggs S, Patterson S, Chang D. Analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy, *European Journal of Cancer Supplements*: 2007;5:6:8.

Baselga J, Mendelsohn J. Receptor blockade with monoclonal antibodies as cancer therapy. *Pharmacol Ther.* 1994;64:203-212.

Berlin J, et al. Panitumumab therapy with irinotecan, 5-fluorouracil, and leucovorin (IFL) in patients (pts) with metastatic colorectal cancer (mCRC). *Ann Oncol*. 2004;15 (suppl 13):265a.

Boyle, P, Ferlay, J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol*. 2005;16:481-488.

Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet. 1998;352:1413-1418.

Cunningham D, Humblet Y, Sienna S ea. Cetuximab monotherapy plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337-345.

Denne JS. Sample size recalculation using conditional power. *Statistics in Medicine*. 2001;20:2645-2660.

de Gramont A, Figer, A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol.* 2000;22:229-237.

de Jong KP, Stellema R, Karrenbeld A, Koudstaal J, Gouw AS, Sluiter WJ, Peeters PM, Slooff M, De Vries EG. Clinical relevance of transforming growth factor alpha, epidermal growth factor receptor, p53, and Ki67 in colorectal liver metastases and corresponding primary tumors. *Hepatology.* 1998;28:971-979.

Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomized trial. *Lancet*. 2000;355:1041-1047.

EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16 (3):199-208.

Gold M. Washington Panel on Cost Effectiveness in Health and Medicine. *Med Care*. 1996;34(12 Suppl):DS197-9.

Goldberg RM, et al. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer; *J Clin Oncol.* 2004:22:23-30.

Gullick WJ. Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. *Br Med Bull.* 1991;47:87-98.

Hecht JR, Patnaik A, Malik A et al. ABX-EGF monotherapy in patients (pts) with metastatic colorectal cancer (mCRC): An updated analysis. *Proc Am Soc Clin Oncol.* 2004;22:247s. Abstract 3511.

Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor Receptor-positive tumors: A new paradigm for cancer therapy. *Cancer.* 2002;94:1593-1611.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335-2342.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2004. http://www.icmje.org/.

Jemal A, Murray T, Ward, E et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55:10-30.

Kindler, HL, Shulman, KL. Metastatic colorectal cancer. *Curr Treat Options Oncol*. 2001;2:459-471.

Lachin JM, Foulkes MA. Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification. *Biometrics.* 1986;42:507-519.

Maindrault-Goebel F, Louvet, C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. *Eur J Cancer.* 1999;35:1338-1346.

Malik I, Hecht JR, Patnaik A, et al. Safety and efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer. *Proc ASCO 23*: 3520 (abstr), 2005.

McLeod, HL, McKay, JA, Collie-Duguid, ES, Cassidy, J. Therapeutic opportunities from tumour biology in metastatic colon cancer. *Eur J Cancer*. 2000;36:1706-1712.

Meropol NJ, Berlin J, Hecht JR, et al. Multicenter study of ABX-EGF monotherapy in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 2003:22:256 Abstract 1026.

Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. *Statistics in Medicine*. 1998;17(8):873-890.

Panitumumab Investigator's Brochure, Version 5.0. Thousand Oaks, CA: Amgen Inc.; 17 September 2004.

Panitumumab Clinical Trial Directive Annual Safety Report. Thousand Oaks: Amgen Inc.; August 2005.

Pazdur R, Coia L, Wagman LD, Ayoub, JP. Colorectal and anal cancers. In: Cancer management: a multidisciplinary approach. Melville, NY: PRR, Inc, 1999:149-175.

Porebska I, Hartozinska A, Bojarowski T. Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. *Tumour Biol.* 2000;21:105-115.

Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim Results of a Phase III Trial. *J Clin Oncol.* 2003*;* 21:2059-2069.

Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of Irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet.* 1998; 352: 1407-1412.

Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J Clin Oncol*. 2004;22:3003-15.

Saeki T, Salomon DS, Johnson GR, Gullick WJ, Mandai K, Yamagami K. Association of epidermal growth factor-related peptides and type I receptor tyrosine kinase receptors with prognosis of human colorectal carcinomas. *Japan J Clin Oncol.* 1995;25:240-249.

Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol.* 1995;19:183-232.

Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *Am Soc Clin Oncol.* 2004;22:1201-1208.

Shirai H, Ueno E, Osaki M, Tatebe S, Ito H, Kaibara N. Expression of growth factors and their receptors in human early colorectal carcinomas: immunohistochemical study. *Anticancer Res.* 1995;15:2889-2894.

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guideline to evaluate the response to treatment of solid tumors. *J Natl Cancer Inst.* 2000;92:205-216.

Tong WM, Ellinger A, Sheinin Y, Cross HS. Epidermal growth factor receptor expression in primary cultured human colorectal carcinoma cells. *Br J Cancer.* 1998;77:1792-1798.

Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 of the reverse sequence in advanced colorectal cancer. *J Clin Oncol.* 2004;22:229-237.

Wang HM, Rajagopal S, Chakrabarty S. Inhibition of human colon cancer malignant cell behavior and growth by antisense epidermal growth factor receptor expression vector. *Anticancer Res.* 1998;18:2297-2300.

Yang X-D, Jia XC, Corvalan JR, Wang P, Davis CG, Jakobovits A. Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy. *Cancer Res.* 1999;59:1236-1243.

15. APPENDICES

Appendix A. Schedule of Assessments (Non-Treatment Cycle-Related Procedures)

	Screening			Study Treatment				Follow-Up	
	Days			Week Number				Safety[e]	Survival[f]
Study Procedures	D –28[a]	D-7[b]	D-3[c]	1	8[d]	16			
Informed Consent	X			See Appendix B (Week 1 = Cycle 1)			Continues Every 8 Weeks		
Review of Eligibility Criteria	X								
Medical and Medication History	X								
Physical Exam	X							X	
Vital Signs[g]	X							X	
Weight	X							X	
Height	X								
Electrocardiogram	X								
ECOG Performance Status		X						X	
Patient Reported Outcomes		X			X[v]	X[v]		X[u]	
Adverse Event Assessment[h]	X	→	→	→	→	→	→	→	
Recording of Concomitant Medication	X	→	→	→	→	→	→	→	X[t]
Randomization			X[i]						
Survival Assessment									X
Laboratory Procedures									
Hematology[j]		X		See Appendix B (Week 1 = Cycle 1)			Continues Every 8 Weeks	X	
Chemistry[k]		X						X	
Pregnancy Test[l]			X					X	
Immunogenicity Testing[m]								X	
Serum for CEA	X				X	X		X[s,u]	
Blood for Biomarker Development[n]					X	X		X	
Archival Tumor Tissue[o]	X								
Optional Fresh Tumor Tissue[p]	X	→	→	→	→	→	→	→	
Radiological / Response Assessments									
CT Scans (optional MRI)[q]	X				X	X		X[s,u]	
Modified RECIST[r]					X	X		X[s,u]	

[a]Procedures to be performed between day –28 and day –1.
[b]Laboratory procedures to be performed between day –7 and day –1.
[c]Randomization will take place upon confirmation of eligibility via an IVRS. Subjects should commence treatment with study drug no more than 3 days following randomization.
[d]Repeat week 8 procedures every 8 weeks ± 1 week until disease progression (per the modified RECIST criteria) or study drug is intolerable.
[e]Safety follow-up will be performed 30 days ± 3 days after the last study treatment administration.

[f]Subjects will be followed for survival by clinic visit or telephone contact approximately every 3 months ± 28 days after the safety follow-up visit until up to 30 months after the last subject has been randomized. Subsequent cancer treatments will be collected as part of the survival assessment.
[g]Vital signs (blood pressure, respiration rate, pulse, temperature).
[h]Adverse event assessment to include recording of skin or nail-related toxicities.
[i]Randomization will take place upon confirmation of eligibility via an IVRS. Subjects should commence treatment with study drug no more than 3 days following randomization.
[j]Hemoglobin, hematocrit, RBC count, mean corpuscular volume, platelets, WBC count and differential.
[k]Sodium, potassium, chloride, bicarbonate **or CO_2**, BUN, LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid.
[l]Women of childbearing potential will have a serum or urine pregnancy test performed 72 hours before randomization.
[m]Blood samples for Anti-panitumumab Antibody assay will be collected for all subjects prior to study treatment administration and at the Safety Follow-Up visit.
[n]Blood for biomarker development (serum, EDTA blood [plasma and cell pellet], PAXgene blood [RNA]) will be collected within 7 days of each radiological tumor assessment and at the Safety Follow-Up visit.
[o]Paraffin-embedded tumor tissue samples will be obtained prior to randomization for EGFr expression, and biomarker, pharmacogenomic and pharmacogenetic analysis.
[p]Fresh paraffin-embedded tumor tissues, if available, will be collected at anytime during the study for biomarker, pharmacogenomic and pharmacogenetic analysis.
[q]Radiological imaging of the chest, abdomen, pelvis and all other sites of disease by either CT (or MRI if clinically indicated) will be performed at screening. Thereafter, CT scans of all sites of disease will be performed every 8 weeks ± 1 week (CXR is acceptable for imaging the chest if the screening chest CT was normal, as long as the CXR remains normal).
[r]Response assessment per modified RECIST criteria will be performed every 8 weeks ± 1 week until disease progression (per the modified RECIST criteria) regardless of whether treatment is discontinued or delayed. Responding disease will be confirmed no less than 28 days after the criteria for response are first met.
[s]Tumor imaging, assessment and serum CEA analysis will only be performed for subjects who have withdrawn from the study for reasons other than radiographically documented progressive disease and have not had a specified tumor evaluation completed within the previous 8 weeks.
[t]Only subsequent treatments for mCRC will be recorded.
[u]All subjects who discontinue study treatment prior to disease progression should continue to be followed up for disease progression (per modified RECIST) and patient reported outcomes every 8 weeks ± 1 week until disease progression or the end of the study.
[v]Patient Reported Outcome data will be collected every 4 weeks ± 1 week during the study treatment period. If treatment is discontinued prior to disease progression collection of the PRO data will continue every 8 weeks ± 1 week until disease progression or the end of the study.

Appendix B. Schedule of Assessments (Treatment Cycle-Related Procedures)

	Study Treatment				
	Cycle Number				
Study Procedures	1	2	3	4	
Physical Exam	X	X	X	X	**Repeat Cycle 3 and Cycle 4 Procedures Alternately Until Disease Progression or Study Drug(s) are Intolerable**
Vital Signs[a]	X	X	X	X	
Weight	X	X	X	X	
BSA[b]	X	X	X	X	
ECOG Performance Status	X		X		
Adverse Event Assessment[c]	X →	→	→	X	
Concomitant Medication Assessment	X →	→	→	X	
Laboratory Procedures					
Hematology[d]	X	X	X	X	
Chemistry[e]	X	X	X	X	
Immunogenicity Testing[f]	X				
Blood for Biomarker Development[g]	X	X			
Treatment Administration					
Panitumumab	X	X	X	X	
FOLFOX	X	X	X	X	

[a]Vital signs (blood pressure, respiration rate, pulse, temperature).
[b]Body surface area to be calculated at cycle 1 and at the beginning of any cycle during which the subject's weight has changed by 10% from baseline (i.e. cycle 1, day 1).
[c]Adverse event assessment to include recording of skin or nail-related toxicities.
[d]Hemoglobin, hematocrit, RBC count, mean corpuscular volume, platelets, WBC count and differential. This should be performed within 48 hours prior to dosing and results should be available to assess subject's suitability for commencing a treatment cycle.
[e]Sodium, potassium, chloride, bicarbonate **or CO_2**, BUN, LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid. This should be performed within 48 hours prior to dosing and results should be available to assess subject's suitability for commencing a treatment cycle.
[f]Blood samples for anti-panitumumab antibody assay will be collected prior to the first study treatment administration and at the Safety Follow-Up visit for all subjects.
[g]Blood for biomarker development (serum, EDTA blood [plasma and cell pellet], PAXgene blood [RNA]) will be collected prior to study treatment administration on day 1 of cycles 1 and 2

Appendix C. ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix D. EQ-5D Health Questionnaire

Patient Reported Outcomes Assessment Form

Date		
Day	Month	Year

1. *After subject finishes, please review the survey for completeness and check the appropriate box below:*

   1 ☐ All items on the questionnaire were completed

   2 ☐ The questionnaire was started, but one or more items were not completed

   3 ☐ None of the items were completed on the questionnaire

2. *If the subject did not answer some or all of the questions, please indicate the reason below:*

   4 ☐ Subject cannot read or understand the questions

   5 ☐ Subject feels too ill or tired

   6 ☐ Subject did not complete study visit
   (for example, missed visit, early termination, etc.)

   7 ☐ Subject refused

   8 ☐ Logistical problem or error

   9 ☐ Other, please specify _____

3. *If the subject completed at least one question, please indicate how the questionnaire was administered:*

   10 ☐ Subject recorded responses on the questionnaire

   11 ☐ Study coordinator read questionnaire to subject and recorded responses

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*eg, work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

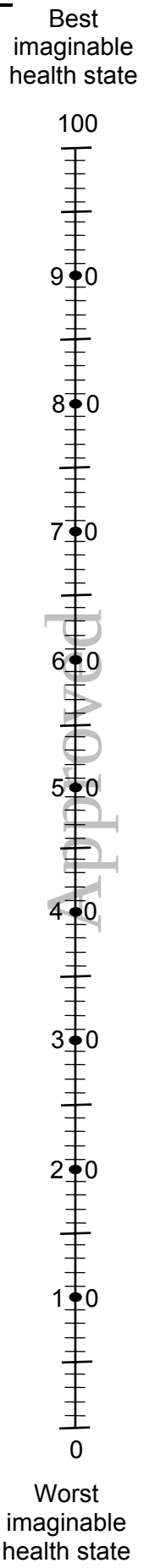
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix E. Adverse Event Assessments

Adverse Event Relatedness

Is there a reasonable possibility that the event may have been caused by investigational product? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is not a reasonable possibility that the event may have been caused by investigational product.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when investigational product is readministered
- does not follow a temporal sequence from administration of investigational product

Yes = There is a reasonable possibility that the event may have been caused by investigational product.

The adverse event:

- follows a temporal sequence from administration of investigational product
- is a known response to the investigational product based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of investigational product
- reappears or worsens when investigational product is readministered

Adverse Event Standard Grading Score

Adverse events will be graded according to the National Cancer Institute's Common Toxicity Criteria (CTC) version 3.0, with the exception of panitumumab-related skin toxicities, which will be graded using CTC version 3 with modifications (Appendix F).

Version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) is available at the following link: **http://ctep.cancer.gov/forms/CTCAEv3.pdf.**

When an adverse event cannot be graded by CTCAE version 3.0, the following severity grade may be used:

1 = mild
2 = moderate
3 = severe
4 = immediately life-threatening
5 = fatal event

Appendix F. Dermatology/Skin/Nail Assessment (from CTCAE version 3.0 with modifications)

Adverse Event (Short Name)	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes (Nail changes)	Discoloration; ridging (koilonychias; pitting) paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema (Erythema)	Painless erythema	Painful erythema	Erythema with desquamation*	Life-threatening; disabling
Pruritis/itching (Pruritis)	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	___
Rash: acne/acneiform (Acne)	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation*	___
Rash/desquamation* (Rash) [Use for non-acneiform rash or non-folliculitis rash]	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritis or other associated symptoms; localized desquamation* or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation* covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
Ulceration (Ulceration)	___	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 cm size; operative debridement, primary closure or other invasive intervention indicated (eg, hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (eg complete resection, tissue reconstruction, flap, or grafting)

***Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.**

Appendix G. Informed Consent Form

(Includes updates from the previous May 2007 Informed Consent Form)

A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

1. BACKGROUND INFORMATION

a. What is this document?

You are invited to participate in a clinical research study of an investigational drug, panitumumab. This document provides you with information about the research study to help you make an informed decision about your participation.

b. What is a research study?

A clinical research study is a “clinical trial” of an investigational drug that is sponsored by a pharmaceutical or biotechnology company. The purpose of such studies is to find out if medications are safe and effective against a disease or medical conditions.

c. What is the purpose of this research study?

The main purpose of this clinical research study is to determine if the study drug (panitumumab), given in combination with a standard chemotherapy regimen (oxaliplatin, infusional 5-FU and leucovorin [FOLFOX]), is more effective at treating metastatic colorectal cancer, than standard chemotherapy alone. This study is also designed to collect more information about the safety of panitumumab, when given in combination with FOLFOX.

You also will be asked to provide blood and tumor tissue samples. These samples will be studied to look for special markers that may help researchers develop blood or tumor tests that can be used for investigation of panitumumab and colorectal cancer.

d. Who is funding this clinical study?

Amgen Inc. (hereinafter referred to as “Amgen”), a for-profit drug company, is funding this clinical study. Amgen is the "sponsor" of the study, which means that Amgen designed the study and drafted the study plan.

e. Why have I been asked to participate in this study?

You have been asked to participate in this study because you have previously untreated metastatic colorectal cancer.

f. How many other people like me (subjects) will be participating in this study?

Approximately 1150 subjects will participate in the research study. Approximately two hundred centers World wide will be involved.

g. What kind of investigational product(s) will be tested in this study?

Panitumumab is considered experimental in this study but the European Regulatory Agencies have recommended its approval as a treatment for colorectal cancer after failure of standard chemotherapy. The American Regulatory Agency has approved panitumumab, trade name Vectibix™, for the treatment of patients with EGFr expressing metastatic colorectal cancer after disease progression on, or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Oxaliplatin, leucovorin and fluorouracil (FOLFOX) are chemotherapy medications that have been approved as a treatment regimen for colorectal cancer by Regulatory Agencies. Panitumumab will be administered in this study along with the FOLFOX chemotherapy regimen.

Panitumumab has already been tested in more than 1700 persons with a mixture of tumor types. Panitumumab is a manufactured antibody – antibodies are proteins that can be found circulating in your blood stream. The growth of colorectal cancer may be affected by the interaction of a growth factor known as "epidermal growth factor" (EGF) with its receptor. Panitumumab is an antibody directed against the receptor for EGF and has been shown to turn off the activity of the receptor and to stop the growth of cancer cells in several laboratory tests. If the same effect is observed in people that receive panitumumab as a treatment, it is possible that their cancer will improve or resolve.

h. What are the chances that I will get the investigational product?

Your chance of receiving panitumumab + the FOLFOX chemotherapy regimen is the same as your chance of receiving the FOLFOX chemotherapy regimen alone. One out of every 2 subjects will be given the investigational product (panitumumab).

i. Will I know which treatment product I am receiving?

This study is 'open-label', which means that both you and your doctor will know whether you are receiving panitumumab + FOLFOX or FOLFOX alone.

j. Who decides whether I get the investigational product or something else?

You will be assigned by chance to receive either panitumumab + FOLFOX or FOLFOX alone.

k. How long is the study?

Once it is determined that you are eligible to participate in the study, you will enter a treatment period and continue to receive panitumumab + FOLFOX or just FOLFOX, for as long as your disease does not worsen or until you are unable to tolerate the treatment. After you have stopped treatment, your research doctor will continue to follow your progress, by telephone contact or from your routine clinic visits, every 3 months for a maximum period of 49 months.

l. How often will I need to visit the hospital, clinic, or doctor's office?

If you decide to participate in this study, you will need to come to the research clinic at minimum, every 2 weeks to complete all the study procedures. The time you spend at the research clinic can vary, however each study visit while you are receiving treatment

will take approximately 4-6 hours or 48 hours depending on the method of chemotherapy administration. In addition, approximately every 8 weeks, you will be required to have radiological examinations (computed tomography [CT], or magnetic resonance imaging [MRI]). This will add approximately 2- 3 hours to your visit. Your research doctor may also ask you to return more frequently to assess your health status while you are receiving treatment with panitumumab + FOLFOX or FOLFOX alone.

When you have stopped treatment, you will be asked to return for one additional visit approximately 1 month after your last study treatment. You will then be contacted via telephone or via your routine clinic visits, approximately every 3 months for a maximum period of 49 months so your research doctor can follow your progress. If you discontinue study treatment before your disease progresses you will continue to have CT or MRI scans approximately every 8 weeks until disease progression or the end of the study (whichever is earlier).

m. What will I be responsible for if I participate in this study?

It is important that you inform your research doctor of any illnesses that occur, and any medications (prescription or over-the-counter) that you take during your participation in this study.

You will be asked not to participate in any other clinical trials involving any other investigational product (study medication or device) whilst you are in the treatment period of this study. You will also be asked not to receive any other chemotherapy, anti-tumor therapy or radiotherapy (except to control pain) for your cancer while you are being treated on this study.

Systemic steroids are only allowed as prescribed by your research doctor.

You will be asked not to schedule any elective surgeries while you are in the treatment period of this study and for 7 days after your last study treatment.

n. What happens when the research study ends?

The treatment period of the study will end when you decide you no longer want to participate; when your doctor decides it is in your best interest not to continue receiving the study treatment; if your doctor has determined that your cancer has got worse, or if the sponsor decides to terminate the study. If this happens, you will be asked to undergo certain tests and procedures approximately 1 month after your last study medication treatment. If there are any abnormal blood test results from the last visit or if your doctor wants to make sure that you have not experienced any unusual effect from the medication, you may be asked to return to the clinic for additional visits. After your treatment is finished you will continue to be followed via telephone or via your routine clinic visits, approximately every 3 months, for a maximum period of 49 months.

2. STUDY PROCEDURES

a. What types of tests or procedures are involved with this study?

Your doctor will evaluate you during a Screening visit to determine if you are a candidate for this study. Various tests and procedures will be performed during the screening visit. Once it is determined that you are eligible for the study, you will enter the treatment

phase. After your last study treatment, you will be asked to return for a safety follow-up visit.

Screening

During screening, your medical history, height, weight, and vital signs will be taken. You will have a physical examination and an electrocardiogram. You will also have a CT or MRI scan of your chest, abdomen and pelvis to assess the extent of your disease.

Approximately 2 tablespoons of blood will be taken for blood analysis. The blood will be used for complete blood count, CEA level (a marker for your cancer) and a chemistry profile. If you are a woman who is able to become pregnant, a urine or serum pregnancy test will be performed to ensure you are not pregnant.

Tumor tissue will be required during your screening. Tissue from a previous biopsy may be used if available. If a biopsy is scheduled at screening as part of the routine investigation of your disease, fresh tissue may be collected instead. Tests will be performed on the tumor tissue that may help researchers in their understanding of panitumumab and/or cancer. These tests may include determining the level of EGF receptor in your tumor cells as well as the evaluation of markers involved in the EGF receptor pathway.

You will also be asked to complete a questionnaire that asks about your general health status.

Treatment

During the treatment period of the study, you will visit the clinic every 2 weeks at which time your study treatment (panitumumab + FOLFOX or FOLFOX alone) will be administered. Panitumumab is administered through a small needle that will be inserted into your vein (intravenous). It will take between 30 and 60 minutes for the panitumumab to be administered.

Approximately 2 tablespoons of blood will be taken for routine laboratory tests every 2 weeks during the treatment phase of the study. The routine laboratory tests include complete blood count, and chemistry profile. An additional 1 teaspoon of blood (approximately) will also be collected before your first treatment cycle and may be used for the analysis of antibodies against panitumumab.

Your vital signs, and weight will be assessed and you will have a physical examination approximately every 2 weeks. Every 8 weeks, you will also have a CT or MRI scan of your abdomen and pelvis and a chest X-ray or a chest CT/MRI scan (depending on the results of your previous chest CT/MRI scan) to assess the extent of your disease. If a chest X-ray is performed and is found to be abnormal, a chest CT/MRI scan will be performed.

You will be asked to complete a questionnaire that asks about your general health status before you begin treatment and approximately every 4 weeks thereafter.

Safety Follow-Up

Approximately one month after your last study treatment administration, a safety follow-up visit will be performed. At this time, approximately 2 tablespoons of blood will be taken for routine laboratory tests including complete blood count, CEA level, and

chemistry profile. An additional 1 teaspoon of blood (approximately) will also be collected and may be used for analysis of antibodies against panitumumab. If you are a woman who is able to become pregnant, a urine or serum pregnancy test will be performed to ensure you are not pregnant.

Your vital signs and weight will be assessed. You will also have a physical examination and you will be asked to complete a questionnaire that asks about your general health status. A CT scan or MRI scan of your abdomen and pelvis and a chest X-ray or a chest CT scan may also be performed to assess the extent of your disease.

CT or MRI scans of your abdomen and pelvis and a chest X-ray or a chest CT/MRI to assess the extent of your disease, as in the study treatment phase, may continue every 8 weeks following stopping treatment, depending on the reason for stopping. Likewise you may be asked to continue completing the questionnaire that asks about your general health status every 8 weeks.

Long-Term Follow-Up

You will be followed approximately every 3 months for a maximum of 49 months either via your routine clinic visit or via telephone to inquire about your health status. If required, any additional CT / MRI scans or X-rays performed during your long-term follow-up may also be requested.

Biomarker Development

Exploratory procedures are designed to develop blood and/or tumor laboratory test(s) that may help to identify subjects who are most likely to be helped by the investigational products. The development of blood tests is important because these tests may be used to track the status of cancer without the need for invasive procedures such as biopsies. Blood tests that may predict tumor response are best developed through the study of tumor and blood in combination to learn what changes in the blood reflect changes in the tumor. One of the goals of this study is to develop tests that will help in the investigation of cancer and/or persons who will have the best possible response to investigational products.

In order to develop new blood tests, additional procedures and studies will be done. A portion of your previously removed tumor (when available) and a portion of any tumor collected during the study for clinical care purposes, along with the corresponding pathology reports, where possible, will be collected and analyzed. These analyses will determine if the tumor cells contain markers that may be linked with disease progression and/or response to investigational products.

For these studies, about 4 teaspoons of blood will be collected at the following times:

- Before you start treatment with panitumumab + FOLFOX or FOLFOX alone;
- Approximately 2 weeks after your first treatment;
- Within 7 days of each radiological assessment of tumor;
- At the safety follow-up visit

These blood and tumor samples along with components of your cells may be stored for up to 20 years. You will retain the right to have the sample material destroyed at any time by contacting the study doctor. If you decide to have your sample destroyed, any data or analysis that were done before the request cannot be removed; however, no additional analysis will be done on your samples, and all of your remaining samples will be destroyed. The sponsor will be the exclusive owner of any data, discoveries, or

derivative materials from the sample materials and is responsible for the destruction of the sample(s) at your request or at the end of the storage period. The study doctor will provide the sponsor with the required study and subject's numbers, so that blood or tumor samples and any components of your cells can be located and destroyed.

By signing this consent form, you are authorizing Amgen to use your samples, the by-products of your samples, and any products developed from the samples for these exploratory research purposes.

3. SAFETY – POTENTIAL RISKS AND DISCOMFORTS

a. What are the general risks of participating in this research study?

More than 1700 subjects have been treated with panitumumab, either alone or combined with other cancer treatments. Since this is an investigational product, not all of the potential adverse effects in humans are known. In addition to the possible adverse effects listed below, there is always the risk of uncommon or unexpected adverse effects that you may experience when panitumumab is given alone or when combined with other therapies.

You will be closely monitored throughout this study by your doctor. Your doctor will discuss with you any questions regarding risks, discomforts, and adverse effects.

If significant new findings develop during the course of the study that might affect your willingness to participate, information will be reported to you as soon as possible. If you have any concerns about this study at any time you should contact Dr. _____(Principal Investigator) at (___) _____ (24 hour phone number).

b. What are the known adverse effects of this study drug?

Very Common: (may occur in 10 or more subjects in 100)

Mild to moderate skin rash has been reported in most subjects treated with panitumumab and has been observed with other drugs that are similar to panitumumab. The skin rash commonly resembles acne. The skin rash often involves the face and upper chest and back but can affect any area of the body. Some rashes have been associated with redness, itching and flaking of the skin. This skin reaction can become severe. In some cases, it may cause infected sores requiring medical and/or surgical treatment, or cause severe skin infections that could be fatal. Prolonged exposure to the sun can make the rash worse. Additionally, dry skin, fissures (cracks in the skin) on the fingers or toes, fingernail bed or toenail bed infection or inflammation have been reported. Once the panitumumab is withheld or discontinued the adverse effects on skin will generally resolve. Your physician may decide to treat the rash and ask you to use particular creams to help reduce the adverse effects of the skin rash.

Other very common adverse effects that you may experience include one or more of the following: diarrhea (sometimes causing severe dehydration), abdominal pain, constipation, swelling of the hands and feet and feeling tired.

In addition to skin infections, other infections (such as urinary tract infection, respiratory tract infection, catheter site and localized infections) have been reported in subjects who are receiving other cancer treatments and panitumumab.

Common: (may occur between 1 and 9 subjects in 100)

Common adverse effects that you may experience include one or more of the following: nausea, vomiting, headache, irritation in the mouth, dehydration, hair loss, heart attack (0.2% of these cases were fatal), cough, shortness of breath, excessive hair growth, dry mouth, chapped lips, a decrease in magnesium, calcium and potassium levels in the blood, nose dryness or bleeding, increased growth of eyelashes, and teary, itchy, dry, red eyes or blurry vision, eye infection and infusion reactions (such as fever, chills, shaking, decrease in blood pressure, slowed heart rate, sudden severe shortness of breath, life-threatening loss of heart or lung function, joint or muscle pain, and rash).

Uncommon: (may occur between 1 and 9 subjects in 1000)

Uncommon adverse effects that you may experience include stroke and blood clots in the legs and in the lungs.

Lung complications known as pneumonitis or fibrosis have been commonly observed in subjects receiving other drugs that are similar to the investigational drug. These complications are generally treatable, but in some cases may result in permanent lung damage. To-date, subjects receiving panitumumab have uncommonly experienced pneumonitis or fibrosis of the lungs.

c. What are the potential adverse effects of this drug?

Many investigational drugs have potential adverse effects and the same is true of panitumumab. Often these potential effects are identified because of the action of similar drugs or the normal response of your body to medication.

Following the administration of panitumumab, you may experience infusion reactions. Infusion reactions may be mild or serious, and there is a possibility that you may develop a severe infusion reaction to panitumumab. You may also develop an allergic reaction such as itching, hives, shortness of breath, wheezing, sudden drop in blood pressure, swelling around the mouth or eyes, palpitation (fast pulse) or sweating. Your doctor will be monitoring you closely for any adverse effects. Severe allergic reactions may rarely occur and if they do, may cause an injury or even lead to death.

There is a possibility that your body's immune system may develop antibodies against panitumumab. These antibodies are known as anti-panitumumab antibodies. Your blood may be checked periodically for the presence of anti-panitumumab antibodies. The presence of anti-panitumumab antibodies may or may not result in an adverse effect. If you develop these antibodies, you may not be able to receive further treatment with panitumumab.

d. Other Information

Some animals treated with panitumumab experienced diarrhea and weight loss. Some of the animals that experienced severe diarrhea developed degeneration of the myocardium (heart muscle), likely due to severe dehydration. Heart damage has been observed in some subjects treated with drugs that are similar to this investigational

product. If you experience any symptoms such as fatigue, shortness of breath, weight gain, swelling of the lower extremities, palpitation, chest discomfort, or other symptoms that you believe is related to the heart, immediately contact your local emergency number and your investigator.

e. Panitumumab and Bevacizumab in Combination with either Oxaliplatin or Irinotecan-based Chemotherapy (Study 20040249-PACCE)

When panitumumab therapy was used in this study with bevacizumab in combination with either oxaliplatin or irinotecan-based chemotherapy, these adverse effects were observed:

The study included more than 400 subjects receiving panitumumab in combination with bevacizumab and either oxaliplatin or irinotecan-based chemotherapy. A recent review of the data in this study showed that subjects who did not receive panitumumab had better survival (lived longer). Some subjects who received panitumumab experienced more severe adverse effects than those who did not get panitumumab. These effects included diarrhea (leading to severe dehydration), dehydration, severe infections and the presence of clots in the lung (pulmonary embolism) that in some cases were fatal.

Potential adverse effects of receiving panitumumab together with bevacizumab and oxaliplatin or irinotecan-based chemotherapy are unknown. This combination of panitumumab with bevacizumab and chemotherapy is not indicated.

Very common: (may occur in 10 or more subjects in 100)

Very common adverse effects observed included: infections (urinary tract infections); inflammation of the bowel; diarrhea (that may lead to severe dehydration); dehydration; constipation; loss of appetite; loss of weight; low potassium level in the blood; low magnesium level in the blood; rash; acne-like skin rash; red and warm skin; mouth sores; cracks or fissures of the skin; dry skin; itchy skin; fever; feeling depressed; vomiting; lower red blood cell counts; hair loss; and upset stomach.

Common: (may occur between 1 and 9 subjects in 100)

Common adverse effects observed included: low calcium level in the blood; nail disorders; flaking skin; skin sores; redness of the hands and feet; red eyes or blurry vision; eye infection and clots in the lung.

f. Panitumumab in Combination with Chemotherapy

Common adverse effects from FOLFOX4 (Oxaliplatin, 5-Fluorouracil and Leucovorin) chemotherapy are listed below

All possible adverse effects of receiving panitumumab and FOLFOX4 chemotherapy are still unknown at this time. Your physician may give you information on how to manage adverse effects that you experience during this study.

A few days after chemotherapy, you may experience a tingling or loss of sensation in your hands and feet, which may worsen when you are exposed to cold temperatures. This sensation is usually reversible within a few months after stopping FOLFOX4 chemotherapy.

You may experience low white blood cell counts, low red blood cell counts, low platelet counts, mouth sores, or bleeding gums, increased nausea, vomiting, and loss of appetite, weight loss, diarrhea and tiredness. You will have some changes in some of your lab tests.

When your white blood cell counts are low, you may develop infection. You may develop a fever a few days after receiving your chemotherapy. Fever occurring more than 48 hours after treatment may be a sign of infection.

You may also experience any one, or more than one, of these adverse effects: skin rash, a darkening of your skin color, redness or swelling on your skin where the infusion needle was placed, changes to your fingernail beds, skin sensitivity to sunshine (it may sunburn easily), teary or irritated eyes and some hair loss.

Chest pain (angina) occurs rarely and your doctor will be monitoring you closely throughout the infusion of the chemotherapy.

In rare cases there have been allergic reactions to the chemotherapy soon after the infusion, including dizziness, fast heart rate, itching and hives, and face swelling and breathing problems.

Oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal.

g. What are the risks associated with procedures done in this research study?

Blood Collection

The risks associated with blood collection commonly include discomfort, pain, redness and swelling and/or bruising where the blood is taken from your arm. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infection are rare occurrences associated with blood collection.

Risks of a MRI Scan

(an imaging test to measure the size of your tumor)

You may feel claustrophobic or anxious. You may experience some discomfort and fatigue from lying in a confined space. There are no known effects from exposure to the magnetic fields. The contrast agent will be injected into the vein and may cause a few people to experience nausea, headache, hot flushes, dizziness and irregular heartbeat as well as discomfort from the injection needle. Please tell your doctor if you have any metal plates or clips in your body.

Risks of a CT Scan

(a computerized picture to locate and measure your tumor)

You may feel some discomfort or anxiety when lying inside the CT scanner. The contrast material (dye) is injected and may cause you to get a metallic taste in your mouth, to feel warm and rarely cause nausea or vomiting. You will be exposed to some radiation through this procedure. There is always a slight risk of damage from being

exposed to any radiation, including the low amount of x-rays used for the CT scan. If you are especially concerned with radiation exposure, please discuss this with your doctor.

h. Can the adverse effects of this study drug or study specific procedures be harmful to my family, my offspring, or me?

It is not yet known if panitumumab causes any adverse effects in pregnant or nursing women, the unborn baby, or in the sperm from the male. Preliminary results in animal studies show that administration of panitumumab during pregnancy may result in loss of fetus.

Women of Childbearing Potential

If you are pregnant, or think you are pregnant, it is important for you to notify the investigator immediately before you receive any panitumumab. If you are pregnant, treatment with the investigational product will be stopped. The sponsor will request the Investigator to obtain initial pregnancy contact information and information on the pregnancy outcome for both the mother and child.

If you participate in this study, you must be willing to agree to the following: have a pregnancy test done before beginning your participation, ensure that there is no possibility that you become pregnant during your study participation, and agree to use an approved method of birth control (double barrier preferred) during the study period and for at least 6 months after your last dose of panitumumab.

If you are a woman who is breastfeeding, you will be asked to discontinue breastfeeding during the course of the study and for 6 months after the last dose of panitumumab.

Sexually Active Male

If your partner is pregnant, or may be pregnant, it is important that you tell your doctor immediately. The **s**ponsor may request the investigator to obtain initial pregnancy contact information and information on the pregnancy outcome for both the mother and child if your partner becomes pregnant while on study.

If you participate in this study, you and your partner must be both willing to use an approved method of birth control (double barrier preferred) during the study period and for at least 1 month after your last dose of panitumumab.

4. POTENTIAL BENEFITS

a. What are the expected therapeutic benefits of this investigational product?

Panitumumab in combination with FOLFOX is an investigational regimen. You may or may not experience any benefit from the addition of the investigational product to the FOLFOX regimen.

b. Will I benefit from participating in this research study? Will others?

Individual subjects will not derive a benefit from taking part in the exploratory procedures. However, future subjects may benefit from what is learned. This

information may help physicians learn more about the use of the investigational product in cancer treatment.

5. ALTERNATIVE THERAPY

a. If I choose not to participate in this study, are there other treatments or medications available to me, instead of this investigational product?

You may choose not to participate in this study. Other treatment options may be available to you. Your doctor will discuss these treatment options with you.

b. Are there benefits with these other treatments? Are there risks?

Your doctor will discuss the benefits and risks of these other treatments.

6. POTENTIAL COSTS/REIMBURSEMENTS

a. What will this study cost me?

Your participation in this study should not result in any additional costs other than those associated with the treatment of your cancer. The sponsor will supply the investigational drugs at no cost to you. All costs related to routine medical treatment of your cancer will be billed to your insurance company or other government health care programs. However, due to the investigational nature of this research study, some insurance companies or government health care programs may limit their obligation to pay for experimental treatments and their consequences. In those cases, you may be responsible for payment of all charges related to the medical care you receive for treatment of your cancer.

b. Will I be reimbursed for any normal expenses that I incur as a result of participating in the study?

The sponsor of the study will cover the costs associated with study specific procedures in this research study, which are not part of your routine care. You will not be paid any money for participating in this study.

c. Will I be compensated for the use of any of my biologic samples?

You should know it is possible that through the use of your sample for exploratory research, a commercial pharmaceutical product may be developed. Amgen, other researchers, or research companies may patent or sell discoveries that result from this research. Neither Amgen nor the principal investigator will compensate you if this happens.

7. CONFIDENTIALITY

a. How will the confidentiality of my records be maintained?

Neither my results nor my samples will be identified with my name. A code will be used in all documentation related to this study.

All exploratory samples will be coded using labels with a unique code number and all analysis results will be further coded by using a different unique bar code from the samples.

b. Who will have access to my medical information if I sign this informed consent form?

It is a requirement that your involvement in this study be noted in your medical records. Direct access to your records will be required by authorized representatives of Amgen to check the information collected for the study.

Your CT / MRI scans and X-rays that may contain confidential information will be sent to a central radiology review facility (RadPharm Inc., Princeton, NJ, USA) for interpretation and reporting results back to Amgen (The confidentiality of the scans will be maintained by RadPharm's staff members).

Your medical records may also be reviewed and copies made by members of either the institutional review board/independent ethics committee responsible for this trial site, a regulatory agency, or an authorized Amgen representative.

By signing this consent form, you (or your legally acceptable representative), authorize access to this confidential information.

Since exploratory sample evaluations are not expected to benefit you directly or to alter your treatment course, these results will not be placed in your medical record and will not be made available to members of your family, your personal physician, or other third parties, except as specified below.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the trial are published, your identity will remain confidential. Using your subject number only, the results and other information from the study may be submitted to regulatory agencies in countries where the investigational product may be submitted for approval.

8. COMPENSATION FOR INJURY

a. What do I do if I think I have an injury/illness related to my participation in this study?

If you think you have an injury/illness that is related to the study, you should immediately notify <<*insert name*>>, the investigator, or one of the staff members working on the study. The investigator and the study staff may be reached at <<*insert address and telephone number*>>.

If you have a study-related injury/illness, the investigator and the study staff will make sure that you receive necessary treatment.

b. If I have an injury/illness related to my participation in the study, will I be compensated in any way?

Amgen will compensate you for reasonable medical expenses for the treatment of any injury/illness that is directly related to the properly administered investigational product. Amgen will not compensate you for treatment that is paid for by a third party.

Amgen also will not compensate you for other injury- or illness-related costs, such as lost wages. You are not waiving any legal rights by participating in this study.

The investigator and/or study staff will provide you with additional information about any financial compensation that may be available.

9. ASSURANCES

If I agree to participate in this study, what can I be assured of:

- Your participation is voluntary, and you are free to withdraw from the clinical research study at anytime without prejudice to your future care. If you decide to withdraw, you should notify your doctor so that your part in the study may be stopped in an orderly manner and that your future care can be discussed.
- <<*Investigator's name*>> or Amgen Inc. may choose to withdraw you from this research study at any time.
- You or your legally acceptable representative will be kept informed, in a timely manner, of any information that may relate to your willingness to continue participation in the study. At the discretion of your doctor(s) and Amgen Inc., you or your legally acceptable representative may be asked to sign a revised informed consent or consent addendum that provides this information.
- You may ask questions at any time about this study. If you feel that you have experienced an adverse reaction to the investigational product(s) or procedures, or if you feel unusually unwell during the study, you should contact <<*contact name, home and business telephone numbers*>>.

If you have any questions about the informed consent process or your rights as a research subject then you should contact <<*contact name, telephone, and address*>>.

10. SIGNATURES

You have had all alternative treatments discussed with you.

All of your concerns and questions about this research study have been answered to your satisfaction.

In signing this document, you confirm that you agree to be part this study and that you have received your own copy of this document.

You agree that Amgen's research using your medical data may lead to the development of commercial pharmaceutical products. Amgen and other researchers may use these data and may patent or commercialize discoveries or inventions that result from this research. Neither Amgen nor other participants in this research will compensate you if this happens.

Subject's signature	Date[1]	PRINT subject's name
Signature of person who conducted the informed consent discussion	Date[1]	PRINT name of the person who conducted the informed consent discussion

[1]Each person who signs the consent must personally enter the date for his/her signature.

Appendix H. Pharmacogenetics Informed Consent Form

Subject Pharmacogenetics Informed Consent

Protocol Number 20050203

A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

1. BACKGROUND INFORMATION

a. What is this document?

You are being asked to take part in a substudy of this clinical protocol. This optional substudy is strictly voluntary. This consent form explains why we are performing this substudy and what your role will be if you choose to participate. This form also describes the possible risks connected with being in this substudy. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to participate in the substudy.

b. What is the purpose of this substudy?

You will be asked to allow the sponsor or its designee to perform genetic (pharmacogenetic) tests on your blood and tumor samples. These tests are being done to help in the investigation of colorectal cancer and/or to study who may have the best possible response to panitumumab.

c. Who is funding this substudy?

Amgen Inc (hereinafter referred to as “Amgen”), a for-profit drug company, is funding this study. Amgen is the "sponsor" of the study, which means that Amgen designed the study and drafted the study plan.

2. SUBSTUDY PROCEDURES

What types of tests or procedures are involved with this substudy?

If you agree to this optional substudy, a portion of the blood and tumor (along with the corresponding pathology report) sample already collected in the main informed consent will be used. No additional blood and tumor samples will be collected for pharmacogenetic analysis. These pharmacogenetic analyses are different from the exploratory study analyses described in the main informed consent because they are being used to evaluate the different inherited gene forms in DNA that influence the responses individuals have to the same drug. Genes contain the instructions for making living organisms and are contained in DNA. Most DNA is identical among human beings, but the small variations we all have in our DNA may explain why individuals have different responses to the same drug.

3. SAFETY—POTENTIAL RISKS AND DISCOMFORTS

What are the general risks of participating in this substudy?

Since the blood sample that was collected for other tests in the clinical study is the source of the genetic material used in this substudy, no additional risks are expected.

Since the tissue sample that is collected will be from material that has already been removed as part of your standard care, no additional risks are expected.

4. POTENTIAL BENEFITS

Will I benefit from participating in this substudy? Will others?

Results of these substudies are for research purposes only and are not expected to benefit you directly or to alter your treatment course. Future subjects may benefit from information learned from this substudy. This information will help physicians learn more about the use of the investigational product to treat colorectal cancer and/or to help investigate colorectal cancer.

5. POTENTIAL COSTS/REIMBURSEMENTS

Through the use of your sample in research, a commercial pharmaceutical product may be developed. If you decide to sign this consent form, you are releasing (giving) to Amgen Inc., your blood and/or tumor sample, the by-products of your sample, and any products developed from the sample or from the use of the sample. Amgen, other researchers, or research companies may patent or sell products, discoveries, data, and/or information that result from this research. Neither Amgen nor the principal investigator will compensate you if this happens. You will have no commercial rights to any products, data, information, discoveries, or derivative materials gained or produced from the sample.

6. CONFIDENTIALITY

a. How will the confidentiality of my records be maintained?

All pharmacogenetic samples will be disguised using labels with a unique code number, and all analysis results will be further disguised by using a different unique bar code from the samples. All genetic research information obtained from your blood sample will be kept strictly confidential.

DNA used for this research may be stored for up to 20 years. This DNA will be stored at a central laboratory and/or at Amgen. During and after the substudy, you will retain the right to have the sample material destroyed by Amgen at any time. If you decide to have your sample destroyed, any data or analysis that were done before the request cannot be removed; however, no additional analysis will be done with your samples, and all of your remaining samples will be destroyed. Otherwise, the sponsor is responsible for the destruction of the sample at the end of the storage period.

b. Who will have access to my medical information if I sign this informed consent form?

Since this optional pharmacogenetic sample evaluation is not expected to benefit you directly or to alter your treatment course, these results will not be placed in your medical record and will not be made available to members of your family, your personal physician, or other third parties, except as specified below.

Unless required by law or regulatory authorities for the purpose of verifying information obtained from this substudy, only Amgen and its authorized personnel and agents will have access to your confidential data. Amgen will not collect or maintain data that identify you by name. The investigator will collect and maintain that information. The results and other information from this substudy may be submitted to regulatory agencies in countries where the licensing application may be submitted. You will not be identified in any reports or publications resulting from this substudy. Because of the need to give these parties access to this information, absolute confidentiality cannot be guaranteed.

7. SIGNATURES

All of your concerns and questions about this substudy have been answered to your satisfaction.

In signing this document, you confirm that you agree to take part in this substudy and that you have received your own copy of this document.

You have been informed and agree that Amgen's research using biologic materials collected from you in this substudy, or materials derived from your biologic materials, may lead to the development of commercial pharmaceutical products. Amgen and other researchers may use these materials and may patent or commercialize discoveries or inventions that result from this research. Neither Amgen nor other participants in this research will compensate you if this happens.

Subject's signature	Date[1]	PRINT subject's name
Signature of person who conducted the informed consent discussion	Date[1]	PRINT name of the person who conducted the informed consent discussion

[1]Each person who signs the consent must personally enter the date for his/her signature.

Appendix I. Guide to Using Modified RECIST Criteria for Review of Disease Response

The RECIST Criteria were developed and published by Therasse et al (2000) and will be employed in this study with modifications based on current practices of the medical community.

Measurable Lesions

Measurable target lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) greater than or equal to 20 mm in the longest dimension using cross sectional imaging techniques such as CT or MRI.

Non-Measurable Lesions

All other lesions (longest diameter less than 20 mm), including small lesions and other truly non-measurable lesions are considered non-measurable and characterized as non-target lesions.

This will include any measurable lesions beyond the maximum number of 10 that were not chosen as target lesions.

Other examples of non-measurable lesions include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions and groups of lesions that are small and numerous.

Lesions clinically measured by the investigator, and not imaged by radiographic methods (ie, skin nodules and palpable lymph nodes) will automatically be considered non-target lesions.

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector CT) should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on chest X-ray should be imaged by CT scan. If the baseline chest scan is abnormal, the same modality should be used throughout the treatment phase. If the chest CT scan performed at baseline is found to be normal, a chest X-ray will be performed at each subsequent tumor imaging. In the event the chest X-ray is found to be abnormal during the treatment phase, a chest CT scan will be obtained and this modality should be used for subsequent tumor imaging.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations. A switch from CT to MRI of the liver is considered the only acceptable change in modality and should not preclude response assessment if, in the judgment of the radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to IV contrast for CT scan during the trial. This change would require the pre-approval of the Medical Monitor.

Ultrasound should not be used for assessment of visceral index lesions for the pre-study documentation of progression following the most recent chemotherapy regimen or the on study efficacy evaluation but can be used to assess superficial lesions such as skin lesions or lymph nodes or masses during on study efficacy evaluation. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules or to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Positron Emission Tomography (PET) with FDG is occasionally used to assess subjects with colon cancer. For this protocol, a response of CR, PR or SD will be determined as assessed by cross sectional imaging techniques (CT or MRI). PET will not contribute to the assessment of response. For the determination of PD, PET could be used to identify new lesions as follows: 1) A new site of abnormal FDG uptake in an area that was previously negative on a baseline PET scan or 2) A site of abnormal PET uptake on a follow-up scan, that has no baseline PET scan for comparison, but corresponds to a new lesion on CT or MRI. If a combined FDG PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

Baseline Documentation of "Target" and "Non-Target" Lesions

Baseline images will be used to prospectively identify all sites of disease present at the start of treatment. Sites of disease will be characterized as either target or non-target lesions.

Up to 10 target lesions (a maximum of 5 per organ) will be chosen to measure over the course of therapy. The distribution of these target lesions should be representative of the subject's overall disease status.

Target lesions should be selected on the basis of their size (greater than or equal to 20 mm in the longest dimension using CT or MRI) and suitability for accurate repeated measurements by imaging techniques. Target lesions must not be chosen from a previously irradiated field unless there has been documented tumor progression in that field prior to randomization.

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of malignant disease), including any measurable lesions that were not chosen as target lesions, should be identified as *non-target lesions* and should also be recorded and assessed qualitatively over the course of therapy.

Evaluation of Objective Response Rate:

The subject response will be assessed based on the response of the target lesions, the response of the non-target lesions and the presence or absence of new lesions. The convention will be used that if a lesion being measured decreases in size to $\leq$ 5 mm in LD, a value of 5 mm will be assigned. If the lesion subsequently increases in size to greater than or equal to 5 mm in one dimension, its true size will be recorded.

Evaluation of Target Lesions at Each Assessment Point	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of the longest diameters (SLD)
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of all or a subset of target lesions, taking as reference the nadir SLD based on all target lesions recorded since the treatment started
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir LD since the treatment started
Unable to Evaluate (UE):	Any target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Scans were not performed at this time point to evaluate the target lesions

Evaluation of non-target lesions at Each Assessment Point	
Complete Response (CR):	Disappearance of all non-target lesions
Stable Disease (SD):	Persistence of one or more non-target lesions not qualifying for either CR or PD
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. If the visit response of target lesions is non-PD and there are no new lesions, progressive disease from non-target lesions alone will be assessed under two conditions: (1) when the SLD of the non-target lesions that are thought to have unequivocal progression has increased by 20% or greater, taking as reference the nadir SLD of these non-target lesions, each of which must measure $\geq$ 10 mm in one dimension at the time of progression; or (2) a significant increase in pleural effusions, ascites or other fluid collections with cytologic proof of malignancy.
Unable to Evaluate (UE)	Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
Not Applicable (NA)	No non-target lesions identified at baseline
Not Done (ND)	Scans were not performed at this time point to evaluate non-target lesions

Matrix for Determining the Response of the Subject at Each Assessment Point Based on the Target and Non-Target Response and the Present of New Lesions

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA**	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA**	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UE	Non-PD/NA**	No	UE
ND	Non-PD/NA**	No	UE
NA*	SD	No	SD
NA*	CR	No	CR

NA* = No target lesions identified at baseline

NA** = No non-target lesions identified at baseline

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should have the reason for treatment discontinuation classified as “non radiographically confirmed disease progression”. In this case progressive disease cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended

that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

Tumor markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a subject to be considered in complete clinical response when all tumor lesions have disappeared.

Response Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met.

A best overall response of SD requires a visit response of SD or better no earlier than 49 days after the date of randomization, otherwise the overall response will be UE.

Appendix J. Pharmacy Guide

Panitumumab

Packaging and Formulation

Panitumumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen's clinical study drug distribution procedures. Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20 mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only.

Labeling

Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

Storage

The supplied investigational drug must be stored at 2-8 ^{o}C in a secured area upon receipt. As panitumumab contains no preservatives, vials are designed for single use only. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

Records of the actual storage condition during the period of the study must be maintained (eg, records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage or trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Preparation

NOTE: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product.

The pharmacist will prepare the panitumumab infusion using aseptic techniques. The dose of panitumumab will be 6 mg/kg and will be based upon the subject's baseline weight. The dose will not be recalculated unless the weight changes at least ± 10% from the weight at cycle 1, day 1. The calculated amount of panitumumab will be removed

from the vials and added to a minimum volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP/PhEur. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. In the event a subject's actual body weight requires greater than a 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. The panitumumab will be infused within 19 hours of dilution. The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion. The sponsor will provide 0.22-micron in-line filters to the sites for panitumumab infusion. The sponsor will conduct initial shipments of drug and 0.22-micron in-line filters and ongoing re-supply.

Supply and Return of Drug

At study initiation and as needed thereafter, panitumumab will be shipped to a responsible person (eg, a pharmacist) at the Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability record. The Proof of Receipt Form should then be returned to Amgen, and the original retained at the site. At the end of the study, or as directed, all panitumumab supplies will be returned to Amgen, whilst filters will be destroyed on site.

Panitumumab and 0.22-Micron filter Accountability

An Investigational Product Accountability Record for the panitumumab and 0.22-micron filters must be kept current and should contain:

- the dates and quantities of panitumumab and 0.22-micron filters received from Amgen
- lot numbers (batch numbers) for product received
- subject's identification (ie subject number)
- date and quantity of panitumumab and 0.22-micron filters dispensed (and remaining, if from individual subject drug units)
- the initials of the dispenser
- dose preparation records
- date and quantity of panitumumab returned to the investigator/pharmacy, if appropriate

All discrepancies must be documented and subsequently reported to Amgen immediately.

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused panitumumab to Amgen. At the end of the study, the Final Investigational Product Reconciliation Statement must be completed and provided to Amgen.

Documentation of the filter lot numbers will be recorded on the 0.22-micron filter accountability record.

These inventories must be made available for inspection by authorized Amgen representatives and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused clinical study supplies.

Other Drugs

All other protocol-mandated drugs for this study (eg, oxaliplatin, 5-FU, leucovorin) are commercially available. These drugs will be formulated, packaged, labeled, and stored according to local manufacturer, supplier, and institutional procedures.

Refer to Section 6.6 for further details.

Appendix K. Pregnancy Notification Worksheet

AMGEN Study No.:	Site No.	Subject ID No.	Subject Initials

PREGNANCY NOTIFICATION WORKSHEET

Did subject withdraw from the study? ❑ No (0) ❑ Yes (1)

Sex ①	① SEX CODES:
	1 Female subject **0** Male subject partner

Estimated Date of Conception		
Day	Month	Year

Investigational Product Administration Start Date			Investigational Product Administration Stop Date		
Day	Month	Year	Day	Month	Year

Fax to:
Date Faxed
Day / Month / Year

The investigator will be contacted for further information.

Please provide the following information:

Investigator Name:	Telephone: ( )
Institution:	Site No:
Address:	

Form Completed By: _____ Date: _____

v4 14Apr04sb

Amendment #2

Protocol Title: A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

Amgen Protocol Number (Panitumumab) 20050203

EudraCT Number:	2006-000170-70
Amendment Date:	21 January 2009

Rationale:

The protocol was amended for the following reasons:

1. To include prospective analyses for KRAS status following new information about KRAS status as a biomarker for panitumumab monotherapy in the pivotal phase 3 randomized clinical trial 20020408, and as part of the conditions for the European approval of panitumumab, which require KRAS status to be investigated in ongoing and future clinical studies with panitumumab in mCRC. As a result, the primary objective of the current study is amended and the sample size considerations revised to ensure adequate power to demonstrate an effect on PFS and OS in the Wild-type KRAS population. This amendment occurs prior to any formal efficacy analysis, knowledge of KRAS information in tumor samples from study subjects, and does not alter the original sample size for the study.
2. Typographical and grammatical errors and omissions updated

Page: 1

Section: Key Sponsor Contact

Replace:

Claire McPhie
Clinical Research Study Manager
Clinical Research Management, Europe
Amgen Ltd
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom
Telephone: +44 1**895 525347**
Fax: +44 1**895 525101**

With:

Pam Dixon
Clinical Research Study Manager
Amgen Ltd
1 Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom
Telephone: **+44 1895 525491**
Fax: **+44 1223 228164**

Page: 1

Section: Amendment Number

Add:

Amendment 2 **21 January 2009**

Page: 2

Section: Investigator's Agreement, first sentence

Add: I have read the attached protocol entitled "A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/ leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer", dated 09 March 2006,

amended 10 October 2007**, and further amended 21 January 2009** and agree to abide by all provisions set forth therein.

Page: 3

Section: Protocol Synopsis, Primary Objective

Replace:

Primary Objective: To assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) **among wild-type KRAS subjects (subjects whose tumors contain non-mutated KRAS) and all randomized subjects.**

With:

Primary Objective: To assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) among **subjects with wild-type KRAS tumors (subjects whose tumors contain non-mutated KRAS) and subjects with mutant KRAS tumors.**

Page: 3

Section: Protocol Synopsis, Secondary Objectives

Replace:

Secondary Objectives: To evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability **among wild-type KRAS and all randomized subjects.**

With:

Secondary Objectives: To evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 3

Section: Protocol Synopsis, Tertiary Objectives

Replace:

Tertiary Objectives: To evaluate time to response and patient reported outcomes (PRO) **among wild-type KRAS and all randomized subjects**.

With:

Tertiary Objectives: To evaluate time to response and patient reported outcomes (PRO) among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 3

Section: Protocol Synopsis, Exploratory Objectives

Replace:

Exploratory Objectives: To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of study drug **among wild-type KRAS and all randomized subjects.**

With:

Exploratory Objectives: To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of study drug among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 3

Section: Protocol Synopsis, Hypothesis

Replace:

Hypothesis: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression-free survival (PFS) compared to chemotherapy (FOLFOX) alone as first-line treatment of mCRC **among wild-type KRAS and all randomized subjects**.

With

Hypothesis:

Primary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression-free survival (PFS) compared to chemotherapy (FOLFOX) alone as first-line treatment of mCRC among **subjects with wild-type KRAS tumors.**

Secondary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression-free survival (PFS) compared to chemotherapy (FOLFOX) alone as first-line treatment of mCRC among subjects with mutant KRAS tumors.

Page: 6

Section: Synopsis, Background Chemotherapy Regimen

Replace:

Chemotherapy: The FOLFOX4 regimen will be administered every 2 weeks as follows:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL sterile water and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in sterile water both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL sterile water as a 22-hour continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL sterile water as a 22-hour continuous infusion

With:

Chemotherapy: The FOLFOX4 regimen will be administered every 2 weeks as follows:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL **D5W** and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in **D5W** both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour continuous infusion

Page: 6

Section: Synopsis, Statistical Considerations

Replace:

Primary Analysis

The primary goal of the statistical analysis is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS) **among the wild-type KRAS subjects (Wild-Type KRAS Efficacy Analysis Set) as well as the all randomized subjects (intention-to-treat [ITT] Efficacy Analysis Set)**, and to characterize and compare overall survival (OS). The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each endpoint. The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

An overall two-sided 5% significance level will be used to compare treatments with respect to both PFS and OS. **PFS in the ITT Efficacy Analysis Set will be compared conditional on first demonstrating a significant difference in PFS in the Wild-Type KRAS Efficacy Analysis Set. OS will be compared only after positives results are obtained for PFS in both the Wild-Type KRAS and ITT Efficacy Analysis Sets, using the same sequential testing scheme, i.e., Wild-Type KRAS followed by ITT. A log-rank test stratified by the randomization factors will be used to compare treatments with respect to both PFS and OS.**

With:

Primary Analysis

The primary goal of the statistical analysis is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS) among **subjects with wild-type KRAS tumors (the Wild-type KRAS Efficacy Analysis Set) as well as subjects with mutant KRAS tumors (the Mutant KRAS Efficacy Analysis Set)** and to characterize and compare overall survival (OS). The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each endpoint. The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors. Significance levels described will be 2-sided unless stated otherwise. PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.

Page: 7

Section: Protocol Synopsis, Statistical Considerations, third paragraph

Add: **Two interim analyses of OS are planned in this study. The first OS interim analysis will be synchronized with the primary PFS analysis. The second OS interim analysis will be conducted with a data cutoff of approximately 9 months later. The second OS interim analysis may be omitted if the data cutoff date of the primary OS analysis is expected to be within 12 months of data cutoff date of the primary PFS analysis.**

Page: 8

Section: Study Design and Treatment Schema

Replace: Within 28 days of day 1

With: Within 28 days of **Randomization**

Page: 9

Section: Study Glossary

Add:

D5W	**Dextrose 5% in water**

ITD	**Intent-to-Diagnosis**

SAP	**Statistical Analysis Plan**

Page: 16

Section: 1.1 Primary Objectives

Replace: The primary objective of this study is to assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) **among wild-type KRAS and all randomized subjects.**

With: The primary objective of this study is to assess whether panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy improves progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for metastatic colorectal cancer (mCRC) among **subjects with wild-type KRAS tumors (subjects whose tumors contain non-mutated KRAS) and subjects with mutant KRAS tumors.**

Page: 16

Section: 1.2 Secondary Objectives

Replace: The secondary objectives are to evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability **among wild-type KRAS and all randomized subjects.**

With: The secondary objectives are to evaluate overall survival (OS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), and safety and tolerability among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 16

Section: 1.3 Tertiary Objectives

Replace: Tertiary objectives are to evaluate time to response and patient reported outcomes (PRO) **among wild-type KRAS and all randomized subjects.**

With: Tertiary objectives are to evaluate time to response and patient reported outcomes (PRO) among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 16

Section: 1.4 Exploratory Objectives

Replace: To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of the study drug **among wild-type KRAS and all randomized subjects.**

With: To investigate potential biomarker development based on assessment of blood cells, tumor cells and the proposed mechanism of action of the study drug among **subjects with wild-type KRAS tumors and subjects with mutant KRAS tumors.**

Page: 25

Section: 2.2.5 Panitumumab Clinical Efficacy Experience, paragraph 8

Add: **On 03 December 2007, the European Commission granted the conditional approval for the use of panitumumab as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.**

Health Canada issued a Notice of Compliance with Conditions for Vectibix® on 3 April 2008. For this approval, Vectibix® is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens.

Australian Therapeutic Goods Administration (TGA) issued an Approval for Registration for Vectibix® on 30 April 2008. For this approval, Vectibix® is indicated for treatment of EGFR expressing, metastatic colorectal carcinoma in

patients who have disease progression following treatment with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy.

Page: 25

Section: 2.2.5 Panitumumab Clinical Efficacy Experience, paragraph 10

Replace: **The information which contributed to the positive opinion in Europe included analyses of the KRAS status of patients in the above phase 3 clinical study, which provided evidence that KRAS status is a biomarker in this setting that may predict which patients are more likely to respond to panitumumab monotherapy (Amado et al., 2007).**

With: **I**nformation **that** contributed to the **approvals** in Europe **and Canada** included analyses of the KRAS status of patients in the above phase 3 clinical study, which provided evidence that KRAS status is a biomarker in this setting that may predict which patients are more likely to respond to panitumumab monotherapy (Amado et al., 2007).

Page: 26

Section: 2.2.5 Panitumumab Clinical Efficacy Experience, paragraph 12

Replace: A clinical trial of chemotherapy plus bevacizumab with and without panitumumab (1:1 randomization) as first line treatment of patients with metastatic CRC is currently ongoing. Oxaliplatin or irinotecan based chemotherapy is used in that study. Recently, safety data from an interim analysis involving 139 subjects in the oxaliplatin containing chemotherapy strata was reviewed by the Independent Data Monitoring Committee (DMC). After review of the data, the DMC recommended that the trial continue without modifications.

With: **Amgen study 20040249 (PACCE) is an open-label, controlled study of bevacizumab and chemotherapy administered with and without panitumumab as first-line treatment of subjects with mCRC. Chemotherapy included oxaliplatin-or irinotecan-based regimens. Based on the results of a planned interim analysis of ~231 PFS events in the oxaliplatin -based cohort, adding panitumumab to bevacizumab and chemotherapy did not prolong progression-free survival and contributed increased toxicity to the multi-agent regimens. Hence, panitumumab was discontinued from the PACCE study.**

Page: 27

Section: 2.4 Hypothesis

Replace: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression free survival (PFS) compared to chemotherapy alone as first-line treatment of mCRC **among wild-type KRAS and all randomized subjects.**

With:

Primary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression free survival (PFS) compared to chemotherapy alone as first-line treatment of mCRC among **subjects with wild-type KRAS tumors.**

Secondary: The addition of panitumumab to chemotherapy (FOLFOX) will increase progression free survival (PFS) compared to chemotherapy alone as first-line treatment of mCRC among subjects with mutant KRAS tumors.

Page: 29

Section: 3.2 Number of Centers

Add: Approximately 200 sites will be participating globally in this study including Western, Central and Eastern Europe, **Canada**, Australia, and South America.

Page: 42

Section: 6.6.2 FOLFOX Regimen Schedule

Replace:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL sterile water and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in sterile water both given over 120 minutes (± 15 minutes) at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL sterile water as a 22-hour (± 1 hour) continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes (± 15 minutes), followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL sterile water as a 22-hour (± 1 hour) continuous infusion

With:

Day 1: oxaliplatin (ELOXATIN™) 85 mg/m^2 IV infusion in 250-500 mL **D5W** and leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion in **D5W** both given over 120 minutes (± 15 minutes) at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour (± 1 hour) continuous infusion

Day 2: leucovorin 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion over 120 minutes (± 15 minutes), followed by 5-FU 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL **D5W** as a 22-hour (± 1 hour) continuous infusion

Page: 43

Section: 6.6.2 FOLFOX Regimen Schedule, paragraph 5

Replace: In the event that FOLFOX4 chemotherapy administration is discontinued for any reason prior to disease progression, panitumumab may continue as monotherapy in subjects who have been randomized to study arm 1. Panitumumab infusions should remain on a once every 14 days (± 3 days) schedule until the subject develops disease progression or is unable to tolerate panitumumab monotherapy.

With: In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy and panitumumab **(for subject randomized to study arm 1) or 5-FU/leucovorin therapy (for subject randomized to study arm 2)** may continue on a once every 14 days (±3 days) schedule until disease progression or intolerance to the study therapy.

Page: 43

Section: 6.6.3.2 FOLFOX4 Dose Modification, paragraph 6

Replace: In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy and panitumumab may continue in subjects who have been randomized to study arm 1, on a once every 14 days (±3 days) schedule until disease progression or intolerance to the study therapy.

With: In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy and panitumumab **(for subjects randomized to study arm 1) or 5-FU/leucovorin therapy (for subjects randomized to study arm 2)** may continue on a once every 14 days (±3 days) schedule until disease progression or intolerance to the study therapy.

Page: 52

Section: 7.1 Screening, paragraph 2, eight bullet, second sub-bullet

Replace:

- Chemistry panel: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) or urea (depending on local institutional practice), lactate dehydrogenase (LDH), magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, phosphorous, and uric acid

With:

- Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice),** blood urea nitrogen (BUN) or urea (depending on local institutional practice), lactate dehydrogenase (LDH), magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, phosphorous, and uric acid

Page: 53

Section: Section 7.3 Treatment Phase, 5th paragraph, eight bullet, second sub-bullet

Replace:

- Chemistry panel: sodium, potassium, chloride, bicarbonate, BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid

With:

- Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice)**, BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid

Page: 55

Section: Section 7.4 Safety Follow-up Visit, second paragraph, seventh bullet, second sub-bullet

Replace:

- Chemistry panel: sodium, potassium, chloride, bicarbonate, BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid

With:

- Chemistry panel: sodium, potassium, chloride, bicarbonate **or CO_2 (depending on local institutional practice)** , BUN or urea (depending on local institutional practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid

Page: 61

Section: 8.2 Replacement of Subjects

Replace: Subjects who are removed or withdrawn from study following randomization will not be replaced. This study will enroll approximately 900 subjects.

With: Subjects who are removed or withdrawn from study following randomization will not be replaced. This study will enroll approximately **1150** subjects.

Page: 62

Section: 9.1.2 Serious Adverse Events, third paragraph

Add: Hospitalization for the performing of protocol-required procedures or administration of study treatment **or for subjects undergoing hospitalization for planned metastasis interventional therapy** is not classified as an SAE.

Page: 63

Section: 9.3 Serious Adverse Event Reporting Procedures, first paragraph

Replace: With 1 exception, serious adverse events will be collected and recorded throughout the study period, beginning with the signing of the informed consent through 30 days after the last dose of investigational product or end of the study (including the follow-up period), whichever is longer. The only exception to this rule is the collection

and recording of serious adverse events that both occur before randomization and are deemed by the investigator to be unrelated to study screening.

With: With 1 exception, serious adverse events will be collected and recorded throughout the study period, beginning with the signing of the informed consent through **to the Safety Follow-Up Visit or** 30 **(+ 3)** days after the last dose of **protocol specified therapy**, whichever is longer. The only exception to this rule is the collection and recording of serious adverse events that both occur before randomization and are deemed by the investigator to be unrelated to study screening.

Page: 64

Section: 9.3 Serious Adverse Event Reporting Procedures, fifth paragraph

Replace: To comply with worldwide serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events will be unblinded before submission to regulatory authorities. Determination of expectedness will be based on the contents of Appendix A in the investigator's brochure for preapproval products and the regional prescribing information for marketed products.

With: To comply with worldwide serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events will be unblinded before submission to regulatory authorities. Determination of expectedness will be based on the contents of Appendix A **and B** in the investigator's brochure for preapproval products and the regional prescribing information for marketed products.

Page: 64

Section: 9.3 Serious Adverse Event Reporting Procedures, fifth paragraph

Add: **Amgen will report serious adverse events (SAEs) and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/institutions and ethics committees in compliance with all applicable regulatory requirements and ICH GCP guidelines.**

Page: 64

Section: 10.1 Study Design

Replace: This is an open-label, randomized, multicenter, phase 3 study to compare the efficacy of panitumumab in combination with chemotherapy to the efficacy of chemotherapy alone for first-line treatment of mCRC **among wild-type KRAS subjects (the Wild-Type KRAS Efficacy Analysis Set) and all randomized subjects (intention-to-treat [ITT] Efficacy Analysis Set).** Subjects will be randomized at a 1:1 ratio to the experimental arm of panitumumab plus FOLFOX and the control arm of FOLFOX alone, stratified by geographic region and baseline ECOG performance status (See Section 3.1). **KRAS status will be retrospectively measured prior to any unblinded efficacy comparisons by KRAS status.**

For each of the two patient populations, the Wild-Type KRAS and the ITT Efficacy Analysis Set (section 10.2.2), the goal of the primary statistical analysis of the study is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS), and to characterize and compare overall survival. The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each endpoint **within each analysis set** (see Section 10.3). The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

An overall 5% significance level will be used to compare treatments with respect to both PFS and OS. **PFS in the ITT Efficacy Analysis Set will be compared conditional on first demonstrating a significant difference in PFS in the Wild-Type KRAS Efficacy Analysis Set.** OS will be compared **only after positives results are obtained for PFS in both the Wild-Type KRAS and ITT Efficacy Analysis Sets, using the same sequential testing scheme, i.e., Wild-Type KRAS followed by ITT.** A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors.

With: This is an open-label, randomized, multicenter, phase 3 study to compare the efficacy of panitumumab in combination with chemotherapy to the efficacy of chemotherapy alone for first-line treatment of mCRC among **subjects with** wild-type KRAS **tumors** (the Wild-Type KRAS Efficacy Analysis Set) and **subjects with mutant KRAS tumors** (**the Mutant KRAS** Efficacy Analysis Set). Subjects will be randomized at a 1:1 ratio to the experimental arm of panitumumab plus FOLFOX and the control arm

of FOLFOX alone, stratified by geographic region and baseline ECOG performance status (See Section 3.1). KRAS status will be retrospectively measured prior to any unblinded efficacy comparisons by KRAS status.

For each of the two patient populations, the Wild-Type KRAS and the **Mutant KRAS** Efficacy Analysis Set (section 10.2.2), the goal of the primary statistical analysis of the study is to assess whether the addition of panitumumab to chemotherapy significantly prolongs progression-free survival (PFS), and to characterize and compare overall survival. The timing of the primary analyses of PFS and OS will be event-driven based on corresponding pre-specified goals for the target number of events for each endpoint within each analysis set (see Section 10.3). The primary analysis of PFS and other modified-RECIST endpoints will be according to blinded central radiology review.

A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors. Significance levels described will be 2-sided unless stated otherwise. PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.

Page: 66

Section: 10.2.2 Analysis Subsets

Replace: **The ITT Efficacy Analysis Set includes** all randomized subjects. Subjects will be analyzed according to treatment randomized regardless of treatment received. **This analysis set is further broken down into the KRAS Evaluable Efficacy Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set whose KRAS status can be assessed), the Wild-Type KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose KRAS status is tested as Wild-Type), the Mutant KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose KRAS status is tested as Mutant) and the KRAS Unevaluable Efficacy**

Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set who have no measurement of KRAS status). These analysis sets will be the primary analysis sets for analyses of PFS and OS.

The Central Tumor Response **Evaluable A**nalysis set is defined as the subset of subjects in the ITT **Efficacy A**nalysis **S**et with at least one uni-dimensionally measurable lesion per the modified RECIST criteria per blinded central radiology review (see Appendix I). **This analysis set is further broken down into the KRAS Central Tumor Response Evaluable Analysis Set, and the Wild-Type, Mutant, and Unevaluable KRAS Central Tumor Response Evaluable Analysis Sets. These will be the primary analysis sets for the analyses of objective response rate, duration of response, and time to response. These** analysis set**s** will also be used for sensitivity analyses of progression-free survival and time to progression. The Evaluable for Local Tumor Response analysis set is defined as the subset of subjects in the ITT **Efficacy A**nalysis **S**et with at least one uni-dimensionally measurable lesion per the local investigator. This analysis set will be used in a comparable manner for analyses based on local tumor assessments. **Breakdown of this analysis set by KRAS status is similar to that of the Central Tumor Response Evaluable Analysis Set.**

A sensitivity analysis may be performed on selected efficacy endpoints to assess the impact of protocol deviations using the Per Protocol (PP) **A**nalysis **S**et, defined as the subjects in the ITT **A**nalysis **S**et without pre-specified, selected important protocol deviations thought to impact on efficacy analyses. **Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.**

The primary PRO analyses will be conducted on the subset of subjects in the ITT **A**nalysis **S**et who have at least 1 post-baseline PRO assessment (PRO All Randomized **A**nalysis **S**et). Secondary analyses for the PRO endpoints may be performed for subjects in the PP **A**nalysis **S**et (PRO Per Protocol **A**nalysis **S**et) who have at least 1 post-baseline PRO assessment. **Breakdown of these two analysis sets by KRAS status is similar to that of the ITT Efficacy Analysis Set.**

The safety analyses will be conducted on all randomized subjects that received at least one dose of panitumumab or chemotherapy (**the All Randomized** Safety **A**nalysis **S**et) analyzed according to treatment received. **Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.**

With: The ITT Efficacy Analysis Set includes all randomized subjects. Subjects will be analyzed according to treatment randomized regardless of treatment received. This analysis set is further broken down into the KRAS Evaluable Efficacy Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set whose **tumor** KRAS status can be assessed), the Wild-Type KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose **tumor** KRAS status is tested as Wild-Type), the Mutant KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Evaluable Efficacy Analysis Set whose **tumor** KRAS status is tested as Mutant), the KRAS Unevaluable Efficacy Analysis Set (includes the subset of subjects in the ITT Efficacy Analysis Set who have no measurement of **tumor** KRAS status), **and the Wild-type Intent-to-Diagnosis (ITD) KRAS Efficacy Analysis Set (includes the subset of subjects in the KRAS Efficacy Analysis Set whose tumor KRAS status is tested as wild-type plus subjects who have no measurement of tumor KRAS status, i.e., the union of the Wild-type and the Unevaluable KRAS Efficacy Analysis Sets)**. The **Wild-type KRAS Efficacy Analysis Set and the Mutant KRAS Efficacy Analysis Set** will be the primary analysis sets for analyses of PFS and OS.

The Central Tumor Response Evaluable Analysis set is defined as the subset of subjects in the ITT Efficacy Analysis Set with at least one uni-dimensionally measurable lesion per the modified RECIST criteria per blinded central radiology review (see Appendix I). This analysis set is further broken down into the KRAS Central Tumor Response Evaluable Analysis Set, and the Wild-Type **KRAS**, Mutant **KRAS**, Unevaluable KRAS **and Wild-type ITD KRAS** Central Tumor Response Evaluable Analysis Sets. The **Wild-type and the Mutant KRAS Central Tumor Response Analysis Sets** will be the primary analysis sets for the analyses of objective response rate, duration of response, and time to response. The **other** analysis sets will also be used for sensitivity analyses of **objective response rate, duration of response, and time to response to estimate treatment effects**. The Local Tumor Response **Evaluable An**alysis **S**et is defined as the subset of subjects in the ITT Efficacy Analysis Set with at least one uni-dimensionally measurable lesion per the local investigator. This analysis set will be used in a comparable manner for analyses based on local tumor assessments. Breakdown of this analysis set by KRAS status is similar to that of the Central Tumor Response Evaluable Analysis Set.

A sensitivity analysis may be performed on selected efficacy endpoints to assess the impact of protocol deviations using the Per Protocol (PP) Analysis Set, defined as the subjects in the ITT Analysis Set without pre-specified, selected important protocol deviations thought to impact on efficacy analyses. Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.

The primary PRO analyses will be conducted on the subset of subjects in the ITT Analysis Set who have at least 1 post-baseline PRO assessment (PRO All Randomized Analysis Set). Secondary analyses for the PRO endpoints may be performed for subjects in the PP Analysis Set (PRO Per Protocol Analysis Set) who have at least 1 post-baseline PRO assessment. Breakdown of these two analysis sets by KRAS status is similar to that of the ITT Efficacy Analysis Set.

The safety analyses will be conducted on all randomized subjects that received at least one dose of panitumumab or chemotherapy (the Safety Analysis Set) analyzed according to treatment received. Breakdown of this analysis set by KRAS status is similar to that of the ITT Efficacy Analysis Set.

Page: 69

Section: 10.2.3 Covariates, third paragraph

Add: Tumor tissue samples obtained will be analyzed to evaluate EGFr expression (eg, by immunohistochemistry). **The following parameters will be obtained using the Dako EGFR pharmDx Kit:**

- **Percent of tumor cells with membrane EGFr staining at each of the following intensities: 0, 1+, 2+, 3+**
- **Percent of tumor cells with cytoplasmic EGFr staining at each of the following staining intensities: 0, 1+, 2+, 3+**
- **Overall EGFr results: negative vs. positive**

Additional EGFr pharmDx variables may be derived from the above parameters. Analyses of EGFr in relation to treatment effects and prognostic value will be reported in the primary analysis. Detailed plans will be documented in a Biomarker SAP addendum, which will be finalized after the interim efficacy analysis, but prior to the primary PFS efficacy analysis.

Page: 69

Section: 10.3 Sample Size Considerations, first paragraph

Replace: For the purpose of sample size and study duration estimation, all time to event endpoints are assumed to be exponentially distributed. **PFS in the ITT Efficacy Analysis Set (section 10.2.2) will be compared conditional on first demonstrating a significant difference in PFS in the Wild-Type KRAS Efficacy Analysis Set. OS will be compared (using the same sequential testing scheme as PFS) only after positive results are obtain for PFS in both the Wild-Type KRAS and ITT Efficacy Analysis Sets.**

With: For the purpose of sample size and study duration estimation, all time to event endpoints are assumed to be exponentially distributed. **PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%.**

Page: 70

Section: 10.3.1 Sample Size Revision

Replace: **The study was initially estimated to require 900 subjects to demonstrate a treatment effect on PFS in the all randomized analysis set alone. However, in September 2007 a retrospective analysis of the phase 3 pivotal study in the 3rd line monotherapy mCRC setting provided evidence that clinical benefit of panitumumab was isolated to patients with non-mutant (wild-type) KRAS status. These results are specific to monotherapy use of panitumumab in a 3rd–line setting, and prospective confirmation of the clinical utility of KRAS for patient selection is required in a 1st-line mCRC setting in combination with chemotherapy. Therefore, the current study was amended, prior to any efficacy analysis, to ensure that sufficient subjects would be enrolled to enable adequate statistical power for analysis within the wild-type KRAS sub-population and the all randomized patient population, within this 1st line mCRC clinical study.**

Achievement of this goal requires an enrollment extension. Although the original accrual had been met at the time of amendment, enrollment is planned to continue beyond the original sample size goal without disruption to maintain continuity for trial integrity. All other aspects of study conduct, ie. protocol eligibility criteria, study treatments, etc., remain unchanged as per the original protocol; thus, the amendment for prospective evaluation of KRAS does not alter the study population enrolled or the risk-benefit of subject participation in the study.

With: The study was initially estimated to require 900 subjects to demonstrate a treatment effect on PFS in the all randomized analysis set alone. However, in September 2007 a retrospective analysis of the phase 3 pivotal study in the 3rd line monotherapy mCRC setting provided evidence that clinical benefit of panitumumab was isolated to patients with non-mutant (wild-type) KRAS status. These results are specific to monotherapy use of panitumumab in a 3rd–line setting, and prospective confirmation of the clinical utility of KRAS for patient selection is required in a 1st-line mCRC setting in combination with chemotherapy. Therefore, the current study was amended, prior to any efficacy analysis, to ensure that sufficient subjects would be enrolled to enable adequate statistical power for analysis within the wild-type KRAS population, within this 1st line mCRC clinical study. Achievement of this goal requires an enrollment extension. Although the original accrual had been met at the time of amendment **1**, enrollment **was continued** without disruption to maintain continuity for trial integrity. All other aspects of study conduct, ie. protocol eligibility criteria, study treatments, etc., remain**ed** unchanged as per the original protocol; thus, the amendment for **the** evaluation of KRAS **did** not alter the study population enrolled or the risk-benefit of subject participation in the study.

Page: 70

Section: 10.3.2 Sample Size and PFS Event Goals

Replace: **In the original protocol dated 09 March 2006, a** PFS hazard ratio (FOLFOX plus panitumumab to FOLFOX) of 0.75 **wa**s hypothesized in the **ITT Efficacy Analysis Set. Importantly, with recent results available from other phase 3 trials, a PFS hazard ratio of 0.80 is deemed more reasonable in this first-line mCRC setting; hence, the protocol amendment assumes this is new hypothesized effect size for the ITT population.** Assuming a median PFS time of 9 months (De Gramont 2000, Goldberg et al 2004) for the FOLFOX arm, this hazard ratio translates into a median of

11.3 months for the FOLFOX plus panitumumab arm. To achieve 90% **unconditional** power to reject the null hypothesis at a 5% significance level **in the ITT Efficacy Analysis Set,** a total of **850 PFS events (non-censored progression free-survival times [based on central review]) or deaths) are required (Lachin and Foulkes, 1986).**

For the Wild-Type KRAS sub-population, a PFS hazard ratio (FOLFOX plus panitumumab to FOLFOX) of 0.714 is hypothesized. Assuming the prevalence of Wild-Type KRAS in the ITT Efficacy Analysis Set is 55%, and the PFS hazard ratio (Wild-Type KRAS over Mutant KRAS) is 0.6 in the FOLFOX alone arm (i.e., median PFS for Wild-Type KRAS is 67% longer in control arm), it is estimated that the median PFS for Wild-Type KRAS FOLFOX is approximately 12.0 months. Hence this hypothesized hazard ratio translates into a median of 16.8 months for the FOLFOX plus panitumumab arm (i.e., 12 vs. 16.8 months) for the Wild-Type KRAS sub-population. To achieve 90% power to reject the null hypothesis at a 5% significance level in the Wild-Type KRAS Efficacy Analysis Set, a total of 380 PFS events are required (Lachin and Foulkes, 1986).

In the original protocol dated 09 March 2006, the enrollment rate was projected at 65 subjects per month with a concave pattern of enrollment of 50% subjects after 2/3 of accrual time had elapsed, and a yearly 5% exponentially distributed lost-to-follow-up. These assumptions turn out to be very close to the real enrollment pattern for those 970 subjects that have been randomized up to the protocol amendment. Hence for the period of enrollment extension, similar assumptions are used with the average accrual rate set at 50 subjects per month.

Based on the above assumptions, it is estimated that 1150 subjects (575 per arm) will need to be randomized (with about 900 from the original protocol and about 250 from the enrollment extension) and accrued over a 19 months (with 14 months under the original protocol and 5 months for the enrollment extension) with a minimum follow-up of approximately 16 months to achieve 380 events for PFS Wild-Type KRAS Efficacy Analysis Set and 850 for PFS ITT Efficacy Analysis Set. With Wild-Type KRAS prevalence of 55% and a KRAS Evaluability rate of 90%, 1150 randomized subjects will produce about 570 subjects that will be tested as Wild-Type KRAS and about 466 subjects that will be tested as Mutant KRAS.

With: **The primary goal of the statistical analysis of the study is to demonstrate whether there is an increase in PFS in subjects treated with panitumumab plus**

FOLFOX versus FOLFOX alone in the Wild-type KRAS Efficacy Analysis Set. Therefore sample size considerations were focused on ensuring sufficient power in the wild-type KRAS stratum alone.

For the Wild-Type KRAS sub-population, a PFS hazard ratio (FOLFOX plus panitumumab to FOLFOX) of 0.714 is hypothesized. Assuming the prevalence of Wild-Type KRAS in the ITT Efficacy Analysis Set is 55%, it is estimated that the median PFS for Wild-Type KRAS FOLFOX is approximately 1**0**.0 months. Hence this hypothesized hazard ratio translates into a median of **14.0** months for the FOLFOX plus panitumumab arm (i.e., **10.0** vs. **14.0** months) for the Wild-Type KRAS sub-population. To achieve 90% power to reject the null hypothesis at a 5% significance level in the Wild-Type KRAS Efficacy Analysis Set, a total of 380 PFS events are required (Lachin and Foulkes, 1986).

In the original protocol dated 09 March 2006, the enrollment rate was projected at 65 subjects per month with a concave pattern of enrollment of 50% subjects after 2/3 of accrual time had elapsed, and a yearly 5% exponentially distributed lost-to-follow-up. These assumptions turn out to be very close to the real enrollment pattern for those 970 subjects that have been randomized up to protocol amendment **1**. Hence for the period of enrollment extension, similar assumptions are used with the average accrual rate set at 50 subjects per month.

Based on the above assumptions, it is estimated that 1150 subjects (575 per arm) will need to be randomized (with about 900 from the original protocol and about 250 from the enrollment extension) and accrued over a 19 months (with 14 months under the original protocol and 5 months for the enrollment extension) with a minimum follow-up of approximately **12** months to achieve 380 events for PFS **in the** Wild-Type KRAS Efficacy Analysis Set. With Wild-Type KRAS prevalence of 55% and a KRAS Evaluability rate of 90%, 1150 randomized subjects will produce about 570 subjects that will be tested as Wild-Type KRAS and about 466 subjects that will be tested as Mutant KRAS. **The study completed enrollment on 1 February 2008 with 1183 subjects accrued, with 586 expected to have wild-type KRAS, 479 to have mutant KRAS, and 118 to have unevaluable KRAS status.**

Page: 71

Section: 10.3.3 OS Event Goals

Replace: To allow estimation of the median survival time in both treatment groups f**or both the ITT population and the Wild-Type KRAS sub-population**, the primary overall survival analysis will **occur when 300 cumulative deaths in the Wild-Type KRAS Efficacy Analysis Set and 600 cumulative deaths in the ITT Efficacy Analysis Set are collected. The study will end when those event goals are achieved (approximately 49 months after first subject is randomized).**

With: To allow estimation of the median survival time in both treatment groups for both the Wild-Type KRAS **and the Mutant KRAS** sub-population, the primary overall survival analysis will occur when **at least 50% of subjects in both randomized treatment groups have an event** in the Wild-Type KRAS Efficacy Analysis Set. The study will end when th**is** event goal **is** achieved (approximately 49 months after first subject is randomized).

Page: 73

Section: 10.5.2.1 Progression-free Survival, second paragraph

Replace: **In protocol amendment 1, the interim analysis will be conducted by the DMC at approximately 258 PFS events to obtain an overall assessment of benefit-risk in the all randomized study population by an examination of overall PFS and safety by treatment; however, the interim analysis will not formally compare PFS, so that a 5% significance level will be preserved for the primary PFS analysis. If warranted from this analysis, the DMC may subsequently recommend that they also obtain an overall assessment of benefit-risk separately within the wild-type KRAS and mutant KRAS sub-populations. Prospective guidelines for DMC actions will be pre-specified in an amended DMC charter for the revised interim PFS analysis and potential subsequent KRAS-stratified PFS analysis.**

With: In protocol amendment 1, the interim analysis **was** conducted by the DMC at approximately 258 PFS events to obtain an overall assessment of benefit-risk in the all randomized study population by an examination of overall PFS and safety by treatment; however, the interim analysis will not formally compare PFS, so that a 5% significance level will be preserved for the primary PFS analysis. Prospective guidelines for DMC actions **were** pre-specified in an amended DMC charter.

Page: 73

Section: 10.5.2.2 Overall Survival

Replace: **No formal interim analysis will be performed for OS in any analysis set.**

With: **Two interim analyses of OS are planned in this study. The first OS interim analysis will be synchronized with the primary PFS analysis. The second OS interim analysis will be conducted with a data cutoff of approximately 9 months later. The second OS interim analysis may be omitted if the data cutoff date of the primary OS analysis is expected to be within 12 months of data cutoff date of the primary PFS analysis. The Haybittle-Peto boundaries of 0.001 will be used as the nominal significance levels for the interim OS analyses. The primary OS in Wild-type KRAS and Mutant KRAS Efficacy Analysis Sets will be compared at a significance level of 5% conditional on a superior result of PFS in the Wild-type KRAS and Mutant KRAS Efficacy Analysis Sets, respectively.**

Page: 74

Section: 10.6.1 General Approach/Considerations

Replace: The analysis objectives and testing strategy are described in Section 10.1, and the estimated timing of event goals in Section 10.3.

Prior to each efficacy analysis, blinded monitoring and modeling of cumulative events **(in the ITT and the Wild-Type KRAS Efficacy Analysis Sets)** will be employed to determine an initial data cutoff date to achieve the planned analysis target total event goal**s.** A prospective lower limit for the**se** target goal**s** will be set. Subsequent to data collection for the data cutoff date, the observed total events will be determined. If this is below the lower limit, then a sufficiently later data cutoff date will be utilized for which the observed total events are at or above the limit. The limits will be prospectively defined in the Statistical Analysis Plan.

Primary efficacy analysis on PFS and OS will use the ITT Efficacy Analysis Set and the Wild-Type KRAS Efficacy Analysis Set. The primary analysis of all tumor measurement related endpoints will be based on **the Central Tumor Evaluable Analysis Set and the KRAS Central Tumor Response Evaluable Analysis Set.** Sensitivity analysis using investigator assessed tumor response or disease progression may be performed, **using similar analysis sets of local review. Additional**

descriptive efficacy and safety analyses may be performed on other analysis sets described in section 10.2.2 to provide a robust assessment of the overall risk-benefit profile of panitumumab.

With: The analysis objectives and testing strategy are described in Section 10.1, and the estimated timing of event goals in Section 10.3.

Prior to each efficacy analysis, blinded monitoring and modeling of cumulative events in the Wild-Type KRAS Efficacy Analysis Set will be employed to determine an initial data cutoff date to achieve the planned analysis target total event goal**.** A prospective lower limit for th**is** target goal will be set. Subsequent to data collection for the data cutoff date, the observed total events will be determined. If this is below the lower limit, then a sufficiently later data cutoff date will be utilized for which the observed total events are at or above the limit. The limits will be prospectively defined in the Statistical Analysis Plan.

Primary efficacy analysis on PFS and OS will use the Wild-Type KRAS Efficacy Analysis Set **and the Mutant KRAS Efficacy Analysis Set**. The primary analysis of all tumor measurement related endpoints will be based on the **Wild-type KRAS** and the **Mutant** KRAS Central Tumor Response Evaluable Analysis Set**s**. Sensitivity analysis using investigator assessed tumor response or disease progression may be performed, using similar analysis sets of local review. **Primary safety analyses will use the Wild-type KRAS and the Mutant KRAS Safety Analysis Sets.** Additional descriptive efficacy and safety analyses may be performed on other analysis sets described in section 10.2.2 to provide a robust assessment of the overall risk-benefit profile of panitumumab.

Page: 74

Section: 10.6.2.1 Progression-Free and Overall Survival

Replace: **PFS in the ITT Efficacy Analysis Set (section 10.2.2) will be compared conditional on first demonstrating a significant PFS difference in the Wild-Type KRAS Efficacy Analysis Set.** OS will be compared **(using the same sequential testing scheme as PFS) only after positives results are obtained for PFS in both the Wild-Type KRAS and ITT Efficacy Analysis Sets.** A log-rank test will be used to compare treatments with respect to both PFS and OS stratified by the randomization factors

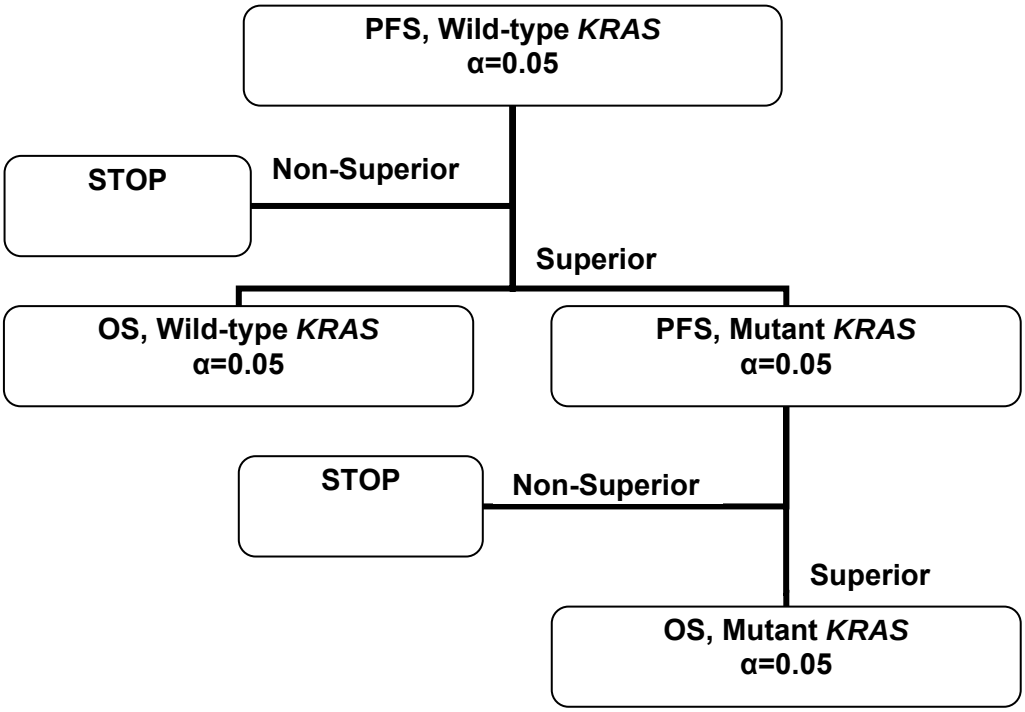
A hazard ratio of test to control and associated 95% CI will be estimated from a Cox model stratified by the randomization factors as captured via IVRS. A piecewise Cox model with pre-defined intervals will be considered given evidence of non-proportional hazards.

Kaplan-Meier (KM) time to event curves will be presented by randomized treatment and actual received treatment for PFS and OS, respectively. KM estimates and 95% CIs will be calculated by randomized treatment for event time quartiles, event-free rates at selected times, and for the difference in event-free rates between treatments at selected times.

Since the Wild-Type KRAS Efficacy Analysis Set is a subgroup of all randomized subjects, a sensitivity analysis of the PFS treatment effect will be conducted to evaluate the impact of baseline treatment arm prognostic factor imbalances. For OS, the impact of second-line treatment will also be assessed. Details will be provided in the amended Statistical Analysis Plan.

With: **PFS in the Wild-type KRAS Efficacy Analysis Set (see Section 10.2.2) will be compared at a significance level of 5%. PFS in the Mutant KRAS Efficacy Analysis Set and OS in the Wild-type KRAS Efficacy Analysis Set will be compared at a significance level of 5% conditional on first demonstrating a significant treatment effect in PFS in the Wild-type KRAS Efficacy Analysis Set. If the analysis demonstrates a significant treatment effect on PFS in the Mutant KRAS Efficacy Analysis Set, then OS in the Mutant KRAS Efficacy Analysis Set will be compared at a significance level of 5%. The PFS and OS efficacy analyses schema is shown in Figure 3. A log-rank test will be used to compare treatments with respect to both OS and PFS stratified by the randomization factors.**

Figure 3. Efficacy Analyses Schema



A hazard ratio of test to control and associated 95% CI will be estimated from a Cox model stratified by the randomization factors as captured via IVRS. A piecewise Cox model with pre-defined intervals will be considered given evidence of non-proportional hazards.

Kaplan-Meier (KM) time to event curves will be presented by randomized treatment and actual received treatment for PFS and OS, respectively. KM estimates and 95% CIs will be calculated by randomized treatment for event time quartiles, event-free rates at selected times, and for the difference in event-free rates between treatments at selected times.

Since the Wild-Type KRAS **and the Mutant KRAS** Efficacy Analysis Set**s are** subgroup**s** of all randomized subjects, sensitivity analys**e**s of the PFS treatment effect will be conducted to evaluate the impact of baseline treatment arm prognostic factor imbalances. For OS, the impact of second-line treatment will also be assessed. Details will be provided in the amended Statistical Analysis Plan.

Page: 76

Section: 10.6.2.7 Safety, first paragraph

Replace: Safety will be analyzed according to treatment received. The primary analysis of safety will summarize all adverse events separately for panitumumab in combination with chemotherapy and during panitumumab monotherapy. A secondary analysis of safety will include all adverse events during the treatment phase (including those from the 30-day safety follow-up).

With: Safety will be analyzed according to treatment received. The primary analysis of safety will summarize all adverse events during the treatment phase (including those from the 30-day safety follow-up). T**he following safety analyses will be performed on all five KRAS Safety Analysis Sets (i.e., KRAS Safety Analysis Set, Wild-type KRAS Safety Analysis Set, Mutant KRAS Safety Analysis Set, Wild-type ITD KRAS Safety Analysis Set, and Unevaluable KRAS Safety Analysis Set) as well as the Safety Analysis Set.**

Page: 91

Section: Appendix A, footnote k

Add: **or CO_2**

Page: 92

Section: Appendix B, footnote e

Add: **or CO_2**