A PHASE II STUDY OF PANITUMUMAB IN COMBINATION WITH FOLFIRI AFTER PROGRESSION ON FOLFIRI PLUS BEVACIZUMAB IN KRAS AND NRAS WILD TYPE METASTATIC COLORECTAL CANCER.

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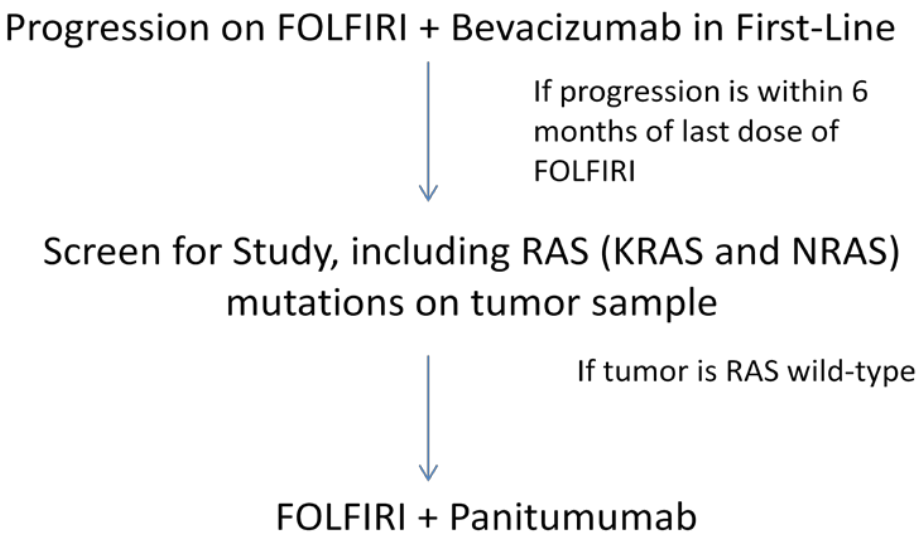
ABBREVIATIONS

Abbreviation	Term
5-FU	5-Fluorouracil
ALT	alanine transaminase (also referred to as SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (also referred to as SGOT)
BEV	Bevacizumab
BUN	blood urea nitrogen
CO_2	total carbon dioxide
CBC	complete blood count
IRINOTECAN	Irinotecan
CR	complete response
CRF	case report form
(CR+PR)	objective complete and partial responses
CTC	Common Toxicity Criteria
ECOG PS	Eastern Cooperative Oncology Group Performance Score
FOLFIRI	Chemotherapy regimen as outlined with 5-FU, LV, and irinotecan
G-CSF	granulocyte-colony stimulating factor
IRB	Institutional Review Board
LV	Leucovorin
pa	Posteroanterior
Pan	Panitumumab
pCR	pathologic complete response rate
PD	progressive disease
PI	Principal Investigator
PR	partial response
SD	stable disease
TS	thymidylate synthase (spelling error)
ULN	upper limits of normal
UPC	Urine Protein Creatinine Ratio
WNL	within normal limits
dThdPase	thymidine phosphorylase

TABLE OF CONTENTS – PHASE II STUDY OF PANITUMUMAB IN COMBINATION WITH FOLFIRI AFTER PROGRESSION ON FOLFIRI PLUS BEVACIZUMAB IN KRAS WILD TYPE METASTATIC COLORECTAL CANCER **3**


Progression on FOLFIRI + Bevacizumab in First-Line
If progression is within 6 months of last dose of FOLFIRI
Screen for Study, including RAS (KRAS and NRAS) mutations on tumor sample
If tumor is RAS wild-type
FOLFIRI + Panitumumab

SCHEMA

1. BACKGROUND AND RATIONALE

1.1. Disease Background

Colorectal cancer is the second leading cause of cancer mortality in the United States (1). Recent advances in the treatment of this deadly cancer have almost doubled the median survival time of those patients. The introduction of Irinotecan and Oxaliplatin along with 5FU has enabled patients to live longer (2-4). Those drugs represent the conventional chemotherapeutic armamentarium for treating metastatic colorectal cancer (MCRC). More recently, added to that armamentarium, came targeted biologic therapies, cetuximab, panitumumab, and bevacizumab with the potential to improve survival even further (5-6). With these molecularly targeted agents, the survival of patients with metastatic disease is now approximating 24 months.

1.2. Drug Background

1.2.1. Panitumumab

1.2.1.1. Panitumumab Pharmacology

Panitumumab is a high affinity (Kd = 5 x 10-11 M) fully human IgG2 monoclonal antibody that is directed against the human EGFR. This fully human antibody was engineered using XenoMouse® technology developed by Abgenix Inc. In this proprietary strain of mice, murine heavy and light chain immunoglobulin genes were inactivated and most of the human heavy and light chain immunoglobulin genes (both kappa and lambda) were inserted. When this strain of engineered mice was immunized with EGFr over- expressing A431 cells, fully human anti-EGFr antibodies were produced, from which panitumumab was selected for further development. (7)

Through the high-affinity interaction of panitumumab with the active site of the EGFr, binding of the ligands EGF, TGFα, amphiregulin, betacellulin, epiregulin, and heparin- EGF is blocked. This inhibition may in turn arrest tumor cell proliferation, inhibit metastasis, and trigger apoptosis (programmed cell death). (7)

1.2.1.2. Preclinical Antitumor Activity of Panitumumab

In murine xenograft tumor models, panitumumab has demonstrated tumor growth inhibition, eliciting both tumor regression and eradication of established tumors (8). When panitumumab was combined with chemotherapeutic agents, eradication and inhibition of the growth of human epidermoid, ovarian, breast, and pancreatic carcinoma cells in vitro and A431 epidermoid, DU145 prostrate, and A549 lung xenografts in vivo were observed. In addition, the administration of panitumumab combined with a multikinase inhibitor, AMG 706, in mice resulted in significantly greater tumor growth inhibition of A431 epidermoid, HT29 colon, and Calu6 non-small cell lung xenografts than with either agent alone.

The antineoplastic effects of panitumumab have been demonstrated in multiple human xenograft tumor models. Panitumumab, at a dose of 1.0 mg/injection administered intraperitoneally (IP) twice weekly for 3 weeks, inhibited the growth of human A431 epidermoid carcinoma xenografts in athymic mice versus the control treatment group, resulting in the complete regression of established (≤ 1.2 cm3) tumors. Lower doses of panitumumab administered twice weekly for 3 weeks inhibited established xenografts more effectively than similar doses of the m225 anti-EGFr antibody.

Non-clinical pharmacology studies indicate that panitumumab antitumor activity is not solely correlated with the total number of EGFr molecules on the tumor cell surface, but are also dependent on the functional activity of this signaling pathway in different tumor cell types (9). A lack of antitumor

activity was observed with panitumumab treatment in a subset of EGFr-expressing human tumor xenografts in vivo. EGFr levels in these tumor cell types may not absolutely correlate with EGFr functional activity, and therefore, tumor cell dependency on this signaling pathway for proliferation, survival, and/or angiogenesis may be more important. The data indicate that expression of EGFr on tumors is frequently accompanied by growth dependency on the EGFr pathway and that blocking the pathway with neutralizing anti-EGFr antibodies, such as panitumumab, may lead to growth arrest and regression (9).

The effects of panitumumab in combination with chemotherapeutic agents (doxorubicin, cisplatin, and docetaxel) have been evaluated in in-vivo models and have indicated additive growth inhibition of tumor xenografts. Panitumumab also has been evaluated in combination with AMG 706, a multikinase inhibitor including VEGF receptor, resulted in significantly greater inhibition of tumor xenografts than either agent alone.

1.2.1.3. Clinical Studies with Panitumumab

The clinical development program for panitumumab is extensive and includes a wide range of studies. Fifteen studies have been initiated and over 1467 patients have been treated with panitumumab at multiple dose levels and 1 of 3 dosing schedules (2.5 mg/kg weekly, 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks). Subjects with a variety of solid tumors (CRC, renal cell, prostate, NSCLC, pancreatic, esophageal) have been treated with panitumumab in either a monotherapy setting or in combination with chemotherapy.

Initially in MCRC, panitumumab, as a single agent, had been shown to have antitumor activity in refractory MCRC in both EGFR-positive and –negative tumors (10,11). However subsequent follow up has shown a significant difference in response comparing patients with mutated *KRAS* oncogene compared to those without a mutation on this oncogene (12,43). The patients with patients a wild-type or unmutated *KRAS* oncogene have a significantly better response to monoclonal antibody targeted therapies against EGFR. As such, panitumumab has been FDA approved for the treatment of EGFR-expressing mCRC after progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

In addition, a recent phase 3, multicenter, randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients (pts) with metastatic colorectal cancer (mCRC). In this study, patients receiving panitumumab had a 46% lower relative progression rate than those receiving BSC alone (hazard ratio=0.54, 95% CI: 0.44, 0.66). By the first scheduled assessment (week 8), a higher percentage of patients alive without progression was observed in the panitumumab versus BSC group (49% versus 30%, respectively); a difference in the percentage of patients alive favoring panitumumab continued through week 32 (AACR abs CP-1,12). In combination with IFL (Amgen Study 20025409), the incidence of grade 3 or 4 diarrhea (58%) was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen, and 1 subject had an episode of grade 4 diarrhea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was better tolerated with an incidence of grade 3 or 4 diarrhea similar to that expected from the literature for this chemotherapy regimen alone (25%) (median PFS=10.9 months) (13,14).. These data suggest that the potential for additive toxicities in the gastrointestinal tract exists when panitumumab is administered in combination with GI-toxic chemotherapy. However, these toxicities could be managed by appropriate selection of the concomitant

chemotherapy regimen.

1.2.1.4. Toxicities

Nonclinical toxicology studies were conducted to support the use of panitumumab for intravenous administration in the oncology setting. All toxicology studies were conducted in cynomolgus monkeys, the only pharmacologically relevant nonhuman species. Panitumumab was administered IV at doses ranging from 0.3 to 30 mg/kg once weekly for 4 weeks and ≤ 15 mg/kg once weekly for 12 weeks. Additionally, a study is ongoing in which panitumumab was administered weekly to monkeys at doses of ≤ 30 mg/kg for 26 weeks. The 30-mg/kg/week dose used in the toxicology studies provides a 6-fold safety margin (AUC-based) to the clinical dose of 2.5 mg/kg once weekly and an approximately 4.5-fold safety margin (AUC-based) to a clinical dose of 6.0 mg/kg once every 2 weeks or 9.0 mg/kg once every 3 weeks. The principal treatment-related findings observed in these studies were diarrhea and skin rash, which were considered to be related to the pharmacologic action of panitumumab. Dehydration and electrolyte disturbances were observed in early studies and were considered likely to be associated with severe diarrhea. Therefore, fluid support was administered in subsequent studies to prevent dehydration.

Reproductive toxicity studies evaluating the effects of panitumumab on embryofetal development and female fertility are ongoing (in-life complete). In the embryofetal development study, panitumumab was administered once weekly at doses of 7.5, 15, or 30 mg/kg to pregnant cynomolgus monkeys during the period of organogenesis. A preliminary review of the data showed that fetal abortions occurred in all dose groups, and thus, panitumumab should not be administered to pregnant women, and women of childbearing potential as well as men should continue to use contraception during panitumumab therapy and for 6 months after the last dose is administered. In the fertility study, panitumumab (7.5, 15, or 30 mg/kg) was administered once weekly to female cynomolgus monkeys before mating and through early pregnancy; based on an initial review of the draft data, minimal-to-severe skin rash and/or diarrhea, decreased food consumption, and body weight loss (sometimes resulting in amenorrhea) were observed in some animals in all dose groups (14).

The mechanism of action of panitumumab is not expected to be mutagenic or carcinogenic, and no structural alerts regarding carcinogenicity have been identified for this drug class. Additionally, panitumumab is neither a growth hormone nor an immunosuppressant. Thus, mutagenicity or carcinogenicity studies are considered unnecessary. This approach is consistent with International Committee on Harmonization (ICH) guidelines.

1.2.1.5 Clinical Safety INFORMATION

Panitumumab Clinical Safety Experience

The below referenced studies reflect the reported adverse events at the time of the last Panitumumab Investigator's Brochure (14). Please refer to the current version of the Panitumumab Investigator's Brochure as well as the updated safety information contained in the Investigational New Drug safety letters for further updates.

Safety analyses from 16 clinical studies in subjects with a variety of solid tumors (n = 1599 receiving panitumumab) indicated that panitumumab is generally well tolerated. Among these studies, 11 enrolled subjects with mCRC (n = 1052 receiving panitumumab as a single agent). In these subjects, dermatologic-related toxicities were the most frequently reported adverse events (91% of subjects), with

most events being mild to moderate. Relatively few subjects (2%) permanently discontinued panitumumab due to dermatologic adverse events.

Infusion reactions to panitumumab (defined as any reported allergic reaction, hypersensitivity, anaphylactoid reaction, chills, fever, or dyspnea, occurring within 24 hours of the first dose that were not otherwise designated as either anaphylactoid or allergic reaction) were infrequent (3% of subjects; < 1% severe); particularly considering that premedication was not mandated in study protocols. Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in the clinical trials and post-marketing experience (including fatal outcomes). Fatal reactions have also been observed in patients with a history of prior hypersensitivity reaction to panitumumab including a case of fatal angioedema occurring more than 24 hours following the administration of panitumumab, Panitumumab antigenicity, as measured by enzyme-linked immunosorbent assay (ELISA) and Biacore assay, was very low and was not associated with clinical sequelae.

Acute renal failure has been observed in patients who develop severe diarrhea and dehydration.

Please refer to the current Panitumumab Investigator's Brochure for further details (14).

1.2.1.6 Panitumumab Safety Monotherapy Studies

An integrated analysis of the safety of panitumumab has been conducted for 1052 subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set). Subjects primarily received panitumumab doses of 2.5 mg/kg once weekly (15%) or 6.0 mg/kg every 2 weeks (82%).

Consistent with the published data on subjects treated with EGFr inhibitors (ie, class/target effect) (Perez-Soler and Saltz, 2005), the most commonly reported treatment-related adverse events in subjects treated with panitumumab were associated with the skin, including pruritus (52%), acneiform dermatitis (51%), erythema (50%), and rash (38%). Most subjects (833 of 1052 subjects, 79%) with any dermatologic toxicity had events that were considered to be mild or moderate. Only 3% of subjects permanently discontinued panitumumab administration for dermatologic toxicities. Dermatologic toxicities typically were observed after initiation of panitumumab, with a median time to first integument toxicity (of any severity) of 10 days (95% CI: 8, 11).

Other common treatment-related adverse events (ie, subject incidence ≥ 10%) included fatigue (15%) and diarrhea (13%).

Subjects in the wild-type KRAS subset received a higher number of panitumumab infusions compared with subjects in the mutant subset (mean [median] 10.0 [8.0] and 4.9 [4.0], respectively). More treatment-related adverse events occurred in the wild-type KRAS subset compared with the mutant KRAS subset, presumably due to the greater number of panitumumab infusions received. These adverse events were mainly skin toxicities (erythema, pruritus, dermatitis acneiform) likely reflecting the increased duration of exposure to panitumumab. No qualitative differences in overall adverse events were observed between the wild-type KRAS subset, the mutant KRAS subset and the overall population, however, treatment related grade 3 adverse events were reported for 25% of subjects in the wild-type KRAS subset compared with 12% of subjects in the mutant KRAS subset. Two percent of wild-type KRAS subjects and 1% of mutant KRAS subjects withdrew for panitumumab-related events.

Infusion reactions to panitumumab were infrequent even though premedication was not mandated in the panitumumab clinical program. Overall, 1% of subjects had an infusion reaction reported by the investigator as an adverse event. Using a definition consistent with the Vectibix USPI (2007), 3% of

panitumumab-treated subjects had a potential infusion reaction; < 1% of subjects had a potential infusion reaction by this definition ≥ grade 3.

1.2.1.7 Safety of Panitumumab in Combination with Chemotherapy

To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN.

In the mCRC setting in combination with IFL (Study 20025409), the incidence of grade 3 or 4 diarrhea (58%) was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen, and 1 subject had an episode of grade 4 diarrhea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was better tolerated with an incidence of grade 3 or 4 diarrhea similar to that expected from the literature for this chemotherapy regimen alone (25%) (14). These data suggest that the potential for additive toxicities in the gastrointestinal tract exists when panitumumab is administered in combination with GI-toxic chemotherapy. However, these toxicities could be managed by appropriate selection of the concomitant chemotherapy regimen.

No clear additive effects were observed in the NSCLC setting where panitumumab was combined with carboplatin/paclitaxel (Study 20025404). One case of pulmonary fibrosis was reported in a subject treated with this combination. Although subjects with evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies (from 2004 onward), this subject, who had a previous history of underlying idiopathic pulmonary fibrosis, was enrolled before the protocol exclusions were implemented.

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 (conducted after 257 progression or death events had occurred), adding panitumumab to bevacizumab and oxaliplatin-based chemotherapy did not prolong progression-free survival and contributed increased toxicity to the multi-agent regimens. Panitumumab treatment was discontinued from the study at that time (22 March 2007).

A final analysis of on-treatment efficacy and safety was performed based on available data as of 31 May 2007. The addition of panitumumab to bevacizumab and oxaliplatin-based chemotherapy showed an unfavorable benefit-to-risk profile with shorter progression-free survival time and increased toxicity. Although panitumumab treatment in the irinotecan-based chemotherapy stratum was also prematurely discontinued, there was no evidence of significant benefit with the addition of panitumumab to bevacizumab and irinotecan-based chemotherapy in first-line treatment of mCRC. Given the unfavorable benefit-to-risk outcome, the PACCE study as designed did not support the use of panitumumab with bevacizumab and oxaliplatin- or irinotecan-based chemotherapy as first-line treatment of metastatic colorectal cancer.

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

1.2.2 5-Fluorouracil

1.2.2.1 Pharmacology of 5-Fluorouracil

5-FU, 5-fluoro-2,4(1H,3H)-pyrimidinedione, is an antineoplastic antimetabolite, is a colorless to faint yellow aqueous, sterile, nonpyrogenic injectable solution for intravenous administration. This antimetabolite has been used since its advent in the 1950s and has cell cycle specific activity in the S-phase. Its main target after conversion to the metabolite FdUMP is the enzyme thymidylate synthase (15). It can be incorporated into both DNA and RNA resulting in alteration and disruption of normal function and ultimately leading to cell death. With regard to colorectal cancer treatment, it has been long the standard of care in the adjuvant setting in combination with leucovorin (16). Given the paucity of active agents in this disease, it was also the mainstay in the metastatic setting. The drug is generally well tolerated with side effects most commonly related to the rate of infusion.

1.2.2.2. Toxicities

Please refer to the FDA approved package insert for more details about a comprehensive list of adverse events. Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment. Other adverse reactions are: Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia. Cardiovascular: myocardial ischemia, angina. Gastrointestinal: gastrointestinal ulceration and bleeding. Allergic reactions: anaphylaxis and generalized allergic reactions. Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache. Dermatologic: dry skin, fissuring, photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet following by pain, erythema, and swelling. Ophthalmic: Lacrimal duct stenosis, visual changes, lacrimation, photophobia. Psychiatric: disorientation, confusion, euphoria. Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails). (17)

1.2.2.3. Clinical Studies with 5-FU

Many studies have been performed with 5-FU in the setting of colorectal cancer. Many of the early studies focused on the schedule of giving the 5-FU: bolus vs. infusional regimens (18, 19). More recently, the focus of studies with 5-FU have been in conjunction with oxaliplatin or irinotecan in regimens such as FOLFOX or FOLFIRI. These latter combinations when compared to a 5-FU/LV in Phase III studies proved to have superior response rates, progression free survival (20, 21) and survival (20). FOLFOX and FOLFIRI appear to be equivalent regimens in the metastatic setting (22, 23).

1.2.3. Irinotecan

1.2.3.1. Pharmacology of Irinotecan

Irinotecan is a water soluble camptothecin analog. Camptothecin is an alkaloid obtained from the *Camptotheca acuminata* tree. The subcellular target of camptothecin and camptothecin analogues in mammalian cells is the nuclear enzyme topoisomerase I (Topo I) which is encoded by a single copy gene mapped to human chromosome 20q11.2-13.1 (27). This enzyme, along with the nuclear enzyme topoisomerase II (Topo II) modulates the topological structure of DNA by inducing transient DNA breaks, thereby relieving the torsional strain that occurs during transcription. Topo I induces single-strand DNA breaks after covalently linking to the 3' terminus of DNA, and subsequently facilitates DNA religation. The camptothecins, along with Topo I and DNA, establish a reversible cleavable complex, inhibiting the religation of DNA. The DNA replication machinery then converts single-strand breaks to lethal double-strand breaks (27). *In vivo*, cellular carboxylesterases cleave the ester bond of irinotecan, which is inactive, thereby producing the active compound SN-38, (7-ethyl-10-hydroxycamptothecin). SN-38 is estimated to be 250-1000 fold more potent as a topoisomerase-I inhibitor than irinotecan (28,29). Mutations of the Topo I gene and stable decrements in Topo I activity are implied in tumor resistance to irinotecan (30,31). Exposure to irinotecan has also been shown to produce a rapid, transient decrease in Topo I concentration *in vitro* and *in vivo*, which in cell cultures correlates with a decrease in irinotecan cytotoxicity throughout the exposure period (30).

1.2.3.2. Toxicities

See section 6.9.2. Below.

1.2.3.3. Clinical Studies with Irinotecan

Significant clinical activity has been reported in phase II trials of irinotecan in patients with small-cell and non-small-cell lung cancer (NSCLC), colorectal cancer, squamous cell carcinoma of the cervix, ovarian cancer, stomach cancer and lymphoma (28). Irinotecan added to 5FU and leucovorin is one of the standards of care in the treatment of MCRC. While bolus irinotecan regimens when given with 5-FU and leucovorin, were found to have a significant effect on mortality (32), the continuous infusion regimens were found to be very effective in both the adjuvant and metastatic settings (33). Currently the preferred method to administer this combination is the bimonthly regimen with infusional 5FU (FOLFIRI). The bimonthly regimen tends to be very well tolerated by patients as well.

1.3. Rationale for Performing the Study

The rationale for this study stems out from the following: 1- FOLFIRI is an active combination in the first and second line treatment of MCRC with a high impact on survival. 2- EGFR is a well established target in colorectal cancer. 3- There is significant preclinical rationale to add panitumumab to irinotecan. Clinically, EGFR targeting monoclonal antibodies, such as panitumumab, enhance the activity of irinotecan in patients in first line therapy (13) as well in patients who are already refractory to irinotecan (34,35). The results of a phase 3 trial evaluating panitumumab in combination with FOLFIRI vs. FOLFIRI alone as a second-line treatment in 1,186 patients with metastatic colorectal cancer (mCRC) showed that panitumumab significantly

improved progression-free survival in combination with FOLFIRI (5.9 mos), compared to FOLFIRI alone (3.9 mos), in patients with *KRAS* wild-type mCRC(36).

The proposed strategy of adding panitumumab to patients having progressed on first line FOLFIRI-Bevacizumab has many advantages. There is a high response rate (> 20%) with the combination of Irinotecan and cetuximab in patients who already failed irinotecan (34,35) equaling or surpassing all of the reported second line response rates (< 25%) from other studies (37,38). Irinotecan, unlike oxaliplatin has no known cumulative toxicity. Therefore this treatment strategy, to deliver second line therapy in a sequential fashion after the patient has progressed on first line FOLFIRI + bevacizumab, is feasible leaving the patients yet with an option for an active combination (FOLFOX) in the third line.

As per the NCCN guidelines, irinotecan in combination with cetuximab is an acceptable second or third line of therapy after a patient has progressed on irinotecan based chemotherapy. This is based on the BOND 1 and BOND 2 study data showing that response rates and median TTP were superior when cetuximab was added to irinotecan vs. cetuximab alone in patients who already failed irinotecan (34,35). These efficacy parameters were comparable to salvage responses with oxaliplatin based regimen. This sets the stage for the rational for our study with panitumumab.

Given the rationale stated above, we propose a phase II study looking at the addition of panitumumab to FOLFIRI upon disease progression with FOLFIRI plus bevacizumab. FOLFIRI is superior to irinotecan alone in patients who failed 5-FU in the first line (39). Thus,5-FU resistance is less relevant and the possible synergism/additivity of 5-FU with oxaliplatin and irinotecan justifies continuing its across lines of therapy. This study hypothesizes the possibility that a cancer becomes resistant to the FOLFIRI regimen, and that adding panitumumab will restore sensitivity to the regimen. This study will provide us with direct prospective data on the activity of FOLFIRI added to a novel targeted agent, panitumumab. The objective of the study is to determine the efficacy of this second line therapeutic regimen in patients with locally advanced, unresectable or metastatic colorectal carcinoma. The regimens consist of mFOLFIRI [5-fluorouracil and irinotecan] and panitumumab.

There is considerable variability of the metastatic colorectal cancer clinical response to anti-EGFR agents. Thus there is a pressing need to identify reliable markers with a predictive value to select the appropriate patients who can benefit from these treatments. There has been reporting of the characterization of molecular markers predictive of anti-EGFR antibodies sensitivity in colorectal cancer. A study including 30 mCRC patients reported that KRAS mutation was highly predictive of tumor resistance to cetuximab (40). The 7 most common KRAS mutations in CRC occur in codons 12 and 13 of the KRAS gene. These mutations can be detected readily in paraffin-fixed tumor tissue by multiple technologies, including direct DNA sequencing or allele-specific PRC as well as with newer immunohistochemical staining. Based on a phase III study which looked at the impact of KRAS codon 12 and 13 mutation status on patients' progression free survival with panitumumab compared to best supportive care, there was an increase from 7.4 to 12.3 weeks in those patients who were had no evidence of mutations (41). On July 17th , 2009, The U.S. Food and Drug Administration (FDA) has recently approved the change in label for panitumumab indicating the utility of *KRAS* gene testing as a predictive

biomarker in patients with mCRC . The Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was a randomized phase 3 study in which panitumumab was given in combination with oxaliplatin and 5FU (FOLFOX4) vs FOLFOX4 alone, and patients were prospectively selected for KRAS exon 2 (codon 12 and 13) wild-type tumors. There was an improvement in progression free survival from 8 to 9.6 months with the addition of panitumumab (HR 0.8; 95% CI 0.66-0.97, p= 0.02) but no statistically significant benefit in overall survival, 23.9 vs 19.7 months, respectively. (42) _Retrospective analysis of this study identified patients with additional RAS mutations such as KRAS exon 3 (codon 61) and exon 4 (codons 117 and 146) and NRAS exon 2 (codons 12 and 13) and exon 3 (codon 61). Patients now identified without any RAS mutations had an improvement in their progression free survival with the addition of panitumumab to FOLFOX4, 10.1 months vs 7.9 months with FOLFOX4 alone (HR 0.72; 95% CI 0.58-0.90 p=0.004) and overall survival from 26 vs 20.2 months (HR 0.78; 95% CI 0.62-0.99 p=0,04).(43) The FIRE-3 trial, a phase III study comparing FOLFIRI and cetuximab or bevacizumab as first-line therapy has prospectively looked at these additional RAS mutations, and there was a greater benefit seen in patients treated with FOLFIRI and cetuximab if they wild-type for all RAS mutations. (44)

Thus, enrollment to this trial requires that patient tumors are checked for RAS mutation (KRAS exon 3 (codon 61) and exon 4 (codons 117 and 146) and NRAS exon 2 (codons 12 and 13) and exon 3 (codon 61)). Only tumors that do not have these mutations will render patients eligible to receive panitumumab and enroll onto this study.

1.4.1 Rationale for correlative study

Initially, our study selected only KRAS wild-type tumors for exon 2 (codon 12 and 13) but not for the additional RAS mutations [KRAS exon 3 (codon 61) and exon 4 (codons 117 and 146) and NRAS exon 2 (codons 12 and 13), exon 3 (codon 61), and exon 4 (codons 117 and 146)]. Thus, we proposed to collect patient tumor samples so that we could retrospectively analyze them for the additional RAS mutations to see if progression-free survival and overall survival are impacted by additional mutations. If patient tumors are analyzed for the additional RAS mutations prior to enrollment, then tissue collection is not necessary.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective for this phase II trial is to determine the median progression-free survival in patients treated with FOLFIRI and panitumumab who have RAS wild-type , metastatic colorectal carcinoma and <u>have already progressed</u> on FOLFIRI + Bevacizumab.

2.2 Secondary Objectives

- To determine the frequency and severity of toxicities of the regimens.
- To determine overall response rate
- To determine the median overall survival and the overall survival rate at 1 year

3. STUDY DESIGN

3.1. Study design

This is an open-label, prospective phase II clinical trial, with a primary endpoint of progression-free survival (PFS). Patients must fail a combination of FOLFIRI and bevacizumab prior to being considered for this study. At the time of consideration, all participants will be screened for RAS mutations and only patients who are considered RAS-wild type [KRAS exon 2 (codon 12 and 13), KRAS exon 3 (codon 61) and exon 4 (codons 117 and 146) and NRAS exon 2 (codons 12 and 13), exon 3 (codon 61), and exon 4 (codons 117 and 146)]will be enrolled on the study. Patients eligible for this study will receive a modified regimen of FOLFIRI as outlined in this study along with panitumumab as outlined in section 6.2. Each cycle will consist of days 1 and 15 as outlined in section 6.2. Patients will be restaged after 2 cycles of therapy. If there is no evidence of progressive disease, patient will continue on study. They will be monitored at regular intervals with serial laboratory testing as well as periodic scans to assess response to treatment as outlined in section 5.5.

3.2 Sample Size and Accrual Rate:

A total of 25 patients will be required to test the null hypothesis that there is no difference in median PFS between the study regimen and the historical control. Please refer to Section 9 for details regarding the statistical methods. We anticipate a uniform accrual rate of 2 patients with KRAS wild type mCRC per month from the 2 participating institutions (The Ohio State University (lead)), no lost to follow-up, and an additional 6 months of planned follow-up after accrual is completed.

4. SELECTION CRITERIA

4.1. Inclusion Criteria

To be eligible for inclusion, each patient must fulfill each of the following criteria:

1. Patients with advanced adenocarcinoma of the colon or rectum not curable with surgery or radiotherapy and have been previously treated for their disease with FOLFIRI plus bevacizumab in the **first line** metastatic setting. Patients will only be eligible if their last line of therapy prior to enrolling onto the study was FOLFIRI and bevacizumab received **no more than 6 months prior** to enrolling in this study. They should have been treated with FOLFIRI plus bevacizumab until disease progression is radiographically documented
2. Patients' tumors will need to be tested for the *RAS* mutation status. Only those patients with wild-type or unmutated *RAS* oncogene are eligible to participate in this study.
3. Provide written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.
4. Prior cetuximab is allowed in the **adjuvant but not in the metastatic setting**, but must have been **completed at least 6 months** before enrolling on this trial.
5. Age $\geq$ 18 years
6. ECOG performance status $\leq$ 1
7. Life expectancy greater than 12 weeks

8. No active brain metastasis. Previously surgically treated or irradiated lesions are allowed if not clinically active.
9. Has a negative serum pregnancy test within 7 days of first dose of study treatment (female patients of childbearing potential).
10. Ability to understand and willingness to sign a written informed consent
11. No history of severe reactions to 5-FU, irinotecan, or a monoclonal antibody
12. Adequate organ and marrow function as defined below:

Leukocytes	≥3000/uL
Absolute neutrophil count	≥1500/uL
Platelets	≥100,000/uL
Hemoglobin	≥9mg/dL
Total Bilirubin	≤1.5 X ULN
AST/ALT	≤3 X ULN (or < 5 x ULN with liver metastases).
Creatinine Clearance	(CrCl) ≥ 30 ml/min (Cockroft-Gault Equation)
Magnesium	≥ lower limit of normal

13. Measurable disease is required according to RECIST 1.1 criteria (45).
14. The effects of Panitumumab on the developing human fetus are unknown. For this reason and because monoclonal antibodies as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and up to 6 months after completing therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.2. Exclusion Criteria

Patients who fulfill any of the following criteria will be excluded:

1. Pregnant or breast-feeding women. Women of childbearing potential with either a positive or no pregnancy test at baseline. Woman or men of childbearing potential not using a reliable and appropriate contraceptive method. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential).
2. Sexually active males unwilling to practice contraception during the study and 6 months beyond.
3. History of interstitial lung disease (eg, pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest CT scan.
4. *KRAS* or *NRAS* mutant tumors.
5. Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as ≥ CTC grade 2 (CTCAE version 4.0))
6. Clinically significant cardiovascular disease that is not well-controlled with medication (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) or myocardial infarction within ≤ 1 year or serious concurrent infection.
7. Bevacizumab within the last 3 weeks before enrollment on trial
8. Patient is more than 6 months since the last dose of FOLFIRI.
9. Patients who have required toxicity related dose reductions of greater than 50% of the original dose of infusional 5-FU and/or irinotecan during the administration of FOLFIRI/bevacizumab .

10. Prior exposure to panitumumab in any setting
11. Prior exposure to cetuximab in the metastatic (Stage IV) setting.
12. Radiotherapy ≤ 14 days prior to enrollment. Patients must have recovered from all radiotherapy-related toxicities.
13. Prior unanticipated severe reaction to fluoropyrimidine therapy, or known sensitivity to 5-fluorouracil, leucovorin, irinotecan, or panitumumab.
14. Treatment for other carcinomas within the last three years, except cured non-melanoma skin and treated in-situ cervical cancer.
15. Concomitant use of strong CYP3A4 inducers are not permitted.
16. Participation in any investigational drug study within 4 weeks preceding enrollment.
17. Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.
18. Incomplete recovery from major surgery within 4 weeks of enrollment.
19. Unwillingness to give written informed consent.
20. Unwillingness to participate or inability to comply with the protocol for the duration of the study.
21. Patients with HIV/AIDS and those severely immunocompromised will be excluded. However, no patients will be tested for HIV.

5. REGISTRATION PROCEDURES

Subsite patients will have eligibility verified and will be centrally registered at The Ohio State University by the OSU Subsite Coordinator. Subsites should call or email the OSU Subsite Coordinator to verify enrollment availability prior to consenting patients.

Following registration, patients should begin protocol treatment within 5 business days. Issues that may cause treatment delays should be discussed with the OSU Principal Investigator as soon as possible. If a patient does not receive protocol therapy following registration, the patient will be replaced. The OSU Subsite Coordinator must be notified immediately if a patient does not receive protocol therapy.

Only patients deemed eligible by the subsite research team should be sent for eligibility verification and registration by the OSU Subsite Coordinator.

To request patient registration, the documents below must be completed by the subsite research team and faxed or securely emailed to the OSU Subsite Coordinator. If secure email is the preferred method and the subsite does not have a confirmed secure email system, the OSU secure email system may be used. Contact the OSU Subsite Coordinator for more information.

Required documents for registration:

- Enrollment Form (Appendix 5)
- Signed Eligibility Checklist (Appendix 6)
- Source documents verifying every inclusion & exclusion criteria
- Required screening items as listed in the Protocol Calendar. Screening tests must be

within the specified window.
- Emails and other signed forms used as source documentation

The OSU Subsite Coordinator will confirm receipt of the registration documents with the subsite contact listed on the Enrollment Form (Appendix 5). If confirmation is not received within 2 hours, it is strongly recommended that the subsite call the OSU Subsite Coordinator to confirm registration documents were received.

Registration requests will be processed as soon as possible and no later than 1 business day after receipt of the registration documents, pending there is no additional information needed to complete eligibility verification. Patients will be registered immediately upon determining they meet eligibility criteria.

The Subsite Coordinator will securely email the subsite contact listed on the Enrollment Form (Appendix 5) with the registration confirmation, and the patient's assigned study number.

6. DETAILED STUDY ASSESSMENTS

6.1. Informed Consent

The investigator must ensure written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study **prior** to undergoing any study-specific procedures.

6.2. Screening Procedures

This study will be conducted in patients with metastatic/unresectable advanced colorectal cancer. Patients may have been treated in the adjuvant setting with prior chemotherapy, but in the metastatic setting, should not have received more than one line of previous chemotherapy or biologic therapy. The patient's tumor sample must be evaluated for *RAS* mutation status prior to enrollment and must be unmutated (wild-type). The patients will be included if upon pathologic confirmation of metastatic disease has been confirmed, radiographic assessment has been completed, and meet the above listed inclusion and exclusion criteria will be eligible. Patients will be evaluated by their treating physician, the study coordinator, and/or the protocol investigator prior to enrollment. The screening procedures will be performed within 28 days prior to the start of treatment. The patients should not have received and bevacizumab within 3 weeks of starting treatment on this study. Pregnancy determination will occur within 7 days prior to study entry.

6.3. Pre-Study Assessment

6.3.1 To be completed within 28 days prior to treatment:

a. Baseline measurements of tumor size based on CT scans and other relevant scanning to be used to document tumor status (includes full assessment of all known metastatic disease)
b. Informed consent
c. Adverse events

d. ECG
e. Malignant Disease/Treatment History
f. Demographic Data
g. General Physical Exam
h. Hematology
i. Concomitant Diseases & Treatments

6.3.2 To be completed within seven days prior to treatment:

a. Medical History
b. Physical examination, and weight
c. Performance status
d. CEA serum level
e. Complete blood count with leukocyte differential
f. Platelet count
g. Serum chemistries, glucose and electrolytes (calcium, inorganic phosphate), liver function tests, uric acid
h. Urinalysis,
i. PT (or INR), PTT.
j. Medication history
k. Pregnancy test (women of childbearing potential) on serum B-HCG

6.3.3 To be completed prior to enrollment in the study:
a. RAS mutation testing

6.4. Assessment during Treatment

The following will be obtained at regular intervals during treatment:

a. History and physical examination Day 1 of each cycle
b. Vital signs and weight assessment will be obtained prior to day 1 and day 15, (within 2 days).
c. Drug toxicity (Adverse Drug Events) will be assessed every two weeks (toxicities will be graded according to the NCI CTC version 4.0).
d. Complete blood count and serum chemistries (electrolytes including magnesium, calcium, potassium, BUN, Creatinine, liver function tests) will be obtained within 48 hours prior to each treatment, days 1 and 15.
e. CEA serum level every as a baseline and once every cycle.
f. Imaging studies including but not limited to CT scans prior to treatment as a baseline and every 8 weeks (+/- 5 days).

6.4.1 On-Study Follow-Up Assessment

The following will be obtained at the end of the study

a. Adverse events/toxicities
b. Monitor for inflammatory or infectious sequela in patients with severe dermatologic toxicities.
c. Performance status
d. Weight

e. Vital signs (blood pressure, pulse rate, respiratory rate, temperature)
f. Physical examination
g. Reevaluation of extent of tumor (same imaging method)

6.4.2 After Study Assessment.

After completion of the study, electrolytes including magnesium, calcium, potassium will be followed every two weeks for the duration of 8 weeks after completion of panitumumab therapy.

6.5. Schedule of Assessments and Procedures

	Screening/Baseline		Every Treatment Cycle[a]		End of Study Visit
Day of Cycle	**Within 28 days prior to first dose**	**Within 7 days prior to first dose**	**1**	**15**	
5-FU bolus then cont infusion (over 46 hours)			X	X	
Irinotecan			X	X	
Panitumumab*			X	X	
Informed Consent [b]	X				
Medical History		X			
Malignant Disease / Treatment History	X				
Demographic Data	X				
General Physical Examination[e]	X	X	X		X
Vital Signs, Height, Weight, ECOG Performance Status		X	X	X	X
CBC[g]	X	X	X[f]	X	X
Complete Metabolic Panel Creatinine Clearance #		X	X[f]		X
Magnesium, potassium[g]		X	X[f]	X	X
CEA		X	X[f]		X
Urinalysis		X	—— as clinically indicated ——		
PT (or INR) & PTT		X	—— as clinically indicated ——		
Serum B-HCG [c]		X	—— as clinically indicated ——		
Tumor measurements (CT Scan)	X		Tumor measurements to be done after every 8 weeks of therapy		X
ECG	X		—— as clinically indicated ——		X

Adverse Events	X		—— recorded throughout study	X
Concomitant Diseases & Treatment	X		—— any changes noted throughout study ———	X
KRAS and NRAS mutation testing [d]	X			

#Creatinine clearance is only required for baseline labs
*Minocycline will be given prophylactically for all patients starting the day prior to starting panitumumab and continue throughout the treatment duration (Please refer to section 6.2 for more details)

a Each cycle is 28 Days, then repeated. Clinic visits can be performed +/- 2 days of treatment.
b Informed consent must be obtained prior to any study-specific procedure
c Only in women of childbearing potential
d Archived tumor samples may be sent when they can be obtained at any time after screening process is started. May already completed prior to 21 days of enrollment.
e Day 1 Cycle 1 is a chemotherapy only appointment. Clinic visit with physician is permitted but not mandatory
f Day 1 Cycle 1 does not require labs to be repeated
g Only CBC, magnesium and potassium to be obtained on day 15
h MRI permitted with approval from PI
i Survival data will be collected after the 8 week study assessment follow-up via chart review and/or phone follow-up every 3 months.

6.6. Efficacy Parameters

Patients will be assessed for tumor response according to the RECIST 1.1 criteria (43) after 8 weeks of treatment, and every 8 weeks thereafter as well at the end of the study. Tumor assessments should also be made on each patient within 2 weeks of study completion, withdrawal or discontinuation, as appropriate, even if the patient demonstrates physical evidence of progressive disease and withdraws from the study before the first scheduled tumor assessment.

6.7. Safety Parameters

6.7.1. Laboratory Tests

Laboratory tests during treatment will be performed according to the Schedule of Assessments and Procedures.

The following laboratory tests during treatment will be performed according to the Schedule of Assessments and Procedures.

- Complete Blood Count including differential, WBC, RBC, hemoglobin, hematocrit, platelet count
- Total bilirubin, AST/ALT, alkaline phosphatase, albumin, and total protein
- Conjugated (direct) bilirubin in the case of abnormal total bilirubin
- Serum creatinine and uric acid
- Glucose
- Electrolytes (sodium, potassium, magnesium)

– Serum calcium and inorganic phosphate
– Urinalysis (pH, protein, glucose and blood) (as clinically indicated)

6.7.2. Physical Exam, Vital Signs and Physical Measurements

A limited physical examination will be done at each visit as per standard clinical practice, which should include breast, lung, heart, abdomen and nodes (cervical, axillary, inguinal), with other areas examined as clinically indicated.

The following vital signs and physical measurements will be measured at each patient visit:

– Pulse
– Blood pressure
– Body temperature
– Weight
– ECOG Performance Status (Appendix 2)
– Monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities

6.8. Premature Withdrawal**

Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

1. Disease progression
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician.
3. If retreatment must be held for > 6 weeks or at the discretion of the investigator (excluding the rest week).
4. Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Nonprotocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol treatment
7. Patient becomes pregnant
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)

**Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violations, administrative reasons or other reasons.

7. STUDY MEDICATION

7.1. Drug Formulation, Packaging, and Storage

7.1.1 5-Fluorouracil:

Storage and Stability- Although fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at controlled room temperature 15° to 30°C (59°to 86°F). Protect from light. Retain in carton until time of use.

Administration- 5FU should be administered only intravenously, using care to avoid extravasation. Extravasation should be handled according to hospital protocol. Patients will be given a bolus of 400 mg/m^2 to be followed by a continuous infusion over 46 hrs at a dose of 2400mg/m^2.

Leucovorin will be administered at a dose of 200 mg/m^2 over 120 minutes prior to the 5-FU bolus. Leucovorin may be run simultaneously with irinotecan infusion via y-site connection.

7.1.2 Irinotecan:

Storage and stability- Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. Irinotecan is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D5W.

Administration- Irinotecan is diluted with 5% dextrose (D5W) to a total volume of 500 mL and infused intravenously over 90 minutes. Nothing else should be added to the bag. Patients will be given a dose of 180 mg/M^2 by intravenous infusion.

7.1.3 Panitumumab (Refer to Appendix 4):

Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of panitumumab will contain 20 mL of a sterile protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 400mg of panitumumab and is for single dose use only. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

The supplied investigational drug must be stored at 2-8° 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 (ie, records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

7.2. Protocol Dosage Regimen and Administration

Prophylactic Skin Treatment: The day before treatment is initiated, patients will be given minocycline at a dose of 100 mg PO bid followed by daily minocycline at a dose of 100 mg PO qd for the duration of therapy. In the STEPP study (Piperdi et al, Abs 394, ASCO GI 2009), patients who received prophylactic therapy (doxycycline) had a significant reduction in the incidence and severity of rash. There was also an improvement in the risk of diarrhea when panitumumab was added to irinotecan in the presence of a prophylactic strategy.

If patient experiences reaction to minocycline, it will be discontinued. The trial will proceed without modification.

It is also recommended patients wear sunscreen and hats and limit sun exposure.

On days one and 15 of a cycle the following drugs will be administered: Irinotecan 180 mg/m^2, 5-FU 400 mg/m^2 bolus, leucovorin 200 mg/m^2, panitumumab 6 mg/kg. Finally the patient will be given a pump to continue to receive their infusional 5-FU at a total dose of 2400mg/M^2 over 46 hours. Panitumumab will be administered first on each treatment day. A cycle of therapy is 28 days and the regimen is repeated on Day 29.

Of note: if a patient has required dose reduction of FOLFIRI chemotherapy with their previous administrations, then such dose reductions will continue at the time of enrollment in this protocol with the exceptions of **sub-optimally** controlled nausea, vomiting, diarrhea, neutropenia, and anemia. Patients with more than 50% reduction of the original dose of infusional 5FU and/or irinotecan will not be allowed on the study (see section 4.2.9). The aforementioned side effects should be attempted to be controlled with the appropriate supportive measures and the full dose of irinotecan should be given.

Premedication for chemotherapy may be administered prior to, during, or after panitumumab administration (if given during panitumumab administration, pre-medications should be given through a separate IV line). Panitumumab will be administered until subjects develop disease progression or are unable to tolerate panitumumab.

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 at least by + 10%. **The total dose may be rounded up or down by no greater than 10 mg**. The panitumumab dose will be diluted in a minimum of 100 mL of pyrogen-free 0.9% sodium chloride solution USP (normal saline solution, supplied by the site). The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. The volume of normal saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. Panitumumab will 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. 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. Strict adherence to aseptic technique will 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.

The doses of irinotecan and 5-FU will be calculated on the basis of milligrams of drug per square meter of body surface area (BSA). As the weight of the patient may change throughout the study, the dose will be recalculated based on the new body surface area prior to the start of each cycle. Refer to Appendix 2: BSA Nomogram for assessment of body surface area

7.3. Duration of treatment

Duration of individual patient treatment will depend on individual response and tolerance. Patients with clearly documented progressive disease must be taken off therapy with FOLFIRI + Panitumumab at time of progression. Patients who are responding (complete or partial), or whose disease is stable, will be treated until progression of disease, intolerable toxicity, patient refusal to continue with study, or investigator decision to remove patient from study in accordance with section 6.8. Patients who have stable disease or better and have completed 6 cycles of therapy, may at the treating physician's discretion, continue with therapy or switch to single-agent panitumumab therapy, for improved tolerance. They may not switch back to FOLFIRI + Panitumumab and will be taken off trial should they have disease progression.

7.4. Dose Adjustment for 5FU and Irinotecan Toxicities

A cycle is 4 weeks – with treatment on days 1 and 15. We do not make up day #15 treatments if a patient should require adjustment or omission based on outlined criteria below.

- This study will take into consideration previous toxicities experienced with FOLFIRI prior to enrollment. The initial dose of FOLFIRI will determined by the investigator at time of trial initiation. Prior to enrollment, if the patient experienced significant toxicity with FOLFIRI and dose adjustments were required, these dose adjustments will continue upon initiation of this trial.

- For toxicities which are considered by the investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia as it can be satisfactorily managed by transfusions.

- For any event that is apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes).

- If on the first day of chemotherapy treatment, the granulocyte count (ANC) is < 1,500 or the platelet count is < 75,000, treatment will be held for up to three weeks until ANC is ≥ 1200 and platelet count is ≥ 75,000. CBC should be obtained at least weekly when treatment is held. Chemotherapy doses will not be reduced based on nadir counts except in febrile neutropenia as defined below.

- If the dose is modified to manage an adverse event, it is recommended that the patient be seen by the investigator prior to re-starting study drug.

- If a rest period is extended due to toxicity, the "complete" cycle should be given afterwards with chemotherapy and panitumumab. If toxicity requires a dosing delay/interruption of both 5-FU and irinotecan of **more than six weeks or at the**

discretion of the investigator, the patient will be **withdrawn** from the study for toxicity reasons.

Table 1: Dose modifications during a course of therapy (day #15 of each cycle).

- Dose adjustments for hematological toxicity during a course of therapy are based on the blood counts obtained in preparation for that day of treatment.
- All dose adjustments are relative to dose given at on day #1 of that cycle.

FOLFIRI Regimen Dose Modification Guideline[a]

Dose Modifications for the Next Cycle Based on the Worst Toxicity Observed[b,f]		
Toxicity Grade[b] (CTCAE v4.0)	5-FU bolus and continuous infusion	Irinotecan
Neutropenia, Thrombocytopenia, and Leukopenia (since prior treatment)		
0 or 1	Maintain dose level	Maintain dose level
2	Discontinue 5-FU bolus	Maintain dose level
3	Discontinue 5-FU bolus and ↓ 1 dose level continuous infusion	↓ 1 dose level
4	Discontinue 5-FU bolus and ↓ 2 dose levels continuous infusion	↓ 2 dose levels
Neutropenic fever or infection[c]	Discontinue 5-FU bolus and ↓ 2 dose levels continuous infusion	↓ 2 dose levels
Diarrhea[d] (since prior treatment)		
0 or 1	Maintain dose level	Maintain dose level
2	Discontinue 5-FU bolus and ↓ 1 dose level continuous infusion	Maintain dose level
3	Discontinue 5-FU bolus and ↓ 1 dose level continuous infusion	↓ 1 dose level
4	Discontinue 5-FU bolus and ↓ 2 dose levels continuous infusion	↓ 2 dose levels
Mucositis/Stomatitis (since prior treatment)		
0, 1 or 2	Maintain dose level	Maintain dose level
3	Discontinue 5-FU bolus	Maintain dose level
4	Discontinue 5-FU bolus and ↓ 1 dose level continuous infusion	Maintain dose level
Vomiting (since prior treatment)		
0, 1 or 2	Maintain dose level	Maintain dose level
3	Maintain dose level	↓ 1 dose level
4	Discontinue 5-FU bolus ↓ 1 dose level continuous infusion	↓ 1 dose level

Palmar-plantar erythrodysesthesia		
0, 1 or 2	Maintain dose level	Maintain dose level
3	Discontinue 5-FU bolus ↓ 1 dose level continuous infusion	Maintain dose level
Other nonhematologic toxicities (except alopecia and skin-related toxicities)[e]		
0, 1 or 2	Maintain dose level	Maintain dose level
3	Discontinue 5-FU bolus ↓ 1 dose level continuous infusion	↓ 1 dose level
4	Discontinue 5-FU bolus↓ 2 dose levels continuous infusion	↓ 2 dose levels

[a] There will be no leucovorin dose reduction. If 5-FU bolus dropped, leucovorin will be discontinued as well.

[b] NCI CTCAE(Version 4.0) (Appendix E)

[c] Absolute Neutrophil Count <1000/mm^3 and Temperature ≥ 38.5°C

[d] Despite maximum supportive care

[e] Bilirubin grade 3 and grade 4 hold dose: once the bilirubin level has resolved to ≤ grade 1 a dose reduction for 5-FU and irinotecan is required.

[f] If the patient's starting dose upon enrollment is not full dose FOLFIRI, future dose adjustments will be made as to reflect the starting dose (i.e. proceed to the next recommend dose)

*There will be no leucovorin dose reduction. If bolus 5-FU dose omitted, leucovorin is also omitted

Table 2. FOLFIRI Regimen Dose Levels (mg/m^2)

DRUG	Starting Dose (mg/m^2)	Dose Level –1 (mg/m^2)	Dose Level –2 (mg/m^2)	Dose Level –3 (mg/m^2)
Irinotecan	180	150	120	Discontinue
5-FU 46 hour infusion	2400	2000	1600	Discontinue

7.5. Panitumumab Dose Modification for Toxicity- (Please refer to Table 3).

The starting panitumumab dose is 6 mg/kg every 2 weeks. 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 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. The

volume of normal saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. **Panitumumab will 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.** If the first infusion is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated.

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 6 Pharmacy Guide for information on panitumumab packing and formulation, labeling, storage, preparation, supply/return, and accountability.

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 according to institutional guideline or investigator's discretion.

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.

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 (CTCAE) version 4.0 (Appendix 4), with the exception of skin- or nail-related toxicities, which must be graded using CTCAE version 3.0 with modifications (see Appendix 4a).

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 4). Dose escalations above 6 mg/kg starting dose are not allowed. Panitumumab dose reductions are listed in Table 3.

Table 3. Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	50
mg/kg	6	4.8	3.0

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

Non-skin- or nail-related toxicities:

Any grade 3 or 4 toxicity with the following exceptions:

- Panitumumab will only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement
- Panitumumab will only be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care (see Section 6.6 and 6.7.1 for diarrhea management guidelines)
- Panitumumab will only be withheld for grade ≥ 3 anemia or grade 4 thrombocytopenia that can not be managed by transfusion(s) or cytokine therapy

Criteria for Re-treatment with Panitumumab

Skin- or nail-related toxicities:

- Panitumumab administration may recommence once:
- The adverse event has improved to ≤ Grade 2 or returned to baseline, and;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; and,
- Systemic steroids are no longer required, and
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

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

Dose Modification Schedule

- Subjects should be assessed for toxicity before each dose. 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 6.5) 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 6.5).

- 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. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose 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 50% 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 50% dose level.

- Subjects who experience toxicity at the 50% 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 6.5). 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 dose 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 50% dose level whose toxicity does not recur should receive the 80% dose at the next dose 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 miss 3 or more consecutive scheduled doses due to toxicity or are unable to receive a dose of panitumumab within 6 weeks of having received their previous dose of panitumumab due to toxicity will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.

- In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, panitumumab should be discontinued until further pulmonary investigation

Panitumumab Delayed- or Missed-Doses

Panitumumab should be administered by IV infusion on the first day of each treatment cycle. However, if panitumumab dose cannot be administered as scheduled, every attempt should be made to administer the drug within 3 days of the scheduled dose (up to 3 days before the scheduled dose or up to 3 days after the scheduled dose). If it is necessary to change a subject's visit from the originally scheduled date, the subsequent visits should continue at the previously scheduled days/dates. If the dose is not administered within the ± 3-day window, the dose will be considered a missed dose, and the next scheduled dose should be given at the time of the regularly scheduled dose. Missed doses will not be made up.

Discontinuation of Panitumumab

Panitumumab will be administered until subjects are unable to tolerate panitumumab, disease progression, death, or study withdrawal by the subject, investigator, or sponsor

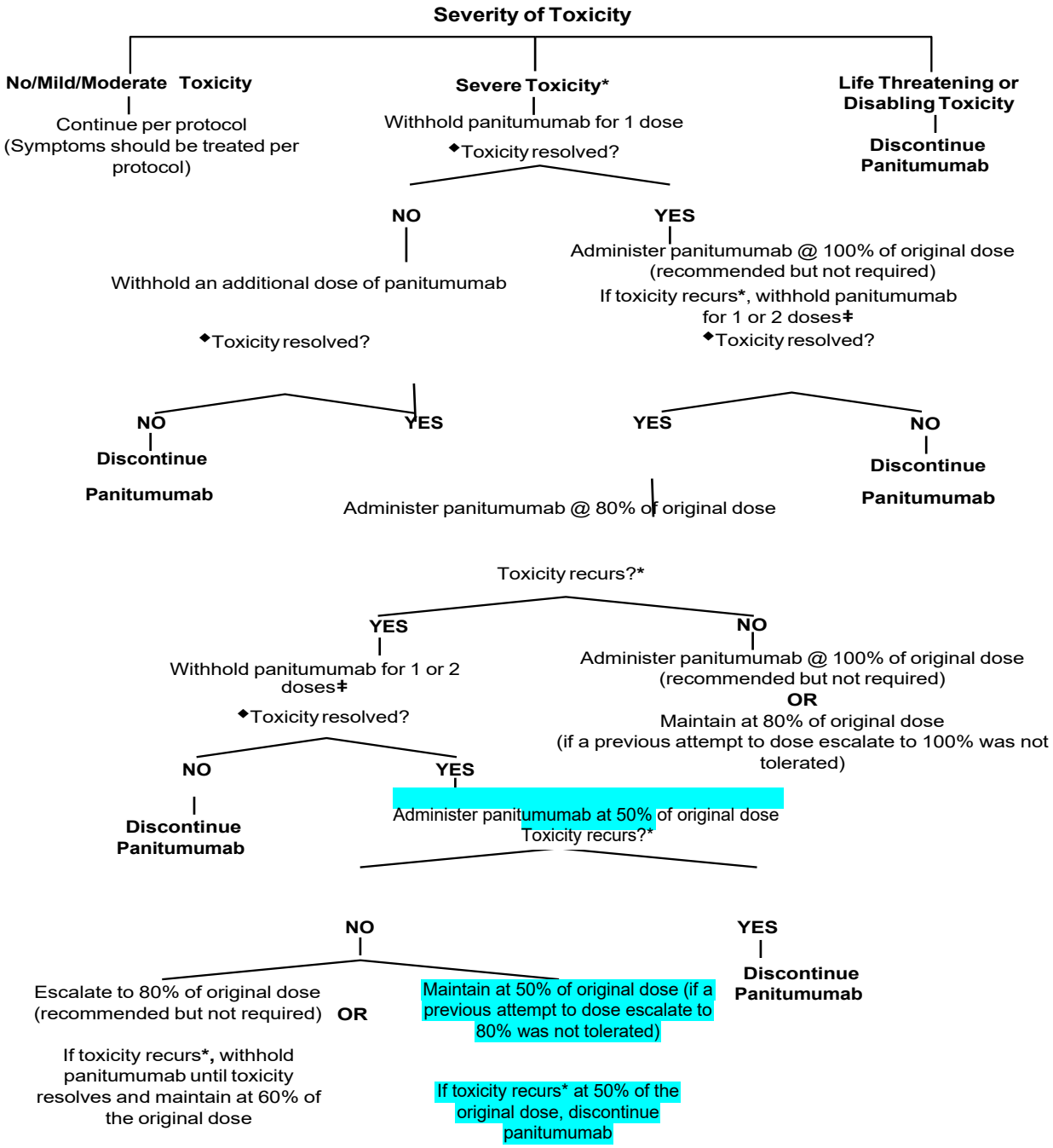
Electrolyte Management

Electrolytes and Magnesium levels will be evaluated as outlined in the schedule of assessment table in Section 5.5 . In the presence of abnormal values, patients will be managed as per standard institutional practice. If hypomagnesemia is present, replacement should be managed with either oral or parenteral replacement, or both, according to institutional practice and to the grade of hypomagnesemia present. It is recommended that 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. Subject's serum potassium and calcium parameters are recommended to be maintained, as per standard institutional practice, within the normal ranges during study treatment.

Electrolytes will be followed for 8 weeks after completion of the trial to insure proper replacement.

Figure 4. Dose modification for panitumumab-associated skin toxicity (see below)



* 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.

Mild/Moderate: Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness. Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL

Severe: Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated. Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences

7.6. Special Instructions Regarding Treatment of Toxicity

Infusion-Related Toxicity and Hypersensitivity:
Careful attention to prophylaxis and bedside monitoring of vital signs is recommended. Discontinue therapy for anaphylaxis. Mild symptoms: (e.g., mild flushing, rash, pruritus): complete infusion, supervise at bedside. No treatment required. Panitumumab is contraindicated in patienst with a history of life-threatening hypersensitivity reaction to panitumumab or any of the excipients.

Moderate Symptoms: (e.g., moderate rash, flushing, mild dyspnea, chest discomfort): Stop chemotherapy infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate of infusion, 20 mg/hr for 15 minutes. Then, if no further symptoms develop, resume infusion at full dose rate until infusion has been completed. If symptoms recur, stop infusion. Remove patient from protocol therapy. Report as an adverse event.

Severe Life-threatening Symptoms: (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilator therapy, generalized urticaria): Stop infusion. Give intravenous diphenhydramine and dexamethasone, as indicated above. Add epinephrine and / or bronchodilators if indicated. If wheezing is present and is not responsive to adrenaline, then administer 0.35 ml of nebulized salbutamol solution (or equivalent). Remove patient from protocol therapy. Report as an adverse event.

Diarrhea
Irinotecan can cause diarrhea, and should be *stopped at diarrhea grade ≥ 2*, and treated symptomatically (recommend IV hydration and use of loperamide for diarrhea, observing loperamide dosage recommendation and treatment start, see below). If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of DPD deficiency should be considered. Irinotecan cannot be re-started until diarrhea has resolved to grade < 2 with the last loperamide dose given at least 24 hours beforehand.
The recommended dosage regimen for loperamide: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night,

the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.
The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Grade ≥ 2 Nausea/Vomiting
For nausea and vomiting the patients must be supplied with anti-emetics in order to help themselves in case nausea or vomiting occurs at home. The choice and dose of anti-emetics will be determined by the treating physician. Adequate secondary prophylactic treatment and IV hydration should be initiated once nausea or vomiting has occurred. If the adverse event recurs despite prophylaxis, then dose modifications should also be according to the table above.

Fever/Infection with or without neutropenia
Chemotherapy should be stopped immediately. Appropriate anti-infective therapy should be initiated. When the ANC has recovered to ≥ 1,500/mm^3 and the fever or infection has resolved, the patient may restart treatment.

Skin Toxicity
With panitumumab, various degrees of skin toxicity, specifically rash and erythema have been reported. Topical emollients have been used with some success in mild cases. If the rash were to develop to have small acneiform pustules, topical antibiotic ointments have been used with varying amounts of success as well. The rash is self-limiting and dissipates upon cessation of the drug in the majority of cases.

It is recommended patients use suncscreen and hats to limit sunexposure while on receiving panitumumab.

Pulmonary Toxicity
Panitumumab may cause pulmonary fibrosis. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, panitumumab should be discontinued until further pulmonary investigation.

7.7. Supportive Therapy

7.7.1. Diarrhea
Loperamide: All patients will be instructed to begin taking loperamide at the earliest signs of diarrhea (i.e. first poorly formed or loose stool, first episode of two or more bowel movements in one day) that occurs more than 12 hours after receiving irinotecan. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night.
Atropine: Diarrhea or abdominal cramping that occurs during or within one hour after receiving irinotecan should be treated with atropine 0.4 mg IM or Subq. Additional antidiarrheal measures may be used at the discretion of the treating physician. Atropine should be used with caution in

patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

7.7.2. Nausea and Vomiting

Antiemetics: Patients should receive antiemetics prior to chemotherapy administration according to institution guidelines.

7.7.3. Myelosuppresion

Growth Factors: Routine prophylactic use of a colony-stimulating factor (G-CSF or GM-CSF) is not permitted. Therapeutic use in patients with serious neutropenic complications such as ANC of < 500 for more than 5 days, fever accompanying grade 3-4 neutropenia, or obvious sepsis may be considered, at the investigator's discretion.

Erythopoietin treatment for moderate to severe anemia (< 10 mg/dl) is permitted in the study.

7.8. Concomitant Medications and Treatments

5-FU and some of its metabolites are converted principally by liver enzymes (carboxylesterase and cytidine deaminase and PyNPase in tumor tissues). At present, it is unknown whether this metabolism is likely to be influenced by other treatments or alcohol, which either induce or inhibit certain liver enzymes.

Laxatives: The use of drugs with laxative properties should be avoided.

7.9. Warnings and Precautions regarding specific agents used in this protocol

7.9.1 5-Fluorouracil:

Cardiovascular: Although uncommon, fluorouracil has been associated with chest pain, anginal attacks, ischemic electrocardiographic changes, myocardial infarction, cardiomyopathy, and very rarely, sudden death. Most commonly, these effects occur when the drug is administered as a continuous infusion and within several hours from the start of the infusion. Patients with pre-existing coronary artery disease (CAD) appear to be at greater risk; however, most reported cases are in those with no previous history of CAD.

Dermatologic: Contact dermatitis, Alopecia, dry skin, fissuring, hand-foot syndrome, nail changes, rash, photosensitivity, and vein pigmentation have been reported in patients receiving intravenous fluorouracil

Hematologic toxicity: primarily neutropenia, occurred significantly more often in patients receiving bolus injections (31% versus 4%, RR 0.14, p less than 0.0001). Anemia and thrombocytopenia occurred in less than 5% of all patients. agranulocytosis, anemia, epistaxis, pancytopenia, and thrombocytopenia have also been reported during treatment with intravenous 5-FU. Factors increasing the risk for hematologic toxicity included a poor performance status and fluorouracil administration by bolus injection, while increased age, female gender, and a good performance status significantly increased the risk for nonhematologic toxicities. In hand-foot syndrome, continuous administration of fluorouracil was an additional prognostic factor.

Gastrointestinal: Commonly occurring symptoms during IV fluorouracil therapy are stomatitis, esophagopharyngitis, nausea, vomiting, anorexia and diarrhea

Neurologic: Neurological effects reported with the administration of fluorouracil include confusion, disorientation, euphoria, nystagmus, headache, and acute cerebellar syndrome.

7.9.2 Irinotecan:

Bone Marrow Suppression: Virtually all phase I and II studies of irinotecan have reported neutropenia that may be dose limiting. Anemia and lymphocytopenia have been observed as well.

GI: Diarrhea- abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; late diarrhea (diarrhea occurring more than 8 hours after irinotecan administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed.

Skin: alopecia, asthenia. irinotecan may cause local irritation at infusion sites. Extravasation necrosis of the skin has not been reported in US studies.

Constitutional: Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, this syndrome is thought to be cholinergically mediated.

Pulmonary: Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported.

Renal: Occasionally, abnormalities of serum Creatinine have been observed.

8. STUDY OUTCOME MEASURES

8.1. Objective Response Rate (ORR)

Objective response of measurable disease will be in accordance with the criteria described in

RECIST 1.1 guidelines (45)

Only measurable lesions which have not been irradiated will be used as indicator lesions. These must have a minimum size of at least one diameter of 10 mm for liver, soft tissue lesions, lung, skin and lymph node lesions.

In responding patients, the response must be confirmed at a minimum of 4 weeks.

8.2. Progression Free Survival (PFS)

PFS will be measured as the time from Study Day 1 to the time the patient is first recorded as having disease progression or death, whichever comes first.

8.3. Overall Survival (OS)

Survival will be recorded as the time from Study Day 1 to the date of death or the last date the patient was known to be alive.

8.4. Duration of Response

Duration of response is defined as the date of first response to the date of first disease

progression or death due to any cause, whichever comes earlier, in the subset of subjects with confirmed objective response (RECIST criteria in Appendix 5).

9. SAFETY PARAMETERS

9.1. Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

9.2. Pregnancy

The patient will be removed from the study if she becomes pregnant during the study and immediately inform the investigator. The investigator should counsel the patient, and discuss the risk of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a patient participating in the study must also be treated as described above.

9.3. Data Safety Monitoring and Submission:

Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial, where applicable, at these disease centered meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources, including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the MCTP protocol files.

Data Submission

The study will be managed per the Multi-Center Trial Program (MCTP) policies. Subsite data must be submitted to the MCTP within 2 weeks of completion of each cycle. Data will be submitted using case report forms and the Data Submission Form cover sheet (refer to Supplemental Forms Document) supplied by the MCTP. Access to the OSU OnCore database may be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents.

Adverse Events
An adverse event is defined in the International Conference on Harmonization (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). The ongoing review of safety data will include review of clinical AEs and SAEs including skin-related toxicity assessment and laboratory studies. The CTCAE version 4.0 will be used to grade all AEs, except panitumumab-related skin toxicity, which will be graded by modified CTCAE version 3.0 Dermatology Skin Assessment (*Appendix 4*). 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.

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 (e.g. 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 is not classified as an SAE.

Reporting Procedures for All Adverse Events
All AEs occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product) will be reported on the case report form. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

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
- Action taken.

Amgen may request follow-up information.

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.

Serious Adverse Events Reporting Procedures
Serious adverse events will be collected and recorded at least throughout the study period, beginning with the signing of the informed consent through 30 days after the end of the treatment phase or through the safety follow-up visit, whichever is longer.

Subsite SAE reporting requirements are located at the end of this section. Subsites are NOT permitted to report directly to the FDA, Amgen, or the OSU IRB.

The investigator should notify the Sponsor (John Hays, MD, PhD) of all serious adverse events occurring at the site(s) in accordance with FDA Regulations. The Sponsor will medically review all SAEs. The Sponsor will ensure the notification of the appropriate Ethics Committees/Institutional Review Boards, of all serious adverse events occurring at the site(s) in accordance with FDA regulations.

The study sponsor is responsible for providing all suspected serious adverse drug reactions (SADRs) related or possibly related to panitumumab to Amgen within 1 month of the event. It is possible that Amgen may request follow-up information from the sponsor.

All suspected unexpected serious adverse reactions (SUSARs) related or possibly related to panitumumab and their follow-up reports must be reported to Amgen within 1 working day of submission to the FDA, IRB or IEC. A copy of any safety report submitted to the FDA, IRB or IEC, should be faxed to Amgen, within 24 hours of such submission. The sponsor is responsible to ensure that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

A copy of any safety report submitted to the FDA, or any other regulatory agency, IRB or IEC, should be faxed with the Amgen Adverse Event fax coversheet to Amgen, within 24 hours of such submission, at:

Amgen Global Safety
Fax: 888-814-8653
AND Principle Investigator: John Hays, MD, PhD
AND The Ohio State University IRB:

REPORTING	FREQUENCY
SADRs	**Within 1 month of the event**
SUSARs	**Within 1 business day of FDA submission**

Investigators should not wait to receive additional information to fully document the event before notifying the sponsor of the SAE. Any SAE, if brought to the attention of the investigator at any time after cessation of study drug, and considered by the investigator to be possibly related to study drug, should be reported.

Subsite SAE Reporting Requirements
Subsites are NOT permitted to report directly to the FDA, Amgen, or the OSU IRB. Subsites must notify the OSU PI and OSU Subsite Coordinator of all SAEs within 24 hours of knowledge of the event. All SAEs must be reported on a MedWatch 3500A and submitted with the SAE Submission Form (Appendix 8) to the OSU Subsite Coordinator within 5 business days of knowledge of the event. All subsite SAEs will be reviewed by the OSU PI. Any subsite SAE that requires reporting to the FDA, Amgen, or the OSU IRB will be sent by the OSU Subsite Coordinator. Subsites should report to their IRB of record per their institutional and IRB policies.

10. STATISTICAL CONSIDERATIONS

HYPOTHESIS AND ENDPOINTS

With median progression-free survival (PFS) as the primary endpoint, the primary objective of this single arm, open-label, phase II study is to determine the median PFS for FOLFIRI and panitumumab in patients with metastatic RAS wild-type colorectal carcinoma who have previously failed FOLFIRI and bevacizumab.

The secondary endpoints of this study are the frequency and severity of toxicities of the regimens, overall response rate, and overall survival rate at 1 year.

10.1. Study design and Sample Size Calculation:

The PRIME study is a phase III clinical trial, in which patients with metastatic colorectal cancer and KRAS (codon 12 and 13) wild-type tumors were randomized to FOLFOX or FOLFOX and panitumumab for first-line therapy. Retrospective analysis of the additional RAS mutations showed that patients with tumors that were RAS wild-type had a 2.2 month improvement in PFS when panitumumab was added to FOLFOX (7.9 vs. 10.1 months [HR 0.72m 95% CI 0.58-0.90, p=0.004]) (43). Patients receiving FOLFIRI plus panitumumab after failing first–line non-irinotecan containing treatment for RAS wild-type metastatic colorectal cancer patients had a reported mPFS of 5.9 months compared to 3.9 months for those treated with FOLFIRI alone (36). Also, per the BOND study, patients who had disease progression on prior irinotecan-based chemoregimens were randomized to either cetuximab monotherapy or cetuximab and irinotecan. Median time to progression was improved by 2.6 months with the combination arm (1.5 vs 4.1 months, comparing cetuximab vs cetuximab and irinotecan) (34). We expect a similar treatment effect for panitumumab and FOLFIRI in our study following FOLFIRI plus bevacizumab failure. As such, we expect our group of patients to have an improved mPFS (6 months) compared to the historical control of a similar patient population treated with irinotecan and cetuximab (3.98 months) in RAS wild-type metastatic colorectal cancer (36).

We anticipate a uniform accrual rate of 2 patients per month, no lost to follow-up, and an additional 6 months of planned follow-up after accrual is completed. A total of 25 subjects will be required to detect the difference between a median PFS of 6 months for our testing treatment and a median PFS of 4 months for the historical control assuming exponential PFS distribution. The one-sided type I error and the power have been set at 0.10 and 80% respectively when calculating the sample size using the online sample size calculator provided by SWOG (http://www.swogstat.org/statoolsout.html).

With a total of 25 patients, we will be able to construct 95% confidence intervals no wider than 20% for proportions. If a specific adverse event occurs with a true probability of 10%, the probability of observing one or more patients with the AE in 25 patients will be about 93%.

10.2. Analysis of Primary and Secondary Efficacy Parameters

Continuous variables will be expressed by means, standard deviations and 95% confidence intervals. Frequencies will be computed for discrete data. Median PFS will be estimated using the Kaplan-Meier estimator with confidence interval calculated based on the Brookmeyer-Crowley method (38). Kaplan-Meier estimator will be used also to estimate OS rate at 1 year.

11. TISSUE COLLECTION AND CORRELATIVE ANALYSIS

11.1 Tissue collection only applies to patients who were enrolled during previous version of the protocol, when only KRAS codon 12 and 13 were assessed for enrollment eligibility. Tissue is collected so that additional RAS mutations can be assessed retrospectively. Thus, if all RAS mutations [KRAS exon 2 (codon 12 and 13),exon 3 (codon 61) and exon 4 (codons 117 and 146) and NRAS exon 2 (codons 12 and 13), exon 3 (codon 61), and exon 4 (codons 117 and 146)] are checked prior to trial enrollment, then no tissue collection is needed. A new biopsy will is not required strictly for purposes of this correlative study. Paraffin-embedded tissue will be obtained from OSU Department of Pathology via the Histology Core Facility as per standard.

Diagnostic samples shall be formalin-fixed and paraffin-embedded according to standard laboratory procedures, with the purpose of storing for future analysis of additional RAS mutations including: KRAS codon exon3 and 4 and NRAS exon 2, 3, and 4.

For participating subsites, no tissues in formalin or ethanol should be sent to the Ohio State University. Participating subsites will use their own standard laboratory protocol and supplies (e.g. formalin, ethanol, paraffin, tissue cassettes, etc) to perform the paraffin-embedding. For surgical specimens, we will defer to handling of the specimen as per the institutional standard practice of grossing the specimen and preparing it for Surgical Pathology evaluation (e.g. surgical margins, histology, lymph node, etc.).

11.2 SPECIMEN SUBMISSION

11.2.1 If the recommended blocks cannot be released to OSU for correlative research, we ask that unstained slides are required to be cut as outlined:

1-Tissue Sections diameter >5 mm, include five sections, 10 um in thickness.

2-Tissue sections diameter< 5mm square, include 15-20 sections 10um in thickness.

3- Please use **NON-PLUS** slides and one H&E (2-4um) for each block.

For these molecular studies, multiple tissue sections can be collected on one glass slide, as the tissue itself is digested and scraped off the slide, thus there is not a need to mount one section per slide. The slides will be air dried (not oven-dried). The slides will be stored at room temperature (>16°C).

11.2.2 Shipping of specimen(s):
Pathology material including copies of pathology reports for the diagnostic/surgical specimens, tissue blocks, H&# stains, or unstained slides to:

John Hays, MD, PhD

Department of Internal Medicine
Divison of Medical Oncology
A445 Starling Loving Hall
320 West 10th Avenue
Columbus, OH, 43210
Clinical office: 614-293-9424
Fax: 614-293-7520
Email: John.Hays@osumc.edu

Shipments should be made Monday through Thursday.
Please notify Dr. Hays by email on or before the day of submission, with the (1) name of the contact person, (2) when to expect the sample, and (3) the overnight shipping carrier and tracking number.
If the submitting institution would like us to return the tissue blocks, please notify Dr. Hays.

12. REFERENCES

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13. APPENDICES

Appendix 1: ECOG Performance Status Scale

Patient performance status will be graded according to the ECOG Scale:

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, e.g. light housework, office work.

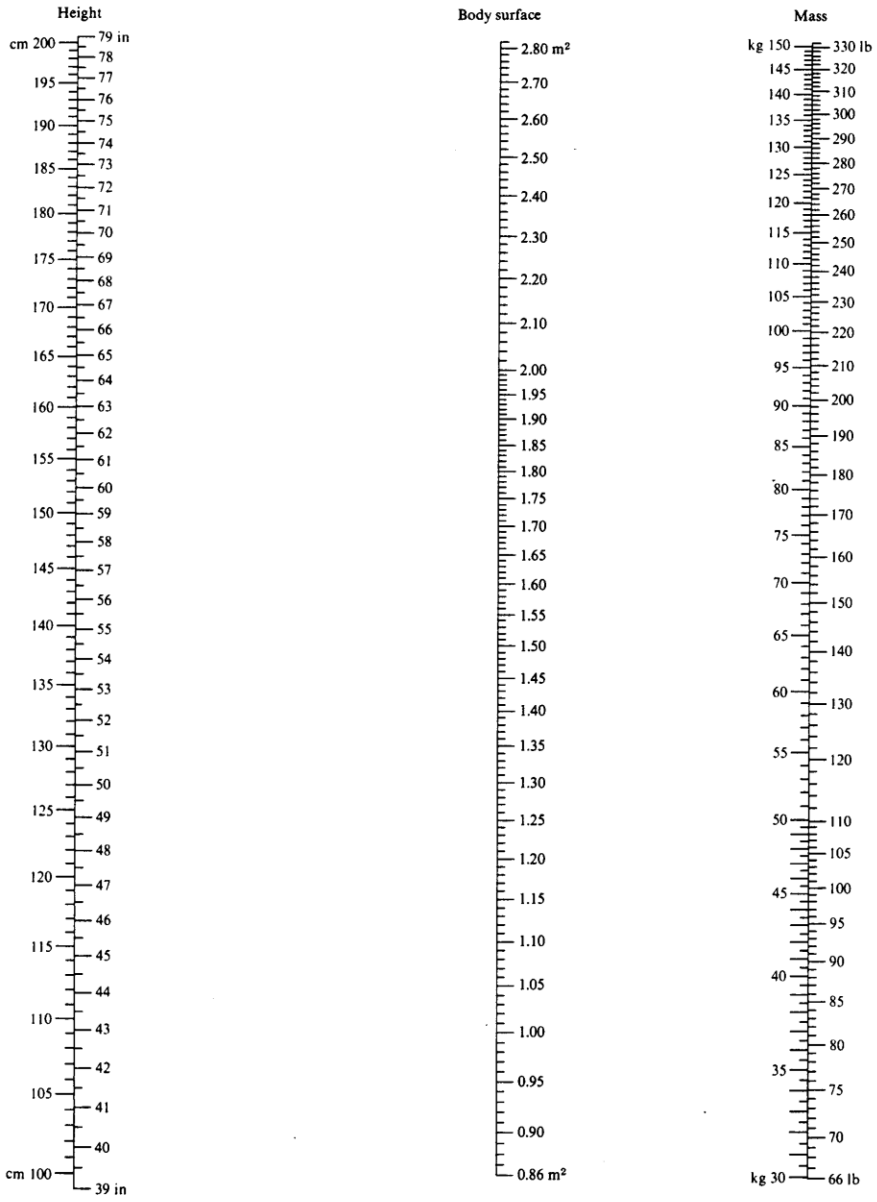
2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Appendix 2: BSA Nomogram

Nomogram for determination of body surface from height and mass†



† From the formula of Du Bois and Du Bois, *Arch. intern. Med.*, **17**, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (S: body surface in cm², M: mass in kg, H: height in cm).

Appendix 3: CTC - Common Toxicity Criteria 4.0

Version 4.0 of the NCI "Common Toxicity Criteria" can be found and downloaded from the CTEP website, http://ctep.cancer.gov/reporting/ctc.html

Appendix 4a. 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 4: Panitumumab Pharmacy Guide

Packaging, Formulation, Labeling and Storage

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

The supplied investigational drug must be stored at 2-8° 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 (ie, records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage of 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. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems, that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

Panitumumab must be prepared as an intravenous 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 of panitumumab is required to be recalculated only when the subject's body weight increases or decreases by > 10% from the original screening/baseline weight. This weight will be considered the new baseline weight from which a + 10% variance is allowed before another recalculation is necessary. The calculated amount of panitumumab (may be rounded to the nearest ten milligrams [eg, 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) will be removed from the vials and added to a minimum volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. 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 + 15 minutes, as tolerated. (6 milligrams/kilogram (mg/kg) intravenously infused over 60 minutes every 14 days. Infuse doses higher than 1000 mg over 90 minutes. Do not give panitumumab as IV bolus. Add doses of up to 1000 mg to a 100 mL bag of 0.9% NS. For doses greater

than 1000 mg, dilute in a 150 mL bag of 0.9% NS. Mix diluted solution by gentle inversion. Do not shake. Administer with a low protein-binding 0.22 micron filter set. Flush line with NS before and after panitumumab**.** The panitumumab will be infused within 19 hours of dilution and will be labeled per site pharmacy standard operating procedures.

Supply and Return

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 toAmgen, and the original retained at the site. At the end of the study, or as directed, all panitumumab supplies, including unused, partially used, or empty containers, will be destroyed at the site or returned to Amgen as directed.

Panitumumab Accountability

An Investigational Product Accountability Record for the must be kept current and should contain:

- The dates and quantities of panitumumab received
- Manufacturing batch or lot numbers for product received
- Subject's identification (subject number)
- Date and quantity of panitumumab dispensed (and remaining, if from individual subject drug units)
- The initials of the dispenser
- Dose preparation records
- Date and quantity of drug returned to the investigator/pharmacy, if appropriate

Any discrepancies must be documented and subsequently reported immediately.

These inventories must be made available for inspection by authorized sponsor representative(s) and regulatory agency inspector(s). The investigator is responsible for the accountability of all used and unused trial supplies.