CITY OF HOPE NATIONAL MEDICAL CENTER
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DUARTE, CA 91010

DEPARTMENT OF MEDICAL ONCOLOGY AND EXPERIMENTAL RESEARCH

TITLE: A Prospective Study of FOLFIRI plus Panitumumab in Extended RAS Wild Type and BRAF Wild Type Metastatic Colorectal Cancer with Acquired Resistance to Prior Cetuximab (or Panitumumab) plus Irinotecan-Based Therapy and Who Failed at Least One Subsequent Non-Anti-EGFR Containing Regimen

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TYPE: Phase II

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INDUSTRY PARTNER/FUNDING SUPPORT: Amgen, Inc.

STUDY SPONSOR AND MONITOR: City of Hope

City of Hope National Medical Center
1500 E. Duarte Road
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Clinical Trial Protocol

A Prospective Study of FOLFIRI plus Panitumumab in Extended RAS Wild Type and BRAF Wild Type Metastatic Colorectal Cancer with Acquired Resistance to Prior Cetuximab (or Panitumumab) plus Irinotecan-Based Therapy and Who Failed at Least One Subsequent Non-Anti-EGFR Containing Regimen

Protocol Version Date:	July 23, 2015
Protocol Version No.:	00
COH Protocol No.:	15117
Agents:	Panitumumab, Folinic acid (leucovorin), 5-Fluoruracil, Irinotecan,
Industry Partner:	Amgen, Inc.
Industry Partner Study ID:	Amgen IST 20149076
IND#:	Exempt

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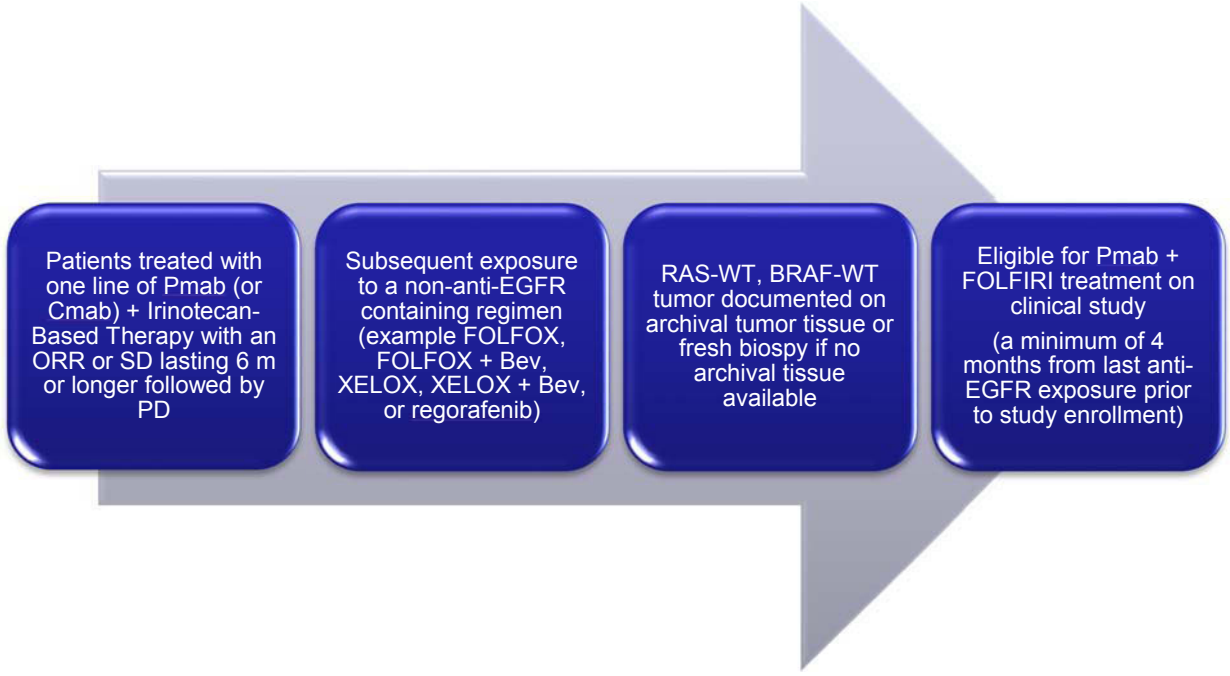
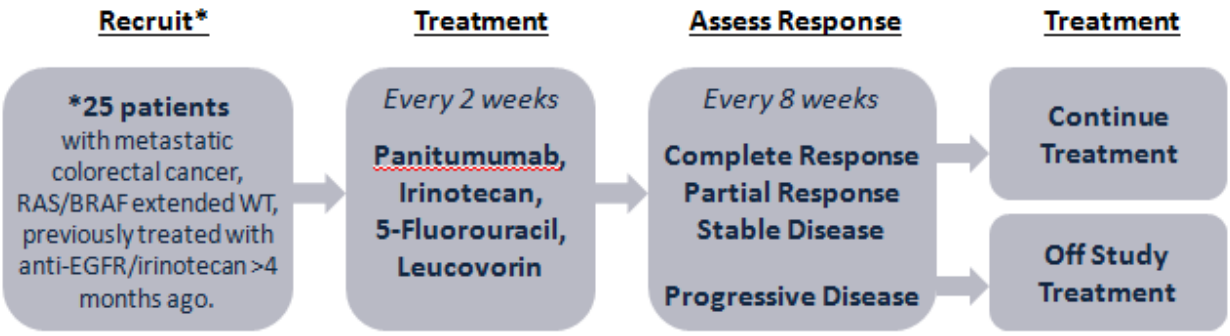
EXPERIMENTAL DESIGN SCHEMA





* Interim assessment after 14 patients accrue. If 1 or more demonstrates a partial response, or if 4 or more achieve a progression free survival of 4 months, then all 25 participants will accrue to the trial.

PROTOCOL SYNOPSIS

Protocol Title:
A prospective study of FOLFIRI plus panitumumab in extended RAS wild type and BRAF wild type metastatic colorectal cancer with acquired resistance to prior cetuximab (or panitumumab) plus irinotecan-based therapy and who failed at least one subsequent non-anti-EGFR containing regimen
Brief Protocol Title for the Lay Public (if applicable):
FOLFIRI Plus Panitumumab Re-Challenge in Extended RAS/BRAF WT Colorectal Cancer
Study Phase:
Phase II
Participating Sites:
City of Hope
Rationale for this Study:
Patients with extended RAS and BRAF wild type colorectal cancer demonstrate a significant clinical benefit from the addition of anti-EGFR therapy to their chemotherapy (FOLFOX or FOLFIRI) in first line or second line settings. With an increasing portion of RAS wild type patients receiving this therapy in the first-line and second line setting, it is important to better define the optimal subsequent lines of treatment in this population. In general, patients who progress after FOLFIRI + anti-EGFR therapy will receive FOLFOX +/- bevacizumab. However, upon progression, no validated options are available for these patients. While regorafenib is approved for patients who fail all cytotoxic therapy, this agent has significant toxicity and minimally relevant clinical efficacy.[1] The question of subsequent anti-EGFR therapy re-challenge merits prospective evaluation. While initial treatment with an anti-EGFR therapy promotes the development and clonal selection of *RAS* mutations in patients with previously *RAS* wild-type tumors, subsequent treatment with a non-anti-EGFR therapy may promote repopulation of the tumor with RAS-WT EGFR-sensitive tissue. In line with this hypothesis, in a prospectively conducted phase II study, 54% of participants undergoing re-challenge with the anti-EGFR therapy, cetuximab, and irinotecan experienced a high objective response rate and a significant a progression free survival exceeding 5 months.[17] In another retrospective analysis, anti-EGFR re-challenge has demonstrated clinical benefit following prior exposure and progression, and this benefit appears to be more significant and successful in patients with a prolonged break between progression on prior anti-EGFR therapy and the start of re-challenge. [19] We therefore hypothesize that an alternate, non-EGFR containing regimen coupled with anti-EGFR withdrawal, after initial anti-EGFR based therapy resistance, will alter tumor repopulation, result in a decline in the *RAS* mutant population, and re-sensitize tumors to anti-EGFR-based therapy. We propose to test this hypothesis in patients with a documented extended *RAS* wild-type and *BRAF* wild-type tumors as these are the most likely to benefit from this strategy. We also propose to conduct this study with panitumumab as no prospective data in similar conditions have been reported with this agent.
Objectives:
Primary Objectives: 1- Estimate the RR and PFS with FOLFIRI + panitumumab in patients with acquired resistance to panitumumab (or cetuximab) + irinotecan-based therapy after a documented clinical

response or prolonged PFS and following progression on a subsequent non-anti-EGFR containing regimen in extended *RAS* wild-type and *BRAF* wild-type patients

Secondary Objectives:

1- Estimate the OS in the re-challenge populations
2- Describe the safety of re-challenge in this population
3- Investigate the impact of PFS, RR on prior anti-EGFR + irinotecan-based exposure on the response and PFS on the current study

Exploratory Objectives:

1- Collect serial plasma samples to investigate the incidence of RAS and BRAF mutation in circulating free DNA at baseline, every 2 months, and at the time to progression (and following progression when feasible).
2- Collect serial plasma samples for future biomarker exploration, including the potential investigation of micro-RNA

Study Design:

Patients who have had previous clinical benefit with first-line anti-EGFR therapy (at least 6 months PFS/PR/CR by RECIST criteria), have subsequently received and progressed on a non-anti-EGFR containing regimen, and have not been exposed to anti-EGFR therapy for at least 4 months will receive panitumumab combined with FOLFIRI (5-fluorouracil, leucovorin, irinotecan) every two weeks with response assessment at 8 week intervals until progression or removal from study treatment due to toxicity.

A modified Gehan 2-stage Phase II design will be employed. In the first stage, 14 participants will be accrued and assessed for response rate and progression free survival. If no objective responses are observed in 14 participants, and fewer than 4 participants are progression-free at the 4 month evaluation, the study will close for futility. If there is at least one response, or at least 4 participants progression-free at 4 months, an additional 11 participants will be accrued.

In addition to response assessment using RECIST 1.1, survival, toxicity information, carcinoembryonic antigen, and blood samples for cell-free DNA and microRNA exploratory analysis will be collected.

Endpoints:

Primary Endpoints:

1- RR and PFS

Secondary Endpoints:

1- OS
2- Toxicity information
3- Impact of PFS, RR on pre-study anti-EGFR + irinotecan exposure with the RR and PFS on the current study

Sample Size:

In the event the study does not close for futility, 25 evaluable patients (received at least 1 cycle of treatment) will be enrolled on this study.

Estimated Time of Accrual

In the event the study does not close for futility, the enrollment will be complete within 2 years from activation (accrual of 1-2 patients per month).

Summary of Eligibility Criteria:

Inclusion Criteria:

- Age: 18 years or older.
- ECOG Performance Status 0-2.
- Life expectancy of $\geq$ 3 months.
- Histologically confirmed colon or rectal cancer with metastatic disease.
- Extended RAS and BRAF wild type status documented on archival tumor tissue or on fresh biopsy if no archival tissue present.
- Measurable disease defined by at least 1 lesion ≥ 1 cm.
- Documented objective response or stable disease lasting for 6 months or more to last prior anti-EGFR (cetuximab or panitumumab) in combination with irinotecan or FOLFIRI.
- Progression within 6 weeks following their last dose of anti-EGFR therapy.
- Treatment with a non-EGFR targeting regimen following progression on anti-EGFR plus irinotecan-based therapy.
- At least 4 months from prior anti-EGFR therapy prior to start of study treatment.
- At least three weeks from any non-anti-EGFR therapy prior to start of study treatment. Any number of prior therapies is permitted.
- Adequate recovery in the investigators opinion from any clinically significant toxicity from prior therapy.
- Adequate organ and marrow function.
- Agreement by men and women of child bearing potential to use effective contraception prior to study entry and for six months after completing the study treatment.

Exclusion Criteria:

- History of intolerance to prior anti-EGFR, irinotecan or 5-fluorouracil treatment.
- Impairment of gastrointestinal function or gastrointestinal disease (e.g., active ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, extensive small bowel resection).
- Major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure.
- Unstable pulmonary embolism, deep vein thrombosis, or other significant arterial/venous thromboembolic event ≤ 30 days before enrollment.
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) $\leq$ 6 months prior to enrollment.
- History of interstitial lung disease (ILD) eg, interstitial pneumonitis, pulmonary fibrosis or evidence of ILD on baseline chest CT or MRI.
- Other active malignancies except cervical carcinomas in situ or clinically insignificant non-melanoma skin cancers.
- Pregnant women and women who are lactating.

Investigational Product Dosage and Administration:

Treatment will be administered every two weeks. Panitumumab will be given over 1 hour at 6mg/kg, followed by irinotecan at 180mg/m^{2}IV, leucovorin at 400mg/m^2, and 5-FU 2400mg/m^{2}over 46 hours. Since this treatment will be provided in heavily pre-treated patients, the treating physician will be allowed to initiate the FOLFIRI at attenuated doses to take into account the patient's history of prior dose-reductions for irinotecan or 5-FU. Starting doses of irinotecan and 5-FU are included below. A clear documentation for the reason for the lower starting dose should be documented. The starting dose of irinotecan can range between 125-180 mg/m^2. The starting dose of 5-FU can range between 1800-2400 mg/m^2. All patients should receive the full dose of panitumumab.

Clinical Observations and Tests to be Performed:

Serum chemistry, hematology, physical exam, vital signs, CT/PET or MRI, carcinoembryonic antigen, blood for RAS/BRAF cell-free DNA and other exploratory biomarkers.

Statistical Considerations:

The primary hypothesis is that the combination of FOLFIRI + panitumumab has activity in patients with *RAS/RAF* WT mCRC when introduced as a re-challenge to patients that had previous clinical benefit with first-line anti-EGFR therapy (at least 6 months PFS/PR/CR by RECIST criteria), have received a subsequent non-anti-EGFR containing regimen, and have not been exposed to anti-EGFR therapy for at least 4 months.

As we will not know a priori the response rate to first-line anti-EGFR therapy, nor the median PFS with previous anti-EGFR therapy, and this study will not be restricted to two prior chemotherapy regimens due to treatment patterns in the US, we can't use the cetuximab estimates for this trial. As a result, a modified Gehan 2-stage Phase II design will be employed.

In the first stage, 14 patients will be accrued. Failure to observe a response if the true response is 20% or above would occur with a probability less than 5% (4.4%). Failure to observe at least 4 patients progression-free at the second evaluation (~4 months), would occur with less than 3% probability if the true 4-month PFS rate is 50%, and would occur with more than 95% probability if the true 4-month PFS rate was 10%, which is higher than placebo treatment 4-month PFS seen on the CORRECT trial.[1] As a result, if no objective responses are observed in 14 patients, and fewer than 4 patients are progression-free at the 4 month evaluation, the study will close for futility. If there is at least one response, or at least 4 patients progression-free at 4 months, an additional 11 patients will be accrued. The interim stopping for futility is such that there is a 46% chance of early stopping if the response rate is 5% and the 4-month PFS rate is 10%. This compares to 48.7% early stopping probability for the standard Gehan design if the true response rate is 5%, but allows us to pass the interim stopping condition if PFS suggests enough activity due to re-challenge to expand to a total of 25 patients.

With a total of 25 patients, the standard error of estimate for the response rate estimate and the 4-month PFS rate estimate will not exceed 10%.

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) will be included in the main analyses of response and PFS, and all the secondary or correlative analysis described below.

Sponsor/Licensee:

Regulatory Sponsor: City of Hope Industry Partnership and Support: Amgen, Inc.
Case Report Forms
Medidata RAVE® Electronic Data Capture system. Forms are detailed in Section 12.1.3.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
ASCO	American Society of Clinical Oncology
AE	Adverse Event
BSC	Best Supportive Care
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRYSTAL	Cetuximab Combined with Irinotecan in First Line Therapy for Metastatic Colorectal Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
ECCO	European Cancer Organisation
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FIRE-3	FOLFIRI plus cetuximab or plus bevacizumab as first-line treatment metastatic colorectal cancer: a randomized, open label, phase 3 trial.
FOLFIRI	5-fluorouracil/leucovorin/irinotecan
FOLFOX	5-fluorouracil/leucovorin/oxaliplatin
5-FU	5-fluoruracil
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
OPUS	Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer
OS	Overall Survival
PD	Progressive Disease
PEAK	FOLFOX + panitumumab vs. FOLFOX + bevacizumab in the first line treatment of metastatic colorectal cancer
PFS	Progression Free Survival
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
PRIME	Panitumumab Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
TRLC	Translational Research Laboratory Core

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Primary Objectives:

1- Estimate the RR and PFS with FOLFIRI + panitumumab in patients with acquired resistance to panitumumab (or cetuximab) + irinotecan-based therapy after a documented clinical response or prolonged PFS and following progression on a subsequent non-anti-EGFR containing regimen in extended *RAS* wild-type and *BRAF* wild-type patients

Secondary Objectives:

1- Estimate the OS in the re-challenge populations
2- Describe the safety of re-challenge in this population
3- Investigate the impact of PFS, RR on prior anti-EGFR + irinotecan-based exposure on the response and PFS on the current study

Exploratory Objectives:

1. Collect serial plasma samples to investigate the incidence of *RAS* and *BRAF* mutation in circulating free DNA at baseline, every 2 months, and at the time to progression (and following progression when feasible).
2. Collect serial plasma samples for future biomarker exploration, including the potential investigation of micro-RNA

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Background:

In a pre-planned prospective-retrospective analysis, Douillard and colleagues have recently reported an updated efficacy analysis of the PRIME study (FOLFOX vs. FOLFOX plus panitumumab) by *RAS* and *RAF* tumor status.[2] *RAS* mutation was *defined* as the presence of exon 2, 3, and 4 *KRAS* or *NRAS* mutations (codons 12, 13, 61, 117, and 146). This expanded *RAS* signature identifies an additional 17% of patients who are *RAS* mutant but lack an exon 2 *KRAS* mutation. Subgroup analyses suggest a detrimental impact on PFS and OS in the panitumumab arm in patients with *KRAS* exon-2 mutations and other non-*KRAS* exon-2 *RAS* mutant patients. In contrast, the addition of panitumumab to FOLFOX in patients lacking any *RAS* mutation had a significant improvement in PFS (HR = 0.72; improvement in median PFS of 2.4 months) and OS (HR = 0.77; improvement in median OS of 5.4 months). The improvement in PFS and OS widened further on the panitumumab arm (HR of 0.68 and 0.74, respectively) upon excluding *BRAF* mutant patients in the *RAS* wild-type population.

The validity of *RAS* mutation signature as a predictive marker of response to anti-EGFR therapy has also been supported by the retrospective analysis of several other randomized clinical trials. Particularly, the FIRE-3 phase III clinical trial of first-line FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab, presented at ECCO 2013, has shown a statistically significant improvement in OS in favor of the cetuximab arm.[3] Patient with tumors lacking any *RAS* mutation experienced a statistically superior OS (33.1 vs. 25.9 months). However, the lack of improvement in PFS on FIRE-3 remains puzzling and suggests a potential role for depth of response in impacting OS. In contrast, patients with non-exon 2 *KRAS* mutations or *NRAS* mutations trended towards a worse clinical outcome on the cetuximab arm. The value of *RAS* status as a marker of response to anti-EGFR agents has also been recently reported on the PEAK trial (FOLFOX +

Panitumumab vs. FOLFOX + bevacizumab in the first line treatment of metastatic colorectal cancer) and study 20020408 (panitumumab vs. BSC in refractory colorectal cancer).[4, 5]

The reproducibility of *RAS* status as a predictive marker of benefit from anti-EGFR agents across the PRIME and FIRE-3 studies (and more recently the 181 clinical trial) validates *RAS* testing as a new standard for anti-EGFR therapy selection in the front-line treatment of metastatic colorectal cancer. *RAS* mutations are estimated to occur in 52% of patients with colorectal cancer, narrowing anti-EGFR candidacy to less than half of the patients with metastatic colorectal cancer.[2] Given the low frequency of *NRAS* mutation and non-exon 2 *KRAS* mutations in colorectal cancer, the ability to conduct prospective clinical trials to validate the predictive value of each individual mutation is not clinically feasible. ASCO and NCCN previously recommended the exclusion of exon-2 *KRAS* mutant colorectal cancers from anti-EGFR therapy based on retrospective data analyses from the OPUS, CRYSTAL, 20020408 study, and NCI-CO17 clinical trials.[6, 7] PRIME and FIRE-3 provide no less compelling data of the predictive value of *NRAS* and low-frequency non-exon 2 *KRAS*-mutations vis-à-vis anti-EGFR therapy.

Both PRIME and FIRE-3 suggest a trend to a worse clinical outcome in *KRAS* exon 2 wild type/ *RAS* mutant patients, supporting the prompt need to exclude these patients from anti-EGFR therapy.

As important, the exclusion of patients with *RAS* mutations identifies a patient population with a robust clinical benefit from the addition of anti-EGFR therapy in the first line setting. The PRIME study showed an improvement in OS of 5.4 and 7.4 months with addition of panitumumab to FOLFOX in patients with *RAS* wild-type and *RAS*/*BRAF* wild-type patients, respectively.[2] An excess of 7 months improvement in OS was similarly noted with FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab in *RAS* wild-type patients on the FIRE-3 study.[3] These are clinically significant improvements in OS that have not been attained with any other biological agent in the first-line treatment of metastatic colorectal cancer in combination with FOLFOX or FOLFIRI, arguably the most commonly used cytotoxic regimens. PRIME and FIRE-3 clearly position anti-EGFR therapy as a first line option in patients without *RAS* mutations when FOLFOX or FOLFIRI are contemplated. Recent reports from CALGB 80405 show similar OS in patients treated with cetuximab-based first line chemotherapy or bevacizumab-based first line chemotherapy in patients who lack *KRAS* exon 2 mutation.[8] Whether a differential positive impact will be seen in favor of the cetuximab arm when the non-exon 2 *KRAS* mutations and *NRAS* and *BRAF* mutations are excluded remains to be reported. Note that no randomized phase III clinical trials to date have shown any survival advantage to the addition of bevacizumab in combination with FOLFOX or FOLFIRI in the first-line treatment of metastatic colorectal cancer.[9-11] Based on the above data, we and others have now incorporated an expanded *RAS* mutation and *BRAF* mutation assay in all our metastatic colorectal cancer patients prior to consideration of anti-EGFR therapy. With an increasing portion of *RAS* wild type patients receiving anti-EGFR therapy in combination with chemotherapy (FOLFOX or FOFLIRI), it is important to better define the optimal second and third line treatments in this population. Particularly, the question of subsequent anti-EGFR therapy re-challenge requires prospective evaluation. In this study, we plan to prospectively investigate the combination of FOLFIRI + panitumumab re-challenge in patients *RAS* wild-type and *BRAF* wild type tumors who derived prolonged clinical benefit from one line of prior irinotecan plus anti-EGFR therapy.

The combination of FOLFIRI plus panitumumab is associated with significant clinical efficacy in the second line treatment of metastatic colorectal cancer.[12] In addition, the addition of the anti-EGFR, cetuximab, has been associated with improvement in OS when combined with FOLFIRI in the first line treatment of metastatic colorectal cancer.[13] This has prompted the acceptance of either cetuximab or panitumumab as a first line treatment in combination with FOLFIRI in the first line treatment of metastatic colorectal cancer.[7] In addition, the recent report of the FIRE-3 study and the updated analysis of the PRIME study detailed above lend further support to a strategy incorporating anti-EGFR treatments in the first line setting. Given the above, it is expected that an increasingly large number of patients will be receiving

panitumumab or cetuximab in combination with FOLFIRI in the first or second line treatment of *RAS* wild type metastatic colorectal cancer. Therefore, developing therapeutic options beyond progression on one line of anti-EGFR therapy + FOLFIRI is considered to be clinically relevant. In general, patients who progress after FOLFIRI + anti-EGFR therapy will receive FOLFOX +/- bevacizumab. However, upon progression, no validated options are available for these patients. While regorafenib is approved for patients who fail all cytotoxic therapy, this agent has significant toxicity and minimally relevant clinical efficacy.[1]

We propose that a re-challenge with panitumumab plus FOLFIRI in patients with a good response to one anti-EGFR line of treatment (namely, FOLFIRI + cetuximab or FOLFIRI + panitumumab) and who had experienced a minimum of 4 months break from anti-EGFR therapy will derive a clinically meaningful benefit. Given the limited activity of 5-FU bolus and increased toxicity in heavily pretreated patients, it will not be included as part of the FOLFIRI regimen.

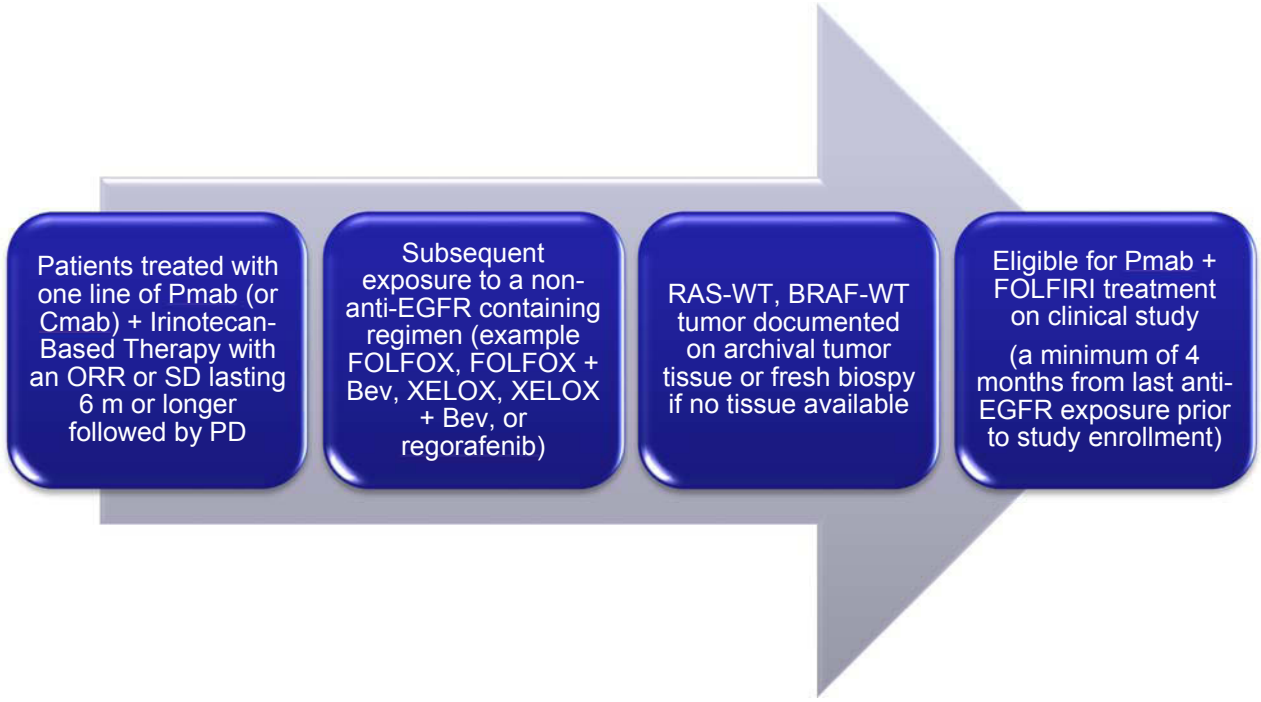
Rationale:

The rationale for a potential benefit from a re-challenge with anti-EGFR therapy is based on two concepts: 1) *RAS* molecular heterogeneity is inherent to most colorectal tumors and *RAS* mutations can be readily detected after anti-EGFR therapy in most patients with initial *RAS* wild-type tumors at or prior to progression; 2) discontinuation of anti-EGFR therapy and subsequent treatment with a non-anti-EGFR containing regimen may re-promote the dominance of *RAS* wild-type clones and therefore reset the tumors to anti-EGFR sensitivity. In support of the first concept, Misale et al. have shown that secondary *RAS* mutations were detected in 60% of tumor samples biopsied at the time of resistance to anti-EGFR therapy and these mutations were also readily detectable in patient sera prior to the development of anti-EGFR resistance.[14] Diaz et al. subsequently confirmed similar findings in patients with *KRAS* wild-type tumors treated with panitumumab monotherapy. 38% of patients with *KRAS* wild-type tumors were shown to subsequently develop a variety of *RAS* mutations during anti-EGFR treatment.[15] Mathematical modeling from the Diaz study indicates that the detected *RAS* mutations were pre-existing prior to panitumumab treatment and that their detection in the sera was a result of clonal selection induced by anti-EGFR therapy.[15] In a follow-up study led by the same group, 24 patients who objectively responded to anti-EGFR therapy and subsequently progressed were assessed for detectable serum mutations involving MAPK pathways. 20/24 patients developed a detectable *KRAS* 12 mutation, 16/24 a *KRAS* 61 mutation, 8/24 an *NRAS* mutation, and 1/24 a *BRAF* mutation. Altogether, 96% of patients with acquired resistance to anti-EGFR therapy developed a detectable mutation involving the MAPK pathway.[16] Based on such findings, one would assume that the detection of readily detectable *RAS* mutations in patients with *RAS* wild-type tumors implies the selection of cetuximab/panitumumab resistant clones responsible for anti-EGFR disease progression - and that such selection would result in a durable resistance to anti-EGFR treatment. However, clinical data with cetuximab + irinotecan re-challenge from a prospectively conducted phase II study suggest that resistance may be reversible after anti-EGFR withdrawal. 39 patients with *KRAS* wild type tumors who had progressed after an initial favorable response to cetuximab + irinotecan-based therapy were treated upon progression with a non-anti-EGFR containing regimen. Upon further progression on non-anti-EGFR based salvage therapy, these patients were prospectively treated with a re-challenge consisting of a cetuximab plus irinotecan-based regimen.[17] 54% of the patients experienced an objective response and the median PFS of the population was 6.6 months.[17] It is hypothesized that the withdrawal of anti-EGFR therapy upon initial progression, coupled by the impact of a non-anti-EGFR containing regimen impacts clonal selectivity of colorectal cancer, re-populating the tumor with predominantly EGFR-sensitive tumors- and therefore, induce a benefit with anti-EGFR re-challenge. In line with this hypothesis, it has been demonstrated that oxaliplatin chemotherapy in colorectal cancer influences clonal repopulation, promoting the dominance of previously minor or dormant lineages.[18] In addition, a recent report from MDACC describes clinical benefit from re-

challenge with anti-EGFR therapy in patients with prior exposure and progression on cetuximab or panitumumab-based therapy. The benefit from re-challenge was more significant in patients with a prolonged break between progression on prior anti-EGFR therapy and the start of re-challenge.[19] We therefore hypothesize that an alternate, non-EGFR containing regimen coupled with anti-EGFR withdrawal, after initial anti-EGFR based therapy resistance, will alter tumor repopulation, result in a decline in the *RAS* mutant population, and re-sensitize tumors to panitumumab-based therapy. We propose to test this hypothesis in patients with a documented extended *RAS* wild-type and *BRAF* wild-type tumors as these are the most likely to benefit from this strategy. We also propose to conduct this study with panitumumab as no prospective data in similar conditions have been reported with this agent.

2.2 Overview of Proposed Study

Eligible patients must have had a prior objective response or a prolonged stable disease (6 months or more) to one prior anti-EGFR based therapy (either cetuximab or panitumumab) in combination with irinotecan (either irinotecan alone or irinotecan plus a fluoropyrimidine). Evidence of progressive disease must have been documented within 6 weeks from their last dose of anti-EGFR therapy. Patients should have been subsequently treated with one or more non-anti-EGFR containing regimens and should be at least 4-month-anti-EGFR-naïve before they can get enrolled on this proposed study. The schema for enrollment is summarized in the figure below.



Patients will be treated on the study with bi-weekly panitumumab in combination with FOLFIRI and the doses recommended by the NCCN guidelines for first or second line treatment. Since patients enrolled on this study are heavily pre-treated, the study will allow some flexibility in the irinotecan and 5-fluorouracil (5-FU) dosing as is detailed in section 5.2. Patients will continue on treatment until evidence of progressive disease or unacceptable toxicity. Response to treatment will be assessed with clinical imaging, which will be performed every 4 cycles (every 8 weeks).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable legal and regulatory requirements.

3.0 PARTICIPANT ELIGIBILITY

3.1 Eligibility Inclusion Criteria

Participant MRN:	Participant Initials: (L,F,M):

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

Informed consent

___ 1. Participant must have the ability to understand and the willingness to sign a written informed consent document.

___ 2. Participant must be willing to comply with study and/or follow-up procedures.

Age Criteria, Performance Status, and Life Expectancy

___ 3. Age: 18 years or older. The safety of the combination of FOLFIRI plus panitumumab has not been adequately assessed in patients younger than 18 years of age and therefore these patients are excluded from this study.

___ 4. ECOG Performance Status 0-2 (Appendix A).

___ 5. Life expectancy of $\geq$ 3 months.

Nature of Illness and Treatment History

___ 6. Histologically confirmed colon or rectal cancer with metastatic disease.

___ 7. Extended RAS and BRAF wild type status documented on archival tumor tissue or on fresh biopsy if no archival tissue present.

___ 8. Measurable disease defined by at least 1 lesion ≥ 1 cm.

___ 9. Documented objective response or stable disease lasting for 6 months or more to last prior anti-EGFR (cetuximab or panitumumab) in combination with irinotecan or FOLFIRI.

___ 10. Progression within 6 weeks following their last dose of anti-EGFR therapy.

___ 11. Treatment with a non-EGFR targeting regimen following progression on anti-EGFR plus irinotecan-based therapy.

___ 12. At least 4 months from prior anti-EGFR therapy prior to start of study treatment.

___ 13. At least three weeks from any non-anti-EGFR therapy prior to start of study treatment. Any number of prior therapies is permitted.

___ 14. Adequate recovery in the investigators opinion from any clinically significant toxicity from prior therapy.

Clinical Labs for Assessing Adequate Organ Function

___ 15. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

___ 16. Hemoglobin (Hgb) ≥ 9 g/dL without transfusions

___ 17. Platelets (PLT) ≥ 100 x 10^9/L without transfusions

___ 18. AST (SGOT) and/or ALT (SGPT) ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN

___ 19. Total bilirubin ≤ ULN

___ 20. Creatinine ≤ 1.5 mg/dL

___ 21. Magnesium ≥ 1.2mg/dL or 0.5 mmol/L

___ 22. Negative serum β-HCG test (female patient of childbearing potential only), to be performed locally within the screening period.

Child Bearing Potential

___ 23. Agreement by females of childbearing potential **and** sexually active males to use an effective method of contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for three months following duration of study participation. The effects of study treatment on a developing fetus have the potential for teratogenic or abortifacient effects. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately.

3.2 Eligibility Exclusion Criteria

Prospective participants who meet any of the following criteria will not be eligible for admission into the study:

History to Previous therapies

___ 1. History of severe anti-EGFR toxicity requiring drug discontinuation or dose-modification within the first 4 months of prior anti-EGFR therapy

___ 2. History of intolerance to irinotecan at dose-intensity of 125 mg/m^2/2 weeks or lower

___ 3. History of intolerance to 5-FU at dose-intensity of 1800 mg/m^2/2 weeks or lower

Concomitant medications

___ 4. Current use (or planned use during the treatment period) of other investigational agents, or biological, chemotherapy, radiation or other anti-tumor therapy. See Inclusion Criteria 12 & 13, for required washout periods from these therapies.

___ 5. Co-medication that may interfere with study results; e.g. immuno-suppressive agents other than corticosteroids, such as systemic cyclosporine and tacrolimus. Consult Principal Investigator for questions, including necessary washout period for the specific drug.

___ 6. No St John's wort supplement or other herbal supplementation is allowed while on trial. Patients are not to take grapefruit juice during study treatment as these may alter the metabolism of irinotecan.

___ 7. Use of drugs known to **inhibit** UGT1A1, such as Atazanavir, Gemfibrozil, Indinavir, or Ketoconazole while on study treatment. (Patients using these drugs must not take these drugs on the day study treatment begins and for the duration of study treatment).

___ 8. Planned use of **strong** CYP3A4 **inhibitors** or CYP3A4 **inducers** (See Table 5.6) while on study treatment unless deemed clinically necessary with no reasonable alternatives and with expressed permission from the principal investigator.

___ 9. If on anticoagulation, participant must be on stable therapeutic dose prior to enrollment.

Other illnesses or conditions

___ 10. Impairment of gastrointestinal function or gastrointestinal disease (e.g., active ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, extensive small bowel resection)

___ 11. Major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure.

___ 12. Unstable pulmonary embolism, deep vein thrombosis, or other significant arterial/venous thromboembolic event ≤ 30 days before enrollment.

___ 13. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 6 months prior to enrollment

___ 14. History of interstitial lung disease (ILD) eg, interstitial pneumonitis, pulmonary fibrosis or evidence of ILD on baseline chest CT or MRI

___ 15. Other active malignancies except cervical carcinomas in situ or clinically insignificant non-melanoma skin cancers.

___ 16. Clinically significant uncontrolled illness or active infections.

___ 17. History of allergic reactions attributed to compounds of similar chemical or biologic composition to irinotecan, 5-FU, leucovorin or any of the products to be administered during dosing.

___ 18. Pregnant women and women who are lactating. FOLFIRI plus panitumumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the administered chemotherapy, breastfeeding should be discontinued if the mother is enrolled on this study.

___ 19. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

Noncompliance

___ 20. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

3.3 Inclusion of Women and Minorities

The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 25 participants, a balance

must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 SCREENING AND REGISTRATION PROCEDURES

4.1 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the participant and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the participant's research chart and medical record.

4.2 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. See Section 10.0 – Study Calendar, for a list of screening procedures and accompanying windows for their administration.

4.3 Registration Requirements/Process

Eligible patients must be registered within 2 weeks prior to start of protocol therapy.

Registration of participants is to be via completion of the following steps:

- Prospective participants must complete the informed consent process, including a signed informed consent, prior to proceeding to study screening.
- Screening procedures and windows are detailed in Section 10 and Table 10, Study Activity Calendar.
- Once all the pre-study requirements have been fulfilled, including a completed eligibility checklist, the study coordinator can register the eligible patient into MIDAS.
- Patients failing to meet all protocol eligibility criteria, including informed consent, may not be registered for the trial.

5.0 TREATMENT PROGRAM

5.1 Treatment Overview

Treatment on study will be in the outpatient setting and will consist of biweekly (every 2 weeks) treatment with panitumumab and FOLFIRI.

A treatment cycle is defined as the period starting from administration of study agents up to the subsequent administration of study agents, and thus will typically be a two week duration. Day 1 of each treatment cycle is defined as the day of treatment administration. Windows for all assessments and treatments are detailed in Section 10.

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10.

The study will enroll 25 evaluable participants with advanced metastatic colorectal cancer, initially enrolling 14 participants for analysis for futility, followed by an additional 11 participants if futility is not demonstrated. A definition of an evaluable participant will consist of a participant with documented *RAS wild type* and *BRAF* wild type tumor receiving at least 1 cycle of FOLFIRI + panitumumab (*RAS and BRAF* will be determined through ONCO48 testing at COH- other CLIA certified assays for these tests will be allowed).

5.2 Treatment Administration Including Initial Starting Doses

See Section 5.6 for required and recommended prophylaxis.

On the day of treatment administration, panitumumab is followed by concurrent administration of irinotecan and leucovorin, followed by 5-FU:

		Starting Dose	Administration
1	Panitumumab	6mg/kg	See section 8.1.9 and 8.1.10**
2	Irinotecan	180mg/m^2 (125-180 mg/m^2)*	As per package insert and COH standard practice (e.g. diluted to 500 ml and infused over 90 min)
3	Leucovorin	400mg/m^2	As per package insert and COH standard practice.
4	5-FU	2400mg/m^2 (1800-2400 mg/m^2)*	As per package insert and COH standard practice. Over 46 hours.

*The treating physician may initiate irinotecan and 5-FU at attenuated doses within the indicated ranges to take into account the participant's history of prior dose-reductions for these agents. A clear justification for the lower starting dose should be documented.

**The panitumumab dose will be calculated based on the participant's actual body weight at baseline and re-calculated at subsequent doses per institutional guidelines. At a minimum, the dose will be re-calculated if the actual body weight changed by at least ± 10% from the last time the dose was calculated.

Modifications to the doses of all agents are detailed in Section 6.2.1 and 6.2.2. Panitumumab dose levels are detailed in Table 6.2.1.

5.3 Planned Duration of Therapy

Participants will receive study treatment until disease progression or other criteria for study removal are satisfied.

5.4 Criteria for Removal from Treatment

Participants may be removed from treatment for any of the following reasons:

- evidence of disease progression
- the participant is deemed intolerant to study treatment because of toxicity, despite dose modification and delay
- participant's request
- participant deemed non-compliant by the investigator

5.5 Participant Follow-Up

Participants will be evaluated as detailed in the study calendar in Section 10. Once taken off study treatment, participants will be asked to provide research blood samples three times at three month intervals. The clinical study coordinator will continue to collect outcome data every 3 months through chart review or by participant outcome to collect survival data. Windows and assessments are detailed in Section 10.

5.6 Supportive Care, Other Concomitant Therapy, Prohibited Medications

Supportive medications as deemed appropriate by the investigated regimen will be allowed. Additional guidelines are provided in the sections that follow:

5.6.1 Prohibited Medications

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of start of study treatment should be recorded. If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- No other investigational therapy should be given to participants
- No anticancer agents other than the study medications administered as part of this study protocol should be given to participants. If such agents are required for a participant then the participant must first be withdrawn from the study.
- Co-medication that may interfere with study results; e.g. immuno-suppressive agents other than corticosteroids, such as systemic cyclosporine and tacrolimus are prohibited during the treatment phase of the study, unless discussed with principal investigator felt to be of low clinical risk to the participant.
- Use of herbal medications may have unknown interactions with the metabolism of the study agents, and therefore are prohibited from use during the treatment phase of the trial.
- Use of drugs known to **inhibit** UGT1A1, such as Atazanavir, Gemfibrozil, Indinavir, or Ketoconazole, are prohibited while undergoing study treatment as they are likely to increase SN-38 levels and increase overall toxicity to irinotecan.
- Strong CYP3A4 Inducers and Strong CYP3A4 Inhibitors (Table 5.6) are **discouraged but not prohibited**. Concomitant use of CYP3A4 hepatic-enyzme inhibitors and inducers can result in increased and decreased blood levels of irinotecan or SN-38. These agents will be allowed if deemed clinically necessary with no reasonable alternatives. If over the course of study treatment the participant receives any of these drugs, efforts should be made to discontinue the use of inhibitors or potent inducers as soon as possible. Such participants may continue study treatment only at the **discretion of the principal investigator.**

Table 5.6 CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors (≥5-fold increase in AUC)	Strong CYP3A4 Inducers	
Atazanavir*	Aminoglutethimide	Nevirapine
Clarithromycin	Bexarotene	Oxcarbazepine
Indinavir*	Bosentan	Phenobarbital
Itraconazole	Carbamazepine	Phenytoin
Ketoconazole*	Efavirenz	Primidone
Nefazodone	Fosphenytoin	Rifabutin
Nelfinavir	Griseofulvin	Rifampin
Ritonavir	Modafinil	Rifapentine
Saquinavir	Nafcillin	St. John's wort
Telithromycin		
Suboxone		

*Drug is prohibited because known to inhibit UGT1A1

5.6.2 Hematopoietic Growth Factors and Blood Transfusions

The use of growth factors and blood transfusions will be allowed, as deemed necessary by the treating physician.

5.6.3 **REQUIRED** Anti-emetics

For FOLFIRI administration, participants will be pre-medicated by 5-HT3 inhibitor and dexamethasone. Additional anti-emetics will be provided as deemed necessary by the treating physician and may be guided by the participant's prior history.

5.6.4 **RECOMMENDED** Preemptive management of panitumumab-associated skin toxicities is recommended:

Clinical trial data with panitumumab therapy indicate that integument and eye toxicities are consistent with what has been observed for other EGFR inhibitors. Most integument- and eye-related toxicity events were mild or moderate in intensity. For participants on panitumumab, dermatologic toxicities should be managed according to institutional standard procedures. The following is provided for reference.

Starting 24 hours before study Day 1 and continuing for at least 6 weeks:

- Skin moisturizer (eg, Lubriderm), apply to face, hands, feet, neck, back, and chest daily in the morning upon rising,
- Sunscreen (para-aminobenzoic acid [PABA] -free, sun protection factor (SPF) 15 or higher, UV-A, and UV-B protection) apply to exposed skin areas before going outdoors,
- Topical steroid (1% hydrocortisone cream) apply to face, hands, feet, neck, back, and chest at bedtime, and
- Oral antibiotic (such as doxycycline 100 mg twice a day) [since doxycycline is a tetracycline derivative, participants should avoid long exposure to direct sunlight or ultraviolet light. Such exposure may result in participants experiencing an exaggerated sunburn reaction (skin erythema). Doxycycline should not be used in participants with a history of hypersensitivity to doxycycline or tetracycline]

The optimal duration of pre-emptive skin treatment is not known and, if implemented, should be individually tailored for each participant. Participants who subsequently experience skin toxicities ≥ grade 2 should be managed appropriately according to the institution's standard procedures.

Examples of various alternative or complementary treatment options suggested in the literature include the following (Perez-Solar and Saltz, 2005; Segaerts and Van Cutsem, 2005; Lynch et al, 2007):

- Avoidance of sun exposure: use of sunscreen with a high SPF that blocks both UV-A and UV-B and wearing a hat
- Prophylactic use of alcohol-free emollient creams and moisturizers to combat dryness (xerosis)
- Topical hydrocortisone (1% or 2.5%) cream and/or Clindamycin 1% gel for mild cases (grade 1); tetracycline oral antibiotics for more severe (≥ grade 2) cases along with the topical treatments for grade 1 events, and use of an oral antihistamine for itch is recommended
- IV antibacterial or antifungals, as clinically appropriate, for superinfection

5.6.5 **RECOMMENDED** Management of Diarrhea:

Use of diarrhea/cholinergic reaction prophylaxis will be provided as deemed necessary by the treating physician and may be guided by the participant's prior history.

Early (acute) Diarrhea: this will be defined as diarrhea occurring during or shortly after their irinotecan infusion. Acute irinotecan-induced diarrhea can be managed with atropine subcutaneously or intravenously as per institutional guidelines. The total dose of atropine should not exceed 1mg. In the event of irinotecan-induced acute diarrhea, atropine can be administered in a prophylactic manner in subsequent cycles.

Delayed diarrhea: irinotecan induced diarrhea typically occurs more than 24 hours after infusion of irinotecan and should be managed aggressively with anti-diarrhea agents. It is recommended that participants received 2 pills of loperamide (4 mg total) at the onset of the first loose bowel movement, followed by 1 pill of loperamide (2mg) every 2 hours until diarrhea-free for 12 hours. If diarrhea occurs at night, participants may take 2 tablets of loperamide (4mg) every 4 hours while awake.

Symptoms of diarrhea and/or abdominal cramping may occur at any time. Diarrhea should be managed aggressively (according to standard institutional practice e.g., with anti-diarrheal medications) in order to prevent dehydration and possible resulting renal insufficiency.

5.6.6 Electrolytes

Electrolytes should be replenished per the discretion of the treating investigator. If hypomagnesemia is present, replacement should be managed with either oral and/or parental replacement, according to institutional practice and to the degree of hypomagnesemia present. It is recommended that the participant's serum magnesium level should be maintained within the normal range, as much as possible, during study treatment.

It is important to assess and manage serum potassium and calcium (adjusted for albumin) in participants who have concomitant hypomagnesemia. Participant's serum potassium and calcium parameters are recommended to be managed, as per local medical practice, and kept within the normal ranges, as much as possible, during study treatment.

Changes in electrolytes, even without blood urea nitrogen (BUN)/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Participants with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.

5.6.7 Management of Panitumumab-associated Infusion Reaction

Infusion-related reactions include cytokine release syndromes/acute infusion reaction and allergic/hypersensitivity reactions as defined by the CTCAE version 4.0. Participants who experience any grade of infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event. For grade 1 or 2 reactions, reduce the infusion rate by 50%. The infusion should be immediately stopped for grade 3 or 4 reactions. Depending on the severity and/or persistence of the reaction consider permanently discontinuing panitumumab.

6.0 EXPECTED TOXICITIES AND DOSE DELAYS/MODIFICATIONS FOR ADVERSE EVENTS

6.1 Expected Toxicities

6.1.1 Panitumumab

Per the package insert for systemic panitumab, the expected toxicities for panitumab are as follows, where the asterisk (*) signifies a common event:

Eye disorders: keratitis, ulcerative keratitis, growth of eyelashes.

Gastrointestinal: stomatitis/mucositis, intestinal obstruction, nausea, diarrhea, vomiting, dry mouth.

General disorders and administration site conditions: Infusion related reaction, fatigue, mucosal inflammation, dehydration, paresthesia.

Infections: paronychia*, conjunctivitis, sepsis, fatal infections/complications including necrotizing fasciitis.

Immune system disorders: hypersensitivity reaction.

Metabolism and nutrition disorders: hypomagnesemia, hypocalcemia, hypokalemia.

Skin and subcutaneous tissue disorders: acneiform dermatitis*, pruritus*, erythema*, rash*, exfoliative rash*, skin ulcer/abscess*, acne, skin exfoliation*, dry skin*, nail disorder*, skin fissure *, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous mucocutaneous skin disease, photosensitivity.

Respiratory: Pulmonary fibrosis/interstitial lung disease, bronchospasm associated with infusion reaction, dyspnea associated with infusion reaction, cough, epistaxis.

Renal: acute renal failure associated from severe diarrhea and dehydration.

Miscellaneous: fever associated with infusion reaction, chills associated with infusion reactions hypotension associated with infusion reaction.

6.1.2 Irinotecan

A list of the adverse events and potential risks associated with the irinotecan, as determined by the Irinotecan Hydrochloride Package Insert follows (* signifies occurs in > 30%):

Blood and lymphatic disorders: febrile neutropenia.

Gastrointestinal: abdominal pain*, constipation*, diarrhea with early onset*, diarrhea with late onset*, anorexia*, nausea, vomiting, ileus, mucositis/stomatitis, colitis, gastrointestinal bleeding, intestinal perforation, megacolon, dyspepsia.

General disorders & administration site conditions: asthenia*/fatigue, fever*, skin irritation at infusion site.

Immune system disorders: infusion reaction.

Infection: neutropenic infection, minor infection.

Hematologic investigations: anemia*, eosinophilia, leucopenia* (including lymphocytopenia), neutropenia*, thrombocytopenia.

Investigations-other: increased bilirubin, increased alkaline phosphatase, increased SGOT/AST, weight loss*.

Metabolism and nutrition disorders: dehydration due to gastrointestinal side effects.

Nervous system disorders: headache, dizziness, insomnia.

Renal disorders: Renal impairment/renal failure due to dehydration.

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, interstitial lung disease.

Skin and subcutaneous tissue disorders: alopecia*, rash, sweating.

Miscellaneous: Cholinergic reaction (associated with bradycardia, flushing, rhinitis, increased salivation, miosis, lacrimation, diaphoresis, abdominal cramping).

6.1.3 Leucovorin

As listed in the package insert the expected toxicities for oral and parenteral leucovorin are:

Allergic Reactions: anaphylaxis and generalized allergic reactions

Skin and subcutaneous tissue disorders: hives (urticaria) associated with anaphylactoid reactions

Leucovorin with 5-FU: Leucovorin can enhance the toxicity of 5-FU. Although the toxicities observed in participants treated with the combination of leucovorin plus 5-FU are qualitatively similar to those observed in participants treated with 5-FU alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in participants treated with the combination.

6.1.4 5-Fluorouracil (5-FU)

Per the package insert for systemic 5-FU, the expected toxicities for 5-FU are as follows, where the asterisk (*) signifies a common event:

Cardiovascular: myocardial ischemia, angina,

Eye disorders: photophobia, visual changes, lacrimation, lacrimal duct stenosis.

Gastrointestinal: stomatitis*, esophagopharyngitis*, diarrhea*, anorexia*, nausea*, vomiting*, gastrointestinal ulceration and bleeding.

Hematologic: leucopenia* (nadir: days 9-14; recovery by day 30),, pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Immune system disorders: anaphylaxis and generalized allergic reactions.

Nervous system disorders: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Skin and subcutaneous tissue disorders: alopecia*, dermatitis (most commonly pruritic maculopapular rash)*, 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 followed by pain, erythema and swelling (hand-foot syndrome); nail changes (nail loss)

Psychiatric: disorientation, confusion, euphoria.

Respiratory: epistaxis.

Miscellaneous: thrombophlebitis.

6.2 Dose Modifications/Delays

6.2.1 General Information

1. The study will use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to grade toxicities, except for skin- and nail-related toxicities, which must be graded using CTCAE version 4.0 with modifications found in Appendix B. A copy of the version 4.0 can be downloaded from:

   http://evs.nci.nih.gov/ftp1/CTCAE/About.html

2. Study agents are always held together, regardless of the attribution of the toxicity.

3. There is no maximum dose reduction for irinotecan or 5-FU.

4. Panitumumab has a maximum of two dose level reductions, and will not exceed the 60% dose level according the following table:

Table 6.2.1.4 Panitumumab Dose Reductions

	Starting Dose	Dose Level -1	Dose Level -2
Percentage (%)	100	80	60
Panitumumab(mg/kg)	6.0	4.8	3.6

5. Dose escalation is never permitted in this study.

6. Whenever treatment is held pending resolution of toxicity to grade 1 or return to baseline, baseline values are from screening (before study treatment) assessments.

7. If the treating investigator wishes to hold the study agent(s) or dose reduce (including increasing the dose reduction) after an adverse event in a manner not outlined in Table 6.2.2, this is permissible following discussion with and written approval by the Principal investigator.*

8. For situations where a participant experiences a toxicity which the treating investigator feels is unlikely related to treatment with either study agent, but which requires hold or reduction of either agent according to Table 6.2.2, maintaining treatment or maintaining treatment dose is allowable per discussion with and written approval by the Principal Investigator.*

9. For holds due to toxicities related to study agent(s), if the participant does not meet criteria to resume treatment **within 28 days of last treatment** administration, the participant must permanently discontinue study treatment (all agents). However, if the participant is clearly benefiting from the study, the investigator may contact the Principal Investigator to determine if

the participant can remain on study and at what dose level. Agreement of the Principal Investigator is to be documented in writing.*

10. For holds for reasons other than treatment related toxicities, such as inclement weather or adverse events unrelated to study agents, if the participant does not meet criteria to resume treatment within 28 days of their last administration, the study agent(s) may be restarted with written approval from the Principal Investigator, as long as there has been no significant evidence of disease progression during the treatment interruption.*

*The principal investigator will document assessment of the impact of these determinations on the study design, objectives and endpoints or risk to participants. If any modifications to the treatment plan might affect the study design, objectives, and endpoints, or impact the risk of participants, a single participant exception will be sought by the IRB. If the treating investigator is the principal investigator, the determination and the rationale for the determination will clearly be documented in the medical record.

6.2.2 Dose Modifications

Table 6.2.2 details the criteria for disrupting treatment, dose modification and treatment discontinuation following an adverse event. See section 6.2.1 for general guidelines including the maximum number of dose reductions. The agent listed in Table 6.2.2 indicates the drug to which the toxicity is likely attributed based on the toxicity profile of the agents. For treatment purposes, the investigator will determine attribution of all toxicities.

Table 6.2.2 Criteria for Disrupting Treatment, Dose Modification or Discontinuation

Adverse Event	Agent most likely attributed to toxicity	Treatment modification
Hematological Toxicities		
Thrombocytopenia Grade 1 (75 x 10^9/L -<LLN)	Irinotecan, 5-FU	Maintain treatment
Thrombocytopenia Grade 2 (50 – <75 x 10^9/L)		Hold all study agents until recovery to ≤ grade 1 (plts ≥ 75 x 10^9/L). Resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose.
Thrombocytopenia Grade 3 (25 – <50 x 10^9/L)		Hold all study agents until recovery to ≤ grade 1 (plts ≥ 75 x 10^9/L). Resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose.
Thrombocytopenia Grade 4 (<25 x 10^9/L)		Hold all study agents until recovery to ≤ grade 1 (plts ≥ 75 x 10^9/L). Resume treatment with a 40% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose.
Neutropenia (ANC) Grade 1 (1.5x 10^9/L -<LLN)	Irinotecan, 5-FU	Maintain treatment
Neutropenia (ANC) Grade 2 (1.0 – <1.5x 10^9/L)		Maintain treatment

Neutropenia (ANC) Grade 3 ($0.5 – <1.0 \times 10^9$/L)		Hold all study agents until recovery to ≤ grade 2 (ANC ≥ 1.0 x 10^9/L). Resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. The investigator may re-escalate to the original dose in the setting of the addition of prophylactic GCSF support.
Neutropenia (ANC) Grade 4 ($<0.5 \times 10^9$/L -<LLN)		Hold all study agents until recovery to ≤ grade 2 (ANC ≥ 1.0 x 10^9/L). Resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Consider G-CSF prophylaxis in subsequent cycles.
Anemia ≥ Grade 3	Irinotecan, 5-FU	Maintain treatment and manage according to BSC. If per the treating investigator anemia is not adequately managed by transfusion, hold treatment and/or apply a 20% dose reduction of irinotecan and 5-FU and continue leucovorin and panitumumab at pre-hold dose.
Serum Electrolytes		
Serum Electrolytes ≥ Grade 2 Calcium , Potassium, Magnesium,	Irinotecan 5-FU (via diarrhea), Panitumumab	Provide supportive care per Section 5.6.6. Maintain treatment per investigator discretion. No dose reduction for panitumumab or FOLFIRI will be made for electrolyte disturbances. Electrolyte disturbances are managed by aggressive electrolyte replacement. Study treatment will be withheld for grade 3 and above hypomagnesemia and/or grade 3 and above hypocalcemia and/or hypokalemia that persists despite aggressive replacement therapy.
Gastrointestinal		
Diarrhea Grade 1 (2-3 stools/day >pretreatment)	Irinotecan, 5-FU, Panitumumab	See Section 5.6.5 for management recommendations. Maintain treatment.
Diarrhea Grade 2 (4-6 stools/day > pretreatment)		See Section 5.6.5 for management recommendations. Maintain treatment Recurrent grade 2 toxicities may be addressed by 20% dose reductions of irinotecan and 5-FU and/or a single dose level reduction of panitumumab if deemed appropriate by the treating investigator.
Diarrhea Grade 3 (7-9 stools/day > pretreatment)		See Section 5.6.5 for management recommendations. Hold study treatment until the diarrhea decreases to ≤ grade 1, and then restart treatment according to the following: First event: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Additional events: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU, and, at the discretion of the investigator, a dose level reduction of panitumumab from the pre-hold dose; leucovorin resumes at pre-hold dose.

Diarrhea Grade 4 (≥10 stools/day > pretreatment)		See Section 5.6.5 for management recommendations. Hold study treatment until the diarrhea decreases to ≤ grade 1, and then restart treatment according to the following: First event: resume treatment with a 30% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Additional events: resume treatment with a 30% dose reduction from pre-hold dose of irinotecan and 5-FU, and, at the discretion of the investigator, a dose level reduction of panitumumab from the pre-hold dose; leucovorin resumes at pre-hold dose.
Mucositis/Stomatitis Grade 1	Irinotecan, 5-FU, Panitumumab	Maintain treatment
Mucositis/Stomatitis Grade 2		Maintain treatment Recurrent grade 2 toxicities may be addressed by 20% dose reductions of irinotecan and 5-FU and/or a single dose level reduction of panitumumab if deemed appropriate by the treating investigator.
Mucositis/Stomatitis Grade 3		Hold study treatment until resolution to ≤ grade 1, and then restart treatment according to the following: First event: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Additional events: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU, and, at the discretion of the investigator, a dose level reduction of panitumumab from the pre-hold dose; leucovorin resumes at pre-hold dose.
Mucositis/Stomatitis Grade 4		Hold study treatment until resolution to ≤ grade 1, and then restart treatment according to the following: First event: resume treatment with a 30% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Additional events: resume treatment with a 30% dose reduction from pre-hold dose of irinotecan and 5-FU, and, at the discretion of the investigator, a dose level reduction of panitumumab from the pre-hold dose; leucovorin resumes at pre-hold dose.
Vomiting or Nausea Grade 1		Maintain treatment
Vomiting or Nausea Grade 2		Hold all study treatments until resolution to ≤ grade 1 and then resume treatment at pre-hold dose.

Vomiting or Nausea Grade 3 or Grade 4, despite appropriate medical management		Hold study treatment until resolution to ≤ grade 1, and then restart treatment according to the following: First event: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin and panitumumab resume at pre-hold dose. Additional events: resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU; leucovorin resumes at pre-hold dose.
Infusion reaction		
Infusion reaction- grade 1 or 2		Provide supportive care per institutional standard practice. For infusion reaction to panitumumab, reduce the infusion rate by 50% for the duration of that infusion. For infusion reaction to irinotecan decrease the infusion rate as deemed appropriate by the investigator. Depending on the severity and/or persistence of the reation, the treating investigator may consider decreasing the infusion rate and administering pre-medications for future administrations.
Infusion reaction Grade 3 or Grade 4		Immediately stop the infusion. Depending on the severity and/or persistence of the reaction the treating investigator may consider permanently discontinuing study treatment and/or reducing the rate of infusion with appropriate premedications.
Respiratory		
Confirmed interstitial lung disease.	Irinotecan, panitumumab	Permanently discontinue all study treatments.
Skin and Subcutaneous Tissue Toxicities **NOTE: Use Appendix B for grading of skin and subcutaneous tissue toxicities.**		
Hand and Foot Grade 1	5-FU	Maintain treatment
Hand and Foot Grade 2 or Grade 3 considered at least possibly related to 5-FU		Hold study treatment until resolution to ≤ grade 1 or baseline, and then restart treatment with a 20% reduction of 5-FU from pre-hold dose; all other agents will resume at pre-hold dose.
Hand and Foot Grade 4 considered at least possibly related to 5-FU		Hold all treatment until resolution to ≤ grade 1 or baseline, then resume treatment with a 30% reduction of 5-FU from pre-hold dose; all other agents will resume at pre-hold dose.
Any skin or nail Grade 2 toxicity considered at least possibly related to panitumumab that meets any of the following criteria: Requires IV antibiotic or IV antifungal treatment, needs surgical debridement, meets the definition of "serious" (defined in Section 7.3)	Panitumumab	Hold all treatments until improvement: IV antibiotic or IV antifungal treatment is no longer required, recovered from surgical debridement, skin or nail related toxicity is no longer serious. First occurrence: resume study agents at pre-hold dose. Additional occurrences: resume panitumumab with a single dose level reduction from pre hold dose, and resume all other agents at pre-hold dose.

Any skin or nail Grade 3 toxicity considered at least possibly related to panitumumab		Hold all treatments until improvement: AE has improved to ≤ grade 2 or baseline, IV antibiotic or IV antifungal treatment is no longer required, recovered from surgical debridement, skin or nail related toxicity is no longer serious. First occurrence: resume study agents at pre-hold dose. Additional occurrences: resume panitumumab with a single dose level reduction from pre hold dose, and resume all other agents at pre-hold dose.
Any skin or nail Grade 4 toxicity considered at least possibly related to panitumumab		Permanently discontinue study agents.
Other unspecified Non-Hematologic Toxicities considered clinically significant and Related to FOLFIRI		
Grade 1	5-FU, irinotecan	Maintain treatment
Grade 2		Hold treatment until resolution to ≤ grade 1 or baseline, then resume treatment at pre-hold dose.
Grade 3		Hold treatment until resolution to ≤ grade 1 or baseline, then resume treatment with a 20% dose reduction from pre-hold dose of irinotecan and 5-FU and resume other study agents at pre-hold doses.
Grade 4		Hold treatment until resolution to ≤ grade 1 or baseline, then resume treatment with a 30% dose reduction from pre-hold dose of irinotecan and 5-FU and resume other study agents at pre-hold doses.
Other unspecified Non-Hematologic Toxicities considered Related to Panitumumab		
Grade 1	Panitumumab	Maintain treatment
Grade 2		Maintain treatment
Grade 3		Hold treatment until resolution to ≤ grade 1 or baseline, then resume according to the following. First occurrence: resume study agents at pre hold dose. Additional occurrences: resume panitumumab with a single dose level reduction from pre hold dose, and resume all other agents at pre-hold dose.
Grade 4		Permanently discontinue study treatment.
Other unspecified Non-Hem Toxicities considered UNRELATED to study agents		
Other unspecified events of any grade considered unlikely to be related or not related to study agents.	UNRELATED	Maintain treatment with study agents. Interruption of study treatment is permitted if the investigator consults with the Principal Investigator to determine that this is in the best interest of the participant.

7.0 DATA AND SAFETY MONITORING, UNANTICIPATED PROBLEMS AND ADVERSE EVENT REPORTING

7.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase II clinical trial where

the risks are at least balanced by the potential benefit to participants and the importance of the knowledge that may result.

7.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Table 7.2.1 City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Expanded Access Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted according to the timelines in Table 1 above. Protocol specific data collection will include the following items: toxicity information, RR, PFS, OS.

7.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as any expected or unexpected adverse event that results in any of the following outcomes:

- Death
- Is life-threatening experience (places the participant at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity

- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the participant population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.4 Reporting of Unanticipated Problems and Adverse Events to COH DSMC and IRB

Unanticipated Problems - Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at *http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf* and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 7.3.1 City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

DSMC Risk Level 3 and Risk Level 4 Protocol Reporting Timelines

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Death while on active treatment or within 30 days of last day of treatment		

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
Death after 30 days of last active treatment/therapy		
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
Within 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days
After 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

COH IRB Adverse Event Reporting Timelines

Required Reporting Timeframe to COH IRB		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment/therapy or within 30 days of the last day of active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2	
Possibly, Probably, Definitely	5 calendar days[1]	Annual[2]
Unlikely, Unrelated	Annual[2]	Annual[2]

[1] These events must be reported in the time frame if they meet the definition of an unanticipated problem.

[2] For studies that are not first in human, Phase I and first in pediatric trials, only grades 3-5 must be reported at annual review.

7.5 Reporting to Amgen

The principal investigator or his designee will immediately advise Amgen of any potential safety issues, including independent or regulatory/institutional/safety monitoring committee actions or change in study conduct for safety reasons, and will consult and work with Amgen on any such potential issues. The timing of and mechanisms for notification to Amgen are detailed in the subsections that follow.

7.5.1 Serious Unexpected Suspected Adverse Events

Within 10 days of the study team learning of the event, the principal investigator or his designee will notify Amgen of any adverse events that meet **all** of the following criteria:

- Serious, (all grade 3 and 4, and all grade 1 or 2 resulting in hospitalization)
- Unexpected to panitumab per the package insert (see also Section 6. 1 of the protocol for a listing of toxicities found in the package insert)
- Suspected (possibly, probably or definitely related) to panitumab.

To notify Amgen, the principal investigator or his designee fax or securely email the completed COH iRIS Safety Report Form **and** the completed study specific SAE Fax Coversheet to Amgen to the email address or fax number on the coversheet. The communication will signify this is for Amgen ISS 20149076.

7.5.2 Non-SAE Unanticipated Individual Safety-Related Events

Within 10 days of the study team learning of the event, the principal investigator or his designee will notify Amgen of any non-SAE unanticipated individual safety related events, to include but not limited to the following:

- misuse/abuse,
- overdose,
- pregnancy/fetal exposure
- lactation exposure
- administration of expired study agent

To notify Amgen, the principal investigator or his designee will fax or securely email the completed COH iRIS Safety Report Form **and** the completed study specific SAE Fax Coversheet to Amgen to the email address or fax number on the coversheet. **NOTE:** In the event of a pregnancy/fetal exposure, the study team will contact the Amgen ISS program manager Leo Lee (leolee@amgen.com) or his designee to request a pregnancy notification worksheet which, when completed, will accompany the aforementioned documents as part of the submission packet to Amgen.

7.5.3 Safety Issues and Safety-Related Changes to Study Conduct

The principal investigator or his designee will immediately advise Amgen of any potential safety issues, including independent or regulatory/institutional/safety monitoring committee actions or change in study conduct for safety reasons (e.g. hold to accrual for safety), and will consult and work with Amgen on any such potential issues.

Safety related changes to study conduct, protocol amendments, etc. will be emailed to the Amgen ISS program manager Leo Lee (leolee@amgen.com).

7.5.4 Protocol Management Team (PMT) Data Safety Monitoring Reports

The principal investigator or his designee will provide all Protocol Management Reports that are submitted to the COH DSMC to Amgen within (+/-) 10 days of their submission to the DSMC. These reports

will be generated and submitted to the DSMC and Amgen at least bi-annually and will therefore substitute for the annual aggregate safety report to Amgen.

PMT/DSM Reports will be emailed to the Amgen ISS program manager Leo Lee (leolee@amgen.com).

8.0 AGENT INFORMATION

The NCCN guidelines include the use of panitumumab with FOLFIRI (irinotecan, 5-FU, leucovorin) in the first line treatment or in the second line treatment for colorectal cancer (extended RAS wild-type). FOLFIRI consists of the combination of **FOL**inic acid, **F**luorouracil, and **IRI**notecan. FOLFIRI is commonly used in the first, second, and third line treatment of metastatic colorectal cancer in combination with cetuximab or panitumumab.

8.1 Panitumumab

A complete description, toxicity, and pharmacology of panitumumab is detailed in the package insert accessible at www.vectibix.com

Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen's clinical investigational product distribution procedures. Panitumumab must be prepared and administered by a qualified and, where applicable, licensed healthcare professional.

8.1.1 Other names:

Vectibix®

8.1.2 Description and molecular weight

Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

8.1.3 Mechanism of action

The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases, including EGFR, HER2, HER3, and HER4. EGFR is constitutively expressed in normal epithelial tissues, including the skin and hair follicle. EGFR is over expressed in certain human cancers, including colon and rectum cancers. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-alpha) leads to phosphorylation and activation of a series of intracellular proteins, which in turn regulate transcription of genes involved with cellular growth and survival, motility, and proliferation. Signal transduction through the EGFR results in activation of the wild-type *KRAS* protein. However, in cells with activating *KRAS* somatic mutations, the *KRAS*-mutant protein is continuously active and appears independent of EGFR regulation. Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR. Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR. In vitro assays and in vivo animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR.

8.1.4 Pharmacokinetics

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (± SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (± SD) AUC0-tau and CL were 1306 ± 374 mcg•day/mL and 4.9 ± 1.4 mL/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

8.1.5 Human Toxicity

See section 6.1.1.

8.1.6 Formulation

Panitumumab is supplied as commercially labeled single-use 5mL vial containing 100 mg (20mg/ml) of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. It is preservative free, sterile, and at pH 5.6 to 6.0.

The solution is a colorless and may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates.

8.1.7 Storage and Stability

Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

The diluted infusion solution of panitumumab should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

Temperature excursions outside of the specified ranges for a duration of over 15 minutes need to be reported to the PI and Amgen; such agent should not be used without written approval from Amgen.

8.1.8 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

8.1.9 Preparation

The panitumumab dose will be calculated based on the participant's actual body weight at baseline and re-calculated at subsequent doses per institutional guidelines. At a minimum, the dose will be re-calculated if the actual body weight changed by at least ± 10% from the last time the dose was calculated.

Inspect the panitumumab prior to removal from the vial. The solution should be colorless and may contain a small amount of visible translucent-to-white particulates. Do not administer if discoloration is observed.

Panitumumab is to be diluted to a recommended total volume of 100 mL in pyrogen-free 0.9% sodium chloride solution USP/PhEur (normal saline solution, supplied by the site), except for doses higher than 1000 mg which should be diluted to 150 mL in 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 that the maximum concentration of the diluted solution does not exceed 10 mg/mL.

Mix diluted solution by gentle inversion. Do not shake. Discard any unused portion remaining in the vial.

The diluted infusion solution of panitumumab should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

8.1.10 Administration

Panitumumab will be administered IV by an infusion pump through a peripheral line or indwelling catheter using **a non-pyrogenic, low protein binding filter with a 0.2 or 0.22-micron in-line filter** infusion set up.

For the 100ml volume, administer the infusion over 60 ($\pm$ 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 $\pm$ 10 minutes.

It is recommended that doses higher than 1000 mg should be diluted to 150 mL in 0.9% sodium chloride solution, USP/PhEur (normal saline solution, supplied by the site) and infused over 90 $\pm$ 15 minutes.

Strict adherence to aseptic technique should be used during panitumumab preparation and administration. The bag should be labeled per site pharmacy Standard Operating Procedures and promptly forwarded to the clinical research center for infusion.

A physician or medical staff involved in study evaluation must be available during the administration of panitumumab to assess and treat adverse events that may arise during dosing.

8.1.11 Supplier

Panitumumab is FDA approved for the treatment of KRAS (exon-2 codons 12 and 13) WT metastatic colorectal cancer in the first line treatment in combination with FOLFOX or as single agent following progression after fluoropyrimidine, oxaliplatin, and irinotecan containing regimens. The commercially labeled agent will be supplied free of charge from Amgen.

8.1.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.1.13 Destruction and Return

At the end of the study, unused supplies of Panitumumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record.

8.2 Irinotecan

Irinotecan (CAMPOSTAR) is an FDA approved chemotherapy agent. Please refer to the Package Insert for additional details not provided in this section:

http://www.sagentpharma.com/Products/Irinotecan/Catalog/Irinotecan_PI.pdf?PHPSESSID=e089d1b1c1dd5c6cbe2ce3165369bfd8

8.2.1 Other names:

CPT-11, Camptosar

8.2.2 Chemical name and molecular formula and molecular weight

Irinotecan hydrochloride trihydrate: (4S)-4, 11-diethyl-4-hydroxy-9-{(4-piperidinopiperidino) carbonyloxy}-IH-pyroano{3',4':6,7}indolzino{1,2-b}quino line-3, 14(4H,12H)dione hydrochloride trihydrate.C33H38N4O6•HCl•3H2O. M.W. 677.19

8.2.3 Mechanism of action

Irinotecan is a topoisomerase I inhibitor.

8.2.4 Human Toxicity

See section 6.1.2.

8.2.5 Formulation

Irinotecan is supplied in three forms: 2 mL vials containing 40 mg of drug, 5 mL vials containing 100 mg of drug, and 15 mL vials containing 300 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

8.2.6 Storage and Stability

Irinotecan vials must be stored in a cool, dry place, protected from light. It is stable to the expiration date on its label. Irinotecan is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D5W.

8.2.7 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent.

8.2.8 Administration

Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90 minutes. Nothing else should be added to the bag.

8.2.9 Supplier

Irinotecan is commercially available.

8.3 Leucovorin

Please refer to the Package Insert for additional details for leucovorin not provided in this section:

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=bffe8bc8-ea2d-4512-b41d-5a2aa30fd11c

8.3.1 Other Names:

Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

8.3.1 Chemical name and molecular formula and molecular weight

5-formyl-5,6,7,8-tetrahydrofolic acid: calcium *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-*L*-glutamic acid.C20H21CaN7O7. M.W. 511.51

8.3.2 Mechanism of Action:

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

8.3.3 Human Toxicity

See section 6.1.3.

8.3.4 Supplier

Leucovorin is commercially available.

8.4 5-fluorouracil (5-FU)

For complete prescribing information, please refer to the FDA approved package insert.

http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=13302

8.4.1 Other Names:

5-Fluorouracil, 5-FU, Adrucil, Efudex.

8.4.2 Chemical name and molecular formula and molecular weight

5-fluoro-2,4 (1H,3H)-pyrimidinedione. C4H3FN2o2 MW 130.08

8.4.3 Mechanism of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

8.4.4 Storage and Stability:

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140EF in a water bath. Do not allow to freeze.

9.0 CORRELATIVE/SPECIAL STUDIES

All participants will undergo serial blood sampling for future possible exploration of the incidence of RAS and BRAF circulating cell free DNA and biomarkers including micro-RNA.

Specimen collection, processing, and storage

Blood will be collected prior to cycle 1, 5, 9, 13 (and every 4 cycles thereafter) of study treatment and at the time of progression. Collection will continue every 3 months (+/-1 month) subsequent to ending treatment for up to 3 additional draws.

The study coordinator should notify the TRLC of possible samples via email to Yafan Wang (e.g. yawang@coh.org) or her designee and preferably at least a day in advance of sample collection.

One 4 ml K_2EDTA purple top tube will be filled at each timepoint. After collection, tubes will be inverted gently several times, and then kept upright on ice or at 4^{o}C and taken to the Translational Research Laboratory Core (TRLC) in Beckman building, room 4320 as soon as convenient. Tubes are to be labeled with participant initials, study number, MRN, and date and time of collection.

The TRLC will process the samples for plasma storage. Blood samples should be centrifuged (10-20 min at 1100-1300g at RT) within four hours of blood collection. Plasma will be distributed into approximately four 500µl aliquots into cryovials and placed on ice within 1 hour of centrifugation. Aliquots should be stored at < -70^{o}C.

Data points will include the following:

- Date and time of blood collection
- Number and volume of aliquots prepared
- Date and time into < -70^{o}C and date and time retrieved from freezer
- Any freeze-thaw that occurs with a sample for any reason
- Any variations or deviations from the orientations in this section, problems, or issues, which should also be promptly communicated to the PI.

10.0 STUDY CALENDAR

Day 1 of each cycle is defined as the day of agent administration. In the absence of a treatment hold, each cycle lasts 14 days but may be extended up to 5 days or reduced by up to 2 days for participant convenience. Safety evaluations are to be performed within 48 hours of agent administration. If there is a delay in treatment and assessments were already performed, only those assessments deemed necessary by the treating investigator need to be repeated within 48 hours of agent administration. The interval for CT scan is +/- 2 weeks.

10.1 Table 10.0 Study Activity Calendar

	Screening[a]	Day 1 of Cycles 1-4 [b]				Day 1 of remaining cycles [b,d]				End of Tx[e]	30-Day Post Drug[f]	Follow-Up[g]
		Cycle 1[c]	Cycle 2	Cycle 3	Cycle 4	Cycle 5, 9	Cycle 6, 10	Cycle 7, 11	Cycle 8,12			
Informed consent [h]	X											
Background information/history[i]	X											
Inclusion/Exclusion criteria [j]	X											
Vital Signs [k]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status[l]	X										X	
Physical exam	X	X	X	X		X		X		X		
Adverse event assessment [m]		X	X	X		X		X		X	X	
Concomitant meds review [n]	X	X	X	X		X		X		X	X	
Hematology[o]	X	X	X	X	X	X	X	X	X	X		
Serum Chemistry [p]	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy Test [q]	X									X		
Carcinoembryonic Antigen (CEA)	X [r]	X		X		X		X		X[s]		
Blood for correlative studies[t]		X				X				X[s]		X[u]
Imaging – PET/CT or MRI [v]	X [w]					X				X[s]		
Response Assessment [x]						X				X[s]		
Study Treatment [y]		X	X	X	X	X	X	X	X			
Progression Assessment												X[z]
Survival												X[aa]

a. To be performed within 14 days from start of study agents, except imaging and CEA to be performed within 21 and 28 days of start of study agents, respectively (footnotes 'w' and 'r').

b. Day 1 is defined as the day of agent administration. Safety evaluations to be performed within 48 hours of agent administration. If there is a delay in treatment and assessments were already performed, only those assessments deemed necessary by the treating investigator need to be repeated within 48 hours of agent administration. In the absence of a treatment hold, each cycle lasts 14 days, but may be extended up to 5 days or reduced by up to 2 days for participant convenience.

c. Screening assessments may serve as cycle 1 day 1 assessments if performed within 7 days of day 1, except in the event that there are indications that the participant's condition is deteriorating, for which laboratory evaluations should be repeated within 48 hours prior to initiation of study agent.

d. Assessments/activities to continue at four cycle repeats, i.e. use Cycle 5 information for Cycle 9, 13, 17 etc. participants will be taken off study treatment at the time of progression.

e. End of treatment assessments to be performed after last study drug administration except where noted in footnote 's'. Assessments may continue where indicated for ongoing reportable adverse events or events resulting in a dose modification.

f. A contact/visit for review of adverse events, ECOG performance status, and concomitant medication review, is to be performed at 30 days +/- 2 days after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug.

g. Every 3 months (+/-1 month). Participants will be followed for samples for correlative studies (at 3 and 6 months only), progression information (for those who do not progress while on therapy), and survival.

h. Informed consent process to be fully documented: e.g. prospective participant had sufficient time for deliberation, all questions were answered, treatment options provided by MD, full study reviewed including risks, and a copy of signed consent given to participant.

i. Background/history – to include a review of treatment history for colorectal cancer, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.

j. Inclusion/exclusion criteria. Source documentation providing investigator's confirmation that patient has met all eligibility criteria must be available prior to registration.

k. Vital signs: Weight, heart rate, blood pressure, respiration rate, temp. Height required only at baseline.

l. See Appendix A for ECOG scale.

m. Adverse events experienced by participants will be collected and recorded from the pre-treatment C1D1 safety assessments up to 30 days of the last dose of study medication. The period for collection and recording of AEs is extended for participant with ongoing "reportable" adverse events that are related to study agent. Adverse event reporting begins for events that occur after start of study treatment. Toxicities will be assessed using CTCAE v.4.0 except for skin and nail toxicities (see Appendix B).

n. Concomitant medication and reason for administration should be documented in the case history.

o. Hematology – erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

p. Serum chemistry – albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), bilirubin (total), calcium, carbon dioxide, chloride, creatinine, glucose, **magnesium,** potassium, protein (total), sodium, urea nitrogen.

q. Serum pregnancy test only for women of child bearing potential.

r. CEA to be performed within 28 days of start of treatment.

s. Do not need to be repeated if performed within 21 days before decision to end treatment.

t. At the time of routine sample collection, one 4 ml purple top (K_2EDTA) tube will be collected, gently inverted several times and then maintained in an upright position at 4^{o}C or on ice, and taken to the TRLC in Beckman, room 4320 within ~ 3 hours and as early as convenient. The TRLC should be notified of planned samples via email to Yafan Wang or (e.g. yawang@coh.org) or her designee preferably at least a day in advance. Tubes are to be labeled with participant initials, study number, MRN, and date and time of collection. (See Section 9.0)

u. During follow up, blood for correlative studies to be taken 3 times only (e.g. 3, 6, 9 months but not after).

v. Imaging studies including a CT chest, abdomen, and pelvis. A PET/CT or MRI can be used if deemed clinically necessary. The interval for scans is +/- 2 weeks.

w. To be performed within 21 days of start of treatment.

x. Response assessment using RECIST 1.1 criteria (Section 11), at time of imaging and as indicated clinically.

y. Study treatment of panitumumab, irinotecan, leucovorin, 5-FU detailed in Section 5.2.

z. Progression assessment for participants who have yet to progress. It will not be a protocol deviation if this assessment is not performed. All visits will be directed by standard of care practices.

aa. Survival assessment to occur via medical record review, review of social security registry, or phone call.

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Response Criteria

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [20] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All participants will be evaluable for toxicity from the time of their first treatment with FOLFIRI plus panitumumab.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does

not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy

resolution/sensitivity. Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.3 Response Criteria

11.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4 Evaluation of Best Overall Response:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.0 DATA REPORTING/PROTOCOL DEVIATIONS

12.1 Data Reporting

12.1.1 Confidentiality and Storage of Records

Electronic data collection will be used for this protocol. The data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized

users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human participants.

12.1.2 Data Collection Forms and Submission Schedule

All data will be collected using electronic data collection, stored as indicated in Section 12.1.1, and will be submitted according to the timelines indicated in Table 14.1.3.

12.2 Table 12.1.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of the last day of cycle
Adverse Event Report Forms	Within 14 calendar days of the last day of cycle
Response Assessment Forms	Within 14 calendar days of the last day of cycle
Other Assessment Forms (concomitant medications, chemistry, hematology, physical exam etc.)	Within 14 calendar days of the last day of cycle
Off Treatment/Off Study Forms	Within 14 calendar days of completing treatment or being taken off study for any reason
Follow up/Survival Forms	Within 30 calendar days of the protocol defined follow up visit date or call

12.3 Protocol Deviations

12.3.1 Deviation Policy

This protocol will be conducted in accordance with COH's "Clinical Research Protocol Deviation Policy" located at http://www.coh.org/dsmc/Documents/Institutional%20Deviation%20Policy.pdf.

Deviations from the written protocol that could increase participant risk or alter protocol integrity require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. IRB pre-approved SSE protocol modifications are considered an amendment to the protocol and not a deviation. The submission of a deviation report is not required.

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression.

12.3.2 Reporting of Deviations

All deviations will be reported to the COH DSMC within five days. The DSMC will forward the report to the IRB following review.

12.3.3 Resolving Disputes

The COH Investigational Drug Service (IDS) cannot release a research agent that would cause a protocol deviation without approval by the PI. Whenever the protocol is ambiguous on a key point, the IDS should rely on the PI to clarify the issue.

In situations where there is misperception or dispute regarding a protocol deviation among the persons involved in implementing the protocol, it is the responsibility of the PI to resolve the dispute and the PI may consult with the DSMC chair (or designee) to arrive at resolution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

The primary hypothesis is that the combination of FOLFIRI + panitumumab has activity in patients with *RAS/RAF* WT mCRC when introduced as a re-challenge to patients that had previous clinical benefit with anti-EGFR therapy (at least 6 months PFS or PR or CR by RECIST criteria), have subsequently received and progressed following a non-anti-EGFR containing regimen, and have not been exposed to anti-EGFR therapy for at least 4 months.

While previous work [12] demonstrated a response rate of 54% with cetuximab-rechallenge in this patient population, enrolled patients were highly selected, with a first-line cetuximab response rate of 90%. In addition, the first-line median PFS was 10 months (range 3-30), and the median PFS on re-challenge was 6.6 months with a range (~2 to ~20) and 95% CI (4.1-9.0 months). As we will not know a priori the response rate to first-line anti-EGFR therapy, nor the median PFS with previous anti-EGFR therapy, and this study will not be restricted to two prior chemotherapy regimens due to treatment patterns in the US, we can't use the cetuximab estimates for this trial. As a result, we will design this study according to:

1. If the response is clearly below 20%, the study will stop early, unless the PFS looks promising (defined below).
2. If the study does not stop early, we will enroll a total of 25 participants to better estimate the response rate, PFS, and compare the PFS to prior anti-EGFR therapy to the PFS (pairwise) on this re-challenge (similarly for responses).
3. Evaluate the role of biological correlatives.

As a result, we will employ a modification of the Gehan 2-stage Phase II design. In the first stage, 14 participants will be accrued. Failure to observe a response if the true response is 20% or above would occur with a probability less than 5% (4.4%). Failure to observe at least 4 participants progression-free at the second evaluation (~4 months), would occur with less than 3% probability if the true 4-month PFS rate is 50%, and would occur with more than 95% probability if the true 4-month PFS rate was 10%, which is higher than placebo treatment 4-month PFS seen on the CORRECT trial.[1] As a result, if no objective responses are observed in 14 participants, and fewer than 4 participants are progression-free at the 4 month evaluation, the study will close for futility. If there is at least one response, or at least 4 participants progression-free at 4 months, an additional 11 participants will be accrued. The interim stopping for futility is such that there is a 46% chance of early stopping if the response rate is 5% and the 4-month PFS rate is 10%. This compares to 48.7% early stopping probability for the standard Gehan design if the true response rate is 5%, but allows us to pass the interim stopping condition if PFS suggests enough activity due to re-challenge to expand to a total of 25 participants.

With a total of 25 participants, the standard error of estimate for the response rate estimate and the 4-month PFS rate estimate will not exceed 10%.

All of the participants who met the eligibility criteria (with the exception of those who received no study medication) will be included in the main analyses of response and PFS, and all the secondary or correlative analysis described below.

13.2 Sample Size Accrual Rate

In the event the study progresses to the second stage, 25 evaluable participants (received at least 1 cycle of treatment) will be enrolled on this study. The enrollment will be complete within 2 years from activation (accrual of 1-2 participants per month).

13.3 Statistical Analysis Plan

Progression-free survival will be estimated using the product-limit method of Kaplan and Meier. As secondary endpoints, we will investigate the impact of PFS and response on prior anti-EGFR therapy and the time since last anti-EGFR exposure on the response rate and PFS on the current study.

Analysis of Correlative Endpoints:

Because of the limited sample size inherent to phase II studies, the analysis of correlative endpoints is primarily exploratory. Standard descriptive methods will be used to summarize the role of mutational status and other studies. If the combination is not found to have sufficient activity, these patterns may help explain the lack of activity. If sufficient activity is found, then participants who experience an objective response will be compared to those who did not in terms of correlates. Estimates of variation will also prove useful for future clinical research on this regimen. Formal testing of these comparisons is not planned. All analysis will clearly document the exploratory nature of these studies, although no attempt will be made to adjust for multiple comparisons inherent in correlative studies.

14.0 HUMAN SUBJECT ISSUES

14.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

14.2 Recruitment of Participants

Participants will be identified from COH medical oncology clinics.

14.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study participants.

14.4 Study location and Performance Sites

This study will be performed at COH.

14.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual response to study agents and any side effects, and this will be linked to the participant's identity using a coded study number. The principal investigator, co-investigators, and laboratory technicians will have access to this information,

but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

14.6 Financial Obligations and Compensation

The study agent, panitumumab, will be provided free of charge by Amgen, Inc.; the remaining study agents, which are standard of care drugs - leucovorin, 5-FU, and irinotecan - will be the responsibility of the research participant and/or the participant's insurance carrier. The standard of care procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

14.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research participants will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research participants who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those participants who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the participant is a candidate for study enrollment.

15.0 PUBLICATIONS

The investigators will provide Amgen the opportunity to review drafts of any proposed publications. However, any manuscripts that result from this publication will be the sole responsibility of the principal investigator and the co-investigators.

16.0 REFERENCES

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3. Stintzing, S., et al., *Analysis of KRAS/NRAS and BRAF mutations in FIRE-3.* ECCO, 2013. **Abstract E17-7073.**
4. Schwartzberg, L., et al., *Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC).* J Clin Oncol, 2013. **31 (suppl; abstr 3631).**
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APPENDIX A: PERFORMANCE STATUS

Performance status will be scored using the ECOG performance scale as detailed below:

ECOG 0	Fully active, able to carry-on all pre-disease performance without restrictions
ECOG 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light and sedentary nature, example light housework and office work
ECOG 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
ECOG 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
ECOG 4	Completely disabled, unable to carry on any self-care. Totally confined to bed or chair.
ECOG 5	Dead

APPENDIX B: DERMATOLOGY/SKIN/NAIL ASSESSMENT

Dermatology/Skin/Nail Assessment (From CTCAE Version 4.0 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