UNIVERSITY OF UTAH
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APK MUTANT: A Single Arm Phase II study of Cetuximab in Third Line for Mutant APC, TP53 and RAS patients with Refractory Metastatic Colorectal Cancer

Principal Investigator	Vaia Florou, MD Assistant Professor, Division of Oncology Huntsman Cancer Institute 2000 Circle of Hope SLC, UT, 84112 vaia.florou@hci.utah.edu
Statistician	Michael Schell, Ph.D Biostatistics and Bioinformatics Department Moffitt Cancer Center, FL Michael.schell@moffitt.org
Sponsor	Huntsman Cancer Institute
Coordinating Center	Huntsman Cancer Institute 2000 Circle of Hope Salt Lake City, UT 84112 HCI-RCO@utah.edu
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Commercial Agent	Cetuximab
Drug Manufacturer	Eli Lilly
Drug Manufacturer Protocol ID	

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DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol	24MAY2021	Not applicable
Protocol Amendment	02NOV2021	SAE Reporting Clarification/Inclusion Criteria
Protocol Amendment	28APR2022	Accrual number and inclusion criteria updates

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

_____

Name of Institution

ABREVIATIONS

Abbreviation	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AV	Atrioventricular
BCVA	Best-corrected distance visual acuity
BICR	Blinded Independent Central Review
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
CQ	Chloroquine

Abbreviation	Definition/Explanation
DILI	Drug-Induced Liver Injury
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NIH	National Institute of Health
PD	Pharmacodynamic(s)
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)

Abbreviation	Definition/Explanation
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RBC	Red blood cell
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SD	Stable disease
SD-OCT	Spectral-domain ocular coherence tomography
$T_{1/2}$	Terminal elimination half-life
TdP	Torsades de Pointes
T_{max}	Time of maximum observed concentration
ULN	The upper limit of normal
VF	Visual field
WBC	White blood cell

1 PROTOCOL SUMMARY

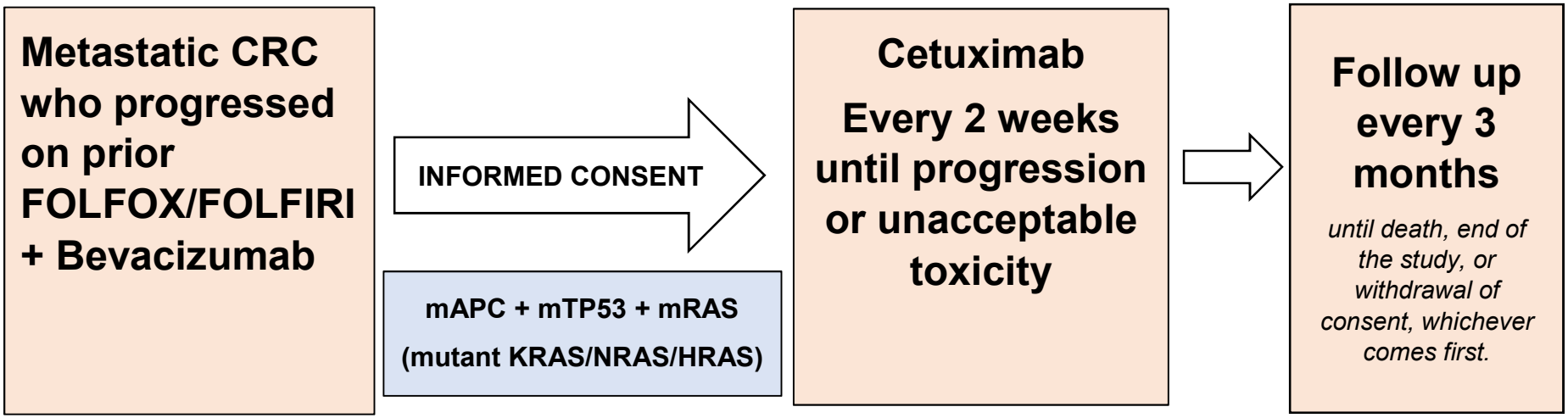
1.1 Synopsis

Title:	APK Mutant: A Single Arm Phase II study of Cetuximab in Third Line for Mutant APC, TP53 and RAS patients with Refractory Metastatic Colorectal Cancer (mCRC)
Protocol Short Title	APK Mutant
Study Description:	Single arm, open label study
Phase:	II
Objectives:	**Primary Objective:** To evaluate the progression free survival (PFS) among patients treated with cetuximab in APC, TP53 and RAS mutated refractory metastatic colorectal cancer. **Secondary Objectives:** To evaluate the overall survival (OS) among patients treated with cetuximab with APC, TP53 and RAS mutated refractory metastatic colorectal cancer. **Exploratory objective**: To correlate APC, TP53, RAS and BRAF status using ultrasensitive cell free DNA (cfDNA) duplex sequencing assay and tissue next generation sequencing to monitoring disease response in patients with metastatic CRC
Endpoints:	**Primary Endpoint:** The primary endpoint is progression free survival (PFS). PFS will be measured from the date of first dose of study drug until first documented radiographic evidence of disease progression by RECIST criteria 1.1, clinical progression per investigator judgement, start of new anti-cancer therapy, or death from any cause. **Secondary Endpoints:** The secondary endpoint is overall survival (OS). OS will be measured from the date of first dose of study drug until death from any cause. Patients who show a response to treatment (CR, PR, or SD) may continue treatment (with disease reassessment every 8 weeks) until disease progression or the occurrence of unacceptable toxicities.
Study Population:	**Key Inclusion Criteria** • Male or female subject aged ≥ 18 years.

	• Histologically confirmed metastatic colorectal adenocarcinoma with mutant APC, TP53 and RAS genes as determined by the local CLIA-certified laboratory are eligible. Patients with wild type RAS, APC or TP53 are ineligible.
	• Progression or unwanted toxicities on at least 2 prior lines of treatment including 5-Flourouracil, oxaliplatin and irinotecan based regimen.
	• Study participants must have measurable disease by RECIST 1.1 criteria by CT or MRI.
	• ECOG Performance Status ≤ 2.
	• Study participants with treated and/or stable brain metastases are allowed.
	• Study participants must have anticipated life expectancy > 3 months.
	• Adequate organ function as defined as:
	  ○ Hematologic:
	  ▪ Absolute neutrophil count (ANC) ≥ ≥1000/μL
	  ▪ Platelet count ≥ 100,000/mm3
	  ▪ Hemoglobin ≥ 9 g/dL
	  ○ Hepatic:
	  ▪ Serum Bilirubin ≤ 2 x ULN or ≤ 3 x ULN for subjects with Gilbert's syndrome.
	  ▪ Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times the upper limit of normal (ULN; or 5.0 times the ULN in the setting of liver metastases)
	  ○ Renal:
	  ▪ Serum creatinine ≤1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed)
	Key Exclusion Criteria:

	• Prior use of systemic anti-EGFR therapy including cetuximab or panitumumab is not allowed. Note: Prior use irinotecan, oxaliplatin, regorafenib or TAS-102 is allowed • Study participants with new or progressive brain metastases (active brain metastases) or leptomeningeal disease who need immediate CNS specific treatment during first cycle of treatment as determined by the treating physician. ○ Note: Brain metastases or cranial epidural disease adequately treated with radiotherapy and/or surgery and stable for at least 4 weeks before the first dose of study treatment will be allowed on trial. Subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the first dose of study treatment. • Known prior severe hypersensitivity attributed to compounds of chemical or biologic composition similar to those of cetuximab, or if the patient had red meat allergy/tick bite history (NCI CTCAE v5.0 Grade ≥ 3). • Live attenuated and inactive vaccinations within 4 weeks of the first dose of study treatment and while on trial is prohibited. COVID-19 vaccines are allowed.
Study Intervention:	Cetuximab 500 mg/m2 IV every 2 weeks infused over 120 minutes
Study Duration:	Approximately 24 months
Participant Duration:	Until RECIST 1.1 disease progression, clinical progression per investigator judgement, or intolerable toxicity whichever comes first

1.2 **Schema**


Metastatic CRC who progressed on prior FOLFOX/FOLFIRI + Bevacizumab
INFORMED CONSENT
mAPC + mTP53 + mRAS
(mutant KRAS/NRAS/HRAS)
Cetuximab
Every 2 weeks until progression or unacceptable toxicity
Follow up every 3 months
until death, end of the study, or withdrawal of consent, whichever comes first.

1.3 Schedule of Events

Protocol Activities	Screening[1]	On-Treatment Period: One Cycle= 14 days			Post Treatment Period		
		Cycle 1[2]	Cycle 2	Cycle 3+ [3]	EOT[4]	Safety Follow up[5]	Long Term Follow-Up
Day of Cycle (Visit Window)	(-28 days)	(± 3 days)	(±3 days)	(±3 days)	(+ 7 days)	(±7 days)	
Informed consent	x						
Demographics	x						
Medical History	x						
Cancer History[6]	x						
Eligibility criteria	x						
Registration[7]	x						
Clinical Assessments							
Vital signs[8]	x	X	X	X	X	X	
Physical examination[9]	x	X	X	X	X	X	
ECOG Performance status	x	X	X	X	X	X	
Adverse event collection	x	X	X	X	X	X	
Concomitant Medications	x	X	X	X	X	X	
Survival follow up[10]							X
Laboratory Studies							
Hematology[11]	X	X	X	X	X	X	

Chemistry panel[12]	X	X	X	X	X	X	
Magnesium level	X	X	X	X	X	X	
CEA[13]	X	X	X	X	X		
Serum pregnancy test[14]	X	X					
Disease Assessments							
Imaging (CT/MRI)[15]	X	Every 8 weeks from C1D1			X[16]		
RECIST 1.1 measurement[17]	X	Every 8 weeks from C1D1			X[17]		
Treatment Compliance							
Cetuximab		X	X	X			
Correlative Studies							
NGS[18]	X						
Blood CfDNA[19]		X at C1D1 and then every 8 weeks (see footnote)					

[1] Screening procedures must be completed ≤ 28 days prior to C1D1 unless noted otherwise.
[2] C1D1 procedures do not need to be repeated if screening procedures were performed ≤ 7 days of the start of treatment.
[3] Treatment will continue until progression or unacceptable toxicity.
[4] The end of treatment visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. All end of treatment procedures should be completed ≤ 7 days after the decision to discontinue treatment has been made
[5] All patients will have a safety follow-up visit 30 days (± 7 days) after last dose of study drug, unless the subject had an EOT visit conducted 30 days after discontinuation of treatment.
[6] History of the malignancy understudy will be collected at the screening visit with special attention to prior regimens (duration of therapy, best response on therapy, date of discontinuation, and reason for discontinuation), surgery, radiation therapy, and sequence.
[7] To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.
[8] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, weight, and body temperature. Height will be captured at screening only.

[9] If necessary to facilitate scheduling, the physical exam may occur one day prior to study treatment.
[10] Subjects will be contacted every 3 months (±14 days) after study treatment discontinuation until death, end of the study, or withdrawal of consent, whichever comes first.
[11] Hematology includes CBC with differential and platelets. Labs may be performed ≤ 3 days prior to a scheduled day one visit except for cycle one day one labs which may be completed ≤ 7 days prior to cycle one day one.
[12] Chemistry includes a Complete Metabolic Panel (Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen). Labs may be performed ≤ 3 days prior to a scheduled day one visit except for cycle one day one labs which may be completed ≤ 7 days prior to cycle one day one.
[13] CEA is the tumor marker that will be drawn on day one of each cycle.
[14] Pregnancy test (serum) must be obtained at screening ≤ 7 days prior to C1D1 for all women of childbearing potential and as clinically indicated while on treatment.
[15] Disease assessment will be repeated every 8 weeks (± 7 days) regardless of dose holds or delays. Subjects who discontinue treatment for reasons other than progression will continue to have disease assessments until documented clinical or radiographic progression or initiation of subsequent therapy.
[16] Scans will be completed per investigator discretion and do not need to be repeated if performed within 8 weeks of the EOT visit.
[17] Recist 1.1 Assessments will be done at each imaging assessment.
[18] Previously completed next generation sequencing data will be collected to confirm APC, TP53, and RAS mutational status. NGS will be performed as part of standard of care testing and does not need to be repeated during the screening period. NGS previously performed in any CLIA certified laboratory will be accepted.
[19] Whole blood will be collected on C1D1 prior to study therapy and then every 8 weeks (± 7 days) coinciding with the disease assessment. When samples are due to be collected on the same day as treatment administration, samples will be collected prior to study therapy.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To evaluate the progression free survival (PFS) among patients treated with cetuximab in APC, TP53 and RAS mutated refractory metastatic colorectal cancer.

Primary Endpoint: The primary endpoint is progression free survival (PFS). PFS will be measured from the date of first dose of study drug until first documented radiographic evidence of disease progression by RECIST criteria 1.1, clinical progression per investigator judgement, start of new anti-cancer therapy, or death from any cause.

2.2 Secondary Objectives

To evaluate the overall survival (OS) among patients treated with cetuximab in APC, TP53 and RAS mutated refractory metastatic colorectal cancer.

Secondary Endpoint: The secondary endpoint is overall survival (OS). OS will be measured from the date of first dose of study drug until death from any cause. Patients who show a response to treatment (CR, PR, or SD) may continue treatment (with disease reassessment every 8 weeks) until disease progression or the occurrence of unacceptable toxicities.

2.3 Exploratory Objectives

To correlate the plasma APC, TP53, RAS, and BRAF status with tissue testing using ultrasensitive cell free DNA (cfDNA) duplex sequencing assay for monitoring disease response in patients with metastatic CRC.

Exploratory Endpoint: The mutation status in the blood or serum is analyzed by duplex sequencing assay. This ultrasensitive assay quantitatively detects the variant allele fraction (VAF) of APC, TP53, RAS, and BRAF in plasma to monitor response to therapy. The tumor is analyzed by using CLIA certified next generation sequencing techniques.

3 BACKGROUND AND RATIONALE

3.1 Metastatic colorectal cancer and Epidermal Growth Factor Receptor Inhibitors

Colorectal cancer (CRC) is the second leading cause of cancer death in United States.[1] Metastatic CRC is usually fatal and treatment options are limited including chemotherapy, targeted therapy and immune therapy. Two well-characterized EGFR inhibitors (EGFRi; cetuximab, panitumumab) are FDA approved as first- and second-line targeted therapies for metastatic colorectal cancer (mCRC).[2-5] Despite approval, utilization has been modest, primarily because of drug restriction to the wild-type (WT) RAS subpopulation.[6] Early colorectal cancer clinical trial studies involving cetuximab/panitumumab, either as monotherapies or as combination therapies, reported that a statistically significant drug response was generally observed in WT KRAS patients—but not in mutant (MUT) KRAS patients. On the other hand, despite selection, about half of patients with a WT KRAS still fail

to respond to EGFRi treatments, [7,8] suggesting that additional genes, beyond KRAS, may negatively contribute to EGFRi response. Recently, mutations in NRAS and BRAF were reported to account for EGFRi therapy resistance in some WT KRAS colorectal cancers. More recently, left-sided colorectal cancers have been reported to be more favorably associated with response to cetuximab/panitumumab than right-sided tumors, as indicated by increased response rate (RR), better progression-free survival (PFS), and/ or overall survival (OS).[9-14] A molecular basis of the laterality of anti-EGFR sensitivity, however, is still poorly understood.

3.1.1 Cetuximab Sensitivity Score (CTX-S)

To model EGFRi sensitivity, a pre-specified cetuximab-sensitivity signature (CTX) score was developed and validated in two independent sets of CRC patient samples derived from clinical trials[15,16] and one set of in vitro cetuximab-treated CRC cell lines.[17] We then used it to stratify 468 tumors in association with concomitant somatic mutations. We found that out of 1321 sequenced cancer-associated genes, mutations in APC and TP53 were the only genes significantly and positively correlated with cetuximab sensitivity scores in all patients (n=468) and MSS patients (n=407) (adjusted FDR P<0.0001 for both genes) (Table 1).[18]

3.1.2 Rationale for selection of APC, TP53, RAS patient population

An integrated analysis–targeted gene sequencing for 1,321 cancer related genes, global gene expression, and microsatellite instability (MSI) analyses was performed across a large cohort of human colorectal cancers (n= 468). Among several mutated genes identified, striking pairwise, statistically significant, correlations were observed between APC, TP53, RAS, and BRAF that ultimately suggested a prognostic role for APC.[16]

Given the paucity of available clinical trial tissue samples with EGFRi exposure, we elected to use a cetuximab sensitivity (CTX-S) gene expression score as a surrogate for cetuximab response data in our colorectal cancer cohort, TCGA, and other published data. We found that the presence of MUT AP had a striking positive effect on the CTX-S scores of KRAS/NRAS–mutated (K/N)-tumors in Moffitt colorectal cancers. Note that because the great majority of RAS mutations in colorectal cancers are KRAS mutations (~40%) and the frequency of NRAS mutations is much lower (~5%), for simplicity, we used K* to represent both KRAS and NRAS mutations (K/N). Although WT RAS tumors (n = 264) had significantly higher CTX-S scores (P < 0.0001 for two-tailed Welch t test) than MUTRAS tumors (n=111) in which the mutant APK subpopulation was excluded, the APK triply mutated tumors (n= 91) had even higher scores (P < 0.0001).[18]

When restricted to Moffitt stage IV tumors (n = 110), a striking difference remained for mutated K* tumors between the APK* and non-APK* subpopulations. In the TCGA colorectal cancers, the mutant APK* tumors and WT RAS tumors had no significant difference in CTX-S scores, but both had significantly higher scores than other RAS-mutated tumors. These data suggest that some APK* patients (heretofore not treated) may be sensitive to CTX treatment.

Based on above data which suggest APC, TP53, RAS as potential biomarkers of cetuximab response, we propose current phase II study to evaluate efficacy of cetuximab in refractory mCRC.

3.2 Investigational Intervention

3.2.1 Cetuximab

Cetuximab is a chimeric human/mouse IgG1 monoclonal antibody that targets epidermal growth factor receptor (EGFR). It binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor– alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

Physical and Chemical Properties

Cetuximab is an epidermal growth factor receptor binding FAB. Cetuximab is composed of the Fv (variable; antigen-binding) regions of the 225 murine EGFr monoclonal antibody specific for the N-terminal portion of human EGFr with human IgG1 heavy and kappa light chain constant (framework) regions. Cetuximab is a clear colorless liquid, with the empirical formula $C_{6484}H_{10042}N_{1732}O_{2023}S_{36}$ and an approximate molecular weight of 152 kDa.

Pharmaceutical Properties and Formulation

Cetuximab is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP. Refer to the most recent version of the Investigator's Brochure for more information.

3.2.2 Pre-Clinical Experience

In vitro assays and in vivo animal studies have shown that ERBITUX inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

3.2.3 Dose Rationale

A pharmacokinetic (PK) study by Tabernero et al. suggested no major differences between cetuximab 250 mg/m2 every week and cetuximab 500 mg/m2 every 2 weeks. Follow up

clinical study in 2008 by Pfeiffer et.al also suggest Cetuximab 500 mg/m2 every 2 week regimen as safe, convenient, and well tolerated regimen in CRC.[19] In addition, a population pharmacokinetic (PK) modeling analyses compared the predicted exposures of cetuximab 500 mg every 2 weeks to observed cetuximab exposures in patients who received cetuximab 250 mg weekly.[20] Also, pooled analyses of overall response rates, progression-free survival, and overall survival from published literature in patients with CRC and Head and Neck cancer, and overall survival analyses using real-world data in patients with mCRC who received either the weekly cetuximab or every 2 week regimens.[21] In these exploratory analyses, the observed efficacy results were consistent across dosage regimens and supported the results of the population PK modeling analyses. Based on above studies, FDA recently approved a new dosage regimen of 500 mg/m2 as a 120-minute intravenous infusion every two weeks for cetuximab.[22]

3.2.4 Clinical Experience

The clinical safety of cetuximab is studied in number of prior phase III clinical trials in mCRC. The most common adverse events are included as below:

Acne-like Rash: The most common adverse event associated with cetuximab administration is acne-like rash. Acne-like rash usually occurs on the face, upper chest, and back, but occasionally extends to the extremities and is characterized by multiple follicular or pustular appearing lesions characterized histologically as a lymphocytic peri folliculitis or suppurative superficial folliculitis. The onset of rash is generally within the first 2 weeks of therapy.

A number of therapeutic interventions have been attempted, including oral and topical antibiotics, topical steroids, and rarely, oral steroids. The value of these measures is unknown since definitive clinical trials have not be performed. The etiology of the acne-like skin rash is believed to be the result of cetuximab binding to EGFR in the epidermis.

Nail Disorder: Nail disorders were reported in 6.4% of patients receiving cetuximab as a single agent. The nail disorder is characterized as paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers. The most commonly affected digits are the great toes and thumbs. According to investigators, the nail disorder persists for up to 3 months after discontinuation of cetuximab. Soaks in aluminum acetate (Burow's) solution BID-QID will prevent secondary infection. Symptom relief may be achieved with standard bandages or with the application of liquid bandages (cyanoacrylate preparations). Preliminary analysis in patients treated at usually doses (400 mg/m2 initial dose, followed by 250 mg/m2 weekly), revealed that the incidence of nail disorders is greater in patients who received more than 6 infusions (approximately 10%) compared to patients treated with 6 or less infusion of cetuximab (approximately 3%).

Allergic Reactions: The majority of the allergic/hypersensitivity reactions described have been grade 1 to 2 toxicities with less occurrences of grade 3-4. All reactions responded promptly to appropriate medical intervention.

Infusion Reaction: Infusion reactions are distinct from allergic or hypersensitivity reactions,

although some of the manifestation are overlapping. Infusion reactions generally develop during or shortly after the infusion. Mild infusion reactions (chills, fever, dyspnea) have been reported in 23% of patients receiving cetuximab as a single agent. Severe infusion reactions (airway obstruction [bronchospasm, stridor, hoarseness], urticaria, hypotension) were reported in 2% of patients receiving single agent cetuximab. Infusion reactions occur most often with the first dose.

Pulmonary Toxicity: Interstitial lung disease has been reported in less than 1% of patients who have received cetuximab for advanced colorectal cancer, and in one patient with head and neck cancer.

Cardiac Toxicity: Recent reports described the occurrence of cardiac dysfunction, chest pain, and/or cardiac ischemia/infarction. These events occurred in patients who were receiving cetuximab in addition to 5-FU-containing therapy. Cardiac ischemia/infarction and acute cardiomyopathy are known side effects of 5-fluorouracil-based chemotherapy. It is presently unclear if the addition of cetuximab may increase the risk of 5-FU-related cardiac events.

Other Toxicities: Other reported or potential toxicities associated with cetuximab include:

Skin—Pruritus (10%), alopecia

Gastrointestinal—Diarrhea (28%, 2% grade 3/4), nausea/vomiting (29%), stomatitis/mucositis (11%), anorexia, constipation

Metabolites—Hypomagnesemia (rarely grade 4 requiring aggressive IV repletion)

Pulmonary—Interstitial pneumonitis was reported in 3 of 633 (<0.5%) patients; one patient died as a consequence.

EENT—Conjunctivitis (7%)

Constitutional—Fatigue/malaise, asthenia, infection

Musculoskeletal—Back pain

Hematologic— Anemia, leukopenia

CNS—Headache (25%, 3% grade 3/4)

4 STUDY DESIGN

This is a prospective, multi-center, phase II study of up to 25 patients to evaluate the efficacy of the EGFR inhibitor, cetuximab in patients with mCRC harboring APC, TP53 and RAS mutations. The study will be conducted at Intermountain Healthcare and Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah.

4.1 Study Duration

The estimated duration of the study from start of screening to last participant completed the study and duration of participation is approximately 24 months

4.2 End of Study

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events.

The study will end when the last subject completes the last visit or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time. If at any time, the sponsor terminates the study any subjects receiving clinical benefit from the study intervention may roll over to an expanded access protocol to ensure continued access to the study medication.

5 STUDY POPULATION

Potential study participants must meet all inclusion criteria and no exclusion criteria to be deemed eligible for trial participation. To ensure subject safety, all subjects must be deemed eligible at the time of study registration and must continue to meet eligibility criteria up to cycle one day one dosing. This eligibility checklist is used to determine subject eligibility and will be filed with the enrolling investigator's signature in the subject research chart.

5.1 Inclusion Criteria

1. _____ Male or female subject aged ≥ 18 years.
2. _____ Histologically confirmed metastatic colorectal adenocarcinoma with mutant APC, TP53 and RAS genes as determined by the local CLIA-certified laboratory are eligible. All RAS mutations are allowed (KRAS, NRAS, HRAS). Patients with wild type RAS, APC or TP53 are ineligible.
3. _____ Progression or unwanted toxicities on at least 2 prior lines of treatment including 5-Flourouracil, oxaliplatin and irinotecan based regimen
4. _____ Study participants must have measurable disease by RECIST 1.1 criteria by CT or MRI.
5. _____ ECOG Performance Status ≤ 2.
6. _____ Study participants with treated and/or stable brain metastases are allowed
7. _____ Study participants must have anticipated life expectancy > 3 months
8. _____ Adequate organ function as defined as:

    - Hematologic:
        - Absolute neutrophil count (ANC) ≥ ≥1000/μL
        - Platelet count ≥ 100,000/mm3
        - Hemoglobin ≥ 9 g/dL
    - Hepatic:
        - Serum Bilirubin ≤ 2 x ULN or ≤ 3 x ULN for subjects with Gilbert's syndrome.
        - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times the upper limit of normal (ULN; or 5.0 times the ULN in the setting of liver metastases)

- Renal:
    - Serum creatinine ≤1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed)

9. _____ For female subjects: Because the teratogenicity of cetuximab is not known, the patient, if sexually active must have a negative serum pregnancy test or surgically sterile or using effective contraception (hormonal or barrier methods) or evidence of post-menopausal status. The post-menopausal status will be defined as having been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women < 50 years of age:
        - Amenorrheic for ≥ 12 months following cessation of exogenous hormonal treatments; and
        - Luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution; or
        - Underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥ 50 years of age:
        - Amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments; or
        - Had radiation-induced menopause with last menses >1 year ago; or
        - Had chemotherapy-induced menopause with last menses >1 year ago; or
        - Underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
10. _____ Female subjects of childbearing potential must have a negative pregnancy test within 7 days prior to enrollment and male subjects with a sexual partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 2 months after last study treatment administration.
11. _____ Male subjects must agree to use a condom during intercourse for the duration of study therapy and for at least 2 months after last study treatment administration.
12. _____ Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to any prior cancer therapy, unless considered clinically not significant by the treating investigator.
13. _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

1. _____ Prior use of systemic anti-EGFR therapy including cetuximab or panitumumab is not allowed but prior use irinotecan, oxaliplatin, regorafenib or TAS-102 is allowed
2. _____ Study participants with prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of the investigational regimen, as determined by the investigator
3. _____ Study participants with new or progressive brain metastases (active brain metastases) or leptomeningeal disease who need immediate CNS specific treatment during first cycle of treatment as determined by the treating physician.

   Note: Brain metastases or cranial epidural disease adequately treated with radiotherapy and/or surgery and stable for at least 4 weeks before the first dose of study treatment will be allowed on trial. Subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the first dose of study treatment.
4. _____ Current evidence of uncontrolled, significant intercurrent illness including, but not limited to, the following conditions:

   - The patient has clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high risk of uncontrolled arrhythmia or uncontrolled cardiac insufficiency.
   - The patient has uncontrolled or poorly-controlled hypertension (>180 mmHg systolic or > 130 mmHg diastolic.
   - Any other condition that would, in the Investigator's judgment, contraindicate the subject'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, [subjects may not receive the drug through a feeding tube], social/ psychological issues, etc.)

5. _____ Known HIV infection with a detectable viral load within 6 months of the anticipated start of treatment.
   Note: Subjects on effective antiretroviral therapy with an undetectable viral load within 6 months of the anticipated start of treatment are eligible for this trial.
6. _____ Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination, radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C.
   Note: Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
7. _____ Medical, psychiatric, cognitive, or other conditions that may compromise the subject's ability to understand the subject information, give informed consent, comply with the study protocol or complete the study.

8. _____ Known prior severe hypersensitivity attributed to compounds of chemical or biologic composition similar to those of cetuximab, or if the patient had red meat allergy/tick bite history (NCI CTCAE v5.0 Grade ≥ 3).
9. _____ Live attenuated and inactive vaccinations within 4 weeks of the first dose of study treatment and while on trial is prohibited. COVID-19 vaccines are allowed
10. _____ The patient is pregnant or breast-feeding.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

5.3 Registration

Subjects must meet all of the eligibility requirements before registration. Study-related screening procedures can only begin once the subject has signed the consent form. Subjects must not begin protocol treatment prior to registration.

Treatment should start as soon as logistically possible after registration.

To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

For sites outside of Huntsman Cancer Institute, submit registration forms to MultisiteRegistrations@hci.utah.edu

5.4 Contraception

Due to the known abortifacient and teratogenic effects of Cetuximab, a form of highly effective contraception is required for the duration of study therapy. Female subjects of childbearing potential must use a form of highly effective contraception from the start of study therapy until 2 months after the last dose of study therapy. Male subjects with a partner of childbearing potential must agree to use a method of highly effective contraception from the start of study therapy until 2 months after the last dose of study therapy.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable.

- Spermicide with a compatible barrier method (i.e. diaphragm, sponge, or male or female condoms).
- Abstinence from heterosexual intercourse.

Due to concern for drug transfer through seminal fluid, male subjects must agree to use a condom during heterosexual and homosexual intercourse from the start of study therapy until 2 months after the last dose of study therapy.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet subject eligibility criteria. These subjects will not be entered into the study or begin study intervention. However, minimal information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes, but may not be limited to, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) experienced during screening, but prior to being deemed ineligible.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at the Investigator's discretion.

5.6 Strategies for Recruitment

Investigators will identify potential subjects in the setting of their outpatient clinics, in tumor boards and referrals from other medical oncologists. All potentially eligible patients irrespective of their age, gender, and race will be screened. This study will be posted on clinicaltrials.gov.

5.6.1 Number of Subjects

Up to 25 patients to get 21 evaluable patients for efficacy as defined in Section 9.2.2.

5.6.2 Number of Study Sites

This is a multi-center study conducted at Intermountain Healthcare and Huntsman Cancer Institute.

6 STUDY INTERVENTION

6.1 Administration Schedule

The treatment plan includes single agent cetuximab. Cetuximab will be administered every 2 weeks (14 days). The initial dose of 500 mg/m2 is to be administered by IV infusion over 120 minutes. Each cycle will be defined as 14 days of treatment.

Sites should make every effort to target infusion timing to be as close to 120 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 120 minutes: -5 min / +10 min).

In an effort to prevent a hypersensitivity reaction, all patients should be premedicated with

diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given approximately 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior tosubsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

Patients should be closely monitored for treatment-related adverse events, especially hypersensitivity reactions, during the infusion and the post-infusion observation hour. For the duration that patients are on protocol therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

6.2 Cetuximab

6.2.1 Investigational Product Supplies

The Investigational Drug Services Pharmacy at Huntsman Cancer Institute and Intermountain Healthcare Principal Investigator will ensure appropriately trained and delegated personnel will receive, inventory, and stored all investigational products per applicable laws and regulations.

6.2.2 Preparation and Dispensing

The investigator or qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment will prepare, handle and dispense all investigational supplies. Appropriate records will be kept to accurately show all dispensing activates and Investigational Product (IP) will be supplied only to subjects deem eligible for study therapy. IP may not be dispensed to subjects who have not been enrolled in the trial.

Drug preparation: The calculated amount of cetuximab should be withdrawn from the appropriate number of vials and injected into an empty sterile container (glass, PVC or non-PVC plastic) for IV infusion. Cetuximab should not be mixed with other drugs or diluted with infusion solutions. Do not shake. Cetuximab should be administered through a 0.22 micrometer in-line filter. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE. Cetuximab can be administered via infusion pump or syringe pump but must not be administered as an IV push or bolus. Cetuximab should be piggybacked to the patient's infusion line. Prime the infusion line with cetuximab before starting the infusion. Use 0.9% saline solution to flush the line at the end of the infusion. In this study cetuximab will be administered at dose 500 mg/m2 as an IV infusion over 120 minutes the initial dose followed by 120 minutes subsequent doses.

Drug dosing guidelines: The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose. It is not necessary to change the dose of chemotherapy or cetuximab administered unless the calculated dose changes by ≥10%.

Drug Disposal: The unused portions of injectable chemotherapeutic agents supplied as single-dose preparations will be discarded within eight hours of vial entry to minimize the risk of bacterial contamination.

6.2.3 Accountability and Compliance

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

Information pertaining to study drug compliance (i.e., date time, and dose) will be recorded in the corresponding electronic case report form (eCRF) by the study team.

Any reason for non-compliance will be documented in the subject's research chart and the corresponding eCRF. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with study visits or study drug.

All doses of Cetuximab will be administered at the investigational site by qualified medical staff. The start and stop times of the infusion, along with the total volume administered, will be recorded in the subjects' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in the rate of infusion will be recorded in the subject's medical records. Any reasons that a dose other than the protocol-specified dose, rate, or dosing schedule was administered should be documented in the subject's research chart.

Depending on the patient's BSA, 7-9 vials for bi-weekly doses will be needed. A suggested initial shipment is 20 vials. Will allow 5-7 business days for shipment of drug from receipt of the request.

All products will be shipped via Federal Express in a temperature-controlled container. Shipments will be made on Monday through Thursday for delivery Tuesday through Friday. There will be no weekend, holiday or Monday delivery of drugs. The cetuximab supplies are study-specific but not patient-specific. Cetuximab ordered may be used for multiple patients on this study.

Inside each shipping container, a disposable electronic unit (TagAlert) to ensure the product has remained at the appropriate temperature during shipping may be included. This unit may be attached to an information card. The LCD display will show "OK" (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarms have been triggered).

6.3 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations (Section 6.5). Doses of Cetuximab that were not administered due to toxicity will not be replaced within the same cycle. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on the dose modifications recommendations. If a toxicity-related dose delay lasts for > 28 days, treatment will be discontinued permanently and the subject should be removed from study treatment. If a subject requires a dose hold for > 28 days for a non-treatment related adverse event or situation (i.e. radiation therapy) the subject may continue on study only after approval and discussion with the Principal Investigator and Medical Monitor.

6.4 Dose Reductions

Following dosing interruption due to treatment-related toxicity, the study drug may need to be resumed at a reduced dose as per the dose modification recommendations. Dose reduction should proceed by decreasing the administered dose by one dose level per Table 1.

Once the study treatment has been reduced for a given patient, all subsequent cycles will be administered at that dose level. Intra-patient dose re-escalation is not allowed except as described in the toxicity management guidelines, Section 6.5

Table 1: Cetuximab Reduction Levels

Dose Level	Cetuximab
Dose Level 0	500 mg/m2
Dose Level -1	400 mg/m2
Dose Level -2	300 mg/m2
Dose Level -3	250 mg/m2

6.5 Dose Modifications Guidelines

Subjects experiencing adverse events attributed to study drug may undergo dose modifications for toxicity management. Dose modification guidelines are provided below for adverse events considered to be related to study medication. If either medication requires reduction below Dose Level -3 for toxicity management, study therapy will be discontinued This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

Hematological toxicities:

- No cetuximab dose modifications will be made for hematologic toxicity.

Gastrointestinal toxicities:

- No cetuximab dose modifications will be made for diarrhea, mucositis, nausea, or vomiting.

Pulmonary Toxicity

- For grade 2 or worsening pulmonary symptoms unrelated to underlying cancer, cetuximab therapy should be stopped and symptoms investigated. Cetuximab therapy may resume when symptoms resolve to ≤ grade 1.
- For ≥ grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates, skip cetuximab until interstitial lung disease is ruled out. Discontinue all protocol therapy if interstitial lung disease is confirmed.

Hypomagnesemia

- Hypomagnesemia has been seen with cetuximab. Should hypomagnesemia occur, magnesium supplementation should be provided. No dose adjustment is required; however, continue careful monitoring.

Cutaneous Toxicity

- Acne is the most common cutaneous toxicity noted with cetuximab. While there is no clear evidence of benefit, over-the-counter or prescription acne medications designed to treat the acne-like rash may be used for patients who experience the acne-like rash associated with EGFR inhibitors. The investigator could also consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended

Table 2: Cetuximab Dose Delays Due to Cutaneous Toxicity

	Cetuximab	**Outcome**	**Cetuximab dose modification**
Grade 3 Rash			
1st occurrence	Skip infusion 1-2 weeks	If improvement	Continue 500mg/m2
		If no improvement	Discontinue cetuximab
2nd occurrence	Skip infusion 1-2 weeks	If improvement	Reduce to 400mg/m2
		If no improvement	Discontinue cetuximab
3rd occurrence	Skip infusion 1-2 weeks	If improvement	Reduce to 300mg/m2
		If no improvement	Discontinue cetuximab
4th occurrence	Skip infusion 1-2 weeks	If improvement	Reduce to 250 mg/m2
		If no improvement	Discontinue cetuximab
5th occurrence	Discontinue cetuximab		
Grade 4 Rash			
	Discontinue cetuximab		

There will be no dose level reductions below a biweekly dose of 250 mg/m^2 for cetuximab. Cetuximab dose reductions are permanent, that is, there will not be any re-escalation of dose. Discontinue cetuximab if doses are skipped for more than 4 consecutive weeks.

Nail disorders

- For grade 3 nail disorders, cetuximab may be skipped for up to 3 weeks and if no improvement, reduce dose to 400 mg/m^2 for 1st occurrence, 300 mg/m^2 for 2nd

occurrence, 250 mg/m^2 for 3rd occurrence and discontinue cetuximab if there is no improvement after 3 weeks.

Hypersensitivity and infusion reactions

- Note that the NCI CTCAE defines these reactions differently: “Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.” See the “Syndromes” section of the CTCAE version 5.0 for a complete list of signs and symptoms of “Cytokine release syndrome/acute infusion reaction;” and see the “Allergy/Immunology” section for a description of hypersensitivity.
- Dose modifications for hypersensitivity reactions to Cetuximab:
    - For grade 1 hypersensitivity reactions (transient rash, drug fever < 38°C): Decrease the infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
    - For grade 2 hypersensitivity reactions (urticaria, drug fever ≥ 38°C and/or asymptomatic bronchospasm): Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to institutional policy.
    - For grade 3 or grade 4 hypersensitivity reactions: Stop the infusion. Discontinue all protocol treatment and notify the Principal investigator or Medical Monitor.

Infusion reactions

- For grade 1 or 2 cetuximab infusion reactions: Stop the infusion until symptoms resolve, then restart cetuximab at a 50% lower rate of infusion. All subsequent doses should be administered at the lower infusion rate.
- For ≥ grade 3 cetuximab infusion reactions: Discontinue cetuximab permanently.

Other non-hematologic toxicities

- For all other ≥ grade 3 non-hematologic toxicities not described above, hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ grade 1 or baseline within 4 weeks, treatment may be resumed with cetuximab at one lower dose level.

Dose Modification for Obese Patients

- There is no clearly documented adverse impact of treatment of obese patients when

dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the patient's actual weight without any modification. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.

6.6 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study. Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded. GCSFs may be used for the management of treatment-emergent neutropenia at the investigator's discretion and according to the current American Society of Clinical Oncology (ASCO) guidelines. The use of hematopoietic growth factors is at the discretion of the treating physician and according to local institutional standards. For example: study participants who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

6.7 Concomitant Medications and Therapies

All administered concomitant medications (including herbal supplements) and non-medicinal therapies (including transfusions) used 28 days prior to Cycle One Day One, and until 30 days after the last dose of study therapy will be recorded in the subject's research chart and corresponding eCRF. All medications, including those used to treat adverse events, chronic conditions or diseases, or as supportive therapy should be documented in the eCRF.

Allowed Therapy

Loperamide: For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with cetuximab, patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. The maximum daily dose of loperamide is 16 mg/day. Patients should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

Antiemetics: Patients should receive antiemetics before cetuximab according to the treating physician and institutional guidelines.

Ancillary Therapy

Hormonal/Other Chemotherapeutic Agents: Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

6.7.1 Radiotherapy

If deemed necessary by the treating investigator, palliative radiation therapy for a single site of bone or brain metastasis is allowed. The radiation field must not affect any of the target lesions designated for disease assessment. Protocol treatment will be held during radiation therapy and will be re-started 2 weeks following the conclusion of therapy.

6.7.2 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Subjects are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy;
- Other investigational agents;
- Radiation therapy (with the exception noted above);
- Any live-attenuated vaccine therapies for the prevention of infectious disease (e.g. MMR, or rotavirus); COVID-19 vaccines are allowed.

If a subject requires treatment with one or more of the listed prohibited medications, the subject may need to be taken off study therapy. Each case will be considered and if possible, the investigator should discuss with the DSMC and Medical Monitor prior to initiating prohibited therapy.

6.8 Duration of Therapy

Subjects will receive study treatment until treatment discontinuation criteria is met. Upon meeting treatment discontinuation criteria, subjects will continue on the study in follow-up until study discontinuation criteria are met.

6.8.1 Criteria for the Discontinuation of Treatment (“Off Treatment”)

Subjects may withdraw from treatment or the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or

procedures. In addition to the drug-specific discontinuation criteria listed in section 6, the following will result in treatment discontinuation:

- The subject requests to discontinue the study treatment and/or study procedures;
- Clinical deterioration that, in the opinion of the investigator, increases the risk to the subject;
- Confirmed disease progression based on radiographic progression per RECIST 1.1;
- Adverse events or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the investigator;
- Pregnancy;
- Patients with grade 4 hypertension must not receive further treatment with cetuximab.

6.8.2 Criteria for the Discontinuation of Study ("Off Study")

Subjects will be taken off study for the following:

- Completed study follow-up period;
- Participant or legally authorized representative requests to be fully withdrawn from the study;
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being;
- The subject is lost to follow-up;
- Screen failure;
- Death.

6.8.3 Withdrawal of consent

Subjects are free to withdraw from the study at any time without prejudice to further treatment. Subjects who withdraw consent for further participation in the study will not receive any further study medications or further study observation.

If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow-up (e.g., survival contact telephone calls). Survival status may be obtained from public records for subjects who have withdrawn from any further follow-up contact.

6.8.4 Long Term Follow-Up

Upon discontinuation of study therapy, subjects will be followed for survival and the initiation of subsequent anticancer therapy from the date of study therapy initiation until death, end of the study, or subject withdrawal of consent, whichever comes first. Subjects or their legally

authorized representatives will be contacted every three months (±14 days) from end of study treatment until death, end of the study, or subject withdrawal of consent, whichever comes first. Survival and subsequent treatment status may be collected by public records, medical records, or by contacting the subject or their legally authorized representative by phone. All efforts should be made to contact the subject at these time points. Refer below for Lost to Follow-Up guidelines.

6.8.5 Lost to Follow-Up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the subject's status at that time. Subjects who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and evaluations should resume according to the protocol.

When a subject is lost to follow-up, site personnel should check hospital records, the subjects' current physician, and a publicly available death registry to obtain a current survival status.

In the event that the subject has actively withdrawn consent, the survival status of the subject can be obtained by site personnel from publicly available death.

7 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 General Assessments

7.1.1 Participant Consent

Before the initiation of any study procedures, all potential subjects or their legal representative must be fully informed of the risks and potential benefits of trial participation and demonstrate understanding. An informed consent document must be signed and dated by the participant or their legal representative indicating that they understand the risks and consent to participation and treatment on the study. The Principal Investigator or their appropriately trained and delegated study personnel conducting the informed consent discussion must also sign and date the document. A copy of the signed document should be provided to the subject.

Procedures, laboratory tests, or imaging performed as part of the standard of care prior to subject consent may contribute to the assessment of eligibility and/or screening procedures if performed during the screening period.

7.1.2 Medical History

The investigator or appropriately trained and delegated study personnel will collect medical history to the extent that supports the assessment of eligibility. The medical history will include any active conditions and any conditions deemed to be clinically significant by the treating investigator. The use of symptom terms should be discouraged; if possible, terms describing the principal condition or syndrome should be used.

When collecting medical history specific attention should be given to:

- Prior history of cancer, family history of cancer
- History of Coronary Artery Disease
- Alcohol history (never used alcohol, current alcohol user, former alcohol user)
- Smoking history (never smoked, current smoker, former smoker)
- Pack years (average number of packs per day and number of years smoked)
- Current employment status (employed, retired, student, unknown, other)
- Insurance status (private insurance, Medicare, Medicaid, VA, military, not insured, self-pay, unknown, other)

7.1.3 Cancer History

The oncologic history of the malignancy understudy will be collected at the screening visit and will include prior regimens (duration of therapy, the best response on therapy, date of discontinuation, and reason for discontinuation), surgery, radiation therapy, and sequence. The details of genomic sequencing, site of metastases will be collected.

7.1.4 Concomitant Medications

All medications currently being used by a study participant, regularly or as needed, must be reviewed and documented by the investigator or qualified designee. Specific attention should be given to medications with a protocol required washout as described in the exclusion criteria and any medication taken 28 days prior to cycle one day one. Refer to Section 6.7.2 for prohibited medications.

During protocol therapy, any medications taken by the patient or used to treat an adverse event will be documented in the subject's research chart and the corresponding eCRF. If a new anticancer therapy is initiated during study follow-up, the new therapy should also be recorded in the subject's research chart and corresponding eCRF.

7.1.5 Tumor Mutation Testing

It is required that all subjects have histological confirmation and documentation of APC, TP53, RAS mutation through local laboratory testing. The mutational status must be confirmed by a Clinical Laboratory Improvement Amendments (CLIA) approved test using either tumor tissue or ctDNA done as part of standard of care testing. Additionally as part of exploratory aim, the blood based cell free DNA assay to test for APC, TP53, KRAS,NRAS, HRAS, BRAF will be assessed every 8 weeks coinciding with CT imaging. The cell free DNA assay is performed using

ultrasensitive duplex sequencing assay at Intermountain Precision Genomics. The duplex sequencing results have a mean duplex depth >22,000x per replicate; and peak duplex depth >35,000x per replicate.

7.2 Safety Assessments

7.2.1 Physical Examinations and Vital Signs

Subjects will have physical examinations to include major body systems, vital signs (blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature), assessment of ECOG performance status (see Appendix 1), weight, and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary to facilitate scheduling, the physical exam may occur one day before study treatment.

7.2.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, dose modification guidelines in the Dose Modification Section will be followed.

7.2.3 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Study Calendar and when clinically indicated. Laboratory tests may be performed up to 3 days before the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center. When applicable, all safety laboratory assessments must be reviewed by the treating investigator before study drug administration. When applicable, results from the pregnancy test must also be available for review before dosing.

Table 3 : Laboratory Assessments

Laboratory Assessments	
Complete Blood Count with Platelet Count and Differential	• White Blood Cell Count • Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes

Chemistry	• Complete Metabolic Panel
	  ○ Sodium
	  ○ Potassium
	  ○ Chloride
	  ○ Carbon Dioxide
	  ○ Alkaline Phosphatase
	  ○ Aspartate Aminotransferase
	  ○ Alanine Aminotransferase
	  ○ Urea Nitrogen

	○ Glucose ○ Creatinine ○ Calcium ○ Protein ○ Albumin ○ Bilirubin • Magnesium level
Pregnancy	• Beta-hCG Qualitative Serum
Tumor Marker	• CEA
Bloodmarker	• CfDNA

7.3 Efficacy Assessments

7.3.1 Disease Assessment

Disease assessments must include all known or suspected sites of disease; therefore, the decision for body areas to be scanned will depend on the extent of disease. The minimum recommended body areas to be scanned is chest, abdomen, and pelvis. Response will be defined by RECIST 1.1 (Appendix 3).

Disease assessments will be evaluated radiologically and conducted at baseline (within 28 days before the first dose of study treatment) and then every 8 weeks thereafter regardless of dose holds or delays. Disease assessments will continue until disease progression. Subjects who discontinue treatment for reasons other than progression will continue to have disease assessments until documented clinical or radiographic progression or initiation of subsequent therapy. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (e.g. symptomatic deterioration) or when clinically indicated. The schedule of tumor assessments should be fixed according to the calendar, starting with cycle one day one, regardless of treatment delays or interruptions due to toxicity.

Brain CT or MRI scans are required at baseline for all subjects with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Consistent imaging modality should be used for all disease assessments.

7.3.1.1 *Photography of Cutaneous Lesions*

Cutaneous lesions not evaluable by CT or MRI will be documented by color digital photography, including a ruler to estimate lesion size. Photographs must be taken in a manner that protects subject identity and confidentiality (e.g. covering eyes or defining marks or characteristics). Cutaneous lesions may be considered target lesions if they meet RECIST v1.1 criteria, otherwise they may be considered non-target lesions. Photographs of cutaneous lesions will be taken at screening and on the same day as a tumor assessment visit, or at the first clinic visit following each tumor assessment

7.4 Correlative Studies

To support exploratory objectives and correlative studies, blood samples will be collected at the time points indicated on the Schedule of Events. Any blood remaining after completion of the indicated testing will be stored for future unspecified research. With the participant's approval and as approved by the Institutional Review Board (IRB), de-identified biological samples will be stored at Huntsman Cancer Institute's and Intermountain Healthcare Biorepository. These samples could be used to research the causes of cancer, its complications, and other conditions for which individuals with cancer are at increased risk, and to improve treatment.

At the time of consent, subjects will be given the opportunity to opt-out of the use of their samples for future research. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, the withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

7.4.1 Blood Samples

A blood sample will be obtained from patients to perform duplex DNA sequencing for APC, TP53, KRAS, BRAF, HRAS, and NRAS mutations. Up to 10 mLs of blood will be collected at the time-points indicated on the Schedule of Events and processed to cfDNA. These samples will be used to identify predictive biomarkers for response and resistance.

7.5 Remote Visits/Telehealth

Some study visits and/or procedures may be conducted remotely in the following circumstances:

- Telehealth visits do not present an increased risk to the participant.
- All necessary data for the trial can be collected.
- Procedures do not include research related imaging, lab samples, and/or pathology which should be conducted in person.

Note: The method of telehealth should be documented in the participants' charts.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse events

21 CRF 312.32, ICH GCP, and OHRP define an adverse event as any untoward medical occurrence whether or not considered treatment-related. This definition extends to the worsening of any preexisting condition or symptom. All adverse events experienced during trial participation should be documented in the subject's research chart and corresponding eCRF

Laboratory abnormalities should not be listed as adverse events unless deemed clinically significant by the investigator or qualified designee. An abnormal test result or findings should not be recorded as an adverse event unless the following conditions are met:

- Associated with clinical symptoms; and/or
- Requires intervention (medical, surgical, or additional diagnostic testing); and/or
- Results in a change in study drug dosing; and/or
- Deemed by the investigator or qualified designee to be an adverse event.

8.1.2 Serious Adverse Events

A serious adverse event is defined as any untoward event that is:

- Fatal;
- Life-threatening;
- Results in persistent or significant disability/incapacity;
- Medically significant;
- Causes a congenital abnormality or birth defect;
- Requires or prolongs inpatient hospitalization.

Investigator judgment must be used to assess an event as medically significant. The event may not be life-threatening or cause disability but may jeopardize the subject and require intervention to prevent the other SAE outcomes.

The following situations should not be reported as an SAE:

- Hospital admission not associated with a precipitating AE such as:
    - Treatment for a preexisting condition not associated with a new AE or the worsening of a preexisting condition;
    - Admission for social or administrative reasons;
    - Optional admission or elective surgery;
    - Observation;
    - Preplanned treatments or surgical procedures as noted at baseline;
    - Admission for the administration of blood products.

8.2 Adverse Event Reporting

The investigator and qualified designees are responsible for the detection, documentation, reporting, and follow-up of all adverse events experienced by subjects during trial participation. AEs and SAEs will be recorded from the initiation of study therapy until 30 days after last dose of study therapy or until new anti-cancer therapy is started. The following information will be required for each adverse event:

- Event severity as graded by the CTCAE v.5;
- The causality assessment to study medication per the below definitions;

- Expectedness
- Event duration;
- Any action taken to treat or manage the event;
- Event outcome.

8.2.1 Severity Assessment

The severity of adverse events should be assessed by CTCAE v.5. If an event is not listed in CTCAE v.5 then the assessment of severity should follow the general guidelines listed in table 3.

Table 4 : Severity Assessment

Grade	Severity Description
1	Mild event that generally does not require intervention.
2	Moderate event that may require intervention.
3	Severe event that requires intervention.
4	Life-threatening event that requires urgent intervention.
5	Death.

Events meeting grade 4 or 5 severity description should be reported promptly as SAEs unless otherwise indicated in Section 8.1.1

8.2.2 Causality Assessment

The Investigator should assess the causality or relationship of AEs and SAEs to study therapy. The Investigator should consider if there is evidence that the investigational product caused the event taking into consideration timing, organ system affected, type of event, and possible alternative etiologies. The relationship of the AE to study treatment will be reported as listed below. These categories will be defined as follows:

- Definitely related – a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to the withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probably related – a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly related – a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely related –a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Not related – there is no evidence of a causal relationship between the study drug and the event and in which other drugs, chemicals or underlying disease explain the event.

Adverse events reported as definitely, probably, and possible, related to study therapy will be reported as related. In cases when the Investigator is unsure of the causality of an AE, the event will be considered related to study therapy unless deemed otherwise by the DSMC.

8.2.3 Expectedness

The Investigator will be responsible for determining whether or not an adverse event was expected or unexpected. Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI) or current Investigator Brochure (IB). Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

8.2.4 Action Taken and Outcome

Start and stop dates will be required for all adverse events and serious adverse events. The action taken in response to the event should also be recorded in the subject's research chart and corresponding eCRF. Event action terms include none, medication administered, non-drug therapy administered, surgery, hospitalization, or other with the option to specify. If a new medication is added the medication should also be added to the concomitant medications log.

All adverse events should be followed until stabilization or resolution. Event outcomes may be classified as resolved, resolved with sequelae, ongoing, or death.

8.2.5 Reporting Serious Adverse Events

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported on the MedWatch 3500A form and submitted to compliance@hci.utah.edu. The HCI Clinical Site Monitor will, in turn, submit the MedWatch form to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

The HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office (RCO). The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety updates, including external safety reports, manufacturer's reports, and updates to the investigator's brochure.

8.2.5.1 *MedWatch 3500A Reporting Guidelines*

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of the event (i.e., expected or unexpected event).

Follow-Up Information

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 7 days of knowledge of event resolution. Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as a follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

8.2.6 FDA Notifications

This study is IND exempted.

8.2.7 IRB Notification

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

8.2.8 Drug Manufacturer Notifications

- All serious adverse events regardless of relationship to study drug must be reported to Eli Lilly.
- SAE reports should be documented on a MedWatch form and can be faxed or emailed the local safety representative using the following information:
    - Local fax number: 866-644-1697
    - Local telephone number: 317-453-3402
    - Email: mailindata_gsmtindy@lilly.com

- Investigator and Institution agree:
    - To provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly.
    - To notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;
    - To notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any “serious” and “unexpected” adverse event experienced by a patient participating in the Study and receiving Study Drug that is possibly related, based on Investigator’s assessment, to the Study Drug.
        - For purposes of this requirement, “serious” means:
            - (1) death;
            - (2) in-patient hospitalization or prolonged hospitalization;
            - (3) life-threatening;
            - (4) persistent or significant disability or incapacity;
            - (5) congenital anomaly or birth defect;
            - or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes and “unexpected” means an adverse drug event that is not consistent with applicable product information in the current labeling for the Study Drug.
            - Serious adverse events should be reported to Lilly using a Medwatch form to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an

adverse event in the Study that is possibly associated with the Study Drug

8.3 Special Situations

8.3.1 Pregnancy or Breastfeeding

Pregnancy and breastfeeding exposure should be tracked from the start of study therapy until at least 5 half-lives after the last dose of study drug.

Although pregnancy is not considered an adverse event, any exposure to the investigational products during pregnancy or breastfeeding must be reported promptly. Exposure may occur by a woman actively receiving study therapy or the partner of a male subject actively receiving study therapy becomes pregnant. Any possible pregnancy or breastfeeding exposure during study therapy and up to 2 months after the last dose of study therapy or up to the start of subsequent anticancer therapy (whichever happens first) must be reported within one business day of awareness regardless of the occurrence of an SAE. Should a woman on study therapy become pregnant, she should immediately discontinue study treatment.

Women exposed to IP during pregnancy or while breastfeeding will be followed for pregnancy outcome and neonate health. Pregnancy outcomes may meet criteria as an SAE if ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly occurs. Congenital anomalies that occur in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death should be reported as an SAE. Any neonatal deaths that occur up to 30 days after birth or breastfeeding exposure should be reported as an SAE. Further follow-up on birth outcomes and neonate health will be handled on a case-by-case base.

8.3.2 Hy's Law Cases

It is important to identify possible cases of Drug-Induced Liver Injury (DILI) early. Total bilirubin, AST, and ALT should be regularly monitored for elevations indicative of liver damage. Subjects who experience a transaminase elevation above three times the ULN should be monitored frequently to determine if the elevation is transient. Transient elevations are an indication of adaption and these subjects may be identified as "adaptors." However, should a transaminase elevation be followed by total bilirubin (TBili) increase, a DILI could be occurring. Any laboratory abnormalities meeting the following criteria should be reported within 24 hours of awareness:

- AST or ALT elevation > 3 x ULN; and
- Total bilirubin > 2 x ULN; and
- Absence of cholestasis; and
- No alternative explanation for the elevations (e.g., impaired glucuronidation capacity caused by genetic [Gilbert syndrome]; viral hepatitis A, B, or C, preexisting or acute liver disease; or another drug capable of causing the observed injury).

Investigators should conduct reasonable investigations to rule out other possible etiologies. Investigators should take into consideration the subject's use of ethanol, acetaminophen,

recreational drugs, herbal supplements, and medical history. A potential Hy's Law case will not be considered a confirmed case until all results and considerations have excluded alternative etiologies.

Possible cases of DILI will be promptly reported to the FDA prior to full work up to rule out other etiologies. Reporting should be completed on a MedWatch 3500A form and should include all available information, including the likelihood that the drug caused the event. Subjects should be closely followed until the resolution of the event.

Subjects who experience possible DILI should be managed per the Dose Modification Guidelines.

8.4 **Data Safety Monitoring Committee**

A Data Safety Monitoring Committee (DSMC) at HCI is charged with ensuring the risk/benefit balance for subjects undergoing study therapy. The purpose of the DSMC is to ensure subject safety and make recommendations for study conduct to ensure subject safety and data integrity. The DSMC is chaired by a medical oncologist and may include, but is not limited to, representatives from medical oncology, oncological sciences, biostatistics, and pharmacy.

The roles and responsibilities of the DSMC are described in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, and approving cohort/dose escalations. Amendments that increase risk, increase treatment exposure, or impact study objectives will also be reviewed by the DSMC. If the DSMC and/or the PI have concerns about unexpected safety issues or AE trends, the study may be stopped and an unplanned safety data analysis may be conducted. Enrollment will not resume until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All trials will be assigned an oncologist member of the DSMC to serve as a medical monitor. In rare cases, an external medical monitor may be assigned. The Medical Monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the RP2D is defined. Approval from the Medical Monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in subjects treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each trial is assigned a research compliance officer who will be responsible for monitoring the trial and reporting to the DSMC. The assessed risk level of the trial will determine the frequency with which monitoring occurs. The Research Compliance Officer monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g., stopping rules), deviations, and any other pertinent information for the full DSMC membership at the regularly scheduled meetings.

Audits will be conducted for all trials one year after enrollment begins and annually thereafter. Audits may be conducted more frequently as requested by the DSMC, Institutional Review Board (IRB), Protocol Review and Monitoring Committee (PRMC), Research Compliance Office management, or the Principal Investigator.

DSMC oversite will be tailored to the assessed risk level of the trial. Trials are categorized amongst three risk levels: high, moderate, and low.

This trial has been classified as high risk and therefore will be monitored by RCO and reviewed by DSMC after the first subject is enrolled and then quarterly thereafter.

9 STATISTICAL CONSIDERATIONS

9.1 Sample size determination

Assuming a parametric exponential survival model, with a minimum 12-month follow-up and a 10% significance level (1-sided), 21 patients will achieve an 90% power for PFS analysis, assuming a null hypothesis median survival of 1.7 months and an alternative hypothesis median survival of 4 months. The null hypothesis is based on the literature for median progression free survival noted in multiple randomized phase III trials who received no additional therapy. The sample size estimation for this and alternative designs are summarized in the following Table 4. (see the line below shaded in Table 4).

Table 5: Statistical Plan

Numeric Results

Test Based on Theta-hat with Fixed Running Time t0 and Without Replacement Sampling.

H0: Theta = Theta0. Ha: Theta = Theta1 < Theta0. Reject H0 if Theta-hat ≤ ThetaC.

Power	N	Time t0	Theta0	Theta1	Target Alpha	Actual Alpha	Target Beta	Actual Beta	Theta C
0.80684	21	12.000	0.4	0.2	0.05000	0.05000	0.20000	0.19316	0.3
0.90532	28	12.000	0.4	0.2	0.05000	0.05000	0.10000	0.09468	0.3
0.80420	15	12.000	0.4	0.2	0.10000	0.10000	0.20000	0.19580	0.3
0.90396	21	12.000	0.4	0.2	0.10000	0.10000	0.10000	0.09604	0.3

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Epstein, Benjamin. 1960. 'Statistical Life Test Acceptance Procedures.' Technometrics. Volume 2.4, pages 435-446.

Juran, J.M. 1979. Quality Control Handbook. McGraw-Hill. New York.

Schilling, Edward. 1982. Acceptance Sampling in Quality Control. Marcel-Dekker. New York.

Report Definitions

Power is the probability of rejecting a false null hypothesis.

N is the size of the sample drawn from the population.

Alpha is the probability of rejecting a true null hypothesis.

Beta is the probability of accepting a false null hypothesis.

Theta0 is the Mean Life under the null hypothesis.

Theta1 is the Mean Life under the alternative hypothesis.

t0 is the test duration time. It provides the scale for Theta0 and Theta1.

r is the number of failures.

Summary:

A sample size of 21 achieves 90% power to detect the difference between the null hypothesis mean lifetime of 0.4 and the alternative hypothesis mean lifetime of 0.2 at a 0.10000 significance level (alpha) using a one-sided test based on the elapsed time. Failing items are not replaced with new items. The study is terminated when it has run for 12.000 time units.

9.2 Population for Analyses

9.2.1 Evaluable for toxicity

Study participants who have received at least one treatment with cetuximab infusion will be evaluable for toxicity.

9.2.2 Evaluable for Efficacy

Study participants who have at received at least 2 doses of cetuximab and have had one set of restaging CT scans or documented clinical progression will be evaluable for efficacy

All study participants who have received one dose of cetuximab will be included in safety data sets.

Study participants who fail to receive at least 2 doses of cetuximab and have at least one set of CT scans or documented clinical progression will be replaced to ensure 21 response evaluable patients.

9.3 Primary Endpoint

The progression free survival (PFS) is the primary endpoint. PFS will be measured from study entry until first documented radiographic disease progression by RECIST criteria 1.1, clinical progression per investigator judgement, start of new anti-cancer therapy, or death from any cause.

9.4 Secondary Endpoints

Overall Survival (OS) will be assessed as the time between trial initiation and death of any cause. Subjects will be followed for OS after the initiation of therapy until death from any cause. Subjects lost to follow-up will be censored at the time of last known follow-up. Subjects still alive will be censored after five years from the date of study therapy initiation. Kaplan-Meier methods will be used to analyze OS.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Human Subjects Protection

The study will be conducted in accordance with the protocol, 21 CFR, HIPAA regulations, the Belmont Principles, ICH Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki. Informed consent will be obtained from all research participants or their legally authorized representative before performing any study procedures using the most recent IRB approved version.

10.1.1 Personal Data Protection

All parties will take all necessary actions required for the protection of subject personal data. Subjects enrolled in the study will be assigned a subject number and will be reference by this number. Directly identifiable data will be omitted from reports, publications, and other disclosures. All personal data will be store at the study site in encrypted electronic and/or paper form stored in a locked and secured facility. The site will be responsible for maintaining a list of subjects linking each subject with their subject number. Data will only be accessed by appropriate personnel and will be password protected or securely stored in a locked room. In the case of a potential breach of personally identifiable data, the site will take responsibility to ensure appropriate action is taken according to institutional practice and applicable laws and regulations.

10.2 Institutional Review

Before the initiation of the study, the Investigator will have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (e.g., recruitment advertisements, questionnaires, if applicable), from the IRB. All correspondence with the IRB should be retained in the Investigator's regulatory file. Changes to the protocol or approved documents may not be made until IRB approval has been received. However, if a change is necessary to eliminate immediate hazards to the subjects, prospective approval is not necessary.

The investigator or designee should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

10.3 Investigator Responsibilities

The Investigator is responsible for ensuring the trial is conducted in compliance with the current IRB approved version of the protocol, GCP, the Declaration of Helsinki, and any applicable national and local laws and regulations.

10.4 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval. However, prospective IRB approval will not be sought when an amendment is required to eliminate immediate risk to

subjects on study. In these cases, amendments will be retrospectively submitted to the IRB for review and approval.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

10.5 Protocol Deviations

A deviation will be defined as any noncompliance with ICH GCP or the clinical protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. As a result of the deviation, a corrective action must be implemented to ensure future deviation does not occur. It is the Investigator's responsibility to identify and report deviations from ICH GCP or protocol requirements. These deviations and corrective action should be documented in the subject's research chart, the associated eCRF, and reported to the IRB per their policy.

11 DATA HANDLING

11.1 Recording and Collection of Data

Primary source documentation will come directly from the subject's medical record. All source documentation should be attributable, legible, contemporaneous, original, accurate, complete, and available. All documentation should be signed and dated by applicable personnel. Relevant source data will be transcribed into the electronic case report forms (eCRFs) and should be completed as soon as possible after data availability. The eCRFs will be part of a computerized database grounded in the protocol requirements and study objectives. The database will be designed to comply with 21 CFR Part 11.

The Investigator has ultimate responsibility for ensuring that all data collected and recorded is accurate and consistent. He/she will need to sign off on all eCRFs to attest that all data recorded on them is true. A separate screening log of all the subjects screened for participation in the study must also be maintained and should include gender, age, eligibility status, the reason for ineligibility (if applicable), and study allocated subject number (if applicable).

11.2 Data Management

To accommodate evaluations, inspections, and/or audits from regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, IP accountability records, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. The Investigator must also agree to the maintain source documents for a minimum of two years after regulatory approval of the investigational product per 21 CFR 312.57. For the duration of record maintenance, records must be stored in a secure location and protected from the elements. If for any reason the Investigator at another participating institution is no longer able to retain study records, the HCI Investigator Sponsor should be notified before any destruction so that the records can be transferred to an acceptable designee. Once retention requirements have been met, the participating site Investigator must get HCI Investigator Sponsor approval before the destruction of any records.

12 PUBLICATION PLAN

In accordance with U.S. regulations and the best interest of research ethics and transparency, this study will be registered on ClinicalTrials.gov before subject enrollment. US Basic Results will also be reported and available on ClinicalTrials.gov within one year of the primary completion date, regardless of formal journal publication. All results will be reported objectively, accurately, balanced, and completely, regardless of the study outcome.

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Appendix 1: ECOG Performance Status[23]

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

Appendix 2: RECIST 1.1

Response to study therapy will be evaluated using RECIST v1.1 criteria. The following definitions and criteria should be used for the baseline evaluations of existing disease, and the ongoing evaluation of tumor responses.

Measurable lesions - lesions that can be accurately measured in at least one dimension with the longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with an x-ray. A lymph node must be ≥15 mm in short axis when assessed by CT scan

Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

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

- All measurable lesions up to a maximum of two lesions per organ and five 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 based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Table 6 : RECIST 1.1 response criteria

Evaluation of target lesions	
Complete Response (CR)	The disappearance of all target lesions (Must persist for a minimum of four weeks)
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD (Must persist for a minimum of four weeks)
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions	
Complete Response (CR)	The disappearance of all non-target lesions
Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response

Per RECIST 1.1 “in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’.” Select the following language as appropriate.

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Table 7 : Best Overall Response Classification

Target Lesions	**Non-Target Lesions**	**Evaluation of New Lesions**	**Best Overall Response**
CR	CR	No	CR
CR	SD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD

Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

The best overall response is the best response observed until progression or recurrence. However, for response (CR or PR) to be reported the response must be confirmed on a subsequent scan at least 4 weeks from the original scan demonstrating response. Best overall response will be determined based on the table below:

Overall response		Best overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.