

Academic and Community Cancer Research United (ACCRU)

BOND-3: A Randomized, Double-blind, Placebo-Controlled Phase II Trial of Irinotecan, Cetuximab, and Bevacizumab Compared with Irinotecan, Cetuximab, and Placebo in RAS-Wildtype, Irinotecan-Refractory, Metastatic Colorectal Cancer

For any communications regarding this protocol, please contact the person listed on the Protocol Resource page. This is a stand-alone document found on the ACCRU website (www.ACCRU.org)

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√ Study contributor(s) not responsible for patient care.

Drug Availability

Commercial Agents: Irinotecan, Cetuximab

Drug Company Supplied: Bevacizumab

Study Participants – Limited: ACCRU Membership

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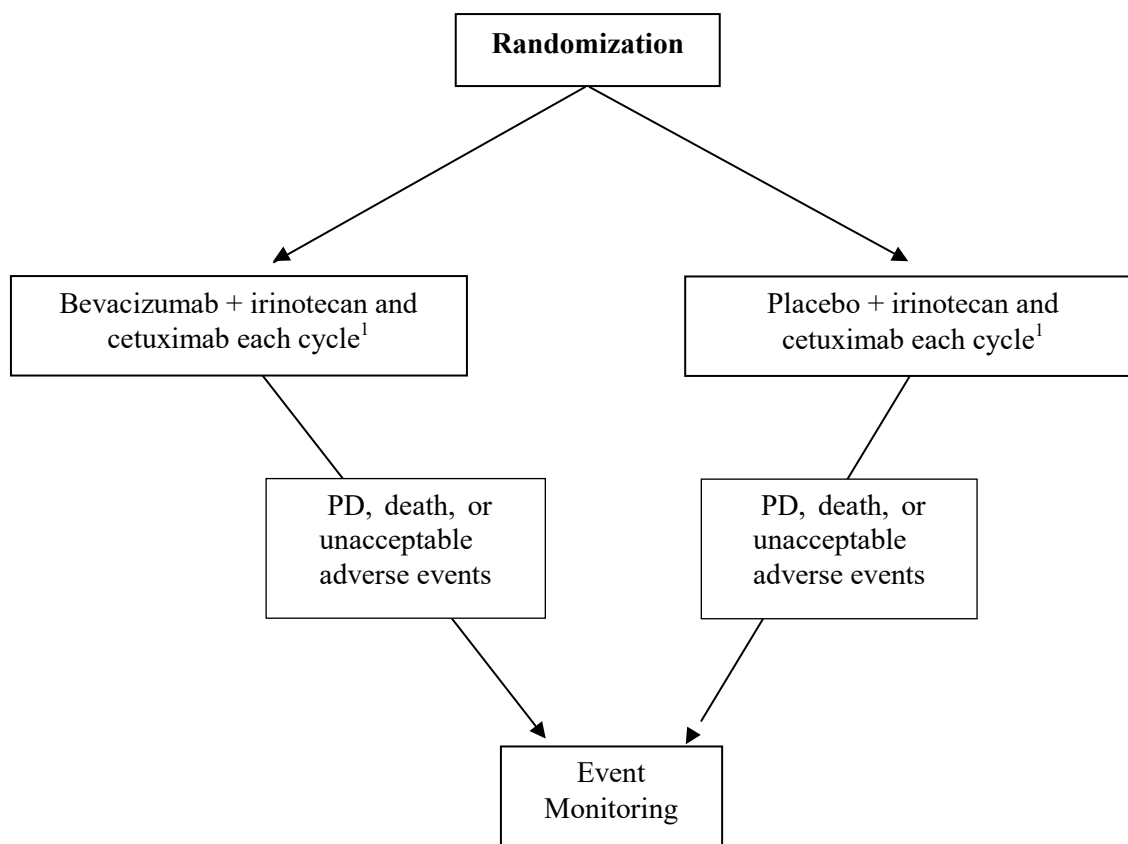
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Schema



¹Cycle length = 14 days.

NOTE: If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

Generic name: Bevacizumab Brand Name: Avastin Availability: McKesson Specialty Pharmacy, Clinical Research Services	Generic name: Placebo Brand Name: NA Availability: Commercial supply
Generic name: Irinotecan Brand Name: Camptosar Availability: Commercial	Generic name: Cetuximab Brand Name: Erbitux Availability: Commercial

Event Monitoring: Is not part of the Active Monitoring phase of a study. It is the time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Participants may not be required to return to the consenting site for study-related reasons or be required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

1.0 Background

1.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death in the U.S. In 2013, an estimated 142,820 cases of CRC will be diagnosed and 50,830 people will die from the disease (American Cancer Society, 2013). Fifteen to 25% of patients with CRC have metastatic disease at the time of diagnosis, and a significant proportion of patients who are initially diagnosed with localized disease ultimately develop metastases (Kindler and Shulman, 2001). While there have been substantive advances in the treatment of metastatic CRC (mCRC) over the past few years, median survival for these patients remains at two years, and less than 6% survive for more than five years (American Joint Committee on Cancer, 2010). Clearly, there is a critical need for new effective treatment regimens to further prolong survival.

1.2 5-Fluorouracil-Based Chemotherapy

Historically, treatment for CRC was limited to 5-fluorouracil (5-FU) and leucovorin (LV), with response rates (RRs) of 23% and median survival time of approximately 10 to 12 months (Advanced Colorectal Cancer Meta-Analysis Project, 1992). 5-FU is incorporated into RNA and DNA and inhibits the enzyme thymidylate synthase (TS), thus interfering with the formation of new strands of DNA during replication. LV is a reduced folate which, when combined with 5-FU, augments 5-FU cytotoxicity by increasing the inhibition of TS by the 5-FU active metabolite FdUMP. Because 5-FU has a short half-life, continuous infusion regimens appear to offer a pharmacological benefit, with the maximal dose intensity of 5-FU delivery being achieved when the drug is administered over 24-48 hours.

In the initial treatment of mCRC, 5-FU/LV is often administered with either irinotecan or oxaliplatin. Irinotecan is converted by carboxylesterase to its active metabolite, SN-38, which binds and stabilizes topoisomerase I, leading to double-stranded DNA breaks and apoptosis. Randomized controlled trials have shown that irinotecan is active both in refractory mCRC as a single agent (Cunningham, et al, 1998) and in the first-line setting when combined with bolus 5-FU/LV (IFL) (Saltz, et al, 2000) or infusional 5-FU/LV (FOLFIRI) (Douillard, et al, 2000). Oxaliplatin is a platinum derivative that leads to the formation of DNA adducts, and has been evaluated in combination with both bolus (i.e., FLOX) and infusional forms of 5-FU/LV (FOLFOX), as well as capecitabine (CAPEOX). All of these studies have found that combination chemotherapy is superior to 5-FU/LV alone. Indeed, FOLFOX has been shown to be superior to IFL in the first-line setting (Goldberg, et al, 2004), but equivalent to FOLFIRI (Tournigand, et al, 2004).

1.3 Cetuximab

Cetuximab is a chimeric human-murine monoclonal antibody that binds selectively to the extracellular region of the epidermal growth factor receptor (EGFR). Binding inhibits ligand-induced, tyrosine kinase-dependent phosphorylation of EGFR and leads to internalization and degradation of the receptor. A reduction in available EGFR at the cell surface subsequently results in reduced activation of downstream signaling pathways.

Cetuximab has been extensively studied in mCRC, with antitumor activity demonstrated both as a single agent and in combination with chemotherapy in multiple lines of therapy.

The BOND-1 trial randomized 329 patients with EGFR+ mCRC who had progressed within three months of an irinotecan-based therapy in a 2:1 ratio to irinotecan + cetuximab or cetuximab alone (Cunningham, et al, 2004). Response rate (RR) was significantly higher with the combination (23% versus 11%), as were median time-to-progression (TTP; 4.1 versus 1.5 months) and median overall survival (OS; 8.6 versus 6.9 months). Cetuximab monotherapy was compared to best supportive care in the CO.17 phase III trial, and RR, PFS, and OS were all statistically higher in the treatment arm (Jonker, et al, 2007). Cetuximab also demonstrated efficacy in the second-line setting in the EPIC study, which randomized 1,298 patients with EGFR+ mCRC who had been previously treated with 5-FU- and oxaliplatin-based therapy to irinotecan + cetuximab or irinotecan alone (Sobrero, et al, 2008). Although the primary endpoint of OS was not statistically different between the arms, both median progression-free survival (PFS) and RR were significantly higher in the combination arm ($P < 0.0001$ for both). Finally, the CRYSTAL trial randomized 1,198 previously untreated mCRC patients to FOLFIRI + cetuximab or FOLFIRI alone, and found a statistically improved median PFS with the addition of cetuximab (8.9 versus 8.0 months, $P = 0.048$) (Van Cutsem, et al, 2009). RR was also significantly higher in the cetuximab-containing arm (46.9% versus 38.7%, $P = 0.004$), but there was no difference in median OS (19.9 versus 18.6 months, $P = 0.31$). EGFR positivity was not an inclusion criterion for this trial due to further research that concluded that it was not, in fact, a predictive marker of cetuximab efficacy.

Following the discovery that EGFR positivity was not predictive of response to anti-EGFR therapy, *KRAS* exon 2 (codons 12 and 13) mutation status emerged as a true biomarker of cetuximab activity. A meta-analysis of 281 irinotecan-refractory patients treated with irinotecan-based therapy in combination with cetuximab across seven studies showed that among the 35% of patients whose tumors harbored a *KRAS* mutation in codon 12 or 13, there were no complete (CR) or partial responses (PR) compared to 2% CR and 41% PR rates among *KRAS* wild-type patients (Di Fiore, et al, 2008). Moreover, median PFS and median OS were significantly worse among *KRAS*-mutated patients (2.7 versus 5.4 months and 8.0 versus 13.2 months, respectively). Subsequently, multiple subgroup analyses of large phase III trials of first-line mCRC demonstrated the same findings, with *KRAS* wild type status predicting superior efficacy outcomes to anti-EGFR therapy, and worse outcomes among *KRAS*-mutated patients (Tveit, et al, 2012; Adams, et al, 2011; Bokemeyer, et al, 2011; Douillard, et al, 2010; Van Cutsem, et al, 2009).

However, not all tumors with wild type *KRAS* codon 12 and 13 respond to anti-EGFR antibodies, and it has now been reported that this resistance could be explained by other mutations within *KRAS* as well as *NRAS*. For example, in a re-analysis of the PRIME phase III trial of FOLFOX +/- panitumumab in first-line metastatic colorectal cancer, 17% of patients without mutations in exon 2 had other mutations in exons 3 and 4 of *KRAS* and in *NRAS* exons 2, 3, and 4 (Douillard, et al, 2013). The presence of these other *RAS* mutations predicted a lack of response to panitumumab, as well as inferior PFS and overall survival in patients receiving FOLFOX + panitumumab compared to FOLFOX alone. Consequently, the National Comprehensive Cancer Network (NCCN) updated their guidelines to restrict use of anti-EGFR antibodies to patients with all-*RAS* wild type tumors only.

1.4 Bevacizumab

Bevacizumab is a fully humanized, monoclonal antibody against the vascular endothelial growth factor (VEGF). Although bevacizumab has limited activity as a single agent for

treatment of mCRC, the addition of the agent to chemotherapy significantly improves patient outcome. The phase III trial that won bevacizumab its FDA approval randomized 815 patients with previously-untreated mCRC to IFL + bevacizumab versus IFL alone, and found statistically significantly superior RR (44.8% versus 34.8%, $P=0.004$), median PFS (10.6 versus 6.2 months, $P<0.001$), and median OS (20.3 versus 15.6 months, $P<0.001$) in the bevacizumab-containing arm (Hurwitz, et al, 2004). The NO16966 trial subsequently confirmed the superiority of adding bevacizumab to an oxaliplatin-based chemotherapy backbone such as CAPEOX and FOLFOX in the first-line setting (Saltz, et al, 2008). Finally, the E3200 trial reported improved median PFS (7.3 versus 4.7 months) and OS (12.9 versus 10.8 months) for previously treated mCRC patients randomized to FOLFOX + bevacizumab versus FOLFOX alone (Giantonio, et al, 2007).

1.5 Study Rationale

Given the multitude of trials reporting a benefit of adding either an anti-VEGF antibody or an anti-EGFR antibody to standard chemotherapy in multiple lines of therapy for mCRC, there is great interest in exploring the addition of both antibody types simultaneously to chemotherapy. Unfortunately, trials in the first-line therapy of mCRC suggest no benefit for the combination of chemotherapy with both an anti-EGFR antibody and bevacizumab (Hecht, et al, 2009; Tol, et al, 2009).

Nonetheless, in patients with irinotecan-refractory mCRC, a randomized trial does suggest a benefit for the combination of irinotecan, cetuximab, and bevacizumab (Saltz, et al, 2007). That randomized phase II trial, BOND-2 (N = 83), evaluated the safety and efficacy of cetuximab and bevacizumab with or without irinotecan in patients with irinotecan-refractory mCRC. The patient population enrolled in the trial had received extensive previous treatment with a median number of prior chemotherapy regimens of three. Patients in Arm A (n = 43) of the study received cetuximab, bevacizumab, and irinotecan. Patients in Arm B (n = 40) received only cetuximab plus bevacizumab. Patients receiving cetuximab, bevacizumab, and irinotecan had a TTP of 7.3 months, RR of 37%, and an OS of 14.5 months. In comparison, patients receiving cetuximab and bevacizumab without irinotecan had a TTP of 4.9 months, RR of 20%, and an OS of 11.4 months. Of note, BOND-2 only enrolled patients with bevacizumab-naïve mCRC.

These response rates compare favorably with those from other studies in patients with refractory mCRC (see Table 1 below). In the BOND-1 study described above, patients with irinotecan-refractory mCRC treated with cetuximab and irinotecan (n = 218) had a median TTP of 4.1 months and a RR of 23% (Cunningham, et al, 2004). These results suggest that, in patients with irinotecan-refractory mCRC, the combination of irinotecan, cetuximab, and bevacizumab may offer superior efficacy when compared to irinotecan and cetuximab. Moreover, the results suggest that, in contrast to first-line therapy, the combination of cetuximab and bevacizumab may offer synergy in later lines of therapy. More recently, other studies suggest a benefit for continuation of bevacizumab into later lines of therapy following progression on first-line chemotherapy and bevacizumab (Arnold, et al, 2012).

Table 1: Cross-study comparison of efficacy from the BOND-1 and BOND-2 trials

STUDY	BOND-2	BOND-1
INVESTIGATIONAL ARM	Irinotecan + Cetuximab + Bevacizumab	Irinotecan + Cetuximab
RR (%)	37	23
PFS (months)	7.9	4.0
CONTROL ARM	Cetuximab + Bevacizumab	Cetuximab
RR (%)	20	11
PFS (months)	5.6	1.5

Consequently, this study proposes a double-blind, placebo-controlled trial of irinotecan, cetuximab, and bevacizumab vs. irinotecan, cetuximab, and placebo in patients with *RAS*-wild-type, irinotecan-refractory mCRC who have also previously received bevacizumab in at least one prior line of therapy. Results from this trial could support the addition of bevacizumab to the approved combination of irinotecan and cetuximab in irinotecan-refractory mCRC. Recent U.S.-wide data suggest that the majority of anti-EGFR use is in irinotecan-refractory mCRC (Abrams, et al, 2012). As such, beyond data supporting first-line use of bevacizumab and continuation of bevacizumab into second-line therapy, results of our proposed trial would support continuation of bevacizumab into third-line therapy with irinotecan and cetuximab.

2.0 Goals

2.1 Primary

2.11 To assess and compare the progression-free survival (PFS) of patients receiving irinotecan, cetuximab, and bevacizumab with patients receiving irinotecan, cetuximab and placebo, in the population of patients with *RAS*-wildtype, irinotecan-refractory metastatic colorectal cancer (mCRC) who also previously received bevacizumab in at least one prior line therapy.

2.2 Secondary

2.21 To assess the adverse event (AE) profile and safety of the proposed treatment in this population.

2.22 To assess and compare the overall survival (OS) between treatment arms in this population.

2.23 To assess and compare the disease control rate (DCR) between treatment arms in this population.

2.24 To assess and compare the overall response rate (ORR) between treatment arms in this population.

- 2.25 To assess and compare the duration of response between treatment arms in this population.
- 2.26 To assess and compare time to treatment failure between treatment arms in this population.
- 2.27 To assess relative dose intensity of treatment agents between treatment arms in this population.

2.3 Correlative

- 2.31 Determine the change in genotype concentrations of prespecified gene mutations in circulating cell-free DNA (cfDNA) collected serially during protocol treatment.
- 2.32 Explore the predictive value of pretreatment mutation status, germline single nucleotide polymorphisms (SNPs), and gene expression signatures for cetuximab sensitivity and resistance.
- 2.33 Explore the predictive value of dynamic changes in mutation status and gene expression signatures for cetuximab sensitivity and resistance.

3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.11 Metastatic or locally advanced (unresectable) colorectal cancer with histological confirmation of adenocarcinoma.
- 3.12 Age \geq 18 years of age.
- 3.13 Measurable disease as defined in Section 11.0.
- 3.14 *RAS* wild-type tumor (Appendix IV).

Note: Evidence of EGFR expression in the tumor is not required.

- 3.15 Previous failure of at least one fluoropyrimidine- and irinotecan-containing chemotherapy regimen for metastatic disease.

Note: Previous failure is defined as disease progression while receiving treatment or within 6 weeks after the last dose of irinotecan. Failure for this assessment is defined as any enlargement of measurable or assessable lesion(s) or the development of any new lesion. A rising tumor marker alone is not sufficient to define failure. Patients can have received irinotecan in any previous line of therapy.

- 3.16 Treatment with bevacizumab in at least one prior line of therapy for metastatic disease.

- 3.17 Negative serum or urine pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
- 3.18 ECOG Performance Status (PS): 0 or 1 (form available on the ACCRU member website at
[REDACTED])
- 3.19a Adequate organ and bone marrow function as defined below (see Section 3.19b)
- 3.19b The following laboratory values obtained ≤ 14 days prior to randomization:
- Total serum bilirubin \leq institutional upper limit of normal (ULN)
 - Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Hemoglobin ≥ 9.0 g/dL (hemoglobin may be supported by transfusion)
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
 - Creatinine within institutional limits of normal
OR
creatinine clearance ≥ 60 mL/min/1.73 m² for patients with creatinine levels above institutional normal.
 - Urinary protein $\leq 1+$
 - Patients discovered to have $\geq 2+$ proteinuria must have a spot urine protein:creatinine ratio (UPCR) < 1.0
 - Partial thromboplastin time (PTT) ≤ 1 x institutional ULN and international normalized ratio (INR) ≤ 1.5 , unless participant is on full dose anticoagulation therapy. Patients on full-dose anticoagulation are eligible if the following criteria are met:
 - Patient has an in-range INR (usually 2-3) on a stable dose of warfarin or other anticoagulant ≤ 14 days or is on a stable dose of low molecular weight heparin
 - Patient has no active bleeding or pathological condition that carries a high risk of bleeding (i.e., tumor involving major vessels or known varices)
 - Patients receiving anti-platelet agents are eligible. In addition, patients who are on daily prophylactic aspirin or anticoagulation for atrial fibrillation are eligible.
- 3.19c Life expectancy > 3 months
- 3.19d Provide informed written consent.
- 3.19e Willing to provide blood samples for mandatory correlative and research purposes (see Sections 6.0 and 14.0).
- 3.19f Willing to provide tissue and blood samples for mandatory banking purposes (see Sections 6.0, 14.0 and 17.0).

- 3.19g Any major surgery or open biopsy completed ≥ 4 weeks prior to randomization.
- 3.19h Any minor surgery or core biopsy completed ≥ 1 week prior to randomization and patient must have fully recovered from the procedure.

Note: Insertion of a vascular access device is not considered major or minor surgery.

3.2 Exclusion Criteria

- 3.21 Presence of a *RAS* mutation in exons 2, 3, or 4 of *KRAS* or *NRAS*. (Patients with mutations in exons 2, 3, or 4 of *KRAS* and/or *NRAS* are excluded)
- 3.22 Prior treatment with cetuximab or panitumumab.
- 3.23 Prior intolerance to irinotecan and/or bevacizumab despite dose reduction.
- 3.24 Known or suspected brain or central nervous system (CNS) metastases, or carcinomatous meningitis.
- 3.25 Active, uncontrolled infection, including hepatitis B, hepatitis C.
- 3.26 Concurrent anti-cancer therapy, including chemotherapy agents, targeted agents, or biological agents not otherwise specified in this protocol.
- 3.27 Anti-cancer therapy ≤ 14 days prior to randomization.
- 3.28 Prior radiotherapy to $>25\%$ of bone marrow.
- Note:** Standard rectal cancer chemoradiation will not exclude subject from study protocol.
- 3.29a Radiation therapy ≤ 2 weeks prior to randomization.
- 3.29b Any of the following, because this study involves agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- *Pregnant women*
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception
- 3.29c Co-morbid systemic illnesses or other severe concurrent disease, history of any psychiatric or addictive disorder, or laboratory abnormality, which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
- 3.29d Patients known to be HIV positive

- 3.29e Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, symptomatic pulmonary fibrosis or interstitial pneumonitis, or psychiatric illness/social situations that, in the opinion of the investigator, may increase the risks associated with study participation or study treatment, or may interfere with the conduct of the study or the interpretation of the study results.
- 3.29f Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
- 3.29g Other active malignancy ≤ 3 years prior to registration.
- EXCEPTIONS:** Non-melanoma skin cancer, prostatic intraepithelial neoplasia without evidence of prostate cancer, lobular carcinoma *in situ* in one breast, or carcinoma-in-situ of the cervix that has been treated.
- 3.29h History of prior malignancy for which patient is receiving other specific treatment for their cancer.
- 3.29i History of allergic reactions attributed to compounds of similar chemical or biologic composition to irinotecan, cetuximab, and/or bevacizumab that led to discontinuation of those agents.
- 3.29j Significant history of bleeding events or pre-existing bleeding diathesis ≤ 6 months of randomization (unless the source of bleeding has been resected)
- 3.29k History of gastrointestinal perforation ≤ 12 months prior to randomization.
- 3.29l Predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline pattern of >3 loose stools daily in subjects without a colostomy or ileostomy. Subjects with a colostomy or ileostomy may be entered at investigator discretion.
- 3.29m Arterial thrombotic events ≤ 6 months prior to randomization
- Note:** This includes transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina or angina requiring surgical or medical intervention in the past 6 months, or myocardial infarction (MI).
- 3.29n Clinically significant peripheral artery disease (e.g., claudication with <1 block) or any other arterial thrombotic event.
- 3.29o Serious or non-healing wound, ulcer, or bone fracture.
- 3.29p History of hypertension not well-controlled ($\geq 160/90$) even though on a regimen of anti-hypertensive therapy.
- 3.29q Evidence of Gilbert's syndrome or known homozygosity for the UGT1A1*28 allele (special screening not required).

4.0 Test Schedule

Tests and procedures	≤14 days prior to registration	Cycle 1, Day 1 ¹	Subsequent cycles, Day 1	End of treatment ¹⁰
Complete medical history and physical exam, weight, vital signs	X			X
Height	X			
Limited physical exam, including weight and vital signs		X	X	
ECOG PS	X	X	X	X
Concurrent medications	X	X	X	X
Adverse event assessment	X	X	X	X ¹¹
Hematology: CBC/differential and platelets	X	X ²	X	X
Serum chemistry: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, total bilirubin, alkaline phosphatase, total protein, albumin, SGOT (AST), SGPT (ALT)	X	X ²	X	X
PT, INR, PTT	X			
Urinalysis ³	X		X ⁴	
Carcinoembryonic antigen (CEA)	X	X ²	X ⁵	X
<i>RAS</i> mutation status (links for commercially available tests in Appendix IV)	X			
Radiologic imaging/tumor measurement	X ⁶		X ⁶	X
B-HCG/serum or urine pregnancy test ⁷	X			
Mandatory blood samples (see Section 14.0) ^{8,R}	X		X ¹²	X
Mandatory tissue sample (see Section 17.0) ^{9,R}	X			

- Cycle = 14 days +/- 3 days.
- Labs do not have to be repeated on Cycle 1, Day 1 if they were done ≤7 days.
- If 2+ protein on urinalysis, obtain additional urine sample for urine protein: creatinine (UPC) ratio – if UPC ≥2, obtain 24-hour urine sample for protein. If ≥3+ protein on urinalysis, obtain 24-hour urine sample for protein.
- Repeated every other cycle starting with cycle 2.
- Repeated every 4 cycles (approximately every 8 weeks).
- ≤ 28 days prior to registration and then repeated every 4 cycles (approximately every 8 weeks). Specify method (e.g., CT, MRI, etc.) Use same imaging throughout the study. Documentation (radiologic) must be provided for participants removed from study for progressive disease.
- For women of childbearing potential only. Must be done ≤7 days prior to Cycle 1, Day 1.
- Mandatory blood samples for future biomarker research. If the sample was not obtained ≤14 days prior to registration, it can be obtained on Cycle 1 Day 1 prior to initiation of protocol therapy. Cryovials are required for this collection (see Section 14.0).
- Mandatory archival tissue for future research. Submit all available archived specimens, if feasible. Submit the associated operative and pathology reports ≤60 days of registration.
- End of treatment evaluation should occur within 30 days (+/-3 days) after the last dose of study treatment. The visit at which a response assessment shows disease progression may be used as the end of treatment visit.

11. Follow for AE monitoring for a total of 30 days (+/- 3 days) from the last dose of study treatment. Participants with an AE that is ongoing at the end of treatment visit should be contacted at least monthly until the event has resolved or until the subject begins treatment with a new anti-cancer therapy.
 12. At the time of the first restaging (prior to Cycle 5) and second restaging (prior to Cycle 9)
- R Research funded.

5.0 Stratification Factors:

- 5.1 Prior chemotherapy regimens for metastatic disease: 1 vs. ≥ 2 .
- 5.2 Bevacizumab received in the immediate prior treatment regimen: Yes vs. no.

6.0 Registration/Randomization Procedures

6.1 Registration

- 6.11 To register a patient, access the ACCRU web page [REDACTED] go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training." Prior to initiation of protocol treatment, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [REDACTED]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [REDACTED]: click on "Registration, Installation & Entry Instructions".

- 6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19e and 14.11).

- 6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using online ACCRU Regulatory Management Systems

(ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

- 6.14 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:
- IRB approval at the registering institution
 - Patient eligibility
 - Existence of a signed consent form
 - Existence of a signed authorization for use and disclosure of protected health information
- 6.15 At the time of registration, the following will be recorded:
- Patient has given permission to store and use his/her blood and tissue sample(s) for future research to learn about, prevent, or treat cancer.
 - Patient has given permission to store and use his/her blood and tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
 - Patient has/has not given permission for ACCRU to give his/her blood and tissue sample(s) to outside researchers.
- 6.16 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.
- 6.17 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.
- 6.18 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.19a All required baseline symptoms (see Section 10.5) must be documented and graded.
- 6.19b Study drug is available on site.
- 6.19c Cryovials available on site.
- 6.2 Randomization Procedures**
- 6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.
- 6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon (Pocock and Simon, et al, 1975) dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.
- Bevacizumab + irinotecan + cetuximab
 - Placebo + irinotecan + cetuximab

6.3**Procedures for Double-Blinding the Treatment Assignment**

- 6.31 After the treatment assignment has been ascertained by the registration/randomization application, the registration specialist will notify the designated data manager/nurse/pharmacist at the patient's institution.

The name of this contact person is to be entered in the designated space on the eligibility checklist so the Registration Office personnel have it for each patient at the time of registration. Make sure this contact person will be available at the time of registration so he or she can take a call from the registration specialist if necessary. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the sources of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment "active or placebo" to the designated contact at the patient's institution.

- 6.32 The treatment assignment will be to bevacizumab + irinotecan + cetuximab or placebo + irinotecan + cetuximab. The bevacizumab/placebo solution will be prepared and labeled by the unblinded pharmacist as "Bevacizumab OR Placebo" so that the contents are not discernible to the person administering the treatment.
- 6.33 The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Protocol Treatment

- 7.1** Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

17.11 Pretreatment medication

- 7.111 Pretreatment anti-emetic medications should be administered per institutional standard of care. Suggestions for pretreatment include ondansetron 16 mg (or similar agent) and dexamethasone 12 mg PO or IV, and consideration of fosaprepitant or an aprepitant tri-fold pack. Other anti-emetics may be administered as clinically indicated.
- 7.112 Diphenhydramine 50 mg (or similar agent) IV should be administered prior to each dose of cetuximab in an effort to prevent an infusion or hypersensitivity reaction. Premedication is recommended prior to subsequent doses, but a lower dose may be used based on patient tolerance to the previous dose and investigator discretion. Pretreatment with acetaminophen may also be used.

7.2 Drug/Placebo Administration

7.21 Sequence of administration

7.211 Cetuximab should be the first agent delivered, and should be administered per institutional standard of care, but the following procedure may be considered:

- The first dose of cetuximab should be administered after diphenhydramine premedication (see above) and infused over 120 minutes.
- If well-tolerated, subsequent infusions may be administered over approximately 90 minutes (not to exceed 10 mg/minute).
- Cetuximab should be administered with the use of a low protein-binding 0.22 micron in-line filter, and 0.9% normal saline should be used to flush the IV line at the end of the infusion.

7.212 Following cetuximab infusion, bevacizumab/placebo should be given according to institutional standard of care, but the following procedure may be considered:

- The initial dose of bevacizumab/placebo should be infused over 90 minutes, the second dose over 60 minutes, and all subsequent doses over 30 minutes if prior infusions are tolerated without infusion-associated adverse events.
- For patients in whom elective surgery is contemplated, bevacizumab/placebo should be discontinued for at least 8 weeks prior to surgery.
- Bevacizumab/placebo may be resumed after at least 8 weeks following surgery. For patients in whom non-elective surgery is required, bevacizumab/placebo should be held as long as possible prior to surgery and for at least 8 weeks following surgery. Other protocol treatment may be given while bevacizumab/placebo is held at the discretion of the treating physician.

7.213 Lastly, irinotecan infusion should follow bevacizumab/placebo and should be given over 90 minutes or per institutional standard of care.

7.22 Protocol treatment administration table

Agent ¹	Dose Level	Route	Day
Cetuximab	500 mg/m ²	IV	Day 1 of each cycle ² (±3 days)
Bevacizumab OR Placebo	5 mg/kg (bevacizumab) OR normal saline in a volume equal to bevacizumab volume		
Irinotecan	180 mg/m ^{2,3}		

1. Administer cetuximab first, then bevacizumab, then irinotecan (see Section 7.3).
2. Cycle = 14 days
3. If during previous irinotecan chemotherapy the irinotecan dose was reduced due to toxicity, this lower tolerated dose should be used as the starting dose.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 14 days during treatment and again within 30 days (+/-3 days) after the last dose of study treatment.

7.4 Protocol treatment by a Local Medical Doctor (LMD) is not allowed.

7.5 Breaking Codes in Double-Blinded Studies

7.51 The treatment code may *not* be broken except for emergencies.

7.52 In the event of an emergency, call the ACCRU Registration Office at (507) 284-2753 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day.

8.0 Dosage Modification Based on Adverse Events

These modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose levels (Based on Adverse Events in Tables 8.2, 8.3 and 8.4)

Dose Level	Bevacizumab / Placebo ^a	Irinotecan	Cetuximab
0*	5 mg/kg	180 mg/m ^{2b}	500 mg/m ²
-1	5 mg/kg	150 mg/m ²	400 mg/m ²
-2	5 mg/kg	120 mg/m ²	300 mg/m ²
-3	5 mg/kg	100 mg/m ²	200 mg/m ²

* Dose level 0 refers to the starting dose.

- a. Bevacizumab/placebo dose is always 5 mg/kg IV. Bevacizumab may be skipped or discontinued, but the dose is not reduced or escalated.
- b. For patients starting out at the maximum irinotecan dose. If starting out at a lower dose that was previously tolerated in a prior treatment regimen, further dose reductions for adverse events should proceed to the next lower dose level from the starting dose. If starting out at a lower dose that was previously tolerated in a prior treatment regimen, consideration can be given to escalating the irinotecan dose during subsequent protocol therapy after discussion with the Study Chair.

Use the following definitions to determine actions in the Action columns of the following tables:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.2 Dose modifications for **irinotecan**

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**1
BASED ON INTERVAL ADVERSE EVENT		
Investigations	Neutrophil count decreased	
	Grade 1 (< LLN – 1.5 x 10 ⁹ /L) OR Grade 2 (< 1.5 x 10 ⁹ /L - 1.0 x 10 ⁹ /L)	Maintain dose level
	Grade 3 (<1.0 x 10 ⁹ /L – 0.5 x 10 ⁹ /L) OR Grade 4 (<0.5 x 10 ⁹ /L)	Hold irinotecan, cetuximab, and bevacizumab/placebo. When ANC has recovered to ≤grade 2, resume treatment and decrease irinotecan by one dose level. Cetuximab and bevacizumab/placebo should continue at the same dose level as previous. If ANC <1.0 x 10 ⁹ /L after 4 weeks, discontinue irinotecan. Continuation of cetuximab and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
	Platelet count decreased	
	Grade 1 (<LLN – 75 x 10 ⁹ /L)	Maintain dose level
	Grade 2(<75 x 10 ⁹ /L – 50 x 10 ⁹ /L) OR Grade 3 (<50 x 10 ⁹ /L – 25 x 10 ⁹ /L)	Hold irinotecan, cetuximab, and bevacizumab/placebo. When platelets have recovered to ≤ grade 1, resume treatment and decrease irinotecan by one dose level. Cetuximab and bevacizumab/placebo should continue at the same dose level as previous.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**1
BASED ON INTERVAL ADVERSE EVENT		
	Grade 4 (<math> < 25 \times 10^9/L </math>)	<p>Hold irinotecan, cetuximab, and bevacizumab/placebo. When platelets have recovered to \leq grade 1, resume treatment and decrease irinotecan by two dose levels (if only one dose level remaining, decrease by one dose level). Cetuximab and bevacizumab/placebo should continue at the same dose level as previous.</p> <p>If platelets $< 75 \times 10^9/L$ after 4 weeks, discontinue irinotecan. Continuation of cetuximab and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the study chair.</p>
Blood and lymphatic system disorders	Febrile neutropenia ^{2,3}	
	<p>Grade 3 (ANC $< 1.0 \times 10^9/L$ with single temperature $> 38.3^\circ C$ [$101^\circ F$], or sustained temperature $\geq 38^\circ C$ [$100.4^\circ F$] for > 1 hour)</p> <p>OR</p> <p>Grade 4 (life-threatening consequences; urgent intervention indicated)</p>	<p>Hold irinotecan, cetuximab, and bevacizumab/placebo. When ANC has recovered to $> 1.0 \times 10^9/L$, fever resolved, and any infection under control, resume treatment and decrease irinotecan by one dose level. Cetuximab and bevacizumab/placebo should continue at the same dose level as previous.</p> <p>If ANC $< 1.0 \times 10^9/L$ after 4 weeks, and/or fever or infection not resolved after 4 weeks, discontinue protocol therapy.</p>

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**1
BASED ON INTERVAL ADVERSE EVENT		
Gastrointestinal disorders	Diarrhea	
	Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome occurring during or shortly after receiving irinotecan	Follow institutional standard of care, such as administering atropine 0.25-1 mg IV or SC. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).
	Late Diarrhea (e.g., developing >24 hours after irinotecan)	
	Grade 1 (increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline)	Maintain dose level
Grade 2 (increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline)	Maintain dose level if resolved to ≤grade 1 by Day 1. If ≥grade 2 diarrhea present on Day 1 of cycle despite optimal anti-diarrheal therapy, decrease irinotecan by one dose level. Cetuximab and bevacizumab/placebo should continue at the same dose level as previous.	

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**1
BASED ON INTERVAL ADVERSE EVENT		
	Grade 3 (increase of ≥ 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL) <i>Or</i> Grade 4	Decrease irinotecan by one dose level if resolved to \leq grade 2 by Day 1. If \geq grade 3 diarrhea present on Day 1 of cycle despite optimal anti-diarrheal therapy, hold irinotecan and check weekly, then treat based on interval toxicity. Cetuximab and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator's discretion. If \geq grade 3 diarrhea after 4 weeks despite optimal anti-diarrheal therapy, discontinue irinotecan permanently. Continuation of cetuximab and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the lead PI.
Gastrointestinal disorders (continued)	Nausea or Vomiting	
	Grade 1	Maintain dose level
	Grade 2	Maintain dose level if resolved to \leq grade 1 by Day 1. If \geq grade 2 vomiting present on Day 1 of cycle despite optimal anti-emetic therapy, decrease irinotecan by one dose level. Cetuximab and bevacizumab/placebo should continue at the same dose level as previous.
	Grade 3 <i>Or</i> Grade 4	Decrease irinotecan by one dose level if resolved to \leq grade 2 by Day 1. If \geq grade 3 vomiting present on Day 1 of cycle despite optimal anti-emetic therapy, hold irinotecan and check weekly, then treat based on interval toxicity. Cetuximab and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator's discretion. If \geq grade 3 vomiting after 4 weeks despite optimal anti-emetic therapy, discontinue irinotecan permanently. Continuation of cetuximab and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the study chair.

<i>→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←</i>		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**1
<i>BASED ON INTERVAL ADVERSE EVENT</i>		
Other	Other irinotecan-related, clinically significant, non- hematologic toxicities	
	Grade 1 <i>Or</i> Grade 2	Maintain dose level
	Grade 3 <i>Or</i> Grade 4	Decrease irinotecan by one dose level if resolved to \leq grade 1 by Day 1. If \geq grade 2 on Day 1 of cycle despite optimal medical management, hold irinotecan and check weekly, then treat based on interval toxicity. Cetuximab and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator's discretion. If \geq grade 2 after 4 weeks despite optimal medical management, discontinue irinotecan permanently. Continuation of cetuximab and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the study chair.

Footnotes follow on next page

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

** Use the following definitions to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

1. Refers to dose used in next cycle
2. At the treating physician's discretion, GCSF or pegylated GCSF should be used, and considered for use in subsequent cycles, according to standard of care, the most recent version of the product label, and all applicable guidelines.
3. In case of febrile neutropenia or grade ≥ 2 infection at any time, GCSF should be used according to all applicable guidelines.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events $>$ Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in subsequent cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels -1, -2, and -3) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in the reported clinical data.

8.3 Dose modifications for **cetuximab**

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
Skin and subcutaneous tissue disorders	Rash acneiform OR Rash maculopapular OR Nail disorders	
	Grade 1 OR Grade 2	Maintain dose level. Initiate symptom management with topical and/or oral antibiotics (e.g., minocycline, topical clindamycin, topical silver sulfadiazine, hydroxyzine) according to institutional standard of care.
	Grade 3	Hold cetuximab for up to 4 weeks and assess weekly. Initiate symptom management with topical and/or oral antibiotics (e.g., minocycline, topical clindamycin, topical silver sulfadiazine, hydroxyzine) according to institutional standard of care. Upon recovery to ≤grade 2, resume cetuximab at same previous dose. For subsequent occurrences, hold cetuximab again for up to 4 weeks and assess weekly. Upon recovery to ≤grade 2, resume treatment and decrease cetuximab by one dose level. If subsequent recurrence of ≥grade 3 rash while patient is already at lowest dose level, discontinue cetuximab permanently. Irinotecan and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator's discretion after discussion with the study chair.
	Grade 4	Discontinue cetuximab permanently. Irinotecan and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator's discretion after discussion with the study chair. If ≥grade 3 after 4 consecutive weeks despite optimal medical management, discontinue cetuximab permanently. Continuation of irinotecan and bevacizumab/placebo on protocol can be considered at the treating investigator's discretion after discussion with the study chair.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
General disorders and administration site conditions Immune system disorders	Infusion related reaction / cytokine release syndrome	
	Allergic reaction Grade 1	Decrease cetuximab infusion rate by 50%. All subsequent infusions should be administered at this lower rate.
	Grade 2	Immediately stop cetuximab infusion and provide supportive care according to institutional standards. Upon recovery to ≤grade 1, may resume cetuximab infusion on the same day at 50% lower rate with close monitoring at the treating investigator's discretion. Use lower rate and administer premedication for all subsequent infusions. If recurrence despite premedication and slower rate, discontinue cetuximab.
	Grade 3 <i>Or</i> Grade 4	Immediately stop infusion and provide supportive care according to institutional standards. Discontinue cetuximab and notify the study chair.
Metabolism and nutrition disorders	Hypomagnesemia	
	All grades	Provide intravenous magnesium supplementation per institutional standard of care. No dose adjustment of cetuximab required; however, continue careful monitoring.

<p>→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←</p>		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
Other	Other cetuximab-related, clinically significant, non-hematologic toxicities	
	Grade 1 <i>Or</i> Grade 2	Maintain dose level
	Grade 3 <i>Or</i> Grade 4	Decrease cetuximab by one dose level if resolved to ≤grade 1 by Day 1. If ≥grade 2 on Day 1 of cycle despite optimal medical management, hold cetuximab and check weekly, then treat based on interval toxicity. Irinotecan and bevacizumab/placebo may continue at the same dose level as previous at the treating investigator’s discretion. If ≥grade 2 after 4 weeks despite optimal medical management, discontinue cetuximab permanently. Continuation of irinotecan and bevacizumab/placebo on protocol can be considered at the treating investigator’s discretion after discussion with the study chair.

* Located [REDACTED]

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

1. Refers to dose used in next cycle

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events > Grade 2, then the dose may be increased, at the investigator’s discretion, one level at a time, in subsequent cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels -1, -2, and -3) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in the reported clinical data.

8.4 Dose modifications for bevacizumab/placebo

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
<i>BASED ON INTERVAL ADVERSE EVENT</i>		
General disorders and administration site conditions	Infusion related reaction / cytokine release syndrome	
	Grade 1	Continue bevacizumab/placebo infusion and monitor vital signs, administer supportive care per institutional standards and treating investigator's discretion. May reduce rate of infusion by 50% at investigator discretion.
	Grade 2	Immediately interrupt infusion and provide supportive care according to institutional standards. Upon recovery, may resume infusion on the same day at reduced rate with close monitoring at treating investigator's discretion. Premedication for subsequent infusions is recommended. If second occurrence, discontinue bevacizumab/placebo.
	Grade 3 <i>Or</i> Grade 4	Immediately interrupt infusion and provide supportive care according to institutional standards. Discontinue bevacizumab/placebo and notify the study chair.
Renal and urinary disorders	Proteinuria	
	Grade 1: 1+ proteinuria (30 - < 100 mg/dL); urinary protein < 1 g/24 hours	Continue bevacizumab/placebo
	Grade 2: 2+ proteinuria (>100-< 500 mg/dL); urinary protein 1-3.4 g/24 hours	Continue bevacizumab/placebo. Obtain additional urine sample for urine protein: creatinine (UPC) ratio ² <ul style="list-style-type: none"> • UPC ratio ≤ 1.9: Continue bevacizumab/placebo. • UPC ratio ≥ 2: Hold bevacizumab/placebo and collect a 24-hour urine sample for urinary protein prior to next visit. May resume bevacizumab/placebo when urine protein is <2.0 g/24 hours.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
	Grade 3: Urinary protein ≥ 3.5 g/24 hours	<p>Hold bevacizumab/placebo. Collect a 24-hour urine sample for urinary protein. May resume when urinary protein is < 2.0 g/24 hours. Consider nephrology consult.</p> <p>If urine protein > 2.0 g/24 hours after 4 weeks despite optimal medical management, discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.</p> <p>Discontinue bevacizumab/placebo permanently. Consider nephrology consult. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.</p>
	Nephrotic syndrome	Discontinue protocol therapy. Consider nephrology consult.
Vascular disorders	Hypertension	
	Grade 1 (Prehypertension: systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	Continue bevacizumab/placebo
	Grade 2 (Stage 1 hypertension: systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg; medical intervention indicated; recurrent or persistent [≥ 24 hours]; symptomatic increase by > 20 mmHg [diastolic] or to $> 140/90$ mmHg if previously WNL; monotherapy indicated)	Continue bevacizumab/placebo. Initiate antihypertensive medication (e.g., DHP calcium channel blocker such as amlodipine).

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
<i>BASED ON INTERVAL ADVERSE EVENT</i>		
	Grade 3 (Stage 2 hypertension: systolic BP ≥160 mmHg or diastolic ≥100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated)	Hold bevacizumab/placebo. Add additional antihypertensive medication according to institutional standard of care or treating investigator's discretion (e.g., ACE inhibitor or angiotensin receptor blocker). Other protocol therapy may be continued at treating investigator's discretion. When BP controlled to ≤ grade 2, resume bevacizumab/placebo at full dose. If ≥ grade 3 after 4 weeks despite optimal medical management, discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
	Grade 4 (life-threatening consequences [e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis]; urgent intervention indicated)	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
Vascular disorders	Thromboembolic event	
	Grade 1: Venous thrombosis (e.g., superficial thrombosis) OR Grade 2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Continue bevacizumab/placebo at treating investigator's discretion. Medical intervention as clinically indicated per institutional standards and treating investigator's discretion.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
	Grade 3: Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombosis), medical intervention indicated	Hold bevacizumab/placebo. Other protocol therapy may be continued at treating investigator’s discretion. Resume when medically stable and on stable dose of anticoagulation.
	Grade 4: Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator’s discretion after discussion with the study chair.
Cardiac disorders Vascular disorders Nervous system disorders	Arterial thrombotic events (e.g., acute coronary syndrome, myocardial infarction, peripheral ischemia, visceral arterial ischemia, ischemia cerebrovascular)	
	Grade 2 OR Grade 3 OR Grade 4	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator’s discretion after discussion with the study chair.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
<i>BASED ON INTERVAL ADVERSE EVENT</i>		
Nervous system disorders	Reversible posterior leukoencephalopathy syndrome (RPLS)	
		<p>For signs and symptoms suggestive of RPLS (e.g., confusion, headache, seizures, cortical blindness), hold bevacizumab/placebo. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, bevacizumab/placebo should be permanently discontinued.</p> <p>If RPLS is ruled out via MRI, the decision on resuming bevacizumab/placebo should be based on the nature of the signs/symptoms. For grade 4 events with likely relationship to bevacizumab/placebo, discontinue bevacizumab/placebo; for grade 3 events, bevacizumab/placebo may be resumed if toxicities completely resolve within 4 weeks.</p> <p>Other protocol therapy may be continued at the discretion of the treating physician after discussion with the study chair.</p>
Cardiac disorders	Left ventricular systolic dysfunction	
	Grade 3 <i>Or</i> Grade 4	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
Gastrointestinal disorders	Intra-abdominal fistula or perforation	
	Any grade	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
<i>BASED ON INTERVAL ADVERSE EVENT</i>		
Other	Hemorrhage / Bleeding	
	Grade 1 <i>Or</i> Grade 2	Continue bevacizumab/placebo at treating investigator's discretion. Initiate wound care and medical therapy according to institutional standard of care.
	Grade 3 <i>Or</i> Grade 4	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
Injury, poisoning, and procedural complications	Wound dehiscence	
	Grade 1 <i>Or</i> Grade 2	Continue bevacizumab/placebo at treating investigator's discretion. Initiate wound care and medical therapy according to institutional standard of care.
	Grade 3 <i>Or</i> Grade 4	Discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator's discretion after discussion with the study chair.
Other	Other bevacizumab/placebo-related, clinically significant, non-hematologic toxicities	
	Grade 1 <i>Or</i> Grade 2	Continue bevacizumab/placebo

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←		
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION** ¹
BASED ON INTERVAL ADVERSE EVENT		
	Grade 3 <i>Or</i> Grade 4	Hold bevacizumab/placebo and restart at full dose if resolved to ≤grade 1 by Day 1. If ≥grade 2 on Day 1 of cycle despite optimal medical management, continue to hold bevacizumab/placebo and check weekly, then treat based on interval toxicity. Irinotecan and cetuximab may continue at the same dose level as previous at the treating investigator’s discretion. If ≥grade 2 after 4 weeks despite optimal medical management, discontinue bevacizumab/placebo permanently. Continuation of irinotecan and cetuximab on protocol can be considered at the treating investigator’s discretion after discussion with the study chair.

* Located at [REDACTED]

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

1. Refers do dose used in previous cycles.
2. Obtain at least 4 ml of a random urine sample. Determine spot urine protein concentration (mg/dL) and spot urine creatinine concentration (mg/dL) quantitatively (i.e., not by urine dipstick). Divide results of protein concentration by creatinine concentration to obtain the UPC ratio

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels -1, -2, and -3) will be at the discretion of the treating physician after discussion with the overall PI, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in the reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006;24:3187-3205.

- 9.3** Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- 9.4** Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, supportive measures and antidiarrheal medication should be initiated as soon as possible. If fever or neutropenia is present, consider hospitalization and antibiotic therapy.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Reporting Period

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial.
- 10.12 Identify and grade the severity of the event using the CTCAE version 4.0.
- 10.13 Determine whether the event is expected or unexpected (see Section 10.2).
- 10.14 Determine if the adverse event is related to the study intervention (agent, medical treatment, or procedure) (see Section 10.3).
- 10.15 Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- 10.16 All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agent(s) and Commercial Agent(s) on, SEPARATE Arms**

- An AE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines in the appropriate **IND/IDE** Reporting Table in Section 10.4.
- An AE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol. **Refer to Commercial** Reporting Table in Section 10.4.

10.32 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

When a commercial agent is used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), **the entire combination (arm) is then considered an investigational**

intervention for reporting. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4.

10.33 EXPECTED Serious Adverse Events: Protocol-Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditiously reported.
Vascular Disorders	Hypertension	≤ grade 3
	Arterial thromboembolic events	Any grade
	Venous thromboembolic events	≤ grade 3
Renal and urinary disorders	Proteinuria	≤ grade 3
Gastrointestinal disorders	Gastric perforation, abscesses	Any grade
	Gastric fistula	Any grade
Injury, poisoning and procedural complications	Wound complication	≤ grade 3
Respiratory, thoracic and mediastinal disorders	Bronchopulmonary hemorrhage	≤ grade 3
Nervous system disorders	Reversible posterior leukoencephalopathy syndrome	Any grade
	Intracranial hemorrhage	≤ grade 2
Cardiac disorder	Heart failure	≤ grade 3

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event regardless of hospitalization.

- * Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.
- * Report an expected event that is greater in severity or specificity than expected as an expedited event.
- * An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the

commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- **Reportable categories of Death**
 - Death attributable to a CTCAE term.
 - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
 - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
 - Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.334 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage, or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 Expedited Reporting via the ACCRU Adverse Event Expedited Report Form for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)		
<p>NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). <p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.33 of the protocol.</p>		
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.</p>		
Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization \geq 24 hrs	7 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required	
<p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. ○ "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE. 		
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p>Expedited 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 3, 4, and Grade 5 AEs <p>Expedited 7 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization <p>²For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.</p> <p>Effective Date: May 5, 2011</p>		

Additional Instructions:

1. Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via expedited mechanisms if the event occurs following treatment on a trial under an IND.
2. Use the ACCRU protocol number and the protocol-specific patient ID provided during trial registration on all reports.

The above expedited reports (24-hour and 3 or 7 day) must be submitted via the **ACCRU Adverse Event Expedited Report Form**. Submit reports to the ACCRU SAE Coordinator via fax [REDACTED]

3. Once the ACCRU SAE Coordinator receives the report via fax, the ACCRU SAE Coordinator will forward a copy of the above expedited reports to:

- **The ACCRU IND Coordinator** who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
- **Genentech:** Genentech will be informed in writing of any SAE within 24 hours/1 business day of receipt of the fax. The fax will be sent by the ACCRU SAE Coordinator to Genentech Drug Safety at: [REDACTED]
 - The ACCRU SAE Coordinator will provide relevant follow-up information to Genentech Drug Safety as soon as it becomes available.
 - Serious AE reports that are related to the bevacizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
 - Serious AE reports that are unrelated to the bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
 - Additional Reporting Requirements to Genentech (from ACCRU) include the following:
 - Any reports of pregnancy following the start of administration with bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
 - All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech (from ACCRU).
 - Special situation reports
 - In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within (30) calendar days:
 - Data related to the Product usage during pregnancy or breastfeeding
 - Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted

medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol

- Lack of therapeutic efficacy
- Drug interaction

Use of a medicinal Product in an Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

Occasionally Genentech may contact ACCRU for additional information, clarification, or current status of the patient for whom an adverse event was reported,

10.424 **Pregnancy**

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE.

Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the bevacizumab should be reported as an SAE.

10.425 **Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject, including, pregnancy occurring in the partner of a male study subject] who participated in the study, the should be reported as an SAE adequately to Genentech drug Safety during follow up period.

10.5 Other Required Reporting

10.51 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation are stated in the table below*:

System Organ Class	Adverse/Event Symptoms	Baseline	Each Evaluation
Investigations	Neutrophil count decreased		X
	Platelet count decreased		X
Gastrointestinal disorders	# Stools per day	X	
	Diarrhea		X
Vascular disorders	Hypertension	X	X
Skin and subcutaneous tissue disorders	Rash acneiform		X
	Rash maculo-papular		X
Metabolism and nutrition disorders	Hypomagnesemia		X

* Grading is per CTCAE v4.0 unless otherwise specified.

10.52 Case Report Forms

Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

- 10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
- 10.523 Grade 5 AEs (Deaths)
- 10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- 10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Genentech AEs of Special Interest

AEs of Special Interest for bevacizumab are defined by Genentech as a potential safety problem identified as a result of ongoing safety monitoring of their product. As such, **surveillance AEs in Appendix II MUST be undertaken at each treatment evaluation. Development of one of these AEs (\geq grade 1 unless otherwise noted) MUST be reported on the AE case report forms in terms of CTCAE v4.0 grade and attribution.**

- 10.531 Reconciliation: ACCRU agrees to conduct reconciliation for the

product. Genentech and the Sponsor will agree to the reconciliation periodicity and format but agree at a minimum to exchange quarterly line listings of cases received by the other party. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by ACCRU to Genentech within five (5) calendar days from request by Genentech

If discrepancies are identified, (ACCRU) and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

- 10.532 Study Close-out: Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech by ACCRU. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study and to Genentech Drug Safety CTV oversight mail box at:

Email: [REDACTED]

and

Email: [REDACTED]

11.0 Treatment Evaluation Using RECIST Guideline

Note: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer, et al, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks (e.g. 4 cycles).

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

- 11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥ 1.0 cm with CT scan, CT component of a PET/CT, or MRI.

- 11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- 11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

11.22 Non-Measurable Disease

- 11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

NOTE: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
 - i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
 - ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
 - iii. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that

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

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

NOTE: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

- 11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR):

All of the following must be true:

- a. Disappearance of all target lesions.
- b. Each target lymph node must have reduction in short axis to <1.0 cm.
- c. Normalization of tumor biomarkers (i.e., CEA).

- Partial Response (PR):

At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.41).

- Progression (PD):

At least one of the following must be true:

- a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
- b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR, nor sufficient

increase to qualify for PD taking as reference the MSD

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR):

All of the following must be true:

- Disappearance of all non-target lesions.
- Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD:

Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD):

At least one of the following must be true:

- At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
- Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.).
- See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)

PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.431

** **NOTE:** This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 **Symptomatic Deterioration:** Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to “symptomatic deterioration” if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors:

None

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 Patients who develop new CNS disease only will be considered to have PD and will go to Event Monitoring.

13.5 Patients who develop PD at any time should go to Event Monitoring. These patients can be treated with alternative treatment options at the treating investigator’s discretion if their clinical status is good enough to allow further therapy.

13.6 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study.

- If the patient received treatment, all data up until the point of confirmation of

ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background / methodology section)	Where to find specific details for specimen submission
Blood/blood products	Mandatory	Quarterly (Section 14.252)	Future biomarkers research and banking (Section 14.2)	Section 14.2
Blood/blood products	Mandatory		Banking (Section 14.2)	Section 14.2

14.2 Blood/Blood Products Handling

14.21 Kits are *not* required for this study; however cryovials will be supplied.

14.211 The requisition form and processing instructions will be found on the ACCRU study-specific web page, under Forms. Cryovials should be requested by each site that is participating on the study prior to first enrollment and as needed throughout the course of the study. To request cryovials, please contact:



Cryovials will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will not cover the cost for rush delivery of cryovials.**

14.22 All samples should be collected Monday-Friday.

14.23 Collect and process all blood/blood products according to the directions below

14.231 Time period from blood draw to freezing of plasma must be less than 4 hours. Tubes can be kept at room temperature until processing. Please accurately record time of blood draw and time of processing.

14.232 Draw venous blood into one 10 mL EDTA tube labeled cfDNA and immediately gently invert the tubes 8-10 times. Write the protocol number, patient ID number, and draw date number on the tube.

- 14.233 Immediately centrifuge for 10 minutes at 1500 (+/- 150) x g. NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.
- 14.234 Pipette the plasma layer (top clear layer) into a new 15 mL tube labeled “cfDNA/patient ID number”. Do not ship. NOTE: Do not dip the tip of the pipette into the plasma/cell interface. Leave a thin plasma layer intact over the interface.
- 14.235 Centrifuge the 15 mL tube containing the plasma only for 10 minutes at 3000 (+/- 150) x g.
- 14.236 Transfer using a fresh pipette, the supernatant into a second 15 mL tube labeled “cfDNA super.do not ship”. NOTE: Leave about 0.3 mL of supernatant in the centrifuged 15 mL tube. This leftover 0.3 mL contains cellular debris.
- 14.237 Using a fresh pipette, transfer 1 mL of plasma from the “super.do not ship” tube into max four (4) 2 mL cryovials labeled “cfDNA.ship.patient ID number/protocol number/date of blood draw.”
- 14.238 Freeze immediately upright at -70°C or colder until shipping.
- 14.239 Ship the frozen samples quarterly to the address on the requisition form. [REDACTED] See the instructions for the FedEx account number to use to ship the samples priority overnight.

14.24 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Baseline / Before Treatment	At time of 1st and 2nd restaging	At Treatment Discontinuation	Additional processing required at site after blood draw?	Storage / shipping conditions ¹
Mandatory	EDTA (purple)	10 mL (1)	Plasma and buffy coat for future research	X	X	X	Yes	Freeze immediately upright at ≤ -70° C

1. After all samples have been processed according to instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

- 14.251 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), [BAP Requisition Form and processing instructions (see Forms Packet)], and specimen collection labels are completed and filled in correctly.

- 14.252 Specimens will be shipped in batches on a quarterly basis.
- 14.253 Ship specimens and requisition forms used to log recording time of blood draw and processing via Priority Overnight service, **Monday – Friday**, to BAP Freezer according to instructions. **Do not send samples on weekends or just prior to federal holidays.**



- 14.254 BAP Freezer will receive the samples and immediately forward the specimens to the



14.3 Study Methodology and Storage Information

- 14.31 Blood/blood product samples will be collected for future biomarker studies. Analysis will be completed when funding is secured.
- We will address the following questions as part of the hypothesis generation stage:
- 14.311 Identify predictive and prognostic markers (DNA, cfDNA, RNA, cfRNA) and assess their associations with toxicity, prognostic value, and response to treatment.
- 14.312 Define key molecular subtypes and assess their associations with toxicity, prognostic value, and response to treatment.
- 14.313 Determine the prognostic and predictive values of immune signatures.
- 13.314 Investigate stem cell signatures and their association with RR, PFS, OS and dependent on location/Braf/MSI.
- 14.32 Use of Circulating Cell-Free DNA (cfDNA) to Monitor Response and Determine Mechanisms of Resistance to Cetuximab

Predictors of clinical benefit from and markers of resistance to EGFR antibodies are urgently needed in order to better select patients for treatment and identify those unlikely to respond. In addition, mechanisms of acquired resistance remain unclear and need to be understood if effective new therapies are to be developed for patients who have progressed. Given the procedural risks, cost, and patient inconvenience of post-treatment tumor biopsies, the analysis of cfDNA obtained from plasma may provide a non-invasive means of interrogating the biology underlying response and resistance to EGFR inhibition. Indeed, recent years have witnessed several high profile publications demonstrating the potential power of

cfDNA genotyping. Studies on cfDNA specimens from 24 colon cancer patients demonstrated that resistance arose via point mutations in *KRAS*. (Diaz LA, Jr., Williams RT, Wu J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature* 2012;486:537-40.) In a second study, these same mutations were found in two of two patient biopsy samples after progression on EGFR inhibitors and cfDNA detection appeared to predict resistance to treatment up to 10 months prior to radiographic progression. (Misale S, Yaeger R, Hobor S, et al. Emergence of *KRAS* mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature* 2012;486:532-6.)

We have developed a new technology for non-invasive quantification of specific tumor mutations in cfDNA isolated from plasma specimens by droplet digital PCR (ddPCR). ddPCR emulsifies input DNA into ~20,000 droplets that are PCR amplified and fluorescently labeled, and then read in an automated droplet flow cytometer. Each droplet is individually assigned a positive or negative value based on the fluorescent intensity. The number of positive and negative droplets is read by a flow cytometer and is used to calculate the concentration of an allele. To gauge feasibility, we studied serial plasma specimens from patients with genotype-defined lung cancer or melanoma to determine whether changes in cfDNA were representative of tumor biology (**Figure 1**). In a patient with *EGFR*-mutant NSCLC receiving chemotherapy after failing erlotinib (**Figure 1A**), an increase in plasma L858R and T790M was seen with development of new brain metastases, followed by decreased plasma levels when treatment on a clinical trial was initiated. In a second case of *EGFR*-mutant NSCLC receiving chemotherapy (**Figure 1B**), plasma L858R decreased as the patient's pleural drainage resolved, though CT imaging of the non-measurable disease showed disease stability. In a patient with *KRAS*-mutant NSCLC and bone metastases (**Figure 1C**), chemotherapy caused a decrease in plasma G12C levels concordant with improved pain control and decreased opiate requirement. Lastly, a patient with *BRAF*-mutant melanoma had progression on experimental immune therapy followed by response to vemurafenib (**Figure 1D**), seen in the rise and fall of plasma V600E levels. This pilot experience suggests cfDNA genotyping has value for serial assessment of disease status, even in patients without objectively measurable disease on CT.

This data also suggests that such a non-invasive assay could be used to characterize the biology of resistance. For the colorectal cancer patients enrolled in this study, genotype concentrations of *KRAS*, *NRAS*, and *BRAF* mutations will be evaluated initially. As more ddPCR assays are validated and new knowledge about resistance mechanisms emerges, the mutations to be studied can be broadened to include genes such as *PIK3CA*, *PTEN*, *EGFR*, among others. Remaining plasma will be banked for this purpose of future research.

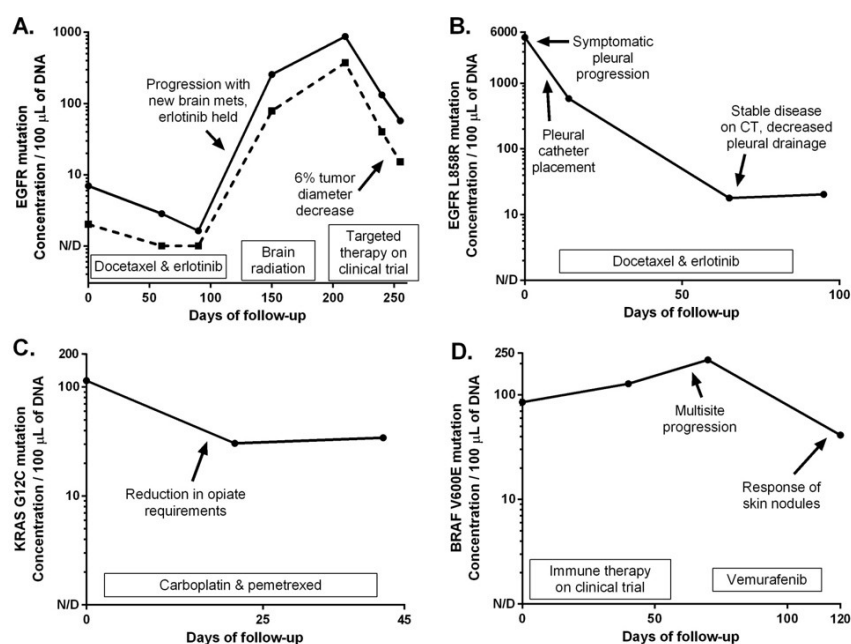


Figure 1. Serial measurement of plasma genotype for disease monitoring. A wide dynamic range is seen in some cases (A, B). Decreases in plasma genotype can be seen both in cases of objective tumor shrinkage (A, D) and in cases of symptomatic response with no measurable disease (B, C). Concurrent *EGFR* L858R (A, solid line) and T790M (A, dashed line) mutations trend in parallel.

14.33 Droplet Digital PCR (ddPCR)

ddPCR involves dilution of DNA molecules into an aqueous/oil suspension containing the necessary reagents for PCR. After disturbance of the suspension, thousands of aqueous compartments (or “droplets”) within the oil emulsion are formed, and PCR reactions are cycled and quantified using a flow cytometer. We have built our ddPCR so that standard TaqMan reagents can be used. In brief, TaqMan PCR reaction mixtures will be assembled from a 2 \times ddPCR Mastermix (Bio-Rad) and custom 40 \times TaqMan probes/primers made specific for each assay. Nineteen μ L of assembled ddPCR reaction mixture plus 6 μ L of ultra pure distilled water will be loaded into sample wells of an eight-channel disposable droplet generator cartridge (Bio-Rad). An additional seventy μ L of droplet generation oil (Bio-Rad) will be loaded into the oil well for each channel. Droplets will be transferred to a 96-well PCR plate and amplified to end-point by conventional PCR. After PCR, the 96-well PCR plate will be read on the QX-100 droplet reader (Bio-Rad) and analyzed by the QuantaSoft analysis software suite (Bio-Rad) that accompanies the droplet reader. Each plasma sample will be analyzed in triplicate with an increasing quantity of input DNA (e.g. 1 μ L, 2 μ L, and 4 μ L). Results will be normalized to the mean concentration of mutant alleles per μ L DNA input, and reported as copies of mutant allele per 100 μ L of DNA.

14.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Bevacizumab (Avastin®)

Investigator brochure will be available on the ACCRU website.

15.11 **Background:** Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.12 **Formulation:** Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is >95%.

Bevacizumab is supplied in 100 mg (4 mL) and 400 mg (16 mL) glass vials, each with a concentration of 25 mg/mL. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

15.13 **Preparation and storage:** Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE.**

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. **Do not administer or mix with dextrose solution.** From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours

at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

- 15.14 **Administration:** Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Do not initiate bevacizumab for 28 days following major surgery and until surgical wound is fully healed.

Refer to Section 7 for protocol-specific administration instructions. Guidelines recommended by the manufacturer are included for reference.

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

- 15.15 **Pharmacokinetic information:**

Distribution: V_d : 46 mL/kg (limited extravascular distribution)

Half-life elimination: ~20 days (range: 11-50 days)

Clearance: 2.75-5 mL/kg/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.

Time to steady state: 100 days

- 15.16 **Potential Drug Interactions:**

Overall the results from the drug-drug PK interaction investigations showed no interaction between bevacizumab and the anti-cancer agents tested. Co-administration of bevacizumab with various chemotherapeutic and other anti-cancer agents resulted in similar values of CL and V_c for bevacizumab, suggesting that the exposure of bevacizumab are not affected by concomitant dosing with doxorubicin, capecitabine, capecitabine/oxaliplatin (XELOX), 5-FU/leucovorin, 5-FU/leucovorin/irinotecan (IFL), 5-FU/leucovorin/oxaliplatin (FOLFOX4), erlotinib, carboplatin, cisplatin, oxaliplatin, paclitaxel, gemcitabine, temozolomide or interferon- α 2a.

The effect of bevacizumab on the disposition of several agents (doxorubicin, 5-FU, irinotecan [and its active metabolite SN38], capecitabine, oxaliplatin, carboplatin, cisplatin, paclitaxel, gemcitabine, erlotinib, temozolomide and interferon alfa-2a) has been investigated. Accumulating data do not suggest that bevacizumab affects disposition of anti-neoplastic agents.

Increased Effect/Toxicity: Bevacizumab may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Bevacizumab may also

enhance the adverse/toxic effect of Irinotecan, Sorafenib, and Sunitinib. Sunitinib may enhance the adverse/toxic effect of Bevacizumab. Specifically, the risk for a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased.

- 15.17 **Known potential adverse events:** Consult the investigator's brochure and package insert for the most current and complete information. U.S. Boxed Warnings include severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding. Avoid use in patients with serious hemorrhage or recent hemoptysis. Percentages reported as Monotherapy and as part of combination chemotherapy regimens.

Common known potential toxicities, >10%:

Cardiovascular: Hypertension, venous thromboembolism, peripheral edema, hypotension, arterial thrombosis

Central nervous system: Pain, headache, dizziness, fatigue, taste disorder, peripheral sensory neuropathy, anxiety

Dermatologic: Alopecia, palmar-plantar erythrodysesthesia, exfoliative dermatitis, xeroderma.

Endocrine & metabolic: Ovarian failure, hyperglycemia, hypomagnesemia, weight loss, hyponatremia, hypoalbuminemia

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, stomatitis, gastrointestinal hemorrhage, dyspepsia, decreased appetite, nausea, vomiting

Genitourinary: Proteinuria, urinary tract infection, pelvic pain

Hematologic & oncologic: Hemorrhage, neutropenia, leukopenia pulmonary hemorrhage, lymphocytopenia

Infection: Pneumonia, catheter infection, or wound infection

Neuromuscular & skeletal: Myalgia, back pain.

Renal: Increased serum creatinine

Respiratory: Upper respiratory tract infection, epistaxis, dyspnea, rhinitis

Miscellaneous: Postoperative wound complication (including dehiscence)

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Thrombosis, deep vein thrombosis, syncope, intra-abdominal venous thrombosis, left ventricular dysfunction, pulmonary embolism

Central Nervous System: Voice disorder

Dermatologic: Acne vulgaris, dermal ulcer, cellulitis

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Xerostomia, rectal pain, colitis, intestinal obstruction, gingivitis, gastrointestinal fistula, gastroesophageal reflux disease, gastrointestinal perforation, oral mucosa ulcer, gastritis, gingival pain, gingival hemorrhage

Genitourinary: Vaginal hemorrhage

Hematologic & oncologic: Febrile neutropenia, neutropenic infection, thrombocytopenia, hemorrhage

Infection: Tooth abscess

Neuromuscular & skeletal: Weakness, dysarthria

Ophthalmic: Blurred vision
Otic: Tinnitus, deafness
Respiratory: Pneumonitis
Miscellaneous: Gastrointestinal-vaginal fistula, anal fistula, infusion-related reaction

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Angina pectoris, antibody development (anti-bevacizumab and neutralizing), bladder fistula, bronchopleural fistula, cerebral infarction, conjunctival hemorrhage, endophthalmitis (infectious and sterile), fistula of bile duct, fulminant necrotizing fasciitis, gallbladder perforation, gastrointestinal ulcer, hemolytic anemia (microangiopathic; when used in combination with sunitinib), hemoptysis, hemorrhagic stroke, hypersensitivity, hypertensive crises, hypertensive encephalopathy, increased intraocular pressure, intestinal necrosis, intraocular inflammation (iritis, vitritis), mesenteric thrombosis, myocardial infarction, nasal septum perforation, ocular hyperemia, osteonecrosis of the jaw, ovarian failure, pancytopenia, polyserositis, pulmonary hypertension, rectal fistula, renal failure, renal fistula, renal thrombotic microangiopathy, retinal detachment, retinal hemorrhage, reversible posterior leukoencephalopathy syndrome, sepsis, tracheoesophageal fistula, vaginal fistula, vitreous hemorrhage, vitreous opacity

- 15.18 **Drug procurement:** Genentech will supply commercial drug labeled for investigational use to McKesson. Each participating ACCRU treating location will order the drug from McKesson. Fax the Drug Order Request Form (found in the Forms Packet) request to:



Each participating ACCRU treating location will be responsible for monitoring the supply of bevacizumab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site according to procedures in place at each institution.

- 15.19 **Suggested nursing guidelines:**

15.191 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur, stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.

- 15.192 Monitor urine dipstick or UPC as required by the test schedule.
- 15.193 Evaluate IV site regularly for signs of infiltration.
- 15.194 Bleeding in the absence of thrombocytopenia is a dose-limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.
- 15.195 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially close.
- 15.196 Patients may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.
- 15.197 Monitor for skin rash, instruct patient to report to MD.
- 15.198 Monitor blood pressure. Administer antihypertensives as ordered by MD.
- 15.199a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to MD immediately.
- 15.199b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.
- 15.199c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.
- 15.199d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.
- 15.199e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.
- 15.199f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.
- 15.199g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS

changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

- 15.199h Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.
- 15.199i Warn female patients of the risk of rectovaginal fistula.
- 15 199j Agent may cause increased cardiotoxic effects of anthracyclines as well as toxic effects of irinotecan, sorafenib, and sunitinib. Patients who on are on dual therapy with these agents should be monitored closely.

15.2 Irinotecan (Camptosar®, CPT11)

- 15.21 **Background:** Irinotecan and its active metabolite (SN-38) bind reversibly to topoisomerase I-DNA complex preventing relegation of the cleaved DNA strand. This results in the accumulation of cleavable complexes and double-strand DNA breaks. As mammalian cells cannot efficiently repair these breaks, cell death consistent with S-phase cell cycle specificity occurs, leading to termination of cellular replication.
- 15.22 **Formulation:** Commercially available for injection 20 mg/mL (2 mL, 5 mL, 25 mL) [contains sorbitol 45 mg/mL; do not use in patients with hereditary fructose intolerance].
- 15.23 **Preparation, storage, and stability:** Store intact vials at room temperature (15 to 30°C or 59 to 86°F) and protect from light. Doses should be diluted in 250-500 mL D5W or 0.9% NaCl to a final concentration of 0.12-2.8 mg/mL. Solutions diluted in D5W are stable for 24 hours at room temperature or 48 hours under refrigeration at 2°C to 8°C. Solutions diluted in 0.9% NaCl may precipitate if refrigerated. Do not freeze.
- 15.24 **Administration:** Administer by I.V. infusion, usually over 90 minutes.
- 15.25 **Pharmacokinetic information:**
 - Distribution:** V_d : 33-150 L/m²

Protein binding, plasma: Predominantly albumin; Parent drug: 30% to 68%, SN-38 (active metabolite): ~95%

Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; SN-38 undergoes conjugation by UDP- glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. Conversion of Irinotecan to SN-38

is decreased and glucuronidation of SN-38 is increased in patients who smoke cigarettes, resulting in lower levels of the metabolite and overall decreased systemic exposure. SN-38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele). Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. The lactones of both Irinotecan and SN-38 undergo hydrolysis to inactive hydroxyl acid forms.

Half-life elimination: SN-38: Mean terminal: 10-20 hours

Time to peak: SN-38: Following 90-minute infusion: ~1 hour

Excretion: Within 24 hours: urine: Irinotecan (11% to 20%), metabolites (SN-38 <1%, SN-38 glucuronide, 3%)

15.26 Potential Drug Interactions:

Cytochrome P450 Effect: Substrate (major) of CYP2B6, 3A4, P-glycoprotein, SLCO1B1 and UGT1A1

Increased Effect/Toxicity: CYP2B6 and CYP3A4 inhibitors may increase the levels/effects of irinotecan. Bevacizumab may increase the adverse effects of irinotecan (e.g., diarrhea, neutropenia). Ketoconazole increases the levels/effects of Irinotecan and active metabolite; discontinue ketoconazole 1 week prior to irinotecan therapy; concurrent use is contraindicated.

Decreased Effect: CYP2B6 and CYP3A4 inducers may decrease the levels/effects of irinotecan.

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John's wort decreases therapeutic effect of irinotecan; discontinue ≥ 2 weeks prior to irinotecan therapy; concurrent use is contraindicated.

15.27 Known potential adverse events: Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, >10%:

Cardiovascular: Vasodilation

Central nervous system: Cholinergic toxicity (includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever, pain, dizziness, insomnia, headache, chills

Dermatologic: Alopecia, rash

Endocrine & metabolic: Dehydration

Gastrointestinal: Late onset diarrhea, early onset diarrhea, nausea, abdominal pain, vomiting, cramps, anorexia, constipation, mucositis, weight loss, flatulence, stomatitis

Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia

Hepatic: Bilirubin increased, alkaline phosphatase increased

Neuromuscular & skeletal: Weakness, back pain

Respiratory: Dyspnea, cough, rhinitis

Miscellaneous: Diaphoresis, infection

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Edema, hypotension, thromboembolic events

Central nervous system: Somnolence, confusion

Gastrointestinal: Abdominal fullness, dyspepsia

Hematologic: Neutropenic fever, hemorrhage, neutropenic infection

Hepatic: AST increased, ascites and/or jaundice

Respiratory: Pneumonia

Rare known potential toxicities, <1% (Limited to important or life-threatening):

ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial pulmonary disease (IPD), intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, myocardial ischemia, neutropenic typhilitis, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus, pulmonary toxicity (dyspnea, fever, reticulonodular infiltrates on chest x-ray), renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhilitis, ulceration, ulcerative colitis,

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Suggested nursing guidelines:**

15.291 If possible, check for any history of hypersensitivity reaction to any previous drug formulated with polysorbate 80.

15.292 Cholinergic symptoms of lacrimation, nasal congestion, diaphoresis, flushing, abdominal cramping, and diarrhea can occur at the beginning, during, or immediately after the CPT-11 infusion. It is suggested that the patient remain in the treatment area for a minimum of one hour following the completion of the very first CPT-11 infusion. If diarrhea occurs within one hour of infusion, refer to Section 9.2 or 15.16 for management.

15.293 Patient education is extremely important. Impress on the patient the importance of compliance with treatment of diarrhea management (see Section 9.4). Stress the need for prompt recognition and early intervention. Motivate the patient to report any complications immediately. The cholera-like syndrome can be unresponsive to conventional antidiarrheals and can result in severe dehydration.

15.294 Ondanestron and diphenhydramine should provide good relief from the nausea/vomiting/cramping. Avoid prochlorperazine on the day of

treatment due to its association with akathisia (motor restlessness). Prochlorperazine may be taken between treatments.

- 15.295 Advise avoidance of excess caffeine, a GI stimulant. Avoid magnesium-based antacids such as Mylanta, Maalox, Rolaids, MOM, Mag-Ox 400, and Tylenol with antacid.
- 15.296 The pulmonary toxicity seen is usually manifested by dyspnea beginning 42-175 days after treatment and occurs at a cumulative dose ranging from 400-1000 mg/m (median 750). Instruct patient to report any cough or SOB.
- 15.297 Patients are at risk for developing eosinophilia and will improve on steroid therapy.
- 15.298 Hepatic enzyme elevations have been transient and did not require intervention.
- 15.299a Monitor CBC closely. Leukopenia occurs primarily as neutropenia but can be severe and dose limiting. The simultaneous occurrence of grade 4 diarrhea and grade 4 neutropenia is rare but may render the patient more susceptible to polymicrobial sepsis and potentially death.
- 15.299b Advise patients of probable hair loss.

15.3 Cetuximab (Erbix®)

- 15.31 **Background:** Cetuximab is a recombinant human/mouse chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding 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. EGFR signal transduction results in KRAS wild-type activation; cells with KRAS mutations appear to be unaffected by EGFR inhibition.
- 15.32 **Formulation:** Commercially available for injection 2 mg/mL (50 mL, 100 mL).
- 15.33 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature (2 to 8°C 38 to 46°F), do not freeze or shake. Reconstitution is not required. Appropriate dose should be added to empty sterile container; do not shake or dilute. Preparations in infusion containers are stable for up to 12 hours under refrigeration (2 to 8°C 38 to 46°F) and up to 8 hours at room temperature (20 to 36°C or 68 to 77°F).
- 15.34 **Administration:** Administer via I.V. infusion; loading dose over 2 hours; weekly maintenance dose over 1 hour. Do not administer as I.V. push or bolus. Do not shake or dilute. Premedication with antihistamines is recommended. The maximum infusion rate is 10 mg/minute. Administer through a low protein-

binding 0.22 micrometer in-line filter. Use 0.9% NaCl to flush line at the end of infusion. For biweekly administration (unlabeled frequency and dose), the initial dose was infused over 120 minutes and subsequent doses infused over 60 minutes.

15.35 **Pharmacokinetic information:**

Distribution: V_d : ~2-3 L/m²

Half-life elimination: ~112 hours (range: 63-230 hours)

15.36 **Potential Drug Interactions:**

There are no known interactions where it is recommended to avoid concomitant use.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe infusion reactions and cardiopulmonary arrest. Cetuximab is contraindicated in patients with known severe reactions to Cetuximab.

Common known potential toxicities, >10%:

Central nervous system: Fatigue, pain, peripheral sensory neuropathy, headache, insomnia, fever, confusion, anxiety, chills, depression

Dermatologic: Skin rash, acneiform, eruption, xeroderma, pruritus, nail disease

Endocrine & metabolic: Hypomagnesemia, dehydration

Gastrointestinal: Nausea, abdominal pain, constipation, diarrhea, vomiting, stomatitis, xerostomia

Neuromuscular & skeletal: Ostealgia, arthralgia

Respiratory: Dyspnea, cough

Miscellaneous: Fever, infusion-related reactions

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Cardiopulmonary arrest

Central nervous system: Taste disorder

Dermatologic: Alopecia, skin disorder

Immunologic: Antibody development

Infection: Sepsis

Renal: Renal failure

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Abscess, aseptic meningitis, blepharitis, cardiac arrest, cardiac arrhythmia, cellulitis, cheilitis, conjunctivitis, corneal ulcer, hypertrichosis, hypotension, interstitial pulmonary disease, increased eosinophils (a type of white blood cell) in the blood with or without scarring or inflammation of the lungs, keratitis, leukopenia, loss of consciousness, MI, pulmonary embolism, radiation dermatitis, shock, skin fissure, skin infection, stridor

- 15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.
- 15.39 **Suggested nursing guidelines:**
- 15.391 Patients should be closely monitored during the infusion for signs of anaphylaxis and standard resuscitative medications should be available during and for one hour following the cetuximab infusion.
- CAUTION:** Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses (as far out as the 8th dose). The infusion reaction may occur during the infusion, or be delayed until any time after the infusion. A nurse should be present in the immediate treatment area throughout the infusion and observation period. A physician should be in close proximity to the patient treatment area. Should an infusion reaction occur, the patient should be treated according to institutional guidelines. Patient should be instructed to report any delayed reactions to the investigator immediately. Patients who have had severe reactions should not receive further doses of Cetuximab.
- 15.392 Vital signs should be taken prior to, during, post and 1-hour post infusion.
- 15.393 Patient should be observed for 1 hour following the loading dose and each maintenance dose.
- 15.394 Premedicate with 50 mg of IV diphenhydramine, or other specific premedications called for in the protocol, prior to each dose.
- 15.395 Patients should be taught to wear sunscreen and hats and limit sun exposure while receiving treatment.
- 15.396 Recommend that all infusions be run on a volumetric pump. Infusion rate **MUST NEVER EXCEED 10MG/MINUTE (5 ML/MINUTE)**.
- 15.397 Monitor CBC and instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.
- 15.398 Monitor LFTs.
- 15.399a Fever and chills may occur. Discuss with MD about premedication with an antipyretic.
- 15.399b Monitor for signs and symptoms of gastrointestinal side effects, including nausea, constipation, diarrhea and vomiting. Administer antiemetics and antidiarrheals as indicated and evaluate their effectiveness.

- 15.399c Instruct patient to report rash.
- 15.399d Hypomagnesemia is a complication of cetuximab therapy. Instruct patients to report any of the following signs or symptoms as these may be signs of the disorder:

Neuromuscular: muscle weakness, muscle cramps, painful swallowing

CNS: Irritability, combativeness, disorientation, psychosis, vertigo, seizures

Cardiac: irregular and/or fast heartbeat

Any or all of the symptoms may or may not be present in the patient with this condition. If patients present with any of these symptoms, inform MD and a magnesium level should be checked.

- 15.399e Sensory neuropathy has been seen. Assess and inform the physician if this develops.

15.4 Placebo

- 15.41 Each institution will use 100ml bags of normal saline as the placebo agent. A volume of normal saline equal to the volume of bevacizumab will be added to the 100 mL bag of normal saline. The initial placebo dose will be given by IV over 90 minutes, the second dose over 60 minutes, and all subsequent doses over 30 minutes. Each institution will use normal saline from their commercial inventory. The ACCRU Research Base Pharmacy will not provide normal saline to the ACCRU sites.

- 15.42 Label as directed in Section 6.32.

16.0 Statistical Considerations and Methodology

16.1 Study Design Overview

This randomized Phase II trial is designed to primarily compare progression-free survival (PFS) in patients with *RAS* wild-type, irinotecan-refractory metastatic colorectal cancer who have also previously received bevacizumab in at least one prior line of therapy, who receive irinotecan and cetuximab plus bevacizumab (experimental arm) versus irinotecan and cetuximab plus placebo (control arm). The BOND-1 study (Cunningham, et al, 2004) reported a median time to progression of 4.1 months in patients with irinotecan-refractory metastatic colorectal cancer who received irinotecan plus cetuximab. The BOND-2 study (Saltz, et al, 2007) randomized irinotecan-refractory mCRC patients to bevacizumab and cetuximab with or without irinotecan. They reported a median time to progression of 7.3 in patients who received irinotecan, cetuximab and bevacizumab. Therefore, to design the current trial, we assumed median PFS of 4.1 months in the control arm.

16.2 Sample Size, Accrual Rate, and Study Duration

- 16.21 **Sample Size:** The study design to be utilized is fully described in Section 16.3. There will be 30 patients randomized to each treatment group of the study (total of 60 patients).
- 16.22 **Accrual Rate and Accrual Duration:** We anticipate accruing 4 patients per month. With a minimal follow-up of 6 months, we anticipate that the study will take approximately 15 months to accrue if there are no major issues of patient safety.
- 16.23 **Primary Endpoint Completion Date for ClinicalTrials.gov Reporting:** For purpose of ClinicalTrials.gov reporting, the primary endpoint completion date for this study is the time the last patient registered has been followed for at least 6 months.

16.3 Statistical Design and Analysis for the Primary Endpoint

16.31 Primary Endpoint:

The primary endpoint is progression-free survival (PFS), defined as time from the date of randomization to the date of 1st documented disease progression or death due to any cause, whichever occurs first. For patients who died without documented progressive disease, if the date of last disease evaluation which shows progression-free status is within 6 months before death date, PFS will be coded as event occurs at the death date. Otherwise PFS will be censored at the last disease evaluation date.

For patients who are alive and progression-free at the time of primary efficacy analysis, the following censoring rules will be implemented:

- Primary rule – PFS will be censored at the date of last disease evaluation which shows progression-free status.
- Secondary rule for sensitivity analysis – PFS will be censored at the earlier date of
 - Last disease evaluation which shows progression-free status
 - Protocol-specified treatment discontinuation due to severe toxicity
 - Start of alternative treatment due to reasons other than progressive disease or severe toxicity

The primary endpoint analysis will be conducted based on the intent-to-treat (ITT) population. Sensitivity analysis will be conducted based on the per-protocol (PP) population and applying the secondary rule for determining the censoring time.

The followings are the definitions of the various analysis populations:

- Intent-to-Treat (ITT) population: All randomized patients regardless of whether they received any treatment and regardless of their final eligibility status. Patients will be analyzed in the group to which they were randomized.

- Per-Protocol (PP) population: All randomized patients meeting the eligibility criteria who received at least one dose of the treatment and did not have any major treatment violations. Patients will be included in the analysis in the group closest in principle to the initial treatment they actually received.
- Safety Analysis (SA) population: All patients who received any quantity of study treatment. Patients will be grouped according to treatment received.

16.32 Statistical Design:

A total of 55 events will provide 80% power to detect a treatment effect of hazard ratio (HR) = 0.562 (corresponding to median PFS of 4.1 and 7.3 months in control and experimental arm, respectively) with a one-sided log-rank test, at the significance level of 0.10. With the assumptions of accruing 4 patients per month and minimal follow up of 6 months, total of 60 patients (30 per arm) will be randomized. The sample size calculation was conducted using EAST v6.4. There is no interim analysis is planned.

Decision Rules: The primary efficacy analysis will be conducted when there are at least 55 events observed for PFS (approximately 28 months after the first patient has accrued). At the conclusion of the trial, the experimental regimen will be concluded to be superior to the control regimen, if the p-value of log-rank test is less than 0.1 (equivalent to $HR < 0.708$).

16.33 Study Operating Characteristics:

The table below shows the study operating characteristics assuming the time-to-event endpoint of PFS follows exponential survival function. The proportion of times that the study would conclude that the experimental regimen is superior to the control regimen is tabulated by the various true HRs.

If the true HR is	1.00	0.89	0.78	0.67	0.56
Then the probability of declaring the experiment regimen is superior to control regimen is ...	0.1010	0.2082	0.3554	0.5705	0.7911

16.34 Analysis Plan:

The distribution of PFS by group will be estimated using the method of Kaplan-Meier. Six and 12 month PFS rates by treatment group with confidence intervals will be estimated based on Kaplan-Meier curves. The HR with confidence interval will be estimated based on stratified Cox models (stratified by levels of stratification factors), without and with adjusting for baseline clinical/pathological factors.

16.4 Supplementary Analysis Plans (Secondary Endpoints):

All analyses of secondary endpoints will be conducted in the ITT population, with the exception of safety endpoints, which will be conducted in the Safety population, or otherwise specified.

- 16.41 Adverse events: Adverse events: The maximum grade of each adverse event and its attribution will be recorded for each patient. The frequency tables will be reviewed to evaluate for patterns of toxicity. The overall adverse event rates for Grade 3 or higher adverse events will be compared between the two treatment groups using Chi-square test (or Fisher's exact test if the data in the contingency table is sparse)
- 16.42 Overall survival (OS): OS is defined as time from randomization to the date of death due to any cause. The distribution of OS by group will be estimated using the method of Kaplan-Meier. Twelve, 18- and 24-month survival rates by treatment group with confidence intervals will be estimated based on Kaplan-Meier curves. The HR with confidence interval will be estimated based on stratified Cox models (stratified by levels of stratification factors), without and with adjusting for baseline clinical/pathological factors.
- 16.43 Disease control rate (DCR): Disease control status will be determined using tumor assessment data collected from date of initiation of the treatment to the date of treatment discontinuation. Disease control is defined as maintaining CR or PR or SD as the tumor assessment result during the defined time window. DCR is defined as number of patients with success of disease control divided by total number of patients in the analysis population, excluding patients who refuse treatment before the initiation of any treatment. DCR will be compared between two treatment groups using Chi-square test (or Fisher's exact test if the data in the contingency table is sparse). Logistic regression models will be used to estimate the odds ratio (OR) and confidence interval without and with adjusting for baseline clinical/pathological factors.
- 16.44 Overall response rate (ORR): Overall response rate (ORR): Overall response status will be determined using tumor assessment data collected from date of initiation of the treatment to the date of treatment discontinuation. Overall response is defined as achieving CR or PR as the best tumor assessment result during the defined time window. ORR is defined as number of patients with CR or PR as the best overall response divided by the total number of patients in the analysis population, excluding patients who refuse treatment before the initiation of any treatment. ORR will be compared between the two treatment groups using Chi-square test (or Fisher's exact test if the data in the contingency table is sparse). Logistic regression models will be used to estimate the odds ratio (OR) and confidence interval without and with adjusting for baseline clinical/pathological factors.
- 16.45 Duration of response (DOR): DOR is defined as time from the date of first tumor assessment with the response status being CR or PR to the date of 1st documented progressive disease. If a patient never achieves CR or PR during treatment, the DOR will be censored with zero DOR time. If a patient is off protocol treatment due to severe AE or other non-PD reasons, the DOR time will

be censored at the date of treatment discontinuation. The distribution of DOR by treatment group will be estimated using the method of Kaplan-Meier. Six and 12 month durable response (i.e. maintaining CR or PR without PD) rates by treatment group with confidence intervals will be estimated based on Kaplan-Meier curves. The HR with confidence interval will be estimated based on stratified Cox models (stratified by levels of stratification factors), without and with adjusting for baseline clinical/pathological factors.

- 16.46 Time to treatment failure (TTF): TTF is defined as time from the date of randomization to the date of treatment discontinuation due to PD, death, or severe AE. If a patient discontinues protocol treatment for reasons other than PD, he/she will be censored at the date of treatment discontinuation. The distribution of TTF by treatment group will be estimated using the method of Kaplan-Meier. Six month event-free rates by treatment group with confidence intervals will be estimated based on Kaplan-Meier curves. The HR with confidence interval will be estimated based on stratified Cox models (stratified by levels of stratification factors), without and with adjusting for baseline clinical/pathological factors.
- 16.47 Relative dose intensity (RDI): RDI is defined as the total dose of protocol therapy a patient actually received (i.e., summation of actually received dose at each cycle) divided by the total planned dose (i.e., summation of planned dose level at each cycle). Separate RDIs will be calculated for irinotecan and cetuximab. Agent-specific RDI will be summarized by means, 25th percentiles, medians, 75th percentiles, and min and max values, all of which will be compared between the two treatment groups by the Wilcoxon Rank sum test.
- 16.48 Correlative: One of the objectives of this correlative study is to determine the change in genotype concentrations of pre-specified gene mutations in circulating cfDNA collected serially from baseline to treatment with cetuximab to progression. We plan to estimate the mean and median change in mutation concentration for each pre-specified gene, and provide the corresponding 95% confidence intervals. With a total of 60 patients, we have 80% power to detect an average change in the concentration of RAS mutations equaling at least 0.62 times the standard deviation using a one-sided t-test and 5% type I error.

We plan to estimate the distribution of progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier method and calculate confidence limits using the Greenwood formula. We will apply Cox proportional hazards models to explore the predictive value of pretreatment mutation status for cetuximab sensitivity and resistance, using PFS and OS as the outcome variables.

We will also explore the dynamic change in mutation concentration while the patient is receiving cetuximab treatment. We will use scatter plots and box plots to illustrate such change.

16.5 Monitoring the Study

16.51 Adverse Event Stopping Rule:

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered to be clinically relevant and at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”), in either treatment group, that satisfy the following:

If 5 or more patients in the first 20 treated patients (or 25% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Study Reporting;

16.61 This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity and administrative information will be provided to the DSMB every 3 or six months, with the first report due at the first reporting period after study initiation

16.62 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the “ClinicalTrials.gov” web site. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov.

16.7 Minorities Distributions (sex, race, ethnicity):

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

We expect about 8% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table.

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	2	2
Not Hispanic or Latino	24	34	58
Ethnic Category: Total of all subjects	24	36	60
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	0	0	0
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	0	0
White	22	33	55
Racial Category: Total of all subjects	24	36	60

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Racial Categories: **Not Hispanic or Latino**
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue block with corresponding H&E (OR 15 unstained slides with corresponding H&E)*	Mandatory*	≤60 days after registration	Banking (Section 17.5)	Section 17.3

17.2 All Diagnostic Slides from Original and/or Recurrent Tissue:

None

17.3 Paraffin Embedded Tissue Blocks/Slides

17.31 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original and/or recurrent) surgery or biopsy. **A corresponding H&E slide for each submitted block must be provided.**

17.32 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 15 five micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). The remaining unstained slides will be processed as described in 17.38. For samples containing less than 1 square millimeter of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake, or place covers slips on the slides. Please do not use sticky labels on the slides.**

17.33 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue block with corresponding H&E slide (OR 15 unstained slides with corresponding H&E(s)).

- Research Tissue Specimen Submission Form
- Surgical Pathology Report
- Operative Report (*optional*)

Note: Please include the ACCRU patient ID number on all materials listed above.

- 17.34 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.
- 17.35 Tissue specimens must be shipped ≤ 60 days after registration.
- 17.36 Verify that the appropriate sections of the Research Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Research Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).
- 17.37 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:



17.4 Frozen Tumor tissue:

None

17.5 Study Methodology and Storage Information

- 17.51 Banking of tumor tissue, according to the patient consent permission, is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU colorectal cancer studies.)
- 17.52 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.
- 17.53 Blocks requested to accommodate individual patient management will be returned promptly upon request.
- 17.54 Return of Genetic Testing Research Results:
- For this study, DNA and/or RNA specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are

obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study Form	≤ 2 weeks after registration
Baseline Adverse Event Form	
RECIST Measurement Form-Baseline	
Research Blood Submission Form (see Section 14.0)	
Baseline Research Tissue Submission Form (see Section 17.0)	
OP and Path Reports (see Section 17.0) ¹	
End of Active Treatment/Cancel Notification Form	Submit ≤ 2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy to the ACCRU Ops Office, Attn. QAS for RU021302I. This is in addition to the pathology material requirements for tissue submission (Section 17.0).

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment Form	X	X
Adverse Event Form	X	X
RECIST Measurement Form ¹	X	X
Research Blood Submission Form	X(see Section 14.0)	X
End of Active Treatment/Cancel Notification Form		X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)	
ADR/AER	At each occurrence (see Section 10.0)	

1. Submit copy of documentation of response or progression to the [REDACTED]

Follow-up Material(s)

CRF	q. 3 months until PD	After PD q. 3 mos.	Death	New Primary
	Event Monitoring Form ^{1,2}	X	X	X

1. Submit copy of documentation of response or progression to [REDACTED]
2. Until 24 mos. after the last patient was enrolled.

19.0 Budget

- 19.1** Costs charged to patient: Routine clinical care costs will be the responsibility of the patient and/or the patient's insurance company. This includes costs associated with the administration of the study drugs. Cetuximab and irinotecan will be obtained through commercial suppliers.
- 19.2** Other budget concerns: Bevacizumab will be provided by Genentech at no charge.
- 19.3** Tests to be research funded:
- 19.31 Mandatory blood samples for future research.
- 19.32 Mandatory archival tissue samples for future research.
- 19.4** Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies to determine which items are considered standard of care versus research at their site. Refer to the payment synopsis for funding provided per accrual to cover study costs, as well as any additional invoiceables that may be allowed.

20.0 References

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