Academic and Community Cancer Research United (ACCRU)

A Randomized Phase II Study of Regorafenib Followed by Anti-EGFR monoclonal antibody therapy Versus the Reverse Sequencing for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin and irinotecan (REVERCE II)

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site ([redacted]).

Study Chairs

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Statistician: [redacted]

Drug Availability
Commercial Agents: Cetuximab, Panitumumab, Irinotecan
Drug Company Supplied: Regorafenib- IND exempt

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

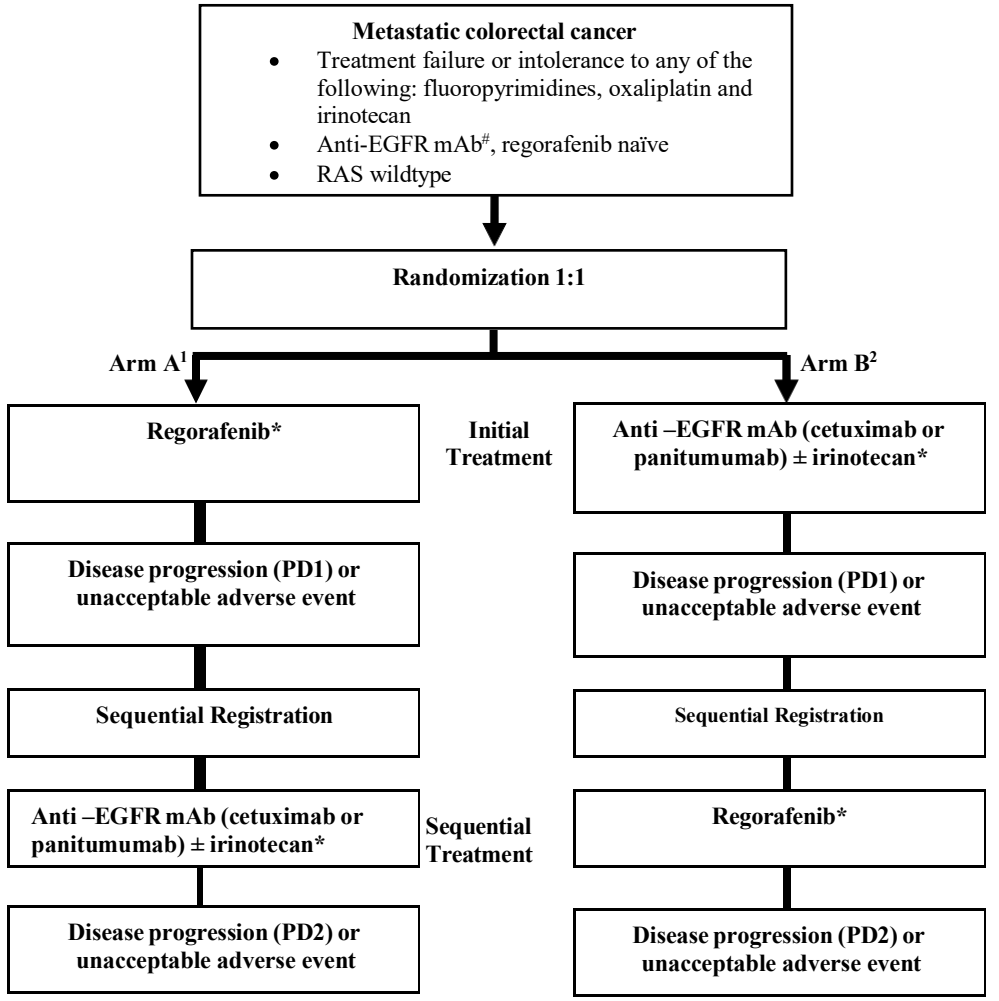
Research Coordinating Center

[redacted]

Document History	**(effective date)**
Initial Version	August 21, 2019
Amendment 1	June 22, 2020
Amendment 2	June 30, 2023

Index

Schema



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1. Arm A: regorafenib followed by anti-EGFR mAb

2. Arm B: anti-EGFR mAb followed by regorafenib

*Cycle length=28 days
#mAb= monoclonal antibody

Needs to discontinue treatment (section 8.45) ⟶ EM**
Patient refusal
Treating physician's decision

** EM= Event Monitoring (on either treatment arm)

Generic name: Regorafenib Brand name(s): Stivarga® Availability: McKesson	Generic name: Cetuximab Brand name(s): Erbitux® Availability: Commercial
Generic name: Panitumumab Brand name(s): Vectibix® Availability: Commercial	Generic name: Irinotecan Brand name(s): Camptosar®, CPT11 Availability: Commercial

1.0 Background

Worldwide, nearly 1.3 million patients are diagnosed with and more than 600 000 patients die from colorectal cancer every year [1]. In patients with advanced (metastatic or recurrent disease), systemic chemotherapy has been established as the standard treatment and associated with a poor prognosis, with a median overall survival of approximated 30 months [2]. Unresectable colorectal cancer (CRC) is treated with systemic chemotherapy as the first choice, but is difficult to cure as shown by the fact that the progression-free survival is approximately 10-12 months with initial chemotherapy and approximately 4-6 months with second-line chemotherapy, requiring third- and fourth-line treatment in most patients [3,4].

1.1 Efficacy of cytotoxic agents, anti-EGFR therapies in CRC

Antibodies that target the epidermal growth factor receptor (EGFR) have been studied in clinical studies primarily involving previously treated patients since the beginning of development. In a US phase II study, IMCL CP02-9923, patients with metastatic CRC unresponsive to chemotherapy including irinotecan, the response rate of combination therapy with irinotecan and cetuximab (Cmab) was 15.2%. BOND-1, a European phase II randomized study evaluated Cmab alone or in combination with irinotecan in patients with colorectal cancer unresponsive to chemotherapy including irinotecan, where the response rate was 22.9% and significantly higher in the combination group than 10.8% in the monotherapy group[5]. The progression-free survival was also improved in the combination group (4.1 vs. 1.5 months, respectively), despite the apparent resistance to irinotecan [5]. These findings suggest that anti-EGFR therapy can potentially re-induce irinotecan sensitivity in irinotecan resistant colon cancer. In the CO-17 study, Cmab monotherapy significantly prolonged survival time in patients with irinotecan-, fluoropyrimidine-, and oxaliplatin-resistant colorectal cancer, compared with best supportive care (BSC) [6]. Based on these findings, Cmab was approved for monotherapy or combination therapy with irinotecan for the treatment of irinotecan-resistant, EGFR-positive metastatic colorectal cancer in the US and Europe.

EPIC, a phase III study that consisted of 1298 patients with treatment refractory advanced CRC, investigated irinotecan monotherapy in comparison to the combination of irinotecan with Cmab as second-line treatment [7]. The combination group demonstrated a significant improvement in response rate (4.2% vs. 16.4%) and progression-free survival (2.6 vs. 4.0 months), but no difference in overall survival (10.9 months vs 10.0 months, combination versus monotherapy respectively). The lack of survival benefit may be attributed to the 46.9% of patients randomized to irinotecan monotherapy that received Cmab as post-study therapy. In the CRYSTAL trial, Cmab in combination with FOLFIRI demonstrated a significant improvement in response rate and progression-free survival compared to FOLFIRI [8].

Similarly, panitumumab (Pmab), a full humanized anti-EGFR monoclonal antibody, was approved for the treatment of advanced CRC based on the results of a comparative study that showed it significantly prolonged progression-free survival in patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan when given alone as the third-line treatment compared with placebo [9]. In addition, a randomized phase III study (Study 20050181) was conducted to compare FOLFIRI and FOLFIRI + Pmab as the second-line

treatment[10]. The concomitant use of Pmab resulted in a significant improvement in progression-free survival in wild-type *KRAS*, with a median of 5.9 months in the combination group versus 3.9 months in the non-combination group (hazard ratio: 0.73, 95% CI: 0.59-0.90, p=0.004). The overall survival trended towards an improvement favoring the combination group, but was not statistically significant (median OS 14.5 vs. 12.5 months, HR: 0.85, 95% CI: 0.70-1.04, p=0.12). In the PRIME study [11], the addition of Pmab to FOLFOX therapy resulted in significant improvement in progression-free survival in wild-type *KRAS* (9.6 vs. 8.0 months, hazard ratio: 0.80, 95% CI: 0.66-0.97, p=0.02) tumors. The results from these clinical trials have shown that anti-EGFR antibodies improve progression-free survival in patients with advanced CRC, regardless of treatment line.

1.2 Efficacy of anti-EGFR antibodies and RAS mutation

After anti-EGFR antibodies were approved for the treatment of colorectal cancer, several reports have suggested that these antibodies are not effective in patients with mutations in *KRAS*, a downstream effector of EGFR [12,13]. In the CRYSTAL study, post hoc analysis revealed an additive effect from Cmab in patients without *KRAS* mutation, which was absent in patients whose tumors exhibited *KRAS* mutations [8]. Similarly in the CO-17 study for third-line treatment in CRC, a significant clinical benefit from Cmab was observed in patients without *KRAS* mutation, (median survival time: 9.5 vs. 4.8 months, hazard ratio: 0.55, p<0.001, median progression-free survival: 3.7 vs. 1.9 months, HR 0.40, p<0.001) but was absent in those with a *KRAS* mutation [14]. In a randomized study of Pmab in third-line treatment, *KRAS* analysis was performed in 427 patients, showing that PFS was significantly prolonged from 7.3 weeks to 12.3 weeks in patients with tumors that were wild-type *KRAS* (HR 0.45, p<0.001), but not in those with *KRAS* mutation [9]. Furthermore, in the 181 trial, Pmab did not improve patient outcomes in those with *KRAS* mutated tumors. In the PRIME study, which evaluated the addition of Pmab to FOLFOX chemotherapy, the presence of RAS mutations predicted a lack of response to Pmab-FOLFOX, while patients whose tumors were without RAS mutations experienced an improvement in overall survival to the addition of Pmab to FOLFOX. Furthermore, RAS mutations were associated with inferior progression-free survival and overall survival from the addition of Pmab[15]. Based on these findings, a consensus has been achieved that anti-EGFR antibodies should be used only in patients whose tumors are RAS wildtype [2].

1.3 Anti-EGFR antibody-related adverse events

EGFR may control proliferation and differentiation of keratinocytes in normal skin. Inhibition of EGFR results in cessation of proliferation and migration of keratinocytes, leading to apoptosis. In addition, inflammatory cytokines are released, and the entire epidermis may become thin, fragile, vulnerable, and unable to retain moisture [16]. Rash acneiform is the most common skin disorder, and usually occurs within 1 to 3 weeks after administration of an anti-EGFR antibody. The most commonly affected area is the upper trunk, including the face, anterior chest, back, and forearm. The severe rash acneiform is often associated with itching and pain. It is replaced by skin dryness and cracking approximately 4 weeks after administration. Paronychia characterized by impaired nail growth and periungual pain may occur 8 weeks or later and be complicated by granulation or abscess in serious cases [16,17]. Grade 3 or higher skin toxicity has been reported in 9.4% to 16.7% of patients treated with cetuximab [5-8], partly contributing to

premature discontinuation of treatment. Another significant adverse drug reaction is severe infusion reaction, with an incidence of less than 5% and interstitial pneumonia (1-2%). In addition, hypomagnesemia, hypokalemia, and hypocalcemia have been reported, requiring monitoring of serum electrolytes before, during, and after treatment and appropriate supplementation as needed.

1.4 Efficacy of regorafenib for colorectal cancer

Regorafenib is an oral multi-kinase inhibitor and inhibits receptor tyrosine kinases involved in neovascularization (VEGFR 1-3, TIE2), tumor microenvironment (PDGFR-β, FGFR), and oncogenesis (KIT, PDGFR, RET, BRAF) [18]. Regorafenib was recently shown to provide a survival benefit in metastatic colorectal cancer patients who have progressed after all standard therapies in the CORRECT trial [19]. This led to its approval in September 2012 by the FDA for use in the United States. Despite the observed benefits in a patient population with no current standard, toxicities such as Palmar-planter erythrodysesthesia syndrome (PPES) (which occurs early in the first 1-2 weeks) and fatigue have widely limited its use in the US [19]. ReDOS (Regorafenib dose optimization study), a randomized phase II trial, evaluated a dose escalation strategy compared to the standard dosing evaluated in the CORRECT study. The study demonstrated superiority in the proportion of patients who initiated the third cycle in the weekly dose escalation arm compared to patients who received standard dosing of 160mg per daily (43% vs 25%) [20]. A survival benefit was also observed favoring the dose escalation arm (9.0 versus 5.9 months; p=0.094) [20]. Based off these results, the NCCN has recommended the weekly dose-escalation strategy for regorafenib.

1.5 Regorafenib-related adverse events

In the CORRECT study, the common grade 3 or higher adverse events related to regorafenib were hand- foot-skin reaction (16.6%), fatigue (9.6%), hypertension (7.2%), diarrhea (7.2%), and rash/exfoliation (5.8%). Drug-related adverse events led to discontinuation of treatment in 8.2% in the regorafenib group and 1.2% in the placebo group [19]. It has been reported that adverse events, primarily hand- -foot-skin-reaction, occurred the most frequently in the first course, and the incidence decreased thereafter due to appropriate dose reduction [21].

1.6 Position of molecularly targeted drugs in guidelines and standard treatment

In the National Comprehensive Cancer Network (NCCN) treatment guidelines (2013 version 3), which serve as the guidelines for standard cancer therapy in the US, the following standard treatment options are presented for first- to fourth-line treatment of colorectal cancer based on the results of the abovementioned clinical studies, and selection of an appropriate option according to the patient's condition and previous chemotherapy is advised [22].

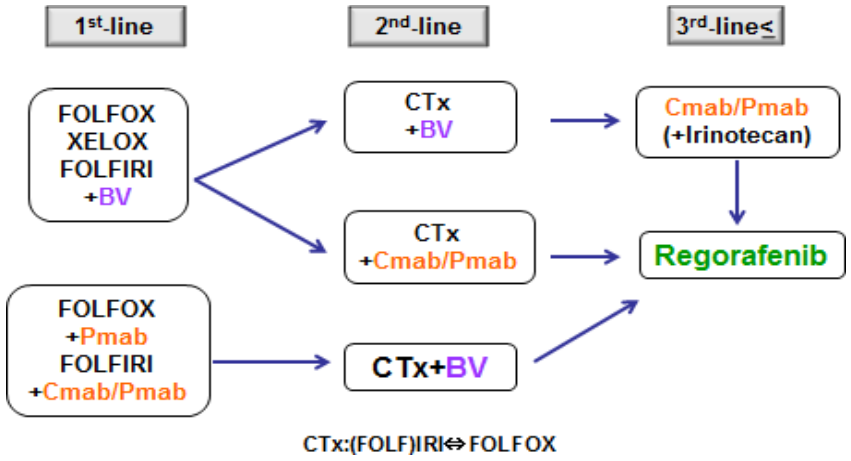
- First-line treatment: FOLFOX (XELOX)/FOLFIRI ± bevacizumab (BV) or Cmab*/Pmab*, 5-FU + l-LV (capecitabine) ± BV
- Second-line treatment: FOLFOX (XELOX) ± BV, FOLFIRI ± BV, FOLFIRI ± Cmab*/Pmab*, irinotecan ± Cmab*/Pmab*, Cmab*/Pmab* alone
- Third-line treatment: Cmab*/Pmab* ± irinotecan, FOLFOX

- Fourth-line treatment: regorafenib

* For patients with no *KRAS* mutation (codon 12, codon 13)

Treatment flow in patients with wild-type *KRAS* is shown in the following schematic diagram:

Chemotherapy flow in wild-type *KRAS* colorectal carcinoma



The results from CALBG 80405 failed to show any significant survival difference between the addition of cetuximab or bevacizumab with chemotherapy (physician's choice) for treatment naïve metastatic colorectal cancer, suggesting either biologic therapy with FOLFOX or FOLFIRI chemotherapy are appropriate therapeutic options [23].

As second-line treatment options following first-line treatment using BV, backbone chemotherapy is changed (oxaliplatin to irinotecan or vice versa), and BV may be continued or replaced by an anti-EGFR antibody (wild-type *KRAS*). Since the TML study showed that continued BV treatment resulted in significantly prolonged survival time[24], and it was shown that anti-EGFR antibodies were useful in third-line treatment [5,6,9], sequential treatment with BV in first- and second-line treatment followed by an anti-EGFR antibody in third-line treatment is widely used. For patients unresponsive or intolerable to all of these drugs, regorafenib is used as the standard treatment based on the results of the CORRECT study [19].

1.7 Background for Investigation of Biomarkers

1.71 Biomarkers related to treatment efficacy of or resistance to anti-EGFR antibodies

It is established that the presence or absence of *RAS* mutation is a predictive factor for the efficacy of anti-EGFR antibodies for colorectal câncer [2,8,15]. In the CO-17 study, however, the response rate of Cmab was as low as 12.8% in patients with wild-type *KRAS*, and approximately 40% of patients treated with Cmab had disease progression within 2 months after the start of treatment [14], suggesting that there may be non-*KRAS* factors involved in resistance to anti-

EGFR antibodies in colorectal cancer. As the biomarker related to the efficacy of or resistance to anti-EGFR antibodies, BRAF, PIK3CA, NRAS, and KRAS (mutations other than codon 12 and codon 13: codon 61, codon 146, etc.), which are downstream of EGFR, have been studied and are suggested to be related to resistance to anti-EGFR antibodies [25]. However, none have been established as biomarkers, warranting further studies.

One recent research topic is an attempt to detect genetic mutations in tumors by a highly sensitive measurement technique using tumor cell-derived DNA (cell-free DNA or circulating free DNA) in blood specimens. It was reported that this technique was successfully used to detect KRAS mutations in tumor cell-derived DNA in blood specimens from patients with wild-type KRAS under anti-EGFR antibody treatment [26,27]. This may have resulted from proliferation of KRAS mutant clones following anti-EGFR antibody therapy and is thus of interest as a mechanism of resistance to anti-EGFR antibodies. In addition, KRAS mutations were examined by BEAMing using tumor tissue DNA and plasma DNA from colorectal carcinoma patients enrolled in the CORRECT study, a phase III study of regorafenib, showing that the agreement rate of KRAS mutations was 76%, and disagreement of KRAS mutations was mostly wild type in the tumor tissue and mutation in the plasma specimen [19]. This may have resulted from proliferation of KRAS mutant clones following anti-EGFR antibody therapy, and is thus of interest as a possible mechanism of resistance to anti-EGFR antibodies. BEAMing is a digital PCR technique with an estimated sensitivity of 0.01% (one mutant DNA among 10,000 wild-type DNA can be detected). It is thus expected that plasma DNA can be used to detect genetic mutations in tumors by improving the sensitivity.

Another potential mechanism of resistance to anti-EGFR antibodies, through a different signaling pathway, is also suggested. Heregulin is a ligand for HER3, a tyrosine kinase on the cell membrane. It is suggested that heregulin, which is overexpressed in the established Cmab-resistant cell lines, may not only activate HER3, but also dimerize to activate HER2 and thereby activate cell proliferation signaling pathways originating from these molecules [28]. In a clinical study, it was reported that among 70 colorectal cancer patients treated with Cmab, those with no response to Cmab had significantly higher plasma heregulin concentrations. In addition, both progression-free survival and overall survival were significantly shorter in patients with high heregulin expression (>1,600 pg/mL) than in those with low expression (<1,600 pg/mL) [28]. Other possible mechanisms of resistance to anti-EGFR antibodies are cell proliferation resulting from abnormal ligand expression for HER2, HGF-cMET pathway, and VEGF [29]. The present study is designed to detect mutations using circulating free DNA at each point of sequential treatment and comprehensively examine multiple serum proteins, including these EGFR ligands, with an aim of producing findings that may be useful in elucidating the mechanism of resistance to anti-EGFR antibodies and contribute to future individualized therapy.

1.72 Biomarkers related to treatment efficacy of or resistance to regorafenib

No biomarker predictive of the efficacy of or related to resistance to regorafenib has been established, raising important issues. In the CORRECT study,

regorafenib significantly prolonged survival time and progression-free survival. The progression-free survival curve greatly improved in the regorafenib group compared with that in the placebo group after the two curves overlapped until 50% of patients had an event, suggesting that more responsive patients can be selected[19]. Regorafenib has various effects, including inhibition of neovascularization (VEGFR 1-3, TIE2), effect on tumor microenvironment (PDGFR-β, FGFR), and direct effect on oncogenesis (KIT, PDGFR, RET, BRAF). Since it is suggested that the efficacy of BV, an anti-VEGF-A antibody, is correlated with the blood VEGF-A level, it may be valuable to assess VEGF-related biomarkers for regorafenib.

In the CORRECT study, blood samples from 611 (80%) of 760 enrolled patients were examined[30]. In the assessment of OS, regorafenib was more effective in patients with high expression of Tie-1 protein (regorafenib vs. placebo: hazard ratio: 0.56 in patients with high expression, 0.87 in those with low expression, P for interaction 0.035). In the assessment of PFS, regorafenib tended to be more effective in patients with low expression of von Willebrand factor (VWF) protein (regorafenib vs. placebo: hazard ratio: 0.39 in patients with low expression, 0.67 in those with high expression, P for interaction 0.02). OS tended to be poor in patients with high levels of IL-8 and placental growth factor (PlGF) (high vs. low IL-8, HR 3.48, $p<0.001$; high vs. low PIGF: HR 1.81, $p=0.002$). Patients with high IL-8 levels also tended to have a poor outcome in terms of PFS. It is suggested that these biomarkers may be related to the efficacy of regorafenib or prognosis, but further validation is required in other cohorts.

Stanniocalcin-1 (STC1), a glycoprotein hormone that plays an integral role in stromal and angiogenic tumor microenvironment and has been identified as a potential plasmatic biomarker.

1.8 Reason for Including Bevacizumab-naive Patients in the Study

Bevacizumab (BV) is widely used as the standard first- and second-line treatment. However, since BV is not recommended for patients with a history of serious arterial thromboembolism (within approximately 6 months), uncontrolled hypertension, a risk of hemorrhage, severe protein urine, or delayed postoperative wound healing, it is assumed that some patients have received chemotherapy alone or in combination with an anti-EGFR antibody rather than BV in first- and second-line treatment. Therefore, previous treatment with BV is not a requisite for participation in the study.

1.9 Significance of the Study

As mentioned above, the current standard treatment is sequential treatment with an anti-EGFR antibody followed by regorafenib [22]. However, regorafenib, which is orally administered once daily, may be more convenient and thus preferable for patients than anti-EGFR antibodies, which require intravenous infusion every week or every other week. In addition, since anti-EGFR antibodies and regorafenib have different toxicity profiles as described in, sequential treatment with regorafenib followed by an anti-EGFR antibody is expected to provide a new treatment option with different convenience and toxicity profile if it is as effective as standard sequential treatment in terms of survival.

REVERCE, a Japanese randomized phase II trial, demonstrated a significant 5.8 month survival benefit from the sequencing of regorafenib prior to cetuximab therapy (17.4 versus 11.6 months, HR 0.61, 95% CI 0.39-0.96, p=0.0293) compared to patients that received the reverse therapeutic sequence [31]. Recently, the PARADIGM study (presented at the ASCO Annual Meeting 2022) demonstrated a survival benefit in patients that received the combination of anti-EGFR antibody with chemotherapy as first-line treatment for metastatic colorectal cancer. In the subgroup analysis, patients with right sided colon cancer did not derive a benefit from first-line anti-EGFR antibody with a numerically worse median OS. Based off the recent results from the PARADIGM study, patients with left sided metastatic colorectal cancer will likely receive anti-EGFR antibody therapy as first line treatment, whereas in those with right-sided disease, the potential sequencing of regorafenib prior to anti-EGFR antibody therapy remains of interest.

The proposed phase II trial is to confirm the observed survival benefit from regorafenib sequencing prior to anti-EGFR monoclonal antibody therapy in REVERCE in a US patient population in patients with right sided colon cancer. In addition, biomarkers will be assessed as described in Section ***2-3*** to investigate whether biomarkers can be used to select subjects for a phase III study on an exploratory basis.

2.0 Goals

2.1 Primary

2.11 To compare the overall survival between patients with right sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.2 Secondary

2.21 To compare the first progression free survival (PFS1) between patients with right sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.22 To compare the second progression free survival (PFS2) between patients with right sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.23 To compare the sequential treatment progression free survival (stPFS) between patients with right sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.24 To assess the frequency and severity of adverse events between patients withright sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.25 To compare the objective response rate (ORR), while on initial treatment, between patients with right sided (primary tumor) metastatic colon cancer who

were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody followed by regorafenib.

2.26 To compare the objective response rate (ORR), while on sequential treatment, between patients with right sided (primary tumor) metastatic colon cancer who were randomized to receive regorafenib followed by anti-EGFR monoclonal antibody therapy compared to those that receive anti-EGFR monoclonal antibody prior to regorafenib.

2.3 Correlative Research

2.31 To assess plasma pharmacodynamics biomarkers of response and resistance to therapy.

2.32 To explore any correlation between tissue and blood-based biomarkers and clinical outcomes.

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologically proven, unresectable distant metastatic or locally advanced Colorectal adenocarcinoma with primary tumor site from right-sided disease only (cecum, ascending colon, hepatic flexure, and transverse colon).

3.13 KRAS, NRAS wild type.

3.14 BRAF v600E wildtype.

3.15 Measurable disease as defined in Section 11.0.

3.16 ECOG Performance Status (PS) 0, 1, or 2. (Form is available on the ACCRU web site: [redacted]

3.17 Life expectancy of ≥ 3 months per estimation of treating physician.

3.18 The following laboratory values obtained ≤7 days prior to randomization.

- Absolute neutrophil count (ANC) ≥1200/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine ≤1.5 x ULN
- INR/PTT ≤ 1.5 x ULN
  NOTE: Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
- Alkaline phosphatase limit ≤2.5 x ULN (≤5 x ULN for patients with liver involvement of their cancer)

3.19a Negative serum pregnancy test done ≤7 days prior to randomization for women of childbearing potential only. NOTE: Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgment of the treating physician.

3.19b Provide informed written consent.

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19d Disease progression on or intolerable to any of the following: fluoropyrimidine, oxaliplatin and irinotecan.

3.19e Able to swallow and retain oral medication.

3.19f Willing to provide tissue and blood samples for correlative research purposes (see Sections 6.0, 14.0 and 17.0).

3.19g Willing to allow transfer of tissue and blood samples, clinical information, and outcome data collected from this trial for future research. (see Sections 6.0, 14.0, and 17.0).

3.2 Exclusion Criteria

3.21 Prior treatment with regorafenib, cetuximab or panitumumab.

3.22 Major surgical procedure, open biopsy, or significant traumatic injury ≤28 days prior to randomization.

3.23 Congestive heart failure > New York Heart Association (NYHA) class 2.

NOTE: Class 3 is defined as marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100m). They are comfortable at rest. Class 4 is defined as patients with severe limitations. Experiences symptoms even while at rest. Mostly bed bound.

3.24 Unstable angina (angina symptoms at rest), new-onset angina (begun ≤3 months prior to randomization) or myocardial infarction ≤ 6 months prior to randomization.

3.25 Cardiac arrhythmias requiring anti-arrhythmic therapy. Note: Pacemakers, beta blockers or digoxin are permitted.

3.26 Uncontrolled hypertension. (Systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).

3.27 History of or current pheochromocytoma.

3.28 Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism ≤6 months prior to randomization.

3.29a Ongoing infection > grade 2 NCI-CTCAE v5.0.

3.29b Known history of chronic hepatitis B or C.

3.29c Patients with seizure disorder requiring medication.

3.29d Symptomatic metastatic brain or meningeal tumors unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of randomization and is clinically stable with respect to the tumor at the time of randomization. Note: Patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies).

3.29e History of organ allograft (including corneal transplant).

3.29f Evidence or history of bleeding diathesis or any hemorrhage or bleeding event >CTCAE v5.0 grade 3 ≤4 weeks prior to randomization.

3.29g Non-healing wound, ulcer, or bone fracture.

3.29h Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

3.29i MSI-H patients who have not received prior PD-1 mAb therapy.

3.29j Concurrent anti-cancer therapy ≤3 weeks from randomization (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization).3.29k Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.

3.29l Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.

3.29m History of known persistent proteinuria of CTCAE v5.0 Grade 3 or higher (≥ 3.5 g/24 hrs).

3.29n Any malabsorption condition.

3.29o Unresolved toxicity greater than CTCAE v5.0 Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity ≤Grade 2.

3.29p Albumin levels <2.5 g/dl.

3.29q Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

NOTE: Men and women of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.

3.29r Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the treating physician, 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.

3.29s Known history of human immunodeficiency virus (HIV) infection or active hepatitis B or C infection requiring treatment with antiviral therapy.

3.29t Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29u Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer ≤ 3 years prior to randomization EXCEPT for cervical cancer in-situ, treated ductal carcinoma in situ of the breast, curatively treated nonmelanoma skin carcinoma, noninvasive aerodigestive neoplasms, or superficial bladder tumor [Ta (Non-invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)]. Note: All cancer treatments for cancers that were distinct in a primary site other than colorectal must be completed at least 3years prior to randomization (i.e., signature date of the informed consent form).

3.29v Pleural effusion or ascites that causes respiratory compromise (≥CTCAE v5.0 Grade 2 dyspnea).

3.29w Any condition which, in the treating physician's opinion, makes the subject unsuitable for trial participation.

4.0 Test Schedule

4.1 Treatment with regorafenib

NOTE: Subjects should follow this test table while taking regorafenib regardless of treatment arm.

Tests and procedures		Active Monitoring Phase											
	≤7 days prior to randomization	Cycle 1				Cycle 2				Prior to dosing each cycle beginning cycle 3+ (+/- 7 days)	Prior to dosing at restaging (C3 and every other cycle after) until progression (+/- 7 days)	End of Initial Treatment Mandatory Sequential Registration (if regorafenib is initial treatment)[12]	End of All Treatment (within 30 days after last dose)
		Week1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 4 (Day 22)	Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 4 (Day 22)				
History and exam, weight, ECOG PS, blood pressure	X	X[7]	X	X	X	X	X	X	X	X		X	X
Height	X												
Adverse event assessment	X				X				X	X		X	X
Hematology[5] CBC/ differential, ANC, INR/PTT[13]	X	X[9]				X				X			
Chemistry[5] SGOT (AST), alk phos, T. bili, serum creatinine, calcium, glucose, Na, K, SGPT (ALT), Mg	X	X[9]		X		X		X		X			
Albumin[5]	X	X[9]				X				X			
Tumor Blood Bio-Markers (CEA)	X					X					X		
Tumor measurement[1] (CT scan of chest, abdomen and pelvis), CT	X										X		X[6]

component of a PET/CT, (MRI if CT is not feasible)													
ECG[4]	X												
Serum pregnancy test[2]	X	X[9]											
Mandatory blood sample-plasma[10,R]		X				X							
STC1 biomarker blood collection[R]		X		X									
Mandatory tissue sample-archival tumor paraffin(see Section 17.0)[8, R]		X											
Patient Medication Diary (Appendix I)[3]		X	X	X	X	X	X	X	X	X		X	X
Optional Blood sample –cfDNA Guardant 360[10, 11, R]													X

1. CT scans preferred (MRI if CT is not feasible), CT component of a PET/CT, of the chest, abdomen and pelvis. Use same imaging throughout the study. Tumor measurements at baseline (≤28 days prior to randomization) and every 8 weeks beginning on cycle 3 day 1 prior to treatment until progression.
2. For women of childbearing potential only.
3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution during each scheduled visit.
4. Performed at screening and then as needed.
5. Hematology and chemistry tests to be done prior to each cycle.
6. If patient goes off study during Cycle 1 and last CT scan was done >28 days prior, the CT scan must be done.
7. If baseline history, exam, weight, ECOG PS, and blood pressure were performed ≤3 days of C1D1, they do not need to be repeated for C1D1.
8. Receipt of archival tumor tissue is not required for study randomization and initiation of therapy. However, it is mandatory to receive the required tissue ≤ 90 days from randomization. See section 17.0.
9. If screening tests occur ≤ 7 days prior to C1D1, they do not have to be repeated prior to dosing.
10. Kits are required for this collection. Refer to Section 14.0.

11. Patients have the option to complete cfDNA testing at study completion and will be allowed to register with protocol ACCRU-GI-1611. Site will access results through the Guardant Health portal: [redacted]. Sites will be notified by Guardant Health via email when results are available in the portal. Refer to Section 13.7. See detailed instructions on the ACCRU website under Manuals and Forms.
12. At the time of disease progression or intolerance from initial treatment, patients will be re-registered (See 6.3) to Sequential Treatment Phase. Tests should be completed after re-registration and prior to dosing of sequential treatment. Patients will then move to the cetuximab or panitumumab ± irinotecan test table (4.2).
13. If the INR/PTT is normal at screening (and subject is not on warfarin) this test will not need to be repeated unless indicated per investigator assessment. If a subject is on warfarin with stable INR/PT at baseline, the INR/PT should be assessed on Day 5 (+/- 3 days). If value is above the therapeutic range, the dose should be modified and the assessment should be repeated weekly until it is stable.

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4.2 Treatment with anti-EGFR mAb (cetuximab or panitumumab) ± irinotecan

NOTE: Subjects should follow this test table while taking anti-EGFR mAb (cetuximab or panitumumab) ± irinotecan regardless of treatment arm.

Tests and procedures		Active Monitoring Phase								
	≤7 days prior to randomization	Cycle 1		Cycle 2		Prior to dosing each cycle beginning cycle 3+ (+/- 7 days)	Prior to dosing at restaging (C3 and every other cycle after) until progression (+/- 7 days)	Day 15 (While on anti-EGFR mAb +/- irinotecan)	End of Initial Treatment Mandatory Sequential Registration (if anti-EGFR mAb +/- irinotecan is initial treatment)[11]	End of ALL Treatment (within 30 days after last dose)
		Week1 (Day 1)	Week 3 (Day 15)	Week 1 (Day 1)	Week 3 (Day 15)					
History and exam, weight, ECOG PS, blood pressure	X	X[6]	X	X	X	X			X	X
Height	X									
Adverse event assessment	X		X		X	X			X	X
Hematology[4]: CBC/ differential, ANC, INR/PTT[12]	X	X[8]	X	X	X	X		X		

Chemistry[4]: SGOT (AST), alk phos, T. bili, serum creatinine, calcium, glucose, Na, K, SGPT (ALT), Mg	X	X[8]	X	X	X	X		X		
Albumin[4]	X	X[8]		X		X				
Tumor Blood Bio-Markers (CEA)	X			X			X			
Tumor measurement[1] (CT scan of chest, abdomen and pelvis), CT component of a PET/CT, (MRI if CT is not feasible)	X						X			X[5]
ECG[3]	X									
Serum pregnancy test[2]	X	X[8]								
Mandatory blood sample-plasma[9, R]		X		X						
STC1 Biomarker blood collection		X	X							
Mandatory tissue sample-archival tumor paraffin(see Section 17.0)[7, R]		X						X		
Optional Blood sample –cfDNA Guardant 360[9,10, R]										X

1. CT scans preferred (MRI if CT is not feasible), CT component of a PET/CT, of the chest, abdomen and pelvis. Use same imaging throughout the study. Tumor measurements at baseline (≤28 days prior to randomization) and every 8 weeks beginning on cycle 3 day 1 prior to treatment until progression.
2. For women of childbearing potential only.

3. Performed at screening and then as needed.
4. Hematology and chemistry tests to be done prior to each cycle.
5. If patient goes off study during Cycle 1 and last CT scan was done >28 days prior, the CT scan must be done.
6. If baseline history, exam, weight, ECOG PS, and blood pressure were performed ≤3 days of C1D1, they do not need to be repeated for C1D1.
7. Receipt of archival tumor tissue is not required for study randomization and initiation of therapy. However, it is mandatory to receive the required tissue ≤ 90 days from randomization. See section 17.0.
8. If screening tests occur ≤ 7 days prior to C1D1, they do not have to be repeated prior to dosing.
9. Kits are required for this collection. Refer to Section 14.0.
10. Patients have the option to complete cfDNA testing at study completion and will be allowed to register with protocol ACCRU-GI-1611. Site will access results by creating an account at [redacted] Sites will be notified by Guardant Health via email when results are available in the portal. Refer to Section 13.7. See detailed instructions on the ACCRU website under Manuals and Forms.
11. At the time of disease progression or intolerance from initial treatment, patients will be re-registered (See 6.3) to Sequential Treatment Phase. Tests should be completed after re-registration and prior to dosing of sequential treatment. Patients will then move to the regorafenib test table (4.1).
12. If the INR/PTT is normal at screening (and subject is not on warfarin) this test will not need to be repeated unless indicated per investigator assessment. If a subject is on warfarin with stable INR/PT at baseline, the INR/PT should be assessed on Day 5 (+/- 3 days). If value is above the therapeutic range, the dose should be modified and the assessment should be repeated weekly until it is stable.

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5.0 Stratification and Grouping Factors:

5.1 Stratification Factors

5.11 Prior bevacizumab treatment in the metastatic setting: yes vs no.

5.13 Treating physician decision on using Irinotecan with anti-EGFR mAb for this study: yes vs no.

5.2 Grouping Factors

5.21 Initial Treatment Received: Regorafenib vs. Anti-EGFR

6.0 Randomization Procedures

6.1 Site Procedures

6.11 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU webpage at [redacted] Refer to Study Resources→ Applications. Near the bottom of the page there will be a link to the "Research Registration Application Training." After training is complete, study staff must complete the "Attestation of Training" and send to the ACCRU Registration Office at [redacted]

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the 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 the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization 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.

6.2 Randomization Procedures

6.21 To register a patient, access the ACCRU web page at [redacted] go to the Study Resources → 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 email [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section → Application section. Please refer to the "Research Registration Application Training" or Quick Reference Guide for instructions.

Prior to initiation of protocol study intervention, 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 at [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 the Research Registration Application training on the ACCRU website under Study Resources → Applications.

6.22 Prior to accepting the registration, the registration 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

6.23 Correlative Research

Mandatory

A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

Optional

An optional correlative research component is part of this study. There will be an option to select if the patient is to be registered onto this component (see Section 14.0).

- Patient has/has not given permission to give his/her blood sample for research testing.

6.24 At the time of randomization, the following will be recorded:

- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood 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 to store and use his/her

tissue sample(s) for future research to learn about, prevent, or treat cancer.

- Patient has/has not given permission to store and use his/her 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 sample(s) to outside researchers.

6.25 Treatment cannot begin prior to randomization and must begin ≤14 days after randomization.

6.26 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.27 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.28 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.29 a Study drug is available on site.

6.29b Blood draw kit is available on site.

6.3 Randomization Procedures

6.31 The factors, defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.32 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 two treatment groups using the Pocock and Simon [39] dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups. At entry, physicians must declare whether each patient will receive irinotecan in protocol treatment (ie, irinotecan+anti-EGFR therapy versus anti-EGFR therapy alone). The stratification factors is defined as 6.21.

6.4 Sequential Treatment Phase

NOTE: Re-registration must occur ≤28 days from documentation of progression or intolerance.

6.41 Upon local confirmation of progression or intolerance, patients will be allowed to re-registered to receive the sequential treatment in the treatment arm.

6.42 To re-register a patient, email [redacted] a completed sequential treatment phase eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and4:30 p.m. central time Monday through Friday.

6.43 Treatment cannot begin prior to re-registering to the sequential treatment phase and must begin ≤7 days after registration for the sequential treatment phase.

7.0 Protocol Treatment

Drugs will be administered in accordance with the information on the respective package inserts. Treatment will be given according to the schedule specified in the protocol. The terms "delay," "modification," and omission" are defined as follows:

Delay: A delay indicates dose was postponed or not received when expected.
Modification: Indicates a change in dose level during the current cycle. However, if a modification was issued after the last dose was received in the current cycle, the modification should be reported on the subsequent cycle.
Omission: Indicates a dose was skipped and not made up, or that the drug was discontinued.

Arm A, treatment with regorafenib followed by anti-EGFR therapy (± irinotecan).
Arm B, treatment with anti-EGFR therapy (± irinotecan) followed by regorafenib.

Treatment on regorafenib will be continued in accordance with Section7.11 "Planned treatment with regorafenib" until any of the "Criteria for discontinuing treatment with regorafenib" (Section 8.34) is met.

Treatment on Anti-EGFR therapy (± irinotecan) will be continued in accordance with Section 8.4**, "**Combination therapy of Anti-EGFR therapy (cetuximab (Cmab) **OR** panitumumab (Pmab) and irinotecan" until any of the "Criteria for discontinuing treatment including Cmab or Pmab" (Section 8.44) is met.

Patients assigned to Anti-EGFR therapy will receive either cetuximab or panitumumab per treating physician discretion and will be dosed per prescribing guidelines. Patients cannot switch between cetuximab and panitumumab during the course of the study. The use of irinotecan is per treating physician discretion and will be dosed per prescribing guidelines. If treating physician chooses to add irinotecan, irinotecan must be included in treatment starting at cycle 1.

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

Agent	Dose	Route	Frequency	ReRx
Regorafenib	80mg daily (Starting dose) See table 7.11	PO	Daily for Days1-21 of 28 day cycle	Every 28 days
Cetuximab*	500mg/m^2	IV	Days 1, 15	Every 28 days
Panitumumab*	6mg/kg	IV	Days 1, 15	Every 28 Days
Irinotecan	180mg/m^2	IV	Days 1, 15	Every 28 days

* Patients assigned to Anti-EGFR therapy will receive **EITHER** cetuximab **OR** panitumumab, not both

7.11 Planned treatment with regorafenib

Regorafenib Dose Escalation

Cycle 1:

Week	Dose[1]
1 Starting Dose	80 mg*
2	120 mg
3	160 mg
4	Off

***starting dose level**
1 Dose escalation/reduction should follow section 8.1

Cycle 2 and beyond:

Week	Dose
1	Remain at highest tolerated dose from Cycle 1 (up to 160 mg)
2	
3	
4	Off

Regorafenib tablets should be taken once a day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) meal. Regorafenib should be taken with a meal at the same time every day. Some examples of low fat meals are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

If vomiting occurs shortly after regorafenib are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

7.2 Planned treatment with Anti-EGFR therapy (cetuximab (Cmab) or panitumumab (Pmab)) and irinotecan. Refer to 8.4 for treatment initiation requirements.\

7.21 Dose levels of panitumumab and cetuximab

Dose reduction level	Dose of panitumumab	Dose of cetuximab
Initial dose level	6 mg/kg	500 mg/m^2
-1	4.8 mg/kg	400 mg/m^2
-2	3.6 mg/kg	300 mg/m^2
-3	2.4 mg/kg	200mg/m^2

7.22 Dose levels of irinotecan

Dose reduction level	Dose of irinotecan
Initial dose level	180 mg/m^2
-1	150 mg/m^2
-2	120 mg/m^2
-3	100 mg/m^2

7.3 Study treatment with regorafenib, cetuximab, panitumumab, and Irinotecan may be administered up to 3 days before or after the scheduled Day 1, Day 15 of each cycle due to administrative reasons.

NOTE: Future treatment dates may need to be adjusted as a result of the ±3 days.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in the following tables for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, 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 Regorafenib Dose Escalation/Reduction

Dose level	If No SDRT	If + SDRT**
80 mg*	Proceed to next dose level	-
120 mg	Proceed to next dose	Decrease to 80 mg
	level	
160 mg	-	Decrease to 120 mg

***starting dose level**
****SDRT = Significant Drug Related Toxicities**

8.11 After week 8, if toxicities have resolved to ≤ Grade 0-1, re-escalation is allowed 40 mg at a time every 4 weeks to a maximum of 160 mg and at the discretion of the treating physician.

8.12 Patients with dose reductions below 80 mg should go off treatment and go to event monitoring.

8.13 Any patients with toxicities requiring >4 week delay should go off treatment and then to event monitoring.

8.2 Regorafenib Dose Modifications

8.21 Regorafenib may be dose reduced per the table 8.21 in case of intolerable toxicity such as weight loss, fatigue, rash or anorexia.

Table 8.21 Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/AST/bilirubin

NCI-CTCAE v5.0[a]	Dose Delay	Dose Modification [b]	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating physician. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating physician's discretion.	

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 5.0
b. Excludes alopecia, non-refractory nausea/vomiting, lymphocyte count decreased, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.
c. If no recovery after a 4 week delay*, treatment should be permanently discontinued unless subject is deriving clinical benefit.
* Modify according to study specific cycle length

If greater than 2 dose level reductions are required, regorafenib will be discontinued and the rest of the study follow up may be continued. The following tables outline dose adjustments for toxicities related to regorafenib except hand-foot skin reaction, hypertension and liver function test abnormalities.

The table above outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except PPES and hypertension. In addition to these recommended dose modifications, subjects who develop diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary. This is in order to minimize the risk of postural hypotension and renal failure.

8.22 Regorafenib may be dose reduced per Table 8.22b in case of Palmar-plantar erythrodysesthesia using Table 8.22a for grading guidelines.

Table 8.22a: Grading for Palmar-plantar erythrodysesthesia syndrome

	Grade 1	Grade 2	Grade 3
NCI-CTCAE v5.0 Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain

Further description / examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

Table 8.22bRecommended dose modification for Palmar-plantar erythrodysesthesia syndrome reaction[a]

Grade of event (NCI-CTCAE v5.0)	Occurrence	Suggested Dose Modification
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1[b,d]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level [b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level.[b,d]
	4th occurrence	Discontinue therapy
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level.[b,d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one additional dose level[b,d]
	3rd occurrence	Discontinue treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the treating physician.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is not permitted.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg.
f. Refer to Section 9.0 for management strategies for Palmer-plantar erythrodysesthesia syndrome reactions.

8.23 Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at least weekly during the first 5 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is >140 mm Hg systolic or >90 mm Hg diastolic (NCI CTCAE v5.0), then the subject must contact

study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the treating physician. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Tables Section 8.1 and 8.2 outline suggested dose reductions.

Table 8.23: Management of Treatment-Emergent Hypertension

Grade (CTCAE v5.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP120 - 139 mmHg	None	Continue regorafenib Consider increasing blood pressure (BP) monitoring
or diastolic BP 80 - 89 mmHg)		
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by >20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: If BP previously within normal limits, start anti-hypertensive monotherapy If patient already on anti-hypertensive medication, titrate up the dose.	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication AND/OR Increase current anti-hypertensive medication AND/OR Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve[a] When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.
4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy

a. Patients requiring a delay of >4 weeks should go off protocol therapy
If BP remains controlled for at least one cycle. Patients requiring >2 dose reductions should go off protocol therapy.
b. If BP remains controlled for at least one cycle, dose re-escalation permitted per treating physician's discretion.
c. Patients requiring >2 dose reductions should go off protocol therapy.

8.24 Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered related to regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table below should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome.

Table 8.24: Dose delay/modifications for ALT and/or AST and/or bilirubin increases related to study drug

Increases in AST/ALT (per NCI-CTCAE v 5.0)	**1st Occurrence**	**Restart**	**Re-occurrence**
AST and/or ALT ≤5 X ULN (< Grade 3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3 X ULN (≤ Grade 1) or baseline.		
ALT and/or AST >5 X ULN (≥ Grade 3)	Interrupt dosing, with weekly monitoring until transaminases return to <3 X ULN or baseline.	If the potential benefit for reinitiating regorafenib/ placebo is considered to outweigh the risk of hepatotoxicity: Reduce one dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST >20 X ULN (≥ Grade 4)	Discontinue		
ALT and/or AST >3 X ULN (≥ Grade 2) with concurrent bilirubin >2 X ULN	Discontinue treatment and measure serum liver tests weekly until resolution. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		
During the first 2 cycles of treatment, ALT, AST and bilirubin must be monitored every 2 weeks.			

8.3 Criteria for discontinuing treatment with regorafenib

Treatment with regorafenib will be discontinued if any of the following criteria for discontinuation is met:

1. When regorafenib is considered to be ineffective
    - Radiographically confirmed disease progression.
    - Significant worsening of symptoms or physical findings (disease progression should be radiographically confirmed whenever possible).

2. When treatment with regorafenib cannot be continued
    - It is necessary to reduce the dose of regorafenib to less than dose level -2 according to the criteria for dose reduction/modification of treatment.
    - Treatment cannot be resumed within 28 days after modification of treatment due to an adverse event.
    - A 3rd episode of grade 3 hand-and-foot syndrome occurs despite symptomatic treatment and dose reduction of regorafenib.
    - Grade 4 hypertension.
    - Grade 4 or higher increase in AST/ALT, 2nd episode of grade 3 increase in AST/ALT or bilirubin > upper limit of normal x 2 and AST or ALT > upper limit of normal x 3.
    - Other grade 4 non-hematological toxicity.
    - The treating physician decides that treatment with regorafenib cannot be continued due to safety concerns.
3. Patient's request for discontinuation of treatment with regorafenib.
4. After enrollment, the patient is found to be ineligible for the study, and it is concluded that further treatment with regorafenib is detrimental to him/her.
5. Transfer to another institution for any reason during treatment with regorafenib.

8.4 Combination therapy of Anti-EGFR therapy (cetuximab (Cmab) OR panitumumab (Pmab)) and irinotecan

Treatment with cetuximab/panitumumab or irinotecan will be started if it is confirmed that all criteria for treatment are met prior to treatment initiation. If all criteria for starting treatment with Cmab/Pmab are met, but any of the criteria for starting treatment with irinotecan is not met, only Cmab/Pmab can be administered. If the case is reversed, however, irinotecan should not be administered alone (without Cmab/Pmab).

8.41 Criteria for starting treatment with Cmab or Pmab

Event	Criteria for starting treatment with Cmab / Pmab
Skin symptom (rash acneiform, dry skin, paronychia, etc.)	Grade 2 or lower (Local infection is considered grade 3 if oral antimicrobial treatment is required, but not if oral antibiotic treatment is given based on the anti-inflammatory effect.)
Infusion-related reaction	Grade 1 or lower
Other	At the discretion of the treating physician, treatment can be delayed due to an adverse event not listed above if necessary.

8.42 Criteria for starting treatment with irinotecan

Event	Criteria for starting treatment with irinotecan
Neutrophil count	≥ 1200/mm^3
Platelet count	≥ 7.5× 10^4/mm^3
AST, ALT	≤ upper limit of normal x 3 (≤ upper limit of normal x 5 in subjects with liver metastasis)
T-bil	≤ upper limit of normal x 1.5
Pyrexia	Absence of pyrexia (≥ 38°C)
Diarrhea, oral mucositis	Grade 1 or lower
Other	At the discretion of the treating physician, treatment can be delayed due to an adverse event not listed above if necessary.

8.43 Criteria for changing the dose level at the second and subsequent doses for Cmab or Pmab and Irinotecan

If any of the events listed below occurs after the previous dose, the next dose will be reduced or discontinued. Dose reduction will be performed one level at a time. When treatment with irinotecan is discontinued in accordance with the criteria for dose reduction/discontinuation during combination therapy with Cmab/Pmab and irinotecan, treatment with Cmab/Pmab will be continued as protocol treatment if none of the criteria for discontinuing protocol treatment are met. Treatment with irinotecan alone should not be continued. The dose should not be increased once reduced.

8.431 Criteria for changing the dose level of Cmab or Pmab at the second and subsequent doses and the dose level

Event	Cmab \ Pmab
1st episode of grade 3 or higher skin symptom	No dose reduction
2nd and subsequent episodes of grade 3 or higher skin symptom	1-level dose reduction
The treating physician concludes that the dose should be reduced due to an adverse event not listed above.	1-level dose reduction

8.432 Criteria for changing the dose level of irinotecan at the second and subsequent doses and the dose level

Event	Grade	Irinotecan
Neutropenia, thrombocytopenia	4	1-level dose reduction
Grade 3 neutropenia or grade 3 thrombocytopenia for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhea, fatigue, oral mucositis	3	
The treating physician concludes that the dose should be reduced due to an adverse event not listed above. (Specify the reason on the case report form.)	3	

Irinotecan should be discontinued if dose reduction is necessary more than -2 level.

8.44 Criteria for discontinuing treatment including Cmab or Pmab

Treatment with Cmab/Pmab plus irinotecan or Cmab/Pmab alone will be discontinued if any of the criteria for discontinuation listed below is met. When treatment with irinotecan is discontinued due to an irinotecan-related adverse event, treatment with Cmab/Pmab alone will be continued if none of the following criteria are met:

1. When treatment including Cmab/Pmab is considered to be ineffective
   - Radiographically confirmed disease progression per RECIST 1.1.
   - Significant worsening of symptoms or physical findings (disease progression should be radiographically confirmed wherever possible).
2. When treatment with Cmab/Pmab cannot be continued
   - It is necessary to reduce the dose of Cmab/Pmab to less than dose level -3 according to the criteria for dose reduction/modification of treatment.
   - Treatment cannot be resumed within 28 days after modification of treatment due to an adverse event.
   - The 3rd episode of grade 3 skin toxicity occurs despite symptomatic treatment and dose reduction of Cmab/Pmab.
   - Grade 3 or higher infusion-related reaction related to Cmab/Pmab.
   - Grade 4 non-hematological toxicity.
   - The treating physician concludes that treatment with Cmab/Pmab cannot be continued due to safety concerns.
3. Patient's request for discontinuation of treatment with Cmab/Pmab.
4. After entry, the patient is found to be ineligible for the study, and it is concluded that further treatment including Cmab/Pmab is detrimental to him/her.
5. Transfer to another hospital for any reason during treatment including Cmab/Pmab.

8.5 Management of neutropenia, leukopenia and thrombocytopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the treating physician with close follow up and modification of study drug if required.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for PEGylated G-CSF) of the last dose of study treatment unless absolutely necessary. Platelet transfusions, if indicated, should be done according to local hospital guidelines. Study treatment can be interrupted for CTCAE grade 1 /2 neutropenia or thrombocytopenia as per treating physician's judgement. In case of CTCAE grade 3/4 neutropenia, leukopenia or thrombocytopenia, study treatment should be interrupted for a maximum of 4 weeks. Study treatment can be restarted at the same dose if an adverse event of neutropenia, leukopenia or thrombocytopenia has been recovered up to CTCAE grade 1 or less.

8.6 Criteria for Discontinuing Protocol Treatment

Protocol treatment will be continued until any of the criteria for discontinuing protocol treatment is met, and the study will be completed when it is decided to discontinue treatment.

1. Any of the criteria for discontinuing initial treatment (regorafenib for patients in Arm A and anti-EGFR±irinotecan for patients in Arm B) is met, and sequential treatment cannot be resumed within 28 days
2. Any of the criteria for discontinuing sequential treatment (anti-EGFR±irinotecan for patients in Arm A and regorafenib for patients in Arm B) is met.
3. Patient's request for discontinuation of protocol treatment.
4. Treating physician's decision

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's 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) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

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, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

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.

9.5 Prevention and treatment of hand-foot skin reaction

- Use of creams (urea-based or non-ureabased), avoid pressure points, use insole cushions, steroid cream, analgesics, keep rest, etc
- Symptomatic treatment, including drugs for complications (e.g., ointment and Minomycin for skin symptoms), bisphosphonates, and morphine, can be given simultaneously if there are no interactions with anticancer drugs used.

9.6 Unacceptable concomitant therapies/supportive therapies

During the treatment period, chemotherapy other than protocol treatment, radiation therapy, immunotherapy, or surgical therapy should not be given, because protocol treatment may be affected. In addition, no investigational product that may affect protocol treatment is allowed. Avoid to use of strong inhibitors and inducers of CYPA34. For any other medications that must be carefully administered in combination with protocol treatment, see the package insert.

10.0 Adverse Event (AE) Reporting and Monitoring

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 Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0

c. Determine whether the event is expected or unexpected (see Section 10.2).
d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.53 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.

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)/treatment.

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

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/device and the adverse event.

10.31 **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 10.53). *

Note: These exceptions only apply if the adverse event does not result in hospitalization.

If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Gastrointestinal Disorders	Diarrhea	Any Grade
	Dyspepsia	
	Nausea	
	Vomiting	
	Colitis Pancreatitis	Grades 1-3
General disorders and administrations site conditions	Anorexia	Any Grade
	General disorders and administrations site conditions-Other (Asthenia)	
	Dehydration	
	Fatigue	
	Malaise	
	Weight loss	
Hepatobiliary disorders	Cholecystitis	Grades 1-3
Infections and infestations	Lung Infection	Grades 1-3
	Sinusitis	
	Skin infection	
	Urinary tract infection	
Investigations	Alkaline phosphatase increased	Any Grade
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Lymphocyte count decreased	

Metabolism and nutrition disorders	Hyperkalemia	Any Grade
	Hypocalcemia	
	Hypomagnesemia	
	Hyponatremia	
Musculoskeletal and connective tissue disorders	Arthralgia	Any Grade
	Back pain	
	Musculoskeletal and connective tissue disorder – Other (muscle spasms)	
Skin and subcutaneous tissue disorders	Alopecia	Any Grade
	Rash acneiform	
	Rash maculo-papular	
	Palmar-plantar erythrodysesthesia syndrome	

*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.

10.312 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 Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - 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 “Disease Progression” under the (SOC) General Disorders and Administration Site Conditions. 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.

10.313 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 Myeloctyic 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.

10.314 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.

10.315 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. The funding sponsor will be notified by ACCRU within 24 hours of notification.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
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)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 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).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch 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.

[1]Serious 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:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For 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.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AE's are reported in the package insert or the literature, including AE's resulting from a drug overdose.

2. Follow site-specific reporting guidelines.

3. All SAEs occurring after start of administration of regorafenib, regardless of their causal relationship to the study drug shall immediately, within 24 hours at the latest, be reported. Submit a complete FDA 3500A MedWatch form and all deidentified supporting documents to Bayer by fax: [redacted] The FDA 3500A MedWatch form can be found at [redacted] or on the ACCRU web site along with the MedWatch Fax Cover Sheet (found on the ACCRU website).

   Also submit the MedWatch form 3500A to the ACCRU SAE Coordinator by email at [redacted]

3. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any

pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v5.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Diarrhea	# stools per day	X
	Nausea	X	X
	Vomiting	X	X
General Disorders	Fatigue	X	X
	Palmar-plantar erythrodysesthesia syndrome	X	X
Skin and Subcutaneous Tissue Disorders	Rash maculo-papular	X	X
Vascular disorders	Hypertension	X	X
Investigations	Blood bilirubin increased	X	X
	Alanine aminotransferase increased	X	X
	Asparatate aminotransferase increased	X	X

10.53 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:

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332Any 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.

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 measurable 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)[33]. 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.

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 ≥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).

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.

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 8 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. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, 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 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.

- 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.

- 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:
  a. Disappearance of all non-target lesions.
  b. 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:
  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. 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.)

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 tables:

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.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
	No	Non-CR/Non-PD
Non-Target Lesions & Non-Target Lymph Nodes		
Not All Evaluated*		
Unequivocal PD		
Any		
Non-CR/Non-PD		

*See Section 11.431

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

12.1 ECOG Performance Status: 0 vs. 1 vs. 2

12.2 Primary tumor location: cecum vs. ascending vs. hepatic flexure vs. transverse vs. splenic flexure vs. descending vs. sigmoid vs. rectosigmoid vs. rectum. vs other

12.3 Microsatellite instability or mismatch repair deficiency tested: yes vs. no.

12.31 If yes,
MSI-High (MSI-H/dMMR) vs. MSS/MSI-L/pMMR

12.4 ERBB2 (HER2) amplification tested: yes vs. no.

12.41 If yes, ERBB2 amplified vs. ERBB2 equivocal vs. ERBB2 not amplified.

12.5 BRAF analysis done: yes vs. no.

12.51 If yes, wild-type vs. mutated.
12.511 If mutated, V600E mutation: yes vs. no.

12.6 KRAS analysis done: yes vs. no.

12.61 If yes, wild-type vs. mutated.

12.6 NRAS analysis done: yes vs. no.

12.61 If yes, wild-type vs. mutated.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after randomization, it is determined that at the time of randomization, 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 (or off study, if applicable).

- 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.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are so severely violated that evaluability for the primary endpoint 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.

13.3 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. No further data submission is necessary.

13.4 Patients who are CR, PR, or SD will continue treatment per protocol with evaluation every 8 weeks, until disease progression or intolerance.

13.5 Patients who develop PD while receiving therapy on the initial treatment may be re-registered to the sequential treatment phase, or may go to event-monitoring, per physician discretion. If a patient develops PD while receiving sequential treatment, they will be followed for survival (i.e. event monitoring phase) every 3 months (±7 days) for 3 years after randomization (per Section 18.0).

13.6 Patients who go off protocol treatment on the initial treatment for reasons other than PD may be re-registered to the sequential treatment phase, or may go to event-monitoring, per physician discretion. If a patient goes off protocol treatment while receiving sequential treatment, they will be followed for survival (i.e. event monitoring phase) every 3 months (±7 days) for 3 years after randomization (per Section 18.0).

13.7 Patients have the option to complete cfDNA testing at study completion and are encouraged to register with protocol ACCRU-GI-1611 (COLOMATE). The results of the cfDNA test will be used in protocol ACCRU-GI-1611 (COLOMATE) to identify genomic alterations and facilitate enrollment on COLOMATE companion clinical trials. Sites will access results by creating an account at [redacted] Sites will be notified by Guardant Health via email when results are available in the portal. See detailed instructions on the ACCRU website under Manuals and Forms.

14.0 Body Fluid Biospecimens

14.1 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 [1]	Prior to dosing on Day 15 of Cycle 1	Prior to dosing on day 1 of cycle 2		End of Treatment[2]	Additional processing required at site after blood draw?	Storage /shipping conditions[3]
Mandatory	EDTA K2 (Purple)	10 mL (1)	Platelet Poor Plasma and White blood cells	X		X			Yes	Freeze /dry ice
Mandatory	EDTA K2 (Purple)	10ml (1)	Platelet Poor Plasma	X	X				Yes	Frozen
Optional	Strec k tube[4]	10 mL (2)	Whole blood					X	No	Room temperature

1. May occur prior to treatment on Cycle 1 Day 1.
2. Discontinuation of study treatment.
3. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.3 for detailed shipping instructions.)
4. Patients have the option to complete cfDNA testing at study completion and are encouraged to re-register with protocol ACCRU-GI-1611. See Section 13.7.

14.2 Kits are required for this study.

NOTE: You will be ordering and receiving kits from two different locations.

14.21 EDTA K2

14.211 Each kit will contain supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits for **EDTA K2** by Specimen collection kits can be ordered through Mayo Clinic Research Client Request Portal (MCRPCRP). A small but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed per institution policy. Do not send unused kits back to BAP. Kit requests must be filled in completely and accurately for quick processing. For questions regarding your kit order contact [redacted]

Please prepare to submit your kit order by reviewing educational material in the following order

[redacted]

[redacted]

Once you have reviewed all material, proceed by creating your account, submitting your access request(s) and submitting your kit request through the portal.

14.213 Kits will be sent via FedEx Ground at no cost to the participating institutions. **Allow up to two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.214 Kits 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 kits.**

14.22 Guardant 360 (Streck Tube)

14.221 In order to receive an initial kit shipment and access to the Guardant portal, fill out the Guardant Site Setup form for each treating location and email it to ACCRU at [redacted]

14.222 ACCRU will notify Guardant Health once each site is activated and will help facilitate portal access requests and the initial kit shipment. Guardant Health will provide portal access to [redacted] will ship the initial supply of kits to each site. Following the initial shipment, each site can request that kits be refreshed/replaced by completing the "Kit Reorder Form" and emailing it to Guardant Health Client Services Team at [redacted]

14.3 Shipping and Handling

NOTE: You will be shipping kits to two different locations.

14.31 EDTA K2

14.311 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit) and specimen collection labels are completed and filled in correctly.

14.312 Processing the EDTA tubes

Gently invert the EDTA 10 times to mix the blood**. Process the blood within 2 hours after collection.**
Centrifuge EDTA tubes at 2000 x g x 5 minutes to separate the blood components. Using a graduated pipette, carefully transfer the plasma into a 15mL conical tube being careful to not disturb the

cell pellet of buffy coat. Centrifuge the conical tube at 2000 x g x 5 minutes. Use a new graduated pipette to aliquot the platelet poor plasma into 1 mL platelet poor plasma into (4) 2mL cryovials, labeled with study ID, Subject ID, collection date and time and (PPP) and freeze at -80°C, Using a new graduated pipette, carefully transfer the white blood cells and place them into (1) 2mL cryovial labeled with study ID, Subject ID, collection date and time and with (B)and freeze at -80°C.

14.313 Specimens must be shipped the same day they are drawn

Place the frozen aliquots in the frozen shipper. Completely fill the box with dry ice pellets and be sure to label the weight of the dry ice on the shipping label. See kit instructions for specific details.

14.314 Ship specimens via Priority Overnight service, Monday – Thursday, to BAP Freezer according to kit instructions. Do not send samples on weekends or just prior to federal holidays. If a patient can only be seen on Fridays, email the Biospecimen Manager (found on resource page) with the sample information and FedEx tracking number.

14.315 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Freezer.

14.316 BAP Freezer will receive the samples and immediately forward specimens to the ACCRU Research Base BAP Shared Resource, Stabile SL-16. At study completion, specimens will be forwarded to the Duke Phase I Biomarker Laboratory located at Duke University for future processing.

14.32 Guardant 360 (Streck Tube)

14.321 Complete the Test Requisition Form and barcode labels.

14.322 Ship tubes the same day as collection with properly prepared gel pack. Do not freeze gel packs. Use as is.

14.323 Place the kit into the preprinted FedEx Clinical Pak and call FedEx for a pickup to be shipped to Guardant Health.

14.324 Detailed Blood Draw and Shipping Instructions are located on the ACCRU website under Manuals and Forms.

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research

14.411 Soluble protein (blood-based) biomarkers

Blood (platelet poor plasma, and white blood cells (buffy coat)) will be collected at baseline and C2D1 for future analysis. The Duke Phase I Biomarker Laboratory located at Duke University may analyze for the following, but are not limited to soluble HGF, c-MET, EGF, HBEGF, HER1-3, FGFa, FGFb, VEGFA-D, PlGF, VEGFR2, GAS6, AXL, SDF1, Ang2, and TIE-2. Additional biomarkers may also be explored using multiplex array technology. Final biomarker selection will reflect the best science at the time of analysis.

14.412 Plasma for mutational analysis

Blood (platelet poor plasma) will be stored for future analysis of cell free DNA (cfDNA) and will be collected at baseline, and C2D1. The Duke Phase I Biomarker Laboratory located at Duke University may analyze for the following, but are not limited to *HER2* amplification, *EGFR* amplification, BRAF mutations, and extended KRAS/NRAS testing (exons 2, 3, and 4). Final biomarker selection will reflect the best science at the time of analysis.

14.413 Future use of patient samples

Any remaining biological materials (platelet poor plasma, and buffy coats) at the end of the study will be retained for possible use in future biomarker research.

14.5 Return of Genetic Testing Research Results

Results of CLIA-certified assays (e.g., Guardant360) are permitted to be shared with patients and their treating physicians. Because the results generated by other 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 **Regorafenib (BAY73-4506, Stivarga®)**

- Refer to package insert for complete, up-to-date information.

15.11 Background

Regorafenib is a novel oral multi-kinase inhibitor that targets tumor cells and the tumor microenvironment. It inhibits tumor growth, progression and metastasis by inhibiting the proliferation of tumor cells, the formation of new tumor vasculature and stromal signaling in the microenvironment of the tumor.

15.12 Formulation

Commercially available in 40 mg tablets.

15.13 Preparation and storage

Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F).

15.14 Administration

Regorafenib tablets should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Regorafenib should not be taken with grapefruit juice.

15.15 Pharmacokinetic information

a) Absorption – A high-fat meal increased the mean AUC of the parent drug by 48% compared to the fasted state and decreased the mean AUC of the M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) active metabolites by 20% and 51%, respectively. A low-fat meal increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively (as compared to the fasted state).

b) Distribution – Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins.

c) Metabolism – Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites measured at steady state are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), both of them having similar *in vitro* pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

d) Excretion – Elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a

longer mean (range) elimination half-life of 51 hours (32 to 70 hours).

e) Feces (71%; 47% as parent compound; 24% as parent compound; 24% as metabolites); Urine (19%).

15.16 **Potential Drug Interactions**

Avoid concomitant use of strong CYP3A4 inducers (i.e. rifampin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) and strong CYP3A4 inhibitors (i.e. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole).

15.17 **Known potential toxicities**

Consult the package insert for the most current and complete information.

Serious Adverse Effects

Hepatotoxicity: [U.S. Boxed Warning]: Severe liver toxicity and hepatic failure (sometimes resulting in death) have been observed in clinical trials; hepatocyte necrosis with lymphocyte infiltration has been demonstrated with liver biopsy. Monitor hepatic function at baseline and during treatment. Interrupt therapy for hepatotoxicity; dose reductions or discontinuation are necessary depending on the severity and persistence.

Most Common Adverse Events, >10%:
Cardiovascular: Hypertension
Central nervous system: Fatigue, dysphonia, pain, fever, headache.
Dermatologic: Palmar-plantar erythrodysesthesia, rash, alopecia
Endocrine & metabolic: Hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia, hypothyroidism
Gastrointestinal: Appetite decreased, lipase increased, diarrhea, mucositis, weight loss, amylase increased, nausea, vomiting
Hematologic: Anemia, lymphopenia, thrombocytopenia, INR increased, hemorrhage, neutropenia
Hepatic: AST increased, ALT increased, hyperbilirubinemia
Neuromuscular & skeletal: Stiffness
Renal: Proteinuria
Miscellaneous: Infection

Less Common Adverse Events, 1% - 10%:
Cardiovascular: Myocardial ischemia and infarction
Gastrointestinal: Taste disturbance, xerostomia, gastroesophageal reflux

Neuromuscular & skeletal: Tremor
Respiratory: Dyspnea

Rare Adverse Events (Important or life-threatening), <1%:
Bradycardia, erythema multiforme, gastrointestinal fistula, hypertensive crisis, liver injury (severe), liver failure, reversible posterior encephalopathy syndrome (RPLS), skin cancer (keratoacanthoma, squamous cell carcinoma), Stevens-Johnson syndrome, toxic epidermal necrolysis

15.18 **Drug procurement:** Bayer will supply the drug to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order regorafenib from Clinical Research Services by submitting the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

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

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

15.19 **Nursing Guidelines**

15.191 Liver toxicity and liver failure have resulted from this agent. Monitor LFT's closely and instruct patients to report any abdominal pain, jaundice or significant fatigue to the study team. Dose reduce or interrupt treatment as per protocol.

15.192 Hypertension has been seen. Monitor blood pressure as outlined in protocol.

15.193 Instruct patient to report a rash, or signs and symptoms of palmar-plantar erythrodysesthesia to the study team. Rarely SJS and TENS have been seen with this agent. Instruct patients to seek immediate medical attention if they experience rash with fever, blisters, sloughing of tissue (especially in the mouth and vaginal, anal regions). Treat symptomatically and monitor for effectiveness.

15.194 Warn patients of possibility of alopecia.

15.195 Gastrointestinal side effects can include, diarrhea, nausea,

vomiting, decreased appetite, weight loss, mucositis and less commonly taste changes, dry mouth, and reflux. Treat symptomatically and monitor for effectiveness.

15.196 Cytopenias are seen with agent. Monitor CBC w/diff and instruct patient to report signs, symptoms of infection or any unusual bruising or bleeding to the study team.

15.197 Secondary skin cancers have been reported. Instruct patients to report new or changing lesions to study team.

15.198 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.

15.2 **Cetuximab (Erbitux®)**

- Refer to package insert for complete, up-to-date information.

15.21 **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.

15.22 **Formulation**: Commercially available for injection 2 mg/mL (50 mL, 100 mL).

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature (2 to 8ºC 38 to 46ºF), 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 8ºC 38 to 46ºF) and up to 8 hours at room temperature (20 to 36ºC or 68 to 77ºF).

15.24 **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.

15.25 **Pharmacokinetic information**:
Distribution: $V_{d:}$ ~2-3 L/m^2
Half-life elimination: ~112 hours (range: 63-230 hours)

15.26 **Potential Drug Interactions**:
There are no known interactions where it is recommended to avoid concomitant use.

15.27 **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 sever 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
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, keratitis, leukopenia, loss of consciousness, MI, pulmonary embolism, radiation dermatitis, shock, skin fissure, skin infection, stridor

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

15.29 **Nursing guidelines**

15.291 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.

15.292 Vital signs should be taken prior to, during, post and 1 hour post infusion.

15.293 Patient should be observed for 1 hour following the loading dose and each maintenance dose.

15.294 Premedicate with 50 mg of IV diphenhydramine, or other specific premedications called for in the protocol, prior to each dose.

15.295 Patients should be taught to wear sunscreen and hats and limit sun exposure while receiving treatment.

15.296 Recommend that all infusions be run on a volumetric pump. Infusion rate **MUST NEVER EXCEED 10MG/MINUTE (5 ML/MINUTE).**

15.297 Monitor CBC and instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.

15.298 Monitor LFTs.

15.299a Fever and chills may occur. Discuss with MD about premedication with an antipyretic.

15.299b Monitor for signs and symptoms of gastrointestinal side effects, including nausea, constipation, diarrhea, and vomiting. Administer antiemetics and antidiarrheals and/or stool softeners as indicated and evaluate their effectiveness.

15.299c Instruct patient to report rash.

15.299d 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.

15.299e Sensory neuropathy has been seen. Assess for this and inform MD if this develops.

15.3 **Panitumumab (Vectibix®)**

- Refer to package insert for complete, up-to-date information.

15.31 **Background**: Panitumumab is a recombinant human IgG2 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 intracellular tyrosine kinases, resulting in inhibition of cell survival, growth, proliferation and transformation. 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 20 mg/mL (5 mL, 20 mL).

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store unopened vials at refrigeration temperature, do not freeze or shake, protect from light. Dilute in 100-150 mL of normal saline to a final concentration of less than or equal to 10 mg/mL. Do not shake, invert gently to mix. Preparations in infusion containers are stable for 24 hours under refrigeration or for 6 hours at room temperature.

15.34 **Administration:** Doses less than or equal to 100 mg, infuse over 1 hour: doses > 1000 mg, infuse over 90 minutes; reduce infusion rate by 50% for mild-to-moderate infusion reactions (grades 1 and 2); discontinue for severe infusion reactions (grades 3 and 4). Administer through a low protein-binding 0.2 or 0.22 micrometer in-line filter. Flush with NS before and after infusion.

15.35 **Pharmacokinetic information**:
Half-life elimination: ~7.5 days (range: 4-11 days)

15.36 **Potential Drug Interactions**:
Increased Effect/Toxicity: 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: Dermatologic toxicities and severe infusion reactions.
Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue
Dermatologic: Skin toxicity, erythema, Acneiform rash, pruritus, exfoliation, paronychial, rash, fissures, acne
Endocrine & metabolic: Hypomagnesemia
Gastrointestinal: Abdominal pain, nausea, diarrhea, constipation, vomiting
Respiratory: Cough
Less common known potential toxicities, 1% - 10%:
Dermatologic: Dry skin, nail disorder
Endocrine& metabolic: Dehydration
Gastrointestinal: Stomatitis, mucositis
Ocular: Eyelash growth, conjunctivitis, ocular hyperemia, lacrimation increased, eye/eye lid irritation
Miscellaneous: Antibody formation, infusion reactions

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Abscess formation, allergic reaction, anaphylactoid reaction, angioedema, chills, dyspnea, fever, hypocalcemia, hypoxia, pulmonary embolism, pulmonary fibrosis, pulmonary infiltrate, sepsis, septic death

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

15.39 **Nursing Guidelines:**

15.391 Patient may experience typical EGFR inhibitor related rash, which is generally acneiform in nature and may be associated with pruritus and erythema. Treat symptomatically and monitor for effectiveness.

15.392 Premedication is generally not required with panitumumab administrations as infusion related reactions are rare. If patients do experience a transfusion related reaction, stop the infusion, inform the MD and treat as necessary. Patient then may need premedication prior to future infusions.

15.393 Panitumumab must be infused via infusion pump through a 0.2 or 0.22 micron in-line filter infusion set up. Flush with 0.9% sodium chloride injection, USP before and after infusion.

15.394 Hypomagnesmia is seen with this agent. Monitor magnesium level prior to each infusion. If level is below normal, inform the MD.

15.395 Patients may experience nail related changes, including discoloration, ridging, paronychias, and/or loss of the nail itself.

Instruct patients to report nail changes to the study team, as intervention may be indicated.

15.396 Gastrointestinal side effects including nausea, diarrhea, constipation and vomiting have been seen. Treat symptomatically and monitor for effectiveness.

15.397 Monitor patients closely and instruct them to report any side effects to the study team as all side effects of panitumumab in combination with chemotherapy are not known at this time.

15.398 Panitumumab is a protein and should be handled carefully to avoid break down of the product. This includes both when mixing from the vial and when administering the product via IV infusion.

15.4 Irinotecan (Camptosar®, CPT11)

- Refer to package insert for complete, up-to-date information.

15.41 **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.

15.42 **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].

15.43 **Preparation, storage, and stability**: Store intact vials at room temperature (15 to 30ºC or 59 to 86ºF) and protect from light. Doses should be diluted in 250-500 mL D_5W 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 2ºC to 8ºC. Solutions diluted in 0.9% NaCl may precipitate if refrigerated. Do not freeze.

15.44 **Administration:** Administer by I.V. infusion, usually over 90 minutes.

15.45 **Pharmacokinetic information**:
Distribution: V_d: 33-150 L/m^2
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 glucoronidation 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%)

15.46 **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 ≥ weeks prior to irinotecan therapy; concurrent use is contraindicated.

15.47 **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, anaphylactic like 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 typhlitis, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus, pulmonary toxicity (dyspnea, fever, reticulo-nodular infiltrates on chest x-ray), renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhlitis, ulceration, ulcerative colitis

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

15.19 **Nursing Guidelines:**

15.191 Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic symptoms may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). These symptoms are expected to occur more frequently with higher irinotecan doses. Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Patients should contact their physician if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours.

15.192 Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis.

15.193 Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if anaphylactic reaction occurs.

15.194 Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan (in combination and as monotherapy). Risk factors include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during CAMPTOSAR therapy.

15.195 Hold CAMPTOSAR if neutropenic fever occurs or if the absolute neutrophil count drops

15.196 Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of CAMPTOSAR.

16.0 Statistical Considerations and Methodology

16.1 Overview

This randomized phase II trial is designed to compare the overall survival (OS) in patients with metastatic colorectal cancer, who randomized to regorafenib followed by anti-EGFR therapy (either cetuximab or panitumumab) ±irinotecan (arm A, R+E) vs. anti-EGFR therapy ±irinotecan followed by regorafenib (arm B, E+R). Prior studies have shown that the median OS of patients in this disease population who received anti-EGFR follow by regorafenib is around 7.5 months [20,32]. It is hypothesized that the sequence of regorafenib followed by anti-EGFR can increase the median OS to 14.5 months. In addition to OS, this trial will also compare the first progression-free survival 1 (PFS1), the second progression-free survival (PFS2), sequential treatment progression-free survival (stPFS), objective response rates (ORR) and adverse event rates between two arms.

This study's original design had no restriction on tumor sidedness. Due to the results of the PARADIGM trial, this study has been amended to reflect treatment patterns where patients will likely receive anti-EGFR therapy as first line therapy. In PARADIGM, the study aimed to test the superiority of panitumumab versus bevacizumab in combination with standard double first-line chemotherapy for patients with newly diagnosed metastatic colon cancer with RAS WT mCRC and left sided tumors. The addition of panitumumab significantly improved overall survival compared to patients who received bevacizumab amongst those with left sided tumors (HR, 0.82; 95.798% CI, 0.68-0.99, p = .031) and the full analysis of all patients (HR, 0.84; 95% CI, 0.72-0.98; p = .030). However, in patients with right sided disease, no improvement in overall survival was observed in patients who received panitumumab (HR 1.09). Given the absence of survival benefit observed in patients with right sided colon cancer, the potential clinical benefit from sequencing therapy remains of interest.

The study has been amended to enrollment of patients with right-sided tumors in Amendment 2. Patients with left-sided tumors who were enrolled prior to Amendment 2 will continue being followed per protocol but their data will not be utilized for the primary endpoint analysis.

Evaluable Population: The Evaluable Population comprises all patients who are eligible, consented, randomized, received any protocol treatment, and have right-sided tumors.

Safety Population: The Safety Population comprises all patients who received any protocol treatment.

16.11 Primary Endpoint: The primary endpoint is overall survival. The primary objective for this trial is to compare the overall survival (OS) between evaluable patients who were randomized to arm A and arm B. Overall survival is defined as the time from randomization to death from any cause. Patients who are alive at the time of statistical analysis will be censored at the last known alive date.

16.12 Secondary Endpoints: Each secondary endpoint will be compared between arms. These include first progression free survival (PFS1), second progression free survival two (PFS2), sequential treatment progression free survival (stPFS), objective response rate of initial treatment and sequential treatment, and incidence of adverse events from initial treatment, sequential treatment and whole period.

16.2 Statistical Design

6.21 The primary goal is to compare the OS between evaluable patients who were randomized to R+E (arm A) and E+R (arm B). The null hypothesis is that R+E (arm A) does not show a significantly superior OS outcome compared to E+R (arm B). The alternative hypothesis is that R+E has improvement in OS compared to E+R.

16.22 Power and Sample Size

We will enter 26 evaluable patients to each arm of the study using a 1:1 randomization scheme (52 evaluable patients in total), unless the study is stopped early. Stratification factors are defined in section 5.0. With 26 evaluable patients per arm, we have 80% power to detect an improvement in median OS from 7.5 months to 14.5 months, assuming a 1-sided significance level of 0.1, and exponential survival.

An additional 8 patients (4 in each arm) will be enrolled to account for ineligibility, major violation, loss of follow-up, etc. The total expected accrual for primary analysis (i.e. patients with right-sided tumor) is 60. Including the 12 patients with left-sided tumors who enrolled prior to Amendment 2, the total expected accrual is 72 patients.

16.23 Final Analysis and Decision Rules

Efficacy analysis will be conducted when at least 42 death events, across both arms combined, have been observed. If the 1-sided p-value from stratified log-rank test is > 0.1 (hazard ratio > 0.673) for arm A vs. B, (R+E) treatment regimen will be considered inefficacious. Conversely, if the 1-sided p-value from stratified log-rank test is ≤ 0.1 (hazard ratio ≤ 0.673) for Arm A vs. B, the (R+E) treatment regimen will be considered promising for future study. Evaluable patients will be used for this analysis (see 16.1 for evaluable definition). The stratified log-rank test will be used for decision making except when there are 0 events in any of the strata; in that case, the un-stratified log-rank will be used for decision making.

Analysis time point	Number of events[1]	Critical p-value		Hazard Ratio	
		Futility	Efficacy	Futility	Efficacy
100%	42	> 0.1	≤0.1	> 0.673	≤ 0.673

16.24 Operating Characteristics

The table below shows the operating characteristics assuming the OS follows the exponential survival function along with a one-sided significance level of 0.1. The proportion of times that regorafenib followed by anti-EGFR (R+E) would be concluded to be superior at the final analysis are tabulated by true median OS times and equivalent true hazard ratios for OS by treatment groups.

True median overall survival (months)[3]		True Hazard Ratio (Arm A vs. B)	% of times that R+ E is deemed superior at the final analysis [4]
R + E[1] (Arm A)	E + R[2] (Arm B)		
7.5	7.5	1	10.3
9.5	7.5	0.789	30.0
11	7.5	0.682	47.8
12.5	7.5	0.6	63.7
14.5	7.5	0.517	79.4

[1] R + E: regorafenib followed by anti-EGFR ±irinotecan

[2] E + R: anti-EGFR ±irinotecan followed by regorafenib

[3] Although we use the median OS to illustrate each scenario, the hypothesis testing is based on the entire survival curve.

[4] Proportions are based on 50,000 replicates in a simulation study

16.25 Accrual Time and Study Duration

We plan to accrue a total of 72 patients (approximately 30 patients per arm with right-sided tumor + 12 patients enrolled with left-sided tumor) in 51 months with a minimum follow-up of 7.5 months to achieve 42 OS events. The length of accrual time is based on an accrual rate of 0.2 patients per month for the first 33 months and 3 patients per month for the remaining accrual period.

16.26 Other Considerations

Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence when the sufficient number of OS events has been observed (see 16.23). Such a decision will be made by the Statistician and Study Chair, in accordance with CCS Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity.

16.31 Primary Endpoint

16.311 Definition

The primary endpoint for this trial is to compare the overall survival (OS) between evaluable patients who were randomized to arm A and arm B. Overall survival is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method and compared between treatment groups using the stratified log-rank test. The median OS and 95% confidence interval will be reported. Patients will be censored at the date patient was last known to be alive.

16.312 Over Accrual

If more than the target number of patients are accrued, the additional evaluable patients will be used for decision making.

16.32 Secondary Endpoints

16.321 First Progression-Free Survival (PFS1)

Progression-free survival one (PFS1) is defined as the time interval between randomization date and the date of first progression while on initial treatment or until death whichever is first, where disease progression will be determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The median PFS and 95%

confidence interval will be reported. Patients with no defined events observed during the follow-up period will be censored at the last disease assessment date prior to the initiation of sequential treatment, if applicable.

16.322 Second Progression-Free survival (PFS2)

Second progression-free survival (PFS2) is defined as the time interval from re-registration to the sequential treatment phase until the date of progression while on sequential treatment or until death, whichever occurred first. Disease progression will be determined based on RECIST 1.1 criteria. PFS2 will be estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The median PFS2 and 95% confidence interval will be reported. Patients will be censored at the last disease assessment date while on sequential treatment .

16.323 Sequential Treatment Progression-Free Survival (stPFS)

Sequential treatment progression-free survival is defined as the time from randomization until progression while on the sequential treatment or until death, whichever occurred first. Patients who did not experience an event during follow-up will be censored at the last disease assessment date.

Patients who completed initial treatment but did not begin sequential treatment will be censored at the date of last disease evaluation prior to discontinuation of initial treatment. Patients who began sequential treatment but discontinued protocol treatment prior to progression will be censored at the last disease assessment date while on sequential treatment. Analysis methods will mirror those of the other PFS endpoints.

16.324 Objective Response Rate

The objective response rate to initial treatment will be estimated by the number of patients who achieve a best response to initial treatment of complete response or partial response (CR or PR) divided by the total number of evaluable patients. Point estimates and the corresponding 95% confidence intervals for the true success proportions will be calculated.

16.325 Sequential Treatment Objective Response Rate

The objective response rate to sequential treatment is defined as the number of patients who achieve a best response to sequential treatment of complete response or partial response (CR or PR) while on sequential treatment divided by the total number of evaluable patients who initiated sequential treatment. Point estimates and the corresponding 95% confidence intervals for the true success proportions will be calculated.

16.326 Adverse Events

Adverse events by patient will be summarized by frequencies and severity using CTCAE version 5.0. We will also closely monitor adverse events throughout the study.

16.327 Correlative Research
Serial blood collections – prior to cycle 1, every 8 weeks at the time of restaging scans and disease progression will be collected to post-hoc evaluate for plasma biomarkers prognostic or predictive to response and acquired treatment resistance

16.4 Data & Safety Monitoring

16.41 Review

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules

The stopping rules specified below are 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, in either arm, we observe events considered to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

If at any time, 3 of the initial 15 treated patients or 20% or more of all patients (i.e. when accrual is greater than 30 patients) have experienced a grade 4+ adverse event.

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

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
FFPE tissue block with corresponding H&E slide or up to twenty-five (25) 4-micron, unstained slides and up to three (3) corresponding H&E slides from **primary tumors present prior to study entry** (if available)	Mandatory	Baseline	Correlative studies (Section 17.3)	Section 17.2

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 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 surgery at the time of diagnosis. Biopsy material obtained at the time of metastatic diagnosis may be submitted, if blocks from the surgical resection are inadequate or unavailable. **A corresponding H&E slide for each submitted block must be provided**. The H&E slide for each block should be reviewed by the institution's pathologist to assess tissue quality prior to submission.

17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut up to 25 (twenty-five) 4-micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections, and thickness of sections. NOTE:** do **NOT** place "sticky" labels directly on slides, **the institution label needs to be visible**. H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). The H&E slides should be reviewed by the institution's pathologist to assess tissue quality prior to submission. For samples containing less than 7 square millimeters 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 should 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.**

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

- Paraffin embedded tissue blocks with corresponding H&E slide(s) (OR up to 25 (twenty-five) unstained slides with corresponding H&E slide(s)).
- Specimen Submission: Tissue form

- Surgical Pathology Report
- Operative Report *(optional)*

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

17.24 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.

17.25 Tissue specimens must be shipped ≤90 days from date of randomization.

17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

17.28 When an appropriate request is submitted, the ACCRU Operations Office will forward the block(s) to the Duke Phase I Biomarker Laboratory located at Duke University for processing as outlined in Section 17.3.

17.3 Study Methodology and Storage Information

Submitted tissue samples will be analyzed as follows:

17.31 At the completion of the study, any unused/remaining material will be stored in the Duke Phase I Biomarker Laboratory located at Duke University for future research according to the patient consent permission Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.32 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 studies).

17.33 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.34 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.35 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

Access the RAVE system through the iMedidata portal at [redacted] All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document.

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after randomization
On-Study	
On-Study: Prior Surgery[2]	
On-Study: Prior Radiation[2]	
On-Study: Prior Systemic Therapy[2]	
Adverse Events: Baseline	
RECIST Measurements: Initial Treatment (Baseline)	
Laboratory Tests & Results: Baseline	
Op and Pathology Reports[1]	
Supporting Documentation: Baseline[3]	
Patient Status: Baseline	
Specimen Submission: Blood -Baseline (see Section 14.0)	
Specimen Submission: Tissue-Baseline (see Section 17)	≤2 weeks after randomization
Notice of New Primary[2]	
Off Treatment	Submit ≤2 weeks after randomization if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[2]	Submit only if applicable during all phases of the study

1. Submit Op and Path Reports via the Supporting Documentation: Baseline form.
2. Submit only if applicable.
3. Submit copy of imaging report

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention)	X[2]	X
Treatment (Intervention): Dose Modifications, Omissions and Delays[3]	X	X
Adverse Events: Solicited	X	X
Adverse Events: Other[3]	X	X
RECIST Measurements: Initial Treatment[3]	X[1]	X[1]
RECIST Measurements: Sequential Treatment (Baseline)[3]	X	X
RECIST Measurements: Sequential Treatment[3]	X	X
Supporting Documentation[3]	X[1]	X
Laboratory Tests and Results	X	X
Specimen Submission: Blood	X (see Section 14.0)	X (see Section 14.0)
Patient Status: Treatment (Intervention)	X	X
End of Initial Treatment		X
Off Treatment		X
Notice of New Primary[3]	X	
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Optional Specimens • Consent Withdrawal: All Follow-Up	X	X
Lost to Follow-Up[3]	X	
ACCRU Deviation Form[3]	X	

1. Attach a copy of imaging report for each restaging scan and documentation of response or progression in RAVE on the Supporting Documentation Form.
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Submit only if applicable.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q.3 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	At each occurrence
Adverse Events: Late[3]					At each occurrence
Supporting Documentation[3]					At each occurrence
Lost to Follow-Up[3]					At each occurrence
Notice of New Primary[3]					At each occurrence
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Optional Specimens • Consent Withdrawal: All Follow-Up					At each occurrence
ACCRU Deviation Form[3]					

1. If a patient is still alive 3 years after randomization, no further follow-up is required.
2. Attach a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.
4. Please use the "Add Event" function to record the first instance of non-protocol treatment received. If the patient has never had any non-protocol treatment, record as "no" at the end of the Event Monitoring Phase.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

- Pharmacogenomic collection
- Mutational collection
- cfDNA Guardant360
- Tumor tissue collection

19.3 Other budget concerns:

19.31 Regorafenib will be supplied by Bayer Pharmaceuticals. Cetuximab, pantiumumab, and irinotecan will not be supplied, but is commercially available.

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Appendix I: ACCRU-GI-1809 SUBJECT MEDICATION DIARY: Regorafenib

Name:	Patient ID Number:
Cycle:	
You will take:	

ORAL MEDICATION DIARY

Subject Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a check "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose or double up the next dose.

ACCRU-GI-1809 SUBJECT MEDICATION DIARY – **Regorafenib**

Cycle #_____

Study Drug/Dose	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Regorafenib/ mg							

Study Drug/Dose	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Regorafenib/ mg							

Study Drug/Dose	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Regorafenib/ mg							

Study Drug/Dose	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Regorafenib/ mg							

Date:_____ Subject's Signature_____

Area Below Only To Be Completed only by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					

Comments:

_____

_____

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