Academic and Community Cancer Research United (ACCRU)

PULSE: A Randomized, Phase II Open Label Study of PanitUmumab RechaLlenge Versus Standard Therapy after Progression on Anti-EGFR Therapy in Patients with Metastatic and/or Unresectable RAS Wild-Type Colorectal Cancer

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

ACCRU: [redacted]

Sponsor/Investigator: [redacted]

Study Co-chairs: [redacted]

Correlative Science Co-chair: [redacted]

Statistician: [redacted]

Drug Availability

Commercial Agents: Trifluridine/tipiracil (TAS-102), regorafenib

Drug Company Supplied: Panitumumab (IND Exempt)

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

Research Coordinating Center

[redacted]

Document History	**(effective date)**
Initial Version	April 29, 2019
Amendment 1	August 4, 2020

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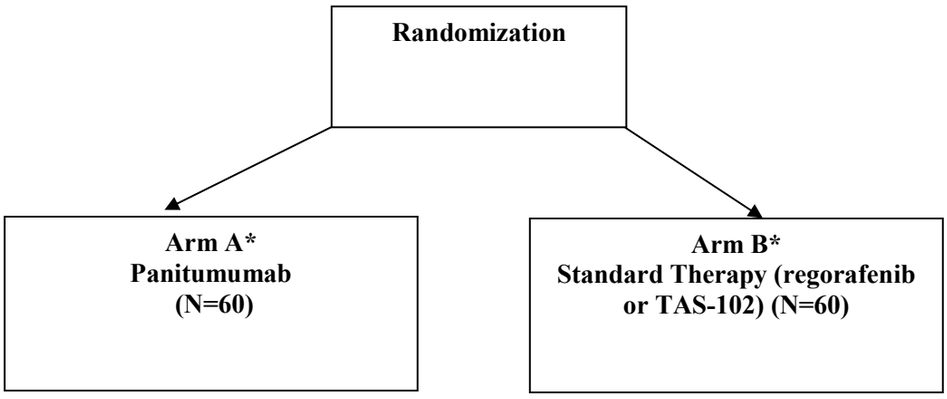
Schema

NOTE: Patients must be registered to ACCRU-GI-1611(COLOMATE) and have received the COLOMATE Companion Trial Recommendation Form prior to being registered on this study.



PD at any time
Unacceptable adverse events → EM**
Patient refusal
Investigator's decision

** EM= Event Monitoring

*Cycle length = 28 days
*Treat until progression or maximum of 24 cycles

Generic name: Panitumumab Brand name(s): Vectibix Availability: Amgen	Generic name: TAS-102 Brand name(s): TAS-102 Trifluridine FTD)/ Tipiracil (TPI) (TAS-102, Lonsurf®) Availability: Commercial
Generic name: Regorafenib Brand name(s): Stivarga Availability: Commercial	

1.0 Background

1.1 Treatment

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States [1]. Current FDA-approved treatment options for refractory metastatic CRC include regorafenib and trifluridine/tipiracil (TAS-102). Compared to placebo, regorafenib and TAS-102 both offer a median progression free survival (PFS) benefit of less than 10 days, and an overall survival (OS) benefit of less than 2 months (*see* **Table 1**) [2, 3]. The objective response rate (ORR) for both therapies is less than 2%.

Table 1. Treatment Options for Patients with Treatment Refractory Metastatic CRC

Clinical trial	Therapies	Patients (N)	ORR (%)	Median PFS (months)	Median OS (months)
CORRECT	Regorafenib	505	1.0%	1.9	6.4
	Placebo	255	0.4%	1.7	5.0
RECOURSE	TAS-102	534	1.6%	2.0	7.1
	Placebo	266	0.4%	1.7	5.3

Approximately half of all patients with metastatic CRC have *KRAS* or *NRAS* (*RAS*) wild-type tumors, and these patients are eligible to receive the epidermal growth factor receptor (EGFR) monoclonal antibodies panitumumab or cetuximab. Anti-EGFR therapies improve survival in the first line [4-6], second-line [7, 8], and treatment refractory settings [9-11], but nearly all patients develop resistance. In recent years several reports have suggested that patients with *RAS* wild-type metastatic CRC who develop EGFR antibody resistance may benefit from EGFR antibody rechallenge [12-14]. In a prospective non-randomized phase II study of cetuximab rechallenge (n=39), the response rate was 54%, with a median PFS of 6.6 months [15]. Despite these encouraging results there is limited evidence from randomized trials establishing the clinical value of this approach. Efforts are ongoing to better understand sub-populations who may benefit from EGFR antibody rechallenge.

1.2 Drivers of EGFR Antibody Resistance

To establish the benefit of EGFR antibody rechallenge, it is critical to avoid treatment in patients with known drivers of EGFR antibody resistance. These genomic drivers of primary and acquired EGFR antibody resistance are well described. The first-line PRIME and CRYSTAL trials established mutations in *KRAS* and *NRAS* exons 2-4 as predictive biomarkers for lack of benefit from anti-EGFR antibody therapy [16, 17]. Based on these findings, the FDA labels for cetuximab and panitumumab were updated to exclude anti-EGFR therapy in patients with known *RAS* mutations. Other genomic alterations may also predict resistance to anti-EGFR therapy. *BRAF* V600E mutations are found in 5-10% of metastatic CRC tumors. Several retrospective studies suggest that *BRAF* mutations predict poor response to anti-EGFR therapy [18-20], though these studies are often limited by small patient numbers. *ERBB2* (also known as HER2) amplification may also predict resistance to anti-EGFR therapies [21-23].

Blood-based genomic profiling has identified several drivers of acquired resistance. *MET* amplification emerges under the selective pressure of anti-EGFR therapy, and may be targetable with FDA-approved and investigational anti-MET therapies [12, 24-28]. EGFR ectodomain (ECD) mutations prevent binding of EGFR antibodies, and may be sensitive to novel anti-EGFR therapies [22, 29, 30]. *KRAS* and *NRAS* mutations are the most common drivers of acquired resistance [31-33]. *RAS* mutated clones are dependent on the presence of EGFR antibodies for their selective advantage, and their frequency declines when EGFR antibodies are withdrawn [12]. In a series of 130 patients with *RAS* wild-type metastatic CRC treated with EGFR antibodies, plasma samples were able to detect acquired *RAS* and *EGFR* mutations in blood. This same analysis demonstrated exponential decay of the *RAS* and *EGFR* relative mutant allele frequency (rMAF), with a half-life of 3.4 months and 6.9 months, respectively [34]. Accordingly, these results provide a rationale for the study of EGFR antibody rechallenge.

1.3 Blood-based molecular profiling to Identify Patients for EGFR Antibody Rechallenge

Several recent studies have demonstrated that molecular profiling of cell free DNA (cfDNA) could be useful for identifying patient sub-populations most likely to benefit from EGFR antibody rechallenge. As part of an investigator-initiated trial at Duke University (NCT02008383), comprehensive blood-based genomic profiling was performed on patients with EGFR-refractory, *RAS* wild-type metastatic CRC. This profiling effort utilized the Guardant360^{TM} assay (Guardant Health, Redwood City, CA), a >70-gene NGS-based blood test. Among the 69 patients with EGFR-refractory disease who received blood-based genomic profiling, 18 patients (26%) had no detectable resistance-conferring mutation or amplification [35].

Recent studies have further shown that cfDNA profiling is an effective diagnostic tool to identify patients likely to benefit from EGFR antibody rechallenge. In a single-arm phase II study conducted in Italy (CRICKET), 28 patients with *RAS* wild-type metastatic CRC who received first-line FOLFIRI/cetuximab and second line FOLFOX/bevacizumab were assigned to third line irinotecan/cetuximab [36]. Six patients (21.5%) experienced partial response, with a median PFS of 3.4 months and a median overall survival (OS) of 9.8 months. Utilizing droplet digital (dd) PCR, 12 patients had a baseline *RAS* mutation detected in blood, and 13 patients had no baseline *RAS* mutation detected. The response rate for patients who were *RAS* wild-type in blood was 38%, with a median PFS of 4.0 months and a median survival of 12.5 months. The use of cfDNA to identify patients likely to benefit from EGFR antibody rechallenge is further supported by results of a phase II randomized trial comparing the novel EGFR antibody admixture SYM004 versus investigator choice (IC) therapy in patients with EGFR refractory metastatic CRC [37]. In the intent-to-treat (ITT) population, there was no survival benefit for SYM004 compared to IC. However, a retrospective analysis of patients who were *RAS*/*BRAF*/*EGFR* mutation negative in blood found improved survival in patients treated with SYM004 compared with IC (median OS, 12.8 and 7.3 months, respectively).

Collectively, these results support the potential clinical benefit of EGFR antibody rechallenge, and suggest that cfDNA profiling may identify patients most likely to benefit.

2.0 Goals

2.1 Primary

2.11 To compare the overall survival (OS) in molecularly selected patients with metastatic CRC receiving panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib).

2.2 Secondary

2.21 To compare the progression free survival (PFS) in molecularly selected patients with metastatic CRC receiving panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib).

2.22 To define the objective response rate (ORR) in patients receiving panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib).

2.23 To define the clinical benefit rate (CBR= complete response + partial response + stable disease ≥ 6 months) in patients receiving panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib).

2.24 To compare the safety and tolerability of panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib).

2.25 To compare QOL between panitumumab rechallenge versus standard therapy (TAS-102 or regorafenib) as measured by the linear analogue self-assessment (LASA) questionnaires.

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 Registration – Inclusion Criteria

3.11 Registered to COLOMATE ACCRU-GI-1611 and:
a) COLOMATE Companion Trial Recommendation Form indicates patient qualifies to be screened for a COLOMATE companion trial.
b) COLOMATE Companion Trial Recommendation Form date of completion is ≤ 30 days prior to randomization.

3.12 Age ≥18 years.

3.13 Histologically and/or cytologically confirmed adenocarcinoma of the colon or rectum that is metastatic and/or unresectable.

3.14 Documented wild-type in *KRAS* and *NRAS* (codons 12, 13, 59, 61, 117, and 146) and in *BRAF* codon 600, based on tumor tissue taken from primary or metastatic site prior to receipt of anti-EGFR therapy.

3.15 Progression, intolerance, or contraindication to a fluoropyrimidine (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody (bevacizumab, ramucirumab, or aflibercept), and an anti-PD-1 monoclonal antibody (nivolumab or pembrolizumab) if tumor has deficient mismatch repair proteins (dMMR) or is microsatellite instability-high (MSI-H).

3.16 Disease progression after treatment with an anti-EGFR monoclonal antibody (cetuximab and/or panitumumab) for at least 4 months (minimum of 8 biweekly treatments or 16 weekly treatments at full or partial dose).

NOTE: Treatments do not need to be administered consecutively.

NOTE: Dose reductions or delays are permitted.

3.17 Greater than 90 days has elapsed between the most recent treatment with an anti-EGFR therapy (cetuximab or panitumumab) and blood collection for COLOMATE ACCRU-GI-1611.

3.18 At least one site of disease that is measurable by RECIST criteria (as defined in Section 11.0) that has not been previously irradiated; if the patient has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation.

3.19a Life expectancy ≥ 3 months per estimation of investigator.

3.19b ECOG Performance Status (PS) 0, 1, or 2. (Form is available on the ACCRU web site).

3.19c The following laboratory values obtained ≤7 days prior to randomization.

- Absolute neutrophil count (ANC) ≥1500/mm^{3}without colony stimulating factor support
- Platelet count ≥75,000/mm^3
- Hemoglobin >8.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)

- Calculated creatinine clearance must be > 30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\text{(140 - age)(weight in kg)(0.85)}}{\text{(72)(serum creatinine in mg/dL)}}$

3.19d Women of child bearing potential and male partners of women of child bearing potential must agree to use two medically accepted methods of contraception, one of them being a barrier method during the study and for 2 months after the last dose of study drug(s).

3.19e Negative serum pregnancy test done ≤7 days prior to randomization, for women of childbearing potential only.

NOTE: Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Postmenopause is defined as amenorrhea ≥ 12 consecutive months. NOTE: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, ovarian suppression or any other reversible treatment.

3.19f Ability to complete questionnaire(s) by themselves or with assistance.

3.19g Capable of understanding and complying with the protocol requirements and has signed the informed consent document.

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

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

3.19j Willing to allow transfer of tissue and blood samples, clinical information, and outcome data collected from this trial for future research (see Sections 6, 14, and 17*).*

3.2 Registration – Exclusion Criteria

3.21 Radiation therapy, hormonal therapy, biologic therapy, experimental therapy, or chemotherapy for cancer < 21 days prior to randomization.

3.22 Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin).

3.23 Maximum mutant allele frequency (highest allele frequency reported for any gene mutation) (MAF) less than 2% by Guardant360 assay.

NOTE: Refer to COLOMATE Companion Trial Recommendation Form for information regarding 3.23 and 3.24.

3.24 Detection of at least one of the following gene mutation(s) or amplification(s) by Guardant360 assay.

- *BRAF* mutation mutant allele frequency (MAF) > 0.5%
- *EGFR* mutation (MAF > 0.5%). Note: EGFR S492R, K467, and R451C mutations are not an exclusion
- *ERBB2* (HER2) mutation (MAF > 0.5%) or amplification
- *KRAS* mutation (MAF > 0.5%) or amplification
- *MET* mutation (MAF > 0.5%) or amplification

- *NRAS* mutation (MAF > 0.5%) or amplification

3.25 Prior treatment with both TAS-102 and regorafenib (prior treatment with either TAS-102 or regorafenib is permitted).

3.26 Unable to swallow oral tablets (crushing of study treatment tablets is not allowed).

3.27 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. Note: This includes impaired heart function or clinically significant heart disease.

3.28 Not recovered to baseline or CTCAE v5.0 ≤ Grade 1 from toxicity due to all prior therapies except alopecia, oxaliplatin-related neuropathy, asymptomatic electrolyte abnormalities, and other non-clinically significant adverse events.

3.29a 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

3.29b Patients with known CNS metastases. Note: Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive (based on repeat imaging ≥ 30 days after completion of definitive treatment), patients are asymptomatic, and no steroids to control symptoms related to CNS metastases have been administered for at least 30 days.

3.29c Major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days prior to randomization (≤ 56 days for hepatectomy, open thoracotomy, major neurosurgery) or anticipation of need for major surgical procedure during the course of the study.

3.29d Serious, non-healing wound, ulcer, or bone fracture.

3.29e History of stroke (cerebrovascular accident), transient ischemic attack (TIA), myocardial infarction (MI), unstable angina, cardiac or other vascular stenting, angioplasty, or cardiac surgery ≤ 6 months prior to randomization.

3.29f History of cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers, calcium channel blockers, or digoxin ≤ 6 months prior to randomization.

3.29g Known history of congestive heart failure – New York Heart Association (NYHA) ≥ Class II.

3.29h Known history of HIV seropositivity, acute or chronic active hepatitis B or C infection, or other serious chronic infection requiring ongoing treatment.

3.29i History of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest CT scan.

3.29j Subjects with any previously untreated or concurrent cancer that is distinct in primary site or histology from colorectal cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Note: Subjects surviving a cancer that was curatively treated and without evidence of disease or biochemical relapse (undetectable PSA for prostate cancer) for 3 or more years before randomization are allowed. All cancer treatments must be completed at least 3 years prior to randomization.

3.29k Uncontrolled hypertension (systolic pressure > 150 mm HG or diastolic pressure > 90 mm Hg [NCI-CTAE v5.0] on repeated measurement despite optimal medical management.

3.29l Evidence or history of bleeding diathesis or coagulopathy.

3.29m Any hemorrhage or bleeding event ≥ NCI CTCAE v5.0 Grade 3, ≤ 4 weeks prior to randomization.

3.29n Ongoing active infection > Grade 2 NCI-CTCAE v5.0.

3.29o Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulation given during the course of this trial.

EXCEPTION: Cetuximab

3.29p Any known history of malabsorption condition.

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

3.29r Use of any herbal remedy (e.g. St. John's wort) ≤ 7 days prior to randomization.

3.29s Use of strong CYP3A4 inducers or inhibitors ≤ 7 days prior to randomization. See Appendix III.

4.0 Test Schedule

Tests and procedures	Screening Phase		Active Monitoring Phase				
	≤28 days prior to randomization	≤7 days prior to randomization	Baseline (Prior to Cycle 1 Day 1 treatment)	Day 15 of each cycle[8] (± 3 days)	Prior to dosing on Day 1 of ≥ cy 2 (± 3 days)	Prior to dosing at restaging (C3 and every other cycle after)	End of Tx (within 30 days after last dose of study drug)
History and exam, wt, ECOG PS	X			X	X		X
Height	X						
Adverse event assessment	X			X[1]	X[1]		X
CBC/ differential: WBC, hemoglobin, hematocrit, platelets, neutrophil count, lymphocyte count, monocyte count, eosinophil count		X	X[11]	X	X		X
Chemistry: Sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, calcium, SGOT (AST), SGPT (ALT), total bilirubin, alk phos, albumin, total protein		X	X[11]	X	X		X
Magnesium		X		X[5]	X[5]		X[5]
Tumor Blood Bio-Markers (CEA)		X			X (C2 only)	X (at each restaging)	
Serum Pregnancy test[2]		X	X[11]			X	
Tumor measurement (CT or MRI of the chest, abdomen and pelvis)[3]	X					X	
COLOMATE Companion Trial Recommendation Form[12]	X						
Mandatory blood sample – whole blood[4, 9,R]			X				
Mandatory blood sample –plasma[4,9, R]			X		X (C2 only)	X (at each restaging)	X
Mandatory tissue sample– archival tumor paraffin[6,R]			X				

Tests and procedures	Screening Phase		Active Monitoring Phase				
	≤28 days prior to randomization	≤7 days prior to randomization	Baseline (Prior to Cycle 1 Day 1 treatment)	Day 15 of each cycle[8] (± 3 days)	Prior to dosing on Day 1 of ≥ cy 2 (± 3 days)	Prior to dosing at restaging (C3 and every other cycle after)	End of Tx (within 30 days after last dose of study drug)
Mandatory Patient Questionnaire Booklet (Appendix II)[10]			X		X		X
Patient Medication Diary (Appendix IV)[13]					X	X	X
Optional Blood sample-cfDNA Guardant 360[4,7,R]							X

1 The adverse event assessment will be evaluated at the end of each cycle prior to the beginning of the next cycle and at day 15 visit for the first 6 cycles. Please note: only the maximum grade will be needed for data entry.
2 For women of childbearing potential only. Must be done ≤ 7 days prior to randomization.
3 Use same imaging throughout the study.
4 Kits are required for this collection. Refer to Section 14.0.
5 Only for patients receiving panitumumab.
6 Receipt of archival tumor tissue is not required for study randomization and initiation of therapy. However, it is mandatory to receive the required tissue within 90 days from randomization. See section 17.0.
7 Patients have the option to complete cfDNA testing at study completion and will be allowed to re-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.
8 May discontinue day 15 visit beginning cycle 7. Additional visits and laboratory studies are permitted as per institutional practice and as clinically appropriate.
9 Patient must be registered prior to collection.
10 Patient questionnaire will be completed at baseline and each cycle (Appendix II). Patient questionnaire booklets **must** be used; copies are not acceptable for this submission. The booklet order form is located on the ACCRU website under Manuals and Forms.
11 If screening tests occur ≤ 7 days prior to C1D1, they do not have to be repeated prior to dosing.
12 The COLOMATE Companion Trial Recommendation Form must indicate that the patient has met molecular eligibility to screen. The patient must be registered to the companion study ≤30 days from date of COLOMATE Companion Trial Recommendation Form completion. If the COLOMATE Companion Trial Recommendation Form recommends a different companion study, patient may still enroll.
13 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
R Research funded.

Event Monitoring: survival follow-up will be done every 3 months (± 7 days) until 3 year after randomization.

5.0 Stratification Factors:

5.1 Primary tumor location: right (cecum, ascending colon, hepatic flexure, and transverse colon) vs left (splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum).

5.2 Prior TAS-102 or regorafenib: Yes vs No.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, fax ([redacted]) a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

NOTE: ACCRU-GI-1611 (COLOMATE) treating physician will provide COLOMATE Companion Trial Recommendation Form which will include the Patient ID that must be used for this study.

6.12 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.

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using 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.

6.14 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.15 At the time of registration, the following will be recorded:

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

6.16 Treatment cannot begin prior to randomization and must begin ≤ 7 days after randomization.

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

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

6.19a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.19b Study drug is available on site.

6.19c Blood draw kit is available on site.

Exclusion: Guardant 360 kit does not need to be on site at the time of registration.

6.19d Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.2 Randomization Procedures

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

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to

one of the following treatment groups using the Pocock and Simon [39] dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

- Panitumumab
- Standard Therapy (regorafenib or TAS-102)

7.0 Protocol Treatment

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

Arm	Agent	Dose Level	Route	Day	ReRx
A	Panitumumab	6 mg/kg	IV	Day 1 Day 15	Every 28 Days
B	TAS-102	35 mg/m^2 (max 80 mg/dose)	Oral	Twice daily, days 1-5 and days 8-12	Every 28 Days
	Regorafenib	160 mg (alternative dosing permitted minimum 80 mg and max 160 mg)	Oral	Once daily, days 1-21	Every 28 Days

7.11 Arm A: Patients assigned to Arm A will receive panitumumab.

7.12 Arm B: Patients assigned to Arm B will receive either TAS-102 or regorafenib per treating physician discretion and will be dosed as per prescribing guidelines and at investigator discretion. Patients who have received TAS-102 prior to registration may only receive regorafenib. Patients who have received regorafenib prior to registration may only receive TAS-102. Patients cannot switch between TAS-102 and regorafenib during protocol treatment.

7.2 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation as per the study calendar during treatment. Additional visits during treatment are not mandated by the study protocol, but are advised to optimize symptom management and provide optimal care.

7.4 Treatment by a local medical doctor (LMD) is not allowed

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

8.0 Dosage Modification Based on Adverse Events

Subjects will be monitored continuously for AEs from the date of first dose of study drug and for 30 days after the last dose of study drug. Subjects will be instructed to notify their treating physician of any and all AEs. All AEs should also be managed with supportive care at the earliest signs of toxicity. Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator. Suggested supportive care measures for the management of adverse events are outlined in Section 9.0.

Subjects experiencing one or more AEs due to study drug(s) may require dose modification(s) as described in Sections 8.1, 8.2, and 8.3. 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. At the discretion of the Investigator, dose modifications are permitted outside of those provided in the protocol if the Investigator feels it is in the interest of the subject's safety (e.g., due to multiple toxicities, persistent toxicities, intercurrent illness, or short term compliance or monitoring issues, etc.). Subjects may need to be followed at least weekly when the study drug is held for clinically significant toxicity until the toxicity returns to Grade ≤ 1 or is determined to be controlled, chronic, or irreversible.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the Lead PI. The reason for interruption should be documented in the patient's study record.

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

8.1 Panitumumab: This section applies to adverse events associated with panitumumab. For adverse events associated with regorafenib, please refer to Section 8.2 and for TAS-102, please refer to Section 8.3.

* Located at [redacted]

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

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped
- **Dose Modifications – Dermatologic Toxicity**

- **Table 8.11. Dose Modifications during Vectibix Treatment**

Occurrence of Skin Symptom(s): ≥ grade 3[a]	Administration of Vectibix	Outcome	Dose Regulation
Initial occurrence	Stop 1 or 2 doses	Improved (< grade 3)	Continue infusion at 100% of original dose
		Not recovered	Discontinue
At the second occurrence	Stop 1 or 2 doses	Improved (< grade 3)	Continue infusion at 80% of original dose

		Not recovered	Discontinue
At the third occurrence	Stop 1 or 2 doses	Improved (< grade 3)	Continue infusion at 60% of original dose
		Not recovered	Discontinue
At the fourth occurrence	Discontinue	--	--

[a] Greater than or equal to Grade 3 is defined as severe or life-threatening

Management of Skin Toxicities

Proactive skin treatment including skin moisturizer, sunscreen (SPF > 15 UVA and UVB), topical steroid cream (not stronger than 1% hydrocortisone) and an oral antibiotic (e.g., doxycycline), as prescribed by the physician, may be useful in the management of skin toxicities. Patients may be advised to apply moisturizer and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night. Treatment of skin reactions should be based on severity and may include a moisturizer, sunscreen (SPF > 15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics, as prescribed by the physician.

Pulmonary Toxicity

In the event of acute onset or worsening of pulmonary symptoms, consider withholding panitumumab. If Interstitial Lung Disease is confirmed, discontinue panitumumab.

For Toxicities other than Dermatologic or Pulmonary

Withhold panitumumab for any grade 3 or 4 panitumumab-related toxicity with the following exceptions:

• Panitumumab will only be withheld for symptomatic grade 3 or 4 hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement

• Panitumumab will only be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care.

Diarrhea management (refer to the 9.4 for management)

Electrolytes

Subjects should be evaluated and managed as per local medical practice. If hypomagnesemia is present, replacement should be managed with either oral and/or parental replacement, according to

institutional practice and to the degree of hypomagnesemia present. It is recommended that the subject's serum magnesium level should be maintained within the normal range, as much as possible, during study treatment. It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesemia. Subject's serum potassium and calcium parameters are recommended to be managed, as per local medical practice, and kept within the normal ranges, as much as possible, during study treatment.

Criteria for Re-treatment with Panitumumab

• For dermatologic toxicities (see Table 8.11)

• For toxicities other than dermatologic: If panitumumab was withheld, administration may recommence once the adverse event has improved to ≤ grade 1 or returned to baseline. The reason for dose change of panitumumab is to be recorded on each subject's CRF(s).

8.2 Regorafenib: This section applies to adverse events associated with regorafenib. For adverse events assorted with panitumumab, please refer to Section 8.1 and for TAS-102, please refer to Section 8.3.

NOTE: This drug is standard of care and FDA approved and, therefore, these are suggested but not mandated.

Discontinue regorafenib for the following conditions:

- Any grade arterial thromboembolic event,
- GI or other perforation or fistula formation,
- Intra-abdominal abscess,
- Wound dehiscence requiring medical or surgical therapy,
- Severe or life-threatening hemorrhage.

Regorafenib Dose Modifications

Dose Modification Level	Regorafenib (Orally, daily, mg, days 1-21 of each 28 day cycle)		
Initial dose	***160***	***120***	***80***
-1	120	80	40
-2	80	40	discontinue
-3	40	discontinue	
-4	Discontinue		

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT		
Skin and subcutaneous tissue disorder	Palmar-plantar erythrodysesthesia syndrome	
	Grade 1	Maintain current dose
	Grade 2	1st occurrence: Hold until grade ≤ 1, then resume at current dose. If there is no recovery after a 4-week delay, treatment with regorafenib will be permanently discontinued. 2nd or 3rd occurrence: Hold until grade ≤ 1, then resume at one dose level lower. Dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event. If there is no recovery after a 4-week delay, treatment with regorafenib will be permanently discontinued. 4th occurrence: Discontinue
	Grade 3	1st occurrence: Hold until grade ≤1 for a minimum of 7 days then resume at two dose levels lower. Dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event. If there is no recovery after a 4-week delay, treatment with regorafenib will be permanently discontinued. 2nd occurrence: Discontinue
	Grade 4	Discontinue
Vascular disorder	Hypertension	
	Grade ≤ 2 asymptomatic	Maintain current dose
	Grade 3 asymptomatic	Maintain current dose
	Grade 2 or 3 symptomatic	1st occurrence: Hold until symptoms have resolve, then resume at one dose level lower. 2nd occurrence: Discontinue
	Grade 4	Discontinue
Investigations	Alanine aminotransferase (ALT), and/or Aspartate aminotransferase (AST), and/or Blood bilirubin increased[a]	
	Grade ≤ 2	Maintain current dose
	Grade 3	1st or 2nd occurrence: Hold until recovery to grade ≤ 2, then resume at one dose level lower if potential benefit outweighs the risk of hepatotoxicity. 3rd occurrence: Discontinue
	Grade 4	Discontinue
	Platelet count decreased	
	Grade 2	Maintain current dose.
	Grade 3	Hold until recovery to grade ≤ 1, then resume at one dose level lower.
	Grade 4	Hold until recovery to grade ≤ 1, then resume at two dose levels lower.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Neutrophil count decreased	
	Grade 2	Maintain current dose.
	Grade 3	Hold until recovery to grade ≤ 1, then resume at one dose level lower.
	Grade 4	Hold until recovery to grade ≤ 1, then resume at two dose levels lower. Discontinue after second occurrence.
	Febrile neutropenia	
	Grade 3	Hold until resolution of fever and neutropenia to grade ≤ 1, then resume at two dose levels lower. Discontinue after second occurrence.
	Grade 4	Hold until resolution of fever and neutropenia to grade ≤ 1, then resume at two dose levels lower. Discontinue after second occurrence.
Gastrointestinal disorders	Diarrhea	
	Grade 1	Maintain current dose
	Grade 2	Hold until recovery to grade ≤ 1, then resume at one dose level lower.
	Grade 3	1st or 2nd occurrence: Hold until recovery to grade ≤ 1, then resume at one dose level lower. 3rd occurrence: Discontinue
	Grade 4	1st occurrence: Discontinue or hold until recovery to grade ≤ 1, then resume at two dose levels lower. 2nd occurrence: Discontinue
	Mucositis oral	
	Grade 1	Maintain current dose
	Grade 2	Hold until recovery to grade ≤ 1, then resume at one dose level lower.
	Grade 3	1st or 2nd occurrence: Hold until recovery to grade ≤ 1, then resume at one dose level lower. 3rd occurrence: Discontinue
	Grade 4	1st occurrence: Discontinue or hold until recovery to grade ≤ 1, then resume at two dose levels lower. 2nd occurrence: Discontinue
	Small intestinal or colonic obstruction	
	Grade 2	Hold regorafenib for partial obstruction requiring medical intervention. Resume all study drugs at current dose when obstruction is resolved to grade ≤ 1.
	Grade 3 or 4	Hold for all study drugs for complete obstruction. If surgery is necessary, subject may resume all study drugs at current doses after full recovery from surgery with permission of Principal Investigator.
General disorders and administration site conditions	Fatigue	
	Grade 1	Maintain current dose
	Grade 2	Hold until recovery to grade ≤ 1, then resume at one dose level lower.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Grade 3	1st or 2nd occurrence: Hold until recovery to grade ≤ 1, then resume at one dose level lower. 3rd occurrence: Discontinue
	Grade 4	1st occurrence: Discontinue or hold until recovery to grade ≤ 1, then resume at two dose levels lower. 2nd occurrence: Discontinue

[a] Discontinue regorafenib for the following:

- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN).
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN.
- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction.

* Located at [redacted]

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

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

8.3 TAS-102: This section applies to adverse events associated with TAS-102. For adverse events associated with panitumumab, please refer to Section 8.1 and for regorafenib, please refer to Section 8.2.

NOTE: This drug is standard of care and FDA approved and, therefore, these are suggested but not mandated.

Complete blood cell counts prior to day 1 and on day 15 of each cycle are recommended. A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m2 twice daily. Do not escalate TAS-102 dose after it has been reduced.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT		
Hematologic	Neutrophil count decreased at cycle start	
	Grade 2-3	Delay treatment until ANC is ≥ 1500/mm^3, then resume at same dose.
	Grade 4	Delay treatment until ANC is ≥ 1500/mm^3. If recovery ≤ 1 week, resume at same dose. If recovery > 1 week, resume at 5mg/m^2/dose lower than previous dose.
	Neutrophil count decreased during cycle	
	Grade 4	Withhold treatment until ANC is ≥ 1500/mm^3. If recovery ≤ 1 week, resume at same dose. If recovery > 1 week, resume at 5mg/m^2/dose lower than previous dose.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Febrile neutropenia at cycle start	
	Grade 3	Delay treatment until ANC is ≥ 1500/mm^3 and fever is resolved. After recovery, resume at 5mg/m^2/dose lower than previous dose.
	Febrile neutropenia during cycle	
	Grade 3	Withhold treatment until ANC is ≥ 1500/mm^3 and fever is resolved. After recovery, resume at 5mg/m^2/dose lower than previous dose.
	Platelet count decreased at cycle start	
	Grade 2-3	Delay treatment until platelet count is ≥ 75,000/mm^3. After recovery, resume at same dose.
	Grade 4	Delay treatment until platelet count is ≥ 75,000/mm^3. If recovery ≤ 1 week, resume at same dose. If recovery > 1 week resume at 5mg/m^2/dose lower than previous dose.
	Platelet count decreased during cycle	
	Grade 2-3	Withhold treatment until platelet count is ≥ 75,000/mm^3. After recovery, resume at same dose.
	Grade 4	Withhold treatment until platelet count is ≥ 75,000/mm^3. If recovery ≤ 1 week, resume at same dose. If recovery > 1 week resume at 5mg/m^2/dose lower than previous dose.
General Disorders and administration site conditions	Fatigue	
	Grade 3	Delay until resolved to grade ≤ 1. Resume at 5mg/m^2/dose lower than previous dose.
	Grade 4	Discontinue[a]
Gastrointestinal disorders	Mucositis oral	
	Grade 3	Delay until resolved to grade ≤ 1. Resume at 5mg/m^2/dose lower than previous dose.
	Grade 4	Discontinue[a]

[a] For all Grade 3 or 4 AEs except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication.

* Located at [redacted]

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

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

9.0 Ancillary Treatment/Supportive Care

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

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology

(ASCO) 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 Management of regorafenib-related Adverse Events

At first occurrence of palmar-planter erythrodysesthesia syndrome (PPES), independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing creams should be administered.

9.51 Recommended prevention/management strategies for skin toxicities consistent with PPES are summarized below:

Control of calluses

Before initiating treatment with regorafenib:

- Check condition of hands and feet.
- Suggest a manicure/pedicure, when indicated.
- Recommend pumice stone use for callus or ‘rough spot’ removal.

During regorafenib treatment:

- Avoid pressure points.
- Avoid items that rub, pinch or create friction.

Use of creams

- Over the counter moisturizing creams or ointments are allowed

- For grades 2 or 3, topical analgesics (e.g. lidocaine 5% patches, lidocaine/prilocaine cream TID, lidocaine 2-5% creams) are to be considered for pain control.
- Topical corticosteroids like clobetasol 0.05% should be instituted for subjects with Grade 2 or 3 PPES.
- For grade 2/3 Oral NSAIDs (celecoxib, ibuprofen) may be used for pain control

Tender areas should be protected as follows:

- Use of thick socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g. silicon, gel)
- Foot soaks with tepid or cool water
- Use soft shoes or slippers (Crocs, TempurPedic slippers), avoid high heels and wood soles/heels

Suggested PPES Reaction Treatment

- CTCAE v5 Grade 1 ((Minimal skin changes or dermatitis (e.g., erythema, edema or hyperkeratosis) without pain)) - Continue regorafenib at current dose.
- CTCAE v5 Grade 2 ((Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental ADL (or intolerable grade 2, defined as grade 2 AE that does not decrease to grade ≤1 after 2 weeks of therapy OR that is considered intolerable per patient))
  - Oral (NSAIDs or narcotics) OR topical analgesia (lidocaine cream or patches PRN.
- CTCAE v5 Grade ≥3 ((Ulcerative dermatitis or skin changes with pain interfering with function. Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkertosis) with pain; limiting self-care ADL))
  - Topical steroid cream BID AND topical anesthetics
  - Oral (NSAIDs or narcotics) OR topical analgesia (lidocaine cream or patches PRN.

9.6 Hypomagnesemia: Panitumumab should be held for severe and/or life threatening hypomagnesemia. Consider IV replacement and magnesium oxide 400 mg PO BID.

9.7 Panitumumab-related skin rash. The treating physician may elect to preemptively treat subjects receiving panitumumab to mitigate or prevent skin toxicities. Doxycyline 100mg every 12 hours or equivalent, emollient, and hydrocortisone 1% cream is recommended, but not required for skin rash prophylaxis (Refer to Section 8.1)

9.8 Hypertension: Early and aggressive medical management of hypertension is strongly recommended to minimize the need for dose holding and/or dose reductions. Addition or adjustment of blood pressure medications should be considered for blood pressure values persistently > 140/90. Symptomatic or asymptomatic patients with poorly controlled blood pressure (>150/100 on 3 measurements over 2 weeks) for over one month (despite the addition and

adjustment of anti-hypertensive therapy) should have regorafenib held until their blood pressure is ≤140/90.

9.9 Prohibited Concomitant Therapy

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices
- Anti-cancer therapy, including but not limited to chemotherapy and hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal non-CNS sites which are not considered target lesions per RECIST 1.1, which may be given after consultation with the medical monitor, provided that there remain other sites of assessable disease accessible by RECIST 1.1
- Strong inhibitors or inducers of CYP3A4. Known strong inhibitors of CYP3A4 include, but are not limited to, ketoconazole, itraconazole, clarithromycin, erythromycin, atazanivir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole. Known inducers of CYP3A4 include, but are not limited to phenytoin, carbamazepine, barbiturates, and St. John's Wort. Partial and more complete lists of strong inhibitors and inducers may be found in other reference material.
- Caution is required when using drugs that are human thymidine kinase substrates, e.g., zidovudine.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

NOTE: Please see Appendix V for specific AE reporting regarding the study drug panitumumab for ACCRU personnel only.

ACCRU is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

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

Definitions

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment through the safety follow-up visit are reported using the Event CRF.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Results in death (fatal)

Immediately life-threatening

The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

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. All SAEs that occur after the subject has signed the main informed consent through the safety follow-up visit or 30 days after the last dose of protocol-specified therapy, whichever is later, will be reported to Amgen and recorded in the case report form. SAEs must be reported to Amgen within 24 hours of discovery.

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).

Events NOT Meeting the Adverse Event Definition
Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

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

Assessment of Causality
The investigator is obligated to assess the relationship between investigational product, protocol-required therapies or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
The investigator will use clinical judgment to determine the relationship.
Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
There may be situations in which a serious adverse event has occurred and the

investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be recorded.
If a subject dies during participation in the study or during a recognized follow-up period as defined in Section 13.0, the investigator will provide a copy of any postmortem findings including histopathology.
New or updated information will be recorded in the originally completed Event CRF.
The investigator will submit any updated serious adverse event data within reporting timeline.

10.31 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements:

Note: These exceptions only apply if the adverse event does not result in hospitalization, immediately life-threatening or resulted in persistent/significant disability or death.

If the adverse event results in hospitalization, immediately life-threatening or resulted in persistent/significant disability or death, 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 expeditiously reported.
Gastrointestinal Disorders	Diarrhea	Any Grade
	Dyspepsia	
	Nausea	
	Vomiting	
	Colitis	Grades 1-3
	Pancreatitis	
General disorders and administrations site conditions	Anorexia	Any Grade
	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	

10.311 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 that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 " Disease progression"** under the system organ class (SOC) of 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.

10.312 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.

10.313 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.

10.314 Pregnancy

The investigator should report all pregnancies, including those of partners of male patients, within 24 hours to ACCRU by submitting the Pregnancy Notification Worksheet located on the ACCRU website under Manuals and Forms. The funding sponsor will be notified by ACCRU within 10 calendar days. The sponsor may ask for follow up evaluation of the pregnancy, fetus, and child.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.
In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

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

10.4 Expedited 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 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

Follow site-specific reporting guidelines.
Commercial agent expedited reports must be submitted to the FDA via MedWatch.3500A

[redacted]

Instructions for completing the MedWatch 3500A:
[redacted]

Submit copies along with the ACCRU MedWatch Cover Sheet found on the ACCRU Website to the ACCRU SAE Coordinator via fax [redacted] The ACCRU SAE Coordinator will forward to the funding sponsor via fax [redacted]

The ACCRU SAE Coordinator will forward to [redacted] as appropriate. 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 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each Evaluation
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal disorders	Diarrhea	X	X
Skin and subcutaneous tissue disorders	Rash acneiform	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs 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.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Late occurring adverse events are any adverse events that occur during Survival Follow-Up reporting periods. These are reported in compliance with Section 4.0 and Section 18.

11.0 Treatment Evaluation Using RECIST Guideline

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) [38]. 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 ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

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

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

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to

less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

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

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

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</u>

can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

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

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

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

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI 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.

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

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

- Complete Response (CR): All of the following must be true:

  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.)

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

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

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
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.

12.0 Descriptive Factors

12.1 ECOG PS: 0 vs. 1 vs. 2.

12.2 Disease characteristics: Unresectable vs. Metastatic.

12.3 Prior treatment: TAS-102 vs. regorafenib vs. neither.

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

12.5 Microsatellite instability or mismatch repair deficiency tested: Yes vs. no.

12.51 If yes, MSI-High (MSI-H) vs. microsatellite stable/MSI-Low (MSS/MSI-L); loss of mismatch repair protein (MMR deficient, dMMR) vs. mismatch repair proteins intact (MMR proficient, pMMR).

12.6 *ERBB2* (HER2) amplification tested: Yes vs. no.

12.61 If yes, *ERBB2* amplified vs. *ERBB2* equivocal vs. *ERBB2* not amplified.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who have CR, PR, or SD will continue treatment per protocol for a maximum of 24 cycles. Subsequent treatment is at the discretion of their attending physician.

13.2 Patients who develop PD while receiving therapy or choose an alternative therapy will go to the event-monitoring phase and be followed for survival (i.e. event-monitoring phase) every 3 months (±7 days) for 3 years after randomization (per Section 18.0). Subsequent treatment is at the discretion of their attending physician.

13.3 Patients who go off protocol treatment for any reason will go to the event-monitoring phase and be followed for survival (i.e. event monitoring phase) every 3 months (±7 days) for 3 years after randomization (per Section 18.0). Subsequent treatment is at the discretion of their attending physician.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the

physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (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.

- If the patient never received treatment, on-study material must be submitted. The patient will not be followed for survival.

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

13.6 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 Off Treatment Form must be submitted. The patient will not be followed for survival.

13.7 Patients have the option to complete cfDNA testing at study completion and are encouraged to re-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 1 of Cycle 2	Restaging[2]	End of Treatment[3]	Additional processing required at site after blood draw?	Storage /shipping conditions[4]
Mandatory	EDTA K2 (Purple)	10 mL (1)	Whole Blood	X				No	Freeze /dry ice
Mandatory	EDTA K2 (Purple)	10 mL (4)	Platelet Poor Plasma and	X	X	X	X	Yes	Freeze /dry ice

			White blood cells						
Optional	Streck tube[5]	10 mL (2)	Whole blood				X	No	Room temperature

1. May occur prior to treatment on Cycle 1 Day 1.
2. At time of radiographic assessments (i.e., every other cycle beginning on cycle 3) which may occur ≤14 days prior to day 1 of new cycle (estimated 4 restagings per patient).
3. Discontinuation of study treatment.
4. 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.) 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 completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. A small but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed of per institution policy. Do not send unused kits back to BAP. **Supply Order Forms must be filled in completely and legibly for quick processing.**

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.**

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx account number or 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 kits and access to the Guardant portal, fill out the Guardant Site Setup form for each treating location and email to [redacted]

14.222 Sites will create an account at [redacted] Once account is created, Guardant Health will ship the sites their kits and their own pre-printed Test Requisition Form(TRFs). Once that happens, kits and TRFs can be refreshed/replaced by contacting Guardant Health Client Services Team at [redacted] or [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. Tube labels MUST match requisition form.

14.312 Specimens must be shipped the same day they are drawn.

14.313 Ship the EDTA tube in a combo shipper with the EDTA going into the side with a properly prepared cold pack. Place the frozen aliquots in the side for dry ice. 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 – Friday, to BAP Freezer according to kit instructions. Do not send samples on weekends or just prior to federal holidays.

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 (provided in kit).

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 Whole blood for pharmacogenomics

Whole blood will be stored for future pharmacogenetic assays (e.g., genetic polymorphisms such as those known to regulate angiogenesis, inflammation, immunity, auto-immunity, and antibody or drug action of clearance) that may correlate with efficacy and tolerability. The Duke Phase I Biomarker Laboratory located at Duke University may analyze the DNA for the presence of markers of interest using standard laboratory protocols.

14.412 Soluble protein (blood-based) biomarkers

Blood (platelet poor plasma, and white blood cells (buffy coat)) will be collected at baseline, every restaging, and progression 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.

14.413 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, every restaging, and at the 30-day post-treatment visit. 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.

14.414 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

IND exempt

- Investigator brochure
  Will be sent hard copy to sites by ACCRU. Sites will email Research Protocol Specialist with shipping address.

15.1 Panitumumab (Vectibix®)

15.11 **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.

15.12 **Formulation**: Panitumumab is supplied as a sterile, colorless, preservative-free solution in a single-dose vial. The vial is designed to deliver 20 mg/mL (5 mL, 20 mL).

15.13 **Preparation, storage, and stability**: Store unopened vials at refrigerated temperature 2 to 8ºC (36º to 46ºF), do not freeze or shake, protect from light. Dilute in 100-150 mL of 0.9% sodium chloride injection, USP to a final concentration of less than or equal to 10 mg/mL. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not shake, invert gently to mix. Preparations in infusion containers are stable for 24 hours under refrigeration (2º to 8ºC or 36º to 46ºF) or for 6 hours at room temperature. Do not freeze the diluted solution.

15.14 **Administration:** Doses less than or equal to 1000 mg, infuse over 1 hour: doses > 1000 mg, infuse over 90 minutes. For doses that are less than or equal to 1000 mg, if the first infusion is well tolerated, subsequent infusions may be administered over 30 to 60 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 0.9% sodium chloride injection, USP before and after infusion.

15.15 **Pharmacokinetic information**:
Half-life elimination: ~7.5 days (range: 3.6 to 10.9 days)

15.16 **Potential Drug Interactions**:
Increased Effect/Toxicity: There are no known interactions where it is recommended to avoid concomitant use.

15.17 **Known potential adverse events:**

Most common known potential toxicities, > 10%:
General disorders: Fatigue/asthenia, pyrexia, mucosal inflammation, peripheral edema, weight loss, decreased appetite
Dermatologic: Skin toxicity, erythema, pruritus, dry skin, dermatitis acneiform, paronychia, rash, skin fissure, acne, conjunctivitis, alopecia
Endocrine & metabolic: Hypomagnesemia, hypokalemia
Gastrointestinal: Nausea, diarrhea, constipation, vomiting, abdominal pain, stomatitis
Respiratory: Dyspnea, cough
Musculoskeletal: Back pain
Nervous system disorder: Paresthesia
Psychiatric: Insomnia

Common known potential toxicities, 1% - 10%:
Cardiovascular: Pulmonary embolism, epistaxis, deep vein thrombosis, flushing
Central nervous system: Chills, headache, dizziness
Dermatologic: Exfoliative rash, nail disorder, skin exfoliation, palmar-plantar erythrodysesthesia syndrome, hyperhidrosis, macular rash, hypertrichosis, maculopapular rash, skin toxicity, onychoclasis pruritic rash, abnormal hair growth, pain of the skin, skin lesion, dermatitis, generalized rash
Endocrine & metabolic: Dehydration, decreased blood magnesium, hypocalcemia, hyperglycemia, hyperphosphatemia
Gastrointestinal: Dyspepsia, dry mouth, rectal hemorrhage, gastroesophageal reflux disease, lower abdominal pain, apthous ulcer, oral pain, cheilitis
Immunologic: Hypersensitivity
Ocular: Increased lacrimation, dry eye, abnormal eyelash growth, blepharitis, ocular hyperemia, eye irritation, eye pruritus
Hematologic: Leukopenia
Infections and infestations: Urinary tract infection, pustular rash, folliculitis, cellulitis, localized infection
Musculoskeletal: Pain in extremity
Psychiatric: Anxiety

Uncommon known potential toxicities, <1%
Eye disorders: Eyelid irritation, keratitis, ulcerative colitis
Gastrointestinal: Chapped lips, dry lip
Infections and infestations: Eye infection, nail infection, eyelid infection
Procedural complication: Infusion related reaction
Nervous system disorder: Cholinergic syndrome
Respiratory, thoracic and mediastinal disorders: Nasal dryness
Skin and subcutaneous tissue: Ingrowing nail, onycholysis, hirsutism, angioedema, skin necrosis, Stevens-Johnson syndrome/ toxic epidermal necrolysis,
Immunologic: Hypersensitivity reaction

Respiratory: Interstitial lung disease

15.18 **Drug procurement:** Each participating ACCRU treating location will fill out the pharmacy contact sheet posted in ARMS. ACCRU will send sites a site specific Drug Order Form. Sites will then send completed Drug Order Form to email address listed on the form.

Each participating ACCRU treating location with be responsible for monitoring the supply of panitumumab 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.

15.19a Temperature excursions that occur at the site should be reported by the site using the Temperature Excursion Form found on the ACCRU web site for this study and emailed to 'send to' address on the form.

15.19b **Nursing Guidelines:**

15.19b1 Patient may experience typical EGFR inhibitor related rash, which is generally acneiform in nature and may be associated with pruitis and erythema. Treat symptomatically and monitor for effectiveness.

15.19b2 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.

15.19b3 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.

15.19b4 Hypomagnesmia is seen with this agent. Monitor magnesium level prior to each infusion. If level is below normal, inform the MD.

15.19b5 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.

15.19b6 Gastrointestinal side effects including nausea, diarrhea, constipation and vomiting have been seen. Treat symptomatically and monitor for effectiveness.

15.19b7 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.

15.19b8 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.

15.2 Regorafenib (BAY 73-4506, Stivarga®)

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

15.21 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.

15.22 Formulation

Commercially available as light pink, oval-shaped 40 mg tablets. Tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets.

15.23 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).

15.24 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.

15.25 Pharmacokinetic information

a) Absorption – Following a single 160 mg dose of Regorafenib in patients with advanced solid tumors, regorafenib reaches a geometric mean peak plasma level (C_{max}) of 2.5µg/mL at a median time of 4 hours and a geometric mean area under the plasma concentration vs time curve (AUC) of 70.4µg*h/mL. 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) Elimination – 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) Excretion – Approximately 71% of radiolabeled dose was excreted in feces (47% as parent compound; 24% as metabolites); and 19% of the dose was excreted in urine (17% as glucuronides).

15.26 **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, nefazodone, posaconazole, telithromycin and voriconazole).

Co-administration of Regorafenib with a Breast Cancer Resistance Protein (BCRP) substrate increased the plasma concentrations of the BCRP substrate. Monitor patients closely for signs and symptoms of exposure related toxicity to the BCRP substrate (e.g. methotrexate, fluvastatin, atorvastatin).

15.27 **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, hemorrhage
Central nervous system: Fatigue, dysphonia, pain, fever, headache.
Dermatologic: Skin toxicity, Palmar-plantar erythrodysesthesia, rash
Endocrine & metabolic: Hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia

Gastrointestinal: Appetite decreased, lipase increased, diarrhea, mucositis, weight loss, amylase increased
Hematologic: Anemia, lymphopenia, thrombocytopenia, INR increased, neutropenia
Hepatic: AST increased, ALT increased, hyperbilirubinemia
Renal: Proteinuria
Miscellaneous: Infection, pain (including gastrointestinal and abdominal pain)

Less Common Adverse Events, 1% - 10%:
Hepatic: Hepatic failure

Rare Adverse Events (Important or life-threatening), <1%:
Gastrointestinal: Gastrointestinal perforation, gastrointestinal fistula,
Cardiovascular: Cardiac ischemia or infarction
Neurologic: Reversible posterior leukoencephalopathy syndrome (RPLS)
Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis

Additional risks:
Hypersensitivity reactions: Hypersensitivity reactions have been reported during post-approval use of regorafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Wound Healing Complications: No formal studies of the effect of regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as regorafenib can impair wound healing, discontinue treatment with regorafenib at least 2 weeks prior to scheduled surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Discontinue regorafenib in patients with wound dehiscence.

Embryo-Fetal Toxicity: Based on animal studies and its mechanism of action, regorafenib can cause fetal harm when administered to a pregnant woman. There are no available data on regorafenib use in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with regorafenib and for 2 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with regorafenib and for 2 months after the final dose.

15.28 **Drug procurement:** Commercial supplies. Each participating ACCRU treating location shall obtain supplies from normal commercial supply chain or wholesaler.

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

15.29 **Nursing Guidelines**

15.291 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.

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

15.293 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.

15.294 Inform patients of possibility of alopecia.

15.295 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.

15.296 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.

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

15.298 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.

15.3 **TAS-102 Trifluridine (FTD)/Tipiracil (TPI) (TAS-102, Lonsurf®)**

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

15.31 Background

TAS-102 is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy

15.32 Formulation

- FTD/TPI (TAS-102) tablet (15 mg) contains 15 mg trifluridine and 6.14 mg tipiracil as active ingredients. The appearance is white round tablet.
- FTD/TPI (TAS-102) tablet (20 mg) contains 20 mg trifluridine and 8.19 mg tipiracil as active ingredients. The appearance is pale red round tablet.

15.33 Preparation and storage

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). If stored outside of original bottle, discard after 30 days. TAS-102 is a cytotoxic drug. Follow applicable special handling and disposal procedures.

15.34 Administration

Recommended to take within 1 hour after completion of the morning and evening meals. Anyone other than the patient who handles their medication should wear gloves.

15.35 Pharmacokinetic information

After twice daily dosing of TAS-102, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 to 35 mg/m^2. After administration of TAS-102 35 mg/m^2 twice daily, the mean elimination of half-life ($t_{1/2}$) of trifluirdine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

Protein Binding
Trifluridine: >96% (primarily to albumin); Tipiracil: <8%

Metabolism
Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY)

Excretion
Following a single dose of TAS-102, the mean 48-hour cumulative urinary

excretion was 1/5% for unchanged trifluridine, 19.2% for FTY, and 29.3% for unchanged tipiracil.

15.36 **Potential Drug Interactions**

Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme. Tipiracil is not metabolized in either human liver or hepatocytes.

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

15.37 **Known potential toxicities**
Consult the package insert for the most current and complete information.

Most common known potential toxicities, >/= 10%:
Blood and lymphatic: Anemia, neutropenia, thrombocytopenia
Gastrointestinal: Diarrhea, nausea, vomiting, abdominal pain
General: Fatigue, pyrexia, infection
Metabolism and nutrition: Decreased appetite

Common known potential toxicities, >/=1% - <10%:
Cardiovascular: Pulmonary emboli
Gastrointestinal: Stomatitis
Nervous System: Dysgeusia

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

Blood and lymphatic: Severe myelosuppression
Respiratory: Interstitial lung disease

15.38 **Drug procurement:** Commercial supplies. Each participating ACCRU treating location shall obtain supplies from normal commercial supply chain or wholesaler.

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

15.39 **Nursing Guidelines**

15.391 Instruct patients that agent should be taken within 1 hour after completion of morning and evening meal.

15.392 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.393 GI side effects are common, including nausea, decreased appetite,

diarrhea, vomiting, and abdominal pain.

15.394 Cytopenias are common. Monitor CBC w/diff and instruct patients to report any signs or symptoms of infection and/or unusual bruising or bleeding to the study team.

15.395 Rarely Pulmonary embolism has been reported with this agent. Instruct patient to report any shortness of breath or chest pain to study team and/or seek out emergency medical attention.

15.396 Although uncommon, inform patients of the possibility of alopecia.

16.0 Statistical Considerations and Methodology

16.1 Overview and Study Design

This is a randomized Phase II study which is designed to compare the overall survival (OS) in patients with EGFR refractory *RAS* wild-type metastatic CRC, who are randomized to panitumumab or standard therapy (TAS-102 or regorafenib). Prior studies have shown that the median OS is around 6.5 months for patients in this disease population receiving TAS-102 or regorafenib and PFS is around 1.9 months for patients receiving TAS-102 or regorafenib in this disease population [40, 41]. It is hypothesized that panitumumab can increase the median OS to at least 10 months. In addition to OS, this trial will also compare the overall response rate, PFS, adverse event rates, and self-reported quality of life outcomes (measured by LASA) between the panitumumab arm and standard therapy (TAS-102 or regorafenib).

16.11 Primary Endpoint

The primary endpoint for this study is overall survival (OS) which is defined as the time from randomization to death from any cause. Patients who are alive will be censored at the last known alive date.

16.12 Interim Analysis

One interim analysis for futility will be conducted when at least 42 patients across both arms combined have provided documentation of death. Overall survival will be used as the endpoint for the interim analysis. The interim futility boundary was selected using EAST software. Un-stratified log-rank p-value will be used for decision making . The trial will continue accrual while the interim analysis is being conducted. If the 1-sided p-value > 0.529 for panitumumab compared to standard therapy (TAS-102 or regorafenib), which corresponds to a hazard ratio (HR) > 1.022, the panitumumab will be considered as futile and the accrual will be suspended. Otherwise, if the 1-sided p-value $\leq$ 0.529 (HR $\leq$ 1.022), the study will continue to full accrual and the final analysis will be conducted as described below.

16.13 Final Analysis

Efficacy analysis will be conducted when at least 83 death events, across

both arms combined, have been observed. 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. If the 1-sided p-value is > 0.15 for panitumumab compared to standard therapy (TAS-102 or regorafenib), which corresponds to a hazard ratio (HR) > 0.797, panitumumab will be considered as inefficacious; if the 1-sided p-value ≤0.15 (equivalently, HR ≤0.797), panitumumab will be considered as promising for future study. All eligible patients who sign the consent form, are randomized, and received any protocol treatment are considered evaluable for this endpoint.

16.14 Decision Rules

Analysis time point	Number of events[1]	Critical p-value		Hazard Ratio	
		Futility	Efficacy	Futility	Efficacy
50%	42	> 0.529	N/A	> 1.022	N/A
100%	83	> 0.15	≤0.15	> 0.797	≤ 0.797

[1] Documentation of death

16.15 Power and Sample Size

The primary goal is to compare the OS between patients who are randomized to panitumumab and those randomized to standard therapy (TAS-102 or regorafenib). The null hypothesis is that the panitumumab arm does not show a superior OS outcome compared to standard therapy (TAS-102 or regorafenib). The alternative hypothesis is that the panitumumab arm has improvement in OS compared to standard therapy (TAS-102 or regorafenib).

We will enter 53 evaluable patients to each arm of the study using a 1:1 randomization scheme (106 evaluable patients in total); unless the study is stopped early. Stratification factors are defined in section 5.0. With 53 evaluable patients per arm, we have 80% power to detect an improvement in the median OS from 6.5 to 10 months (HR=0.65), assuming a 1-sided significance level of 0.15 and an accrual rate of 8 patients per month. The trial has a single interim analysis for futility, adopting the Rho family (Rho=1.5) beta spending function for controlling the overall type II error rate and will be considered non-binding.

16.151 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 0.15.

The table below includes the operating characteristics according to the monitoring plan outlined above. The proportion of times that 1) the study would stop early at the interim analysis due to futility of panitumumab, and 2) the study would conclude panitumumab is superior to TAS-102 or regorafenib at the final analysis, are tabulated by true OS median survival times and equivalent true

hazard ratios for OS by treatment groups.

True median overall survival (months)[1]		True Hazard Ratio	% of times the study will be stopped for futility at the interim analysis [2]	% of times that panitumumab is deemed superior at the final analysis [2]
TAS-102 or regorafenib	panitumumab			
6.5	6.5	1	47.7	14.1
6.5	7.2	0.90	34.3	26.8
6.5	7.9	0.82	24.3	41.9
6.5	8.6	0.76	16.5	56.7
6.5	9.3	0.70	11.2	69.9
6.5	10	0.65	7.5	79.4

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

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

16.2 Sample Size

We plan to randomize at least 106 eligible patients (53 to panitumumab; 53 to standard therapy (TAS-102 or regorafenib). We anticipate randomizing an additional 14 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is projected to be 120 patients.

16.3 Accrual Time and Study Duration

The anticipated accrual rate is approximately 8 patients per month. Therefore, the accrual period for this randomized Phase II study is expected to be around 15 months. The final analysis can begin as soon as the 83rd OS event has occurred; approximately 25 months after the study begins under the alternative hypothesis.

16.4 Data & Safety Monitoring

16.41 The principal investigator(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 trial is monitored continually by the study team. 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 study statistician. Any safety issues requiring protocol changes are communicated through protocol amendments.

16.42 Adverse Event Monitoring and Stopping Rules

The monitoring rule specified below is based on the knowledge available at study development. We note that the Adverse Event Monitoring Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension 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 also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual may be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria for **each arm separately**:

- If at any time, 4 of the initial 10 treated patients, or 33% or more of all patients (when accrual is greater than 10 patients) have experienced a grade 4+ adverse event at least possibly related to treatment.

16.43 Data Safety Monitoring

This trial will be monitored by the Mayo Clinic Cancer Center Data and Safety Monitoring Board (MCCC DSMB) every 6 months.

16.5 Definitions and Analyses of Secondary Endpoints

All these endpoints will be assessed individually and will also be compared between the 2 arms. Descriptive statistics will be provided. P-values will be reported but will be considered descriptive.

16.51 Progression Free Survival (PFS)

Progression free survival is defined as the time from randomization to documentation of disease progression or death due to any cause, whichever is first. For patients who are progression-free and alive, PFS will be censored at the last disease evaluation. If the patient did not have any disease evaluation post randomization, PFS will be censored at one day after randomization. The distribution of progression free survival will be estimated using the method of Kaplan-Meier (Kaplan 1958). Progression free survival will be compared between the 2 treatment arms using the log-rank test.

16.52 Overall Response Rate (ORR)

Overall response rate is defined as the number of patients with a complete response (CR) or partial response (PR) (as defined by the RECIST 1.1) divided by the number of evaluable patients in each arm at 12 months post registration. ORR will be compared between the 2 treatment arms. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson.

16.53 Clinical Benefit Rate

Clinical benefit rate is defined as the number of patients with a complete response (CR), partial response (PR), or stable disease for ≥ 6 months (as defined by the RECIST 1.1) divided by the number of evaluable patients in each arm. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson.

16.54 Adverse Events

All eligible patients who have initiated treatment will be considered evaluable for adverse event analyses. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine adverse event patterns. The overall adverse event rates for grade 3 or higher adverse events will be compared using Chi-Square or Fisher's Exact tests.

16.55 Patient-reported Outcomes

Patients reported quality of life (QOL) outcomes will be collected using the Linear Analog Self-Assessment (LASA) Questionnaire. Data will be collected each cycle. Mean values of the first question (regarding overall QOL) at each cycle will be plotted, and stratified by arm. Additional analyses using data collected from the LASA questionnaire may be performed.

16.56 Over Accrual:

If more than the target number of patients are accrued, the additional patients will be used to evaluate the stopping rule or used in any decision making processes. They will also be included in final point estimates and confidence intervals.

16.6 Correlative Research

16.61 Blood-based Biomarker Studies

16.611 Cell free tumor DNA (cfDNA)

Cell free DNA will be analyzed at baseline, each restaging and at progression. A report will be generated for each clinical specimen, which may include (but not limited to) the presence or absence of relevant gene mutations or amplifications, along with the allele frequency. Mutations of interest include *KRAS* and *NRAS* exons 2, 3, and 4, *BRAF, PIK3CA, EGFR, AKT, PTEN, MAP2K1,* and *MET*. Amplifications of interest include *MET, EGFR, KRAS,* and *ERBB2*. Genes and alterations analyzed will be based on best available science at the time of analysis. We will also explore the association between genetic alterations and clinical outcomes.

16.612 Circulating protein studies

Plasma samples will be analyzed for multiple soluble protein analytes, which may include (but not limited to) HGF, c-MET, EGF, HBEGF, TGF-α, EGFR, HER2, and CD73. Additional biomarkers may also be explored using multiplex array technology. We will explore the association between soluble protein expression and clinical outcomes.

16.62 Tumor Tissue Studies

Comprehensive mutational analysis will be performed on archived formalin fixed paraffin embedded (FFPE) tumor samples. This analysis may include, but is not limited to Next Generation Sequencing (NGS) and IHC where appropriate. We will explore the association between genetic alterations and gene expression and clinical outcomes.

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:

[redacted]

17.28 When an appropriate request is submitted, the ACCRU Operations Office will forward the block(s) to the [redacted] At study completion specimens will be sent 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 (see Section 6. 5). 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 (see Section 6. 5), 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

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

18.1 Submission Timetable

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Systemic Therapy	
Adverse Events: Baseline	
RECIST Measurements: Baseline	
Laboratory Tests & Results: Baseline	
Supporting Documentation: Baseline[2]	
Specimen Submission: Blood (Baseline) (see	

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Section 14.0)	
Specimen Submission: Tissue (Baseline) (see Section 17.0)	
Patient Status: Baseline	
Notice of New Primary[1]	
OP and Path Reports (see Section 17.0)[2]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet-PRO/QOL: Linear Analogue Self Assessment (LASA)	≤ 2 weeks after registration - Patient questionnaire booklet must be used; copies are not acceptable for this submission.
PRO/QOL : Booklet Compliance[3]	≤ 2 weeks after registration - This form must be completed only if the (name of booklet/s – or whatever verbiage you want to use to describe the booklet/s) contains absolutely NO patient provided assessment information.
ACCRU Deviation Form[1]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Submit only if applicable.
2. Upload via the Supporting Documentation: Baseline form. COLOMATE Companion Trial Recommendation Form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
3. This form must be completed **only** if the Linear Analogue Self Assessment (LASA) contains absolutely **NO** patient provided assessment information.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment (within 30 days after last dose of study drug)
Treatment (Intervention)	X	X
Treatment (Intervention): Dose Modifications, Omissions and Delays[1]	X	
Adverse Events: Solicited	X	X
Adverse Events: Other[1]	X	X
RECIST Measurements[2]	X	X
Supporting Documentation[2]	X	X
Laboratory Tests and Results	X	X
Specimen Submission: Blood (see Section 14.0)	X	
Patient Status: Treatment (Intervention)	X	X
Notice of New Primary[1]	X	X
Consent Withdrawal (choose appropriate form)[1] • Consent Withdrawal: Specimen Only	X	X

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment (within 30 days after last dose of study drug)
Off Treatment		X
ACCRU Deviation[1]	X	X
Patient Questionnaire Booklet[3] – PRO/QOL: Linear Analogue Self Assessment (LASA) (if applicable)	X	X
PRO/QOL : Booklet Compliance[4] (if applicable)	X	X

1. Submit only if applicable.
2. Upload documentation of response or progression on the Supporting Documentation form.
3. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
4. This form must be completed **only** if the Linear Analogue Self Assessment (LASA) contains absolutely **NO** patient provided assessment information.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD or alternative therapy	At PD	After PD or alternative therapy q. 3 mos.	Death	New Primary
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	At each occurrence
Adverse Events: Late[3]					X
Supporting Documentation[2, 3]					
Notice of New Primary[3]					X
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up					X
Lost to Follow-Up[3, 4]					
ACCRU Deviation Form[3]	X[3]	X[3]	X[3]	X[3]	

1. If a patient is still alive 3 years after randomization, no further follow-up is required.
2. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.
4. Patients are eligible to be confirmed lost to follow-up after 2 years of unsuccessful contact with the patient.

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 Panitumumab will be supplied by Amgen. TAS-102 and regorafenib will not be supplied, but is commercially available.

20.0 References

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[38]

Appendix I: ACCRU-GI-1623 PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet
(Baseline and Each Cycle)

You will be given booklets to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed prior to dosing at each cycle and at the end of treatment (within 30 days after your last dose).

2. This booklet contains the following questionnaire:
    a. Linear Analogue Self Assessment (LASA)

3. Directions on how to complete each set of questions are written on the top of the page.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. Please complete the booklet and return it to your study staff. It is very important that you return the booklet to us.

Thank you for taking the time to help us.

Appendix II: ACCRU-GI-1623 LINEAR ANALOGUE SELF ASSESSMENT

Patient Name: _____ Date: _____
Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

7. the frequency of your pain?

0	1	2	3	4	5	6	7	8	9	10
No pain										Constant pain

8. the severity of your pain, on the average?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

9. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Constant

Tiredness

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10
No support										Highest level of support

11. your financial concerns?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

12. your legal concerns (will, advanced directives, etc.)?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

Appendix III: ACCRU-GI-1623 (PULSE) Examples of CYP3A4 Inducers and Inhibitors

Please see [redacted] for examples of CYP3A4 therapies. This list is not comprehensive. Contact your investigational/central pharmacy for any questions.

(Strong and moderate classifications may be referenced on Lexi-Comp Online, drug information reference [redacted]

CYP3A4 INHIBITORS	
GENERIC NAME	TRADE NAME
Indinavir	Crixivan
Nelfinavir	Viracept
Ritonavir	Norvir
clarithromycin	Biaxin
itraconazole	Sporanox
ketoconazole	Nizoral
Nefazodone	Serzone
Saquinavir	Invirase
telithromycin	Ketek
Aprepitant	Emend
erythromycin	Ery-Tab
Fluconazole	Diflucan
grapefruit juice	
Verapamil	Calan
Diltiazem	Cardizem
Cimetidine	Tagamet
Amiodarone	Cordarone
chloramphenicol	Chloroptic
Delavirdine	Rescriptor
diethyldithiocarbamate	Imuthiol
fluvoxamine	Luvox
gestodene	Minesse
mibefradil*	Posicor
mifepristone	Mifeprex
norfloxacin	Noroxin
norfluoxetine	N/A
star fruit	
voriconazole	VFEND
amprenavir[1]	Agenerase
atazanavir[1]	Reyataz
fosamprenavir[1]	Lexiva
seville oranges	

CYP3A4 INDUCERS	
GENERIC NAME	TRADE NAME
efavirenz	Sustiva
nevirapine	Viramune
barbiturates	Luminal
carbamazepine	Tegretol
glucocorticoids	
modafinil	Provigil
nevirapine	Viramune
oxcarbazepine	Trileptal
phenobarbital	Luminal
phenytoin	Dilantin
pioglitazone	Actos
rifabutin	Mycobutin
rifampin	Rifadin
St. John's wort	
troglitazone*	Rezulin

Appendix IV(A): ACCRU-GI-1623 (PULSE) PATIENT MEDICATION DIARY: Regorafenib

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

ORAL MEDICATION DIARY

Patient 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 "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-1623 (PULSE) PATIENT MEDICATION DIARY – **Regorafenib**

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:_____ Participants 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					

Appendix IV(B): ACCRU-GI-1623 (PULSE) PATIENT MEDICATION DIARY:TAS-102

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

ORAL MEDICATION DIARY

Patient 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 time dose taken on the line under the date.
- If you miss a dose, place a "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-1623 (PULSE) PATIENT MEDICATION DIARY – **TAS-102**

Study Drug/Dose	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
TAS-102/___mg **AM**							
TAS-102/___mg **PM**							

Study Drug/Dose	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
TAS-102/___mg **AM**							
TAS-102/___mg **PM**							

Study Drug/Dose	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
TAS-102/___mg							
TAS-102/___mg							

Study Drug/Dose	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
TAS-102/___mg							
TAS-102/___mg							

Date:_____ Participants 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					

Appendix V: Submission of Safety Data Regarding the Study Drug Panitumumab

NOTE: For ACCRU personnel only

For Interventional studies with IMP*:

Safety Data	**Timeframe for Submission to the Funding Sponsor**
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Sent to funding sponsor at time of regulatory submission
Serious Adverse Events (SAEs)	Not required, unless contractually specified per study
Adverse Events not meeting serious criteria	Not required, unless contractually specified per study
Events of Interest	Not required, unless contractually specified per study
Pregnancy/Lactation	Within 10 calendar days of Sponsor awareness
Event listing for reconciliation	As specified per contract

*Specific requirements are to be outlined in the Research Agreement

For all studies – aggregate reports*(as applicable):

Safety Data	**Timeframe for submission to the Funding Sponsor**
Annual Safety Report (eg, EU Clinical Trial Directive [CTD] **DSUR**, and US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc)
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the Research Agreement