Academic and Community Cancer Research United (ACCRU)

Regorafenib Dose Optimization Study (ReDOS): A Phase II Randomized Study of Lower Dose Regorafenib Compared to Standard Dose Regorafenib in Patients with Refractory Metastatic Colorectal Cancer (mCRC)

For any communications regarding this protocol, please contact the protocol resource person on the following page.

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Drug Availability

Commercial Agents: Clobetasol Propionate Cream
Drug Company Supplied: Regorafenib – IND Exempt

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

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Document History	(effective date)
Activation ACCRU	March 27, 2015
Addendum 1	June 2, 2015
Addendum 2	July 3, 2015
Addendum 3	June 24, 2016
Addendum 4	March 17, 2017
Addendum 5	December 1, 2017
Addendum 6	February 16, 2018

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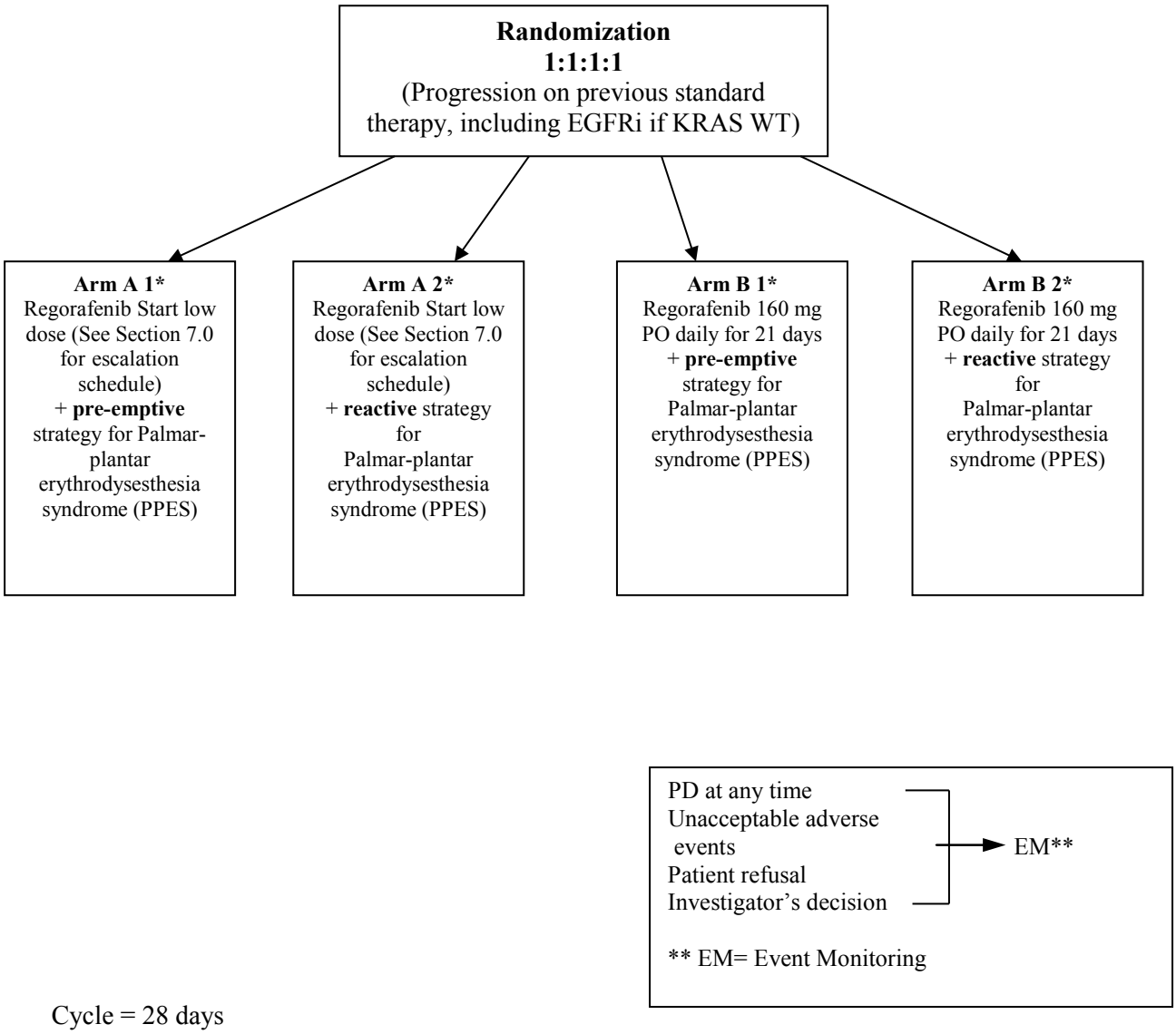
Schema



Cycle = 28 days

* Pre-emptive strategy: Clobetasol 0.05% cream for first 12 wks is prophylactically applied to hands and soles of patients. Reactive strategy: Patients will be treated per investigator discretion when they develop Palmar-plantar erythrodysesthesia syndrome.

Generic name: Regorafenib Brand name(s): Stivarga® Availability: Biologics, Inc.	Generic name: Clobetasol Propionate Cream Brand name(s): Temovate Availability: Commercially available

1.0 Background

1.1 Worldwide, nearly 1.3 million patients are diagnosed with and more than 600 000 patients die from colorectal cancer every year (Ferlay et al, 2013). Regorafenib is a novel oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in angiogenesis, oncogenesis and tumor microenvironment (Kies et al, 2010). Regorafenib was recently shown to provide a survival benefit in metastatic colorectal cancer patients who have progressed after all standard therapies (Grothey, et al). This led to its approval in September 2012 by the FDA for use in the United States. Despite the observed benefits in a patient population with no current standard, toxicities such as Palmar-planter erythrodysesthesia syndrome (PPES) (which occurs early in the first 1-2 weeks) and fatigue have widely limited its use in the US. Multiple practices across the US have adopted, and despite the absence of supportive data, various dosing or interval scheduling including starting at lower doses and escalate as tolerated, every other week dosing intervals and other.

In this study, we propose to design a novel strategy to optimize the dose of regorafenib in patients with refractory mCRC to allow maintenance of the observed benefits while improving the tolerability profile. The proposed strategy, arm A (combining A1 and A2) consists of starting regorafenib at 80 mg/day for 1 week (week1), then if no significant drug-related toxicities escalate to 120 mg/ day for another week (week 2), then again if no significant related toxicities escalate to a total dose of 160 mg/day (week 3) followed by a week break (week 4 of cycle 1). If at the end of week 1, week 2 or week 3 toxicities are unacceptable as defined by the study, the decision will be to deescalate by 40 mg/day and there will be no further dose escalations. A comparative arm, arm B (combining B1 and B2) will include a standard dose/schedule regorafenib of a 160 mg/day starting on day 1 of cycle 1. The primary goal of this study is to compare the proportions of patients on each arm who complete 2 cycles of protocol treatment and initiate cycle 3. We will also assess other outcome and quality of life measures and toxicity profile with a focus on regorafenib related toxicities. We will also assess a potential strategy to reduce the severity of PPES. Additionally, we will perform limited PK analysis in both arms.

To explore a potential strategy to reduce the severity of PPES, Clobetasol 0.05% cream for first 12 weeks will be prophylactically applied to palms and soles of patients in arm A1 and (pre-emptive strategy). Patients in arm A2 and B2 will be treated per investigator discretion when they develop PPES (reactive strategy). All patients will be required to fill HFS14 quality of life questionnaire on C1D14, C2D1, C2D14, and C2D28 intervals.

1.2 QOL Tools

1.21 QOL is an important outcome and covariate in this trial because the treatments are expected to differ in terms of their symptom profiles and impact on patient well-being. Previous data has indicated that the most prevalent QOL issues with these patients are fatigue, pain, weight loss, and other symptoms, as well as more general aspects of QOL such as ability to enjoy life and contentedness in QOL (Odom et. al. 2010). We hypothesize that patients receiving regorafenib will experience greater deficits in QOL as reflected by scores on the HSF14, the BFI and the LASA. These questionnaires have specific application to this population.

The HSF14 has been specifically designed to capture changes in QOL related to PPES. Cronbach's alpha for this questionnaire is 0.93. It involves 14 questions

with three domains: hand, feet, and social. The final score for this questionnaire ranges from 2-100, where a higher score indicates greater QOL impairment (Sibaud et. al., 2011). For comparison to other QOL questionnaires, the HSF14 will be converted to a 0-100 scale, where a higher score indicates better QOL.

The Brief Fatigue Inventory (BFI), a 9-item questionnaire, has been validated as a short and comprehensive instrument to assess severity of fatigue and fatigue-related impairment in cancer patients. The reliability estimated with Cronbach's alpha ranges from 0.82 to 0.97. Recently, both the German version and the Japanese version of the BFI has been validated with test-reliability (mean scores of 0.93) and impairment (mean scores of 0.87) for the German version and reliability with Cronbach's alpha at 0.96 for the Japanese version. Minor differences were seen in the validation of the German version compared to the original version.

Linear Analogue Self Assessment (LASA) items have been validated as general measures of global QOL dimensional constructs in numerous settings (Grunberg et al., 1996; Gudex et al, 1996; Hyland et al., 1996; Srivatanakul, 1983; Wewers, 1990). A series of LASA items have been constructed and validated at Mayo Clinic for use in cancer patients (Bretscher et al, 1999). These items have been seen to be important prognostic factors for cancer patient survival and should be included as covariates in survival analysis (Sloan, JCO, 2012).

1.3 Correlative Research

1.31 Regorafenib clinical pharmacokinetics

Regorafenib and its metabolites M2 and M5 have been assessed pharmacokinetically in several phase I studies, both with regorafenib dosed 21 days on/7 days off (Mross K et al. 2012; Strumberg D et al. 2012; Sunakawa Y et al. 2014), and with continuous dosing (Kies MS et al. 2010; Finn RS et al. 2013). Based on safety, efficacy and PK analysis (higher exposure on dosing days), the final dose taken into phase III studies was 160 mg 21 days on/7 days off.

Regorafenib is moderately fast absorbed after oral administration with median t_{max} of 3 to 4 hours, and mean C_{max} of 2.5 mg/L. Steady-state is expected to occur within 7 days after first administration. The overall mean terminal half-life at steady state is 20-30 hours, with a $t_{max,ss}$ of 5 hrs. Mean $C_{max,ss}$ and $AUC_{(0-24)ss}$ with 160 mg dosing were 3.9 mg/L and 58.3 mg•h/L. In the dose escalation phase I studies, regorafenib PK at doses above 60 mg was less than dose proportional. Accumulation of regorafenib from day 1 to day 21 was consistent with linear pharmacokinetics (Mross K, et al .2012).

Regorafenib has 2 major active metabolites, M2 and M5. While both regorafenib and M2 have elimination half-lifes of 20-30 hrs, the M5 active metabolite has a half-life of 60 hrs (range 40-100 hrs).

Regorafenib and its active metabolites have substantial variability in their plasma exposure – expressed as either the maximum concentration shortly after administration (C_{max}) or the area under the concentration-time curve (AUC) – after oral regorafenib administration. The coefficient in variation (standard

deviation/mean) of C_{max} ranges from 61.9% to 173.5%, showing considerable interpatient variability in the absorption. This is not unexpected since regorafenib's absorption is influenced by the fat content in the diet (Section 15.15). Similarly, the AUC has substantial variability with the CVs ranging from 77.8 to 182.4%. This is also not unexpected since regorafenib undergoes enterohepatic recirculation, and is susceptible to a multitude of drug interactions since it is a CYP3A4 and UGT1A9 substrate (Section 15.15). Furthermore, within-patient variability is present such that an individual patient can have dose-to-dose variability in their pharmacokinetics.

No relationship was suggested between AUC or C_{max} of regorafenib, M2 or M5 and adverse events in phase 1 trials, but it was suggested that an exposure of ≥ 60 mg daily of regorafenib was associated with greater efficacy (regorafenib IB).

1.32 Rationale for regorafenib pharmacokinetic studies

Regorafenib has clinical activity in CRC, but many patients discontinue treatment in the first 2 cycles due to adverse events (Grothey A et al. 2013). In the few phase I studies to date, small patient numbers underwent any PK evaluation at steady state beyond cycle 1, to understand a possible connection between toxicity and PK parameters.

Because this clinical trial seeks to optimize the regorafenib dose and overall exposure in patients with refractory mCRC, it is critical that we evaluate the pharmacokinetic parameters of regorafenib and its metabolites, and assess whether their PK variability is clinically relevant. To our knowledge, no large pharmacokinetic correlative studies – or those studies evaluating if plasma regorafenib concentrations are associated with its efficacy or toxicity –have been conducted to date.

Therefore, as detailed in Section 14.1, we have developed a clinic-friendly sampling schedule to collect the PK trough levels (C_{min}) for the study drug and its metabolites, to maximize patient compliance. In the low dose (dose escalation) cohort, as the regorafenib dose is planned to be escalated weekly in cycle 1 from 80 to 120 to 160mg, trough levels will be collected on days 7, 14 and 21, when each regorafenib dose would be expected to reach steady state. These visits coincide with regular clinic visits for safety/toxicity evaluation. In cycle 2, PK will be collected on days 1 and 21. To be able to compare the low dose, escalating cohort with the standard dose cohort, similar time-points for PK analysis were chosen.

2.0 Goals

2.1 Primary

2.11 Evaluate the proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A (pooled arm A1 and A2) and arm B (pooled arm B1 and B2).

2.2 Secondary

2.21 Evaluate outcome measures for efficacy in each arm including progression-free survival (PFS), time to progression (TTP), and overall survival (OS).

2.22 Compare between arms the cumulative dose and dose intensity received within the first two cycles.

2.23 Evaluate the proportion of patients in each arm that exhibit grade 3 Palmar-plantar erythrodysesthesia syndrome (PPES) and/or fatigue, and make comparisons between regorafenib dosing strategies and pre-emptive vs. reactive strategies to address PPES.

2.24 Compare QOL between treatment arms (regorafenib dosing strategies and pre-emptive vs. reactive PPES strategies) as measured by the HFS14, BFI, and LASA questionnaires.

2.3 Correlative Research

2.31 Evaluate and compare trough (C_{min}) PK during the first 2 treatment cycles for regorafenib and active metabolites M2, M5 between the low dose (dose escalation) and the standard dose cohorts, and correlate with toxicity profile.

2.32 Evaluate the correlation between PK parameters and tumor response/stable disease after the first two cycles.

2.33 Evaluate the correlation between PK parameters and PFS and OS.

2.34 Evaluate if trough (C_{min}) concentrations are associated with patient-specific factors (such as – but not limited to – age and concomitant medications).

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological or cytological documentation of adenocarcinoma of the colon or rectum.

3.13 Advanced or metastatic colorectal cancer with no curative options available and progression on previous standard therapy, including an EGFR inhibitor if KRAS wild-type.

3.14 Measurable or non-measurable disease as defined in Section 11.0.

3.15 ECOG Performance Status (PS) 0 or 1. (Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html).

3.16 Life expectancy of ≥ 3 months.

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

- Absolute neutrophil count (ANC) >1500/mm^3
- Platelet count >100,000/mm^3
- Hemoglobin >9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferease (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine ≤1.5 x ULN
- INR/PTT ≤ 1.5 x ULN
  NOTE: Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
- Alkaline phosphatase limit ≤2.5 x ULN (≤5 x ULN for patients with liver involvement of their cancer)

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

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

3.19b Provide informed written consent.

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

3.19d Willing to provide blood samples for correlative research and banking purposes (see Sections 6.0 and 14.0).

3.2 Exclusion Criteria

3.21 Prior treatment with regorafenib.

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

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

3.24 Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months) or myocardial infarction less than 6 months prior to randomization.

3.25 Cardiac arrhythmias requiring anti-arrhythmic therapy. Note: Pace makers, beta

blockers or digoxin are permitted.

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

3.27 History of or current pheochromocytoma.

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

3.29a Ongoing infection > grade 2 NCI-CTCAE version 4.0.

3.29b Known history of chronic hepatitis B or C.

3.29c Patients with seizure disorder requiring medication.

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

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

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

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

3.29h Renal failure requiring hemo-or peritoneal dialysis.

3.29i Dehydration CTCAE (version 4.0) grade ≥1.

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

3.29k Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.

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

3.29m Persistent proteinuria of CTC Grade 3 or higher (≥ 3.5 g/24 hrs).

3.29n Patients unable to swallow oral medications.

3.29o Any malabsorption condition.

3.29p Unresolved toxicity greater than CTCAE (version 4.0) Grade 1 attributed to any

prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity ≤Grade 2.

3.29q Albumin levels <2.5 g/dl.

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

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

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

3.29s 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.

3.29t Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

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

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

3.29w Pleural effusion or ascites that causes respiratory compromise (≥CTCAE version 4.0 Grade 2 dyspnea).

3.29x Concurrent anti-cancer therapy ≤4 weeks from registration (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization).

3.29y Current use of clobetasol propionate.

3.29z Use of any herbal remedy (e.g. St. John's Wort [Hypericum perforatum]).

3.29aa Patients unable to ambulate or who have amputations or paralysis of any extremity.

3.29bb History of contact dermatitis to clobetasol propionate or similarly fluorinated steroids or other steroids with the propionate ester.

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase										
	≤7 days prior to randomization	Cycle 1[13]				Cycle 2[13]				After week 8: Every 4 weeks until progression (+/- 3 days)	At PD, withdrawal or removal
		Week1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 4 (Day 22)	Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 4 (Day 22)		
History and exam, weight, ECOG PS[12], blood pressure	X	X[12]	X	X	X	X	X	X	X	X	X
Height	X										
Adverse event assessment[8]	X		X	X	X	X	X	X	X	X	X
Hematology [8, 11]: CBC/ differential, ANC, INR/PTT [8, 10]	X	X				X				X	
Chemistry [8, 11]: SGOT (AST), alk phos, T. bili, serum creatinine, calcium, glucose, Na, K, SGPT (ALT)	X	X		X[7]		X[7]		X[7]		X	
Albumin	X										
Urine proteinuria or urine protein creatinine ratio	X										
Tumor measurement[8] (CT scan of chest, abdomen and pelvis) (MRI if CT is not feasible)	X[1]								X[1]	X[1]	X[1,9]
ECG[6]	X										
Serum pregnancy test	X[2]										
Mandatory blood sample (see Section 14.0)	X[4,R]	(Day 7) X[4,R]	(Day 14) X[4,R]	(Day 21) X[4,R]		(Day 1) X[4,R]		(Day 21) X[4,R]			
Patient Medication Diary (Appendix II)[3]		X	X	X	X	X	X	X	X	X	
Patient Questionnaire Booklets (Appendices IV, V, VI)	X[5]		X[5, 8]			X[5, 8]	X[5, 8]		X[5, 8]		

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

3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution weekly during Cycles 1 and 2 and every 4 weeks thereafter.
4. Kits are required for this collection. Samples will be collected for PK analysis of C_{min} of regorafenib, M2 and M5 at the following time points: Cycle 1, days 7, 14 and 21 prior to treatment; Cycle 2, days 1 and 21 prior to treatment. Samples will be collected for research banking at the following time points: Baseline, prior to treatment; Cycle 2, days 1 and 21, prior to treatment. See Section 14.0 for specific instructions.
5. Patient questionnaires will be completed at baseline (appendices IV and V only), Cycle 1 Day 14, Cycle 2 Day 1, Cycle 2 Day 14 and Cycle 2 Day 28. Cycle 2 Day 14 and Cycle 2 Day 28 patient questionnaire can be sent home with the patient to complete and return at their next clinic visit if needed. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
6. Performed at screening and then as needed.
7. AST, ALT and total bilirubin will be checked at baseline and every other week during Cycles 1 and 2.
8. +/- 1 day. Applies to days 1, 8, 15, and 22; includes baseline tests and procedures for Day 1 Cycle 1.
9. If patient goes off study during Cycle 1 and last CT scan was done >28 days prior, the CT scan must be done.
10. If a subject is on warfarin with stable PT/INR at baseline, the PT/INR should be assessed on Day 5 (+/- 3 days). If value is above the therapeutic range, the dose should be modified and the assessment should be repeated weekly until it is stable.
11. Hematology and chemistry tests to be done prior to each cycle.
12. If baseline history, exam, weight, ECOG PS, and blood pressure were performed ≤3 days of Cycle 1 Day 1, they do <u>not</u> need to be repeated for Cycle 1 Day 1.
13. It is suggested that patients start treatment Tuesday-Friday to avoid PK collection on Sundays.

R Research funded (see Section 19.0*)*

5.0 Stratification Factors: None

6.0 Registration/Randomization Procedures

6.1 Randomization Procedures

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

The instructions for the registration/randomization application are available by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Correlative Research

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

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

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office ([redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

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 randomization, the following will be recorded:

- Patient has 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 10.5) 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 Blood draw kit is available on site.

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

6.2 Randomization Procedures

6.21 The registering membership will be used as the only stratification factor for this study.

6.22 After the patient has been registered into the study, the patient will be assigned to one of the following treatment groups, in 1:1:1:1 fashion, using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon, 1975).

- Arm A 1: Regorafenib Cycle 1: 80 mg daily Week 1/120 mg daily Week 2/160 mg daily week 3 then 1 week off followed by Cycle 2+ (160 mg for 21 days/1 week off) + pre-emptive strategy for PPES starting Cycle 1 Day 1
- Arm A 2: Regorafenib Cycle 1: 80 mg daily week 1/120 mg daily week 2/160 mg daily week 3 then 1 week off followed by Cycle 2+ (160 mg for 21 days/then 1 week off) + reactive strategy for PPES
- Arm B 1: Regorafenib 160 mg daily for 21 days/then 1 week off + pre-emptive strategy for PPES starting Cycle 1 Day 1
- Arm B 2: Regorafenib 160 mg daily for 21 days/then 1 week off + reactive strategy for PPES

7.0 Protocol Treatment

7.1 Treatment Schedule

Arm	Agent	Dose	Route	Frequency	ReRx
A 1	Regorafenib	80 mg daily (Starting dose) See Section 7.11	PO	Daily for 21 days of 28 day cycle	Every 28 days
	Clobetasol (**pre-emptive**)	0.05% cream thin layer to palms and soles, avoid washing hands or feet for 1 hour after application	Topical	BID for first 12 weeks	BID for first 12 weeks starting Day 1 of regorafenib dose
A 2	Regorafenib	80 mg daily (Starting dose) See Section 7.11	PO	Daily for 21 days of 28 day cycle	Every 28 days
	Clobetasol (**reactive**)	0.05% cream thin layer to palms and soles, avoid washing hands or feet for 1 hour after application	Topical	BID (per physician discretion; recommend no longer than 12 weeks from initiation)	BID (per physician discretion upon occurrence of PPES Grade ≥1; recommend no longer than 12 weeks from initiation)
B 1	Regorafenib	160 mg (Starting dose)	PO	Daily for 21 days of 28 day cycle	Every 28 days
	Clobetasol (**pre-emptive**)	0.05% cream thin layer to palms and soles, avoid washing hands or feet for 1 hour after application	Topical	BID for first 12 weeks	BID for first 12 weeks starting Day 1 of regorafenib dose
B 2	Regorafenib	160 mg (Starting dose)	PO	Daily for 21 days of 28 day cycle	Every28 days
	Clobetasol (**reactive**)	0.05% cream thin layer to palms and soles, avoid washing hands or feet for 1 hour after application	Topical	BID (per physician discretion; recommend no longer than 12 weeks from initiation)	BID (per physician discretion upon occurrence of PPES Grade ≥1; recommend no longer than 12 weeks from initiation)

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

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).

- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

7.11 Arm A Regorafenib Dose Escalation

Cycle 1:

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

***starting dose level**

Cycle 2 and beyond:

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

7.12 Arm B Regorafenib Dose (all cycles)

Week	Dose
1 Starting Dose	160 mg
2	
3	
4	Off

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 at least every 7 days during treatment and every 28 days during active monitoring.

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

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in the following tables for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

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

8.1 Arm A Regorafenib Dose Escalation/Reduction

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

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

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

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

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

Regorafenib may be dose reduced per the table in Section 8.2 in case of intolerable toxicity such as weight loss, fatigue, rash or anorexia.

8.2 Arm B Regorafenib Dose Levels (Based on Adverse Events in **Tables 8.3**.)

Dose Level	Drug	Dose
0*	Regorafenib	160 mg daily, Four 40-mg tablets
-1	Regorafenib	120 mg daily, Three 40-mg tablets
-2	Regorafenib	80 mg daily, Two 40-mg tablets

***** Dose level 0 refers to the starting dose.

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

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

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade.

In the case of two or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment.

8.3 Regorafenib Dose Modifications

Table 8.31 Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/AST/bilirubin

NCI-CTCAE v4.0[a]	Dose Interruption	Dose Modification [b]	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0
b. Excludes alopecia, non-refractory nausea/vomiting, lymphocyte count decreased, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.
c. If no recovery after a 4 week delay*, treatment should be permanently discontinued unless subject is deriving clinical benefit.
* Modify according to study specific cycle length

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

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

Table 8.32: Grading for Palmar-plantar erythrodysesthesia syndrome			
	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description / examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

Table 8.33 Recommended dose modification for Palmar-plantar erythrodysesthesia syndrome reaction[a]		
Grade of event (NCI-CTCAE v4.0)	**Occurrence**	**Suggested Dose Modification**
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1[b,d]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level [b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level.[b,d]
	4th occurrence	Discontinue therapy
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level.[b,d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one additional dose level[b,d]
	3rd occurrence	Discontinue treatment permanently.
a. More conservative management is allowed if judged medically appropriate by the investigator. b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is not permitted. c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently. d. Subjects requiring > 2 dose reductions should go off protocol therapy. e. The maximum daily dose is 160 mg. f. Refer to Section 9.0 for management strategies for Palmer-plantar erythrodysesthesia syndrome reactions.		

8.34 Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at least weekly during the first 5 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is >140 mm Hg systolic or >90 mm Hg diastolic (NCI CTCAE v4.0), then the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Tables Section 8.1 and 8.2 outline suggested dose reductions.

Table 8.34: Management of Treatment-Emergent Hypertension

Grade (CTCAE v4.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	Continue regorafenib Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by >20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: If BP previously within normal limits, start anti-hypertensive monotherapy If patient already on anti-hypertensive medication, titrate up the dose.	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication AND/OR Increase current anti-hypertensive medication AND/OR Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve[a] When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.
4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy

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

8.35 Liver Function Abnormalities

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

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

Table 8.35: Dose modifications/interruption for ALT and/or AST and/or bilirubin increases related to study drug

Increases in ASL/ALT (per NCI-CTCAE v 4.0)	**1st Occurrence**	**Restart**	**Re-occurrence**
AST and/or ALT ≤5 X ULN (< Grade 3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3 X ULN (≤ Grade 1) or baseline.		
ALT and/or AST >5 X ULN (≥ Grade 3)	Interrupt dosing, with weekly monitoring until transaminases return to <3 X ULN or baseline.	If the potential benefit for reinitiating regorafenib/ placebo is considered to outweigh the risk of hepatotoxicity: Reduce one dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST >20 X ULN (≥ Grade 4)	Discontinue		
ALT and/or AST >3 X ULN (≥ Grade 2) with concurrent bilirubin >2 X ULN	Discontinue treatment and measure serum liver tests weekly until resolution. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		
During the first 2 cycles of treatment, ALT, AST and bilirubin must be monitored every 2 weeks.			

8.4 No dose modifications expected for clobetasol propionate.

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 ASCO 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence Based Clinical Practice Guideline. Journal of Clinical Oncology, Vol 24, No 19 (July 1), 2006: pp. 3187-3205.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

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

9.41 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, but patients cannot apply these within 1 hour before and after clobetasol applications.
- 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 (in reactive arm). Avoid systemic steroids.
- For grade 2/3 Oral NSAIDs (celecoxib, ibuprofen) may be used for pain control
- Continue clobetasol during dose interruptions or decreased dosing/rechallenge
- Continue analgesia with topical analgesics or oral NSAIDs during dose interruptions or decreased dosing/rechallenge

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 v4 Grade 1 ((Minimal skin changes or dermatitis (e.g., erythema, edema or hyperkeratosis) without pain)) - Continue regorafenib at current dose.
- CTCAE v4 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)) – See Section 8.33.
  - Oral (NSAIDs or narcotics) OR topical analgesia (lidocaine cream or patches PRN.
- CTCAE v4 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)) – Interrupt regorafenib dose and monitor
  - Topical steroid cream BID AND topical anesthetics
  - Oral (NSAIDs or narcotics) OR topical analgesia (lidocaine cream or patches PRN.

9.5 Prevention/management strategies for diarrhea: Diarrhea can be a common side effect of regorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status). Anti-diarrhea medications may be introduced if symptoms occur. Previous trials have shown that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours. In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4).

Important: Expedited adverse event reporting requires submission of a MedWatch 3500A report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 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

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

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

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

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

10.31 **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.

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

System Organ Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be 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 **Persistent or Significant Disabilities/Incapacities**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.312 **Death**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.
  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
  - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
  - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
  - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 **Second Malignancy**

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

10.4 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>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.3

Effective Date: May 5, 2011

Additional Instructions:

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

2. Submit form 3500A to the FDA, MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at 1-800-332-0178 or online at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

3. **ACCRU Sites*:*** Follow site-specific reporting guidelines. Provide copies by fax [redacted] to the ACCRU SAE Coordinator. The ACCRU SAE Coordinator will then electronically send the report to Bayer:

Electronic Mailbox: [redacted]
Facsimile: [redacted]
Address: [redacted]
Mail only [redacted]
[redacted]
Address: [redacted]
FDX or UPS only: [redacted]

Reports for all Bayer products can also be phoned in via our Medical Communications Department

Phone: [redacted]

The Site Investigator shall report to ACCRU within 24 hours of the investigator's awareness of other events such as:

- An adverse event related to study specific procedures
- Any new and important event related to treatment with the study drug(s).
- Any pregnancy during which a female patient was exposed to the study drug(s)
- Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).
- Any other relevant safety information including but not limited to reports on drug interaction, overdose, drug abuse or misuse, drug dependency, withdrawal syndrome, medication error, occupational exposure and lack of drug effect (LODE) occurring at any time during the treatment phase.

Pregnancy: If a pregnancy occurs, follow the patient throughout the pregnancy until the outcome of the pregnancy is available. Subsequent follow-up will depend on the outcome of the pregnancy. If there is an abnormal outcome or pregnancy complications, additional follow-up may be requested to obtain further information.

Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports (DSUR) / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees;

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

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

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

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

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

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation Using RECIST Guideline

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

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

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks.

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).

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.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

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

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

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

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

11.42 Non-Target Lesions & Non-Target Lymph Nodes

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

11.43 Response Criteria

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

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

11.432 Evaluation of Target Lesions

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

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

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

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

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

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

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

11.44 Overall Objective Status

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

For Patients with Measurable Disease

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

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

*See Section 11.431
** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

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

*See Section 11.431

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

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

12.0 Descriptive Factors

12.1 BRAF analysis done: Yes vs. no.

12.11 If yes, wild-type vs. mutated.

12.2 KRAS analysis done: Yes vs. no.

12.21 If yes, wild-type vs. mutated.

12.3 ECOG Performance Status: 0 vs. 1.

12.4 Age: <70 vs. ≥70.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 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. Event monitoring will be required per Section 18.0 of the protocol.

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

13.3 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 Patients will continue treatment until progression, unacceptable adverse events, or patient refusal. Treatment will then be discontinued and the patient will go to event monitoring and be followed per Section 18.0.

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

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

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

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Specimens for This Protocol

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for specimen submission**
Blood/blood products (EDTA whole blood)	Mandatory	Multiple draws (see Section 14.21for schedule)	Defined translational studies (Section 14.211)	Section 14.2
Blood/blood products (EDTA whole blood)	Mandatory	Baseline Prior to Treatment and Multiple Draws	Banking (Section 14.212)	Section 14.2

14.12 Kits are required for this study.

14.121 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.122 Participating institutions may obtain kits 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. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry**. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource.**

14.123 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.124 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.13 All samples must be collected Monday –Friday.

14.14 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood is drawn and sample type.

14.15 Collect and process all blood/blood products according to the directions below and the kit instructions for the table below.

14.151 Baseline and Cycle 2 EDTA Tube: Centrifuge the EDTA tubes in a refrigerated centrifuge within 2 hours or less after collection all time points. Centrifuge sample 3000 rpm x 10 minutes. Carefully pipette 1.0 mL of plasma into each of the 3 cryovials. Next pipette the white blood cells being careful to not disturb the underlying cell layer into the 4th cryovial. Carefully tighten the caps. Discard the EDTA collection tube.

14.152 Serial Draws: Centrifuge the EDTA tubes in a refrigerated centrifuge within 2 hours or less after collection all time points. Centrifuge sample 3000 rpm x 10 minutes. Carefully pipette 1.0 mL of plasma into each of the 3 cryovials. Carefully tighten the caps. Discard the EDTA collection tube.

14.153 Freeze all cryovials at -70°C or colder until shipped.

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, Prior to Tx	Cycle 1, Day 7 Prior to Tx, Cycle 1 Day 14 Prior to Tx, Cycle 1 Day 21 prior to Tx	Cycle 2 Day 1 Prior to Tx and Cycle 2 Day 21 Prior to Tx	Additional processing required at site after blood draw?	Storage /shipping conditions
Mandatory	EDTA	10 ml (1)	Plasma (PK)		X	X	Yes	Freeze/dry ice
Mandatory	EDTA	10 ml (1)	Plasma, White Blood Cells (banking)	X		X	Yes	Freeze/dry ice

14.16 Shipping

14.161 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. Enter information from the Blood Specimen Submission Form.

14.162 Ship all plasma and white blood cells via Priority Overnight service on dry ice.

14.163 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.**

14.164 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 airbill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Freezer.

14.165 BAP Freezer will receive the samples and immediately forward specimens to the ACCRU Research Base BAP Shared Resource, Stabile SL-16, Attention: BAP Supervisor.

14.2 Study Methodology and Storage Information

14.21 Blood/blood product samples will be collected for pharmacokinetic analysis.

PK analysis for regorafenib and M2 and M5 will be performed as follows:

- Cycle 1 day 7: 0, prior to dosing (C_{min}, trough levels)
- Cycle 1 day 14: 0, prior to dosing (C_{min}, trough levels)
- Cycle 1 day 21: 0, prior to dosing (C_{min}, trough levels)
- Cycle 2 day 1: 0, prior to dosing (C_{min}, trough levels)
- Cycle 2 day 21; 0, prior to dosing (C_{min}, trough levels)
- Window sampling times are predose ≤12 hours.

14.211 A portion of the plasma, 0.5 ml (500 mcl), for each sample will initially be analyzed for the amount of regorafenib in Dr. Jeannine McCune's laboratory using standard laboratory protocols. The samples will be shipped upon request to

[redacted]

[redacted]

According to patient consent information, remaining white blood cells/plasma will be stored frozen at -70/-80ºC by BAP until specific analyses are identified. 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 the majority of ACCRU studies.)

14.212 Ongoing research is likely to identify putative biomarkers for regorafenib efficacy and/or toxicity in the near future. Given the key importance of such biomarker identification, our study offers a unique opportunity to validate such discoveries given its size and prospective nature. As such, and as part of ongoing ACCRU research, we will collect plasma and white blood cells for future research studies, according to patient consent information, on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU (scientific) and IRB review and approval prior to any samples being used.

14.3 Return of Genetic Testing Research Results

For this study, DNA (White Blood Cells) is only being banked, and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND exempt

- Investigator brochure - Available on the ACCRU website.

15.1 Regorafenib (BAY 73-4506, Stivarga®)

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

15.12 **Formulation**: Regorafenib 40-mg tablets contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talk, titanium dioxide E171 (color index 77891), Macrogol/PEG 33350, lecithin (soy), iron oxide yellow – E172 (color index 77491), iron oxide red – E172.

Regorafenib will be provided by Bayer as coated, not divisible, gray-orange-red, oval tablets (length 16 mm, width 7 mm, thickness 4.9-5.6 mm). Tablets are in an immediate-release dosage form with rapid dissolution characteristics under the in vitro test conditions.

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 28 tablets and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets.

15.13 **Preparation and storage**: Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F). The study drug must be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff.

15.14 **Administration:** Regorafenib tablets should be taken at the same time every day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) meal. Regorafenib should not be taken with grapefruit juice.

15.15 **Pharmacokinetic information**:

a) Absorption – A high-fat meal increased the mean AUC of the parent drug by 48% compared to the fasted state and decreased the mean AUC of the M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) active metabolites by 20% and 51%, respectively. A low-fat meal increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively (as compared to the fasted state).
b) Distribution – Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins.
c) Metabolism – Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites measured at steady state are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), both of them having similar *in vitro* pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

d) Excretion – Elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (range) elimination half-life of 51 hours (32 to 70 hours). Elimination occurs through: Feces (71%; 47% as parent compound; 24% as parent compound; 24% as metabolites); Urine (19%).

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

15.17 **Known potential toxicities**:

Serious Adverse Effects:

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

Most Common Adverse Events, >10%

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

Less Common Adverse Events, 1% - 10%

Cardiovascular: Myocardial ischemia and infarction
Gastrointestinal: Taste disturbance, xerostomia, gastroesophageal reflux
Neuromuscular & skeletal: Tremor
Respiratory: Dyspnea

Rare Adverse Events (Important or life-threatening), <1%

Bradycardia, erythema multiforme, gastrointestinal fistula, hypertensive crisis, liver injury (severe), liver failure, reversible posterior encephalopathy syndrome (RPLS), skin cancer (keratoacanthoma, squamous cell carcinoma), Stevens-Johnson syndrome, toxic epidermal necrolysis

15.18 **Study agent procurement:**
Bayer HealthCare Pharmaceuticals will supply regorafenib tablets to Biologics, Inc. Each participating ACCRU treating location will order the drug from Biologics, Inc. Fax the Drug Order Request Form (found in the forms packet) to:

[redacted]

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

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

15.19 Nursing Guidelines

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

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

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

15.194 Warn patients of possibility of alopecia.

15.195 Gastrointestinal side effects can include, diarrhea, nausea, vomiting, decreased appetite, weight loss, mucositis and less commonly taste changes, dry mouth, and reflux. Treat symptomatically and monitor for effectiveness.

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

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

15.198 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

15.2 Clobetasol Propionate Cream (Temovate®)

15.21 Background: Clobetasol propionate cream has anti-inflammatory, antipruritic and vasoconstrictive properties. Topical corticosteroids may depress the formation, release, and activity of endogenous chemical mediators of inflammation (kinins, histamine, liposomal enzymes, prostaglandins) through the induction of phospholipase A2 inhibitor proteins (lipocortins) and sequential inhibition of the release of arachidonic acid. Clobetasol has very high range potency.

15.22 Formulation: Clobetasol propionate 0.05% cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

15.23 Preparation and storage: Once the drug has been received it must be kept in a secure, dry location. Clobetasol propionate must be stored in its original packaging at a temperature between 15°C and 30°C (59°F and 77°F). Cream should not be refrigerated.

15.24 Administration: Apply a thin layer of clobetasol propionate cream to the palms of the hands and soles of the feet. Avoid washing hands and feet for one hour after application of clobetasol propionate cream. The use of clobetasol propionate is for external use only. Avoid contact with the eyes and mucous membranes. Do not apply to face or intertriginous areas. Do not use if there is atrophy at the treatment site. Minimize contact to nonaffected areas of the body. The treated skin should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.

15.25 Pharmacokinetic information:
Absorption: Percutaneous absorption is variable and dependent upon many factors including vehicle used, integrity of epidermis, dose, and use of occlusive dressings (not recommended)

Metabolism: Hepatic

Excretion: Urine and feces

15.26 Potential Drug Interactions: Due to the topical use of clobetasol propionate, drug-drug interactions are thought to be minimal.

15.27 Known potential toxicities:
Precautions:
Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy. Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids.

Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products. If irritation develops, clobetasol propionate cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing. If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of clobetasol propionate cream should be discontinued until the infection has been adequately controlled.

Adverse reactions, significant
Frequency not always defined; may depend upon formulation used, length of application, surface area covered, and the use of occlusive dressings.

Central nervous system: Localized burning (5% to 40%), stinging sensation (<2% to 5%), numbness of fingers (<2%), local pain (1%), intracranial hypertension (systemic effect reported in children treated with topical corticosteroids)
Dermatologic: Pruritus (<2% to 3%), eczema asteatotic (2%), erythema (<2%), folliculitis (<2%), skin atrophy (<2%), telangiectasia (<2%), xeroderma (<1% to 2%), atrophic striae (children)
Endocrine & metabolic: Adrenal suppression, Cushing's syndrome, glucosuria, growth suppression, HPA-axis suppression, hyperglycemia
Local: Skin fissure (<2%), local irritation (1%)
Respiratory: Upper respiratory tract infection (8%), nasopharyngitis (5%), streptococcal pharyngitis (1%)
<1% (Limited to important or life-threatening): Alopecia, exfoliation of skin, skin rash, urticaria

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

15.29 Nursing Guidelines

15.291 As therapy is a topical preparation, side effects are expected to be minimal.

15.292 Instruct patients to apply a thin layer to palms of hands and soles of feet.Patients should be instructed not to wash these areas for a minimum of 1 hour after application.

15.293 Instruct patients to avoid contact with the eyes and mucous membranes.

15.294 Patients may experience a local burning/stinging sensation depending on the strength.

15.295 Rarely after prolonged use and discontinuation, patients may display symptomatic signs of glucocorticoid insufficiency. Instruct patients to report any excessive fatigue, facial puffiness (moon face) to the study team.

15.296 Rarely after prolonged use, patients may experience elevated glucose levels, instruct diabetics to monitor sugar levels and report any fluctuations to the study team.

16.0 Statistical Considerations and Methodology

16.1 Study Design

This is a randomized phase II study of regorafenib starting at low dose (Arm A, combining A1 and A2) compared to standard dose of regorafenib (Arm B, combining B1 and B2) in patients with refractory metastatic colorectal cancer (mCRC). Patients will be randomized 1:1:1:1 to one of the following 4 arms:
A1: Regorafenib start low dose and pre-emptive Clobetasol for PPES
A2: Regorafenib start low dose and reactive Clobetasol for PPES
B1: Standard dose of regorafenib and pre-emptive Clobetasol for PPES
B2: Standard dose of regorafenib and reactive Clobetasol for PPES
(see Schema)

16.2 Sample Size, Accrual Time and Study Duration

Accrual time is anticipated to be 18 months, with approximately 2 months of follow-up per patient until occurrence of the primary endpoint and approximately 6 months of planned follow-up overall per patient. The sample size will be 110 patients, with approximately 28 patients randomized per regorafenib and strategy treatment sub-arm (A1, A2, B1, B2). An additional 13 patients overall will be enrolled to account for drop-out, cancels, ineligibles, etc., to give a total sample size of 123 patients. The total study duration (accrual and follow-up) is expected to be approximately 2 years.

16.3 Statement for Primary Endpoint

The primary endpoint is the proportion of patients in each arm who complete 2 cycles of protocol treatment and initiate cycle 3. The proportion will be calculated among evaluable patients separately by arm (Arm A vs. Arm B). Evaluable patients are defined as patients who are eligible, consented, received any protocol treatment. In the CORRECT trial, among patients who were randomized to regorafenib, 45% continued treatment beyond cycle 2. Other than disease progression, majority of patients discontinued regorafenib due to adverse events not associated with progression. It was noted that most adverse events occurred during Cycles 1-2 of the treatment (Grothey A et. al., 2013, Lancet). Assuming 45% of patients would complete 2 cycles of protocol treatment and initiate cycle 3 in the control (standard dose; pooled arms B1 andB2) group, and desiring an improvement to 63% in the experimental (starting low dose) group (pooled arms A1 and A2), a one-sided test with alpha = 0.20 and power of 80% will require a sample size of 110 patients enrolled to both regorafenib arms (A and B). We will enroll 13 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 123 patients. A Fisher exact test will be used to detect a difference in proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 between arms (starting low dose [pooled arm A1 and A2] vs. standard dose [poled arm B1 and B2]). The proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 will be computed by arm with its 95% confidence interval using exact method.

16.4 Supplementary Analysis Plans (includes all secondary and translational goals)

16.41 Overall survival (OS) is defined as time from randomization to death due to any cause. OS will be estimated with Kaplan-Meier survival curves and differences between regorafenib arms (A vs. B) tested using log-rank tests, though we note these analyses are not powered for formal non-inferiority assessments. See Section 2.21.

16.42 Progression-free survival (PFS) is defined as the time from randomization to the earlier of disease progression or death due to any cause, where progressed disease (PD) is as defined by RECIST 1.1 (see Section 11.0). PFS will be estimated with Kaplan-Meier survival curves and differences between regorafenib arms (A vs. B) tested using log-rank tests, though we note these analyses are not powered for formal non-inferiority assessments. See Section 2.21.

16.43 Time to progression (TTP) is defined as the time from randomization to disease progression, where progressed disease (PD) is defined by RECIST 1.1 (see Section 11.0. TTP will be estimated with Kaplan-Meier survival curves and differences between regorafenib arms (A vs. B) tested using log-rank tests, though we note these analyses are not powered for formal non-inferiority assessments. See Section 2.21.

16.44 The cumulative (total) dose of regorafenib received by patients and dose intensity in the first two cycles will be summarized with descriptive statistics and compared between regorafenib arms (A vs. B) using the t-test (if approximately normally distributed) or the Wilcoxon rank sum test (if not approximately normally distributed). Dose intensity is defined as the cumulative (total) dose of regorafenib divided by the expected total dose. See Section 2.22.

16.45 The proportion of patients overall and within each arm experiencing grade 3 or 4 HFS or fatigue will be computed with 95% confidence intervals, and differences between regorafenib dosing strategies (pooled across HFS strategies) tested using a Fisher Exact test. The incidence of grade 3 or 4 HFS will also be descriptively compared between those receiving a pre-specified preemptive vs. reactive approach for hand and foot syndrome (pooled across dosing strategies), and tested using a Fisher Exact test. See Section 2.24. Adverse event reports will be shared with Dr. Lacouture of Memorial Sloan Kettering Cancer Center 1-2 times per month for review.

16.46 Furthermore, patients will be descriptively compared between treatment arms and between HFS treatment strategies (pre-emptive vs. reactive) according to self-reported outcomes given on the HFS14 questionnaire. See Section 2.24. Results from the cycle 1 and 2 HSF14 questionnaires will also be summarized descriptively as they relate to the pre-emptive versus reactive PPES strategies, with comparisons made within and between arms using the t-test or Wilcoxon rank sum test as appropriate, as well as taking time-dependence into account. Changes in QOL (according to the LASA questionnaire as measured by the overall QOL question) from baseline will also be compared between the treatment arms using the t-test or Wilcoxon rank sum test. We hypothesize that patients receiving regorafenib will experience greater deficits in QOL as reflected by scores on the HSF14, the BFI and the LASA. These questionnaires have specific application to this population. See Section 2.24.

16.47 Pharmacokinetic Analysis

The samples will be analyzed for the regorafenib concentrations using liquid chromatography mass spectrometry, with the anticipated method being a modified version

of that published by Van Erp et al. The samples will be analyzed for M2 and M5, if cost-free standards can be obtained from Bayer.

After quantitation, the average regorafenib concentration will be calculated by arms (Arm A vs. B) at each time point.

As exploratory analysis, this average concentration will be correlated with toxicity and efficacy endpoints. Further descriptive characteristics of the pharmacokinetics will also be calculated, An example includes (but is not limited to) within-patient variability in the trough concentrations pharmacokinetic parameters will also be calculated, both overall and within cycles, as a ratio of the maximum:minimum value.

16.5 Adverse Event Stopping Rule

Because this study randomizes patients to either a standard of care treatment or a lower dose of the same treatment, stopping rules for toxicity will not apply. However, as noted below in Section 16.7, regular meetings of the DSMB will review all toxicity and adverse event data while patients are being treated.

16.6 Accrual Monitoring Stopping Rule

There is no stopping rule related to accrual.

16.7 Study Monitoring

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

16.8 Missing Data

Patients with missing data will be excluded from relevant analyses; no imputation of missing data will be performed.

16.9 Primary Endpoint Completion Time Estimation

Given 18 months of accrual and 2 months of follow-up per patient to observe the primary endpoint, a total of 20 months will be required to observe all primary endpoint events, with subsequent time required for data cleaning and analysis (approximately 2 months).

17.0 Pathology Considerations/Tissue Biospecimens:
None

18.0 Records and Data Collection Procedures

Access the RAVE system through the iMedidata portal at https://login.imedidata.com. All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document.

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Radiation[2]	
On-Study: Prior Systemic Therapy[2]	
Adverse Events: Baseline	
RECIST Measurements: Baseline	
Measurements (Non-Measurable Disease Only): Baseline	
Op and Pathology Reports[1]	
Supporting Documentation: Baseline	
Patient Status: Baseline	
Specimen Submission: Blood -Baseline (see Section 14.0)	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet: Baseline	≤ 2 weeks after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Booklet Compliance	≤ 2 weeks after registration - This form **must** be completed only if the Patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.

1. Submit Op and Path Reports via the Supporting Documentation: Baseline form.
2. Submit only if applicable.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention)	X[4]	X
Treatment (Intervention): Dose Modifications, Omissions and Delays	X[5]	
Adverse Events: Solicited	X	X
Adverse Events: Other		
RECIST Measurements	X[1]	X[1]
Measurements (Non-Measurable Disease Only)	X[1]	X[1]
Supporting Documentation	X[1]	
Specimen Submission: Blood- Cycle 1	X (see Section 14.0)	
Specimen Submission: Blood – Cycle 2	X (see Section 14.0)	
Patient Questionnaire Booklet: Treatment	X[2]	
Booklet Compliance	X[3]	
Patient Status : Treatment (Intervention)	X	
Off Treatment		X
Notice of New Primary[5]	X	
Consent Withdrawal (choose appropriate form)[5] • Consent Withdrawal: QOL Only • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up	X	
Lost to Follow-Up[5]	X	
Deviation Form[5]	X	

1. Attach a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.
2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
3. This form must be completed **only** if the Patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
4. Complete at each evaluation during Active Treatment (see Section 4.0).
5. Submit only if applicable.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PD	At PD	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	At each occurrence
Adverse Events: Late[3]					At each occurrence
Lost to Follow-Up[3]					At each occurrence
Notice of New Primary[3]					At each occurrence
First Non-Protocol Treatment[4]					At each occurrence
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: QOL Only • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up					At each occurrence

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

19.0 Budget

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

19.2 Tests to be research funded: Mandatory blood samples for correlative research.

19.3 Other budget concerns:

19.31 Regorafenib will be supplied by Bayer Pharmaceuticals. Clobetasol propionate will not be supplied, but is commercially available.

19.32 Remuneration will be provided to patients for the first 2 cycles of treatment.

20.0 References

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