FOX CHASE CANCER CENTER
TEMPLE HEALTH

GI-094 A Pilot Phase II, single arm, open label, investigator-initiated clinical trial of Regorafenib plus 5-Fluorouracil/Leucovorin (5FU/LV) beyond progression on Regorafenib monotherapy in metastatic colorectal cancer (mCRC)

Brief Title: Regorafenib plus 5-FU/LV beyond progression in mCRC

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Protocol Version Date: 12/14/2018
Amendment#7

Synopsis

[Title]	Regorafenib plus 5-FU/LV treatment beyond progression in mCRC patients
Clinical study phase	Pilot Phase II
Study objective(s)	The goal is to investigate PFS and OS in mCRC patients who progressed on regorafenib monotherapy and are treated with regorafenib/5-FU/LV combination therapy
[Background treatment]	Standard multi-agent combination chemotherapy and regorafenib monotherapy
Indication	Metastatic Colorectal Cancer including cancers with wild-type or mutant KRAS/NRAS/BRAF genes
Diagnosis and main criteria for inclusion	mCRC with prior progression on standard multi-agent combination chemotherapy and progression on regorafenib monotherapy.
Study design	Single arm open label pilot phase II trial of Regorafenib PO plus 5-FU/LV infusion in mCRC patients who progressed on prior Regorafenib monotherapy as well as 5-FU containing chemotherapy combinations. Dose of Regorafenib is 160 mg PO daily D1-D21 of 28 day cycle or last tolerated dose while on Regorafenib monotherapy. 5-FU dose D1 and D15 is 400 mg/m^2 over 10 mins, Leucovorin 400 mg/m^2 over 2 hours, 5-FU 2400 mg/m^2 IV infusion over 46 hours (or last tolerated dose of infusional 5-FU).
Type of control	Historical control (no control arm for the single arm study)
Number of subjects	15
Plan for statistical analysis	Descriptive pilot study
Institutional enrollment	The study will be performed at Fox Chase Cancer Center and Fox Chase Cancer Center at Temple University Hospital
Publications	Results will be submitted by the PI and collaborating investigators to society meetings such as ASCO, GI ASCO, AACR and eventually the work will be submitted for publication in a journal as a full manuscript after the study is concluded.

Contents

1. Introduction

1.1 Metastatic Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer diagnosis in the United States and the most prevalent malignancy of the digestive tract (1). Worldwide, approximately 1.3million patients are diagnosed with CRC, and 694,000 deaths are attributed to the disease each year (2). Screening tests are both widely available and effective at detecting this disease at an early stage. As a result of screening efforts, fewer than 25% of patients diagnosed with CRC in the United States have evidence of metastatic spread at initial presentation (1). Unfortunately, 50 to 60% of patient diagnosed with CRC eventually develop metastases, and the majority of these patients have unresectable disease (3). Whenever possible, the standard of care for patients with CRC is complete surgical resection for possible cure. This is typically followed by adjuvant chemotherapy in patients with stage III disease, stage IV disease with resectable metastases or stage II disease with high-risk features (4). If complete resection is not possible, however, patients are offered systemic chemotherapy. Sometimes in this setting neoadjuvant therapy results in downsizing of disease, making surgical resection possible with improved long-term outcomes. The mainstays of first and second line treatment for patients with stage IV unresectable metastatic CRC (mCRC) consists of fluoropyrimidine-based combination chemotherapy with FOLFOX (leucovorin, 5-FU, oxaliplatin), Cape-Ox (capecitabine, oxaliplatin), or FOLFIRI (leucovorin, 5-FU, irinotecan). Patients with tumors that retain wild-type *KRAS/NRAS* can benefit from the addition of monoclonal antibodies that target the epidermal growth factor receptor (EGFR), such as cetuximab or panitumumab. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) receptor is generally offered to patients who develop progressive disease while undergoing treatment with an EGFR antagonist or as a component of initial therapy for *KRAS/NRAS* mutated tumors (4).

1.2 Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI) (1). Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

1.3 Preclinical

In vivo, regorafenib exhibited anti-angiogenic and anti-proliferative effects in human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced

Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian). (1) Immunohistochemical *ex-vivo* studies with a phospho –specific monoclonocal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody. (1) These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

1.4 Clinical Experience

Three phase III global randomized studies have evaluated the efficacy of regorafenib. The CORRECT (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) trial is an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 760 patients with mCRC whose disease has progressed after approved standard therapies. Metastatic colorectal cancer patients were randomized to regorafenib plus best supportive care (BSC) or placebo plus BSC. Treatment cycles consisted of 160 mg of regorafenib (or matching placebo) once daily for three weeks on / one week off plus BSC. The primary endpoint of this trial was overall survival. Secondary endpoints included progression-free survival, objective tumor response rate and disease control rate. The safety and tolerability of the two treatment groups were also compared.

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.773 (95% confidence interval [CI], 0.635 to 0.941; 1-sided $p = .0051$). Patients treated with regorafenib had a median overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression-free survival was 1.9 months (95% CI, 1.88 to 2.17) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.493 (95% CI, 0.418 to 0.581; 1-sided $p< .000001$). There was a substantial difference in disease control rate in the regorafenib and placebo groups (44% vs. 15%; $p<.000001$). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of mets, number of lines of prior therapy, and kras status.

The most frequent grade ≥ 3 adverse events in the regorafenib group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety from the CORRECT study supported FDA approval in September 2012.

A second randomized international, double-blind, placebo-controlled study enrolled patients with mCRC whose disease progressed after approved standard therapies was

conducted in Asia Pacific (China, Hong Kong, Taiwan, Republic of Korea, and Vietnam). This multicenter phase III study randomly (CONCUR - A placebo CONtrolled, randomized, double blind Clinical study Using Regorafenib in Asian CRC patients after failure of standard therapies) assigned 136 Asian patients to regorafenib at 160 mg daily and 68 to placebo.The primary endpoint of the study was overall survival. Sixty percent of patients enrolled received previous targeted therapy.

The study met its primary endpoint, with regorafenib demonstrating a median overall survival of 8.8 months compared to 6.3 months for placebo compared –and with 45% reduction in the risk of death compared with placebo ((hazard ratio 0.55, 95% CI 0.40-0.77, one-sided p=0.00016 $P = 0.0002$). Adverse events in CONCUR were consistent with the known safety profile of regorafenib in metastatic colorectal cancer.

The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on/1 week off cycle) or placebo, plus best supportive care.

The results showed that treatment with regorafenib led to a statistically significant 3.9-month improvement in progression-free survival (PFS), compared with placebo (4.8 months vs. 0.9 months; hazard ratio [HR] = 0.27; $p < .0001$). Overall survival was statistically similar between groups as expected due to a trial design that allowed crossover to regorafenib for disease progression (85% for placebo and 31% regorafenib randomized patients). The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control group. The most common grade ≥3 adverse events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%). The efficacy and safety of the GRID study data supported FDA approval February 2013.

1.5 Rationale for Combination

Our preclinical data support the concept that there is synergy between 5-FU and regorafenib in mCRC subtypes and anecdotal patient cases we have treated have suggested that there is disease control by combining regorafenib plus 5-FU beyond progression on regorafenib

1.6 Preclinical

We have observed synergistic effects with the addition of regorafenib to 5-FU in colorectal cancer cell lines with KRAS mutation, BRAF mutation, p53 mutation, p53 deletion or wild-type p53 status (**Figure 1**, Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015).

Regorafenib (uM)	5-FU(uM)	Combination Indices			
		HCT116$^{p53-/-}$	HCT116	SW480	HT29
2	10	1.91±0.04	2.09±1.97	1.00±0.1	2.23±0.19
2	20	2.88±0.56	>>1	0.88±0.13	2.29±0.24
2	40	2.12±0.35	>>1	1.10±0.10	1.31±0.08
4	10	2.23±0.45	0.90±0.01	1.28±0.11	1.85±0.28
4	20	2.55±0.38	0.86±0.03	1.40±0.15	1.88±0.30
4	40	2.06±0.30	1.53±0.81	1.62±0.09	1.63±0.14
8	10	1.23±0.14	1.37±0.04	1.29±0.15	0.84±0.05
8	20	1.21±0.09	0.85±0.07	1.19±0.34	0.88±0.08
8	40	0.72±0.04	0.63±0.01	0.76±0.09	1.13±0.14

Figure 1: Regorafenib synergizes with chemotherapy. (Combination index (CI) values of regorafenib in combination with 5-fluorouracil for 48 h in various non-constant ratios against colon cancer cell lines. Combination index <1, D1 and >1 indicates synergism, additivity or antagonism, respectively. Red numbers indicate synergy (CI<1). Additional details of the case can be found in Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015.

Of note, while it is known that mismatch repair deficient colorectal cancers are generally more resistant to 5-FU than microsatellite stable tumors, the HCT116 mismatch repair deficient cells used in our study were sensitive to the regorafenib plus 5-FU combination regardless of whether p53 was wild-type or deleted (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015). We performed cell culture experiments to assess alterations in specific biomarkers that may correlate with observed sensitivity patterns. Potent inhibition of Mcl-1 expression was observed in regorafenib-treated colorectal cancer cells and the reduced expression was still present when 5-FU was added in combination across the panel of cell lines tested (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015). Reduced Mcl-1 and Bcl-XL (although reduction of Bcl-XL was less robust and noted primarily in the combination therapy conditions) could be a contributing factor to the observed sensitivity patterns (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015).

1.7 Clinical experience

Our clinical experience reported as clinical case reports showed that two patients diagnosed with metastatic colorectal cancer who exhausted all approved standard therapies had stable disease following treatment with the combination of regorafenib and either 5-FU or capecitabine (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015). Both these patients showed disease progression despite treatment with first-line FOLFOX and second-line FOLFIRI combination chemotherapy regimens. After failing these fluoropyrimidine-based regimens, both patients received additional cytotoxic and targeted therapies with eventual disease progression. These therapies included capecitabine plus dabrafenib and trametinib,

regorafenib monotherapy, and regorafenib with panitumumab. After exhausting available options, both patients were offered regorafenib with either 5-fluorouracil (5-FU) or capecitabine. The first patient was transitioned to regorafenib 160 mg PO daily for days 1-21 of a 28 day cycle with capecitabine 1000 mg PO twice daily for days 1-14 of a 21 day cycle while the second patient received 160 mg PO daily for days 1-21 of 28 day cycle plus infusional 5-FU every 2 weeks at 2400 mg/m2 over 46 hours, bolus 5-FU 400 mg/m2 on day 1 and leucovorin. This regimen produced stable disease in both patients with acceptable toxicity (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015).

The first patient had stable disease for at least one month after starting therapy with regorafenib and capecitabine. Disease control was reflected in both radiographic and serologic measures of CRC activity. The duration of the stable disease response to treatment was cut short, however, by severe pneumonia and pulmonary hemorrhage resulting in the patient's demise. It remains uncertain whether this fatal bleed occurred as a treatment-related adverse event because the patient was concurrently receiving therapeutic-dose enoxaparin for her pulmonary embolus and otherwise had advanced metastatic disease. This patient did not experience toxicities commonly associated with regorafenib or capecitabine, therefore, did not require any dose reductions or delays during the short course of therapy.

A more prolonged period of disease control following therapy was observed in the second patient, who received regorafenib with 5-FU for approximately 17 months. This patient had evidence of stable disease for at least 2 months before starting to accumulate new metastatic foci. Despite developing progressive disease, the patient opted to continue on this treatment, and for the next 11 months, his tumor markers remained largely suppressed. The patient ultimately passed away 17 months following his first dose of regorafenib with 5-FU due to a disease-related complication. While on treatment with regorafenib and 5-FU, this patient did experience modest treatment-associated toxicity and therefore required some dose reductions and several treatment delays. Of note the patient had disease control for many months on the regorafenib plus 5-FU combination as documented by a non-rising CEA while on therapy (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015). CEA rose when patient had interruptions to therapy due to sepsis related to indwelling catheters but CEA became stable when the regorafenib plus 5-FU therapy was restarted (Figure 2).

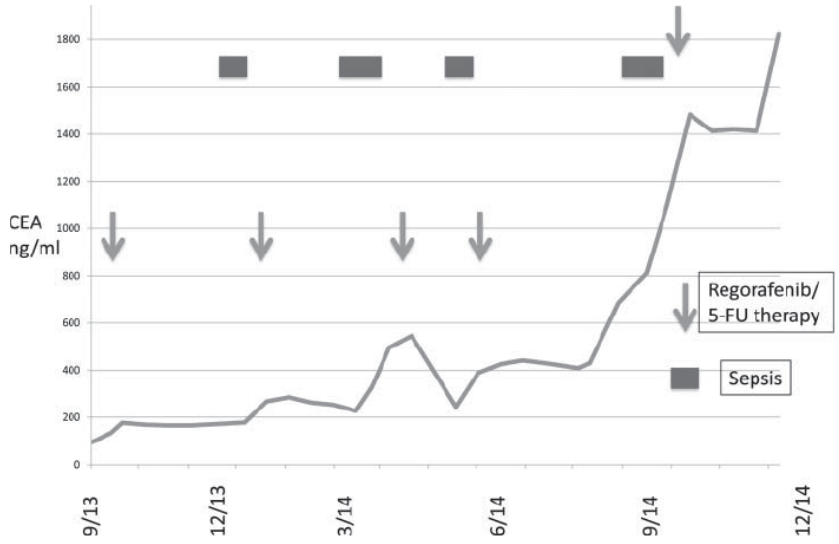

Figure 2. Serologic response to prior systemic therapies and regorafenib plus capecitabine in a patient with metastatic colorectal cancer who had progressed on prior standard combination therapies. CEA (carcinoembryonic antigen) is displayed as a function of time in the patient's treatment course. Additional details of the case can be found in Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015.

Despite the multitude of clinical trials, there has not been active clinical investigation in the safety and efficacy of combining regorafenib with capecitabine or 5-FU in treatment refractory mCRC. This regimen holds considerable theoretical appeal, as fluoropyrimidines are the backbone of effective first and second-line therapy. Regorafenib, on the other hand, has been proven to prolong OS in patients who failed initial therapy and may blunt the side effects of cytotoxic chemotherapy. Further investigation into this possible later-line regimen is certainly warranted given the observation of stable disease from the combination of regorafenib and 5-FU or capecitabine despite progression on prior therapy with either agent alone. Our preclinical experiments support a rationale for the combination with evidence for synergy across a range of various CRC subtypes (KRAS mutant, BRAF mutant, KRAS/BRAF wild-type, MSI), and there is also reduction of prosurvival molecules such as Mcl-1 observed in CRC cells treated with combination (Marks et al., *Cancer Biol. Ther.* 16:1710-1719, 2015).

2 Study objectives

2.1 Primary Objective:

The goal is to investigate PFS at 2 months in mCRC patients who progress on regorafenib monotherapy and are treated with regorafenib and 5-FU/LV combination therapy.

2.2 Secondary objective:

Characterize overall survival time, best overall response, duration of response, and disease control rate in mCRC patients who progress on regorafenib monotherapy and are treated with regorafenib and 5-FU/LV combination therapy. Safety profile of the combination therapy will also be assessed by frequencies and grades of toxcities due to the combination

therapy

3 Study design

This is a single arm open label pilot phase II trial of Regorafenib PO plus 5-FU/LV infusion in 15 mCRC patients who progressed on prior Regorafenib monotherapy as well as 5-FU containing chemotherapy combinations.The study will enroll mCRC patients with prior progression on standard multi-agent combination chemotherapy and progression on regorafenib monotherapy.

All 15 patients will have response evaluation after every 2 cycles on therapy. The study will be terminated and the null hypothesis accepted if none (0) of the first 10 patients are both alive and progression free at 2 months. Alternatively, if one (1) or more of the first 10 patients are alive and progression free an additional 5 patients will be accrued.

There is no randomization in this single arm pilot study. There is no stratification although the study will collect demographic information, prior therapies, location of baseline metastasis (liver, lung, other) and information on genomic analysis of the CRCs including KRAS/NRAS/BRAF/MSI as standard of care.

All patients are expected to have confirmed histologic diagnosis of metastatic colorectal cancer. Response assessment (radiologic tumor assessment) by RECISTv1.1 criteria will be done after every 2 cycles (8 weeks) while patients are on study. Tumor marker analysis (CEA, CA19.9) will be performed at the time of screening. For patients with elevated levels at screening, analysis will be performed every 2 weeks while the patients are on study.

The dose of Regorafenib is 160 mg PO daily D1-D21 of 28-day cycle or last tolerated dose while on Regorafenib monotherapy. 5-FU dose D1 and D15 is 400 mg/m^2 over 10 mins, Leucovorin 400 mg/m^2 over 30 min, 5-FU 2400 mg/m^2 IV infusion over 46 hours (or last tolerated dose of infusional 5-FU).

4 Patient Selection Inclusion & Exclusion

4.1 Inclusion criteria

4.1.1 mCRC with prior progression on standard multi-agent combination chemotherapy and regorafenib as a standard approved monotherapy. Progression on prior regorafenib is required for inclusion in this clinical study. Prior regimens may include FOLFOX -/+ bevacizumab, FOLFIRI -/+ bevacizumab or -/+ cetuximab (if KRAS wild-type) or panitumumab (if KRAS wilt-type). Other prior regimens may include 5-FU or capecitabine -/+ bevacizumab, irinotecan -/+ cetuximab or panitumumab, FOLFIRI -/+ ziv-aflibercept or ramicirumab.

4.1.2 Patients treated with oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy. Patients who

progress more than 6 months after completion of oxaliplatin containing adjuvant treatment must be retreated. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be allowed in the study.

4.1.3 Patients previously treated with regorafenib, lonsurf or capecitabine as the last prior regimen can start on this study as long as there is at least 1 week of period between the last dose of previous treatment and day 1 in this study provded the patients are eligible. Patients who were on FOLFOX or FOLFIRI regimens must have at least 2 weeks period between the last dose and the first dose in this clinical study. Patients previously treated with Avastin, Zaltrap, cetuximab, pembrolizumab, panitumumab, nivolumab Erbitux, and Vectibix must have at least 4 weeks period between the last dose of previous chemotherapy and the first dose in this clinical study.

4.1.4 Measurable metastatic disease that is refractory.

4.1.5 ECOG performance status 0-2.

4.1.6 Patients are included regardless of KRAS/NRAS, BRAF, p53, or MSI status

4.1.7 Age ≥ 18 years.

4.1.8 Life expectancy of at least 8 weeks (2 months).

4.1.9 Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

4.1.10 Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements:

- Total bilirubin ≤ 1.5 x the upper limits 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)
- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine ≤ 1.5 x the ULN
- International normalized ratio (INR)/ Partial thromboplastin time (PTT) ≤ 1.5 x ULN, unless patient is on therapeutic anticoagulation
- Platelet count > 100000 /mm^3, hemoglobin (Hb) > 9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm^3. Blood transfusion to meet the

inclusion criteria will not be allowed.

4.1.11 Subject must be able to swallow and retain oral medication.

4.1.12 Up to 5 of the 15 patients will be allowed to have had other approved or investigational drugs ***after*** prior progression of Regorafenib monotherapy. (all patients enrolled in this trial must have had prior progression on regorafenib therapy). This may include TAS102, off-label therapy that may have been prescribed based on tumor genomic profiling or any investigational agents on a clinical trial.

4.1.13 No more than grade 2 toxicity with last previous cycle of regorafenib mono therapy.

4.2 Exclusion criteria

4.2.1 Patients receiving any concurrent investigational agents

4.2.2 Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.

4.2.3 Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.

4.2.4 Active or clinically significant cardiac disease including:

- Congestive heart failure – New York Heart Association (NYHA) > Class II.
- Active coronary artery disease.
- Suspected Long QT syndrome defined as QTc interval > 500 milliseconds at baseline.
- Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
- Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.

4.2.5 Evidence or history of bleeding diathesis or coagulopathy.

4.2.6 Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.

4.2.7 Subjects diagnosed with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 3 months of start of study treatment.

4.2.8 Patients with any previously untreated or concurrent cancer that is distinct

in primary site or histology except cervical cancer in-situ, treated ductal carcinoma in situ of the breast, curatively treated nonmelanoma skin carcinoma, noninvasive aerodigestive neoplasms, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed; all cancer treatments must be completed at least 3 years prior to registration.

4.2.9 Patients with phaeochromocytoma.

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

4.2.11 Ongoing infection > Grade 2 NCI-CTCAE v4.0.

4.2.12 Symptomatic metastatic brain or meningeal tumors.

4.2.13 Presence of a non-healing wound, non-healing ulcer, or bone fracture.

4.2.14 Major surgical procedure or significant traumatic injury within 28 days before start of study medication

4.2.15 Renal failure requiring hemo-or peritoneal dialysis.

4.2.16 Dehydration Grade ≥1 NCI-CTCAE v4.0.

4.2.17 Patients with seizure disorder requiring medication.

4.2.18 Persistent proteinuria ≥ Grade 3 per NCI-CTCAE v4.0 (> 3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample).

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

4.2.20 Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).

4.2.21 History of organ allograft (including corneal transplant).

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

4.2.23 Any malabsorption condition.

4.2.24 Women who are pregnant or breast-feeding.

4.2.25 Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.

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

4.3 Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Pregnancy

Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment, and for at least 3 months after the completion of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have a negative pregnancy test within *72 hours* prior to receiving the first dose of the investigational agent(s). If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

4.5 Patient Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional

registration questions, please email **FCCC.MONITOR@fccc.edu** or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5 Treatment Plan

5.1 Treatments to be administered

Agent	Dose	Route	Schedule	Cycle Length
Regorafenib	160 mg **Or** last tolerated dose while on Regorafenib monotherapy (last tolerated dose has to be either 40, 80, 120 or 160 mg to be included in the trial)	PO	D1-D21, daily	4 weeks (28 days)
5-FU	400 mg/m^2 bolus over 10 mins followed by 2400 mg/m^2 continuous infusion over 46 hours **Or** last tolerated dose of infusional 5-FU	IV	D1 and D15 of each cycle	
Leucovorin	400 mg/m^2 over 30 mins **Or** last tolerated dose of leucovorin	IV	D1 and D15 of each cycle	

5.2 Regorafenib

Four 40-mg regorafenib tablets should be taken in the once a day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30%) fat meal. 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.

5.3 Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

5.3.1 Excluded therapies and medications

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than the study treatment.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study treatment.
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy.
- Bone marrow transplant or stem cell rescue.
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cycloosporin, and digoxin). Warfarin is metabolized by the cytocrome enzyme CYP2C9 and it's levels may be especially affected by regorafenib

5.3.2 Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (**including contrast media**) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

Co-administration of a strong CYP3A4 inducer (rifampin) with a single 160 mg dose of regorafenib decreased the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. **Avoid concomitant use of regorafenib with strong CYP3A4 inducers** (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort)

Co administration of a strong CYP3A4 inhibitor (ketoconazole) with a single 160mg dose of regorafenib increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. **Avoid concomitant use of regorafenib with strong inhibitors of CYP3A4 activity** (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

5.3.3 Permitted concomitant therapy:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates or danusumab
- Therapeutic or prophylactic anticoagulation

  Subjects who are treated with an agent such as warfarin or heparin require close monitoring (day 1 and day 15 of each cycle) of their INR/PTT. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

- A standard antiemetic regimen for the prophylaxis of acute emesis is recommended on the day of chemotherapy at least 30 minutes prior to the administration of chemotherapy. Such a regimen may include a serotonin ($5\text{-}HT_3$) antagonist (e.g. granisetron or ondansetron) with or without a corticosteroid (e.g. dexamethasone). The investigators should also consider providing subjects with a standard antiemetic regimen for treatment of delayed or breakthrough emesis as needed.

5.4 Duration of Therapy

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Disease Progression
- Pregnancy. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans or MRI or bone scans while pregnant)
- If, in the investigator's opinion, continuation of the trial would be harmful to the

subject's well-being.

- Subject is lost to follow-up.
- Death.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to regorafenib or 5-FU (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

5.5 Duration of Follow-up

Safety follow-up will be performed 30 days (+/-3 days) after discontinuation from the study. Patients removed from the study for unacceptable toxicity would move into safety follow-up and would be followed 30 days (+/-3 days) after discontinuation or until resolution or stabilization of the adverse events, whichever occurs last.

Survival follow-up: For patients who discontinued the study for reasons other than disease progresson, radiologic tumor evaluation must be done every 6 to 9 weeks. Patients will be followed-up every every 3 months for 2 years, every 6 months for next 2 years and annually until death. Telephone call is appropriate if patient is unable to be seen in clinic for survival follow-up.

6 Dose Modifications

The starting dose of regorafenib is 160 mg once daily or the last tolerated dose of regorafenib monotherapy. Study medication will be administered on a 3 weeks on/1week off schedule (3 weeks out of every 4). The strating dose of 5FU is 2400mg/m^2 or the last tolerated dose of 5-FU

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

The modifications of regorafenib and 5FU will follow the following predefined dose levels*:				
	Regorafenib		5-FU	Leucovorin
Dose level 0	160 mg po daily	Four 40-mg tablets of regorafenib	2400mg/m^2	400mg/m^2
Dose level - 1	120 mg po daily	Three 40-mg tablets of regorafenib	No bolus administration and 1920mg/m^2	320 mg/m^2
Dose level - 2	80 mg po daily	Two 40-mg tablets of regorafenib	No bolus administration 1536mg/m^2	256 mg/m^2
Dose level -3	40mg po daily	One 40-mg tablets of regorafenib	No bolus administration 1229 mg/m^2	205 mg/m^2

* except for those starting at the last tolerated dose.

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.

If more than 3 dose reductions are required for subjects starting at 160 mg po daily of regorafenib, 400mg/m^2 of leucovorin and 2400mg/m^2 of 5FU, subjects would come off protocol therapy. For patients who start at 120mg po daily dose two dose reduction are allowed. For patients who start at 80mg po daily dose one dose reduction is allowed while patients who start at 40mg po daily, no dose reduction is allowed. If a dose reduction has been performed, dose re-escalation can be considered (up to the maximal 160 mg daily dose for regorafenib, 400mg/m^2 of leucovorin and 2400mg/m^2 for 5FU) at the discretion of the treating physician provided that the toxicity(ies) has resolved to baseline.

Similar to regorafenib patients will start 5FU and leucovorin at the last tolerated dose level. Patients who start treatment at 2400mg/m^2 of 5FU and 400mg/m^2 of leuvovorin, 3 dose reductions will be allowed as shown in the table above. Patients who start at dose lower than 2400mg/m^2 of 5FU and 400mg/m^2 of leuvovorin, their dose would be reduced by 20% from the last dose for every dose reduction. If dose reductions are required beyond dose level -3, the patient will be off-treatment.

The exact combination of administered dose may depend upon the last tolerated dose. For example it is possible that a patient would start on 80mg po daily regorafenib dose, 400mg/m^2 of leucovorin and 2400mg/m^2 of 5FU if these were the last tolerated doses. If a dose reduction is required in this case 5 FU and leucovorin will be reduced by 20% (1920mg/m^2 ; 320mg/m^2 respectively), and regorafenib will be reduced to 40mg po daily. If further dose reduction is required this patient will be off-treatment unless treating

physician thinks that the toxicity can be alleviated by just reducing the 5FU and leucovorin dose. Similarly when the lowest allowed dose in the study, which is 40mg daily for regorafenib, 205mg/m^2 for leucovorin and 1229mg/m^2 for 5-FU is reached for one drug while the lowest allowed dose for the other drugs is not reached and further dose reduction is warranted, patient will be off-treatment unless the treating physician thinks that the toxicity can be alleviated by reducing the dose of the drug that has not reached the lowest dose level. Maximum 3 dose reductions are allowed for both the drugs. If a third dose reduction is needed the patient will be off-treatment

When treatment is delayed due to toxicities both drugs will be held and the treatment will be restarted with appropriate dose modification of both drugs.

6.1 Specific Toxicities and Modifications

The following tables outline dose adjustments for toxicities related to study drug except hand-foot skin reaction, hypertension and liver function test abnormalities.

Hematological toxicities will be addressed through standard dose modifications for 5-FU at the investigator's discretion. At the beginning of any cycle, treatment will be delayed for ANC < 1000, platelet count < 75,000, or Hgb < 7.0. A 20% reduction in 5-FU dose will be done for grade 3 toxicity.

6.1.1 The table below outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except HFSR and hypertension.

Table 6-1: 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	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, 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.

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.

6.1.2 Grading for Hand-Foot-Skin-Reaction

Table 6-2: Grading for Hand-Foot-Skin-Reaction

	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndromea	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.

6.1.3 Suggested regorafenib dermatologic toxicity modification

Table 6.3 Recommended dose modification for hand-foot-skin 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, c]

	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, treat at reduced dose level [b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. [c] 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 permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
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.

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

Recommended prevention/management strategies for skin toxicities consistent with HFSR 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

- Non-urea based creams may be applied liberally.
- Keratolytic creams (e.g. urea-based creams, salicylic acid 6%) may be used sparingly and only to affected (hyperkeratotic) areas.
- Alpha hydroxyl acids (AHA) based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.

- Topical analgesics (e.g. lidocaine 2%) are to be considered for pain control.
- Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 HFSR. Avoid systemic steroids.

Tender areas should be protected as follows:

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g. silicon, gel)
- Foot soaks with tepid water and Epson salts

6.1.4 Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at least weekly at the study site during the first 6 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, Table 6-4 outlines suggested dose reductions.

Table 6-4: Management of Treatment-Emergent Hypertension

Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**
1 Prehypertension (systolic BP 120 - 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.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (eg, 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 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.		

6.1.5 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 6-5 should be followed.

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

Table 6.5: Dose Modification/interruption for alanine aminotransferase and/or aspartate aminotransferase increases related to study drug

Increases in ASL/ALT (per NCI-CTCAE v 4.0)	1st Occurrence	Restart	Recurrence
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 >	Interrupt dosing, with	If the potential	Discontinue

5 X ULN (> Grade 3)	weekly monitoring until transaminases return to < 3 X ULN or baseline.	benefit of reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level and measure serum transaminases weekly for at least 4 weeks.	
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 transaminases weekly until resolution. Exception: subjects with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		

6.1.6 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. 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.

7 Study Agent Information

7.1 Regorafenib

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

7.2 5FU

5FU is a commercially availabile drug and will be procured as such by FCCC. See 5-FU package insert for most up-to-date information on 5FU.

7.3 Destruction and Return of Regorafenib

At the end of the study, unused supplies of regorafenib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer. Patient returned study medication may be destroyed on site, as per institutional SOPs after documentation on the drug accountability document. Expired study medication may be destroyed on site, as per institution SOPs, during the study. A completed "Unused Study Drug Disposition Form Destruction or Return Confirmation" should be sent to Bayer at the following address:

E-mail: Karen.marini@bayer.com
OR
Mail: (VP of Medical Affairs named in contract) at
Bayer HealthCare Pharmaceuticals
100 Bayer Boulevard
Whippany, NJ 07981

7.4 Records to be kept at Site; Dispensing and Accountability

It is the responsibility of the Site Principal Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

8 Study Calendar

		Cycle 1				Cycle 2[k]						
	Screening (within -28 days of C1D1)	D1[l]	D8	D15	D22	D1	D8	D15	D22	End of Treatment	Saftey follow-up[i]	Survival Follow Up[f]
Regorafenib (Days 1-21 of each cycle)		----------X----------				----------X----------						
5-FU/LV (Q2 weeks)		X		X		X		X				
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds	X	X----------X								X	X	
Physical exam[d]	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[c,d]	X	X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight[d]	X	X	X	X	X	X	X	X	X	X	X	
ECOG[d]	X	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts[d]	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[a,d]	X	X	X	X	X	X	X	X	X	X	X	
INR/PTT[d]	X	X		X		X		X		X	X	
Urinalysis[d,g]	X	X		X		X		X		X	X	
EKG	X											
CEA & CA 19-9[e]	X	X		X		X		X		X	X	
AE evaluation	X	X----------X								X	X	
Radiologic evaluation	X	Radiologic measurements should be performed after every 2 cycles (8 weeks, +/- 1 week). It could be scheduled for the first day of the next cycle but must be done before the drugs administration. Documentation (radiologic) must be provided for patients removed from study for progressive disease.										X[J]
β-HCG[b]	X											
Overall Survival												X

FOOTNOTES

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus,potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
b: Serum pregnancy test (women of childbearing potential only) must be performed 72 hours prior to beginning therapy.
c: Vital Signs: Heart Rate, Blood Pressure, Respiration rate, Temperature.
d: After cycle 2, these assessments will be performed at D1 and Day15 of every cycle.
e: if CEA and CA 19-9 are elevated at screening, CEA and CA 19-9 will be performed every 2 weeks.
f: Follow every 3 months for 2 years, every 6 months for next 2 years and annually until death. Telephone call is appropriate if patient is unable to be seen in clinic.
g: Color and appearance, pH and specific gravity, bilirubin, glucose, ketones, leukocytes, Nitrite, Occult blood, Protein, Urobilinogen
h: AE evaluation beyond cycle 2 will be only on day 1 and day 15 of every cycle.
i. 30 days after the End of treatment
j. every 6-9 week until disease progression.
k. Beyond cycle 2 cycles will be repeated as per cycle 2 schedules until end of treatment. Beyond cycle 2 labs would not be performed on day 8 and day 22 and no visit is necessary.
l. Each scheduled visit has a window of +/-1 week

9 Adverse Events

9.1 Definitions

Adverse Events (AE) are any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011).* All AEs including those due to due to regorafenib and 5FU will be recorded.

Serious Adverse Event (SAE) is an AE that results in the following outcomes-

- Death
- Life threatening adverse event
- Requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours),
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Congenital anomaly/ birth defect.

A **"life-threatening**" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

NOTE: Important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes.

9.1.1 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

9.1.2 Attribution/Relationship to regorafenib and 5FU

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

9.1.3 Expectedness

An **Expected Adverse Event** is one where the specificity or severity is consistent with the current information available from the resources.

An **Unexpected Adverse Event** is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subject (s) predisposing risk factor profile for the adverse event.

9.2 Recording and Reporting Responsibilities

9.2.1 Investigative Site Recording Responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to regorafenib and 5FU, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.
3. The attribution and expectedness must be recorded on the MedWatch form. If this information is not available at the time of initial reporting, a final report must be documented with attribution and expectedness. It may be necessary to submit follow up reports to the Sponsor should the event require further investigation. All subsequent SAEs must be recorded for up to 30 days after the last treatment.

9.2.2 Investigative Site Reporting Responsibilities:

1. The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the sponsor within 24 hours of becoming aware of the event. All subsequent SAEs must be reported for up to 30 days after the last treatment.

   Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent by email to **SAE.FCCC@fccc.edu.**

2. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the ISRU, draft revisions will be made in track changes and submitted to the ISRU for consideration. Any consent revisions must receive ISRU approval **prior** to submission to the IRB.

3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor-Investigator

4. If the results of an investigator or ISRU investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

5. Investigative site should report Reportable New Information (RNI) to their local IRB. This information should also be sent to ISRU. Unexpected events during the clinical study that are considered to be reportable should be reported to IRB as RNI. Serious unexpected events that are associated with the treatment are considered to be reportable. Expected AEs that are experienced multiple times such that the frequency or severity of the AEs are more than expected in the patient population according to the investigator brochure are considered to be reportable.
6. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

Participating sites should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

9.2.3 Sponsor Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
    a. Unexpected (in terms of nature, severity, or frequency) given
        i. (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
        ii. (b) the characteristics of the subject population being studied;
    b. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
    c. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.
3. All participating sites must be notified of all amendments approved by FCCC IRB; or if the study is suspended such that the participating sites cannot accrue patients in the study until further notification.
4. All participating sites must be notified when the study is closed by IRB.
5. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.
6. SAEs in this study are not reportable to FDA but will be collected by ISRU in MedWatch3500a form for Data safety
7. Reportable New Information: Unexpected events during the clinical study that are considered to be reportable should be reported to IRB as RNI. Serious unexpected events that are associated with the treatment are considered to be reportable. Expected AEs that are experienced multiple times such that the frequency or severity of the AEs are more than expected in the patient population according to the investigator brochure are considered to be reportable. All participating sites should be made aware of any RNI.

9.2.4 OCR Reporting Responsibilities to Bayer:

The following will be reported to BAYER by fax and/or email within 24 hours of becoming aware of any Serious Adverse Reactions with a potential relationship to Regorafenib.

(1) any other relevant safety information including but not limited to:

a. reports of drug exposure via mother / father with and without adverse events (exposure during conception, pregnancy, childbirth and breastfeeding) including their outcome;

b. if linked to a serious adverse event, reports of misuse, abuse, overdose , medication error and other uses outside what is foreseen in the protocol, drug dependency, occupational exposure, suspected transmission of an infectious agent, withdrawal syndrome, drug interactions with respect to the STUDY DRUG;

(2) any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports / 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 (e.g. reportable non-serious cases);

9.2.5 Expedited Reporting of Other Safety Information:

The Investigator/ Sponsor shall report to Bayer within 24 hours of the investigator's awareness of other events such as:

- 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;

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform Bayer and record the cause of death in detail within 24 hours.

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

Facsimile:	(973) 709-2185
Address: **Mail only**	Global Pharmacovigilance - USA Bayer HealthCare P.O. Box 915 Whippany, NJ 07981-0915
Address: **FDX or UPS only**	100 Bayer Blvd., Whippany, NJ 07981 67 Whippany Road, Whippany NJ 07981 for UPS

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

Phone:	1-888-842-2937

9.3 Pregnancy

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

The outcome of any pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

In the event of a confirmed pregnancy in a patient participating in the study, the site Investigator must immediately notify the Fox Chase Cancer Center Study Monitor who will notify Dr. Vijayvergia.

10 Measures of Effect

For the purposes of this study, patients should be re-evaluated for response after every 2 cycles. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1 Definitions

Evaluable for adverse events: All patients who received any on-study treatment with Regorafenib and 5-FU/LV will be evaluable for adverse events from the time of their first treatment with Regorafenib and 5-FU/LV.

Evaluable for objective or best overall response: Only those patients who have measurable disease present at baseline, have received any on-study treatment with Regorafenib and 5-FU/LV, and have had their disease re-evaluated will be considered evaluable for response.

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, received any on-study treatment with Regorafenib and 5-FU/LV, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline, during study treatment and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It

may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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. MRI is also acceptable in certain situations (e.g. for body scans).

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

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

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.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD /not evaluated	No	PR	
SD	Non-CR/Non-PD /not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

10.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met

for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11 Statistical Considerations

11.1 Study Design/Endpoints

We will conduct a single-arm, Simon's optimal two-stage phase II clinical trial, two-stage phase II clinical trial to evaluate the efficacy of the combination therapy in patients who progressed on prior Regorafenib monotherapy as well as 5-FU containing chemotherapy combinations. The primary outcome variable is progress-free survival at two months or greater. The treatment will be of no interest if the proportion of patients who are both alive and progression free at 2 months (p) is less than 5% (the null hypothesis). Alternatively, the combination therapy will be of interest if the proportion of patients who are alive and progression free at 2months is at least 30%. Fifteen patients would be needed to test the null hypothesis at the 3.6% level of significance with 87% power.

The study will be terminated and the null hypothesis is accepted if none (0) of the first 10 patients are alive and progression free at 2 months. Alternatively, an additional 5 patients will be accrued if one (1) or more of the first 10 patients are alive and progression free after 2 months on the combination therapy. Accrual will pause after 10 patients are enrolled for interim analysis unless the criteria for accruing next 5 patients is already met.The probability of early stopping under the null hypothesis is 60% and there is a 2.8% chance of early stopping in error. If the trial progresses until 15 patients are evaluated and 3 or more patients are alive and progression free at 2 months, then the null hypothesis will be rejected and the combination therapy deemed worthy of further consideration.

We have established rules to terminate study accrual in the case of an excess number of patients with a severe drug related toxicity (SDRT) using the methods of Ivanova et al. (2005). We anticipate that the true probability of a patient experiencing at least one SDRT will not exceed 30%. SDRT will be defined as any grade 3 or 4 drug related toxicity that is not resolved within 30 days such that the patient cannot be treated during this time due to the toxicity. Accrual will be halted if the number of observed patients with SDRTs is equal to, or exceeds, S_n out of n patients (see table 11.1). The chance of early study suspension is 64% if the true SDRT probability is 50% and 14.0% if it is 30%.The probability of early study termination under several true SDRT probabilities is presented in Table 11.2.

Table 11.1. Stopping rules for Toxicity												
Number of Patients, *n*	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, S*n*	3	4	4	4	5	5	6	6	6	7	7	8

Table 11.2. Probability of study termination due to excess toxicity under a number of scenarios.	
True Severe Toxicity Probability	Probability of early stopping
0.30	0.14
0.50	0.64
0.70	0.97

In secondary analyses we will use standard descriptive statistics (e.g., means, medians, frequencies, proportions and 95% confidence intervals) to characterize best overall response (BOR) and disease control rate (CR, PR or stable disease at two-months). Kaplan-Meier methods will be used to analyze progression free survival time, overall survival time, and duration of response. Toxicity data will be compiled in frequency tables by cateogory and grade to evaluate the safety profile of the combination therapy.

11.2 Sample Size/Accrual Rate

The study will enroll 15 patients. It is expected to enroll 1 patient per 2 months.

11.3 Stratification Factors

There is no stratification although demographic information will be collected.

11.4 Analysis of Secondary Endpoints

Samples will be collected as indicated above

11.5 Reporting and Exclusions

11.5.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Regorafenib and 5-FU/LV.

11.5.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there

are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

Evaluable for adverse events: All patients who received any on-study treatment with Regorafenib and 5-FU/LV will be evaluable for adverse events from the time of their first treatment with Regorafenib and 5-FU/LV.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received any on-study treatment with Regorafenib and 5-FU/LV, and have had their disease re-evaluated will be considered evaluable for response. The best overall response (BOR) is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, received any on-study treatment with Regorafenib and 5-FU/LV, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Evaluable for primary efficacy analyses: Patients who (1) were evaluable for objective response, and (2) either had had their disease re-evaluated at the two month follow-up or died or progressed before two months will be included in the primary efficacy analysis for PFS. Individuals who are lost to follow-up before two months and were alive and progression-free at last observation will be considered failures.

11.6 Planned interim analyses

Interim monitoring will be performed. The study will be terminated if none (0) of the first 10 patients are both alive and progression free at 2 months on the combination therapy.

Stopping rules for excess toxicity are described in section 12.1.

12 Data and Safety Monitoring Plan

12.1 Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor-Investigator who will review the data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor-Investigator as applicable.

12.2 Data Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed by the Fox Chase Cancer Center Data & Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the Sponsor-Investigator. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data & Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

12.3 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

12.4 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit

The ISRU is responsible for compiling and submitting data to the Sponsor-Investigator and statistician on an ongoing basis for monitoring as described in the DSMP and reporting to the Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

12.5 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

12.6 Study Agents

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

12.7 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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