NCT02466009
Regorafenib in Adults ≥ 65 Years with Metastatic Colorectal Cancer: A Phase II Study

Test drug:	Regorafenib		
Study purpose:	Toxicity in Geriatric Population		
Clinical study phase:	II		
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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Synopsis

Title	Regorafenib in Adults ≥ 65 Years with Metastatic Colorectal Cancer: A Phase II Study
Clinical study phase	Phase II
Primary study objective	To assess grade 3-5 toxicity rates of regorafenib in older adults with implementation of focused education and support initiatives
Indication	Refractory metastatic colorectal cancer (mCRC)
Diagnosis and main criteria for inclusion	1. Histologically or cytologically confirmed colorectal carcinoma 2. Evidence of measurable (by RECIST criteria) metastatic disease 3. Age 65 years or over 4. Progression of disease on previous therapy, deemed not a candidate for further standard therapy by treating oncologist, or patient declines other options 5. ECOG PS 0-1
Study design	Single-arm, open label Phase II study
Type of control	Historical
Number of subjects	60
Plan for statistical analysis	Adverse events will be grouped by system organ class and graded using NCI CTCAE version 4.0. Descriptive statistics for grade 3/4 toxicity rates and all-grade skin (HFS) toxicity will be assessed. Relative dose intensity for regorafenib will be calculated. Based on expected grade 3-4 toxicity rates of 40-50%, a sample size of 60 patients will give approximately 10% margin of error with 95% confidence interval. Secondary outcomes for efficacy will be response rate (RR), progression-free survival (PFS) and overall survival (OS). Kaplan-Meier curves will be used to estimate median PFS and OS.

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List of abbreviations

ADL	Activities of Daily Living
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	*bis in die*, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board

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MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NM	Nano molar
NYHA	New York Heart Association
PD	Progressive Disease
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFS	Progression free survival
PO	*per oris*, oral
PR	Partial Response
PS	Performance Status
PTT	Partial thromboplastin time
QD	*quaque die*, once daily
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

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1. Introduction

Background

More than half of all patients diagnosed with colorectal cancer are above the age of 65. Yet, only about 20% of patients in this age group were enrolled in the clinical trials on which our treatment decisions are based. Furthermore, it is well-established that adverse events and diminished quality of life are more likely to accompany treatment in this age group. This lack of data leads to variations in treatment patterns among older adults making them less likely to receive standard therapies. It is therefore important to design trials specifically for older patients which incorporate tools to measure health status factors that can be used to identify patients most likely to benefit from treatment.

Rationale of the study

Limited evidence exists to guide risks and benefits of the multi-kinase inhibitor, regorafenib, in the older adult. Participants in the Phase III CORRECT trial that led to approval of regorafenib in previously treated mCRC had a median age of 61. The small number of older patients (38 subjects ≥ 75 years of a total n=503) in this study had a disproportionately higher risk of any ≥ grade 3 toxicities (66% for ≥ 75 years vs. 52% for < 65 years). More safety information is needed – especially since many older patients are not candidates for combination cytotoxic chemotherapy and may be candidates for the use of regorafenib earlier in the course of the disease than their younger counterparts.

The management of older colon cancer patients must be tailored to the patient's overall functional status, risk of toxicities and comorbidities. Advanced age alone should not preclude patients from receiving standard anti-cancer therapy and the patient's physiologic age should guide treatment decisions. Tools such as the Comprehensive Geriatric Assessment (CGA) which is incorporated in this study need to be developed to aid the oncologist and patient in the shared decision process of treatment planning.

A special focus of this study will be to provide intensive education and support for preventing and managing skin toxicity (hand-foot syndrome) along with other common toxicities. This will be done according to standard guidelines developed by the sponsor. It is known that the elderly are particularly vulnerable to toxicities and we feel it is important that close and regular monitoring is provided for all participants in the study. Our hope is that this study will serve as a model for use of regorafenib in the geriatric patient population.

This study is timely because the use of combination cytotoxic chemotherapy (FOLFOX or FOLFIRI) versus monotherapy remains an issue of active debate in the management of older patients with metastatic colon cancer. The FOCUS2 trial, the largest randomized clinical trial in older patients with metastatic colon cancer, was recently published. The study randomized older patients with untreated metastatic colon cancer to capecitabine/5-FU with or without oxaliplatin with an initial empiric 20% dose reduction. The addition of oxaliplatin resulted in improved response rates and a trend towards improvement in PFS but no improvement in OS. The rate of grade 3 or higher toxicity was not increased with the addition of oxaliplatin at this lower dose. For now, the benefit of combination chemotherapy for adults ≥ 65 years of age is questionable

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and considered on an individual patient basis. Additional treatment options, such as regorafenib, would be helpful and need to be evaluated carefully in this patient population.

Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI).

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.

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). 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. These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

Clinical Experience

Two 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 had 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

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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 (versus placebo) group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety results from the CORRECT study supported FDA approval in September 2012.

The regorafenib treatment arm in the CORRECT study included 309 patients < 65 years (307 evaluable for safety), 155 patients 65-74 years and 38 patients ≥ 75 years. The OS hazard ratio was 0.72 (95% CI 0.56-0.91) in patients <65 years and 0.86 (95% CI 0.61-1.19) in patients ≥ 65 years. The rate of grade ≥ 3 adverse events was 52% for patients <65 years, 57% for patients 65-74 years and 66% for patients ≥ 75 years. Dose modification was necessary for 76% of patients < 65 years, 73% for patients 65-74 years and 84% for patients ≥ 75 years. This underscores the importance of close monitoring and good supportive care for older patients on regorafenib.

Comprehensive Geriatric Assessment

All participants will undergo an abbreviated cancer-specific comprehensive geriatric assessment (CGA) at baseline, at 4 weeks , and then every 3 months while on study (+/- 7 days). Common assessment instruments in oncology (e.g. Karnofsky performance status) do not address critical geriatric domains that predict morbidity and mortality in the older patient (e.g., functional status, comorbidity and social support). A prospective study of 500 older adults with cancer demonstrated that traditional oncology functional assessment tools could not identify older adults at risk for chemotherapy toxicity. However, a predictive model that includes geriatric assessment questions could identify such individuals.

This validated cancer-specific CGA includes a compilation of reliable and validated tools to assess geriatric domains such as comorbidity, functional status, physical performance, cognitive ability, psychological state, nutrition, medication review and social support. The CGA can detect unsuspected conditions that may affect cancer treatment in more than 50% of older patients. Repetto et al. demonstrated that CGA added information to standard oncology performance measures such as Karnofsky performance score which is a one-item measure of function that was validated in younger patients. CGA has great potential to identify areas of

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vulnerability and interventions that could help improve outcomes (e.g. reducing therapy-related toxicity) in older cancer patients. The initial study of this tool illustrated feasibility as demonstrated by a short mean time to completion of 27 minutes. Furthermore, 90% of patients were satisfied with the questionnaire length, and 78% were able to complete the self-administered portion on their own.

The abbreviated cancer-specific CGA was also found to be feasible for use by the Cancer and Aging Leukemia Group-B (CALGB 360401). Previous clinical studies, including the FOCUS2 trial, have demonstrated that factors within a CGA can better assess toxicities and aid with management decision. Based on these data, therefore, our study will incorporate CGA to assess the relative safety profile of regorafenib in the elderly population. The specific instruments used in our study have been slightly modified from the CGA data published by Hurria et al but address identical geriatric domains of interest. This CGA format is currently used in the SOCARE (Specialized Oncology Care and Research in the Elderly) multi-disciplinary clinic based at the University of Rochester Medical Center that is run by Dr. Supriya Mohile. Staff at all sub-sites will be trained to conduct the CGA in a similar and replicable manner. This training will be overseen by Dr. Mohile and her experienced staff.

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COMPREHENSIVE GERIATRIC ASSESSMENT

DOMAIN	TOOL	SCORE SIGNIFYING IMPAIRMENT
Background Information	➢ Demographics: ➢ Education ➢ Marital status ➢ Living Arrangements ➢ Health status ➢ Employment status ➢ Driving status ➢ Age ➢ Zip code ➢ Gender ➢ Ethnicity ➢ Race ➢ Insurance/health care ➢ Income ➢ Social Services	
Physical function	➢ ADL ➢ IADL ➢ Fall history	➢ Any ADL or IADL impairment ➢ Any history of fall
Objective physical performance	➢ SPPB	➢ ≤ 9
Comorbidity	➢ Average number of comorbid conditions	➢ >5
Nutrition	➢ BMI ➢ MNA	➢ <21 ➢ ≤ 11
Social support	➢ OARS Medical Social Support	➢ Any deficit noted
Polypharmacy	➢ Number of total medications	➢ ≥5 medications
Psychological	➢ GDS	➢ ≥ 5
Cognition	➢ BOMC ➢ Mini Cog	➢ >10 ➢ abnormal
Screening	➢ VES-13	➢ ≥3
Quality of Life	➢ FACT-C ➢ FACT-F ➢ MDASI	

ADL: Activity of daily living
MNA: Mini nutritional assessment
SPPB: Short physical performance battery
BMI: Body mass index
VES: Vulnerable elderly survey
MDASI: MD Anderson Symptom Inventory
GDS: Geriatric Depression scale
IADL: Instrumental activity of daily living
BOMC: Blessed orientation-memory-concentration
FACT-C: Functional Assessment of Cancer Therapy-Colon
FACT-F: Functional Assessment of Cancer Therapy-Fatigue

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2. Study objectives

Primary Objective

- To measure grade 3-5 toxicity of regorafenib in older adults with mCRC with implementation of focused education and support initiatives

Secondary Objectives

- To evaluate efficacy of regorafenib in older adults with mCRC (RR, PFS, DCR and OS)
- To explore association between baseline CGA findings and risk of toxicities
- To explore the association of toxicities with CGA domain changes over time
- To assess patient-reported QOL on regorafenib over time

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4. Study Design

Given 54% grade 3/4 toxicity and required dose modification among 76% of patients in the regorafenib arm (randomized phase III CORRECT trial), we will initiate treatment at a reduced dose of 120mg in this geriatric study population on a similar 3 weeks on/1 week off schedule. Dose escalation to 160mg will be recommended after the first cycle (4 weeks) at the discretion of the treating physician. There is good precedent for starting at reduced doses in similar trials – the FOCUS2 study team utilized 80% starting chemotherapy doses in their study among the elderly with metastatic CRC and dose escalated if tolerated.

Participants will undergo a comprehensive geriatric assessment (CGA) at baseline, at 4 weeks and then every 3 months (+/- 7 days) while on study to assess for any deterioration in geriatric domains (functional status, comorbidities, nutrition, psychological state, social support and cognitive ability). All sites have personnel experienced in performing geriatric assessments and the University of Rochester as the lead site will conduct training to ensure that all sites will conduct the assessments in the same way.

All patients will receive intensive one-on-one education about prevention/management of skin toxicity, diarrhea, fatigue and other toxicities at initiation and follow-up visits (see section 7 & 8 for review of treatment strategies). Starter packs with moisturizing cream (10% urea content), socks and patient-friendly 'Tips for Skin Care' will be distributed. On-treatment visits will occur weekly for first two cycles and every 4 weeks after that. Alternate weekly visits may be substituted with a home nursing visit for BP check and symptom evaluation if it is not feasible for patient to attend clinic visits weekly. Pill adherence diaries will be provided to patients and pill counts will be performed at the end of every cycle.

Restaging CT/MRI scans will be completed every 12 weeks (+/- 7 days) (or sooner if treating oncologists suspects progression of disease based on clinical symptoms). Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (see Appendix A). Subjects will have a Safety Follow-up visit within 30 days after their last dose of study drug or prior to the initiation of another antineoplastic therapy, whichever occurs first. After treatment discontinuation, survival status will be assessed periodically (see Table of Assessments).

5. Study Population / Eligibility/Re-Screening

Re-screening may be allowed. Subjects who are re-screened must be consented as if they were a new patient. If a patient re-screens, they will be assigned a new subject ID when entered into Red Cap.

Inclusion Criteria

- Histologically or cytologically confirmed colorectal adenocarcinoma
- Evidence of measurable (by RECIST criteria) metastatic disease

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- Age 65 years or over
- Progression of disease on standard therapy or deemed not a candidate for further chemotherapy by treating oncologist or patient declines other options.
- ECOG PS 0-1
- Life expectancy of at least 3 months.
- 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.
- Adequate bone marrow, kidney and liver 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- transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer).
    - Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer).
    - Creatinine ≤ 1.5 x the ULN.
    - International normalized ratio (INR)/ Partial thromboplastin time (PTT) ≤ 1.5 x ULN.

    Platelet count ≥ 100000 /mm3, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.
- Subjects (men) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subject must be able to swallow and retain oral medication.

Exclusion Criteria

- Previous treatment with regorafenib.
- Systemic therapy for metastatic CRC within 28 days of initiating study treatment.
- Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.
- Active or clinically significant cardiac disease including:
    - Congestive heart failure – New York Heart Association (NYHA) > Class II.

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  - Active coronary artery disease.
  - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers, calcium channel 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.

- Evidence or history of bleeding diathesis or coagulopathy.
- Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.
- Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of informed consent.
- History of other active malignancy within past 2 years (excluding non-melanoma skin cancer).
- Patients with phaeochromocytoma.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Ongoing infection > Grade 2 NCI-CTCAE v4.0.
- Symptomatic metastatic brain or meningeal tumors.
- Presence of a non-healing wound, non-healing ulcer, or bone fracture.
- Major surgical procedure or significant traumatic injury within 28 days before start of study medication.
- Renal failure requiring hemo- or peritoneal dialysis.
- Dehydration Grade ≥1 NCI-CTCAE v4.0.
- Patients with seizure disorder requiring medication.
- Persistent proteinuria ≥ Grade 3 NCI-CTCAE v4.0 (> 3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample).
- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
- Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).
- History of organ allograft (including corneal transplant).
- Known or suspected allergy or hypersensitivity to the study drug.
- Any malabsorption condition.

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- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

Excluded Therapies and Medications, Previous and Concomitant

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (regorafenib) being used for colon cancer.
- Prior use of regorafenib.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 28 days before start of study medication.
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.

6. Withdrawal of Subjects from Study

Withdrawal

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.
- 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 (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.

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- 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.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, dose levels]) are provided in Section 13. Premature Termination of the Study).

Screen Failures/Withdrawals

A subject who discontinues study participation prematurely for any reason is defined as a "withdrawal" if the subject has already been assigned to treatment or administered at least one dose of study drug.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "withdrawal" (see above) is regarded as a "screen failure".

Replacement

No withdrawn subjects will be replaced.

7. Treatment[s]

Treatments to be administered

All patients will receive regorafenib 120mg daily for 3 weeks on and 1 week off with cycle 1. Dose escalation to 160mg will be permitted after the first cycle at the discretion of the treating physician. Subjects will continue study treatment until disease progression or other reasons for removal from treatment (section6).

Treatment assignment

Regorafenib

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 28 tablets and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F).

The study drug must be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff.

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Study Treatment

The initial screening period is 14 days from the date of consent. Once approved, by the coordinating site, an additional 14 day period is granted for scheduling, in which subjects must start treatment.
Regorafenib will be administered as monotherapy during the study. 120 mg qd (starting dose) will be administered for 3 weeks on /1 week off. One cycle is 28 days. Study treatment must be initiated within 14 days of registration.

Three 40-mg regorafenib tablets (starting dose) should be taken 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.

Dose Modification Levels

The starting dose of regorafenib is 120 mg once daily. Study medication will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4].

Dose escalation to 160mg is recommended after the first cycle (4 weeks) at the discretion of the treating physician.

Doses will be held 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 tables that follow. Doses held for toxicity will not be made up but will be counted as missed doses. Dose modifications will follow predefined dose levels. Sites may also follow their institutional practice for dose modifications. Missed doses are to be omitted rather than made up. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

The modifications of regorafenib will follow the following predefined dose levels:		
Dose level +1	160mg po qd	Four 40-mg tablets of regorafenib
Dose level 0 (starting dose)	120 mg po qd	Three 40-mg tablets of regorafenib
Dose level - 1	80 mg po qd	Two 40-mg tablets of regorafenib
Dose level - 2	40 mg po qd	One 40-mg tablets of regorafenib

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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 a dose reduction has been performed, intra-subject dose re-escalation can be considered (up to the maximal 160 mg daily dose) at the discretion of the treating physician provided that the toxicity(ies) has resolved to baseline.

The following tables outline dose adjustments for toxicities related to study drug other than diarrhea, hand-foot skin reaction, hypertension and liver function test abnormalities. More information on dose reductions for diarrhea, hand-foot skin reaction, hypertension, and liver function test abnormalities follows Table 7-1.

Table 7-1: Recommended dose modification for toxicities except diarrhea, hand-foot-skin reaction, hypertension and ALT/ST/bilirubin

NCI-CTCAE v4.0[a]	Dose Interruption	Dose Modification[b]	Dose for Subsequent Cycles
Grade 0-1	Treat on time	No change	No change
Grade 2[c]	Treat on time	No change	No change
Grade 3	Hold 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	Hold 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 non-clinically significant and asymptomatic laboratory abnormalities.
c. If subject is experiencing multiple grade 2 toxicities, treatment can be interrupted at discretion of treating oncologist until toxicities are ≤ grade 1 and then resumed at reduced dose (by 1 level)
d. If no recovery after a 4 week delay, treatment should be permanently discontinued unless subject is deriving clinical benefit.

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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 in order to minimize the risk of postural hypotension and renal failure.

8. Prevention/Management Strategies for Diarrhea, Hand-Foot Skin Reaction, Hypertension, and Liver Function Test Abnormalities

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 diarrhea can 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.

Hand-Foot Skin Reaction

Table 8-1: 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.

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Table 8-2 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 reinforce supportive measures for symptomatic relief
Grade 2	1st occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[b, c] When resuming treatment, treat at reduced dose level.
	2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[b, c] When resuming treatment, treat at reduced dose level.
	3rd occurrence	Discontinue therapy
Grade 3	1st occurrence	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	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 reinforcement 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.

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- 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

Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured weekly during the first 8 weeks of treatment (either in the office or with nursing services).

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 8-4 outlines suggested dose reductions.

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Table 8-3: 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.		

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Liver Function Abnormalities

For patients with observed worsening of 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 8-5 should be followed.

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

Table 8-4: 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 > 5 X ULN (> Grade 3)	Interrupt dosing, with weekly monitoring until transaminases return to < 3 X ULN or baseline.	If the potential benefit of reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level and measure transaminases weekly for at least 4 weeks.	Discontinue
ALT and/or AST > 20 X ULN (> Grade 4)	Discontinue		
ALT and/or AST > 3 X ULN (> Grade 2) with concurrent bilirubin > 2 X ULN	Discontinue treatment and measure 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.		

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9. University of Rochester [UR] Site Administration

The Wilmot Cancer Institute, Clinical Trials Office at the University of Rochester will serve as the Coordinating Center for this multi-site study. The lead PI of the Coordinating Center is affiliated with the UR and is also the UR enrolling site PI. Both the lead PI and Coordinating Center will assume responsibility for the overall conduct and management of the study, including the following responsibilities:

- Ensure all approval of protocol documents, including model consent forms are distributed to enrolling sites and approved by enrolling site IRBs prior to implementation.
- Maintain a regulatory file for the Coordinating Center and for each enrolling site.
- Monitor subject enrollment and participation.
- Ensure informed consent is obtained from each subject and consent is in compliance with federal, state and local regulations, as well as the study protocol.
- Ensure compliance with the study protocol (including timely reporting of all research events) and data validity and integrity.
- Convey study-related information to enrolling sites, sponsors and study-specific committees, as needed.
- Respond to enrolling site protocol inquires and questions.
- Provide enrolling site staff continued training on the conduct of the study, as necessary.
- Ensure all enrolling sites are notified when enrollment is complete, and all study-related activities are complete.
- Verify each enrolling site closed the study with their IRB.
- Ensure the data set and any stored samples are appropriately de-identified or coded and managed per the study protocol.

Distribution of Study Documents to Enrolling Sites and Obtaining Enrolling Site IRB Approval

Protocol documents (submitted both at the time of initial approval and via amendment) should be submitted and approved by the Coordinating Center's IRB prior to distribution to enrolling sites. Once enrolling sites receive the study documents, they then must submit applications to their respective IRB for approval prior to initiation of the study at their site.

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Any changes to protocol documents requested by the enrolling site and/or their IRB should be reviewed and approved by the Coordinating Center prior to re-submission to the enrolling site's IRB. Any substantive changes to study documents by the enrolling site should be appropriately justified. Every effort should be made to avoid changing the protocol for individual enrolling sites; however, in certain circumstances it may be appropriate for sites to include site-specific addendums in order to comply with their institution's policies and procedures. Editorial changes to the consent form are also generally permissible as long as they do not change the content or intent of the document.

Once the study and/or amendment has been approved by the enrolling site IRB, a copy of the approval notification and all related approved study documents must be provided to the Coordinating Center prior to initiation of the study at the enrolling site.

Study Monitoring & Auditing

All aspects of the study will be monitored closely by the site PI's, the Coordinating Center and the Sponsor. Monitoring will be conducted according to GCP and standard operating procedures for compliance with applicable government regulations. As a participating site, the Investigator grants permission to the Coordinating Center and/or appropriate regulatory authorities to conduct routine remote monitoring and/or on-site monitoring of all appropriate study documentation if requested.

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) can occur at any time during or after completion of the study. The investigator should notify the Coordinating Center immediately of any such inspection.

Documentation of monitoring will be maintained by the Coordinating Center.

Essential Study Documentation

The Coordinating Center will be responsible for maintaining essential documentation for the Coordinating Center as well as for the enrolling sites. These essential documents permit the conduct of the study and demonstrate compliance with the protocol and regulatory requirements. Copies of all regulatory documents from each enrolling site should be scanned and emailed to: Cynthia_Doane@urmc.rochester.edu. The regulatory team at the Coordinating Center will track and monitor these documents.

Examples of these documents include but are not limited to:

- Dated IRB approval notifications for site protocols, informed consent forms, recruitment materials, and case report forms (including initial approvals, amendments and progress reports); include all approved versions;
- Signed clinical trial agreements between all involved parties;
- Signed and dated CVs;

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- Investigational product label samples, handling instructions, shipping records and accountability records;
- All versions of the Investigator's Brochure, if applicable;
- Monitoring reports; and
- Reportable research events.

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Drug logistics and accountability

The drug will be shipped directly to the Investigational Pharmacy at the Coordinating Center, which will in turn dispense the medication to the other enrolling sites.

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

Accountability

The investigator at each site or a responsible party designated by the investigator must maintain a careful record of the inventory and disposition of the agent, including dates and lot numbers of all study drug received. All study drug supplies issued to, used by, and returned by each patient must be recorded using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Destruction and Return

At the end of the study, unused supplies of Regorafenib, opened or unopened should be destroyed according to institutional policies in accordance with the requirements outlined in the study contract ONLY after study drug accountability has been completed and with approval of the study PI. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to the Coordinating Center.

A completed "Unused Study Drug Disposition Form Destruction or Return Confirmation" should be sent to the Coordinating Center. The Coordinating Center will ensure all forms from sites are sent to Bayer at the following address:

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Bayer:
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

UR Coordinating Center Pharmacy Contact:

Noel Forrett, Pharm D
University of Rochester
Cancer Center Pharmacy, Room 1.0773
601 Elmwood Avenue
Rochester, NY 14642
Phone: 585-275-6357
Fax: 585-292-1701
Email: Noel_Forrett@urmc.rochester.edu

Subject information and consent

Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. Voluntary written informed consent must be obtained before registration or performance of any study-related procedure not part of normal medical care.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form.

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The Coordinating Center will first approve consent form/amendment changes through their IRB and once approved, will distribute to enrolling sites. Once these changes have been approved by the enrolling site IRB, a copy of the approval notification and all related approved study documents must be provided to the Coordinating Center prior to use. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form.

Registration and Data handling

All patients will be registered through the Coordinating site, Clinical Trials Office, which is located at the:

James P. Wilmot Cancer Institute
University of Rochester Medical Center
Rochester, NY 14642

Each site will receive access to the study-specific, REDCap database at the University of Rochester.

It is the expectation that all data has source documentation available at the enrolling sites. Site personnel will be responsible for entering their patient data regularly into this database.

At the time of registration, the signed informed consent form and documents that support eligibility should be emailed in pdf format to the data manager, Matt Poquadeck, at the Coordinating Center: matt_poquadeck@urmc.rochester.edu.

The signed consent form and supporting documents can also be faxed to the Coordinating Center at (585) 442-0137. Please inform the data manager by email that the eligibility forms have been faxed.

Any question regarding eligibility or that may arise during the conduct of the study should be addressed to:

Name: Aram Hezel, MD
Email: Aram_Hezel@urmc.rochester.edu
Phone: (585) 275-9484

10. Treatment compliance

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks

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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 strongCYP3A4 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).

Permitted concomitant therapy includes:

- 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

The following are not permitted:

- Other investigational treatment during or within 28 days before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy for colorectal cancer
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. phenytoin, quinidine, carbamazepine, Phenobarbital, cycloosporin, and digoxin).

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- Liver function tests should be obtained before initiation of regorafenib and monitored at least every 2 weeks during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated

Follow-up Period

Follow-up Prior to Progression

- Patients who come off treatment for reasons other than progression of disease will have physical exams performed at least every 3 months or earlier as clinically indicated until the follow-up period is terminated (see Reasons for Follow-up Termination). Frequency of radiographic studies will be at the discretion of the treating physicians.
- After disease progression, follow-up assessments will occur every 6 months and will include subsequent anti-neoplastic therapy and survival status of the patient until the follow-up period is terminated (see Reasons for Follow-up Termination). Physical exams, and all other assessments, are at the discretion of the treating physicians.

Reasons for Follow-up Termination

Patients will remain in the follow-up period until any of the reasons below are satisfied:

- Completion of the study
- Patient death
- Patient withdraws consent from the follow-up period
- Patient is lost-to follow-up

Termination of Follow-up

Patients whose follow-up period terminates should have the final date of contact recorded in the End of Study CRF in REDCap.

- For patients in follow-up at completion of the study, please use the study termination date
- Patients found to be deceased in the follow-up period should have their date of death recorded in the End of Study CRF.
- For patients who withdraw consent from follow-up, use the date the patient withdrew consent. Notify the Coordinating Center's data manager of the patient withdrawal of consent from follow-up, along with supporting documentation, should this occur.
- For patients who meet the criteria to be lost-to follow-up, enter the last date of known contact with the patient, along with comments in the CRF indicating the patient is lost-to follow-up.

Lost-to Follow-up

All efforts should be made to assess the survival status of each patient until the follow-up period is terminated. A patient will be considered lost-to follow-up when 1) the patient is due for a follow-up contact as per the Table of Assessments, and 2) at least 2 attempts to contact the patient have occurred since the follow-up was due. Documentation of these 2 attempts should be sent to the Coordinating Center's data manager (see Registration and Data Handling).

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Timing of assessments

See Table of Assessments

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		Cycle 1				Cycle 2				Cycle 3				Cycle 4						
Study Day [a]	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W[b]	FU Prior to Progression[c]	Safety FU 30 days after last treatment dose	FU After Progression[d]
	STUDY[k]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
REQUIRED STUDIES																				
PHYSICAL																				
History and Physical Exam[e]	X	X	X	X	X	X	X	X	X	X				X				X	X	X
Weight and Performance Status[e]	X	X	X	X	X	X	X	X	X	X				X					X	
Blood Pressure[e]	X	X	X	X	X	X	X	X	X	X				X					X	
Disease Assessment	X													X				X	X	X
Toxicity Evaluation/Support[e]		X	X	X	X	X	X	X	X	X				X					X	
Comprehensive Geriatric Assessment[f]	X				X												X			
Pill count					X				X				X				X			
LABORATORY[L]																				
CBC/Differential	X	X		X		X		X		X				X				X[J]	X	
Comprehensive Metabolic Panel[g]	X	X		X		X		X		X				X				X[J]	X	
- Phosphorus	X	X		X		X		X		X				X				X[J]	X	
INR	X																			
aPTT	X																			
SCANS																				
CT/MRI of Chest[h]	X												X					X		
CT/MRI of Abdomen and Pelvis[h]	X												X					X		
TREATMENT																				
Regorafenib[i]		X	X	X		X	X	X		X	X	X		X	X	X				

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[a] Except for week 1 visit, there is a window of +/- 5 days for subsequent follow up visits.
[b] Patients with stable disease and on protocol treatment beyond cycle 4 will be followed every 4 weeks until disease progression.
[c] Patients off protocol treatment secondary to reasons other than progression will have physical exams performed at least every 3 months or earlier as clinically indicated until closure of the study. Frequency of radiographic studies will be determined by the treating physicians.
[d] After disease progression subsequent anti-neoplastic therapy and survival status will be assessed every 6 months for the remainder of the study or until death.
[e] Alternate weekly visits may be substituted with a home visit or phone call for BP check and symptom evaluation if it is not feasible for patients to attend clinic visits weekly.
[f] Comprehensive geriatric assessment (CGA) will be performed at baseline, at 4 weeks, and then every 12 weeks during the study protocol (+/- 7 days). The baseline CGA can be performed at the week 1 visit prior to dispensing Regorafenib. These questionnaires can be completed at the study visit or given to the patient to take home, complete, and send back, or mailed to the patient to be completed prior to the next visit.
[g] CMP to include Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Blood Urea Nitrogen (BUN), Creatinine (Cr), Glucose, Calcium (Ca), Magnesium (Mg), Total Protein, Albumin, Alkaline Phosphatase, Total Bilirubin, Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST).
[h] Pre-study imaging must have been completed within 30 days prior to registration. Restaging imaging will be performed every 12 weeks (+/- 7 days) when patients are on protocol treatment until disease progression and is defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
[i] Treatment will be given 3 weeks on/1 week off and will continue until disease progression or other reason for discontinuation of protocol treatment.
[J] Lab work is required every 4 weeks after cycle 4 as long as patient remains on study
[k] Initial screening period is 14 days from the date of consent. Once approved, by the coordinating site, an additional 14 day period is granted for scheduling, in which subjects must start treatment [L] Pre study labs can be used for week 1.

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Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication.
- Started before signing of the informed consent.
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 11 (Definitions).

Efficacy

Efficacy variables to be measured include response rate (RR), progression-free survival (PFS), disease control rate (DCR) and overall survival (OS).

Response rate (RR) is defined as the percentage of subjects with a partial response (PR) or complete response (CR) as defined by RECIST criteria (see Appendix A). PFS will be measured from the date of randomization until disease progression or death from any cause. DCR will be the rate of CR, PR and stable disease (SD) combined together. OS will be measured from the date of randomization until death from any cause.

11. Safety

All subjects who receive at least one dose of study treatment will be valid for the safety analysis.

All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation) and changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature).

All AEs whether considered drug-related or not, will be reported in with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

Adverse events

Investigators should refer to the Safety Information section of the current IB for regorafenib, including the DCSI (development core safety information), for the expected side effects of regorafenib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

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Therapeutic monitoring should be performed following dose selection or modification of regorafenib, in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.

All concomitant medications must be recorded in the subject's source documentation.

Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE if worsens compared to baseline).

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

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

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c. Requires inpatient hospitalization or prolongation of existing hospitalization.

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours.
- The admission is pre-planned.
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE.
  (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another medically important serious event as judged by the investigator.

Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 11 (Definitions).

Intensity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

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CTCAEv4 Grade 5: death due to an AE.

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no".

An assessment of "no" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

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- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable

Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

Assessments and documentation of adverse events

Adverse events and grade will be recorded at each follow-up visit. Serious adverse events will be collected and reported from the time patient signs informed consent until the End of Treatment safety follow-up visit. Non-serious adverse events will be collected from the time of first study drug dosing until the End of Treatment safety follow-up visit.

Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 11(Definitions).

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to the Coordinating Center within 24 hours. The Coordinating Center will then inform the DSMC and Bayer and will report to the RSRB using

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the "reportable event" form in the ROSS system. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

Non-reportable research events across all sites (including UR site) will be submitted in summary at the time of the Coordinating Center's Continuing Review.

The Investigator may report serious adverse drug reactions (SADRs) using either:

An ADEERS form (Adverse Event Expedited Reporting System) available at
http://ctep.cancer.gov/reporting/adeers.html

OR

A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

UR Coordinating Center

Electronic Mailbox:	Matt_Poquadeck@urmc.rochester.edu
Facsimile:	(585) 442-0137
Address -- Mail only:	Matt Poquadeck University of Rochester Wilmot Cancer Institute Clinical Trials Office 601 Elmwood Ave, Box 704 Rochester, NY 14642

The Coordinating Center will ensure that all reports are then passed on to Bayer. All reports shall be sent electronically to:

Bayer

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address -- Mail only:	Global Pharmacovigilance - USA Bayer HealthCare Pharmaceuticals Inc. P.O. Box 915 Whippany, NJ 07981-0915
Address – FDX or UPS only:	100 Bayer Boulevard, Whippany, NJ 07981

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone:	1-888-842-2937

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Expected adverse events

Overview listings of frequent adverse events are shown in the most current version of the investigator's brochure (IB) / summary of product characteristics.

If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the Coordinating Center and Bayer according to the applicable reference document and according to all local regulations.

Adverse events of special safety interest

As with any new chemical entity, there is always potential for unexpected adverse events, including hypersensitivity reactions.

Based on data studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify the Coordinating Center as outlined in Section 11 (Reporting of Serious Adverse Events).

Reportable adverse events include:

- Acute renal failure (NCI-CTCAE version 4.0 ≥ grade 3) or severe proteinuria (NCI-CTCAE version 4.0 ≥ grade 3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (NCI-CTCAE version 4.0 ≥ grade 3)
- Stevens-Johnson Syndrome and erythema multiforme
- Hepatic failure
- Reversible posterior leukoencephalopathy syndrome
- Gastrointestinal perforation or fistula

Pregnancies

The investigator must report to the Coordinating Center any pregnancy occurring in a study subject's partner during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

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.

The MedWatch form should be used to submit this information and is available at http://www.fda.gov/medwatch/

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Further safety

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform the Coordinating Center and will record the cause of death in detail (using the SAE Form) within 24 hours.

Appropriateness of procedures / measurements

The assessments described in the previous sections are widely used and generally recognized as reliable, accurate, and relevant for determining the safety and efficacy of therapies in this disease.

Safety Analyses

The Data Safety Monitoring Committee (DSMC) at the James P. Wilmot Cancer of the University of Rochester will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the investigators and study team.

The DSMC will provide oversight of study progress and safety by review of accrual and adverse event data at semi-annual meetings or more frequently if concerns arise. Any adverse effects requiring expedited review per protocol will be submitted to the chair of this committee for determination as to whether further action is required. This committee will meet after 6 patients have been enrolled and received at least one cycle of therapy. If >3 of these first 6 patients have delays in treatment administration due to toxicity, accrual will be held pending review and discussion with the investigators.

The study team will record and monitor adverse event rates utilizing the University of Rochester Cancer Center Clinical Trial database. If the study has two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review a summary of SAEs, discuss events with study investigators and conduct a detailed review. The DSMC will determine if further action is required. A copy of the DSMC reports will always be sent to all participating sites for review and submission to their local IRB.

12. Statistical Methods and Determination of Sample Size

Statistical and analytical plans

The primary end-point is grade 3-5 toxicity incidence rates. Adverse events will be grouped by system organ class and graded using NCI CTCAE version 4.0. Descriptive statistics (counts and percentages) for grade 3 and 4 toxicity rates and all-grade skin toxicity will be assessed and evaluated in relation to CGA domains.

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Relative dose intensity (dose reductions, dose delays, or inability to tolerate treatment) for regorafenib will be calculated. Specific toxicities associated with dose reductions, delays and/or early discontinuation of treatment course will be identified.

Efficacy outcomes will be response rate (RR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Best response will be classified per RECIST criteria into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Disease control will be the combination of CR + PR + SD. Kaplan-Meier survival curves will be used to estimate median PFS and OS. All statistical tests will be conducted using SAS version 9.2 (SAS Institute Inc).

Analysis of CGA results will be descriptive and will describe mean, median and standard deviations of scores at baseline and at follow up time points. CGA deficits will be captured at baseline and follow up time points. Each domain will be evaluated individually and scores will be compared between baseline and follow up time points. Overall CGA deficits will be examined and proportion of patients who decline in more than 1 domain will be determined for each time point.

Determination of sample size

Based on data from the CORRECT trial, an anticipated grade 3-4 toxicity rate of 40-50% is expected for our study. This is slightly lower than the observed grade 3-4 toxicity rate seen among patients > 65 years in the CORRECT trial. However, we hypothesize that starting at a lower dose and instituting extensive supportive care will lower the observed toxicity rate in our patient population. Using a sample size of 60 subjects with an expected toxicity rate of 45%, we will have a 90% CI of [0.341, 0.564] and an approximate 12% margin of error. Our plan is to accrue 3-4 patients per month among the four participating sites.

13. Premature Termination of the Study

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

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For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties (Coordinating Center and enrolling site).
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.

14. Ethical and Legal Aspects

Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Investigator Requirements:

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; **the investigator may not modify or alter the procedures described in this protocol.**

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by the Coordinating Center. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Coordinating Center approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator and reported to the Coordinating Center by faxing: 585-442-0137.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

15. Publication policy

The Coordinating Center recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the Coordinating Center (who will then forward this to Bayer) at least

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thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the Coordinating Center (including Bayer) and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between the Coordinating Center and the investigator/institution.

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

16. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

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18. Appendices

Appendix A – RECIST 1.1 Criteria

	RECIST 1.1
Measurable Disease: Tumor Lesions	Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded with a minimum size of): - 10mm by CT /MRI scan (scan slice thickness no greater than 5mm) - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable) - 20mm by chest X-ray
Measurable Disease: Malignant Lymph Node	Sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) Measure **SHORT** axis: - Target lesion if short axis ≥ 1.5cm - Non-target if short axis 1.0 to <1.5cm or pathological - Normal lymph node if short axis < 1.0cm Add **ACTUAL** short axis measurement to sum of longest diameters of non-nodal lesions.
Target Lesions	All measurable lesions: - Up to 5 target lesions max in total - Up to 2 target lesions max per organ
Non-Target Lesions	All other lesions (site of disease). Measurements are not required and these lesions should be followed as: - Present - Absent - Unequivocal progression
New Lesions	The appearance of new malignant lesions denotes disease progression.
Methods for Evaluation of Measurable Disease	All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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Appendix B: Investigators Brochure

Will be provided upon request

Appendix C: Comprehensive Geriatric Assessment Tools


CGA Team Assessment 12Apr20


CGA Patient Assessment 12Apr20

Appendix D: Handout on 'Tips for Skin Care' for patients


STIVARGA® for Patients _ Managing H

Appendix E: Handout on 'Planning Low-Fat Meals' for patients


STIVARGA - Helping You Plan Your Low-Fat

Appendix F: Subject Diary


Regorafenib Subject Diary IRB Approved.pd

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