Multi Institutional Phase II Trial of Single Agent Regorafenib in Refractory Advanced Biliary Cancers

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Title page

Multi institutional phase II trial of single agent regorafenib in refractory advanced biliary cancers.

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title	**Multi institutional phase II trial of single agent regorafenib in refractory advanced biliary cancers.**
Clinical study phase	*Phase II*
Study objective(s)	**Primary Objective** • To determine the 6 month overall survival in patients with advanced refractory BC receiving regorafenib. **Secondary Objectives** • To determine the frequency and severity of adverse events and tolerability of the regimen in patients with advanced refractory BC receiving regorafenib • To evaluate the disease control rate (CR + PR+ SD) as defined by the RECIST 1.1 criteria in patients with advanced refractory biliary cancers (BC) receiving regorafenib at 8 weeks. • To determine the progression-free survival in patients with advanced refractory BC receiving regorafenib **Exploratory Objectives** • To explore potential correlations between blood biomarkers and clinical outcome

Background treatment	The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is currently an unmet medical need for patients with advanced BC who have failed one prior systemic therapy. The second line setting therefore offers a unique opportunity to evaluate the activity of relevant molecularly targeted therapies and to identify potential predictive biomarkers. The fact that aberrant activation of the Ras/Raf/MAPK pathway occurs in more than 60% of BC indicates the importance of these pathways in biliary carcinogenesis and highlights potential new strategies in the treatment of this disease. Furthermore anti-angiogenic agents such as the VEGF-antagonist bevacizumab, and the multikinase inhibitor sorafenib have been tested in BC in the first line setting with modest activity. Regorafenib is an oral multi-kinase inhibitor that targets both receptor tyrosine kinases (RTKs), as well as the tumor cell proliferation/survival signaling pathway kinases (RAS/RAF/MEK/ERK). In addition, regorafenib inhibits VEGFR-2/3, TIE-2, c-KIT, and PDGFR-ß receptor phosphorylation. Given the pivotal role of VEGF, the Ras/Raf/MAPK pathway, and PDGFR- ß in biliary cancer biology, evaluation of the regorafenib in the second line setting represents a rational approach.
Indication	Patients with advanced biliary tumor who have failed at least one prior line of systemic therapy.
Diagnosis and main criteria for inclusion	• Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible. • Patients must have failed no more than 2 prior line of systemic chemotherapy for advanced biliary cancer. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing one line of systemic chemotherapy used to treat the disease recurrence. • Patients must have measurable disease, as defined by RECIST 1.1 criteria. • Patients must not have been treated with any VEGF inhibitors.
Study design	This is a multi-institutional phase II single arm single-stage design trial using regorafenib as a single agent.

Type of control	Patients will receive regorafenib 160 mg QD (21 days on and 7 days off). After 2 cycles (1cycle= 28 days), response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).
Number of subjects	*39*
Plan for statistical analysis	Overall survival (OS) will be defined as the time from starting on trial to date of death due to any cause. The final analysis will be conducted after the follow-time of the last patient exceeds 6 months. OS at 6 months is the primary endpoint of the trial and will be estimated using the Kaplan-Meier method. The two-sided 95% confidence interval (CI) for median OS will be computed using log-log transformation. The sample size was determined based on the Simon's two-stage minimax design. With one-sided 10% of type I error rate and 90% power, a sample of evaluable 39 patients will be evaluated; 28 in first stage and additional 11 patients in second stage. If 8 or more out of 28 survive 6 months or more, the study goes on the second stage. The experimental treatment will be deemed to have good activity if ≥16 out of 39 patients survive 6 months or more.

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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
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

1. Introduction

1.1 Background

Biliary cancer (BC) typically includes intra and extrahepatic cholangiocarcinoma and cancers of the gallbladder. In the United States, an estimated 2600 intrahepatic cholangiocarcinomas were diagnosed in 2010.[1],[2] In addition, about 10,000 cases of extrahepatic bile duct cancer are diagnosed annually in the United States, two-thirds of which are gallbladder cancers.[1] Unfortunately, most patients have advanced disease at presentation and relapse despite surgery.[3]

Data regarding chemotherapy have historically been disappointing in advanced BC, but new combinations show promise. ABC-02, a randomized phase III study recently published by Valle et al, enrolled more than 300 patients and compared gemcitabine plus cisplatin with gemcitabine alone.[4] The median overall survival (OS) and progression-free survival (PFS) were greater for gemcitabine plus cisplatin than for gemcitabine alone without significantly increased toxicity (OS: 11.7 *v* 8.2 months; log-rank *P* = .002; PFS: 8.5

v 6.5 months; *P* = .003). This drug combination set a new international standard of care for advanced biliary tract cancers. However, the survival for advanced BCs still rarely exceeds one year. This has led to a search for molecular targets for therapy. However, advances have been slow in part because of the tumor heterogeneity of BCs.[5]

VEGF Pathway

The vascular endothelial growth factor (VEGF)/VEGF receptor tyrosine kinase (RTK) signaling pathway plays a pivotal role in tumor angiogenesis by promoting vascular and lymphatic endothelial cell proliferation, survival, and invasion, resulting in neovascularization, tumor growth, and metastasis.[6]

VEGF has been found to be overexpressed in biliary tract cancers and has thus been suggested as a potential prognostic marker and therapeutic target.[7, 8] VEGF expression in biliary tract cancer has also been found to be an independent negative predictive marker. [9] Increased VEGF expression has been reported to be associated with significant vascularization of human intrahepatic cholangiocarcinomas, as assessed by microvessel density. In comparison, hypovascularity of cholangiocarcinoma may be related to a downregulation of VEGF together with an upregulation of the angiogenesis inhibitor thrombospondin-1.[10] Interestingly, VEGF-A expression was more frequently encountered in peripheral cholangiocarcinoma (69 vs 25%, $p < 0.0001$) and correlated with increased vascular density.[11] This could suggest a potential benefit for antiangiogenic therapies in peripheral cholangiocarcinomas.

Based on the pre-clinical data, VEGF inhibitors have been studied in bile duct cancers. Bevacizumab, a monoclonal antibody to VEGF, has been used in combination with gemcitabine/oxaliplatin or erlotinib and has shown promising results.[12, 13] The combination of gemcitabine and oxaliplatin with the addition of bevacizumab for first line treatment showed impressive overall survival of 12.7 months and progression free survival of 7.0 months. [12] Bevacizumab has also been studied in combination with erlotinib as a second line treatment.[14] The results were modest with response rate of 13% and overall survival of 4 months.

Tyrosine kinase inhibitors (TKI) of VEGF have also been tested in advanced biliary tract tumors. Sorafenib, a small molecule inhibitor of several protein kinases including VEGFR has been studied as first line treatment in biliary cancers. So far there have been 2 studies using sorafenib in advanced biliary cancers.[15, 16] The results were moderately effective but with a high rate of toxicity.

Raf-MEK-ERK Pathway

The Raf-MEK-ERK signaling pathway controls fundamental cellular processes including proliferation, differentiation and survival.[17] This pathway is an important mediator of response to growth signals and angiogenic factors, and is often aberrantly activated in human tumors due to the presence of activated RAS, mutant BRAF, or overexpression of growth factor receptors.[18] Activated RAS triggers the phosphorylation and activation of the RAF kinase, which then phosphorylates MEK1 and MEK2 on two serine residues. [19] Because this pathway is frequently dysregulated in human cancers, intense efforts are under way to develop selective inhibitors of the ERK pathway as anticancer drugs. In preclinical data, MEK inhibitors have been shown to improve survival in mice with KRAS mutant BC. [20] However, the frequency of RAS and RAF mutations in biliary cancer is still

unclear. In one study evaluating 69 patients with BC, 31 (45%) patients had KRAS mutations.[21] Other studies have shown RAS mutation in BC ranging from 3-54% [22, 23]

Incidence of BRAF mutation in BC is unclear as well. In one study, BRAF mutations were identified in 22% of human cholangiocarcinoma samples. Significantly, these mutations were mutually exclusive of KRAS alterations, which occurred in 45% of tumors within the same series.[21] BRAF mutations are frequently associated enhanced sensitivity to MEK inhibition and may constitute a key survival mechanism for those cells.[24, 25] A better understanding of the frequency and impact of BRAF mutations in cholangiocarcinoma is needed since other studies have found no BRAF mutations in BC. [26]

Downstream of BRAF, the MAPK pathway appears active in 75% of BC, as evidenced by P-MAPK immunostaining.[27] Expression profiling across a panel of seven human BC cell lines demonstrated expression of a number of RAS/MAPK pathway components and have demonstrated sensitivity to MEK inhibitors.[28]
The PDGFR pathway also appears to be a potential target in BC. It has been hypothesized that PDGFR activation mediates resistance apoptosis. Data in human cells has shown increased sensitivity to apoptotic agents once the PDGFR- ß /c-kit pathway was targeted.[29]

1.2 Rationale of the study

The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is currently an unmet medical need for patients with advanced BC who have failed one prior systemic therapy.
The second line setting therefore offers a unique opportunity to evaluate the activity of relevant molecularly targeted therapies and to identify potential predictive biomarkers. The fact that aberrant activation of the Ras/Raf/MAPK pathway occurs in more than 60% of BC indicates the importance of these pathways in biliary carcinogenesis and highlights potential new strategies in the treatment of this disease.[30] Furthermore anti-angiogenic agents such as the VEGF-antagonist bevacizumab, and the multikinase inhibitor sorafenib have been tested in BC in the first line setting with modest activity.
Regorafenib is an oral multi-kinase inhibitor that targets both receptor tyrosine kinases (RTKs), as well as the tumor cell proliferation/survival signaling pathway kinases (RAS/RAF/MEK/ERK). In addition, regorafenib inhibits VEGFR-2/3, TIE-2, c-KIT, and PDGFR-ß receptor phosphorylation. Given the pivotal role of VEGF, the Ras/Raf/MAPK pathway, and PDGFR- ß in biliary cancer biology, evaluation of the regorafenib in the second line setting represents a rational approach.

1.3 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.

1.3.1 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).[31] 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.[31] These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

1.3.2 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 has progressed after approved standard therapies. [32]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.

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. 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%). GRID study data is currently under FDA review.

2. Study objectives

Primary Objective

• To determine 6 month overall survival in patients with advanced refractory BC receiving regorafenib.

Secondary Objectives

- To determine the frequency and severity of adverse events and tolerability of the regimen in patients with advanced refractory BC receiving regorafenib
- To evaluate the disease control rate (CR + PR+ SD) as defined by the RECIST 1.1 criteria in patients with advanced refractory biliary cancers (BC) receiving regorafenib at 8 weeks.
- To determine the progression-free survival in patients with advanced refractory BC receiving regorafenib

Exploratory Objective

- To explore potential correlations between blood biomarkers and clinical benefit

3. Investigator[s] and other study participants

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4. Study design

This is a multi-institutional single arm, *Simon's two-stage* trial using regorafenib as a single agent in patients who have failed at least one prior line of systemic therapy in advanced biliary tumors. 39 patients will be accrued. Patients will receive regorafenib 160 mg QD (21 days on and 7 days off). After 2 cycles (1cycle= 28 days), response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Primary endpoint is 6 month overall survival.

4.1 Eligibility

4.1.1 Inclusion criteria

- Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable, locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible.
- Patients must have failed no more than 2 prior line of systemic chemotherapy for advanced biliary cancer. Patients who received adjuvant chemotherapy and had

evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing one line of systemic chemotherapy used to treat the disease recurrence.

- Age ≥ 18 years.
- Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment of 0 or 1
- Measurable and non-measurable disease will be allowed.
- Patients must not have been treated with any VEGF inhibitors.
- Life expectancy of at least 12 weeks (3 months).
- For patients who have received prior cryotherapy, radiofrequency ablation, therasphere, ethanol injection, transarterial chemoembolization (TACE) or photodynamic therapy, the following criteria must be met: 28 days have elapsed since that therapy (lesions that have not been treated with local therapy must be present and measureable
- 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.
- All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF).
- Adequate bone marrow, liver and liver function as assessed by the following laboratory requirements:
    - Total bilirubin ≤ 2.0 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
    - Calculated creatinine clearance > 30 ml/min.

      $$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times t\ (\text{kg}) \times [0.85\ (\text{if female})]}{72 \times \text{creatinine (mg/dL)}}$$

    - International normalized ratio (INR)/ Partial thromboplastin time (PTT) ≤ 1.5 x ULN. (Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is

stable based on a measurement that is pre-dose as defined by the local standard of care.

- Platelet count ≥ 75,000 /mm3,
- hemoglobin (Hb) ≥ 9 g/dL,
- absolute neutrophil count (ANC) 1000/mm3.
- Blood transfusion to meet the inclusion criteria will be allowed.

- Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subject must be able to swallow and retain oral medication.

4.1.2 Exclusion criteria

- Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
- Other investigational treatment during or within 21 days before starting study treatment
- Child Pugh B or C
- 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.
  - Active coronary artery disease.
  - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
  - Unstable angina (anginal symptoms at rest), new-onset angina within 3 months, or myocardial infarction within 6 months.
- 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.
- No active malignancy except for nonmelanoma skin cancer or *in situ* cervical cancer. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before the trial are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form).
- 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.
- Renal failure requiring hemo-or peritoneal dialysis.
- 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 any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- 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.

4.1.3 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
- Prior use of regorafenib or other anti VEGF drugs.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 21 days 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 medication.
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

4.2 Withdrawal of subjects from study

4.2.1 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.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/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.
- Progression of disease
- 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.
- 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 3 or 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.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

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

4.2.2 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reasons except death, disease progression and severe toxicity is defined as a dropout.

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 “dropout” (see above) is regarded a “screening failure”.

4.2.3 Replacement

Dropout patients will need to be replaced.

Patients will be considered inevaluable for the primary endpoint of 6 month of OS if they are not able to complete first cycle. Inevaluable patients will be replaced

5. Treatment[s]

5.1 Treatments to be administered

All patients will receive regorafenib

Arm 1: Regorafenib

Agent	Dose	Route	Day	Schedule*
Regorafenib	160mg	PO	QD	21 days

One cycle = 28days

5.1.1 Regorafenib

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 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.

5.1.2 Dosage and administration:

Regorafenib tablets for oral administration are formulated as light pink oval shaped tablets debossed with “BAYER” on one side and “40” on the other. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate, and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film –coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

5.1.3 Study Treatment

Regorafenib is administered as monotherapy during the study, 160 mg qd will be administered for 3 weeks on /1 week off. One cycle is 28 days.

Four 40-mg regorafenib tables should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Some examples of low fat breakfasts 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.

5.1.4 Dose Modification for management of adverse events

5.1.4.1 Dose Reduction Levels

The starting dose of regorafenib is 160 mg once daily. Study medication will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4].

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

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 2 dose reductions are required, regorafenib will be discontinued and patient will need to come off of the trial. 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 except hand-foot skin reaction, hypertension and liver function test abnormalities.

Table 6-1: Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/ST/bilirubin

NCI-CTCAE v4.0[a]	**Dose Interruption**	**Dose Modification** [b]	**Dose for Subsequent Cycles**
Grade 0-2	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.
* Modify according to study specific cycle length

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

In addition to these recommended dose modifications, subjects who develop diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary. This is in order to minimize the risk of postural hypotension and renal failure.

Table 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.			

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

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.		

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.

Alanine or aspartate aminotransferase (AST/ALT): for any grade increase in AST or ALT, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of AST or ALT is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted at the same dose level upon return of the AST and ALT to baseline or grade 2.

For any grade increase in bilirubin, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of bilirubin is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted at the same dose level upon return of the bilirubin to baseline or Grade 1.

Table 6-5: Dose modifications/interruption for ALT and/or AST and/or bilirubin increases related to study drug

Observed elevations	**1st Occurrence**	**Restart**	**Re-occurrence**
ALT and/or AST >5 X ULN (≥ G3)	If patient had Grade 0 or 1 AST or ALT increase at baseline, hold the drug until AST or ALT returns to Grade 1 or baseline. If patient had Grade 2 (asymptomatic) AST or ALT increase at baseline, continue treatment at same dose and follow AST or ALT weekly for 4 weeks. Hold	Reduce one dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue

	the drug if patient develops symptoms or if AST or ALT ≥ 10 x IULN; restart treatment with one dose level reduction when AST or ALT returns to baseline AND patient is asymptomatic		
ALT and/or AST > 20 X ULN (≥ G4)	Discontinue		
Bilirubin (G=2)	If patient had a normal bilirubin at baseline, hold the drug until bilirubin returns to Grade 1 or baseline If patient had Grade 1 bilirubin at baseline, continue treatment at same dose and follow bilirubin weekly for 4 weeks. Hold the drug if patient develops symptoms or if bilirubin > 2 x ULN and AST or ALT ≥ 5 x ULN Restart treatment when bilirubin returns to grade 1 or baseline and patient is asymptomatic.	Restart with one dose reduction	Discontinue
Bilirubin (G=3)	Discontinue		Discontinue
During the first 2 cycles of treatment, ALT, AST and bilirubin must be monitored every 2 weeks.			

Bilirubin and AST/ALT: for any grade increase in bilirubin AST or ALT, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of AST or ALT is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted at the same dose level upon return of the AST and ALT to baseline or grade 2.

5.1.4.2 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status).

Anti-diarrhea medications may be introduced if symptoms occur. Previous trials have shown that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours.

5.2 Drug logistics and accountability

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.

5.2.1 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) 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.)

5.2.2 Destruction and Return

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.

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

Fax: 973-709-2193
OR
Mail: (VP of Medical Affairs named in contract) at
Bayer HealthCare Pharmaceuticals
6 West Belt
Wayne, NJ 07470

5.3 Treatment compliance

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form.

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.

5.4 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 Stivarga 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 Stivarga 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 Stivarga increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoide concomitant use of Stivarga 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

- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. 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.

The following are not permitted:

- Other investigational treatment during or within 21 days before starting study treatment

- 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, cyclosporine, and digoxin). Warfarin is metabolized by the cytochrome enzyme CYP2C9 and it's levels may be especially affected by regorafenib

- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

6. Procedures and variables

6.1 Calendar

Required studies must be done within 28 days prior to starting on the treatment.

		Cycle 1 **+/- 2 Days**				Cycle 2 **+/- 2 Days**				Cycle 3[1] **+/- 2 Days**					
REQUIRED STUDIES	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Pre-Progression Follow-Up [1]	Post-Progression Follow-Up [2]
PHYSICAL [1]															
History and Physical Exam (informed consent)	X	X	X	X	X	X	X			X				X	X
Weight and Performance Status	X	X	X	X	X	X	X			X				X	
Toxicity Notation	X	X	X	X	X	X	X			X				X #	X #
Blood Pressure		X	X	X	X	X	X								
LABORATORY [1]															
CBC, Differential, Platelets	X	X		X		X		X		X					
CA-19-9	X									X					
Serum Chemistry [3]	X	X		X		X		X		X					
U/A [7]	X														
PT/INR	X														
X-RAYS AND SCANS [1, 4]															
CT/MRI for Disease Assessment [5]	X									X				X	
EKG	X														
SPECIMEN SUBMISSION															
Blood sample (for correlatives)[6]	X									X					
TREATMENT															
Regorafenib		X	X	X		X	X	X		X	X	X			

1 Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 4.2.1

2 After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 3 months for up to two years or death.

3 Sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST, ALT

4 To be performed every 8 weeks until progression. Must be performed using same method as prestudy.
5 Scan must be performed +/- 1 week of each assessment.
6 Draw 1 x10mls EDTA tubes at baseline, Cycle 3 Day 1 (+/- 2 days), and at the treatment discontinuation visit if patient continues on after cycle 3 day1. (see section 13.)
7. Spot urine must not show 2+ or more protein in urine or the patient will require a repeat urine analysis. If repeat urinanalysis shows 2+ protein or more, a 24- hour urine collection will be required and must show total protein excretion <3500 mg/24 hours

Toxicity should be evaluated until resolution of any adverse events.

6.2 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), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

All AEs whether considered drug-related or not, will be reported with following information: 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.

6.2.1 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.

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.

6.2.1.1 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.

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.

6.2.1.2 Classifications for adverse event assessment

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

6.2.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 6.2.1.1

6.2.1.2.2 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.

CTCAEv4 Grade 5: death due to an AE.

6.2.1.2.3 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 causality assessment should be done separately for each study treatment.

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.

[Causal relationship to protocol-required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

6.2.1.2.4 Action taken with study treatment

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

The study treatment action should be recorded separately for each study treatment.

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

6.2.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

6.2.1.2.6 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

7. CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1 guidelines

7.1 Measurability of Lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm 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 non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, 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 by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be

7.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an

explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related

to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

7.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

8. Statistical methods and determination of sample size

8.1 Sample Size Determination

Overall Survival (OS) at 6 month is the primary endpoint on this study. OS is defined in section 8.2. Dropouts/screen failures defined in section 4.2.2 and those who are lost

follow-up prior to 6 months from starting on trial except death are not evaluable for the primary endpoint, and they will be replaced by new patients. The study will test the null hypothesis of ≤30% of OS at 6 month against the alternative of ≥50% of OS at 6 month (HR = 0.578 under exponential model). The sample size was determined, based on the Simon's two-stage minimax design. With one-sided 10% of type I error rate and 90% statistical power, a sample of evaluable 39 will be evaluated: 28 in first stage and additional 11 in second stage. If 8 or more out of 28 survive 6 months or more, the study goes on the second stage.. REGORAFENIB will be deemed to have good activity if ≥16 out of 39 patients survive 6 months or more from starting on trial. The continuation of accrual may be allowed while the analysis for early stopping being conducted. We expect to accrue 2 or more patients per month among 6-7 participating institutions and will follow up patients 6 months or more.

Dropouts/screen failures defined in section 4.2.2 and those who are lost follow-up prior to 6 months from starting on trial except death, disease and severe toxicity are not evaluable for the primary endpoint, and they will be replaced by new patients

8.2 Statistical Analysis

Overall survival (OS) is defined as the time from starting on trial to date of death due to any cause and progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever comes first. The final analysis will be conducted after the follow-time of the last patient exceeds 6 months. The primary endpoint of the study is OS at 6 month. The experimental treatment will be deemed to have good activity if ≥16 out of 39 evaluable patients survive 6 months or more. OS will be estimated using the Kaplan-Meier method and the two-sided 95% confidence interval (CI) for median OS will be computed using log-log transformation.

The secondary endpoints in this study include the disease control response (DCR) defined as (CR + PR+ SD), toxicity, and PFS. DCR rate will be reported with 95% CI computed by the Clopper-Pearson method. The frequency and severity of adverse events and tolerability of the regimen will be summarized using descriptive statistics. PFS with 95% CI will be estimated. As exploratory objective, the association between biomarkers and clinical outcomes (DCR rate, OS and PFS) will be examined using multiple logistic regression and the multivariable Cox regression model. A p-value of <0.05 will be considered statistically significant. Frequency and severity of adverse events will be summarized using descriptive statistics.

9. Safety Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

The PMC monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any

agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.
Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or
more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

Internal Monitoring Plan

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely according to Moffitt's Monitoring Policies.

9.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (grade 1-4, or mild/moderate/severe)
- Its relationship to the study drug(s) (suspected/not suspected)
- Its duration (start and end dates or if continuing at final exam)
- Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between Investigator Brochure updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

9.2 Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for routine treatment or monitoring of the studied indication
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to Bayer expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in ONCORE, the electronic data capture system and a Medwatch Form online at http://www.fda.gov/medwatch The SAE must be reported by email (affiliate.research@moffitt.org) to the MCRN within 2 working days.

9.3 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 6.2.1.1.

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 Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

The Investigator may report serious adverse events (SAEs) as described below.

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

All reports shall be sent electronically to:

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

Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA
Mail only: Bayer HealthCare Pharmaceuticals Inc.

P.O. Box 1000
Montville, NJ 07045-1000

Address: 340 Changebridge Road
FDX or UPS only Pine Brook, NJ 07058

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

Phone: 1-888-765-3203-2937

9.4 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 from phase I/II 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 sponsor as outlined in Section 7.6.1.4.

These events are:

- 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

9.5 Pregnancies

The investigator must report to Bayer any pregnancy occurring in a study subject, or in his 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 a study subject, the outcome of the 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.

For all reports, the forms provided are to be used.

9.6 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 Bayer and record the cause of death in detail (using the SAE Form) within 24 hours.

10. 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 any interim analysis
  - 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.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- 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 4.2.1.

11. Data recording

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient
understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

11.2 Required Documentation

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center.
Sites must provide a copy of their informed consent to the MCRN coordinating center for review and approval prior to submission of any documents to the site's IRB. Any changes re- quested by the site's IRB must be provided to the MCRN staff for review and approval prior to resubmission to the IRB.

The MCRN Coordinating Center must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Responsibility Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, Conflict of Interest statements, etc) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc) as needed Signed protocol specific Task Order

A study initiation visit (or teleconference) will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and MCRN research coordinator is required

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The MCRN utilizes the EDC system, OnCore. OnCore training will be scheduled if indicated with the appropriate staff from the site.

11.3 Registration Procedures

All subjects must be registered with the MCRN Coordinating Center to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility can not be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number and randomization information if indicated. Within 24-48 hours after registration, It is the site's responsibility to:

- Enter the demographic and on-study patient information into the OnCore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with supporting documentation to the MCRN via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM(EST).

11.4 Data Management and Monitoring/Auditing

All participating sites are required to enter and submit data through the Oncology Research Management software (OnCore) electronic data system.Data will be monitored for subject eligibility and protocol compliance, as well as for accuracy and completeness,

To obtain access to OnCore, the site research staff must complete an OnCore Access Request Form and a Moffitt Information Systems Confidentiality Agreement and submit both to the Coordinating Center. Once the completed forms are received, the site coordinator will receive a VPN access key, logon/password, and information on how to access OnCore using the VPN. The MCRN Coordinating Center will provide OnCore training to the site once initial access is granted and on an ongoing basis as

needed. Written instructions will be provided electronically for each site to download prior to the initial training with updates sent as appropriate.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol

11.6 Emergency Modifications

Moffitt Cancer Center and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior H. Lee Moffitt Cancer Center or their respective institution's approval/favorable opinion.

For Institutions Relying on Moffitt's IRB:
For any such emergency modification implemented, a Moffitt IRB modification form must be completed by Moffitt Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to: To Moffitt Principal Investigator for agreement and the Affiliate institution's IRB for review and approval. (Once IRB"s response is received, this should be forwarded to the MCRN).

11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on

Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

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 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 entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12. Ethical and legal aspects

12.1 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).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to Bayer.

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 Bayer. 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/Bayer 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.

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 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.

12.2 Subject information and consent

Each subject / legal representative or proxy consenter 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 / legal representative or proxy consenter 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 / legal representative or proxy consenter 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.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters 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. The investigator will inform the subject / legal representative or proxy consenter 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. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

12.3 Publication policy

Bayer 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 Bayer at least 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 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 Bayer 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.

12.4 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.

13. Correlative studies

13.1 Required Participation

Regorafenib is a multi-kinase inhibitor that is believed to block tumor growth through effects on both tumor cells and the angiogenic compartment. At present, there is no way to predict which patients will benefit from this compound. Biomarker studies will be performed to investigate the mechanisms by which regorafenib works in an attempt to identify markers predictive of drug benefit in patients with advanced biliary tumors. In the current study, both genetic and non-genetic biomarker analyses are planned on blood specimens. Utmost care will be taken to protect patient identity during biomarker analyses. Collection, processing, handling, and shipping of biomarker samples will be performed as described in the laboratory manual

13.2 Details on Potential Biomarker Studies by Specimen

Plasma samples: The Duke Molecular Reference Laboratory at Duke University Medical Center is one of several core facilities for CALGB. It acts as a molecular profiling laboratory for blood-based biomarkers of targeted therapies, particularly targeted anti-angiogenic agents. Drs. Andrew Nixon and Herbert Hurwitz serve as co-directors of the facility and direct the overall research of the laboratory. The laboratory has quality control procedures in place to address many of the issues involved in clinical trials research including sample quantity, sample integrity, and sample heterogeneity. The services provided align with our programmatic focus around the interrogation of blood and urine samples by either multiplex or standard ELISA technologies. Each study utilizes unique combinations of cancer therapeutics, affecting multiple signaling pathways. The optimal design for this study addresses the specific drug targets of the study as well as attempting to capture the relevant co- and counter-regulated proteins. Based on our experience, we have chosen important pathway components, identified the appropriate assay, built multiplex panels, and established QA/QC parameters regarding these assays.

In the past, the gold standard for detection of growth factors and cytokines in blood was the use of ELISAs; however, multiplex technology offers an attractive alternative approach for cytokine and growth factor analysis. This novel technology allows for the measurement of multiple analytes simultaneously from a single sample. The advantages of multiplex technology compared to traditional ELISA assays are conservation of patient sample, increased sensitivity, and significant savings in cost, time and labor. Furthermore, all plate designs are validated in order to 1) limit cross-reactivity of the antibodies 2) optimize sensitivity and specificity and 3) maximize the linearity of the assay's dynamic range.

Several systems exist, the plate-based platforms being the Meso Scale Discovery (MSD) multiplex system and the SearchLight system, produced by Aushon Biosystems (formerly of ThermoFisher Scientific). The assay design in both cases is similar to a sandwich ELISA,

except multiple capture antibodies are pre-spotted into individual wells of a 96-well plate. Samples or standards are added which bind to the specific capture antibodies and are detected using various outputs. Over the past 2 years, we have optimized the design of customized multiplex ELISA plates via extensive collaborations with the SearchLight. We have devoted considerable effort to this and have developed an appropriately designed panel for the simultaneous evaluation of up to 40 regulators of tumor and normal angiogenesis. Table 1 lists the analytes that can be evaluated. Modifications to this list may occur during patient accrual, but the programmatic theme related to angiogenesis will remain constant. Standard ELISA assays are also included to evaluate soluble TGF □RIII and IGF-1 as additional blood markers.

All multiplex plate designs have been validated in order to limit cross-reactivity of the antibodies, optimized for sensitivity and specificity, and maximize the linearity of the assay's dynamic range. The CVs of the multiplex arrays are approximately 15-20%, depending on the particular assay. Any study samples that fall outside the linear portion of the standard curve are retested. Samples that read below the limit of detection are retested, if possible. Samples that read above the linear portion of the standard curve are serially diluted and retested to obtain accurate measurements. Any analyte that does not meet the aforementioned criteria will result in the sample being re-evaluated. Analytes of interest that are not available in our multiplex plates can be evaluated using commercial ELISA kits or "home-brew" ELISAs.

Table 1. Plasma-based marker identification

Soluble Angiogenic Factors*	Matrix-Derived Angiogenic Factors	Markers of Coagulation	Markers of Vascular Activation and Inflammation
bFGF	MMP2	Tissue Factor	Gro-□
HGF	MMP9	PAI-1 Active	IL-6
PlGF	TGF □1	PAI-1 Total	IL-8
VEGF-A	TGF □2	CRP	P-selectin
VEGF-C	Osteopontin	D-dimer	E-selectin
VEGF-D	TSP1	Von Willebrand Factor	SDF-1 □
ANG-2	TSP2		ICAM-1
PDGF-AA	BMP9		VCAM-1
PDGF-BB	sEndoglin		MCP-1
IGFBP1	PEDF		E-cadherin
IGFBP2			
IGFBP3			
sVEGFR1			
sVEGFR2			

*Standard ELISA assays will also be included to evaluate soluble TGFbRIII, and IGF-1 as additional blood markers.

Lastly, all samples have appropriate chain-of-custody documentation to ensure compliance with FDA and IRB regulations. We have systems in place detailing the location, transfer,

and use of any and all human research subject samples. Any discrepancies or omissions in flow sheets and/or sample labels are resolved upon receipt of the sample in the lab. All sample and data handling procedures will be fully compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). We have sample handling protocols that provide step-by-step details for sample isolation, sample handling, and sample receipt/shipment. Samples are housed in ultra low temperature freezers (-80°C). The freezers are monitored daily and are equipped with an alarm system designed to alert laboratory personnel upon freezer malfunction. Additionally, we have implemented a secondary, independent alarm system on all ultra low freezers currently used to store all patient samples. Use of these redundant systems greatly reduces the chance of freezer failure, which could potentially result in the loss of irreplaceable samples from hundreds of clinical trial patients.

13.3 Special Instructions

For plasma samples:

1. Draw 1 x10mls EDTA tube
2. Invert tubes 10 times to mix blood
3. Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
4. Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
6. Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml cryovial. For the EDTA, aliquot into pink capped cryovial. Total of 3 pink capped cryovials needed for EDTA plasma. For the sodium citrate, aliquot into blue capped cryovial. Total of 2 blue capped cryovials needed for sodium citrate plasma.
7. Label and freeze at -80°C* (see labeling instructions below)

13.4 Shipping

- ***All biomarker samples (whole blood, plasma, serum and urine) must be shipped on dry ice by overnight delivery Monday through Thursday (no holidays) to the following address:***

Attention: Phase I Biomarker Laboratory
ATTN: Andrew Nixon, PhD
Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710

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