NU 13S02
Multicenter, Open-Label Phase II Study of Daily Oral Regorafenib for Chemotherapy-Refractory, Metastatic and Locally Advanced Angiosarcoma

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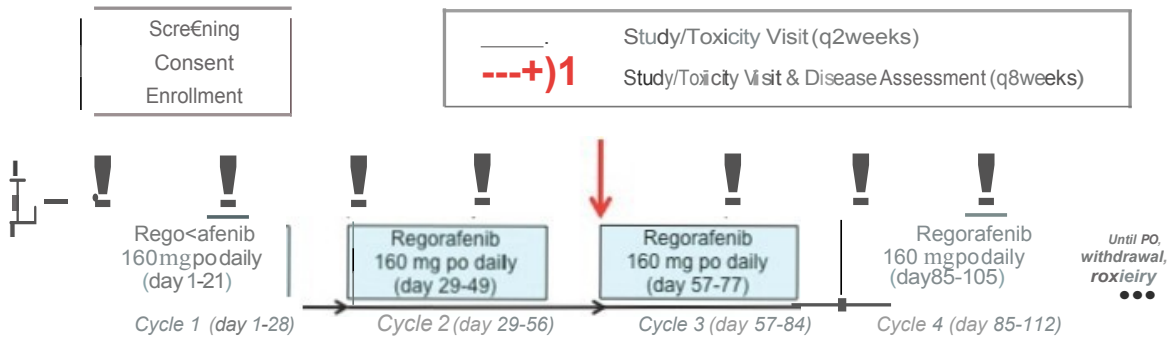
SYNOPSIS

Title	Multicenter, Open-Label Phase II Study of Daily Oral Regorafenib for Chemotherapy-Refractory, Metastatic and Locally Advanced Angiosarcoma
Short Title	Regorafenib for Advanced Angiosarcoma
Phase/Design	Phase II, open-label
Study Center(s)	Lead Site: Northwestern University – Robert H. Lurie Comprehensive Cancer Center Participating Sites: Mayo Clinic (Rochester, MN) Mayo Clinic (Jacksonville, FL) Washington University University of Iowa Sarcoma Oncology Research Center
Study Objective(s)	Primary: Progression-free survival at 4 months Secondary: Progression-free rate at 3 and 6 months Progression-free survival Overall survival (up to 5 years) Response rate (by RECIST v 1.1) Rate and duration of tumor control (CR+PR+SD) Safety and tolerability
Sample Size	1st stage: N = 12 2nd stage: N = 19
Diagnosis & Main Inclusion Criteria	• Histologically-confirmed, metastatic or locally advanced, unresectable angiosarcoma with measurable disease • Progressive disease with prior ifosfamide, doxorubicin or taxane therapy • No prior sorafenib
Treatment Plan	Patients will be treated with regorafenib 160 mg PO daily for the first 3 weeks of each cycle (1 cycle = 4 weeks) until disease progression. Response evaluation will be every 2 cycles (approximately 2 months) using RECIST v 1.1.
Plan for statistical analysis	Optimal two-stage Simon design. First stage includes 12 patients. If > 3 patients have PFS > 4 months, and additional 19 will be enrolled for a total of 31 patients.

SCHEMA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Cycle 2 (day 29-56)
Cycle 3 (day 57-84)
Cycle 4 (day 85-112)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
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
PT/INR	Prothrombin time/ International Normalized Ratio
QD	*quaque die*, once daily
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

1.0 INTRODUCTION

Angiosarcoma is an aggressive soft tissue sarcoma of endothelial differentiation. Angiosarcoma has a particularly poor prognosis with 5 year overall survival rates of approximately 30-40%. Deaths are almost universally attributable to distant metastatic disease. Median overall survival of metastatic angiosarcoma is less than one year (1). In addition to clinically aggressive behavior, survival is limited by a paucity of efficacious systemic therapies. The identification of novel, active agents is urgently needed to improve the duration and quality of life for angiosarcoma patients.

1.1 BACKGROUND

Treatment of locally advanced and metastatic angiosarcoma is inadequate. Three phase II trials have been conducted in this setting. The first, ANGIOTAX, examined weekly paclitaxel in 30 patients with metastatic or unresectable angiosarcoma between April 2005 and October 2006 (1). Progression-free survival at 4 months was 45%. Response rate was less than 20% and median overall survival was 8 months. Despite these sobering results, retrospective analysis has demonstrated that weekly paclitaxel is slightly more active than single agent doxorubicin – the mainstay of metastatic soft tissue sarcoma therapy (2). A small retrospective series of 25 locally advanced or metastatic angiosarcoma patients treated between January 2008 and November 2010 suggests single agent gemcitabine may also have modest activity in this disease (3).

The inability of traditional cytotoxins to durably control angiosarcoma coupled with the observation this malignancy displays endothelial differentiation prompted interest in targeted anti-vascular therapies. Consequently, the two additional phase II trials in this setting have examined agents that antagonize the VEGF-VEGFR signaling axis. Agulnik and colleagues reported their phase II experience with bevacizumab in unresectable and metastatic angiosarcoma (4). Between August 2005 and April 2011, 23 angiosarcoma patients were treated with single agent bevacizumab. The median progression-free and overall survival were 3 months and 1 year, respectively. Responses were rare with only 2 (9%) experiencing a partial response. The French Sarcoma Group reported the third phase II trial in angiosarcoma examining the multi-targeted tyrosine kinase inhibitor, sorafenib, in 41 patients treated between June 2008 and June 2009 (5). Although progression-free and overall survival rates were disappointing, a 40% tumor control rate and 23% response rate were observed in patients previously treated with cytotoxic chemotherapy.

Taken together, these data suggest both (A) conventional cytotoxic therapy is inadequate in angiosarcoma and (B) the most promising approach observed in phase II trials is multi-targeted tyrosine kinase inhibition after failure of conventional cytotoxic therapy. As discussed in detail below, regorafenib is a highly promising agent in angiosarcoma. Similar to bevacizumab and sorafenib, regorafenib antagonizes the endothelial VEGF-VEGFR axis. However, in contrast to these agents (and other tested VEGFR antagonists such as sunitinib), regorafenib also displays potent activity against the endothelial Tie2 tyrosine kinase receptor – a newly identified therapeutic target in human angiosarcomas. Consequently, we have hypothesized that regorafenib will display clinically meaningful activity in patients with refractory, locally advanced and metastatic angiosarcoma.

1.2 RATIONALE FOR THE STUDY

The greater activity of sorafenib in advanced angiosarcoma compared to bevacizumab and sunitinib prompted the hypothesis that this enhanced activity

derived from a broader range of kinase inhibition. In particular, the greater activity of sorafenib was hypothesized to result from inhibition of the Tie2 kinase receptor. Sorafenib displays modest activity against Tie2 in cell-based assays (IC_{50} 330 nM).

To determine if Tie2 receptor kinase antagonism may be a viable therapeutic strategy in advanced angiosarcoma, expression of Tie2 signaling components (Tie1, Tie2, Ang1 and Ang2) was assessed in 51 human angiosarcomas. Strikingly, moderate to strong expression of both the Tie2 receptor and its agonist ligand, Ang1, was observed in > 80% of human samples (6). To extend these observations, the effects of VEGFR and Tie2 antagonism on angiosarcoma growth were assessed in vitro and in mouse xenograft models (7). As hypothesized, a highly selective Tie2 receptor tyrosine kinase inhibitor inhibited tumor cell proliferation in vitro and tumor growth in vivo. Moreover, the Tie2 antagonist displayed synergistic antiproliferative activity when combined with a VEGFR antagonist in a model of aggressive, high-grade angiosarcoma. More recently, stable and selective knock-down of the Tie2 receptor has been shown to reduce angiosarcoma cell proliferation in vitro and potently inhibit tumor growth in vivo (Kozak, unpublished results). These data strongly suggest concurrent, potent inhibition of VEGFR and Tie2 represents an attractive therapeutic strategy in angiosarcoma.

Regorafenib displays potent VEGFR inhibition with IC_{50}s generally half that observed with sorafenib. Moreover, regorafenib displays approximately 10-fold greater potency against the Tie2 receptor (as assessed in cellular kinase activity assays) compared to sorafenib (8,9). Beyond these favorable characteristics, regorafenib also possesses far greater activity than sorafenib (and other related TKIs) against additional potential targets in angiosarcoma including PDGFRs, RAF, KIT and FGFR (9). Taken together, these data raise the possibility that regorafenib will have considerable activity in the treatment of angiosarcoma.IC_{50}

The proposed single-arm phase II trial will assess progression-free survival at 4 months as the primary efficacy endpoint. If this trial meets efficacy criteria, it would be prudent for subsequent phase III or other large-scale confirmatory trials to employ an interim analysis to provide a double-check on the efficacy results.

1.3 REGORAFENIB

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 (9,10). 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. Regorafenib activity corresponds to long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI).

1.3.1 Preclinical experience

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). (9) Immunohistochemical ex-vivo studies with a phospho –specific monoclonal 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. (9) 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 (11). 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 (12). 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 recently prompted FDA approval of regorafenib for treatment of previously treated patients with locally advanced, unresectable or metastatic GIST.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary study objective is to define the progression-free survival (PFS) at 4 months with daily oral regorafenib (160 mg) in previously treated locally advanced/metastatic angiosarcoma patients.

2.2 SECONDARY OBJECTIVES

2.2.1 Progression-free rate at 3 and 6 months
2.2.2 Progression-free survival
2.2.3 Overall survival (up to 5 years)
2.2.4 Response rate (by RECIST v 1.1)
2.2.5 Rate and duration of tumor control (CR+PR+SD)
2.2.6 Safety/tolerability of regorafenib

3.0 SELECTION OF SUBJECTS

The target population for this phase II study is patients with locally advanced or metastatic angiosarcoma who have progressed after prior ifosfamide, doxorubicin or taxane therapy. This will be a multi-center trial with Northwestern University serving as the lead site. Potential patients may be referred to the Principal Investigator, Dr. Mark Agulnik, at (312) 695-0990, or the local investigator at each participating site.

Eligibility will be evaluated by the study teams according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. All registrations will be centralized through the Clinical Research Office at Northwestern University. Please refer to Section 11 and the Appendices for complete instructions regarding registration procedures.

3.1 INCLUSION CRITERIA

3.1.1 Age ≥ 18 years.
3.1.2 Life expectancy of at least 4 months
3.1.3 Histologically confirmed angiosarcoma
3.1.4 Tumor deemed unresectable or metastatic

3.1.5 Measurable disease per RECIST v 1.1
3.1.6 ECOG PS 0 or 1
3.1.7 Progressive disease under last palliative therapy with a history of prior ifosfamide, doxorubicin or taxane therapy for angiosarcoma. Up to 4 prior therapies are allowed.If patient refuses or if IV chemotherapy is contraindicated, patients will be eligible if they fail one systemic therapy. Note: *It will be up to the treating investigator to define what constitutes a "therapy" in each case, and final decisions on how prior therapy should be counted will be at the discretion of the Principal Investigator*.
3.1.8 All acute toxic effects of any prior treatment have resolved to Grade 1 or less (by NCI-CTCAE v 4.0) at the time of registration. *NOTE: Exceptions to this criterion will include alopecia and fatigue.*
3.1.9 Patients must meet the following laboratory requirements to be considered eligible:

3.1.9.1	Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
3.1.9.2	ALT and AST ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
3.1.9.3	Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
3.1.9.4	Lipase ≤ 1.5 x the ULN
3.1.9.5	Serum creatinine ≤ 1.5 x the ULN
3.1.9.6	PT/INR ≤ 1.5 x ULN
3.1.9.7	Platelet count ≥ 100000 /mm^3
3.1.9.8	Hemoglobin ≥ 9 g/dL
3.1.9.9	Absolute neutrophil count > 1500/mm^3
3.1.9.10	If baseline UPC ≥ 1, a 24-hour urine protein must be assessed. Patients must have a 24-hour urine protein value< Grade 3 (> 3.5 g/24 hours) to be eligible.

NOTE: Subjects may not have had a transfusion within 7 days of screening assessment.

NOTE: Patients who are prophylactically 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 PT/INR is stable based on a measurement that is pre-dose as defined by the local standard of care.

3.1.10 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 age ≥ 50 years and no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.*
3.1.11 Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at registration 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.*
3.1.12 Subject must be able to swallow and retain oral medication.
3.1.13 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.*

3.2 EXCLUSION CRITERIA

3.2.1 Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg on repeated measurement) despite optimal medical management.

3.2.2 Active or clinically significant cardiac disease including:
- 3.2.2.1 Congestive heart failure – New York Heart Association > Class II
- 3.2.2.2 Active coronary artery disease
- 3.2.2.3 Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin
- 3.2.2.4 Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before registration, or myocardial infarction within 6 months before registration

3.2.3 Evidence or history of bleeding diathesis or coagulopathy.

3.2.4 Any hemorrhage or bleeding event ≥ Grade 3 within 4 weeks prior to registration.

3.2.5 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. *Note: Subjects with recent DVT who have been treated with therapeutic anticoagulating agents for at least 6 weeks prior to study treatment are eligible*

3.2.6 Subjects with any previously untreated or concurrent cancer unrelated to angiosarcoma. *NOTE: Exceptions include cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed. All treatments must have been completed at least 3 years prior to registration.*

3.2.7 Patients with pheochromocytoma.

3.2.8 Patients with severe hepatic impairment (Child-Pugh Class C)

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

3.2.10 Ongoing infection > Grade 2.

3.2.11 Evidence of significant central nervous system disease including seizure disorder requiring medication, symptomatic metastatic brain or meningeal tumors.

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

3.2.13 Renal failure requiring hemo-or peritoneal dialysis.

3.2.14 Dehydration > Grade 1.

3.2.15 Interstitial lung disease with ongoing signs and symptoms at the time of registration.

3.2.16 Pleural effusion or ascites that causes respiratory compromise (≥ Grade 2 dyspnea).

3.2.17 History of organ allograft (including corneal transplant).

3.2.18 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.

3.2.19 Any malabsorption condition.

3.2.20 Evidence of abdominal fistula, GI perforation or intraabdominal abscess.

3.2.21 Women who are pregnant or breast-feeding.

3.2.22 Concurrent anti-cancer therapy (chemotherapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (regorafenib).

3.2.23 Prior use of regorafenib.

3.2.24 Prior use of sorafenib.

3.2.25 Use of cytotoxic chemotherapy within 21 days of registration.

3.2.26 Use of targeted therapy within two half-lives of registration.

3.2.27 Radiation directed at target lesion within 28 days of registration.

3.2.28 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before registration.

3.2.29 Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.
NOTE: Prophylactic anticoagulation as described below is allowed:
- Low dose warfarin (1 mg orally, once daily) with PT-INR $\leq$ 1.5 x ULN is permitted. Infrequent bleeding or elevations in PT-INR have been reported in some subjects taking warfarin while on regorafenib therapy. Therefore, subjects taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
- Low dose aspirin ($\leq$ 100 mg daily).
- Prophylactic doses of heparin.

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

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

3.2.32 Unable or unwilling to discontinue use of strong inducers and inhibitors of CYP450 listed in Appendix for at least 14 days prior to the first dose of study treatment and for the duration of the study (Appendix A). CYP3A4 substrates can be administered, but investigators will need to be aware of possible increased or decreased effectiveness of the non-study drug and this should be recorded in concomitant medications. BCRP and PgP inducers and inhibitors should be used with caution if another alternative drug is not able to be used (Appendix A and B)
Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

4.0 TREATMENT PLAN

4.1 OVERVIEW

The eligible study population will consist of adult patients with histologically confirmed, measurable, unresectable or metastatic angiosarcoma who have progressive disease after prior treatment with ifosfamide, doxorubicin or a taxane. Patients will be treated with daily oral regorafenib (160 mg) for 3 weeks on followed by 1 week off (1 cycle = 4 weeks). Patients will continue treatment until disease progression or withdrawal due to unacceptable toxicity. Once off-treatment, patients will be followed for overall survival up to 5 years. An optimal two-stage Simon design will be employed. The first stage will include 12 patients. If > 3 patients achieve a PFS > 4 months, an additional 19 patients will be enrolled for a total of 31 patients.

4.2 TREATMENT ADMINISTRATION

Regorafenib will be administered orally at a dose of 160 mg regorafenib for 3 weeks on followed by 1 week off. One cycle is 4 weeks (28 days). Patients will be instructed to take 4 40mg regorafenib tables every morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast. Patients will be given examples of low fat breakfasts, such as:
- 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).

4.3 DOSE MODIFICATION & MANAGEMENT OF TOXICITY

4.3.1 Dose Reductions/Re-escalations

The starting dose of regorafenib is 160 mg once daily. Study medication will be administered on a schedule of 3 weeks on followed by 1week off (1 cycle = 4 weeks). 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 Table 1 below. 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.

NOTE: In some cases, dose re-escalation may be permitted at the discretion of the treating investigator. Please refer to the tables below for details regarding when this is acceptable and under what conditions.

Table 1: Pre-defined dose modification levels

Dose Level	Dose	# of Regorafenib Tablets
Dose level 0 [1]	160 mg PO qd	4 40mg tablets
Dose level - 1	120 mg PO qd	3 40-mg tablets
Dose level - 2	80 mg PO qd	2 40-mg tablets

[1] Standard starting dose

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade unless that toxicity is unequivocally deemed not to be causally related to study treatment. In such cases, the investigator may dose reduce according to the toxicity deemed most causally related to study treatment.

Table 2 below outlines dose adjustments for toxicities related to study drug *except* hand-foot skin reaction, hypertension and liver function test abnormalities.

Table 2: Dose Modifications for Toxicities*

Toxicity Grade [a]	Dose Interruption	Dose Modification [b]	Dose for Subsequent Cycles
Grade 0-2	None – 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. According to the National Cancer Institute – Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v 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.
* Dose modifications are for toxicities *except hand-foot-skin reaction, hypertension, and ALT/AST/bilirubin abnormalities. Refer to the tables below for management of these.*

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.

4.3.2 Management and Dose Modifications for HFSR

Table 3: Grading for Hand-Foot-Skin Reaction

	Grade 1	Grade 2	Grade 3
CTCAE v 4.0: Palmar-plantar erythrodysesthesia syndrome [a]	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 4: Recommended Dose Modification for Hand-Foot-Skin Reaction[a]

CTCAE v 4.0 Grade	Occurrence	Suggested Dose Modification
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence No improvement within	*Tolerable* Grade 2: No change *In-tolerable* Grade 2: Decrease 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]
	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.

4.3.2.1 Supportive care guidelines for HFSR

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:

4.3.2.1.1 **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.

4.3.2.1.2 **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.

4.3.2.1.3 **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

4.3.3 Management and Dose Modifications for Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subjects 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, then the subject will be instructed to contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed

according to local institutional 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 5 outlines

suggested dose reductions.

Table 5: Recommended Dose Modifications for Hypertension		
CTCAE v4.0 Grade	**Antihypertensive Therapy**	**Regorafenib Dosing**
Grade 1: Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
Grade 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.
Grade 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]
Grade 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.		

4.3.4 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 should be followed.

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

Table 6: Dose Modifications/Delays for Liver Function Abnormalities

Observed Elevations	1st Occurrence	Restart	Re-occurrence
AST and/or ALT ≤ 5 X ULN (< G3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3 X ULN (≤ G1) or baseline.		
ALT and/or AST >5 X ULN (≥ G3)	Interrupt dosing, with weekly monitoring until transaminases return to < 3 X ULN or baseline.	If the potential benefit for reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: Reduce one dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST > 20 X ULN (≥ G4)	Discontinue		
ALT and/or AST > 3 X ULN (≥ G2) with concurrent bilirubin > 2 X ULN	Discontinue treatment and measure serum liver tests weekly until resolution. *Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.*		
ALT, AST, and bilirubin must be monitored prior to initiation of regorafenib treatment. During the first 2 cycles (2 months) of treatment, ALT, AST and bilirubin will be monitored at least every 2 weeks.			

4.3.5 Prevention/Management Strategies for Diarrhea

Diarrhea can be a common side effect of regorafenib. The preventive/management strategies for diarrhea should be consistent with local institutional 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.

4.4 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 appropriate eCRF (including start/stop dates, dose frequency, route of administration, and indication).

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

Co administration of a strongCYP3A4 inhibitor (ketoconazole) with a single 160mg dose of regorafenib increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of regorafenib with strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

4.4.1 Permitted Concomitant Therapies

- 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 30% of total bone marrow is irradiated to a total of 20 Gy (EQD2). Protocol treatment should be held 7 days before, during and 7 days after palliative radiation, or at the discretion of the site radiation oncologist. Palliative radiation cannot include target lesions.
- Palliative surgery: Protocol treatment should be held 7 days before and until the wound is healed. If treatment is not resumed within 3 weeks, the case will be reviewed byQAM and PI to determine whether or not subject can restart treatment. Palliative surgery cannot include surgery on target lesions.
- 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 prophylactically treated with an agent such as warfarin or heparin will be allowed to participate. Close monitoring (day 1 of each cycle) is mandatory. *NOTE: Therapeutic doses of anti-coagulants are not permitted.*

4.4.2 Concomitant Therapies Not Permitted:

- Other investigational treatment during study treatment.
- *Prior* use of sorafenib.
- Use of cytotoxic chemotherapy within 21 days of registration.
- Use of targeted therapy within two half-lives of registration.
- Radiation directed at target lesion within 28 days of registration.
- Concurrent 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. phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporin, and digoxin). *NOTE: Warfarin is metabolized by the cytochrome enzyme CYP2C9 and it's levels may be especially affected by regorafenib; therefore, only prophylactic doses of warfarin are permitted.*
- Use of drugs that induce CYP3A4 including (but not limited to):
    - Glucocorticoids (cortisone, hydrocortisone, prednisone, methylprednisone, dexamethasone)
    - Anticonvulsants (phenytoin, carbarnazepine, phenobarbital, oxcarbazepine)
    - HIV antivirals (efavirenz, nevirapine)
    - Antibiotics (rifampin, rifabutin, rifapentine)
    - St. John's Wort
    - Modafinil
    - Pioglitazone

4.8 STUDY DURATION AND WITHDRAWAL CRITERIA

Patients will continue treatment until disease progression or development of unacceptable toxicity. In addition, patients may be discontinued from treatment and/or withdrawn from the study for other reasons, as outlined below. 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 appropriate eCRF and in the subject's medical records. Patients will be followed once off-treatment for up to 5 years for overall survival endpoints.

4.8.1 Mandatory Withdrawal Criteria

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 within the same timelines as an SAE, although a pregnancy per se is not considered 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.*
- The *investigator concludes* that continuation of the trial would be harmful to the subject's well-being.
- Subject is *lost to follow-up*.
- *Death* occurs.

4.8.2 Possible Withdrawal Criteria

Subjects **may be** withdrawn from the study for any of 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. 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 investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.
- *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 4.
- Use of *illicit drugs or other substances* that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

5.0 STUDY PROCEDURES

Table 7: Study Visit Parameters

	Baseline (-28days)	On Treatment								Off Treatment	Follow-Up [i]
	Screening [j]	Cycle 1 [l, n]				Cycle 2 [g,l,n]				Cycle 3+ [g,l,n]	End of study treatment	
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9+**		
Regorafenib 160 mg [e]		*On*			*Off*	*On*			*Off*	*Continue [e]*		
Informed consent	X											
Medical history [h]	X											
Physical examination	X	X				X				X	X	
Vital signs [a]	X	X	X	X	X	X	X	X	X	X	X	
CBC/Diff	X	X				X				X	X	
PT/INR [b]	X	X [b]				X [b]				X [b]	X [b]	
Clinical chemistry [c]	X	X		X		X		X		X [c]	X	
Pregnancy test [f]	X											
Urine Protein/Creatinine Ratio (UPC)	X											
ECOG PS	X	X				X				X	X	
Disease Measurements [d]	X [d]									X [d]	X[d]	
Study medication dispensing & pill diary collection		X				X				X		
Tolerability/AE reporting	X	X	X	X	X	X				X	X	
Adverse Event Self-Report Survey (AESRS)		X[k]				X				X		
Concomitant medications	X	X				X				X	X	
Phone call[m, i]			X[m]	X[m]	X[m]							X[i]

a- Vital signs to include height (height is recorded at screen visit only), weight, blood pressure, pulse, temperature. **Blood pressure should be monitored weekly for the first six weeks of study treatment. A patient blood pressure log will be maintained to aid in monitoring (See Appendices). Patients will record blood pressure at home during the weeks they are not coming to the clinic for exams.**

b- PT/INR should be closely monitored on day 1 of each cycle.

c- Electrolytes, calcium, magnesium, BUN, serum creatinine, total bilirubin, AST, ALT, alk phos, albumin, amylase, lipase. Should be done every 2 weeks during Cycles 1 and 2; if no abnormalities are seen, may be done on day 1 only of subsequent cycles. Mid-cycle labs may be performed at a local laboratory if needed to accommodate patient travel logistics..

d **Imaging should be done as clinically indicated** (i.e. CT, MRI and visual measurements), which satisfy RECIST v 1.1 to evaluate disease (such as in extremity, head and neck). Imaging studies will be done at baseline (within 4 weeks (28 days) before the first dose) and repeated after every 2 cycles of treatment (prior to each odd cycle) for tumor response evaluation.

ePatients will receive regorafenib daily x 3 weeks followed by 1 week off (1 cycle = 4 weeks).

f- Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to registration.

g- Assessments including physical examination, vital signs, ECOG PS, clinical chemistry, CBC/Diff and PT/INR should immediately precede initiation of the next cycle of therapy. Clinically indicated scans should be performed during the off week immediately preceding initiation of odd numbered cycles.

h- Medical history findings (i.e. previous diagnoses, diseases or surgeries) will be collected, including those not pertaining to the study indication, beginning before registration, that are considered relevant to the study.

i- Once off treatment, patients will be followed approximately every 6 months by phone for survival endpoints. Follow-up will continue up to 5 years.

j- Screening assessments must be completed within 15 days prior to registration, unless otherwise specified. Screening assessments may be used for C1D1 assessments if completed ≤ 15 days before study drug initiation.

k- Adverse Event Self-Report Survey (AESRS) should be disseminated to each patient on day 1 of cycle 1, but no data is collected.

l- Unless otherwise noted, on-therapy windows for testing will be as follows: imaging scans should be completed within +/- 1 week of the target time point, and labs and physical examination within +/- 3 days of the target time point .

m- Subjects will be instructed to follow-up weekly with the study team IF they are experiencing any side effects.

n- Day 1 of each cycle should be every 28 days. In the event that this day falls on a holiday or other such event, study team should use +/- 3 day window to complete pre-treatment procedures, and dispense protocol agents to patients with instructions to commence treatment on day 1. Any missed doses will not be made up and should be skipped to maintain a 28-day cycle.

6.0 ENDPOINT ASSESSMENT

6.1 DEFINITIONS AND RESPONSE CRITERIA

Response and progression will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in RECIST v 1.1.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

6.1.1 Measurable and non-measurable disease

Measurable tumor lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm on CT (with less than 5 mm slice thickness) or ≥ 10 mm by caliper measurement during clinical examination. For superficial lesions measured by caliper, documentation by color photography including a ruler in the field of view is strongly recommended. MRI may be used in clinically appropriate circumstances to measure tumor lesions. Measurable lymph nodes are defined as those that can be accurately measured as ≥ 15 mm in short axis when assessed by CT.

Lesions failing to reach size criteria above and those that are not reproducibly measurable including leptomeningeal disease, effusions/ascites, inflammatory breast disease, diffuse lymphangitic disease and blastic bone lesions are defined as non-measurable. Previously irradiated lesions will also be considered non-measurable except if unequivocal progression is documented and radiation was greater than 28 days prior to study entry.

6.1.2 Target and non-target lesions

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameter for all target lesions (long axis for tumor lesions and short axis for lymph nodes, if included) will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted.

6.1.3 Guidelines for evaluation of response

Target lesion measurements should be obtained at baseline (within 4 weeks from initiation of regorafenib). Repeat measurements will be performed using the same technique as that used at baseline. For each measurement, a sum

of diameters will be calculated and non-target lesions will be followed as "present", "absent" or in rare cases "unequivocal progression."

6.1.3.1 Target lesion responses

Target lesions will be evaluated as follows:

6.1.3.1.1 **Complete response (CR):** Disappearance of all target lesions

6.1.3.1.2 **Partial response (PR):** ≥ 30% decrease in the baseline sum diameters of target lesions

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

6.1.3.1.4 **Progressive disease (PD):** ≥ 20% increase in the sum diameters of target lesions, taking as reference the smallest sum diameters while on study. The sum diameters must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions also qualifies as PD.

6.1.3.2 Non-target lesions responses:

Non-target lesions will be evaluated as follows:

6.1.3.2.1 **Complete response (CR):** Disappearance of all non-target lesions with all lymph nodes < 10 mm in short axis.

6.1.3.2.2 **Non-CR/Non-PD:** Persistence of one or more non-target lesions

6.1.3.2.3 **Progressive disease (PD):** Unequivocal progression of non-target lesions (meriting discontinuation of regorafenib). The appearance of one or more new lesions also qualifies as PD.

6.1.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account requirements for confirmation. Please refer to Table 8 below.

Table 7: Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time

should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.

6.1.5 Confirmatory Measurement/Duration of Response

6.1.5.1 Confirmation

To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

6.1.5.2 Duration of overall response/stable disease

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

The duration of overall CR is measured from the time that measurement criteria are first met for CR until the date that recurrent disease is objectively documented.

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

6.2 PRIMARY ENDPOINT ASSESSMENT

The primary endpoint of the study will be progression-free survival (PFS) at 4 months, defined as the absence of progression at 4 months. Patients must complete at least 2 cycles of study treatment to be considered evaluable for this endpoint.

6.3 SECONDARY ENDPOINT ASSESSMENT

The progression-free rate (PFR) at 3 and 6 months will be defined as the number of patients with progression absent at these timepoints divided by the total number of study patients. Median PFS (defined as the duration of time from start of treatment until time of progression or death, whichever occurs first) will be estimated as a secondary endpoint. Overall survival will be defined as the time from start of treatment until death by any cause. Response rate (by RECIST v 1.1) will be calculated using the definitions above. The rate and duration of tumor control will be defined as the number of CR+PR+SD responses. Patients must complete at least 2 cycles of study treatment to be considered evaluable for efficacy endpoints.

To evaluate the safety and tolerability of regorafenib, all subjects who receive at least one dose of study treatment will be considered evaluable for the safety analysis. Safety variables will 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 results of clinically indicated studies outside study guidance, such as ECG or chest x-ray images, as produced at the investigator’s discretion. All AEs whether considered drug-related or not, will be reported with a diagnosis, start/stop dates, action taken, whether treatment

was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator. All observations pertinent to the safety of the study treatment will be recorded and included in the final report. This trial will use the NCI CTCAE v 4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.0 ADVERSE EVENTS AND SAFETY MONITORING

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations and as required by the NCI AdEERS Reporting Guidelines.

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.

7.1 ADVERSE EVENT MONITORING

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. 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. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death occurs.

Therapeutic monitoring should be performed following dose 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.

7.2 DEFINITIONS & DESCRIPTIONS

7.2.1 Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal

relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v. 4 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

7.2.2.1 Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

7.2.2.2 Moderate (grade 2): the event causes discomfort that affects normal daily activities.

7.2.2.3 Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

7.2.2.4 Life-threatening (grade 4): the patient was at risk of death at the time of the event.

7.2.2.5 Fatal (grade 5): the event caused death.

7.2.3 Serious adverse events (SAEs)

All SAEs, regardless of attribution, occurring during the study or within 30 days of the last administration of study drug must be reported upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE (as outlined in 7.3 below). A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1 Results in death.
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.2.3.2 Is life-threatening.
The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

7.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24hours.

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is a congenital anomaly/birth defect.

7.2.3.6 Is an important medical event.
Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

Examples: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Medical History vs. Adverse Event

7.2.4.1 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).

7.2.4.2 Conditions that started before registration and for which no symptoms or treatment are present until after registration are recorded as medical history (e.g. seasonal allergy without acute complaints).

7.2.4.3 Conditions that started before registration and for which symptoms or treatment are present after registration, *at unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).

7.2.4.4 Conditions that *started or deteriorated after registration* will be documented as adverse events.

7.2.5 Exceptions to the Definition of SAE

Certain hospitalizations or prolongation of hospitalizations should not be considered SAEs, including those that meeting the following criteria:

7.2.5.1 An admission resulting in a hospital stay of less than 12 hours.

7.2.5.2 An admission that is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study).

7.2.5.3 An admission that is not associated with an AE (i.e. social hospitalization for purposes of respite care).

7.2.6 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

A UPIRSO includes events that meet ALL of the following criteria:

7.3.3.1.1 Are unanticipated in terms of nature, severity, or frequency;

7.3.3.1.2 Place the research subject or others at a different or greater risk of harm; AND

7.3.3.1.3 Are deemed to be related or possibly related to participation in the study.

7.3 ADVERSE EVENT REPORTING

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the Schedule of Events. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Steps to determine if expedited reporting is required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

7.3.2.1 Identify the type of adverse event using the NCI CTCAE v 4.0.

7.3.2.2 Grade the adverse event using the NCI CTCAE v 4.0.

7.3.2.3 Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

7.3.2.3.1 Definite: AE is clearly related to the study treatment.

7.3.2.3.2 Probable: AE is likely related to the study treatment.

7.3.2.3.3 Possible: AE may be related to the study treatment.

7.3.2.3.4 Unrelated: AE is clearly NOT related to the study treatment.

7.3.2.4 Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
7.3.2.4.1 the current protocol;
7.3.2.4.2 the drug package insert;
7.3.2.4.3 the current Investigator's Brochure.

7.3.3 Documentation of AEs

Each event should be described in detail along with start and stop dates, severity, relationship to regorafenib, action taken and outcome.

Any action on study treatment to resolve the AE is to be documented on the appropriate eCRF using the categories listed below:
- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

In addition, 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

7.3.4 Expedited Reporting of SAEs

Completion of the Medwatch form is the preferred method of reporting. This form can be found at: http://www.fda.gov/medwatch/.

7.3.4.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:
- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.4.2 Reporting to the IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.4.3 Reporting to the FDA

This applies to studies conducted under an IND or IDE, as set forth in the Code of Federal Regulations, Section 312.32

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.4.4 Reporting to Bayer HealthCare

Investigators should report SAEs to Bayer using one of the following methods:

- **Email:** DrugSafety.GPV.US@bayer.com
- **Fax:** (973) 709-2185
- **Mail:** Global Pharmacovigilance - USA
  Bayer HealthCare Pharmaceuticals Inc.
  P.O. Box 1000
  Montville, NJ 07045-1000
- **FedEx or UPS:** Global Pharmacovigilance – USA
  340 Changebridge Road

Pine Brook, NJ 07058

- **Phone call to the Clinical Communications Department:** 1-888-765-3203-2937

7.3.5 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.

8.0 DRUG INFORMATION

8.1 SUPPLY AND STORAGE GUIDELINES

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.

8.2 DOSAGE AND ADMINISTRATION

The starting dose for all subjects on this study will be 160 mg daily (4 40 mg tablets). Regorafenib is administered orally. Please refer to Section 4 for further details regarding administration and dose modifications.

8.3 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. Study drug for all sites will be shipped to the lead site (Northwestern University); the lead site will then be responsible for shipping drug to each of the participating sites. For questions about drug ordering or to request drug, please contact the following individual at Bayer Heatlhcare:

Joy Wang, MA
Bayer Healthcare - U.S. Medical Affairs
Investigator Sponsored Studies & Medical Education
6 West Belt Parkway
Wayne, NJ 07470
Office: 973.487.5333
Email: joy.wang1@bayer.com

8.3.1 Accountability

An adequate record of receipt, distribution, and return of all study drugs must be kept at each site. Patients will maintain a pill diary (see Appendices).

8.3.2 Destruction and Return

At the end of the study, unused supplies of regorafenib should be destroyed according to local institutional policies. A certificate of destruction should be sent to Bayer that outlines how much drug was destroyed. This may be sent via:

E-mail: Karen.marini@bayer.com
OR
Fax: 973-709-2193
OR
Mail: [VP of Medical Affairs named in contract]
Bayer HealthCare Pharmaceuticals
6 West Belt
Wayne, NJ 07470

9.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 PRIMARY OUTCOME OF INTEREST

The primary endpoint will be progression-free survival at 4 months. Standard of care therapy currently provides a median PFS of about 3 months with a SD of approximately 2.5 months.

9.2 SECONDARY OUTCOMES OF INTEREST

Secondary endpoints of interest will include progression free rates at 3 and 6 months, median PFS, overall survival, response rates, duration of responses, rates of stable disease, safety and tolerability. Standard of care therapy currently provides a median overall survival of about 9 months with a SD of approximately 4 months.

9.3 TRIAL DESIGN AND DETERMINATION OF SAMPLE SIZE

A two-stage optimal Simon design will be employed to test the null hypothesis that the probability of progression-free survival of 4 months or greater (P) is $\leq$ 0.22 versus the alternative that the probability $\geq$ 0.45. To test this hypothesis with adequate power, a first stage involving 12 patients will be completed. If > 3 patients achieve progression-free survival of 4 months, the trial will be continued for a total of 31 patients. If > 11 out of 31 patients achieve progression-free survival of 4 months, the trial will reject the hypothesis that $P \leq 0.22$ and conclude that $P > 0.45$,

To determine sample size, the following parameters were employed: *P0* = 0.22, *P1* = 0.45, α = 0.05 and β = 0.20. Computations originally performed using software PASS (www.ncss.com).

N1	R1	PET	N	R	Avg N	α	β	Satisfied
26	9	0.000	26	9	26.00	0.043	0.194	Single Stage
7	0	0.176	26	9	22.66	0.042	0.199	Minimax
12	***3***	***0.739***	***31***	***10***	***16.96***	***0.047***	***0.188***	***Optimum***

Definitions:
N1 – sample size in the first stage
R1 – drug rejection number in the first stage
PET – probability of early termination of study
N – combined sample size of both stages
R – combined drug rejection number after both stages
Avg N – average sample size if this design is repeated many times
α – probability of rejecting that $P < P0$ when this is true
β – probability of rejecting that $P > P1$ when this is true
P0 – response proportion P of a poor drug
P1 – response proportion P of a good drug

9.4 PLANNED ANALYSES

Survival data will be analyzed using parametric (exponential) and non-parametric (Kaplan-Meier) methods. Exact methods for providing confidence intervals for proportions "surviving" landmarks will be used as needed. Statistical software will be SAS (and others as merited) and analysis will be conducted under the supervision of Alfred Rademaker, PhD, in the Biostatistical Core Facility at Northwestern University.

Descriptive statistics (mean, standard deviation, mean change from baseline, etc.) will be presented for laboratory values. Detailed examination of AEs by NCI CTCAE grade and frequency tabulation will be presented. Missing data for partial dates on AEs or concomitant medications may be imputed.

10.0 STUDY MANAGEMENT

10.1 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.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 AMENDMENTS

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bayer. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

10.3 REQUIRED DOCUMENTATION FOR MULTI-SITE STUDIES

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

10.3.1 Signed and completed Letter of Invitation to participate in the study.

10.3.2 Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.

10.3.3 A copy of the official IRB approval letter for the protocol and informed consent.

NOTE: Informed consent form should be submitted to the Clinical Research Office for review/approval prior to submission to the local IRB.

10.3.4 CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study at the site.

10.3.5 Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

10.4 SUBJECT REGISTRATION PROCEDURES

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

Registering a Patient to a Phase II Study

For potential patients this study, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)

• Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

10.5 DATA SUBMISSION

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, for all phase II patients, data are due at the end of every cycle within 10 days.

10.6 DATA MANAGEMENT AND MONITORING/AUDITING

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer NOTIS for additional data submission instructions.

10.7 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.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

10.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

10.6.2.1 Is generally noted or recognized after it occurs.

10.6.2.2 Has no substantive effect on the risks to research participants

10.6.2.3 Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.

10.6.2.4 Did not result from willful or knowing misconduct on the part Of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI)if the variance:

10.6.2.5 Has harmed or increased the risk of harm to one or more research participants.

10.6.2.6 Has damaged the scientific integrity of the data collected for the study.

10.6.2.7 Results from willful or knowing misconduct on the part of the investigator(s).

10.6.2.8 Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

10.8 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 PI is responsible for personally overseeing the treatment of all study patients. The PI 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 (local PI) will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

10.9 PREMATURE TERMINATION OF THE STUDY

The study may be halted prematurely for any of the following reasons:

- 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.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties (including approval from the Data Monitoring Committee at Northwestern University).
- All affected institutions and their IRBs, competent authority (ies), study center, and the 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.

10.10 PUBLICATION POLICY

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to Bayer Healthcare(funding source).
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 30 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 also ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

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APPENDIX I – DATA COLLECTION & SUBMISSION GUIDELINES

Study-specific instructions regarding the entry and submission of data using eCRFs through NOTIS will be provided at the time of training prior to study activation. In addition, instructional videos on data entry using NOTIS and eCRFs are available on the CRO's website at: https://www.cancertrials.northwestern.edu/working-with-the-cro. The Internal and Affiliate Data Compliance Policies of the Lurie Cancer Center's DMC regarding will be strictly enforced.

Please refer to stand-alone document in NOTIS
'NU13S02 Data submission guidelines' for more details.

APPENDIX II – PILL DIARY

Pill diary available as stand-alone document in NOTIS

APPENDIX III – BLOOD PRESSURE LOG

Protocol Number_____Institution _____

Subject Initials_____Subject ID# _____

Date of assessment	Time of assessment	Systolic/Diastolic (mmHg)	Comments
Wk1:			
Wk2:			
Wk3:			
Wk4:			
Wk5:			
Wk6:			

Blood pressure should be recorded weekly during the first six weeks of treatment.

_____ _____

CRA Initials Date of Completion

APPENDIX IV – DATA SAFETY MONITORING PLAN

This trial will be conducted and monitored in accordance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. A copy of the plan can be obtained from the following link:

https://www.cancertrials.northwestern.edu/cpsrms/cpsrms-p-ps

Data is expected to be submitted according to requirements described in appendix I. The QAM will review and assess each submitted eCRF for completeness, protocol adherence/compliance, toxicities, potential subject safety issues, and disease outcome and response. The QAM will routinely query study teams regarding any issues or for outstanding data. The QAM will present SAEs, protocol deviations, data summaries, and any other issues that may impact patient safety or data integrity to the DMC on a semi-monthly basis.

APPENDIX V - ADVERSE EVENTS SELF-REPORT SURVEY

Available as stand-alone document in NOTIS

APPENDIX VI – PROTOCOL HISTORY OF CHANGES

Initial Version approved by Scientific Review Committee – May 10, 2013			
Amendment 1 (pre-IRB submission) – October 10, 2013 *Approved by SRC – October 22, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Throughout	n/a	Adds the Bayer Healthcare study number to the header (ONC-2013-129)	Administrative
Synopsis, 2.1 (Primary Objective), 6.2 (Primary Endpoint Assessment), 9.1 (Primary Outcome of Interest)	Primary objective was progression-free survival (PFS).	Changed primary objective to PFS at 4 months.	This was changed at the recommendation of the company providing regorafenib (Bayer Healthcare). PFS at 4 months is the only endpoint that the study is designed to assess with a pre-identified risk of error, which makes it the logical basis for conclusion of efficacy in this trial.
Synopsis, 2.2 (Secondary Objectives), 6.3 (Secondary Endpoint Assessment), 9.2 (Secondary Outcomes of Interest)	n/a	Adds overall PFS and progression-free rate (PFR) at 3 and 6 months secondary objectives.	PFR has been established as an endpoint for soft tissue sarcoma by the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTCSTBSG) to account for low PR rates in this disease. This was changed at the recommendation of Bayer Healthcare.
1.2 (Rationale)	n/a	Adds a statement that future phase III or other large-scale confirmatory trials should employ an interim analysis as an efficacy double-check if this trial meets efficacy criteria.	Added at the recommendation of Bayer Healthcare.
3.1 (Inclusion Criteria)	n/a	Adds that “Patients who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided	Added at the recommendation of Bayer Healthcare.

		that no prior evidence of underlying abnormality in coagulation parameters exists." Gives recommendations for how to monitor this.	
3.1 (Inclusion Criteria)	No limit on the number of prior therapies for eligibility.	Allows up to 4 prior therapies for eligibility; clarifies that progressive disease must have been under last palliative therapy.	Added at the recommendation of Bayer Healthcare.
Table 4 (Recommended Dose Modification for Hand-Foot-Skin Reaction)	n/a	Removes footnote "e".	Administrative – did not pertain to any part of the table.
Table 6 (Dose Modifications/Delays for Liver Function Abnormalities), Table 7 (Study Visit Parameters)	Stated that ALT, AST and bilirubin will be monitored at least weekly during the first 2 cycles of treatment.	Changes this to require monitoring prior to initiation of regorafenib treatment, and then every 2 weeks during the first 2 cycles; adds that 2 cycles = 2 months. Updates visit parameters accordingly.	Clarification and change requested by Bayer Healthcare.
4.3.5 (Prevention/Management Strategies for Diarrhea)	Stated that the same dose modification algorithm used for skin toxicities should be used for diarrhea.	Revises this to state only that diarrhea prevention and management should be consistent with local institutional practices.	Update requested by Bayer Healthcare.
4.4 (Prior and Concomitant Therapy)	General background given on the interactions of CYP3A4 inducers and inhibitors on regorafenib.	Adds detailed background information on the effects of co-administration of strong CYP3A4 inducers (such as rifampin) and strong CYP3A4 inhibitors (such as ketoconazole) on exposure of regorafenib and its metabolites.	Update requested by Bayer Healthcare.
4.4 (Prior and Concomitant Therapy)	Mentioned that "caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6	Removes this statement.	Per Bayer Healthcare, only strong CYP3A4 inducers and inhibitors are prohibited.

	and CYP2C9. Such concomitant medication should be avoided, if possible."		
4.4.1 (Permitted Concomitant Therapies), 4.4.2 (Concomitant Therapies Not Permitted)	Stated that *therapeutic* anti-coagulation with agents such as warfarin or heparin are allowed.	Revises this to indicate that only *prophylactic* treatment with such agents is permitted.	Changed to be consistent with eligibility criteria (3.2.29).
4,8.1 (Mandatory Withdrawal Criteria)	"Pregnancy" and "investigator conclusion that continuation of the trial would be harmful" listed as *possible* withdrawal criteria.	Changes "pregnancy" and "investigator conclusion that continuation of the trial would be harmful" to events requiring *mandatory* withdrawal. Clarifies that pregnancy *itself* is *not an SAE*, but that it should be reported along the timelines as an SAE.	Added at the recommendation of Bayer Healthcare.
Table 7 (Study Visit Parameters)	Footnote "b" mentioned therapeutic doses of anti-coagulants.	Removes reference to this.	Therapeutic doses of anticoagulants are not permitted.
Table 7 (Study Visit Parameters)	AE/tolerability reporting required on day 1 of each cycle.	Changed to require AE reporting weekly over the phone during cycle 1 (and then day 1 of each cycle thereafter).	Added at the recommendation of Bayer Healthcare.
Table 7 (Study Visit Parameters)	n/a	Adds "& pill diary collection" to be done at the time of dispensation of study medication.	Administrative
8.1 (Supply and Storage Guidelines), 8.2 (Dose and Administration)	n/a	Removes language about the contents of regorafenib tablets.	Removed at the request of Bayer Healthcare.
10.4 (Subject Registration Procedures)	Contained some outdated language and instructions.	Updates the language and instructions pertaining to registration of study patients.	Administrative update
Appendix I	Contained some outdated language and generic instructions.	Updates the language to provide study-specific instructions and timelines for submission of study data via eCRFs.	Administrative update
Appendix IV	n/a	Adds more study-specific detail regarding how the study will be monitored.	Administrative

Appendix VI	n/a	Adds a Protocol History of Changes to summarize changes by amendment.	Administrative
Amendment 2 – September 19, 2014 *Approved by SRC – November 5, 2014*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
List of Abbreviations, 3.1.9.6, and 2nd NOTE in 2.1.9	PTT	PT/INR replaces PTT.	Revised for accuracy.
5.0 (Study parameters table)	Rows entitled "CT C/A/P" and "Other scans"	Combined to form one row entitled "Disease Measurements"	Clarification of disease measurement procedures
5.0 (Study parameters table)	Footnote "d" relating to "CT C/A/P" and footnote "e" relating to "Other scans"	Footnotes "d" and "e" combined into footnote "d" now relating to "Disease Measurements". Footnote "d" revised to add "MRI and visual measurements" as options for other imaging studies that are clinically indicated. All remaining footnotes re-lettered to reflect change.	Clarification of disease measurement procedures
5.0 (Study parameters table)	Footnote "j" reading "Screening assessments must be completed within 2 weeks prior to registration, unless otherwise specified."	Revised to add "Screening assessments may be used for C1D1 assessments if completed ≤ 2 weeks before study drug initiation."	Revised so that patients do not repeat screening assessments unnecessarily.
5.0 (Study parameters table)	n/a	Footnote "k" added, "Adverse Event Self-Report Survey (AESRS) should be disseminated to each patient on day 1 of cycle 1, but no data is collected."	Clarification
5.0 (Study parameters table)	n/a	Footnote "l" added. "Unless otherwise noted, on-therapy windows for testing will be as follows: imaging scans should be completed within +/- 1 week of the target time point, and labs and	Revised to add windows for on therapy testing.

		physical examination within +/- 3 days of the target time point."	
Amendment 3 – May 18, 2015 *Approved by SRC – May 20, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover Page	IND #: TBD	Added IND exemption 120139 EXEMPT**.**	New information
3.1 (Inclusion Criteria)	n/a	Adds how prior therapies are counted is at the discretion of the treating physician and principal investigator.	Clarification
5.0 (Study parameters table)	Urinalysis	Changes urinalysis to urine protein/creatinine ratio (UPC) as this is what is required for eligibility in section 3.1.	Clarification
Amendment 4 – February28, 2017			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Protocol title page and Study summary	Mayo Clinic (Scottsdale), University of Wisconsin and Minnesota included as affiliate sites	Removed Mayo Clinic (Scottsdale), University of Wisconsin and Minnesota as affiliate sites. Added University of Iowa to the summary section	***They are no longer affiliate sites for this study*** ***Correction of error***
Section 3.1.9 Inclusion criteria	List of laboratory requirements to be considered for eligibility with a note that blood transfusion will not be allowed in order to meet criteria	Note modified to state that "subjects may not have had a transfusion within 7 days of screening assessment" for these laboratory tests.	***For clarity and flexibility***
Section 3.2.5 Exclusion criteria	Statement of exclusionary criteria for patients with thrombotic, embolic, venous or arterial events.	*Note added to state an exception, that " Subjects with recent DVT who have been treated with therapeutic anticoagulating agents for at least 6 weeks prior to study treatment are eligible"*	***For clarity and flexibility***

Section 3.2.32 New exclusion criteria added	N/A	Criteria explaining the exclusion of patients that are unable or unwilling to discontinue use of strong inducers and inhibitors of CYP450	***For added clarity, flexibility and safety***
Section 4.4.1 Permitted Concomitant Therapies	Details about possible palliative radiation therapy during study treatment.	Added language: ‘‘Protocol treatment should be held 7 days before, during and 7 days after palliative radiation, or at the discretion of the site radiation oncologist. Palliative radiation cannot include target lesions.” “Palliative surgery: Protocol treatment should be held 7 days before and until the wound is healed. If treatment is not resumed within 3 weeks, the case will be reviewed by QAM and PI to determine whether or not subject can restart treatment. Palliative surgery cannot include surgery on target lesions.’’	***For added clarity, flexibility and safety***
Section 5.0 study procedures table	Previous list of footnotes	<u>Numbering of footnotes corrected and some new footnotes added</u>: Footnote k: “Unless otherwise noted, on-therapy windows for testing will be as follows: imaging scans should be completed within +/- 1 week of the target time point, and labs and physical examination within +/- 3	***For added clarity, flexibility and safety***

		days of the target time point “. Footnote L: “Subjects will be instructed to follow-up weekly with the study team IF they are experiencing any side effects.” Footnote m: “Day 1 of each cycle should be every 28 days. In the event that this day falls on a holiday or other such event, study team should use +/- 3 day window to complete pre-treatment procedures, and dispense protocol agents to patients with instructions to commence treatment on day 1. Any missed doses will not be made up and should be skipped to maintain a 28-day cycle.” <u>In addition,</u> Footnote f regarding assessments :CT C/A/P has been modified to read “ clinically indicated scans” Footnote C regarding CT scans: has been modified to state: “Imaging should be done as clinically indicated (i.e. CT, MRI and visual measurements), which satisfy RECIST v 1.1 to evaluate disease (such as in extremity, head and neck). Imaging studies will be done at	

		baseline (within 4 weeks before the first dose) and repeated after every 2 cycles of treatment (prior to each odd cycle) for tumour response evaluation."	
Section 7.3.4 Expedited Reporting of SAEs	Previous NU protocol template language	Updated to current NU protocol template language	***To align with current NUIIT protocol template and IRB requirements.***
Section 10.4 Subject registration procedures	Previous NU protocol template language	Updated to current NU protocol template language	***To align with current NUIIT protocol template and IRB requirements.***
Section 10.5 Data submission guidelines (new section added)	N/A	Language added from current NU protocol template directing users to refer to the 'stand-alone' document in NOTIS that contains the data submission guidelines. (Previously, an outdated version of these guidelines were included in the Appendix. These have been removed in this amendment)	***To align with current NUIIT protocol template and IRB requirements***
Section 10.6 Data management and monitoring/auditing	Reference to data Safety Monitoring plan in the Appendix.	Updated to refer to Data Safety Monitoring plan in NOTIS.	***To align with current NUIIT protocol template and IRB requirements***
Section 10.7.2 Other protocol deviations	Sub-section Promptly Reportable Non-Compliance(PRNC)	Term replaced with Reportable New Information(RNI)	***To align with current NUIIT protocol template and IRB requirements***
Section 10.10 Publication policy	Previous language stating conditions mandated by Bayer Healthcare	Added language from current NU protocol template	***To align with current NUIIT protocol template and IRB requirements***
Appendix II	Entire pill dairy included in this appendix	Pill dairy removed. Language inserted asking users to refer to NOTIS for pill dairy	***For convenience and to align with current NUIIT protocol template***
Appendix III Blood pressure log	Previous template	Updated with more details.	***For convenience and clarity***
Adverse Event Self-Report Survey(AESRS)	Entire survey was inserted in the appendix	Survey removed. Language inserted stating that the survey is available as a stand-	***For convenience and to align with current NUIIT protocol template***

		alone document in NOTIS.	
Amendment 5-March 6th , 2018			
Section(s) Affected	***Prior Version***	***Changes***	***Rationale***
Title page and Synopsis	Study information along with affiliate site PI information	Added new affiliate site with PI information: Sant P. Chawla, MD Sarcoma Oncology Research Center, CA	***On-boarding of new affiliate site***
Section 5.0	Baseline did not have a definite window stated	Added a -28 day baseline window.	***For convenience and consistency***
Section 5.0 footnote c	The language pertaining to imaging was clubbed together with chemistry laboratory tests, due to a formatting error	The imaging language has now been shifted back to footnote d and all other footnotes readjusted to its previous accurate and corresponding positions in the table.	***Correction of error.***
Section 5.0 footnote j	The Screening assessments had a 2 week window	The screening assessment window has been changed to 15 days	***For convenience***
Section 5.0	Follow-up footnotes were not clearly marked	Follow-up footnotes: (i) and (m) clearly allocated in the table	***For increased clarity***
Section 11 Data Submission	Data submission guidelines for Phase II study	Inserted a window of 10 days for Phase II data , as per CTO policy	***To align with NU CTO policy***

Amendment 6 dated 4.3.19			
Section(s) Affected	***Prior Version***	***Changes in Amend 6***	***Rationale***
Section 3.1.7 Inclusion criteria	Progressive disease under last palliative therapy with a history of prior ifosfamide, doxorubicin or taxane therapy for angiosarcoma. Up to 4 prior therapies are allowed	Added language to state: "If patient refuses or if IV chemotherapy is contraindicated, patients will be eligible if they fail one systemic therapy."	***For flexibility and clarity***