Study of Regorafenib for Urothelial Cancer Following Chemotherapy

Study Protocol & Statistical Analysis Plan

NCT02459119

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STUDY TITLE: A Multicenter, Non-Randomized, Phase II study of Regorafenib for Advanced Urothelial Cancer Following Prior Chemotherapy

Test drug(s):	Regorafenib
[Study purpose:]	Proof of concept
Clinical study phase:	II
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

[Title]	**A Multicenter, Non-Randomized, Phase II study of Oral Regorafenib for Advanced Urothelial Cancer Following Prior Chemotherapy**
Clinical study phase	II
Study objective(s)	Progression-free survival (PFS) at 6 months (PFS6)
[Background treatment]	Platinum based chemotherapy
Indication	Advanced urothelial or transitional cell carcinoma who have failed 1-3 previous treatments
Diagnosis and main criteria for inclusion	Pathologically or cytologically confirmed locally advanced unresectable or metastatic invasive transitional cell carcinoma of the urothelium Progressive disease following 1-3 chemotherapy regimens
Study design	Metastatic UC progressing after prior chemotherapy (N-35) → Archival FFPE slides (15 slides of 10 µM sections, slides of 5 µM sections) ↓ Regorafenib 120 mg po for 21 days of 28 days in cycle 1 increased to 160 mg po daily from cycle 2 or later if no Regorafenib- → Clinical and laboratory daily evaluation day 1 of each 28 day cycle Radiologic evaluation every 8 weeks ↓ Continue therapy until disease progression or intolerable toxicities

Type of control	No control arm in this nonrandomized study
Number of subjects	35 patients; 4 sites
Plan for statistical analysis	A minimum of 32 evaluable subjects will be included in final analysis. Given that 5-10% of patients may be inevaluable, up to 35 patients may be enrolled. The alpha level of the design is 0.05 and the power is 0.8. Chi-square or Fisher's exact test will be employed to determine univariate association of biomarker status with PFS6 and objective response.

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List of abbreviations

ADL	Activities of Daily Living
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	*bis in die*, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NM	Nano molar
NYHA	New York Heart Association

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

1. Introduction

Patients with advanced urothelial carcinoma (UC) have a poor long term prognosis. Those patients who progress after initial responses with first-line platinum based chemotherapy have limited treatment options. Novel therapeutic options are needed for this patient population, especially in the second line setting.

1.1 Background

1.1.1 Systemic therapy for advanced urothelial carcinoma

Advanced UC has not enjoyed major improvements in outcomes for over two decades. Despite initial high response rates (RR) of 40% to 70% with cisplatin-based frontline combination chemotherapy, these regimens are generally not curative, and yield 5-year overall survival (OS) of 4% to 20%.(1-3). Multiple agents have demonstrated limited activity in the second-line setting, with response rates of 5% to 20%, median progression-free survival (PFS) of 2 to 4 months and a median OS of 6 to 9 months (4-13). Hence, there are significant unmet medical needs, particularly in the second-line setting.

A large randomized phase III trial accrued 370 patients and compared vinflunine plus Best Supportive Care (BSC) to BSC alone as second-line therapy (14). This trial permitted patients progressing after frontline platinum-containing chemotherapy for metastatic disease, and those who had received prior perioperative chemotherapy only were excluded. More than 80% had progressed within 6 months after prior chemotherapy and greater than 70% of patients had visceral involvement. Although an extension of survival, the primary endpoint, was not demonstrated with vinflunine compared to placebo by an intention-to-treat analysis (6.9 vs. 4.6 months, P=0.287), there was a statistical improvement in RR (8.6 vs. 0%) and median PFS (3.0 vs. 1.5 months). Approximately 30% of patients in both arms received subsequent undefined systemic therapy after progression, which may have confounded OS. Multivariate Cox analysis adjusting for front-line prognostic factors showed a statistically significant extension of OS with vinflunine (P = .036), reducing the risk of death by 23%. Additionally, in the eligible population (n = 357), the median OS was significantly longer for vinflunine + BSC compared to BSC (6.9 vs. 4.3 months, P=0.04). As a result of this study, vinflunine has been approved by the European Medicine Agency (EMEA) and is the first agent approved by a regulatory agency for this indication. Nevertheless, the activity of vinflunine is modest and appears similar to the activity of other agents that have been evaluated in smaller phase II trials, e.g. taxanes, pemetrexed.

Since both PFS and OS are influenced by baseline clinical factors, interpretation of results of nonrandomized phase II trials needs to occur carefully. Indeed, survival has been shown to vary as a function of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), hemoglobin (Hb) and liver metastasis (LM) (15). Other factors may also impact on outcomes. A retrospective study of a large pooled prospective phase II trial dataset externally validated the independent impact of time from prior chemotherapy (TFPC), in additi
on to Hb, PS and LM, on PFS, although the independent impact of TFPC on OS could not be externally validated in the vinflunine phase III trial (16). However, the pooled phase II trial discovery dataset did demonstrate a strong independent impact of TFPC on OS. One major difference between the discovery dataset and validation datasets may possibly have hampered the external validation of an association of TFPC with OS: the inclusion of patients who had received prior peri-operative chemotherapy only in the discovery dataset, while patients in the validation dataset were required to have received prior chemotherapy for metastatic disease. A 4-variable nomogram has been constructed including Hb, PS, LM and TFPC to predict the activity of second-line therapy (i.e. PFS6) using historically used agents

(17). The comparison of observed vs. expected PFS6 may facilitate interpretation of PFS6 in nonrandomized trials, i.e. an observed PFS6 should be required to be at least similar and preferably superior to predicted PFS6. Notably, PFS6 has been demonstrated to be more robustly associated with OS, and performed better compared to response as an intermediate surrogate for OS (18). Finally, other variables such as number of prior lines of therapy, response to prior therapy, prior perioperative chemotherapy and site of primary (bladder vs. other) have not been identified to be independently prognostic after controlling for the above 4 major prognostic factors (19, 20).

Trials of metastatic UC in the second line setting have commonly utilized response rate (RR) and median PFS as intermediate endpoints to potentially capture OS. However, response may not capture the activity of cytostatic agents and both of these endpoints do not lend confidence with regard to the durability of benefits. We recently demonstrated that PFS at 6 months (PFS6) is strongly associated with OS at 12 months (OS12) and appears more optimal than RR to identify active second-line agents for advanced UC (21). PFS6 rate for this large pooled phase II trial dataset including patients treated with chemotherapy and/or biologic agents was 22%. In the discovery dataset, a significant correlation was observed between PFS6 and OS12 at the trial (R^2=0.55, Pearson correlation=0.66) and individual levels (82%, Ķ=0.45). Response correlated with OS12 at the individual level less robustly (78%, Ķ= 0.36), and the trial level association was not statistically significant (R^2=0.16, Pearson correlation= 0.37). The correlation of PFS6 (81%, Ķ= 0.44) appeared stronger than the correlation of response (76%, Ķ= 0.17) with OS12 at the individual patient level in the external validation phase III trial dataset.

1.1.2 Angiogenesis as a therapeutic target in urothelial carcinoma

No single dominant therapeutic target has emerged. However, angiogenesis appears to be a broad target. UC is target rich malignancy with subsets that probably benefit from agents inhibiting multiple targets. There is robust scientific rationale for targeting the tumor vasculature in urothelial carcinoma. A greater microvessel density in cystectomy specimens has been associated with higher rates of recurrence.(22, 23) Both serum and urine levels of VEGF are increased in urothelial carcinoma and are predictive of recurrence of non-muscle-invasive bladder cancer (NMIBC) (24, 25). Higher serum levels of VEGF are predictive of metastatic disease in urothelial carcinoma.(26) Expression of VEGFR2 is greater in MIBC than NMIBC.(27) Serum levels of VEGF are higher in MIBC than in NMIBC and VEGF has been shown induce proliferation of bladder cancer cell lines.(28)

<u>Vascular endothelial growth factor axis as a therapeutic target</u>
Bevacizumab is a monoclonal antibody that binds and neutralizes VEGF. Bevacizumab has been evaluated in combination with GC in a phase II trial conducted by the Hoosier Oncology Group (HOG).(29) The objective response rate was 72% including 19% with complete responses. The median progression free survival (PFS) was 8.2 months with a median overall survival (OS) of 19.1 months. Thromboembolic events occurred in 21% of patients. Notably, the incidence of thromboembolism was only 8% after the protocol was amended to a lower dose of gemcitabine. Other adverse events associated with bevacizumab included hemorrhage (37%), cardiac events (30%), hypertension (21%) and proteinuria (16%). Bevacizumab has also been evaluated with gemcitabine and carboplatin in a phase II trial in patients who were unfit for cisplatin.(30) The response rate was 49% with 6% achieving a complete response. The median PFS was 6.5 months with a median OS of 13.9 months. Thromboembolic events occurred in 20% of subjects. Given the efficacy outcomes in this phase II trial that appear to be superior to GC alone when comparing across trials, there is significant interest in targeting VEGF to provide an increment in outcomes. The definitive phase III study comparing GC + bevacizumab/placebo

(NCT00942331, CALGB 90601) is currently being conducted in the United States cooperative groups.

Sunitinib is an inhibitor of multiple targets including VEGFR, PDGFR, c-Kit and FLT3. Preclinical studies have shown activity in urothelial carcinoma cell lines and xenografts (31). Sunitinib has been evaluated as a single agent in the first-line setting in cisplatin-ineligible patients and showed a response rate of only 8%.(32) However, Clinical benefit (PR + SD) was 58% and median time to progression (TTP) was 4.8 months and median overall survival 8.1 months. Interestingly, low interleukin (IL)-8 levels and tumor contrast enhancement >40 Hounsfield units at baseline were associated with a better clinical outcome, suggesting their potential as biomarkers. In the second-line setting as a single agent the response rate was 5%.(33) In this phase II trial, 77 patients received sunitinib on one of two schedules (50 mg per day for 4 weeks on and 2 weeks off [cohort A], 37.5 mg per day continuously [cohort B]). A partial response was seen in three of 45 patients in cohort A, and in one of 32 patients in cohort B. Clinical regression or stable disease was achieved in 33 of 77 patients (43%). The progression-free survival (2.4 v 2.3 months; P = .4) and overall survival (7.1 v 6.0 months; P = .4) were similar in both cohorts. There was one treatment-related death, and 47 patients (33 in cohort A, 24 in cohort B) experienced grade 3 or 4 toxicity. Pazopanib, an inhibitor of VEGFR, PDGFR and c-Kit, has been evaluated in urothelial carcinoma. As a single agent in platinum-refractory disease, the objective response rate was reported to be 17%; though toxicity was notable for fistulization potentially due to vigorous response (34). This study used CT and PET/CT on a monthly basis. Several patients not meeting response by RECIST were noted to have decreased metabolic activity on PET/CT suggesting activity of the drug in some patients with stable disease. However, a subset of patients appeared to garner durable benefits: 4 (10%) were progression free after a median follow-up of 19 months. Similar to the first-line sunitinib trial, high baseline IL-8 conferred poor outcomes, and early increases during treatment were also associated with poor outcomes. Thus, inhibition of the VEGF pathway demonstrates activity at least in a subset of patients. A randomized phase II trial is comparing second-line weekly paclitaxel versus Pazopanib (PLUTO trial). A more recent nonrandomized phase II trial combined Pazopanib with weekly Paclitaxel as second-line therapy and suggested a potential increment in outcomes with a high ORR and median OS of 10 months.(35)

Cabozantinib is a TKI targeting VEGFR and MET, has demonstrated promising bone metastasis targeted activity in advanced prostate cancer and is currently under evaluation as salvage therapy for patients with metastatic UC (NCT01688999).(36, 37) Preliminarily, responses have been observed and associated with low peripheral blood regulatory T cells (Tregs). The neoadjuvant setting is also being explored: Nintedanib, a TKI targeting VEGFR and FGFR, is being investigated in a randomized phase II trial in combination with GC to evaluate pathologic complete response (pCR) as the primary endpoint. The neoadjuvant setting is also being explored: Nintedanib, a TKI targeting VEGFR and FGFR, is being investigated in a randomized phase II trial in combination with GC to evaluate pathologic complete response (pCR) as the primary endpoint. A randomized phase II study to evaluate gemcitabine-carboplatin with or without Vandetanib, a VEGF and EGF receptor TKI, is ongoing for the first-line treatment of cisplatin-ineligible patients. The monoclonal antibodies IMC-18F1 and Ramucirumab target VEGFR1 and VEGFR2, respectively. A randomized phase II study is evaluating docetaxel with either Ramucirumab, IMC-18F1 or alone in the second-line setting (NCT01282463). Aflibercept is a recombinant fusion protein that binds multiple VEGF isoforms. TRC105 is antibody targeting CD105 which is a TGFβ coreceptor expressed on the endothelium. TRC105 is being evaluated in a phase II study in UC (NCT01328574).

Angiopoietin-Tie2 axis as a therapeutic target in UC

The angiopoietin ligands in the angiopoietin-tie1/2 signaling pathway have also been documented to be expressed in human subjects with UC (38). The expression of Ang-1 and -2 were assessed by IHC from 52 UCs of the bladder in this. Expression was detected in 18 samples (35%) for Ang-1 and in 23 samples (44%) for Ang-2. Ang-2 expression was also significantly correlated with histological grade, stage and poor prognosis. On multivariate analysis, positive Ang -2 expression was an independent negative predictor for survival (P = 0.042). Another study analyzed the expression of the mRNA of VEGF, Ang-1 and Ang-2 in 113 UCs (39). Multivariate analysis identified Ang-2 as an independent predictor of tumor recurrence and Tie2 expression as an independent favorable prognostic factor for both metastasis and disease-specific survival. These data show the strongest change in expression of VEGF and Ang-1 occurred in non-muscle invasive bladder cancer in comparison with normal bladder epithelium and the invasive tumor stages. One study analyzed the expression of mRNA for VEGF, Ang-1 and Ang-2 in 71 UCs (40). Low-stage superficial UC expressed VEGF and Ang-2 mRNA at a significantly higher level than high-stage muscle invasive carcinomas, and low-grade TCC at an insignificantly higher level than high-grade tumors. Conversely, Ang-1 mRNA was expressed at a significantly lower level in low-grade, low-stage compared to high-grade, high-stage UC. Thus, a significant drop of VEGF and Ang-2 mRNA expression coupled with higher Ang-1 in muscle-invasive cancer may represent a crucial event in progression.

Trebananib (AMG 386) consists of an angiopoietin antagonist-Fc fusion and will be evaluated in combination with docetaxel in platinum-resistant disease (NCT01907308) based on promising activity in a phase I trial in an advanced UC patient. Indeed, one patient with cisplatin-refractory advanced bladder cancer receiving combination carboplatin plus paclitaxel chemotherapy with AMG386, a monoclonal antibody against Tie2, exhibited a complete response at week 8 (41). Moreover, preclinical activity in UC has been demonstrated for CEP11981, a small molecule TKI of VEGF and Tie2 receptors, which has a similar spectrum of targets as Regorafenib(42). CEP11981 at 5 mg/kg significantly inhibited human urothelial carcinoma xenografts compared to controls ($p<0.05$). IHC of xenografts demonstrated no differences in CD31, cleaved caspase-3 or VEGFR2, but TIE2 was significantly down-regulated ($p=0.008$) by CEP-11981, suggesting that the inhibition of TIE2 may be the major mechanism of anti-tumor activity against UC. Thus, CEP-11981 demonstrated a significant pre-clinical activity against human UC xenografts, which was attributable primarily to effects on TIE2 receptor. Although CEP11981 is not being developed clinically, Regorafenib has a similar spectrum of targets, i.e. the VEGFRs and TIE2.

Fibroblast growth factor axis as a therapeutic target

In the last ten years, it has become clear that FGF signaling is altered in a high proportion of bladder tumors. FGFR1 overexpression is frequent in all grades and stages and recent data indicate a role in urothelial epithelial-mesenchymal transition (43). In vitro and in vivo studies have shown that FGFR inhibition has cytotoxic and/or cytostatic effects in FGFR-dependent bladder cancer cells (44). FGFR3 is frequently mutated in low grade, non-muscle-invasive bladder cancer (NMIBC). FGFR3 mutations do occur in metastatic urothelial carcinoma but are less common and found in ~15% of tumors.(45) FGFR3 signaling contributes to angiogenesis. Dovitinib, a small molecule inhibitor of multiple angiogenic factors including FGFR3 has been evaluated as a single agent in a phase II study in subjects having received prior chemotherapy.(46) Tumor tissue was evaluated for FGFR3 mutation and patients were stratified by mutational status. Total accrual was 44 subjects (31 wild-type, 12 mutated and 1 unknown). Only one objective response was seen in a subject with wild-type FGFR3. Dovitinib is also being evaluated in BCG-refractory NMIBC that harbors either FGFR3 mutation or overexpression (NCT01732107). However, more potent and selective pan-FGFR

inhibition by BGJ398 and JNJ-42756493 has preliminarily demonstrated robust responses in UC harboring FGFR3 mutations, FGFR3/TACC3 translocation or FGFR2 truncation.(47-49) Further clinical development of these agents and another monoclonal antibody targeting FGFR3 are planned in randomized trials.

Table: Ongoing or planned randomized trials investigating angiogenesis-promoting targets in urothelial carcinoma

Phase	Therapeutic target	Control arm	Experimental arm	Trial ID
First-line for cisplatin-eligible advanced disease				
III	VEGF	GC + Placebo	GC + Bevacizumab	NCT00942331, CALGB 90601
First-line for cisplatin-ineligible advanced disease				
II	VEGFR, EGFR	GCa	GCa + Vandetanib	NCT01191892
Second or later line for advanced disease				
II	VEGFR	Weekly paclitaxel	Pazopanib	73030316 (PLUTO)
II	VEGFR1 or VEGFR2	Docetaxel	Docetaxel + Ramucirumab Docetaxel + Icrucumab	NCT01282463
II	FGFR3	Docetaxel	R3Mab	Not available
Neoadjuvant therapy				
II	VEGFR, FGFR	GC	GC + Nintedanib	ISRCTN56349930

Index: GC- gemcitabine+cisplatin, GCa- gemcitabine+carboplatin, VEGF- vascular endothelial growth factor, VEGFR- VEGF receptor, EGFR- epidermal growth factor receptor, FGFR- fibroblast growth factor receptor

1.1.3 Regorafenib

Regorafenib is a novel oral multikinase inhibitor of angiogenic pathways including VEGFR1-3, TIE2 and FGFR-1, 2 and 3 as well as the RAF/MEK/ERK signaling pathway (50). Regorafenib is a diphenylurea with a chemical structure and biochemical profile similar to that of sorafenib, a multikinase inhibitor approved for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma. The addition of a fluorine atom to Regorafenib's center phenyl ring leads to a pharmacologically more potent agent with a broader spectrum of antiangiogenic activity than sorafenib. In vitro biochemical assays, using a standard 1-μM Regorafenib dose, revealed potent inhibition of angiogenic and stromal RTKs, including VEGF receptors-1-3, fibroblast growth factor (FGF) receptor-1 and Tie-2 at mean half maximal inhibitory concentration (IC_{50}) values ranging from 4.2 to 311 nM. Potent inhibition of TIE2 autophosphorylation was observed in vanadate-stimulated Chinese hamster ovary (CHO)-TIE2 cells with an IC_{50} of 31 nM, as determined by ELISA and by Western blotting following TIE2 immunoprecipitation. Preclinical activity has been shown at low nanomolar activity against endothelial cells stimulated to grow in the presence of VEGF or FGF. Regorafenib is approved in the dose of 160 mg orally once daily for 3 of every 4 weeks for the therapy of recurrent colorectal cancer and gastrointestinal tumor based on positive phase III trials (51, 52)-see data below. Additionally, other malignancies also appear sensitive to Regorafenib, e.g. renal cell carcinoma (53). The recommended dose from phase I studies was determined to be 160 mg daily 21 days on/7 days off per 28-day cycles (54, 55). The most common grade 3 or 4 AEs were dermatologic AEs (hand-foot skin reaction, rash), hypertension, and diarrhea.

1.2 Rationale of the study

VEGF, FGF and TIE2 receptors appear to be key therapeutic targets in UC as described above. Although multiple trials are evaluating inhibitors of VEGF and FGF pathways,

inhibition of the TIE2 pathway has not been investigated in clinical trials. Given Regorafenib's broad kinase inhibition of all of these 3 critical angiogenic axis molecules, significant activity in UC may be anticipated. Thus, Regorafenib potently inhibits a broader range of angiogenesis-promoting molecules than Sunitinib, Sorafenib, Axitinib and Pazopanib. In particular, based on the impact of expression of TIE2, VEGF and FGF receptors on prognosis and preliminarily promising activity of TIE2, VEGFR and FGFR inhibition in UC in the aforementioned preclinical and clinical trials, the inhibition of all 3 of these pathways by Regorafenib receptors is a highly attractive property that may translate to more robust activity in a broader group of patients. Indeed, the inhibition of both VEGF and TIE2 targets together has been demonstrated to be more active than inhibiting only one of these targets in preclinical studies (56). Advanced UC is a malignancy with severe unmet needs and agents that provide increments in outcomes are necessary while a better understanding of basic biology of the disease accumulates.

However, when starting at the US FDA approved dose of 160 mg once daily for colon cancer and GIST, Regorafenib dose reductions owing to toxicities are common and may be necessary in up to 60-70% of patients (57). The most common adverse events (AEs) of any grade that occurred in ≥10% of patients include fatigue, decreased appetite and food intake, hand-foot skin reaction (HFSR), also known as palmar-plantar erythrodysesthesia or PPE, diarrhea, mucositis, weight loss, infection, and hypertension. Interestingly, most AEs occurred early in the treatment course, during cycles 1 and 2, and their incidence decreased over subsequent cycles of therapy. Further, the dosing of Regorafenib remained relatively stable after three cycles of treatment, and there was no evidence of cumulative toxicity. These data suggest that the incidence of drug-related AEs decreases over time, and that proactive AE management early on may help to decrease the incidence or severity of those AEs that occur during the course of treatment, thus enabling better treatment compliance and adherence to therapy (58). Therefore, a robust rationale may be made to start at a dose of 120 mg once daily for 3 of every 4 weeks and incorporate close monitoring in the initial 2 cycles followed by gradual tapering of monitoring. In addition, the accrual of performance status 0-1 patients only (and excluding PS=2 patients) will mitigate the risk of AEs.

We propose a non-randomized proof-of-concept phase II trial to evaluate Regorafenib for patients with metastatic progressive urothelial carcinoma following 1-3 prior chemotherapy regimens who still have an ECOG performance status 0-1. Given the lack of validated predictive biomarkers for the efficacy of Regorafenib, all patients will be enrolled. Additionally, the initial dose will be 120 mg daily since Regorafenib dose reductions are common in colorectal cancer and GIST patients (see data below).However, dose will be escalated to 160 mg daily from cycle 2 day 1 or later if no Regorafenib-related >grade 1 toxicities are seen in cycle 1. Moreover, close monitoring is incorporated especially during the first 2 cycles, which then gradually tapers (see schedule table below). However, given a disease with substantial unmet needs and the lack of any FDA approved salvage agents for this disease, the potential benefits provided by this strategy are expected to outweigh the risks.

Historical pooled PFS6 is approximately 20% for previously used agents. In this study, those progressing within 6 months of prior therapy will be enrolled with the goal of detecting PFS6 in ≥20% of patients, while PFS6 in <5% will be considered to be of poor interest. Selecting patients following 1-3 prior regimens and within 6 months of prior therapy will ensure timely accrual of a homogeneous population and enrich for patients unlikely to attain PFS6 without active therapy. Thus, outcome results will be more interpretable, given these stipulations. Tumor tissue will be collected to be studied retrospectively to analyze genomics/proteomics to identify an association with PFS6.

Nanostring platform for gene expression analysis of formalin-fixed paraffin embedded tumor
Gene expressing profiling performed by the nanostring technology, which utilizes formalin-fixed paraffin embedded (FFPE) tissue using the nCounter® appears highly promising (59). This technology provides robust data from FFPE tissue using the nCounter® GX Kit and offers high levels of precision and sensitivity (>1 copy per cell) without the need for amplification of ≥100 ng of RNA. Nanostring is a multiplexed (up to 800 genes per reaction) platform, which utilizes digital counting and excellent quantitative reproducibility by employing two ~50 base probes per mRNA that hybridize in solution. Multiple successful applications utilizing the nCounter System to subtype tumors, formulate tumor prognostic signatures, or discover novel targets for therapy have been reported in other malignancies (60-63). Notably, the 50-gene PAM50 signature (Prosigna™) derived from nanostring was approved by the US FDA in 2013 to assess the risk of distant recurrence at 10 years in postmenopausal women with hormone receptor-positive breast cancer. Indeed, the PAM50 gene score, which is enriched for proliferation-associated genes appeared more robust than the Oncotype DX® recurrence score in predicting recurrence (62). Gene expression by nanostring may be proposed for a highly relevant panel of 797 genes including 230 human cancer-promoting genes, 519 kinase genes, 32 bladder cancer specific genes recently reported by TCGA including 4 genes involved in epigenetic regulation, 85 DNA damage repair genes, 3 stem cell relevant genes and 8 internal reference genes (64).

1.3 Regorafenib

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

1.3.1 Preclinical

In vivo, Regorafenib exhibited anti-angiogenic and anti-proliferative effects in human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian). (1) 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. (1) These data suggest that Regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

1.3.2 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. Metastatic colorectal cancer patients were randomized to Regorafenib plus best supportive care (BSC) or placebo plus BSC. Treatment cycles consisted of 160 mg of Regorafenib (or matching placebo) once daily for three weeks on / one week off plus BSC. The primary endpoint of this trial was overall survival. Secondary endpoints included progression-free survival, objective tumor response rate and disease control rate. The safety and tolerability of the two treatment groups were also compared.

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

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

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

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

However, Regorafenib dose reductions are common in colorectal cancer and GIST patients, and advanced urothelial carcinoma patients are ~5-10 years older (by median age). Dose reductions or interruptions appear common (43.8%) in off-study patients despite being initiated on a dose lower (120 mg daily) than the recommended initial dose (33.3%) (57). In the aforementioned pivotal phase III trials in colorectal and GISTs, dose interruptions are reductions occurred quite commonly. In the colorectal cancer trial, 333 (67%) and 304 patients (61%] in the Regorafenib group had an adverse event leading to dose modification or dose interruptions. In the GIST trial, dose modifications occurred in 95/132 patients (72·0%) on Regorafenib.

2. Study objectives

2.1 Primary Objective

Progression-free survival (PFS) at 6 months (PFS6)

2.2 Secondary Objectives

- Measurable disease response rate (RECIST)
- Overall survival
- Comparison of observed PFS6 with expected/estimated PFS6 by nomogram
- Toxicities

2.3 Exploratory objectives

- Association of tumor IHC for Tie2 and VEGFR2 with PFS
- Association of Gene expression in tumor tissue using Nanostring technology

3. Investigator[s] and other study participants

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Dr. Lisle Nabell, MD is a Professor in Department of Medicine, division of Hematology and Oncology at University of Alabama at Birmingham (UAB) and a Scientist at UAB Comprehensive Cancer Center (UABCCC). Dr.Ulka Vaishampayan is the director of urologic oncology at Wayne State University Karmanos Cancer Institute, and has extensively accrued in urothelial cancer trials and published multiple studies. Dr. Lakshmin Nandagopal, MD is an

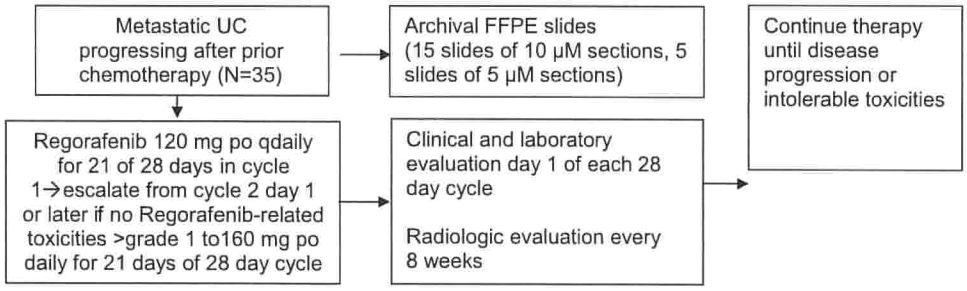
Assistant Professor in the Department of Medicine, Division of Hematology and Oncology at UAB. He will see patients at Kirklin clinic along with Dr. Nabell. Dr. Petros Grivas is a faculty urologic medical oncology physician with Cleveland Clinic where he is active with clinical trials and patient care.

4. Study design

This is a 3-center one-stage phase II trial conducted at the UAB Comprehensive Cancer Center (Birmingham, AL), Wayne State Karmanos Cancer Institute (Detroit, MI), and the Cleveland Clinic (Cleveland, OH). The trial will be managed by the Clinical Trial Network Monitoring Office (CTNMO) housed at the UAB Comprehensive Cancer Center. Progression free survival at 6 months is the primary end- point and the trial will enroll 35 patients. The eligible population includes patients with advanced urothelial cell carcinoma who have progressive disease after 1-3 prior chemotherapy regimens. Regorafenib is taken orally and is administered daily for the first 21 days of each 28 day cycle. The dose of Regorafenib is 120 mg once daily for the first cycle, which will be escalated to 160 mg once daily from the second cycle if no Regorafenib-related toxicities greater than grade 1 occur. Each 28 day cycle will be repeated until disease progression, intolerable toxicities, or patient decision with no limit on number of cycles allowed. Radiological evaluations are performed at each institution using RECIST 1.1 criteria every 2 cycles (8 weeks) or earlier if clinically indicated. Progression free-survival will be defined as the time to first occurrence of any of the following:

1. Clinical symptoms and signs of progression of disease,
2. Progression in measurable disease as defined by RECIST 1.1 criteria,
3. Death.

Trial schema



5. Study Population

5.1 Eligibility criteria

5.1.1 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patients must have pathologically or cytologically proven TCC of the urothelium
- Progressive disease after 1-3 prior chemotherapy regimens (perioperative chemotherapy within 12 months will be considered one regimen)
- Prior regimen must be within 6 months of registration
- Measurable disease by RECIST 1.1
- ECOG Performance status 0 - 2

- Patients with metastatic (lymph node or distant metastasis, i.e. N+ or M1) or locally advanced unresectable (T4b) TCC
- Age 19 years or older
- Life expectancy of at least 12 weeks (3 months).
- Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements:
  - Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
  - Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Serum creatinine ≤ 1.5 x the ULN
  - International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN **unless receiving treatment with therapeutic anticoagulation**. (Subjects 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 INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care. (See Section 3.3)
  - Platelet count > 100000 /mm3, hemoglobin (Hb) > 8 g/dL, absolute neutrophil count (ANC) 1500/mm3. The patient cannot be transfused in order to meet study entry criteria
- Women of childbearing potential must have a negative pregnancy test (urine or serum) performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgment of the investigator.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subject must be able to swallow and retain oral medication.

Commented [YW1]: The definition of this Inclusion criteria does not change.

5.1.2 Exclusion criteria

Patients meeting any of the following exclusion criteria within 4 weeks (unless otherwise stated) of being enrolled are not to be enrolled in the study.

- Component of small-cell cancer or sarcomatoid cancer
- Prior therapy with any systemic infusion or injection therapy (chemotherapy or biologic therapy) within twenty-eight days prior to study entry; greater than or equal to 2 weeks of oral biologic or oral chemotherapy
- Patients must have recovered from toxicities from prior systemic anticancer treatment or local therapies.
- Patients who have undergone major surgery < 4 weeks or minor surgery < 2 weeks prior to registration. Wounds must be completely healed prior to study entry and patients recovered from all toxicities from surgery. Placement of a vascular access device is not considered major or minor surgery in this regard.
- Prior radiation therapy is allowed as long as the irradiated area was not the sole source of measurable disease and radiotherapy was completed with recovery from

toxicity, at least three weeks prior to enrollment. If the irradiated area is the only site of disease, there must be evidence of progressive disease.

- Uncontrolled central nervous system (CNS) metastases (previously treated with radiation and off steroids is acceptable)
- Patient with active or uncontrolled infection.
- Recent or active bleeding diathesis or arterial vascular event within 4 weeks.
- Pregnant or nursing (Fertile patients must use effective contraception during and for up to 3 months after completion of study treatment)
- Patients may not be receiving any other investigational agents.
- Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.
- Active or clinically significant cardiac disease including:
    - Congestive heart failure – New York Heart Association (NYHA) > Class II (section 13.4).
    - Active coronary artery disease.
    - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    - Unstable angina (angina symptoms at rest), new-onset angina within 3 months before consenting or myocardial infarction within 6 months before consenting.
- Evidence or history of bleeding diathesis or coagulopathy.
- Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism **within 6 month before the start of study medication** (except for adequately treated catheter-related venous thrombosis occurring more than one month before the start of study medication)
- Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment within 6 months of informed consent.
- Subjects with any previously untreated or concurrent cancer that is distinct in primary site or histology from breast cancer except cervical cancer in-situ, treated localized basal cell carcinoma, Gleason score > 6 prostate cancer or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed. All cancer treatments for another malignancy must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form).
- Patients with pheochromocytoma.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Ongoing infection > Grade 2 NCI-CTCAE v4.0.
- Symptomatic metastatic brain or meningeal tumors.
- Presence of a non-healing wound, non-healing ulcer, or bone fracture.
- Renal failure requiring hemo-or peritoneal dialysis.
- Dehydration Grade ≥1 NCI-CTCAE v4.0.
- Patients with seizure disorder requiring medication.
- Persistent proteinuria ≥ Grade 3 NCI-CTCAE v4.0 (> 3.5 g/24 hrs, measured by urine protein:creatinine ratio on a random urine sample).
- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.

- Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).
- History of organ allograft (including corneal transplant).
- Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

5.1.3 Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (Regorafenib, other agents being investigated in combination with Regorafenib).
- Prior use of Regorafenib.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 2 weeks of trial entry (signing of the informed consent form).
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Patients being treated with anticoagulant will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. For anticoagulants that require monitoring, standards should be considered and controlled by the investigator. For NOACS an Individual risk benefit in accordance with the applicable labels and/or local guidelines should be carefully assessed

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

5.1.4 Selection of study population

General Guidelines

Eligible patients will be entered on study at the following institutions: the Kirklin Clinic, UAB, Birmingham, AL; Wayne State University Karmanos Cancer Institute, Detroit, MI; (UAB research nurse to be designated by Elizabeth Busby, Director of UAB Oncology Clinical Trials, Clinical Studies Unit (CSU), UAB). All sites should call the Study Coordinator to verify agent availability. Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may

be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

Registration Process
The Clinical Trials Network Monitoring Office (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at participating sites to achieve timely study subject enrolment. Once a study subject has been screened and deemed eligible for study entry by the participating site, a study-specific study subject eligibility checklist, a copy of the dated and signed consent form, and corresponding source documentation are faxed to the participating site study coordinator for eligibility verification. Subsequently, a study-specific number is assigned to the study subject and sent to the participating site. Finally, a Patient Registration Form is completed and faxed by the CTNMO site to the participating study coordinator. Queries regarding data accuracy are forwarded from the participating site coordinator to the CTNMO site for clarification or correction. Once the CTNMO site addresses queries, any corrected data forms or copies of corrected source documentation are faxed to the participating site study coordinator.

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

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

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

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to Regorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.

- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

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

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

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).

5.2.2 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been randomized, assigned to treatment/run-in/wash-out, and administered at least one dose of study drug.

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

5.2.3 Replacement

No withdrawn subjects will be replaced. The study will enroll 35 patients out of which 32 will be evaluable for end point analysis. Any drop out will effectively be replaced through the nature of design.

6. Treatment[s]

6.1 Treatments to be administered

This is a single arm study in which all patients will receive Regorafenib orally. Patients will visit the clinic on the first day of each cycle for assessments for responses and safety. Instructions about medications will be given to the patient as mentioned in sections 6.3.1.

6.2 Treatment assignment

6.2.1 Regorafenib

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets (for randomized studies) or 28 tablets (for open-label studies) 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.

6.3 Blinding

This is a non-randomized study and hence investigators, study staff and patients will know about the treatment being administered. There will no blinding of any involved personnel or participants.

6.3.1 Study Treatment

Regorafenib is administered as monotherapy during the study once daily for 3 of every 4 week cycle. The dose of Regorafenib is 120 mg once daily for the first cycle, which will be escalated to 160 mg once daily from the second cycle if no Regorafenib-associated toxicities greater than grade 1 occur during the first cycle.

Three 40-mg Regorafenib tablets (with potential escalation to 4 tablets or reduction to 2 tablets) should be taken once a day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) meal. Some examples of low fat meals are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

6.3.1.1 Dose Reduction and escalation Levels

The starting dose of Regorafenib is 120 mg once daily. The dose will be escalated to 160 mg once daily from the second cycle if no Regorafenib-associated toxicities greater than grade 1 occur during the first cycle.

Study medication will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4].

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

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

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

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

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

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

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

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

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

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

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

Table 6-2: Grading for Hand-Foot-Skin-Reaction			
	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndromea	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description / examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

Table 6.3 Recommended dose modification for hand-foot-skin reaction[a]

Grade of event (NCI-CTCAE v4.0)	Occurrence	Suggested Dose Modification
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1 [b, c]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, treat at reduced dose level [b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level. [b, d]
	4th occurrence	Discontinue therapy
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level. [b, d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one additional dose level [b, d]
	3rd occurrence	Discontinue treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the investigator.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with Regorafenib will be discontinued permanently.
d. Subjects requiring dose reductions below 80 mg daily should go off protocol therapy.
e. The maximum daily dose is 160 mg.

(For studies with combination therapy, consider including the following statement "The other study treatment may be continued").

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

Recommended prevention/management strategies for skin toxicities consistent with HFSR are summarized below:

Control of calluses

Before initiating treatment with Regorafenib:

- Check condition of hands and feet.
- Suggest a manicure/pedicure, when indicated.

- Recommend pumice stone use for callus or 'rough spot' removal.

During Regorafenib treatment:

- Avoid pressure points.
- Avoid items that rub, pinch or create friction.

Use of creams

- Non-urea based creams may be applied liberally.
- Keratolytic creams (e.g. urea-based creams, salicylic acid 6%) may be used sparingly and only to affected (hyperkeratotic) areas.
- Alpha hydroxyl acids (AHA) based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.
- Topical analgesics (e.g. lidocaine 2%) are to be considered for pain control.
- Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 HFSR. Avoid systemic steroids.

Tender areas should be protected as follows:

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

6.3.1.2. Hypertension

Hypertension is a known AE associated with Regorafenib treatment. Subject will have their blood pressure measured at least weekly at the study site during the first 6 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is > 140 mm Hg systolic or > 90 mm Hg diastolic (NCI CTCAE v4.0), then the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Table 6-4 outlines suggested dose reductions.

Table 6-4: Management of Treatment-Emergent Hypertension		
Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue Regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: • If BP previously within normal limits, start anti-hypertensive monotherapy • If patient already on anti-hypertensive medication, titrate up the dose.	• Continue Regorafenib • If symptomatic, hold Regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When Regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold Regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When Regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Patients requiring a delay of >4 weeks should go off protocol therapy b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion. c. Patients requiring dose reductions below 80 mg daily should go off protocol therapy.		

Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered related to Regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 6-5 should be followed.

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

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

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

6.3.1.3 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of Regorafenib. The preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status).

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

6.4 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.

6.4.1 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

6.4.2 Destruction and Return

At the end of the study, unused supplies of Regorafenib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer.

A completed "Unused Study Drug Disposition Form Destruction or Return Confirmation" should be sent to Bayer at the following address:

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

6.5 Treatment compliance

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

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

6.6 Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's

source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

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

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

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.
- For subject receiving Regorafenib in combination with chemotherapy consider adding the following:
    - A standard antiemetic regimen for the prophylaxis of acute emesis is recommended on the day of chemotherapy at least 30 minutes prior to the administration of chemotherapy. Such a regimen may include a serotonin (5-HT_3) antagonist (e.g. granisetron or ondansetron) with or without a corticosteroid (e.g. dexamethasone). The investigators should also consider providing subjects with a standard antiemetic regimen for treatment of delayed or breakthrough emesis as needed.

The following are not permitted:

- Other investigational treatment during or within 28 days before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cycloosporin, and digoxin). Warfarin is metabolized by the cytocrome enzyme CYP2C9 and its levels may be especially affected by Regorafenib
- Use of any herbal remedy (e.g. St. John's Wort [Hypericum perforatum])
- Please note: Patients should be seen frequently / early during treatment as per Prescribing Information
- Liver function tests should be obtained before initiation of Regorafenib and monitored at least weekly during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated
- Monitor blood pressure weekly for the first 6 weeks of treatment and every cycle or more frequently as clinically indicated.

7. Assessments

7.1 Timing of Assessments

Baseline evaluations are to be conducted within 2 weeks prior to administration of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	-28 days	-14 days	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15 (F)	Day 22	Day 1	Every 2 cycles	28 (± 7 days) post last treat-ment
	Screening		**Cycle 1 and 2**				**Cycle 3 and 4**				**Cycle 5+ (F)**		**EOT (G)**
PROCEDURES													
Informed Consent	X												
History & Physical (by MD)		X	X	X	X		X		X		X		X
BP Exam (E)		X	X	X	X	X	X		X		X		X
ECOG performance status		X	X				X						X
CBC with differential		X	X (C)		X		X				X		X
Chemistries & Electrolytes (&LFTs)		X	X (C)	X (H)	X	X (H)	X		X		X		X
Coagulation Panel (D)		X	X	X	X	X	X		X		X		
Urine or serum pregnancy test		X											
Adverse event and concomitant medication assessment (B)		X	X	X	X		X		X		X		X
DISEASE ASSESSMENT													
CT or MRI chest, abdomen, pelvis (A)	X (A)						X (A)					X (A)	X
Bone Scan (if bone pain or high alkaline phosphatase) (A)	X (A)						X (A)					X (A)	
TREATMENT													
Regorafenib PO QD (3 of 4 weeks)			X	X	X		X	X	X		X		
CORRELATIVE STUDIES													
Request 20 slides from archival biopsy for potential correlative studies	X												
FOLLOW-UP													
Disease progression and survival													X

A. Tumor Assessment: CT/MRI (and bone scan if required) will be conducted every 8 weeks +/- 4 days until PD. If tumor assessments are available during the follow up period for subjects who discontinued study treatment and have not experienced PD, they should be recorded in the CRF.

B. Adverse Events and Toxicities: AE assessment to be started after signing of IC until 30 days after last study treatment (excluding survival assessment)

C. Laboratory evaluations are not required day 1 of cycle 1 if completed within 7 days of starting study drug. In addition, weekly checks of ALT, AST and bilirubin are required during the first two cycles of study treatment
D. If a subject is on warfarin with stable PT/INR at baseline, the PT/INR should be assessed on day 5 (+/- 3 days). If value is above therapeutic range, the dose should be modified and assessment should be repeated WEEKLY until it is stable.
E. BP should be evaluated weekly for the first 6 weeks of treatment
F. After 4 cycles, day 15 assessments can be done at the discretion of the investigator. If for any reason additional assessments are clinically warranted they can be done at the discretion of the investigator.
G. *EOT = End of treatment.* When a patient discontinues the study treatment for any reason (except death, IC withdrawn or lost to follow-up) an end of treatment evaluation should be performed within 14 days after study treatment has stopped. For a patient who discontinues the study due to dose interruption longer than 28 days, the end of treatment evaluation should be performed within 14 days after the day when the decision of discontinuation is made. For patients who discontinue for reasons other than disease progression, tumor measurements and evaluation of tumor response of all measurable lesions should be performed according to RECIST. If Brain metastases are suspected, head CT or MRI must be performed
H. LFTs (alkaline phosphatase, ALT, AST, GGT, and total bilirubin) on Day 8 and Day 22 of Cycle 1 and Cycle 2

7.1.1 Medical history

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

- Not pertaining to the study indication.
- Start before signing of the informed consent.
- Considered relevant to the study.
- Baseline or visit 1 includes height and weight
- Baseline: include smoking history (current status and pack years)

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.4.1.1.

7.1.2 Long term follow up

After study drug treatment ends patients will be evaluated 4 weeks after last dose to assess toxicities and then per investigator discretion using good clinical practice up to study closure to acquire information on survival.
Telephone follow-up is acceptable.
In case of difficulty in contacting a patient during follow up, every attempt should be made to reconnect with the patient or, if it is thought that a patient may have died, to establish a date of death. Patients who withdraw consent from study drug treatment shall enter the long-term follow-up period unless consent to follow-up is specifically withdrawn.

7.2 Efficacy

7.2.1 End points of efficacy

The primary endpoint of the study is to evaluate progression free survival (PFS) at 6 months (PFS6). Secondary endpoints of this study are evaluating measurable disease response rate using RECIST 1.1 criteria, measuring survival and toxicities after receiving Regorafenib. Immunohistochemistry and gene expression using Nanostring technology for a panel of kinase and cancer associated genes to correlate with tumor response may be performed and are potential endpoints based on outcomes.

7.2.2 Exploratory tumor tissue studies and central pathology review

Twenty archival formalin-fixed paraffin-embedded (FFPE) tumor slides will be requested for potential central pathology review and molecular studies. Fifteen slides of 10 µM thickness sections each and 5 slides of 5 µM thickness sections each will be requested from all institutions. In the event of attainment of the primary endpoint (i.e. PFS6 in ≥20% of patients), slides will be obtained and following central pathology review for determining histologic subtype, tumor will be demarcated from adjacent normal tissue on the H+E slide to guide procurement of tumor-enriched samples. The 10 µM sections will be used for RNA isolation toward gene expression profiling for ~800 cancer-promoting, kinase, DNA-damage repair, bladder cancer-specific and stem cell panel genes by the nanostring platform performed centrally in the UAB Comprehensive Cancer Center. A total surface area of tumor 100 mm^2 is adequate to harvest the necessary amount of RNA (100 ng) using the RNAeasy Mini Kit (Qiagen), and the quality of the RNA will be assessed via the 260/280 ratio using nanodrop. Dr Eddy S. Yang at UAB Radiation Oncology Dept. will perform the nanostring studies as described in previous publications utilizing the nCounter by inputting RNA directly into a hybridization reaction containing color-coded molecular barcodes representing the genes of interest [56]. Immunohistochemistry (IHC) is performed on the 5µM section slides for VEGFR2 and Tie2 by previously described methods using appropriate controls.

7.2.3 Measurement of effect

Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every 8 weeks and earlier if clinically required. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)(65). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

All patients will be evaluable for toxicity from the time of their first treatment with Regorafenib. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. Lymph nodes are considered measurable if the short axis diameter is ≥15 mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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

Methods for Evaluation of Measurable Disease
All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

The utilization of endoscopy techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria for the evaluation of Target Lesions
Complete Response (CR): Disappearance of all target lesions
Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

objective progression even after discontinuation of treatment.

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

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

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

Progression-Free Survival
PFS is defined as the duration of time from start of treatment to time of progression or death, whichever comes first.

7.3 Pharmacokinetics / pharmacodynamics

N/A

7.4 Safety

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

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

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

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

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

7.4.1 Adverse events

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

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

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

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

7.4.1.1 Definitions

Definition of adverse event (AE)

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

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

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

Definition of serious adverse event (SAE)

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

a. Results in death.

b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

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

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE

dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

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

e. Is a congenital anomaly / birth defect.

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

Serious adverse events
In addition to the SAE criteria specified in the standard text above, further criteria may be defined; e.g. all Grade-4 laboratory toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) may have to be recorded as SAEs.

7.4.1.2 Classifications for adverse event assessment

The descriptions and grading scales of Adverse events are found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 which will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03.

- "Expectedness": AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are bold and italicized in the CAEPR.
- Attribution of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

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

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

7.4.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.4.1.1.

7.4.1.2.2 Intensity

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

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

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

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-

care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

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

CTCAEv4 Grade 5: death due to an AE.

7.4.1.2.3 Causal relationship

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

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

Possible answers are "yes" or "no".

An assessment of "no" would include:

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

or

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

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

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

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

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

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

Possible answers are "yes" or "no".

7.4.1.2.4 Action taken with study treatment

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

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

7.4.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

7.4.1.2.6 Outcome

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

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

7.4.1.3 Assessments and documentation of adverse events

Safety laboratory samples will be analyzed *at the individual participating site laboratory.* Safety laboratory examinations will include hematology, biochemistry and urine examinations. Table 7.9.1.3:1 presents the laboratory tests to be performed.

Table 7.9.1.3:1 Clinical Laboratory Tests

Category	**Parameters** *<keep parameters written in black; amend others as appropriate>*
Hematology	hemoglobin, hematocrit, platelet count, blood cell count (WBC)

Table 7.9.1.3:1 Clinical Laboratory Tests

Category	**Parameters** *<keep parameters written in black; amend others as appropriate>*
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT),
Chemistry	
Electrolytes	sodium, potassium, calcium, magnesium,
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine; Creatinine clearance (see Section 13.6).
Other	glucose, albumin,

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal findings from these investigations need to be reported as an Adverse Event.

7.4.1.3.1 Assessment of other safety parameters

Physical examination, vital signs, height and weight

A full physical exam will include cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination will be clarified. Wherever possible the same investigator should perform this examination.

A complete physical examination will be done at Screening, Day 1, every visit on study, and at the End-of-Treatment visit. A symptom-directed examination is to be performed on all other visits.

Vital signs

Vital sign measurements blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, temperature and measurement of height (in cm, at screening) and body weight (in kg) and the evaluation of the ECOG performance status (see section 13.2) will be performed at the times specified in the flow chart.

7.4.1.4 Reporting of serious adverse events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Serious Adverse Events (SAEs) are reported by the participating site Lead Investigator within 24 hours to the Clinical Trial Network Monitoring Office (CTNMO) Manager (Pam Dixon) by email (pamdixon@uab.edu) or by fax (205) 975-9875. The 24 hour paging number for the CTNMO Manager is (205) 934-3411, beeper #5904. The CTNMO Manager is then

responsible for reporting SAEs to the UAB IRB and protocol P.I. in accordance with study-specific requirements. SAEs occurring at CTNMO sites are reported to the UAB IRB as "non-UAB" events.

A Serious Adverse Event (SAE) is an AE that 1) results in patient hospitalization or prolongation of hospitalization; 2) results in persistent or significant disability or incapacity; 3) results in death; 4) is a cancer or congenital abnormality or 5) results in the development of drug dependence or abuse. An AE will be considered an SAE when the nature or severity of the event is not consistent with the current Investigator's Brochure. It is also the responsibility of the participating site Lead Investigator to report SAEs to the local site IRB and to submit copies of that report to the CTNMO Manager. It is the CTNMO Manager's responsibility to report the SAE to the Clinical Trials Monitoring Committee, UAB IRB and / or industry sponsor. This submission of IND Safety Reports will be cross referenced according to local regulations to Bayer Investigational Compound Number (IND) at the time of submission

7.4.1.4.1 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. AEs reported must also be reported in routine study data submissions. Safety will be monitored throughout the study by physical examinations, review of adverse events (AEs), and laboratory studies. The frequency of safety monitoring procedures is outlined in Sections 6.6.1 and 6.9.1.3. Criteria that will be used throughout the study for dose interruption, reduction, and discontinuation of chemotherapeutic agents are specified in Section 6.3.1.1.

Data and Safety Monitoring Plan
The UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP) will monitor subjects treated at UAB. The Clinical Trials Monitoring Committee (CTMC) on a weekly basis will closely monitor adverse reactions observed during treatment. The CTMC is responsible for data and safety monitoring of the trial and adherence to the DSMP. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to the DSMP. Reports from the CTMC are reviewed monthly by the QAC.

Protocol Management and Oversight of Participating Site
Dr. Lisle Nabell functions as the sponsor of the trial at UAB and at the participating sites. The participating sites will utilize their respective IRB of record. The Lead Investigator at participating site(s) will be responsible for ensuring that all the required data will be collected and entered onto the Case Report Forms. A monthly teleconference between UAB CTNMO and participating sites will ensure discussion of AEs seen across all sites. UAB PI, CTNMO manager and participating site Lead Investigators will discuss management of AEs and impact of AEs on trial conduct. The CTNMO office will report the outcome of these discussions at CTMC meeting every month. Periodically, monitoring visits will be conducted by CTNMO manager and the participating site Lead Investigator will provide access to his/her original records to permit verification of proper data entry. At the completion of the study, all case report forms will be reviewed by the CTNMO manager and will require his/her final signature to verify the accuracy of the data.

Table 7.9.1.4:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
From signing of informed consent to ≤28	Report all AEs and SAEs regardless of relatedness or whether the trial drug was

days after last trial drug administration	administered. This includes all deaths.
Post-treatment (>28 days after last trial drug administration)	Report only SAEs which are considered related to trial treatment or trial design. Death should be reported as an SAE only when considered related to trial treatment or trial design (because death is an endpoint and will be followed-up separately).

The definition of serious adverse events (SAEs) is given in Section 7.4.1.1.

All adverse events, serious and non-serious, will be collected, documented and reported to the sponsor by the Lead site investigator on the appropriate CRFs / SAE reporting forms (Bayer SAE report form or alternatively the CIOMS form with Bayer cover letter form).

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, CTC AE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 6.9.1.1 and 6.9.1.2.

Adverse events with onset within first administration of Regorafenib therapy and 28 days after last administration of Regorafenib will be considered as on treatment. All AEs, including those persisting after end of study treatment will be followed up until they have resolved or have been sufficiently characterised or the principal investigator decides to not further pursue them.

Serious and non-serious adverse events occurring later than 28 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

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

All serious adverse events will be reported to UAB IRB.

All serious adverse events should be reported to Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

7.4.1.4.2 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use the reporting procedures briefly outlined in the table below.

Expedited Reporting Guidelines – Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3	Grades 4 & 5[2]		Grades 4 & 5[2]
	Un-expected and Expected	Un-expected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Unexpected Without Hospitalization		Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:

24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported.

- Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

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

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

OR

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

All reports shall be sent electronically to:

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

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

Phone:	1-888-842-2937

7.4.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

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

7.4.1.6 Adverse events of special safety interest

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

Based on data studies with Regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify the sponsor as outlined in Section 7.4.1.4.

Reportable adverse events include:

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

7.4.2 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.

7.4.3 Further safety

Progressive disease

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

Death

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

7.5 Appropriateness of procedures / measurements

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

8. Statistical methods and determination of sample size

8.1 Analysis sets

This is a one-stage, non-randomized, phase II trial conducted at UAB Comprehensive Cancer Center, , Wayne State University and Progression-free survival at 6 months (PFS6) is chosen as the primary end-point. A total of 35 patients will be enrolled for this trial. Accrual period will be 6 to 12 months.

8.2 Variables

Al patients will be screened before enrollment and demographic information about age, gender, race, height and smoking status will be collected. Weight, blood pressure measurements, and tumor measurements using CT scans will be noted at baseline visits and subsequent clinic visits.

All patients will be evaluable for toxicity from the time of their first treatment with Regorafenib. CTCAE v 4.03 will be utilized to grade toxicities (Section 13.5). All evaluable patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions will be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

8.3 Statistical and analytical plans

The primary endpoint of the study is the rate of progression free survival (PFS) at 6 months (PFS6). Given the poor prognosis of this patient population and data from other studies of salvage therapy, a PFS6 of ≥20% is felt to be important for this regimen, while a PFS6 <5% is felt to be of poor interest. The trial also enrolls patients who progress within 6 months of last cycle of prior chemotherapy to enhance the interpretability of outcomes, since such patients are unlikely biologically to be progression-free for 6 more months without active therapy that favorably impacts on tumor biology to extend PFS. SAS version 9.3 was used to calculate power. The justification for the proposed sample size is based on an exact test for a binomial proportion with a one-sided significance level of 5%. With 32 evaluable subjects,

we will have approximately 80% power (79.6%) to reject the null hypothesis that PFS6 is < 5% in favor of PFS6 ≥ 20%. Given that 5-10% of patients may be inevaluable, up to 35 patients may be enrolled. If five or more patients remain progression-free at 6 months, this regimen will be considered to be of significant interest.

Chi-square or Fisher's exact test will be employed to determine univariate association of biomarker status with PFS6 and objective response. Descriptive statistics including frequencies and proportions will be calculated to summarize safety and toxicity outcomes. Specifically, the number of adverse events (AE) and serious adverse events (SAE) will be tabulated and summarized. Point estimates and exact binomial (Clopper-Pearson) confidence intervals (CI) will be calculated to estimate the incidence of AEs and SAEs. The precision of these estimates, i.e., width of the confidence interval, will depend on the estimated incidence of each outcome. The table below gives the exact 95% confidence intervals for a range of incidences, assuming 32 evaluable subjects.

Number of subjects experiencing event	Estimated Incidence	95% Exact CI for Incidence		Width of CI
		Lower Limit	Upper Limit	
1	0.031	0.001	0.162	0.161
2	0.062	0.008	0.208	0.200
4	0.125	0.035	0.290	0.255
8	0.250	0.115	0.434	0.319
16	0.500	0.319	0.681	0.362

A secondary objective is comparison of observed PFS6 vs. predicted PFS6 based on previously published nomogram. (17, 66). This internally and externally validated and calibrated nomogram uses PS (performance status), LM (liver metastasis), Hb (hemoglobin) and TFPC (time from prior chemotherapy) to predict PFS6 for an individual subject receiving historically used agents such as taxanes. We will use this nomogram to predict PFS6 for the patients in our study and compare the predicted values to the observed PFS6. The concordance index (c) will calculated as a measure of the nomogram's discrimination ability. Predicted PFS will also be plotted against the observed PFS6 to provide a visual comparison.

9. Data handling and quality assurance

9.1 Data recording

The trial protocol will undergo initial review by the Clinical Trials Review Committee (CTRC) and IRB (Institutional Review Board) of the central coordinating site, UAB Comprehensive Cancer Center. Thereafter, the scientific review committee of each institution will review the protocol followed by IRB approval for each institution. The registration of patients will be conducted as per described in section 5.1.4. The data manager at each institution enters data on the electronic case report forms (eCRFs) directly. Patient eligibility is verified based on the entries in the eCRF. The Clinical Trials Network (CTN) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at CTN affiliate sites of UAB and other participating institutions. The CTN Monitoring Office (CTNMO) will maintain shadow charts for the patients entered on trial. The data entered into the eCRFs for each protocol specific time point will be compared to the source for accuracy and completeness. Queries will be generated as needed. All patients for this trial will be registered into the OnCore system for study patient tracking for this trial for the UAB Comprehensive Cancer Center.

9.2 Monitoring

This protocol will adhere to the policies and requirements of the NCI CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the UAB study coordinator and the procedures for auditing are presented in section 9.4. The Principal Investigator and CTNMO are responsible for distributing all Safety Reports to all coordinating centers for submission to their individual IRBs for action as required.

Each study subject is discussed at the CTN site's monthly Clinical Trials Monitoring Committee meeting by the CTN site research nurses and participating site Lead Investigators and is, in turn, presented at the next monthly Clinical Trials Monitoring Committee meeting by the CTNMO Manager. The P.I. (assisted by the CTNMO Manager) is the primary contact for study-specific questions such as dose modifications, toxicities, and supportive care. The CTNMO Manager is the primary contact for issues regarding patient registration, regulatory documentation, completion of eCRFs, data collection, and data submission electronically. Comprehensive monitoring of studies (100% of patients) is conducted using the electronic data CRFs and supporting source documents that are transmitted to the Department of Biostatistics. Following each monitoring exercise, queries and/or requests for additional documentation are generated by the CTNMO Manager generally within 2 weeks of receipt of the CTN affiliate site and participating site documents. Subsequently, the CTN affiliate site and participating sites review and respond to queries and implements the necessary corrective action(s). Within two weeks, the CTN affiliate site and participating site submits query responses and, if appropriate, a written summary of corrective actions to the CTN Coordinating Center Manager. The CTN Coordinating Center Manager conducts "on-site" monitoring visits at least once a year to verify data from source charts and to provide staff education and to assist in implementing corrective action.

9.3 Data processing

After completion of the study, i.e. when the study has been concluded in accordance with this protocol and the last patient completed his/her last follow-up visit (last patient out), an integrated clinical and statistical study report containing a complete and detailed analysis and summary of all observations, results and conclusions related to or resulting from the study shall be written by the sponsor in consultation with the Principal investigator within twelve (12) months after completion of the study.

The study report shall be compiled in accordance with the ICH-E3 Guideline.

9.4 Audit and inspection

Audits will be conducted on a regular interval. Ten percent of the patient charts will be audited. As part of this process, 10% of the institution's "shadow charts" maintained at the CTN Monitoring office will also be audited. Following the audit of the CTN site "shadow charts", a summary of the audit findings will be forwarded to the CTN site IRB, the UAB IRB, the CTN site Lead Investigator, the CTN Director and the UAB Cancer Center Associate Director for Clinical Research. The site Lead Investigator, in consultation with the CTN director, will have 2 weeks to respond to any deficiencies prior to formal UAB IRB action concerning the audit findings. Data collection and submission is the responsibility of the site Lead Investigator. Any deviations from the study protocol will be documented in the study subject's medical record and research chart. Missing data will be documented. Inspections by regulatory health authority representatives i.e. FDA and IRB(s) are possible. The investigator will notify Bayer immediately of any such inspection.

9.5 Archiving

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

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

10. Premature termination of the study

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

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

For any of the above closures, the following applies:

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

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

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

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

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

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bayer. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects

without prior IEC/IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

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

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

11.2 Subject information and consent

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

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

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

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

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any

revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

11.3 Publication policy

Bayer recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to Bayer at least thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer and the investigator/institution

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

11.4 Confidentiality

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

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

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13. Amendments

13.1 Amendment 1

13.1.1 Overview of Changes

13.1.2 Changes to the Protocol Text

14. Appendices

14.1 Examples of a low fat meal

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

One cup of cereal (i.e. Special K), 8 ounces of skimmed 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).

14.2 Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14.3 Tumor response assessment according to RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) will have a reduction in short axis to < 10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum will also demonstrate an absolute increase of at least 5 mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes will be non-pathological in size (< 10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

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	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

14.4 NYHA Classification for heart failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

14.5 NCI-CTCAE Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v4.03: Publish Date: June 14, 2010
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.6 Cockcroft-gault formula

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results will be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \text{ if } \textit{Female}]}{72 \cdot \text{Serum Creatinine}(\text{in mg/dL})}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot \text{Constant}}{\text{Serum Creatinine}(\text{in µmol/L})}$$

Where *Constant* is *1.23* for men and *1.04* for women.

14.7 MULTICENTER GUIDELINES

Responsibility of the Protocol Principal Investigator (PI)

- The PI will be the single liaison with the Protocol and Information Office (UAB). The PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the PI. There will be only one version of the protocol, and each participating institution will use that document. The PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to UAB are the responsibility of the participating site Lead investigator(s).
- The PI is responsible for the timely review of Adverse Events (AEs) to assure safety of the patients.
- The PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center (CTNMO)

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- The Coordinating Center at UAB is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. Participating institutions will report directly to UAB. The Coordinating Center will submit AE reports to the PI for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites by CTNMO manager.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration are in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, directly to UAB or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters will be distributed to participating institutions.