0S-14-3: Phase II Study of Single Agent Regorafenib in Patients with Advanced/Metastatic Neuroendocrine Tumors

NCT #: NCT02259725

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Study Drug: **Regorafenib (Stivarga)**

Funding Source: **Bayer HealthCare Pharmaceuticals**

Initial version: **6/25/14**
Amended: **11/21/16, 3/13/18**
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Protocol Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Institutional Name: _____

Date: _____

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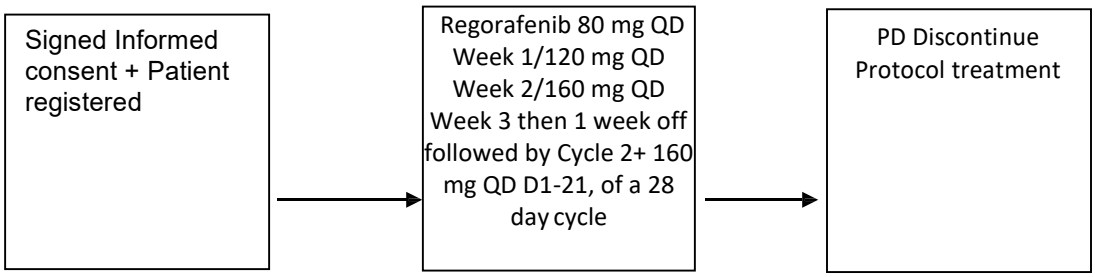
LIST OF ABBREVIATIONS

Examples Include:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CISO	Clinical Investigations Support Office
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MCC	Multi-site Coordinating Center
MTD	Maximum Tolerated Dose
NCCC	Norris comprehensive Cancer Center
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Study of Single Agent Regorafenib in Patients with Advanced/Metastatic Neuroendocrine Tumors
Short Title	Phase II Study of Regorafenib in Advanced/Metastatic Neuroendocrine Tumors
Protocol Number	0S-14-3
Phase	II
Methodology	Open label
Study Duration	Estimate one patient per month accrual. If both cohorts accrue past the interim the study will take 4 years to complete accrual.
Study Center(s)	2
Objectives	1. To assess PFS in advanced/metastatic in patients with carcinoid or pancreatic islet cell tumors 2. To assess OS, RR in advanced/metastatic poor prognosis in patients with carcinoid or pancreatic islet cell tumors 3. To assess toxicity of patients treated with regorafenib 4. To explore markers of angiogenesis as they relate to outcome in carcinoid and pancreatic islet cell tumors.
Number of Subjects	Cohort A (Carcinoid Tumors): 11+13=24 Cohort B (Pancreatic Islet Cell Tumors): 11+13=24

Diagnosis and Main Inclusion Criteria	Advanced metastatic, progressing carcinoid or pancreatic islet cell cancers *Patients may have received one line of prior therapy with octreotide, locoregional therapy. Continuation of concurrent octreotide is allowed. *No prior targeted tx or anti-angiogenic therapy. *Patients will be maintained on octreotide (sandostatin) for the duration of their treatment. *SWOG PS 0-1
Study Product(s), Dose, Route, Regimen	Regorafenib 80 mg QD Week 1/120 mg QD Week 2/160 mg QD Week 3 then 1 week off followed by Cycle 2+ 160 mg QD D1-21, of a 28 day cycle.
Duration of administration	Patients may remain on study until the development of disease, development of intolerable toxicity, or any of the criteria for removal of the study as set forth in the protocol.
Statistical Methodology	The 6-month PFS rate will be the primary endpoint. Two parallel Simon's 2-stage phase II trials will be conducted to evaluate the efficacy of regorafenib in patients with advanced carcinoid (cohort A) or pancreatic islet cell tumors (cohort B). For cohort A, a 6-month PFS rate of 40% would be considered as disappointing and 65% or higher would be encouraging. For cohort B, a 57% rate would be considered as not interesting, and 80% or higher would be promising. We need a total of 24 patients with carcinoid tumors (cohort A) and 24 patients with pancreatic islet cell tumors (cohort B). The study design of both trials has 80% power to demonstrate the efficacy of regorafenib. The type I error rate is 5.1% and 5.3%, for cohort A and B, respectively. We designed the trials with type I error rate a little higher than 5% because the tumors are rare and the sample size should be as small as possible.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Neuroendocrine tumors, which include carcinoid tumors and pancreatic islet cell tumors, are rare malignancies, occurring in only 1-2 people per 100,000 in the United States. As these cancers cause few symptoms and little pain, most patients are diagnosed with disseminated metastases. Patients with metastatic disease have a 5-year survival rate of only 18%.[1] Carcinoid tumors and pancreatic islet cell tumors both arise from neuroendocrine cells and are histologically indistinguishable. Neuroendocrine tumors are usually made up of small cells containing regular, well-rounded nuclei with rare mitoses. These tumors often have a slow rate of progression, yet patients with metastatic disease eventually develop significant morbidity, including pain, diarrhea, constipation, anorexia, weight loss, fatigue, and sometimes episodic flushing, wheezing and right sided valvular heart disease.

For patients with neuroendocrine tumors and localized disease, surgery has shown a survival benefit. For unresectable disease, however, no treatment with survival benefit has been found. Therefore, treatment in this population is currently palliative. Somatostatin analogs are effective in relieving the symptoms of both the carcinoid syndrome and the hormonal hypersecretion seen with pancreatic endocrine tumors.[2] Octreotide may also led to an improvement in PFS as reported in a phase II study, although treatment is not necessarily associated with objective responses. Some patients benefit from interferon-α, but the toxicity of this treatment frequently outweighs the small therapeutic benefit.[3] Chemotherapy is of limited efficacy in the metastatic population, with streptozotocin being the only approved anticancer agent for patients with neuroendocrine tumors, only of the pancreatic islet cell type. The combination of streptozocin and doxorubicin has been investigated in patients with advanced pancreatic islet cell tumors, with a response rate of only 6%. The combination was found to have considerable toxicity, including myelosuppression, asthenia and renal insufficiency. Decreases in hormone secretion and improved physical examinations were seen in patients treated with this combination, however.[4,5] Patients with metastatic carcinoid tumors have also shown resistance to chemotherapeutic regimens consisting of streptozocin and cyclophosphamide, streptozocin and 5-FU, as well as docetaxel and gemcitabine.[6-8] Some single agents and drug combinations have shown limited activity (response rates of 30% or less) in carcinoid patients (fluorouracil, doxorubicin, dacarbazine, cyclophosphamide,fluorouracil plus strotozocin and etoposide plus cisplatin). Complete responses with these regimens are rarely seen. The responses that are seen do not usually last long.[9] There is recent data supporting the role of antiangiogenic agents and mTOR inhibitors in this disease.

Generally, NE tumors are hypervascular and VEGF and VEGF receptors have been found to play critical roles in angiogenesis in these tumors as expression has been demonstrated both in GI and pulmonary carcinoid. In pancreatic islet cell cancers, phase III trials of sunitinib and everolimus compared to placebo have now been reported. Both trials enrolled patients with progressive disease within the previous 12 months and demonstrated clinically and statistically significant improvements in PFS compared to placebo. Both agents have been approved by the US FDA and become standard therapy for pancreatic NET (islet cell carcinoma). For patients who participated in the sunitinib trial, the median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42;

95% confidence interval [CI], 0.26 to 0.66; P<0.001). A Cox proportional-hazards analysis of progression-free survival according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% CI, 0.19 to 0.89; P=0.02). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue.

For patients with pancreatic neuroendocrine tumors who participated in the everolimus study, The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash(49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23%vs. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs. 16 weeks).

In addition, bevacizumab has demonstrated anti-tumor activity and is currently being evaluated in a recently closed SWOG trial, a randomized phase III trial with sandostatin versus interferon and sandostatin. [10,11]

In the recent, double-blind, placebo-controlled, phase 3 RADIANT-4 trial in advanced, progressive, well- differentiated, non-functional neuroendocrine tumors of lung or gastrointestinal origin patients were randomly assigned in a 2:1 ratio to receive everolimus 10 mg per day orally or identical placebo, both with supportive care. The primary endpoint was progression-free survival assessed by central radiology review, analyzed by intention to treat. Overall survival was a key secondary endpoint. A total of 302 patients were enrolled, of whom 205 were allocated to everolimus 10 mg per day and 97 to placebo. Median progression-free survival was 11·0 months (95% CI 9·2–13·3) in the everolimus group and 3·9 months (3·6– 7·4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of progression or death (hazard ratio [HR] 0·48 [95% CI 0·35–0·67], p<0·00001). Although not statistically significant, the results of the first pre-planned interim overall survival analysis indicated that everolimus might be associated with a reduction in the risk of death (HR 0·64 [95% CI 0·40–1·05], one-sided p=0·037, whereas the boundary for statistical significance was 0·0002). The drug was well tolerated the most common toxicities were stomatitis, diarrhea, anemia, fatigue and hyperglycemia. The FDA approved everolimus for progressive, well-differentiated non-functional, neuroendocrine tumors of gastrointestinal or lung origin in patients with unresectable, locally advanced or metastatic disease in February 2016. This has changed the approach and standard treatment options in this patient population.[12]

1.2 Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI).[13]

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.

1.2.1 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). [13] 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.[13] These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

1.2.2 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.

Recently data from a randomized Phase II study of regorafenib in refractory metastatic colorectal cancer was presented at ASCO GI 2018 by Bekaii-Saab et al. This study randomized patients to Arm A: 80 mg regorafenib per day, with weekly dose escalation of 40 mg, up to a dose of 160 mg per day if no significant drug-related toxicities were observed or Arm B: 160 mg regorafenib per day. Arm A, the dose escalation arm had patients staying on regorafenib longer (43% initiating the 3rd cycle versus 25%, p=.028) and had longer overall survival, (9.0 months vs. 5.9 months, p=.094). Progression free survival was not statistically significantly longer for Arm A (2.5 months versus 2.0 months, p=.553), but rates of overall grade 3/4 toxicity did favor Arm A (% palmar-plantar erythrodysethesia syndrome 15 versus 16, hypertension 7 versus 15 and fatigue 13 versus 18).

1.3 Correlative Studies

There are no validated biomarkers to predict efficacy to anti VEGF or anti VEGFR targeted therapy. There are promising markers identified such as VEGF or VEGFR mRNA expression or germline

polymorphisms in these genes which have been shown to be associated with outcomes, however no prospective clinical trial with sufficient patient samples has been tested. There is evidence that VEGF independent pathways may play a critical role in effectiveness of bevacizumab with data showing IL8, CXCR2, IL1beta, or IL6 are associated with outcome either measured by plasma levels or germline polymorphisms.

We will obtain archival tumor tissue and plasma samples at baseline and at the time of progression to explore the biomarkers of benefit from regorafenib.

1.4 Rationale

Regorafenib is a multiple kinase inhibitor (MKI) targeting several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGFR-2, VEGFR-3, TIE-2, PDGFR-ß, c-KIT, RET and FGFR-1) (VEGFR: vascular endothelial growth factor receptor) along with p38α, a member of the MAPK family. In cellular mechanistic assays, regorafenib reduced basal phosphorylation of the MAPK pathway in a panel of human breast, melanoma, and pancreatic tumor cell lines. In other cellular assays, regorafenib was found to be a potent inhibitor of human VEGFR-2, VEGFR-3, TIE-2, c-KIT, and PDGFR-ß receptor phosphorylation. In addition, regorafenib blocks VEGF dependent MAPK activation in human endothelial cells and PDGF dependent cell proliferation in primary human vascular smooth muscle cells. (BAYER Regorafenib package insert)

Given the potential treatment of neuroendocrine tumors with vegf inhibition, we are proposing a phase II study with regorafenib as a single agent in patients with advanced/metastatic NE tumors.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To assess PFS in advanced/metastatic in patients with carcinoid or pancreatic islet cell tumors

2.2 Secondary Objectives

2.2.1 To assess Overall Survival and Response Rate in advanced/metastatic poor prognosis in patients with carcinoid or pancreatic islet cell tumors

2.2.2 To assess the toxicity of patients treated with regorafenib

2.2.3 To explore markers of angiogenesis as they relate to outcome in carcinoid and pancreatic islet cell tumors."

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Advanced metastatic, progressing carcinoid or pancreatic islet cell cancers

3.1.2 No prior chemotherapy or anti-angiogenic therapy. One prior mTOR inhibitor is allowed. Patients may have received one line of prior therapy with somatostatin analogue, locoregional therapy. Continuation of concurrent somatostatin analogue is allowed. Patients will be maintained on somatostatin analogue for the duration of their treatment.

3.1.3 Age ≥ 18 years.

3.1.4 Life expectancy of at least 12 weeks (3 months).

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

3.1.6 All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF). Exceptions to this include alopecia.

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

- Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferease (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Lipase ≤ 1.5 x the ULN
- Amylase ≤ 1.5 x the ULN
- Serum creatinine ≤ 1.5 x the ULN
- International normalized ratio (INR)/ Partial thromboplastin time (PTT) < 1.5 x ULN. (Subjects who are 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 (day 5 of cycle 1 and day 1 of each cycle) is mandatory) will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
)

- Platelet count $\geq$ 100,000 /mm3, hemoglobin (Hb) $\geq$ 9 g/dL, absolute neutrophil count (ANC) $\geq$ 1,500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.

3.1.8 Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2 according to the Modified Diet in Renal Disease (MDRD) abbreviated formula.

3.1.9 Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgement of the investigator

3.1.10 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.

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

3.1.12 SWOG Performance Status 0-1.

3.1.13 Patients must have measurable disease.

Exclusion Criteria

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

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

3.1.16 Active or clinically significant cardiac disease including:

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

3.1.17 Evidence or history of bleeding diathesis or coagulopathy.

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

3.1.19 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.

3.1.20 Subjects with any previously untreated or concurrent cancer that is distinct in primary site or histology from carcinoid or pancreatic islet cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before randomization are allowed. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form).

3.1.21 Patients with pheochromocytoma.

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

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

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

3.1.25 Renal failure requiring hemo-or peritoneal dialysis.

3.1.26 Dehydration Grade $\geq$1 NCI-CTCAE v4.0.

3.1.27 Patients with seizure disorder requiring medication.

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

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

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

3.1.31 History of organ allograft (including corneal transplant).

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

3.1.33 Any malabsorption condition.

3.1.34 Women who are pregnant or breast-feeding.

3.1.35 Any condition which, in the investigator's opinion, makes the subject

unsuitable for trial participation.

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

3.1.37 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.1.38 History of allergic reactions attributed to compounds of similar chemical or biologic composition to regorafenib or other agents used in study.

3.1.39 Uncontrolled, intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.1.40 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).
- Prior use of regorafenib.
- Concurrent use of chemotherapy, radiotherapy or another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form)
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

4.1 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Regorafenib 80 mg QD Week 1/120 mg QD Week 2/160 mg QD Week 3 then 1 week off followed by Cycle 2+ 160 mg QD D1-21, of a 28 day cycle.

Regorafenib tablets should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Some examples of low fat breakfasts are:

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

protein, 93 g of carbohydrate, 520 calories.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Study Calendar. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.2.1.1 Dose Levels and Reductions

Study medication will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4]. A new cycle of therapy can start when all toxicities, (except hand-foot syndrome, alopecia, non- refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities) have resolved to Grade 2 or less. Hand-foot syndrome must have resolved to Grade 0-1.

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.

Strictly follow the modification in the following tables for the first **two** cycles until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Dose Level			If no SDRT	If + SDRT**
Dose level 0*	80 mg po qd	Two 40-mg tablets of regorafenib	Proceed to next dose level	
Dose level 1	120 mg po qd	Three 40-mg tablets of regorafenib	Proceed to next dose level	Decrease to 80 mg
Dose level 2	160 mg po qd	Four 40-mg tablets of regorafenib		Decrease to 120 mg
* Starting Dose ** SDRT= Significant Drug Related Toxicities				

If a subject experience 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

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

Table 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, lymphocyte count decreased, 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 2: Grading for Hand-Foot-Skin-Reaction

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

a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.

Table 3 Recommended dose modification for hand-foot-skin reaction (HFSR)[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 not permitted.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg.

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

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

Control of calluses

Before initiating treatment with regorafenib:

- Check condition of hands and feet.
- Suggest a manicure/pedicure, when indicated.
- Recommend pumice stone use for callus or 'rough spot' removal.
- During regorafenib treatment:
    - Avoid pressure points.

- Avoid items that rub, pinch or create friction.

Use of creams

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

Tender areas should be protected as follows:

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

Hypertension

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

Table 4: Management of Treatment-Emergent Hypertension

Grade of event (CTCAE v4.0)	Antihypertensive Therapy	Regorafenib Dosing
Grade 1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring

Grade 2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: • If BP previously within normal limits, start anti-hypertensive monotherapy • If patient already on anti-hypertensive medication, titrate up the dose.	• Continue regorafenib • If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
Grade 3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
Grade 4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Patients requiring a delay of >4 weeks should go off protocol therapy b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion. c. Patients requiring >2 dose reductions should go off protocol therapy.		

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 5 should be followed.

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

Table 5: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	**Occurrence**	**Recommended measures and dose modification**

≤ 5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue Regorafenib treatment. Monitor liver function weekly until transaminases return to < 3 times ULN (Grade 1) or baseline.
>5 times ULN to ≤ 20 times ULN (Grade 3)	1st occurrence	Interrupt Regorafenib treatment. Monitor transaminases weekly until return to < 3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-initiate Regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with Regorafenib permanently.
>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with Regorafenib permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with Regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exceptions: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.
Weekly LFT monitoring for the first two cycles is required.		

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

4.3 Concomitant Medications/Treatments

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

avoided, if possible.

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

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

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates
- Octreotide
- 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 (day 5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

The following are not permitted:

- Other investigational treatment during or within 30 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 it's levels may be

especially affected by regorafenib

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

4.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Removal of Patients from Protocol Therapy

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation of treatment will be documented and may include:

- Patient withdraws consent (follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician determines continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented in CRF's.

4.6 Duration of Follow Up

Patients will be followed with phone calls every 3 months until death after removal from treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 7 days prior to registration for labs, 28 days for scans unless otherwise stated. The screening procedures include:

5.1.1 Medical history. Complete medical and surgical history, history of infections.

5.1.2 Demographics. Age, gender, race, ethnicity

5.1.3 Review subject eligibility criteria

5.1.4 Review previous and concomitant medications

5.1.5 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.6 SWOG Performance status

5.1.7 Adverse event assessment
Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.8 Hematology, coagulation

5.1.9 Blood draw for correlative studies:
Two purple top tubes to the Lenz lab, See Section 9.0 for details.

5.1.10 Serum chemistries: Phosphorus, Magnesium, LDH and Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.11 Urine Pregnancy test (for females of child bearing potential)

5.1.12 Tumor assessment

5.1.13 Thyroid Function (TSH, T3, T4), 5HIAA, Lipase

5.1.14 EKG

5.1.15 Serum Chromogranin

5.1.16 Ocreotide scan

5.1.17 Urinalysis for proteinuria

5.1.18 Archival tumor tissue

5.1.19 CXR if CT of chest is not done

5.2 Procedures During Treatment

5.2.1 Prior to Each Treatment Cycle

- Physical exam including vital signs (temperature, pulse, respirations, blood pressure), height, weight
- Hematology
- Concomitant medications
- Urine pregnancy test (if woman of childbearing potential)
- EKG, PT/PT-INR, PTT, Thyroid Function (TSH, T3, T4) if clinically indicated
- SWOG performance status
- Urinalysis for proteinuria
- Serum chemistries: Phosphorus, Magnesium, LDH and Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.
- Adverse event evaluation
- 5HIAA
- Pill Diary
- Lipase

5.2.2 Day 8, 15 and 22 of Cycle 1 and 2 only

- BP Monitoring
- Liver Function Tests

5.2.3 Day 15 of all Cycles

- Serum chemistries: Phosphorus, Magnesium, LDH and Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.
- Hematology

5.2.4 One day of week 3 of Cycle 2 only

- Octreotide scan

5.2.5 One Day of Week 3 of every other Cycle (starting with Cycle 2)

- Serum Chromogranin
- Tumor Assessment

5.2.6 Off Study

- Pill Diary
- SWOG Performance Status
- Vital Signs
- Blood draw for correlative studies - Two purple top tubes to the Lenz lab, See Section 9.0 for details

5.3 Follow-up Procedures

Patients will be followed with phone calls every 3 months until death after removal from treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.4 Study Calendar

Cycles will be 28 Days. Regorafenib will be taken orally Days 1-21 of each Cycle. For first cycle all labs and EKG should be done within 7 days of first receiving study drug. For the first cycle, Imaging studies should be done within 28 days of first receiving study drug.

Table 6

Parameter	Pre-Treatment[8]	Day 1 of All Cycles[1][2]	Day 8, Day 15 And 22 of Cycle 1 and 2 only[12]	Day 15 of all Cycles[1][2]	One Day of Week 3 Of every other Cycle (starting with Cycle 2)	Off study	Follow-up
Informed Consent	X						
Pill Diary		X				X	
History & Physical Exam	X	X					
Weight, SWOG Performance Status, Con Meds	X	X				X	
Adverse Event/Toxicity Evaluation	X	X					
WBC (differential), Hgb, Platelets	X	X		X			
Complete Metabolic Panel, Phosphorus, Magnesium, LDH	X	X	Liver function	X			
Lipase	X	X					
Thyroid Function (TSH, T3, T4)	X	X[3]					
PT/PT-INR, PTT	X	X[3,9]					
Urinalysis for proteinuria	X	X					
5HIAA	X	X					
Serum Chromogranin	X				X		
Octreotide scan	X				Cycle 2 only		
EKG	X	X[3]					
CXR (if CT of chest not done)	X[7]				X[7]		
BP Monitoring		X	X				
Radiology, x-ray or Scans for disease measurement[2]	X[8]				X		X[10]
Archival tumor tissue	X[8]						
Plasma	X[8]					X[8]	
Urine Pregnancy Test	X[5]	X[5]					
Survival Follow-up							X[11]

1 If used to follow measurable disease.
2 Within 28 days of Cycle 1, Day 1.
3 As clinically indicated.
4 Paraffin embedded tissue must be available for review.
5 For women of childbearing potential
6 Confirm response within 4 weeks.
7 Not required if CT scan of the chest is done.
8 See section 9. For plasma two purple top tubes to the Lenz lab.
9 Close monitoring (day 5 of cycle 1 and day 1 of each cycle) of PT/PT-INR and PTTis mandatory for patients on agents such as warfarin and heparin.
10 Patients that come off for reasons other than disease progression will have their standard of care scans measured via RECIST until progressive disease, to determine date of disease progression
11 Patients will be followed up via phone call, medical records or database search until death to determine survival time
12 All study visits allow a +/ - 7 day window

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All patients will be included in the toxicity summaries, from the time of their first treatment with study drug.

All patients must be accounted for in the summary of objective response (see Section 10.4 for more details). To formally classify a patient as RECIST-evaluable, only those patients who have measurable disease present at baseline, and have had their disease re-evaluated will be considered evaluable. 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.)

6.1.2 Disease Parameters (RECIST 1.1)

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. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

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.

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

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.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days 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.

Conventional CT and MRI. These techniques 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.

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

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart.

There can be no appearance of new 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. There can be no appearance of new lesions.

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.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

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

6.1.4.3 Evaluation of Best Overall Response

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

Table 7

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	documentedat 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.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.5 **Confirmation of Response:**

Confirmation of response is not required in this trial as response is not the primary endpoint.

6.1.6 **Duration of Response**

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

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

6.1.7 **Progression-Free Survival (PFS)**

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death on study whichever comes first. Patients who go off treatment for reasons other than disease progression or death will be censored at the time of the last CT scan.

6.1.8 **Time to Treatment Failure (TTF)**

Time to treatment failure is defined as from start of treatment until time to progression, death, start of alternate therapy or development of secondary malignancy, whichever comes first.

6.1.9 **Overall Survival (OS)**

Overall survival is defined as from start of treatment until death due to any cause. Otherwise OS is censored on the last day patients are known to be alive.

6.1.10 **The primary endpoint**:

The 6-month PFS rate is the primary endpoint. The 6-month PFS is dichotomous, *yes* or *no*. Radiographic scan for disease measurement that is done within ±14 days of the 6-month landmark (Day 182 since first receiving study drug) will be counted to determine the 6-month PFS status. Patients who are alive and progression-free at 6 months (182 days) since first starting regorafenib will be counted as '*yes*' for the 6-month PFS. Patients who progress or die within 6 months of starting regorafenib will be counted as '*no*' for the 6-month PFS. Patients whose status of progression or death at 6 months is unknown due to early withdrawal, loss-of-follow-up, or other reasons will be also counted as '*no*' for 6-month PFS.

6.2 Safety/tolerability

Analyses of safety/ toxicity will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

7.1 **ADVERSE EVENTS**

7.1 Adverse Event Monitoring

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

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

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

7.2 Definitions

7.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of Adverse Events

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

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

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

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

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

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

7.3.3.4 Results in persistent or significant disability or incapacity.

7.3.3.5 Is a congenital anomaly/birth defect

7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- 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 *unlikely related* to the study treatment.
- Unrelated – The AE is *clearly NOT related* to the study treatment.

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

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the drug package insert;
- the current Investigator's Brochure

7.4 Reporting Requirements for Adverse Events

7.4.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
    - Study Chair/USC PI: Syma Iqbal, MD (iqbal_s@med.usc.edu)
    - Multi-site Coord./DSMC Coord.: Grace Kim (Grace.Kim@med.usc.edu)_
- SAE occurring after consent but before first dose will not require reporting.
- **The Investigator may report serious adverse drug reactions (SADRs) using either:**

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

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.

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 to Bayer 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 (within 24 hours.

All non-USC sites are required to notify the study chair, Dr. Iqbal and the multi-site coordinator of all SAE submissions. Investigators should also report events to their IRB as required.

SAE notification to the FDA:

- USC: study team to work with CISO QA to submit to the FDA using MedWatch 3500A form in accordance within the FDA required timelines

- Non-USC site: study team to notify USC PI within 24hrs of site becoming aware of the event by completing a MedWatch 3500A form. USC will review and submit applicable reports to the FDA and notify Bayer of the FDA submission.

  The study sponsor, USC, will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

IRB reporting

- The Institutional IRB must be notified of "any unanticipated problems involving risk to subjects or others" in accordance with the Institutional policy. Such policies will be provided to the CISO QA prior to enrolling 1st patient. The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- The USC NCCC Data and Safety Monitoring Committee (DSMC) must be notified within 24 hours of submission of such reportable event to the IRB. The patient ID and the study number as well as identifier of the SAE report should be submitted to the DSMC Coordinator via email or Fax to the attention of the DSMC Coordinator at 323-865-0089.
- The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

7.4.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission. This report should also be forwarded to

the DSMC Coordinator. A list of all toxicities will be included in the IND annual report.

7.5 Stopping Rules (Monitoring rules for safety)

Although we expect that regorafenib be well tolerated, the guidelines listed below will be used to raise a flag if the number of patients who experience unacceptable toxicity is large enough to strongly suggest that the true probability of unacceptable toxicity is 33% or higher.

Unacceptable toxicity will be defined as

- Any Grade 3 non-hematologic toxicity not reversible to Grade 1 or less within 96 hours with the exception of Grade 3 diarrhea or
- Any Grade 4 non-hematologic toxicity or
- Any Grade 4 hematologic toxicity not resolving to Grade 1 or less within 5 days, despite supportive care or
- Grade 4 neutropenia associated with fever or
- Grade 4 thrombocytopenia.

An unacceptable toxicity, regardless of attribution, observed during any course, will be used in the decision to suspend accrual. Two cohorts will be monitored separately.

To be evaluable for excessive toxicity a patient must complete a minimum of 2 courses of treatment or have experienced unacceptable toxicity. Patients who do not complete 2 courses and who do not experience any unacceptable toxicity will not be used in the decision to continue or suspend accrual to the trials, for reasons for excessive toxicity. Every time unacceptable toxicity is observed, the number of patients (X) who have experienced unacceptable toxicity will be compared to the number of patients (N) who are evaluable for excessive toxicity. If the number of patients, N, is greater than N_X, the number given in column 2 of the Table XX, below, then accrual will not be suspended. If N is less than or equal to N_X, then accrual will be suspended for review of the data.

Table XX: Criteria for continuing accrual

X: # pts who experienced a DLT in a cohort	3	4	5	6	≥7
N_x: Suspend trial of # evaluable pts. (N) is $\leq N_x$ in a cohort	≤5	≤10	≤15	≤20	suspend

Using this rule with 24 patients, the probability of correctly suspending this regimen for review toxicities is 0.79 if the true chance of unacceptable toxicity is 33%. The probability of falsely suspending this regimen for review toxicities is 0.030, if the true chance of unacceptable toxicity is 10%. Estimations of the probabilities of suspending this regimen are based on 10,000 simulations.

8.0 DRUG INFORMATION

8.1 Regorafenib

- Other names for the drug(s): Stivarga
- Classification - type of agent: Tyrosine Kinase Inhibitor

- Mode of action: Stivarga (regorafenib) is a potent oral multi-kinase inhibitor with a kinase inhibition profile targeting angiogenic, stromal and oncogenic receptor tyrosine kinases (TK). This distinct anti-angiogenic profile includes inhibition of both VEGFR2 and TIE2 TK.

- Storage and stability: Store Stivarga at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]. Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening.

  Discard any unused tablets 7 weeks after opening the bottle. Dispose of unused tablets in accordance with local requirements.

- Protocol dose: 160 mg qd will be administered for 3 weeks on /1 week off. One cycle is 28 days.

- Preparation: None

- Route of administration for this study: P.O.

- Incompatibilities: See 4.3

- Availability: Provided by sponsor free of charge.
- Side effects: asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction (palmar-plantar erythrodysesthesia), diarrhea, mucositis, weight loss, infection, hypertension, dysphonia, gastrointestinal and abdominal pain, rash, fever and nausea. See the package insert for a comprehensive list of adverse events.

8.1.1 **Return and Retention of Study Drug**

Destruction and Return

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

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

E-mail: Karen.marini@bayer.com
OR
Fax: 973-709-2193
OR
Mail: (VP of Medical Affairs named in contract) at

Bayer HealthCare Pharmaceuticals
6 West Belt
Wayne, NJ 07470

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.

The study pharmacist at each participating site will be responsible for maintaining a record of shipment, receipt and dispensation of study medication(s). The study pharmacist will utilize an NCI drug accountability template for documenting dates, and amounts/doses received from the sponsor and dates, patient initials and doses dispensed to the patient.

8.1.2 **Treatment compliance**

The study Research Coordinator(s) and Data Manager(s) will be responsible for drug accountability of dispensed and returned drug in accordance with the CISO SOP 8.0. The CISO standard pill diary in English and Spanish will be used.

9.0 CORRELATIVES/SPECIAL STUDIES

All correlative studies are mandatory. The samples will be collected for correlative studies which will be determined by current scientific knowledge available at the end of the study. For sites not at USC, store all samples for batch shipping.

9.1 Archival Tissue

Slides require 10 slides of unstained tumor 10 um thick from paraffin embedded tumor blocks or fresh frozen tissue. In lieu of slides, a tumor block may be sent. If possible, the tumor block should be large enough to provide the slides described above.

9.2 Plasma Collection

The blood will be collected prior to initiation and at time of progression/off study. The blood collection will require 2 tubes of blood (two purple top tubes).

Dr. Lenz's laboratory will receive and process

information. Heinz-Josef Lenz, MD Laboratory
USC Norris Cancer Center
1441 Eastlake Avenue, Laboratory Room
#5410 Los Angeles, CA 90033
323-865-0572

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

The 6-month PFS rate will be the primary endpoint (see definition at section 6.1.10). Two parallel Simon's 2-stage phase II trials will be conducted to evaluate the efficacy of regorafenib in patients with advanced carcinoid (cohort A) or pancreatic islet cell tumors (cohort B).[14] Two randomized phase III trials [refs 10-11] that were completed for advanced pancreatic islet cell tumors observed the median PFS was about 11 months and 6-month PFS rate was 71% in arm of the anti-VEGF therapy. Two small phase II trials of anti-VEGF agents that were conducted among patients with advanced carcinoid tumor [refs 14-15] showed that the median PFS was about 6 months and 6- month PFS rate was 45%. Therefore 6-month PFS rate of 65% for patients with advanced carcinoid and 80% for patients with advanced pancreatic islet cell tumors would be promising for further investigation. Otherwise observation of 40% and 60% 6-month PFS rate would be considered ineffective in the setting of advanced carcinoid and pancreatic islet cell tumors, respectively.

For cohort A, a 6-month PFS rate of 40% (under the null hypothesis) would be considered as disappointing and 65% or higher (under the alternative hypothesis) would be encouraging. For cohort B, a 57% rate (under the null hypothesis) would be considered as not interesting, and 80% or higher (under the alternative hypothesis) would be promising. The 6-month PFS rates under the null and alternative hypotheses were chosen based on a phase II consortium trial in the similar settings (NCI Protocol #: 8233). We need a total of 24 patients with carcinoid tumors (cohort A) and 24 patients with pancreatic islet cell tumors (cohort B).

10.2 Sample Size and Accrual

In cohort A, 11 patients will be enrolled in stage I. If 5 or more patients remain alive and progression-free at 6 months, we will continue to enroll until a total of 24 patients are enrolled. If 4 or fewer patients out of the first 11 patients remain alive and progression-free at 6 months, we will suspend the accrual. If we observe **14** or more patients are alive and progression-free at 6 months, regorafenib would be considered promising for cohort A as long as it is tolerable.

In cohort B, 11 patients will be enrolled in stage I. If 7 or more patients remain alive and progression-free at 6 months, we will continue to enroll until a total of 24 patients are enrolled. If 6 or fewer patients out of the first 11 patients remain alive and progression-free at 6 months, we will suspend the accrual. If we observe **18** or more patients are alive and progression-free at 6 months, regorafenib would be considered promising for cohort B as long as it is tolerable.

We will not suspend accrual when the number of patients enrolled meets the goal for the number of patients required for stage I in each trial but the decision of suspending the accrual during stage I cannot be reached due to the insufficient follow-up.

The study design of both trials has 80% power to demonstrate the efficacy of regorafenib. The type I error rate is 5.1% and 5.3%, for cohort A and B, respectively. We designed the trials with type I error rate a little higher than 5% because the tumors are rare and the sample size should be as small as possible. The sample size calculation was based on a single-arm 2-stage Simon's Minimax phase II Design. An online program (Clinical Trial Design Systems) developed by Duke Cancer Institute was used to perform the calculation (http://www.dukecancerinstitute.org/research/shared-resources/biostatistics/clinical-trial-

design-systems/).

10.3 Data Analyses Plans

Two cohorts will be analyzed separately. The primary data analysis set will include all patients who enroll the study and start to receive regorafenib for decision making in accrual and warranting further studies. Patients who withdraw the study, are lost to follow-up, or start another therapy before the status of 6-month PFS is determined will be counted as 'no' for the primary endpoint and be included in the primary data analysis set. Patients who drop out the trial before starting regorafenib will be replaced and excluded from the primary data analysis set.

The primary endpoint, 6-month PFS rate will be summarized as a proportion of patients who are alive and progression-free among all patients in the primary data analysis set. The 95% confidence intervals of the 6-month PFS rate will be calculated using the Wilson method. We chose 6-month as the cut-off point because it would be easier to compare with the historical data. The tumor response will be evaluated by CT scans every 2 cycles starting with week 3 of cycle 2. Six-months since starting treatment are 182 days, may not be on the CT scan date. CT scans will not on the strict schedules. Additional scans may be conducted to confirm a complete or partial response. Patients whose systems deteriorate clinically will be counted as progression event without confirmation of CT scans. CT scans that are conducted within ±14 days of the landmark Day 182 will be used to determine the 6-month PFS status if there are no other scans available to determine the status. The detailed status of 6-month PFS will be counted as follows: alive and progression-free, disease progression within 6 months, death within 6 months, and progression at 6 months unknown due to early withdrawal, toxicities, or other reasons.

A sensitivity analysis of PFS at week 24 will be conducted. The PFS rate at week 24 may provide the impact of CT scheduling on estimating the 6-month PFS rate.

In addition, progression-free survival (see definition at section 6.1.7) will be analyzed using Kaplan-Meier curves. The median PFS and 95%CIs will be calculated. The probability of 6-month PFS will be estimated from the KM curve too.

The secondary endpoints including tumor response rate and OS (see definition at section 6.1.9) will be analyzed descriptively.

Tumor response rate will be calculated as a proportion of patients who have either a complete or partial response among all patients in the primary data analysis set. The 95% confidence intervals will be given.

OS will be analyzed in the same way as PFS.

Toxicity profile will be summarized by attribution: regorafenib-related and all reported, course: cycle 1 and all cycles, type, and grade: grade 1-2, 3-4, and 5.

10.4 Reporting and Exclusions

10.4.1 Evaluation of toxicity. All toxicities experienced by patients who receive

any treatment of the study drug(s) will be reported.

10.4.2 Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. 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).

All of the patients who met the eligibility criteria (with the possible exception of those who never received any study drug) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

The primary analysis will be based on all eligible patients and who received any amount of study drug.

10.5 Data analysis plan for the exploratory objective

Biomarkers such as mRNA levels or germline variations of genes related to angiogenesis will be measured once the study is completed and regorafenib is recommended for further studies in the setting. The associations between biomarkers and clinical outcomes (6-month PFS, response, PFS, and OS) will be analyzed in univariate analysis first using appropriate methods. Multivariable analyses will be conducted to evaluate the independent effect of a marker on clinical outcome. All tests will be two-sided at a significance level of 0.05. *P* values will be adjusted for multiple comparisons. The purpose of the correlative study is to generate hypotheses that will be examined for future clinical trials.

11.1 STUDY MANAGEMENT

11.1 Conflict of Interest

All investigators will follow the University conflict of interest policy. Any USC investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must complete a "Statement of Outside Interests Related to Research" Form. The application is reviewed and approved by the Conflict of Interest Review Committee (CIRC) USC conflict of interest policy is available at
http://ooc.usc.edu/conflict-interest-research

11.2 Institutional Review Board (IRB) Approval and Consent Process

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol and all study related documents used in the study (e.g. QOL questionnaire, pill diary, brochure, advertisement etc).

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

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

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person authorized to obtain the informed consent

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Investigation Support Office (CISO)

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Protocol signature page with Investigator signature
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Registration Procedures

Multi-Site Registration:

All participants in the multi-site trial are subject to central registration, which is used for tracking study accrual, checking eligibility, and monitoring adequate participation of women and minorities. Subject registration will be conducted through the coordinating center at the NCCC-CISO. External sites will identify eligible subjects and verify enrollment availability with the MCC prior to consenting patients. The external site is required to notify the MCC of a new signed informed consent within 48 business hours and note the basic consent information on the screening log. A copy of the consent will accompany the complete eligibility packet for verification. The MCC will enter the patient, demographic, and consent information in the applicable USC database. The MCC will assign a study patient sequence ID and communicate this to the external site.

The Coordinating Center Program Hours are 8 am to 4 pm, Monday through Friday, based

on the PST zone. The MCC will be closed on official government holidays unless otherwise indicated. The contact number for the MCC is 323-865-3122. A copy of the registration sheet is located in the Appendix.

External sites will verify eligibility prior to submitting documents to the MCC for central registration. External sites must submit registration requests to the MCC at least one full business day prior to the planned treatment start date. Registration will require the external site to submit to the MCC all of the following:

- A completed registration form with patient demographics:
- Zip code
- Age
- Sex
- Race
- Ethnicity
- Initials
- Date of Birth (DOB)
- A completed Eligibility Checklist signed by the investigator
- A copy of the most recently IRB-approved, patient signed informed consent form
- All required screening tests, within the time parameters specified by the protocol study calendar
- All other de-identified source documents needed to verify all points of eligibility
- Any On-Study forms for registration specified by protocol

These documents must be securely emailed to the MCC staff. With advance notice documents will also be accepted faxed to 323-865-0457. The MCC will verify completeness of documents and confirm eligibility. The MCC will enter the registration information in the USC OnCore® database. The MCC will then fax or securely email the completed Registration Form with the assigned study sequence ID to the external site as confirmation of patient registration.
An external site must maintain a log of all subjects who sign informed consents. The log must also document an explanation for exclusion due to screen failure. The MCC will provide sites with a Patient Tracking Log at the time of site activation. In the event of screen failure, external sites must submit the Screen Failure form to the MCC within one business day of determining screen failure.

Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise.

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology reports, MRI reports, Operative reports, etc.) submitted to the CISO-MCC must have the patient's full name and social security number redacted (blacked out) and the assigned CISO-MCC patient ID number, protocol number, and site number written in. Patient initials only may be included or retained for cross verification of identification.

A registration verification letter will be emailed (preferred) or faxed to the registering site within one working day for patients registered to CISO-MCC multi-site trials. Treatment may not be initiated until the site receives this faxed or emailed verification.

USC Registration:
For patients enrolled at USC, the Research Coordinator must complete the protocol eligibility form to ensure that the patient is eligible. The PI will review the patient eligibility (with assistance from the Research Coordinator- who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

The Research Coordinator or data manager will then register the patient into the Cancer Center database, Café, by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in cafe will need to be completed, for Off Treatment and Off Study.

11.5 RECORDS AND DATA SUBMISSION

A. Confidentiality of Records

The original data collection forms will be kept in secure file cabinets, for USC patients forms will be kept in the Clinical Investigations Support Office (CISO).

B. Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent with the Human Rights and the HIPAA authorization must be given to the patient. Institutional policy regarding distribution and location of original consent documents should be followed. When a study is opened at two or more institutions, a copy of the signed consent and HIPAA should be sent to USC CISO QA team as soon as possible, and not later than within 5 business days of obtaining consent. For patients consented at USC/LAC, institutional policy should be followed: a copy of ICF and HIPAA should be uploaded through True to USC CRO and to CISO QA Team. The original will be kept in the patient research chart maintained by the study assigned Data Manager.

C. Registration Eligibility Worksheet

At the time of registration, the completed Eligibility Worksheet will be submitted to the QA Monitor at CISO for review of eligibility compliance.

D. Data Collection Forms and Submission Schedule

If a treatment trial, protocol data will be entered into eCRFs in Café.
Within two weeks of registration, the data manager will complete the initial set of On Study forms and baseline Toxicities
Within two weeks of completion of each course of treatment, the data manager must complete the Course Assessment, Toxicities, and if appropriate Response data.

- After Off Treatment, within two weeks of each follow up, complete the Follow Up forms.

11.6 Data Management and Monitoring/Auditing

11.6.1 Active Monitoring Program Details

a. **Adherence to Protocol/Per Patient**: It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

b. **Day-to-Day Monitoring – Eligibility:** At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

c. **Day-to-Day Monitoring – Informed Consent:** Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

Day-to-Day Monitoring – Treatment: The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the subjects on study at other institutions to ensure compliance and adherence to the protocol.

d. **Data Management – Patient Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, all written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is the Electronic Patient File (EPF). Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Affinity. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented.

e. **Data Management – Research Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical

and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results, that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

f. **Data Management – Case Report Forms:** It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

11.6.2 Quality Assurance Monitoring Committee (QAMC) Oversight

The Quality Assurance and Monitoring Committee (QAMC) of the NCCC has the responsibility for study auditing and monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual. QAMC procedures are detailed in the NCCC Data Safety and Monitoring Plan available on CISO Website.

11.6.2.1 QAMC Annual Patient Audits

The QAMC is responsible for conducting audits and providing the initial review of the audits, for all open institutional (i.e. USC initiated), CCCP-sponsored trials, and any trials identified by the CIC. These trials are audited by the QAMC once a year. Faculty and staff at the Cancer Center involved in clinical research – but not directly involved in the research under evaluation – are asked to serve as auditors. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are selected at random; however, additional patients may be selected for audit if there is some indication that there might have been a problem or unusual circumstance (possibly related to compliance, toxicity, response or some indication of an irregularity). The audit involves a review of the research chart, hospital medical record (i.e., source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent) and baseline status of the patient; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist. In addition, for Institutional, Investigator Initiated Trials, Data in the CAFÉ database are compared to the information in the medical record.

11.6.2.2 QAMC Annual Protocol Review

All open trials are reviewed at least once a year by the QAMC (or more often if stipulated by the CIC). This annual review includes the following: evaluation of the current accrual

relative to the planned total accrual; examination of gender and minority accrual; examination of all reported violations; review of past audits and correspondence with the PI; review of results of current audit (by an outside agency or by the NCCC QAMC); review of previous correspondence between the PI and the QAMC/DSMC. The QAMC review process is detailed in USC NCCC DSM Plan available on the CISO website.

11.6.3 Data and Safety Monitoring Committee (DSMC) Oversight

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

11.7 Adherence to the Protocol

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

11.7.1 Emergency Modifications

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

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

11.7.2 Non-Emergency departures from protocol

A protocol deviation is any variance from an IRB approved protocol.
If the deviation meets all of the following criteria, it is considered a minor protocol deviation that:

- Is generally noted or recognized only after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

If the deviation meets any of the following criteria, it is considered a protocol violation:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: All protocol violations will be entered in the clinical trial database by the Research Coordinator. In addition, Research Coordinator and Investigator should report all protocol violations within one (1) week of the knowledge of the event using iStar.

11.7.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB as well as to all the sponsoring agencies (FDA, NCI, etc.) for review and for approval prior to implementation. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved.

11.8 Record Retention

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

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

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

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

after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDIX 1

REGISTRATION REQUEST FORM

PROTOCOL NUMBER:0S-14-3

Patient Initials (First-Middle-Last):	
Address (Zip Code):	Birth Date:
	Sex:
Race (Please check all that apply): ☐ American Indian or Alaska Native ☐ Black or African American ☐ White ☐ Asian ☐ Native Hawaiian or Pacific Islander ☐ Other	
Ethnicity (Please check): ☐ Hispanic ☐ Non-Hispanic ☐ Other	
U.S. Resident?: ☐ Yes ☐ No If No, enter Country of Residence:	
Method of Payment (Please check): ☐ Private Insurance; ☐ Medicare; ☐ Medicare & Private Insurance; ☐ Medicaid; ☐ Medicaid & Medicare; ☐ Military or Veterans Administration Sponsored; ☐ Self Pay (No Insurance); ☐ No Means of Payment (No Insurance); ☐ Unknown	
Date IC Signed _____/_____/_____ **Time** _____ **am/pm**	**Date HIPAA Signed** _____/_____/_____
Date of Request Form Submitted:	Site Name:
Site Telephone #:	Site Principal Investigator Name:

By signing below, the investigator attests to the review of the source documents for the protocol eligibility requirements.

_____

Eligibility reviewed by: Investigator Name

_____ _____

Investigator Signature **Date**

Utilize the signed form as the cover sheet for the de-identified source doc submission when requesting MCC eligibility verification and registration