Protocol #: LCI-GI-PAN-REG-001

TITLE: A Pilot Study Testing Single-Agent Regorafenib in Advanced Previously-Treated Adenocarcinoma of the Pancreas

LAY TITLE: A Study of Regorafenib in Advanced Pancreatic Cancer Patients

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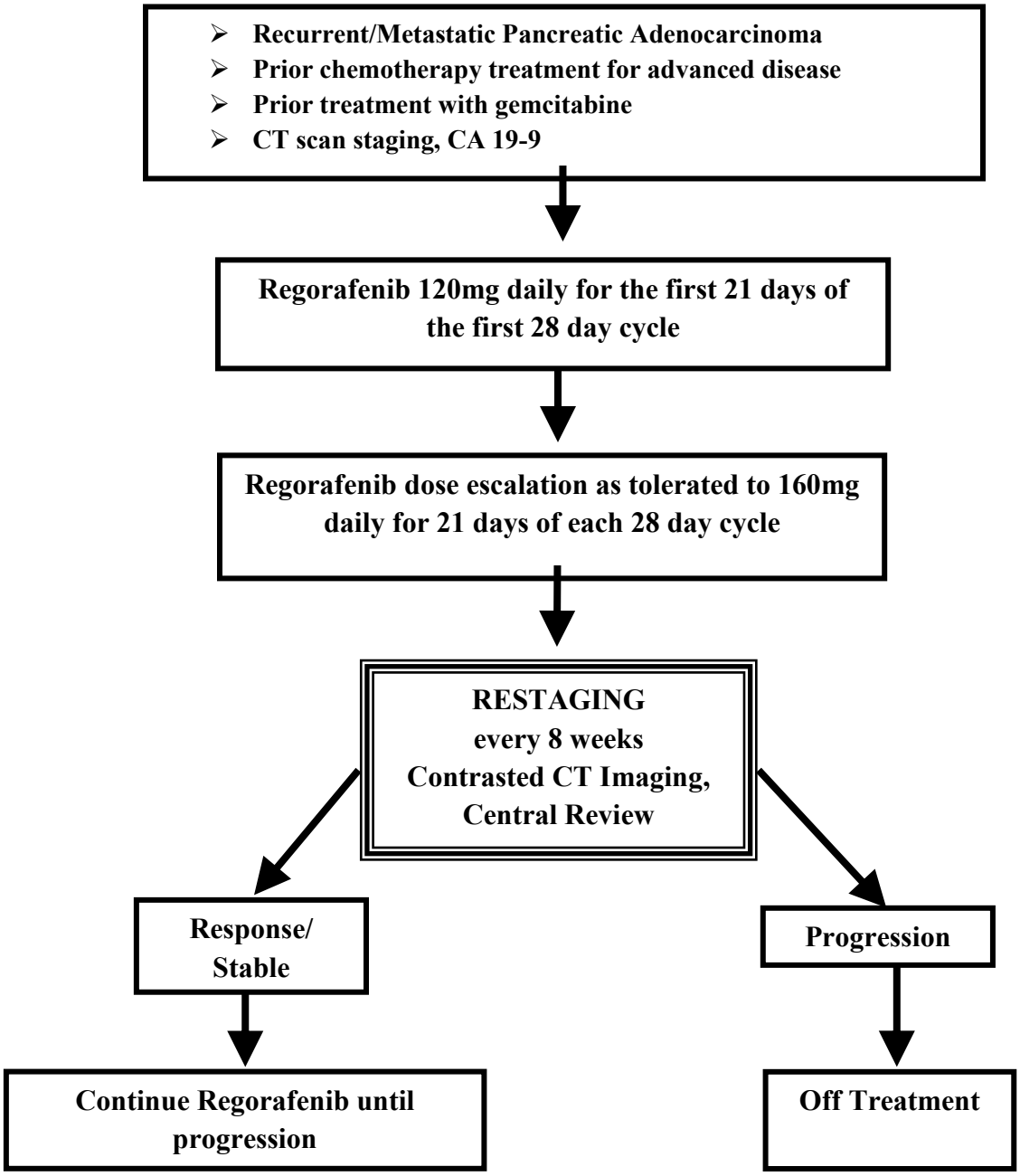
The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Commercial agents: Bayer Regorafenib ***Original Phase 2 /Version 5 /January 14, 2015***

PROTOCOL SUMMARY	
A. Study Title	A Pilot Study Testing Single-Agent Regorafenib in Advanced Previously-Treated Adenocarcinoma of the Pancreas
B. Indication	Advanced, second-line pancreatic cancer
C. Clinical Phase	II
D. Summary of Rationale	Patients who have failed the current standard of care therapy, gemcitabine, have a dismal expected survival of less than 2.5 months and novel approaches are desperately needed. This study tests regorafenib as a single agent in advanced, previously treated pancreatic cancer. Regorafenib is an oral multi-targeted kinase inhibitor that blocks pathways involved in the growth and spread of pancreatic cancer, and preclinical data suggests activity in this disease. Evidence of clinical benefit in this population has the potential to lead to subsequent development of the drug in combination with more standard chemotherapy treatments earlier in the disease course.
E. Study Objectives	The primary study objective is to assess the potential benefit of regorafenib in the treatment of advanced, previously-treated pancreatic cancer. The primary objective is to evaluate the 16-week Progression Free Survival (PFS) rate relative to historical controls. Secondary objectives include critical examination of Response Rate (RR), Disease Control Rate (DCR), Overall Survival (OS), and toxicity. Tissue and blood samples will be collected for analysis of the MUC1 antigen, and future exploratory biomarker analyses.
F. Sample	32 subjects
G. Inclusion/ Exclusion	-Histologically or cytologically-proven metastatic adenocarcinoma of the exocrine pancreas. -Life expectancy of at least 8 weeks. -ECOG Performance Status 0 – 2. -Subjects must have previously undergone at least one documented line of chemotherapy for advanced disease and have had prior treatment with gemcitabine either as part of adjuvant therapy or for advanced disease.
H. Dosage, Route, and Dose Regimen	Subjects will take 120 mg oral regorafenib (tablets) once daily (with a low-fat breakfast) for cycle 1. If well tolerated, the daily dose will be escalated to 160 mg daily. Dose reductions will follow protocol guidelines regardless of whether subject is dose escalated or not. Each cycle is 28 days, with daily dosing for 21 days, followed by a 7 day break.
I. Statistical Analysis	The frequency and proportion of subjects alive and progression free after 16 weeks will be calculated, along with a 95% Clopper-Pearson confidence interval. A one-sided test of proportions, with $\alpha = 0.10$, will be carried out, testing the null hypothesis that the 16-week progression free survival probability is less than 15%.

SCHEMA



- **Endpoints**
- Primary Endpoint: PFS (in terms of 16-week progression free survival rate)
- Secondary Endpoints: RR, DCR, OS, toxicity
- Exploratory Endpoints: Biomarkers in tissue and blood

- **Statistical Plan**
- This will be a single arm, single stage design
  - 32 subjects will be enrolled and the final analysis will be conducted on the population of subjects who begin regorafenib treatment

ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	bis in die, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BSR	Biospecimen Repository
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CHS	Carolinas Healthcare System
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DCE	Dynamic Contrast Enhanced
DC-MRI	Dynamic Contrast-Magnetic Resonance Imaging
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EIA	Enzyme Immunoassay
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration

FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board
LTF	Lost to follow-up
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
MUC1	Mucin1
NM	Nano molar
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFS	Progression free survival
PO	Per Oris, oral
PR	Partial Response

PS	Performance Status
PTT	Partial thromboplastin time
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
RTK	Receptor Tyrosine Kinase
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Stable Disease
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

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1. OBJECTIVES

1.1. Primary Objective

The primary study objective is to assess the potential benefit of regorafenib in the treatment of advanced previously-treated pancreatic cancer. The primary endpoint is progression free survival (PFS) calculated for each subject and the primary objective is to evaluate the 16-week progression free survival rate relative to a historical control.

1.2. Secondary Objectives

Secondary objectives include critical examination of Response Rate (RR), Disease Control Rate (DCR, defined as CR+PR+SD), Overall Survival (OS), and toxicity.

1.3. Exploratory Objectives

Tissue and blood samples will be collected for MUC1 antigen analyses and future exploratory biomarker analyses.

2. BACKGROUND

2.1. Study Disease and Treatment History

Approximately 40,000 people will develop pancreatic cancer in the United States this year, the great majority of whom will die of their disease. Only 15-25% of patients have surgically resectable disease at the time of diagnosis, and most of those that are resected will recur after surgery. For these reasons, cancer of the pancreas is the fourth-leading cause of cancer death in the United States.

Progress in the treatment of advanced pancreatic cancer has been very slow, and novel approaches remain desperately needed. Between the 1950's and the 1990's, 5-fluorouricil was the standard treatment. However, even with leucovorin-modulated 5-FU, response rates were only 5-10%, with median survivals of approximately 5 months. In 1997, a randomized trial comparing 5-FU with the nucleoside analogue gemcitabine suggested a small but clinically and statistically significant benefit for the newer agent.[1] Gemcitabine demonstrated an improvement in the primary endpoint "clinical benefit response," defined as a composite measure of pain, performance status, and weight (24% for gemcitabine vs. 5% for 5-FU), as well as improvements in median OS (5.65 months vs. 4.41 months), and 1-year survival

(18% vs. 2%). This study has solidified gemcitabine as a standard therapy for the initial treatment of advanced pancreatic cancer.

Attempts to improve upon the rather modest benefit of single-agent gemcitabine have met with mixed success. Phase III studies have combined gemcitabine with 5-FU[2], cisplatin[3], irinotecan[4], pemetrexed[5], capecitabine[6], oxaliplatin[7], exatecan[8], cetuximab[9], and bevacizumab[10] without a survival benefit over gemcitabine alone. A randomized phase III study demonstrated a clinically small but statistically significant survival benefit with the addition of the epidermal growth-factor receptor (EGFR) tyrosine kinase inhibitor erlotinib to standard gemcitabine therapy (median OS=6.37 months vs. 5.91 months, HR=0.82, 95% CI: 0.69-0.99).[11] More recently, the addition of nab-paclitaxel to gemcitabine demonstrated an improvement in survival compared to gemcitabine alone (median OS 8.5 months vs. 6.7 months, HR=0.72, 95% CI: 0.617-0.835, p=0.000015), which establishes this combination as an appropriate first-line standard treatment option in patients with advanced pancreatic cancer.[12]

The only non-gemcitabine based regimen to improve outcomes is the multi-agent combination of FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and infusional fluorouracil). A 342 patient randomized study demonstrated a clinically and statistically significant improvement in OS (overall survival) for FOLFIRINOX compared to single-agent gemcitabine (11.1 months vs. 6.8 months, HR 0.57, 95% CI: 0.45-0.73, p<0.0001)[13], which makes it an appropriate front-line choice for healthier patients who can tolerate this relatively toxic regimen.

Unfortunately, the prognosis for patients who have had failure of previous gemcitabine-based therapy is dismal with a median expected survival of less than 2.5 months. The randomized phase III CONKO-003 study tested second-line salvage therapy with oxaliplatin, folinic acid, and 5-fluorouricil compared to best-supportive care, but was stopped early after only 46 patients had been accrued.[14] Although this study suggested the possibility of clinical benefit with oxaliplatin-fluoropyrimidine based therapy, the very small sample size precludes any definitive conclusions. Currently, no standard second-line treatment options exist for advanced pancreatic cancer. Thus, we wish to examine regorafenib in this setting.

2.2. Experience with Regorafenib

2.2.1. Pre-clinical

In vivo, regorafenib exhibited anti-angiogenic and anti-proliferative effects in

human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian). Immunohistochemical ex-vivo studies with a phospho –specific 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. These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

2.2.2. Clinical

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.[15]

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 metastases, number of lines of prior therapy, and K-Ras status.[15]

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%).[15] The efficacy and safety from the CORRECT study supported FDA approval in September 2012.

The efficacy and safety of regorafenib was also 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.[16]

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 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%).[16] The efficacy and safety of the GRID study data supported FDA approval February 2013.

2.3. Study Rationale

Regorafenib is a potent oral inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, TIE-2, FGFR-1, KIT, and the RAF protein kinases. Preclinical studies have demonstrated broad-spectrum antitumor activity in xenograft models, with responses that correlated both with inhibition of the Ras/Raf/MEK/ERK pathway and reductions

in vascular permeability as measured by DC-MRI.[17] Phase I trials have shown that the drug is well tolerated at doses of 160 mg daily on a 3-weeks-on/1-week-off schedule, or 100 mg daily on a continuous schedule, with adverse effects typical of other multikinase inhibitors. Phase III studies include the CORRECT trial, which demonstrated an improvement in overall survival from 5.0 months to 6.4 months compared to placebo in patients with refractory metastatic colorectal cancer.[15] The GRID study tested regorafenib in patients with metastatic gastrointestinal stromal tumors who had failed previous therapy with imatinib and sunitinib, revealing an improvement in PFS from 0.9 months to 4.8 months compared to placebo.[16] The results of these two studies have led to FDA-approval in patients with advanced, previously-treated colorectal cancer and GIST.

Regorafenib has several potential mechanisms of benefit in the treatment of pancreatic cancer. Approximately 90% of all pancreatic cancers exhibit constitutively-active mutations in codon 12 of the K-Ras gene.[18] Raf-kinase inhibition with regorafenib may act as a down-stream target against mutated K-Ras. Pancreatic cancer is characterized by a dense desmoplastic tumor stroma which is involved in the processes of tumor formation, progression, invasion, and metastasis.[19] The tumor microenvironment is thought to be a dynamic compartment mediated by the interaction of pancreatic stellate cells and tumor cells through a variety of autocrine and paracrine growth factors, including TGFβ, PDGF, and FGF. As an inhibitor of PDGFR and FGFR, it is possible that regorafenib may be able to disrupt some of these pathogenic pathways. Although specific antiangiogenic inhibition of the VEGF pathway with axitinib[20] and bevacizumab[10] has been disappointing in patients with pancreatic cancer, regorafenib has a broader antiangiogenic profile, with kinase inhibition of potential escape pathways PDGFR, FGFR, and TIE-2. Regorafenib has demonstrated activity in pancreatic xenograft models, and one patient with pancreatic cancer had prolonged stable disease to treatment with regorafenib (>21 months) in the published phase I experience.[21]

This study tests regorafenib as a single agent in the treatment of locally advanced and metastatic pancreatic cancer patients who have previously failed prior chemotherapy. The prognosis for these patients is particularly grim, no other standard treatment options exist, and novel approaches are desperately needed. Treatment with single-agent regorafenib could be a platform to examine the biology of the disease through exploratory blood and tissue biomarker analyses. Furthermore, if there is evidence of clinical benefit in this population, this study has the potential to lead to subsequent development of the drug in combination with more standard chemotherapy treatments earlier in the disease course.

2.3.1. TAB 004 Studies

In a collaborative study with the Hepatobiliary and Pancreas Surgery Department at Carolinas Medical Center, a novel antibody (TAB 004) based enzyme immunoassay (EIA) has been shown to detect circulating MUC1 in a stage-dependent manner in patients with pancreatic cancer.[23] Furthermore, circulating levels of MUC1 correlated with its tissue expression. This study presents a unique opportunity to use the TAB 004 EIA and evaluate it as an indicator of regorafenib treatment efficacy. Protocol type TAB 004 EIA kits (manufactured at a GMP certified facility) will be provided by CanDiag, Inc.

3. SUBJECT SELECTION

3.1. Eligibility Criteria

a. Histologically or cytologically-proven adenocarcinoma of the exocrine pancreas with locally advanced or metastatic disease.
b. The site of the primary tumor must have confirmed endosonographically, surgically, or radiographically to have been within the pancreas.
c. Patients must have had progression on at least one prior line of chemotherapy for locally-advanced or metastatic pancreatic cancer.
d. Patients must have had tumor progression on or within 3 months of treatment with a gemcitabine regimen for advanced pancreatic cancer, or within 12 months of treatment with gemcitabine as part of adjuvant therapy.
e. All patients must have measurable disease on axial imaging (RECIST 1.1).
f. Age $\geq$ 18 years.
g. Life expectancy of at least 8 weeks at time of eligibility.
h. ECOG Performance Status 0 – 2. Enrollment of patients with PS=2 will be capped at 7 patients.
i. 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.
j. All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of registration . Exceptions to this include alopecia.
k. Adequate bone marrow, renal, and liver function as assessed by the following laboratory requirements:
    - Total bilirubin $\leq$ 1.5 x the upper limits of normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate amino-transferease (AST) $\leq$ 2.5 x ULN ($\leq$ 5 x ULN for subjects with malignant liver involvement or presence of a biliary stent)

- 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 prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care. (See Section 4.2.7)
- Platelet count >100000 /mm3, hemoglobin (Hb) >9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm3. Blood transfusion within 72 hours to meet the inclusion criteria will not be allowed.

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

m. Women of childbearing potential must have a negative urine 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.

n. Patients (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 Investigator.

o. Patient must be able to swallow and retain oral medication.

3.2. Exclusion Criteria

a. Previously received treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.

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

c. Active or clinically significant cardiac disease including:

i. Congestive heart failure – New York Heart Association (NYHA) > Class 2.

ii. Active coronary artery disease.

iii. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.

iv. Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before registration, or myocardial infarction within 6 months before registration.

d. Cerebrovascular arterial event (such as transient ischemic attack or cerebrovascular accident) within 6 months of registration.
e. Evidence or history of bleeding diathesis or coagulopathy.
f. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.
g. Patients with new venous thrombotic or embolic events, such as deep vein thrombosis or pulmonary embolism within 3 months of start of study medication. Older events are permitted if the patient is on stable treatment doses of anticoagulation.
h. Patients with any previously untreated or concurrent cancer that is distinct in primary site or histology except cervical cancer in-situ, treated ductal carcinoma in situ of the breast, curatively treated nonmelanoma skin carcinoma, noninvasive aerodigestive neoplasms, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed. All cancer treatments must be completed at least 3 years prior to registration.
i. Patients with pheochromocytoma.
j. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
k. Ongoing infection ≥ Grade 2 NCI-CTCAE v4.0.
l. Symptomatic metastatic brain or meningeal tumors.
m. Presence of a non-healing wound, non-healing ulcer, or bone fracture.
n. Renal failure requiring hemo-or peritoneal dialysis.
o. Dehydration Grade ≥1 NCI-CTCAE v4.0.
p. Patients with seizure disorder requiring medication.
q. Persistent proteinuria ≥ Grade 3 NCI-CTCAE v4.0 (>3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample). A urine protein test is not required to confirm eligibility unless patient has recent history of proteinuria.
r. Interstitial lung disease with on-going signs and symptoms at the time of informed consent.
s. Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).
t. History of organ allograft. Previous corneal transplant 3 months or more before registration is permitted.
u. Known or suspected allergy or hypersensitivity to the study drugs.
v. Any severe, uncontrolled malabsorption condition.

w. Women who are pregnant or breast-feeding.
x. Any condition which, in the Investigator's opinion, makes the subject unsuitable for trial participation.
y. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.
z. Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (regorafenib).
aa. Prior use of regorafenib.
bb. Concurrent use of 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).
cc. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
dd. Prior radiation therapy or hepatic arterial regional therapy is permitted if more than 4 weeks have passed since completion of the treatment and measurable disease outside of the treated area is present or if progression since treatment has occurred.
ee. Use of St. John's wort (Hypericum perforatum).

3.3. Registration

Subjects will be registered and assigned a Study ID number. The Study ID number will begin with "LCI" and include a two digit number identifying the enrolling investigational site, followed by a two digit number sequentially assigned to the subject. (e.g. "LCI0101" will be the Study ID number assigned to the first subject at the coordinating center.) A Protocol Registration Form will be completed for each subject.

3.4. Subject Withdrawal

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

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- Pregnancy. Pregnancy will be reported as an SAE. (Note: Subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the Investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up after three consecutive months of attempted contact.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to regorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.
- Any other (non-disease related) reason, at the Investigator’s discretion.

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

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

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 12.2.

3.5. Screen Failures

A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates the study before receiving first dose of study drug is regarded a “screen failure”.

All screen failures will be tracked in the CTMS (clinical trial management system).

3.6. Replacement

Subjects who withdraw consent after receiving first dose of study drug will not be replaced. Screen failures may be replaced.

4. INVESTIGATIONAL PLAN AND STUDY PROCEDURES

4.1. Milestone Date Definitions

Eligibility date: the date when the last procedure occurred that confirmed subject eligibility.
Enrollment date: the date of initiation of regorafenib treatment.
Treatment discontinuation date: the date the Investigator decides to discontinue the subject from regorafenib treatment.

4.2. Overall Investigational Plan

This is a single arm, single stage Phase II study designed to evaluate progression free survival in patients with locally-advanced or metastatic pancreatic cancer who have failed at least one prior line of therapy. This study will initially open at LCI. Additional investigational site(s) beyond the coordinating site will be added following activation. A total of 32 subjects will be enrolled to this study over a two year accrual period. Following informed consent and eligibility check, all patients will start oral regorafenib therapy and will continue therapy until progression or patient withdrawal. Treatment must start within 7 days of the eligibility date. Subjects will undergo radiological staging after the first two cycles of regorafenib therapy. Subjects with progressive disease as assessed by RECIST 1.1 will be removed from the study. Subjects who have at least stable disease will continue regorafenib therapy, at the Investigator's discretion, and will be radiologically restaged bimonthly. The overall duration of the study is expected to be no longer than 24 months.

Data from this study will be collected on electronic case report forms (eCRFs).

4.3. Study Procedures

4.3.1. Informed Consent

Written informed consent will be obtained from each subject prior to undergoing protocol-specific evaluations or procedures and prior to receiving treatment. In addition, all subjects will provide authorization for the release of their medical records for research purposes.

4.3.2. Demographics and Medical/Treatment History

Demographics and medical/treatment history will be collected during the screening visit. Medical and treatment history (oncological and relevant non-oncological) will be collected and recorded in the eCRF. Cancer history will be obtained and the following information (including but not limited to) will be reported in the eCRF:

- Date of first histological/cytological diagnosis
- Primary tumor site
- Tumor histology and characteristics
- Prior cancer therapy

All medical history findings that occurred prior to the patient signing informed consent will be documented.

4.3.3. Pregnancy Test

A urine pregnancy test will be performed at screening and as clinically indicated for women of childbearing potential. Women who are pregnant and/or breast-feeding are ineligible for study participation. Women will be counseled regarding risk of teratogenicity and need to use contraception through the course of the study. Men will also be counseled on the need to use contraception for all sexual encounters.

4.3.4. Office Visit

Physical exam and documented evaluation by body system, height (screening only), and weight will be documented during screening, repeated at Week 0 (if not within 7 days of study treatment) and at each treatment visit. Vital signs will be recorded and should include temperature, pulse rate, respiratory rate, blood pressure and oxygen saturation (screening and treatment). ECOG performance status will be assessed during the screening and treatment visits. Blood pressure will be monitored weekly for the first 6 weeks of treatment

and then every two weeks, or as clinically indicated. Office visits will occur according to the Study Calendar in Section 5.

4.3.5. Adverse Event Assessment

All adverse events and serious adverse events will be monitored and documented (regardless of grade or attribution) and reported to applicable agencies on an ongoing basis beginning at screening. Investigators should refer to the Safety Information section of the current IB for regorafenib, including the DCSI (development core safety information), for the expected side effects of regorafenib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

4.3.6. Concomitant Medications

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. Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

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

Co-administration of a 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 regorafenib with strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

Permitted concomitant therapies include:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.

- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the Investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Bisphosphonates.
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (within 7 days of the enrollment date and as clinically indicated) 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.
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporin, and digoxin). Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be especially affected by regorafenib.

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.
- Use of St. John's wort (Hypericum perforatum). Use of other herbal remedies is discouraged, and is permitted only with the specific assent of the Investigator. All herbal and vitamin supplement use must be carefully documented.

4.3.7. Laboratory Tests

The blood-based clinical laboratory tests will include a complete blood count with differential and platelets, a basic metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, and calcium.), and

liver function tests (Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Direct Bilirubin, Total Bilirubin, and Total Protein) which will be performed at screening and then again prior to the first dose of regorafenib if the enrollment date is not within 7 days of eligibility confirmation. After enrollment, a complete blood count with differential and platelets and a comprehensive metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, and total protein) will be performed every 2 weeks according to the Study Calendar. LDH and CA 19-9 will be collected at Week 0 and then every 4 weeks according to the Study Calendar. Amylase, lipase, coagulation panel (INR, PT, PTT), and pregnancy test (in appropriate subjects) will be collected at screening.

4.3.8. Radiology and Tumor Measurements

A CT (computed tomography) scan with oral and intravenous contrast of the chest, abdomen and pelvis will be performed within 28 days prior to the first dose of regorafenib (screening scan). After enrollment, scans will then be performed every eight weeks (+/- 2 weeks). A contrast-enhanced MRI of the abdomen and pelvis and an uncontrasted CT scan of the chest may be substituted if clinically necessary; however, subsequent studies must be performed using the same imaging modality throughout the study period. Scans will be submitted for Central Radiology review per Section 10.1.4.

Every effort will be made to obtain imaging studies and tumor assessments every 8 weeks (+/- 2 weeks) until documented progression for subjects who had a complete response, partial response, or stable disease, and/or discontinued study therapy due to toxicity or reasons other than progressive disease.

4.3.9. Archived Tissue and Blood-based Biomarkers

Tissue and serum will be collected and made available for analysis for exploratory biomarker correlates by LCI. For subjects who have archived tissue, the subject agrees to tissue collection being included in this study by signing the informed consent form. Tissue will be requested after confirmation of study eligibility. Subjects may be asked to undergo an optional core biopsy after providing additional written informed consent. Subjects will not be excluded from this study if they choose not to undergo the optional core biopsy. Core biopsy samples will be collected per standard

operating procedures and submitted fresh within 15 minutes of collection to the Carolinas Medical Center Pathology Laboratory where they will be snap frozen and stored at -80°C or moved to the Carolinas HealthCare System Biospecimen Repository (BSR) until biomarker testing. Core biopsy samples collected at investigational sites other than the Coordinating Site will be processed and shipped on the day of collection, fresh, on dry ice to Carolinas Medical Center Pathology Laboratory:

William Ahrens, M.D.
Carolinas Medical Center
Pathology Laboratory
1000 Blythe Boulevard
Charlotte, NC 28203
Phone: (704) 355-0519

Archived paraffin or fresh frozen tissue samples will be from investigational sites other than the Coordinating Site and stored in the CHS BSR for later study. Although not formally part of the initial protocol, biomarkers related to the angiogenic, RAS-RAF and Mek-Erk pathways, may be tested at a later date. These include, but are not limited to the presence of KRAS, NRAS, HRAS, BRAF, p53, KDR, KIT, FGFR1, and PDGFRA mutations. Additionally, archived tissue will be examined for Mucin1 (MUC1) at the University of North Carolina at Charlotte.

Plasma and serum from subjects will be collected using two ethylene diamine tetraacetic (EDTA) (10 mL) tubes and one serum collection tube. Samples will be processed within one hour of collection, if possible, but may be kept at 4°C for no longer than 4 hours before processing and then stored at -80°C until future testing. Samples will be stored at the CHS BSR.

Samples will be collected at scheduled intervals, according to the schedule in Section 5. Baseline samples will be collected after subject eligibility confirmation, but prior to administration of the first dose of regorafenib. One serum sample will be stored in the CHS BSR for later study while the second serum sample, if possible to obtain, will be provided to the University of North Carolina at Charlotte for MUC1 analysis. Exploratory biomarker arrays may be used to detect changes in baseline, on-treatment and post-treatment levels of sVEGFR-1, sVEGFR-2, sVEGF, HGF, SCF, PLGF, sTie-2, IL16, TGF-β1, PDGF-AA, PDGF-BB, angiopoietin-1, and FGF levels.

Specimen collection and processing data will be recorded in the CTMS. All specimens will be labeled appropriately with the protocol number, subject ID number, and date of collection.

Future tissue and blood-based biomarkers not described in this protocol may also be examined.

4.3.10. Subsequent Therapy and Survival Status

Once subjects complete their Off Treatment visit, they will be followed until all treatment-related toxicities have resolved, returned to baseline, stabilized, or are deemed irreversible. Subject's cancer therapies following completion of treatment on this study and survival status will be documented.

Subjects (or their family members or designees) may be contacted by telephone, in writing, or during clinic visits after treatment discontinuation for collection of long-term follow-up data every month until death or lost to follow-up. Long-term follow-up clinical information may also be obtained through chart reviews.

5. STUDY CALENDAR (see footnotes on next page)

Required Procedures	Screening	Study Week												Off Treatment	Follow-up
		0	1	2	3	4	5	6	8	10 [h]	12 [h]	14 [h]	16 [h]		
	Within 28 days of treatment initiation	Start C#1				Start C#2			Start C#3		Start C#4		Start C#5	Within 30 days of last drug dose	Every month until death or LTF
Informed Consent and HIPAA waiver	X														
Demographics	X														
Medical History	X														
Pregnancy Test (urine) [a]	X													X	
Vital Signs with Blood Pressure[k]	X[j]		X	X	X	X	X	X	X	X	X	X	X	X	
Office Visit	X[j]		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment	X[j]		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X[j]		X	X	X	X	X	X	X	X	X	X	X	X	
Dose Assessment [b]						X			X		X		X		
Basic Study Labs [c]	X[j]			X		X		X	X	X	X	X	X	X	
LDH, CA 19-9 [d]		X[j]				X			X		X		X	X	
Amylase, Lipase & Coagulation Panel	X														
CT Scan [e]	X								X				X		
Translational Blood Biomarkers[i]		X[j]				X								X	
Archived Tissue Collection [f]	X														
Core Biopsy [g]	X														
Subsequent Therapy														X	X
Survival Status														X	X

a: In women of child-bearing potential
b: Dose escalation can be considered up to 160 mg maximum dose, per section 6.1.1.2.
c: Screening and Week 0 (if applicable): Complete blood count, basic metabolic panel, and liver function tests; then subsequent visits: complete blood count and comprehensive metabolic panel per sections 4.3.7.
d: Week 0, then every 4 weeks per section 4.3.7.
e: Screening scan should be within 28 days prior to treatment initiation, then every 8 weeks. Radiography with tumor measurements and central radiology review will be done per section 4.3.8.
f: If available; attempt to collect archived tissue can be made at any time after subject eligibility confirmation.
g: Optional; may be requested at any time if subject consents.
h: After week 16, the schedules for weeks 10-16 repeat themselves for subjects who are still on study (i.e. week 18 as per week 10 schedule, week 20 as per week 12, etc.)
i: Screening biomarker specimens must be collected after eligibility confirmation, but prior to the first dose of regorafenib.
j: Must be performed within 7 days before treatment initiation.
k: Vital signs to include: temperature, pulse rate, respiratory rate, oxygen saturation rate and blood pressure.

6. TREATMENT PLAN

6.1. Drug Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 7.

No investigational or commercial agents or therapies other than regorafenib may be administered with the intent to treat the subject's malignancy. 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. Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

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

Co-administration of a 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 Regorafenib with strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

6.1.1. Regorafenib Dosage and Administration

6.1.1.1. Initial Regorafenib Dosage and Administration (Cycle 1)

Regorafenib will be started within 7 days of the eligibility date . Regorafenib is administered orally as monotherapy at 120 mg daily for 21 days on /7 days off. Subjects will take three 40-mg regorafenib oral tablets (total dose 120 mg) each morning with a low-fat breakfast and approximately 8 fluid ounces (240mL) of

water for 21 days. Under the direction of the Investigator, subjects may take regorafenib at a time other than the morning, as long as it is taken with a low-fat meal as above, and it is taken at the same time each day.
Subjects will not take regorafenib the following 7 days. One cycle is 28 days. Cycle start may be delayed up to 5 days.

6.1.1.2. Regorafenib Dose Escalation (Cycle 2 and Subsequent Cycles)

After the first cycle of therapy on study and at the start of cycle 2, subjects who have no worse than grade 1 toxicity (CTCAE v4) will have a dose escalation up to 160 mg daily, taken for 21 days followed by 7 days off. Subjects with clinically significant grade 2 or higher toxicity considered possibly, probably, or definitely related to regorafenib, OR, in the Investigator's opinion, may adversely impact the safety of the subject will not have a dose escalation (excluding alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities). Subjects who undergo dose escalation up to 160 mg will take four 40 mg regorafenib oral tablets each morning as per section 6.1.1.1. Dose reduction for toxicity will follow standard protocol guidelines (see section 7.2).

Dose escalation by 1 level (i.e. from dose level -1 to dose level 0, or from dose level -2 to dose level -1) can be considered as above at the treating Investigator's discretion at the beginning of each subsequent 28 day cycle for any subject who has no worse than clinically-significant grade 1 toxicity. Doses beyond 160 mg are not permitted. Dose reduction for toxicity will follow standard protocol guidelines, whether or not dose escalation had previously occurred.

6.1.2. Regorafenib Drug Supply

Regorafenib tablets for oral administration are formulated as light pink oval shaped tablets debossed with "BAYER" on one side and "40" on the other. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate, and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film –

coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

Regorafenib will be supplied by Bayer HealthCare through their Investigator Sponsored Study (ISS) Portal located at the following website:

http://www.iss.bayer.com/

The Sponsor-Investigator will provide Portal access to the investigational pharmacist(s) for the purpose of managing drug supply and shipment.

The LCI investigational pharmacy will receive regorafenib tablets packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 28 tablets and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F). Temperature excursions of 15-30°C (59-86°F) are acceptable.

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

Bottles dispensed to subjects will be labeled as "Investigational" and subjects should comply with the following directions:

- Store tablets in the original bottle, once opened use within 28 days
- Take tablet at the same time daily, with breakfast containing less than 30% fat (Appendix A)
- Swallow tablet whole
- If dose is missed, do not take 2 doses in one day

6.2. Treatment Compliance

An adequate record of receipt, distribution, and return of all study drugs must be documented on a Drug Accountability Form.

Study drug will be dispensed to subjects, and the pills bottles returned to LCI Clinical Trials staff according to LCI standard operating procedures. IDS Pharmacy staff will report the number of pills in the bottles returned to LCI Clinical Trials. The number

of pills the subjects take per cycle will be derived from these pill counts rather than reported by the subjects on a pill diary.

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

6.3. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.

6.4. Drug Accountability

All study drugs will be stored at the investigational pharmacy in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

An adequate record of receipt, distribution, and destruction of all study drugs must be documented on a Drug Accountability Form. The Investigator, or a responsible party designated by the Investigator, will maintain a careful record of the inventory using the Drug Accountability Form.

6.5. Destruction

At the end of the study, unused supplies of regorafenib will be destroyed according to LCI IDS pharmacy policies. Destruction will be documented in the Drug Accountability Form and sent to Bayer at the following address:

Email: joy.wang1@bayer.com
Mail: Joy Wang
Bayer HealthCare Pharmaceuticals
100 Bayer Boulevard
Whippany, NJ 07981
Phone: (862) 404-5333

7. TREATMENT-RELATED ADVERSE EVENTS

7.1. Adverse Events Related to Regorafenib

Based on data studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug class, as soon as there is reasonable suspicion of any of the AEs in the following sections, the Investigator should immediately notify the appropriate agencies as outlined in Section 9.

7.2. Prevention and Management of Adverse Events

7.2.1. Dose Modifications for Adverse Events

The starting dose of regorafenib is 120 mg once daily (starting dose level -1) but with a planned dose escalation (to dose level 0) with cycle 2 if less than grade 2 clinically significant toxicity (per the Investigator) is experienced (see section 6.1.1.2). Study medication will be administered on a 21 days on/7 days off schedule (3 weeks out of every 4). Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

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

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade. In the case of two or more toxicities of the same grade, the Investigator may dose reduce according to that deemed most causally related to study treatments. If treatment is held for more than 4 weeks due to toxicity or if dose reductions beyond dose level -2 are necessary, then treatment will be permanently discontinued.

7.2.2. Dose Adjustments for Adverse Events (other than hand-foot-skin reaction, hypertension and liver function test abnormalities)

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

Table 7.1: Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/AST/Total Bilirubin

NCI-CTCAE v4.0[a]	Dose Interruption	Dose Modification[b]	Dose for Subsequent Cycles
Grade 0-1	Treat on time	No change	Dose escalation or No change (see section 6.1.1.2)
Grade 2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating Investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating Investigator's discretion.	

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

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.

7.2.3. Grading and Dose Adjustments for Hand-Foot-Skin Reaction (HSFR)

Table 7.2: Grading for Hand-Foot-Skin-Reaction

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

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

Table 7.3 Recommended dose modification for hand-foot-skin reaction[a]		
Grade of event (NCI-CTCAE v4.0)	**Occurrence**	**Suggested Dose Modification**
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1 [b, c]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, treat at reduced dose level [b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. [c] When resuming treatment, decrease dose by one dose level. [b, d]
	4th occurrence	Discontinue therapy
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. [c] When resuming treatment, decrease dose by one dose level. [b, d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. [c] When resuming treatment, decrease dose by one additional dose level [b, d]
	3rd occurrence	Discontinue treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the Investigator.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the Investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg.

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

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

Control of calluses

Before initiating treatment with regorafenib:

- Check condition of hands and feet.
- Suggest a manicure/pedicure, when indicated.
- Recommend pumice stone use for callus or 'rough spot' removal.

During regorafenib treatment:

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

Use of creams

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

Tender areas should be protected as follows:

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

7.2.4. Grading and Dose Adjustments for 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 7.4 outlines suggested dose reductions.

Table 7.4: Management of Treatment-Emergent Hypertension		
Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: • If BP previously within normal limits, start anti-hypertensive monotherapy • If subject already on anti-hypertensive medication, titrate up the dose.	• Continue regorafenib • If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Subjects 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. Subjects requiring >2 dose reductions should go off protocol therapy.

7.2.5. Dose Adjustments for Liver Function Test Abnormalities

For subjects 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 7.5 should be followed.

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

Table 7.5: Dose modifications/interruption for ALT and/or AST and/or Total Bilirubin increases related to study drug

Observed elevations	1st Occurrence	Restart	Re-occurrence
baseline G0 → G1 or baseline G1 → G2	Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.		Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.
baseline G0 → G2	Delay until ≤ G1 and check AST, ALT, bilirubin 2x/week.	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[a]	Discontinue

Baseline any grade → G3	Delay until ≤ G1 if baseline was G0 or G1 OR until G2 if baseline was G2. Check AST, ALT, bilirubin 2x/week. If ALT or AST > 8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation at the first occurrence.	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[a]	Discontinue
Before regorafenib initiation and during the first 2 cycles of treatment, ALT, AST and bilirubin must be monitored at least every 2 weeks.			
a: If toxicity returns to ≤ Grade 1 after dose reduction, dose re-escalation is permitted at the discretion of the treating Investigator per Section 6.1.1.2 for first occurrence only.			

7.2.6. Prevention and Management of Diarrhea

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

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.

7.3. Adverse Event Grading

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All Levine Cancer Institute staff will have access to a copy of the CTCAE version 4.0.

Grade refers to the severity (intensity) of the AE:

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

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

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

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

CTCAEv4 Grade 5: death due to an AE

7.4. Adverse Event Attribution

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. AEs are considered to be "not related" or "related" to the study drug according to the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

Final attribution should be stated as follows (choose only one):
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.

Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.5. Adverse Event Action and Outcome

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

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

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

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

8. DATA AND SAFETY MONITORING PLAN

8.1. Safety Monitoring

This trial will be monitored according to the processes in effect for all Levine Cancer Institute Investigator- Initiated Trials and will abide by standard operating procedures set forth by both the Carolinas Medical Center Office of Clinical and Translational Research and the Levine Cancer Institute Clinical Trials Department. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. On at least a monthly basis, the Sponsor-Investigator, Study Statistician and Protocol Coordinator will meet to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's)], study drug administration, and validity/integrity of the data. SAEs will be reported to the IRB per their requirements. Major protocol deviations that result in a threat to subject safety or the integrity of the study will be reported to the IRB per their requirements. Following each meeting, a status will be

generated and kept on file in the LCI Clinical Trials Office with study records. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

8.2. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, standard operating procedures (SOPs) of Levine Cancer Institute and Carolinas Medical Center Office of Clinical and Translational Research, the FDA, and other applicable regulations and guidelines (e.g. GCP).

Data will be collected on electronic CRFs in the CTMS.

Subjects will be monitored by Levine Cancer Institute Research Monitors routinely for data quality. This monitoring will be done by comparing source documentation to the CRFs. Any variation between the two data sets will be discussed with the Protocol Coordinator or Sponsor-Investigator.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate study team member and/or Sponsor- Investigator. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

8.3. Communication Between Investigational Sites

Investigational sites will be required to report AEs for all grades and attributions, SAEs, study drug administration, or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. All investigational sites will report AEs using the eCRFs and SAEs using the SAE reporting function in the CTMS to the Sponsor-Investigator. AEs will be reported promptly of the Investigator learning of the event. SAEs will be reported within 24 hours, or next business day, of the Investigator learning of the event. Study drug administration or any other problem should be communicated to the Protocol Coordinator and/or Sponsor-Investigator by email or phone as soon as possible but within 2 business days of the Investigator learning of the event.

9. SAFETY DATA COLLECTION, RECORDING AND REPORTING

All subjects who receive at least one dose of study treatment will be valid for the safety analysis. All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs and SAEs (whether related to regorafenib or not), laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and, in some instances, changes in radiologic images. These assessments should be performed according to the Study Calendar. Adverse events will be evaluated continuously throughout the study. Safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be determined by the Investigator and recorded in the eCRF.

9.1. Unanticipated Problem Definition

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g. Investigator's brochure, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

9.2. Adverse Event (AE) Definition

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre or post-treatment complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented.

An AE does not include:

- relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., "jaundice" due to new or increasing liver metastases, or "tumor pain" or "bone pain" due to progressive disease);
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; and
- pregnancy (Pregnancy during treatment should be reported as an SAE and on the eCRF)

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events if they meet the definition of an adverse event . In addition, laboratory abnormalities marked as **clinically significant** by the Investigator should also be recorded as adverse events on the eCRF. The Investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a **clinically significant** laboratory abnormality occurs.

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered unrelated or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally

related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and on the case report form for this protocol. AEs will be captured from the time of enrollment through 30 days after the date of the last study drug administration.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

9.3 Adverse Drug Reaction (ADR) Definition

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means in view of the investigator and/or company that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility and that the adverse event is associated with the use of the drug.

9.4. "Serious Adverse Event (SAE)" Definition

A Serious Adverse Event includes any event that:

- Results in death.

- Is life-threatening.
  NOTE: The term 'life-threatening' refers to an event during which the subject was at immediate risk of death from the adverse event. It does not refer to an event which hypothetically might have caused death if it had been more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: In general, hospitalization means that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment planned prior to study enrollment is neither an SAE nor an AE.

- Results in persistent or significant disability or incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect.

- Is an important medical event.
  An event may be considered an important medical event when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  SAEs will be captured from the time of enrollment through 30 days after the date of the last study drug administration. SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times, cause the follow-up period for SAEs to be greater than 30 days. This 30-day time period applies even if the subject is taken off study and enrolled onto another protocol during this time period. Similarly, the Sponsor-Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another service at LCI.

  Laboratory abnormalities:

  Laboratory abnormalities that meet the definition of a serious adverse event will be recorded as such on the CRF and reported appropriately. The Investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a clinically significant laboratory abnormality occurs.

  Planned hospitalizations:

  Elective surgeries that have been planned prior to subject enrollment in the study or for conditions existing prior to study enrollment do not need to be captured as

SAEs, unless complications occur or the conditions are worse that the subject's baseline. They should however, be clearly documented on the case report form.

Development of new cancers:

Secondary malignancies are defined as *new* cancers, not transformations or progression of original disease.

Secondary malignancies during 30 day time period:

Any secondary malignancy diagnosed within 30 days of the last dose, regardless of attribution, must be reported as an SAE.

Secondary malignancies after the 30 day time period:

Any secondary malignancy diagnosed greater than 30 days after last day of study drug and thought to be possibly, probably or definitely related to drug must be reported as an SAE

Deaths:

Deaths during 30 day time period:

Any death, expected or unexpected, occurring within 30 days of the last dose of study drug, regardless of attribution, must be reported as an SAE.

Deaths after the 30 day time period:

Deaths occurring greater than 30 days after last day of study drug and thought to be possibly, probably or definitely related to drug must be reported within 24 hours of knowledge of the event.

All SAEs (including event name, grade, start/stop date and attribution) will be documented in the medical record and on the case report form for this protocol.

The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the trial.

9.5. Serious Adverse Drug Reaction (SADR) Definition

A Serious Adverse Drug Reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drug.

The Sponsor-Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the serious adverse event.

9.6. "Unexpected" Definition

An SAE or SADR is to be considered unexpected if the event is not listed in the current Investigator Brochure or is not listed in the severity or specificity observed. Investigators should refer to the Safety Information section of the current IB for regorafenib, including the DCSI (development core safety information), for the expected side effects of, regorafenib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

9.7. SAE Reporting Requirements

All Serious Adverse Events must be reported to the Sponsor-Investigator within 24 hours, or next business day, of awareness via the CTMS with a notification to the Protocol Coordinator and Sponsor-Investigator. Also, all SAEs must be reported to Bayer within 24 hours, or next business day, of the Principal Investigator's awareness and must include the following minimum information:

1. **The name and contact information of the reporter**
2. **The name of the study drug(s)**
3. **A description of the reported SAE**
4. **A patient identified by one or more of the following:**
    a. **Patient initials**
    b. **Patient number**
    c. **Knowledge that a patient who experienced the adverse event exists**
    d. **Age**
    e. **Sex**
5. **An investigator assessment of study drug causality.**

Additional data which would aid the review and causality assessment of the case include but are not limited to:

- The date of onset
- The severity
- The time from administration of study drug(s) to start of the event
- The duration and outcome of the event
- Any possible etiology for the event
- The final diagnosis or syndrome, if known
- Action(s) taken, if any

Expedited Reporting of Other Safety Information:

The Investigator/ Sponsor shall report to Bayer within 24 hours, or next business day, of the investigator's awareness of other events such as:

- An adverse event related to study specific procedures
- Any new and important event related to treatment with the study drug(s).
- Any pregnancy during which a female patient was exposed to the study drug(s)
- Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).
- Any other relevant safety information including but not limited to reports on drug interaction, overdose, or medication error occurring at any time during the treatment phase.

All SAEs will be reported to Bayer HealthCare via MedWatch forms (FDA Form 3500) within 24 hours, or next business day, of the Sponsor-Investigator learning of the event.

All reports shall be sent electronically to:
Electronic Mailbox: DrugSafety.GPV.US@bayer.com
Address: 100 Bayer Boulevard
Whippany, NJ 07981
Phone: (862) 404-5333

All events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE that are related to the study drug (serious adverse drug reactions) and unexpected must be reported to the IRB of record within 10 working days of the Sponsor-Investigator learning of the event.

9.8. Deviation Reporting to the IRB

Protocol deviations involving the informed consent process, subject safety, or adversely impacting data integrity will be reported promptly to the IRB but no later than two weeks from the time of identification of the protocol deviation by the Sponsor-Investigator.

9.9. Deviation Reporting to the Funding Company

Protocol deviations involving subject safety will be reported to Bayer HealthCare promptly but no later than two weeks from the time of identification of the protocol deviation by the Sponsor-Investigator.

10. MEASUREMENT OF EFFECT

10.1. Anti-tumor Effect

Response and progression will be evaluated in this study using the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1.[22]

10.1.1. Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with regorafenib.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one dose of study therapy, and have had their disease re-evaluated (either clinically or radiologically) will be considered evaluable for objective response. These subjects will have their response classified according to the definitions stated below.

10.1.2. Disease Parameters

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. *Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan or MRI. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis $\geq$ 10 mm but <15 mm) should be considered non-target

lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow).

10.1.3. 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 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. The Sponsor-Investigator or designee will be responsible for performing tumor measurements. The tumor measurements will be documented on the eCRF.

10.1.4. Central Radiology Review

Scans will be evaluated by Central Radiology at screening and every 8 weeks for each subject. The Central Radiologist will be notified by the applicable study team member when central review of scans for a subject is due. For subjects receiving their scans at an office other than Charlotte Radiology, the Coordinator will request the images be burned to a disc and de-identified, and mail to the following address:

Attn: Richard Redvanly, M.D.
Charlotte Radiology
1000 Blythe Boulevard, Suite 4
Charlotte, NC 28203

Phone: (704) 365-0343

Tumor logs and the Central Radiology Review request form accompany Central Radiology Review requests.

Central radiology review of scans performed for screening is NOT required to be completed prior to subject enrollment.

Scan data will be abstracted and entered into the eCRF.

10.2. Response Criteria

Response will be evaluated using RECIST 1.1 Criteria.

Complete Response:

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Partial Response:

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease:

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Summary of RECIST:

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category also requires**
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥ 4 weeks 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 nontarget lesions may be accepted as disease progression.				

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. This means that subjects with CR may not have a total sum of the diameters of 'zero'.

Subjects 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 objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. It is included as part of the criteria for determination of Progression Free Survival. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

A total of 32 participants will be enrolled to this study. The primary objective is to evaluate the 16-week progression free survival rate. The CONKO-003 study reported a median OS with best supportive care in this subject population to be 2.3 months.[14] Therefore, the null hypothesis assumes a median PFS of 6 weeks. This corresponds to a 16-week PFS rate of approximately 0.15. A single-stage design will be used to test the hypothesis that the 16-week PFS rate is less than or equal to 0.15. If at least 8 of the 32 subjects are alive and progression free at 16 weeks, the null hypothesis will be rejected (based on an exact binomial test) and regorafenib therapy may be considered for further evaluation in this subject population. Assuming a one-sided alpha = 0.10 significance level, this sample size will provide at least 90% power to reject the null hypothesis, assuming the true 16-week progression free survival rate is 0.35. An increase in the 16-week PFS rate of 0.20 in the context of this Phase II study is considered clinically relevant.

11.2. Endpoint Definitions

11.2.1. 16-Week Progression Free Survival

Progression free survival will be calculated from a recorded binary variable determined for each subject indicating whether or not the patient experienced disease progression or death from any cause during the 16 week period following the start of treatment. Disease progression can be objectively determined as per Section 10.2 or progression can be subjective as determined by the Investigator. Evidence for subjective progressions must be documented in the medical records. The binary variable described above will be calculated for the primary objective.

11.2.2. Progression Free Survival

PFS is defined as the duration of time from enrollment to the study to time of

progression or death. Disease progression can be objectively determined as per Section 10.2 or progression can be subjective as determined by the investigator. Evidence for subjective progressions must be documented in the medical records. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who experience a PFS event immediately following an interval equal to two or more scheduled CT assessments will be censored at the date of the last assessment prior to the first missed assessment.

11.2.3. Overall Survival

Overall survival is defined as the duration from enrollment date to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

11.2.4. Overall Response

Overall response will be determined for each patient as a binary variable indicating whether or not the patient achieved a best overall response of CR or PR as determined by RECIST 1.1 criteria. For the purposes of response determination, a confirmatory scan for CR and PR is not required.

11.2.5. Disease Control

Disease control will be determined for each patient as a binary variable indicating whether or not the patient achieved a best overall best response of CR, PR, or stable disease as determined by RECIST 1.1 criteria.

11.2.6. Safety Endpoints

Safety endpoints will include treatment administration (cycles delivered, cumulative dose administration, and relative dose intensity), AEs, SAEs, deaths while on study therapy, and laboratory determinations.

11.3. Analysis Populations

Efficacy and safety analyses will be conducted on the population of subjects who begin regorafenib treatment. Analysis of overall response rate will be conducted on those patients in the efficacy population with measurable disease present at baseline. The date of initiation of regorafenib treatment will be the enrollment date.

11.4. Analysis Methods

11.4.1. Timing of Analysis

While not planned as a formal multistage analysis, we will be evaluating safety and efficacy in data reviews throughout the course of the study. The analysis for the primary objective will occur after all 32 patients have either progressive disease, died, or have at least 16 weeks of follow up time after the treatment start date. Preliminary analysis of the secondary endpoints (including PFS and OS) will also be done at the time of the primary analysis. However, an updated PFS analysis will also occur once the PFS censoring rate for all enrolled patients reaches 20% or after all patients have at least 1 year of follow up time (whichever occurs first). Additionally, for the purposes of OS, patients will continue to be followed until the OS censoring for all enrolled patients reaches 20% or after all patients have at least 3 years of follow up time (whichever occurs first), and the final analysis will be conducted after this milestone is reached.

11.4.2. Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

11.4.3. Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and subject medical history will be assessed.

11.4.4. Efficacy Analyses

11.4.4.1. Primary Analysis

The frequency and proportion of subjects alive and progression free

after 16 weeks will be calculated, along with a 95% Clopper Pearson confidence interval. A one-sided exact binomial test of proportions, with $\alpha = 0.10$, will be carried out, testing the null hypothesis that the 16-week progression free survival probability is less than 15%. Based on the sample size calculations described in Section 11.1, if at least 8 subjects are alive and progression free at 16 weeks, the null hypothesis can be rejected.

11.4.4.2. Secondary Analyses

Overall and progression free survival will be analyzed using Kaplan Meier techniques. Medians, 25th, and 75th percentiles will be estimated. Selected landmarks for OS (1, 3, 6, and 9 month survival rates) and PFS (1, 3, and 6 month PFS rates) will from the Kaplan Meier curve. Tumor response and disease control rates will be estimated with proportions and associated 95% Clopper Pearson confidence intervals will be calculated.

11.4.5. Safety Analyses

Incident rates for adverse events, SAEs, and deaths while on study therapy will be summarized. Laboratory data will be analyzed quantitatively using methods for longitudinal data.

11.4.6. Exploratory Analyses

Cox proportional hazards models and logistic regression will be used to assess the correlation between baseline characteristics and biomarker expression levels with clinical outcomes.

11.5. Interim Analyses

No interim analyses are planned for this study.

12. STUDY COMPLETION AND TERMINATION

12.1. Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits.
- All subjects have discontinued from the study.
- The IRB, LCI DSMC, Sponsor-Investigator or Bayer HealthCare discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

12.2. Termination

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example:

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

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 3.4.

13. RETENTION OF RECORDS

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

14. ETHICAL AND LEGAL ISSUES

14.1. Ethical and Legal Conduct of the Study

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

Documented approval from appropriate agencies (e.g. DSMC, IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of IRB approval must be obtained and forwarded to Bayer HealthCare.

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

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Bayer Healthcare. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

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

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

14.2. Confidentiality

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

15. PUBLICATION POLICY

The Sponsor-Investigator must send a draft manuscript of the publication or abstract to Bayer HealthCare prior to submission of the final version for publication or congress presentation. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer HealthCare and the Sponsor-Investigator.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

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APPENDICES

APPENDIX A: EXAMPLES OF A LOW-FAT MEAL

Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (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).

APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.