CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

A PHASE II STUDY OF SECOND-LINE THERAPY WITH REGORAFENIB PLUS GEMCITABINE IN METASTATIC PANCREATIC CANCER

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NCI Comprehensive Cancer Center

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CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: **CASE5214**

ClinicalTrials.gov NCT#: NCT02383433

STUDY TITLE: **SECOND-LINE THERAPY WITH REGORAFENIB PLUS GEMCITABINE IN METASTATIC PANCREATIC CANCER – A PHASE II STUDY**

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SUPPLIED AGENT Regorafenib

OTHER AGENT Gemcitabine

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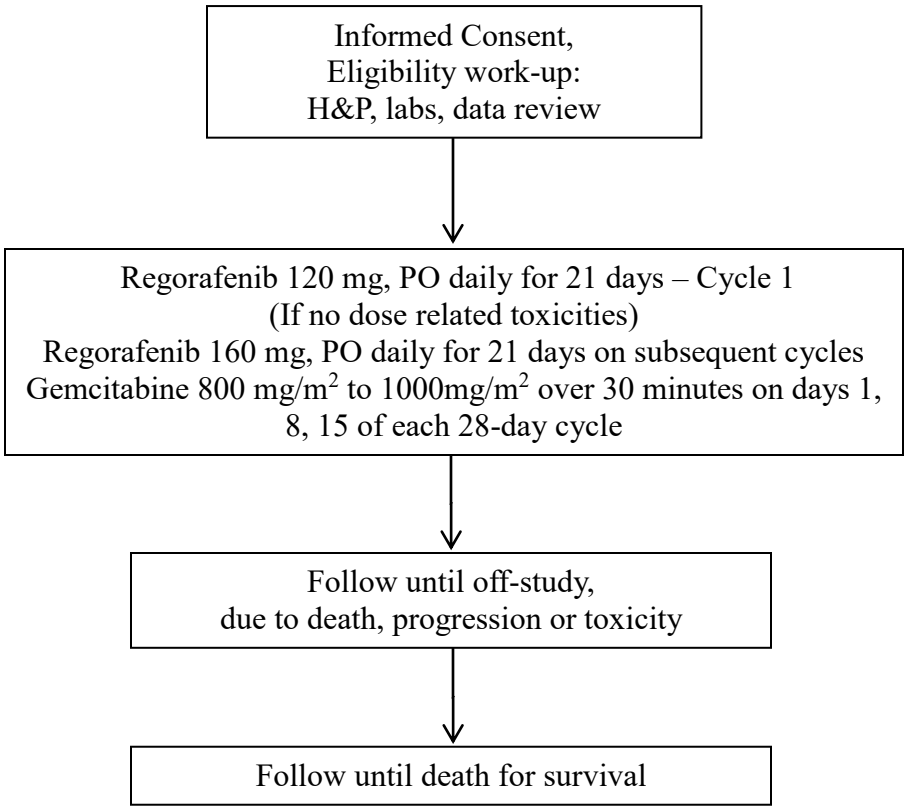
SCHEMA


Informed Consent,
Eligibility work-up:
H&P, labs, data review
Regorafenib 120 mg, PO daily for 21 days – Cycle 1
(If no dose related toxicities)
Regorafenib 160 mg, PO daily for 21 days on subsequent cycles
Gemcitabine 800 mg/m2 to 1000mg/m2 over 30 minutes on days 1, 8, 15 of each 28-day cycle
Follow until off-study,
due to death, progression or toxicity
Follow until death for survival

List of abbreviations

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

IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NM	Nano molar
NYHA	New York Heart Association
PD	Progressive Disease
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFS	Progression free survival
PO	*per oris*, oral
PR	Partial Response
PS	Performance Status
PTT	Partial thromboplastin time
QD	*quaque die*, once daily
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

1.0 INTRODUCTION

1.1 Background on Metastatic Pancreatic Carcinoma

Pancreatic adenocarcinoma is an aggressive gastrointestinal cancer with an estimated annual incidence of over 45,000 cases in the United States, and is also expected to account for over 38,000 deaths in the United States in 2013 making it the fourth leading cause of cancer death for both men and women. Five-year survival rate is around 6 %. The incidence of diagnosis peaks in the seventh and eighth decade of life [1, 2]. Pancreatic adenocarcinoma is characterized by extensive local growth and early metastasis, making surgical control of disease uncommon. As a result, chemotherapeutic agents are often employed in an effort to control growth and spread of the cancer, as well as to prolong life and maximize function for patients with pancreatic cancer.

1.2 Rationale of the Study

Currently, the most widely used first line regimens for metastatic pancreatic cancer in the US involves gemcitabine, which is a nucleoside analog, either alone or in combination with erlotinib, an inhibitor of epidermal growth factor receptor-associated tyrosine kinase. Median survival with gemcitabine based regimen ranges approximately between 5.2-7.2 months. Recently, two new combination therapies consisting of 5-FU/LV plus oxaliplatin and irinotecan (FOLFIRINOX) and Nab-paclitaxel plus gemcitabine have been added to the first line treatment regimen for metastatic pancreatic cancer. FOLFIRINOX was approved by the FDA in 2010 after a large randomized phase 3 trial showed significant improvement in overall survival compared to gemcitabine monotherapy (11.1 vs 6.8 months, $p < 0.001$) [3]. There are, however, many concerns about the toxicity of the FOLFIRINOX regimen. The grade 3/4 toxicity rates were 12.3% for diarrhea, 15.6% for nausea, 17.2% for vomiting, 24% for fatigue, 47.9% for neutropenia, and 5.7% for febrile neutropenia. Patients who were enrolled in the study had an ECOG performance status of 0-1. Therefore, this regimen has not been completely adapted by the medical oncology community. Gemcitabine with nab-paclitaxel is another regimen that has been shown to improve outcomes in the first-line setting, compared with gemcitabine monotherapy, with a median overall survival of 8.5 months vs. 6.7 months (HR=0.72, $p<0.001$) [4]. Unfortunately, results from clinical studies on the use of biologics in pancreatic cancer have been disappointing. One of the studies was a phase III study, CALGB 80303, comparing Bevacizumab plus gemcitabine with gemcitabine plus placebo had a median OS of 5.8 months for Bevacizumab/gemcitabine and 5.9 months for gemcitabine/placebo [5]. Progression free survival (PFS) was 3.8 months versus 2.9 months ($p=0.07$) [5].

There is no optimal treatment for patients whose disease progress after their initial treatment. This is, in part, due to lack of adequate clinical trials in this patient population. Pancreatic cancer is now becoming the second most common cause of all cancer deaths with a median 5 year survival of only 6%. Historically, combination systemic therapy has been shown to be more beneficial than single agent therapy albeit with increased toxicities. Regorafenib in preclinical studies showed some activity in reducing blood vessel formation in pancreatic cancer cell lines. Therefore, we propose this current study to assess the safety and clinical benefit of the combination of regorafenib and gemcitabine as well as to develop other therapeutic options.

1.3 **Background on Regorafenib**

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI) [6]. Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

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) [6]. Immunohistochemical ex-vivo studies with a phospho – specific monoclonocal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody [6]. These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

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 [7].

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.773 (95% confidence interval [CI], 0.635 to 0.941; 1-sided $p = .0051$). Patients treated with regorafenib had a median overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression-free survival was 1.9 months (95% CI, 1.88 to 2.17) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.493 (95% CI, 0.418 to 0.581; 1-sided $p< .000001$). There was a substantial difference in disease control rate in the regorafenib and placebo groups (44% vs. 15%; $p<.000001$). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of mets, number of lines of prior therapy, and *KRAS* status [7].

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

The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on/1 week off cycle) or placebo, plus best supportive care [8].

The results showed that treatment with regorafenib led to a statistically significant 3.9-month improvement in progression-free survival (PFS), compared with placebo (4.8 months vs. 0.9 months; hazard ratio [HR] = 0.27; $p <.0001$). Overall survival was statistically similar between groups as expected due to a trial design that allowed crossover to regorafenib for disease progression (85% for placebo and 31% regorafenib randomized patients). The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining

partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control group. The most common grade ≥3 adverse events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%) [8]. The efficacy and safety of the GRID study data supported FDA approval February 2013.

1.4 Background on Gemcitabine

Gemcitabine (2',2'-difluorodeoxycytidine: dFdC) is a nucleoside analogue that has a broad spectrum of antitumor activity in solid tumors and leukemia [9]. A prodrug with high membrane permeability and a high affinity for deoxycytidine kinase, gemcitabine is converted intracellularly to its active metabolite, difluorodeoxycytidine triphosphate (dFdCTP). dFdCTP achieves higher intracellular concentrations and is retained significantly longer than the triphosphate of other pyrimidine analogues though feedback inhibition of cytidine deaminase, the enzyme responsible for its degradation. It competes with dCTP for incorporation into DNA, where it acts as chain terminator [9]. The drug also depletes intracellular deoxynucleoside triphosphate pools, presumably by inhibiting ribonucleotide reductase. Responses to gemcitabine as a single agent have been shown in several common solid tumors in phase II studies. Dose ranged from 800 to 1,250 mg/m^2 weekly for 3 weeks every 28 days, and toxicity was considered tolerable [10]. A phase III trial in patients with advanced pancreatic cancer demonstrated that gemcitabine 1,000 mg/m^2 weekly was more effective than 5-FU in producing clinical benefit, as measured by a specific scale [11]. Other outcomes including response rate, time to progression and overall survival also favored gemcitabine in this study.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the efficacy (progression-free survival) of regorafenib and gemcitabine in previously treated patients with metastatic pancreatic cancer.

2.2 Secondary Objective(s)

- To assess the safety of regorafenib in combination with gemcitabine
- To assess response rate (RR),
- To assess overall survival (OS)

3.0 STUDY DESIGN

Previously treated histologically confirmed metastatic pancreatic cancer will be eligible for this study. Study is a single arm non-randomized open label phase II study.

Regorafenib will be given daily at 120 mg orally for 21 days out of 28 days for the first cycle and for those patients who do not experience any regorafenib dose related toxicities; the dose may be escalated to 160 mg daily for the subsequent cycles of treatments. Patients will take Regorafenib along with food (low-fat meal)

Gemcitabine will be given intravenously at a starting dose of 800 mg/m^2 and increased to a maximum dose of 1000 mg/m^2 over 30 minutes per each dose on days 1, 8, 15 of each 28-day cycle as tolerated.

Radiographic imaging will be performed at baseline and after every 2 cycles.
Response to treatment will be evaluated based on RECIST 1.1 criteria
Treatment will continue until disease progression, unacceptable toxicity or decision of patient/physician.

4.0 PATIENT SELECTION

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. The checklist must be completed for each patient and must be signed and dated by the treating physician.

Patient's Name _____

Medical Record # _____

Research Nurse /
Study Coordinator Signature: _____ **Date** _____

Treating Physician [Print] _____

Treating Physician Signature: _____ **Date** _____

4.1 Inclusion Criteria

4.1.1 Patients must have histologically or cytologically confirmed metastatic pancreatic adenocarcinoma (or any mixed pathology if adenocarcinoma is predominant).

4.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan.

4.1.3 Prior Therapies: Patients must have received at least one prior systemic chemotherapy regimen for metastatic pancreatic cancer. They should have experienced disease progression or intolerable toxicity from that regimen.

4.1.3.1 Patients who have received prior non-gemcitabine-based systemic chemotherapy for metastatic disease at any time 4 weeks prior to enrollment, or those who are beyond 12 months of exposure to gemcitabine-based chemotherapy regimen are allowed.

4.1.3.2 Prior chemotherapy, radiation therapy, concurrent chemoradiation are allowed if used for treatment of non-metastatic disease.

4.1.3.3 Any chemotherapy must have been completed 4 weeks prior to enrollment.

4.1.3.4 Any radiotherapy must have been completed 2 weeks prior to enrollment.

4.1.4 Age ≥ 18 years. Because the dosing and toxicity data for Regorafenib are not currently available in patient population <18 years, children are excluded from this study.

4.1.5 ECOG performance status 0-1

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

4.1.7 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.

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

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

- Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferease (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Lipase ≤ 1.5 x the ULN
- Serum creatinine ≤ 1.5 x the ULN
- International normalized ratio (INR)/ Partial thromboplastin time (PTT) • 1.5 x ULN. (Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
    - Platelet count ≥ 100000 /mm^3, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm^3. Blood transfusion to meet the inclusion criteria will not be allowed.

4.1.10 Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.

4.1.11 Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.

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

4.2 **Exclusion Criteria**

The presence of <u>any</u> of the following will exclude a patient from study enrollment.

4.2.1 Chemotherapy within 4 weeks prior to entering the study, radiotherapy within 2 weeks prior to entering the study or failure to recover from adverse events to Grade 1 or less due to agents administered more than 4 weeks earlier.

4.2.2 Use of any other investigational agents.

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

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

4.2.5 Active or clinically significant cardiac disease including:

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

4.2.6 Evidence or history of bleeding diathesis or coagulopathy.

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

4.2.8 Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of informed consent.

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

4.2.10 Patients with phaeochromocytoma.

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

4.2.12 Any infection requiring ongoing intravenous antibiotics for management..

4.2.13 Symptomatic metastatic brain or meningeal tumors. Treated and stable, asymptomatic brain metastases, as long as treatment was greater than 4 weeks prior to informed consent, are allowed.

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

4.2.15 Renal failure requiring hemo-or peritoneal dialysis.

4.2.16 Dehydration Grade ≥1 NCI-CTCAE v4.0.

4.2.17 Patients with seizure disorder requiring medication.

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

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

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

4.2.21 History of organ allograft (including corneal transplant).

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

4.2.23 Any malabsorption condition.

4.2.24 Women who are pregnant or breast-feeding.

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

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

4.3 **Inclusion of *Women and* Minorities**

Both men and women and members of all races and ethnic groups are eligible for this trial

5.0 REGISTRATION *or RANDOMIZATION, if applicable*

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Taussig Cancer Institute, Cleveland Clinic and will be provided a study number by referring to the OnCore Database. Patient numbers are to be assigned in numerical order.

6.0 TREATMENT PLAN

6.1 Eligibility and Baseline Evaluation

After obtaining written informed consent and ensuring all eligibility requirements are met, based on clinical history and physical examination, laboratory tests for marrow and organ function, imaging studies and laparoscopic evaluation for extent of disease, as outlined in section 4.0, patients will be enrolled onto the study. A chemotherapy port will be placed to allow central venous administration of chemotherapeutic agents.

6.1.1 Regorafenib

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 40-mg tablets (for randomized studies) or 28 40-mg tablets (for open-label studies) and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F).

Oral Regorafenib 120 mg daily for 21 days of the first 28-day cycle taken along with food (low-fat meal). For those patients who tolerate the first cycle of treatment without any regorafenib dose related toxicities, the dose of regorafenib may be escalated to 160 mg/day for the second and subsequent cycles (3 weeks on and 1 week off; every 4 week cycle).

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

Dose escalation criteria are given below:

Cycle Each cycle 28 days	Adverse Event	Regorafenib Days 1-21	Gemcitabine Days 1, 8, 15
1	N/A	120 mg/day baseline	800 mg/m^2 baseline
2 onward	No ≥grade 2 toxicity in cycle 1	160 mg/day baseline, refer to 6.4.2 for dose modification	1000 mg/m^2 baseline, refer to 6.4.2 for dose modification
2 onward	Any ≥grade 2 toxicity in cycle 1	120 mg/day baseline, refer to 6.4.2 for dose modification	800 mg/m^2 baseline, refer to 6.4.2 for dose modification

This is a phase II open labeled study.
One treatment cycle is 28 days.

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

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

6.1.2 **Gemcitabine**

Gemcitabine will be administered at a starting dose of 800 mg/m^2 and escalated to 1000 mg/m^2 as tolerated by study patients after a stable dose of regorafenib is achieved for 1 cycle, as a 30-minute intravenous infusion, on days 1, 8 and 15 of each 28-day cycle.

6.2 **General Concomitant Medications and Supportive Care Guidelines**

Concomitant medicines will be administered to counter the expected common side-effects of chemotherapy. These may include anti-emetic, anti-allergy, and anti-diarrhea medicines, as well as growth factors for bone marrow support. These will be ordered by the treating physician per the patient's condition and prior history
Further intravenous medicines and fluids may also be used per the treating physician's recommendations. Oral medicines can be prescribed for use at home, as deemed appropriate by the treating physician. These may include anti-emetics, analgesics, anti-pyretics, anti-diarrheals, pancreatic enzyme supplements, appetite stimulants, antacids, H2-blockers, proton pump inhibitors, anxiolytics, anti-depressants, sleep aids, and other common medicines as needed. Referral to health care providers from other specialties, such as palliative medicine, nutrition, psychology, psychiatry, home care services, etc., may be made as needed per the patient's clinical situation.

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

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

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

Permitted concomitant therapy includes:

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

The following are not permitted:

- Other investigational treatment during or within 30 days before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporine, and digoxin). Warfarin is metabolized by the cytocrome enzyme CYP2C9 and its levels may be especially affected by regorafenib
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])
- Please note: Patients should be seen frequently / early during treatment as per Prescribing Information
- Liver function tests should be obtained before initiation of regorafenib and monitored at least every 2 weeks during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated
- Monitor blood pressure weekly for the first 6 weeks of treatment and every cycle or more frequently as clinically indicated.

6.3 **Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment with regorafenib and gemcitabine will continue or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- The investigator considers it, for clinical reasons, to be in the best interest of the patient.
- Unacceptable treatment-related toxicity, NCI CTCAE version 4.0, that fails to resolve with usual supportive measures,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study for a child-bearing participant, or
- Death.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

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

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

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

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

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

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

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

6.4 **Duration of Follow Up**

Patients will be followed from the time of enrollment until death, or patient decision to withdraw from the study. The study calendar, in section 11, describes the schedule of follow-up.

6.5 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

6.5.1 Accountability

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

6.5.2 Destruction and Return

Unused, expired and returned supplies of regorafenib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer.

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

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

6.5.3 Treatment compliance

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

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

7.0 DOSING DELAYS / DOSE MODIFICATIONS

The starting dose of regorafenib is 120 mg once daily. Study medication will be administered on a 3 weeks on/1 week off schedule [3 weeks out of every 4].

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

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

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

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

If more than 2 dose reductions are required, regorafenib only will be discontinued and the rest of the study treatment (gemcitabine) may be continued. If a dose reduction has been performed, intra-subject dose re-escalation can be considered (up to the maximal 160 mg daily dose) at the discretion of the treating physician provided that the toxicity(ies) has resolved to baseline.

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

Table 7-1: Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/ST/bilirubin			
NCI-CTCAE v4.0[a]	**Dose Interruption**	**Dose Modification[b]**	**Dose for Subsequent Cycles**
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0

b. Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.

c. If no recovery after a 4 week delay*, treatment should be permanently discontinued unless subject is deriving clinical benefit.

Other Toxicities

Any treatment-emergent toxicities other than the ones described above will be managed by the treating physician as appropriate. Dose delays and modifications, and treatment cessation will be at the discretion of the treating physician and/or the Principal Investigator. All adverse events will be documented and measures to manage/treat/mitigate them will be documented as well. This is described further in section 8.0.

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

Table 7-2: Grading for Hand-Foot-Skin-Reaction			
	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndrome	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 regorafenib therapy. The other study treatment may be continued
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 regorafenib treatment permanently. The other study treatment may be continued

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. The other study treatment may be continued.
e. The maximum daily dose is 160 mg.

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

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

Control of calluses

Before initiating treatment with regorafenib:

- Check condition of hands and feet.

- Suggest a manicure/pedicure, when indicated.
- Recommend pumice stone use for callus or 'rough spot' removal.

During regorafenib treatment:

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

Use of creams

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

Tender areas should be protected as follows:

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

Hypertension

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

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

Liver Function Abnormalities

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

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

Table 7.5: Dose Modification/interruption for alanine aminotransferase and/or aspartate aminotransferase increases related to study drug

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

	develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		

Prevention/management strategies for diarrhea

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

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

Myelosuppression (Hematological Toxicities)

ANC should be $\geq 1000/mm^3$ and platelets should be $\geq 75,000/mm^3$ prior to each administration of medications.

Dose modification of gemcitabine will be allowed for subsequent doses based on the nadir counts when treatment is held.

Dose Modification of Gemcitabine for subsequent doses:

ANC ($cells/mm^3$)	Platelets ($cells/mm^3$)	Gemcitabine (mg/m^2)
≥ 1000	≥ 75,000	Continue previous dose level
500-999	50,000-74,999	Reduce dose by 20%
<500	<50,000	Reduce dose by 40%

- CBC will be checked weekly for all cycles of Gemcitabine.
- Hold for a maximum of 3 weeks. Perform blood counts weekly until they return to ≥1000 (ANC) and ≥75000 (platelets), to allow resumption of gemcitabine. If counts do not recover to these levels despite 4 weeks of holding gemcitabine, discontinue protocol therapy.
- G-CSF can be administered if persistent neutropenia ≤500/mm3 for more than 7 days with no fever, or neutropenia with temperature $\geq 38.5^0$C.

Non-Hematological Toxicities from Gemcitabine

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity

- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold Gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

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

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

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

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

8.1 Adverse Events and Potential Risks

8.1.1 Regorafenib

Common: Hand-Foot-Skin reaction, Hypertension, Liver function abnormalities, Diarrhea
Rare: Myocardial infarction/ischemia, Taste disturbances, GERD, Tremor

8.1.2 Gemcitabine

Common: Myelosuppression, Dyspnea, Pulmonary toxicity, Hepatic toxicity, Hemolytic Uremic Syndrome, Peripheral edema
Rare: Paresthesias, Increased creatinine, Bronchospasm, TTP

8.2 Definitions

8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily

have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

Internal adverse events are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

8.2.2 The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

8.2.3 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the

subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for

AE reporting.
Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to the Site Principal Investigator.
Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events. SAEs will be reported in OnCore.

8.4.1 FDA Reporting

In accordance with 21 CFR 312.32, the Taussig Cancer Institute Principal Investigator is responsible for notifying the FDA of SAEs that are serious, unexpected (not listed in the Investigator Brochure) and judged to be related (i.e., possible, probable, definite) to the study drug.

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

9.1 Gemcitabine

9.1.1 Gemcitabine

Chemical Name: Gemcitabine, Nucleoside Analogue

Other Names: Gemzar

Classification: Antineoplastic

Molecular Formula: Nucleoside analogue in which the hydrogen atoms on the 2' carbon of deoxycytidine are replaced by fluorine atoms

Mode of Action: The triphosphate analogue of gemcitabine replaces cytidine, during DNA replication. That process arrests tumor growth, as only one additional nucleoside can be attached to the "faulty" nucleoside, resulting in apoptosis.

Other target of gemcitabine is the enzyme ribonucleotide reductase (RNR). The diphosphate analogue binds to RNR active site and inactivates the enzyme irreversibly. Once RNR is inhibited, the cell cannot produce the deoxyribonucleotides required for DNA replication and repair, and cell apoptosis is induced

Metabolism: Metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleoside metabolites

Product description: Gemcitabine is commercially available. Using standard Pharmacy policies and procedures for chemotherapeutic agents, drug will be prepared for intravenous administration to patients.

9.2 **Regorafenib**

9.2.1 Regorafenib

Chemical Name: Regorafenib

Other Names: Stivarga

Classification: Antineoplastic

Mode of Action: Regorafenib is a multikinase inhibitor; it targets kinases involved with tumor angiogenesis, oncogenesis, and maintenance of the tumor microenvironment which results in inhibition of tumor growth. Specifically, it inhibits VEGF receptors 1-3, KIT, PDGFR-alpha, PDGFR-beta, RET, FGFR1 and 2, TIE2, DDR2, TrkA, Eph2A, RAF-1. BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl.

Metabolism: Hepatic via CYP3A4 and UGT1A9, primarily to active metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl)

Product description: Regorafenib is commercially available. For this study, however, it will be supplied by the manufacturer. Using standard Pharmacy policies and procedures for chemotherapeutic agents, drug will be supplied to patients.

10.0 CORRELATIVE / SPECIAL STUDIES

NA

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤ 28 days prior to administration of protocol therapy.

- Informed Consent
- Demographics
- Medical History
- Complete physical examination
- Height
- Weight
- Vital signs including: Temperature, Pulse, Blood Pressure, Respiratory rate
- Concomitant Medications Assessment including all prescription medicines
- ECOG Performance Status ≤ 1
- Baseline Symptoms Assessment
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
    - ß-hCG for women of childbearing potential
- CT or MRI scan of chest, abdomen, and pelvis with and without contrast

11.1.2 All Follow-up visits and procedures are described in the Study Calendar.

Lost to Follow-Up

If the patient does not show up for the scheduled follow-up visit, all reasonable efforts will be made to contact the patient or appropriate family member or personal caregiver to re-schedule follow-up. If patient is deceased, this information will be captured. If patient is unable to follow up in clinic, appropriate reasons will be captured. In this case, or if patient withdraws consent, permission will be sought to continue contact by telephone, letter, or email to capture survival data. Appropriate databases, such as the Social Security Death Index, may be searched to gather survival data.

11.2 Study Calendar

		Cycles 1&2 (Every 28 days per cycle)			Cycles 3 onward (Every 28 days per cycle)			End of treatment	Every 2 months ± 1 week
	Screen	Day 1*	Day 8±1	Day 15±1	Day 1±1	Day 8±1	Day 15±1	4 weeks (± 3 days) from last treatment visit	
Informed Consent	X								
History[1]	X	X		X	X		X	X	X[7]
ECOG PS	X	X	X	X	X		X	X	X[7]
AE assessment[6]		X	X	X	X		X	X	
Physical exam[2]	X	X		X	X		X	X	X[7]
Height	X								
Weight	X	X		X	X		X	X	X[7]
Vitals[3]	X	X	X	X	X		X	X	X[7]
CBC	X	X	X	X	X	X	X	X	
LFTs[4]	X	X	X	X	X		X	X	
BMP, amylase and lipase	X	X		X	X		X	X	
Urinalysis and urine protein	X	X		X	X		X		
aPTT and PT/INR	X	X		X	X		X		
CA 19.9	X	X			X			X	X[7]
β-hCG	X								
CT or MRI[5]	X							X	X[7]
RECIST 1.1 Evaluation[6]	X	Scans for response evaluation to be performed every 8 weeks (+/-3 days)						X	X[7]
Gemcitabine		X	X	X	X	X	X		
Regorafenib		X – to be taken daily for the first 21 days of each 28-day cycle							
Survival data		X						X	X

Abbreviations: ECOG PS: ECOG Performance Status. AE: Adverse Event. CBC: Complete Blood Count, with differential. BMP: Basic Metabolic Panel, including bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, sodium. LFTs: Liver Function Tests, albumin, alkaline phosphatase, total bilirubin, total protein, SGOT [AST], SGPT [ALT].

*Cycle 1, Day 1 assessments need not be performed if the screening assessments were performed within 7 days.
1. Complete or focused clinical history, as determined appropriate by treating physician.

2. Complete or focused physical examination, as determined appropriate by treating physician.
3. Include temperature, pulse, and blood pressure. ***Monitor blood pressure weekly for the first 6 weeks of treatment and every cycle or more frequently as clinically indicated.***
4. Liver function tests (albumin, alkaline phosphatase, total bilirubin, total protein, SGOT [AST], SGPT [ALT]) should be obtained before initiation of regorafenib and monitored at least weekly during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated
5. Contrast enhanced CT or MRI of the chest, abdomen and pelvis based on treating physician's preference. It is recommended (but not required) to obtain the same study as was performed at screening throughout a patient's course. PET scans are NOT acceptable alternatives.
6. Response will be assessed using RECIST 1.1 criteria after 2 cycles of treatment. Imaging (CT or MRI) will be repeated every 2 cycles (every 8 weeks (+/-3 days)).
7. To be performed only up to disease progression or initiation of new cancer-directed therapy. Once disease progression is established, or a new cancer-directed therapy is initiated, only survival data will be captured.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (+/-3 days). In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks (+/-3 days) following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. For primary brain tumors, response and progression will be evaluated using the RANO criteria [*J Clin Oncol* 28: 1963-1972.2010].

12.1.1 Definitions

Evaluable for toxicity All patients will be evaluable for toxicity from the time of their first treatment with the study drugs**.**

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

Evaluable Non-Target Disease Response Patients who have lesions present at baseline that are evaluable, but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable Disease Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$ 10 mm with CT scan, or $\geq$ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

Non-measurable disease All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), 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 reproducible should be selected. 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 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 any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 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 unless the lesion(s) being followed cannot be imaged, but are assessable by clinical exam.
Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-holding techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical

diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if is not routine or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26: 1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in

assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FGD-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

   Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	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.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target lesions

Response	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD [Incomplete response/ Stable Disease (SD)]	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of 'non-target' lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for

progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation **
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation **
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline **
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD ***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesion	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD *
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

12.1.5 Duration of Response

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

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

12.1.6 Overall and Progression-Free Survival

Overall Survival will be calculated as time in days from enrollment (signing of the informed consent) to death.

Progression-free Survival will be calculated as time in days from enrollment (signing of the informed consent) to the earlier of:

- Death, or
- Disease progression, by clinical, imaging, or laparoscopic parameters.

13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.5 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

14.0 STATISTICAL CONSIDERATIONS

All clinical data will be captured in the OnCore database system.

All pertinent baseline demographic and disease characteristics will be captured. Medical and surgical history, with detailed information on pancreatic cancer treatment history, including surgery, chemotherapy, and radiation therapy, will be gathered. During the study, detailed treatment data, clinical, laboratory and radiologic data, and adverse event and efficacy data will be collected.

Categorical data will be summarized as frequency counts and percentages, measured data will be summarized using means, standard deviations, medians, and time-to-event data will be summarized using the Kaplan-Meier method. Chi-square tests, t-tests and ANOVA methods (or their non-parametric counterparts), and the logrank test or proportional hazards models will be used for univariable comparisons that might be performed. Multivariable methods such as logistic regression and proportional hazards will be used to adjust for potential confounders.

No interim analyses planned.

The primary efficacy outcome is progression-free survival (PFS). Limited data are available on PFS in metastatic pancreatic cancer that has progressed on prior chemotherapy. A recent comprehensive analysis estimated that the median PFS with other combination chemotherapy care in this setting is between 1.6 and 2.9 months [11]. We will consider a median PFS of 4 months with regorafenib and gemcitabine as supportive of further investigation. The study will be conducted at the Cleveland clinic main campus and all its ten (10) regional oncology sites. Based our current tumor registry data, 50-60 new patients with stage IV pancreatic cancer are seen each year at the main campus alone, therefore, the estimated accrual time for the study is 18-24 months, and the follow-up time is 6-12 months. With 80% power and a one-sided alpha of 0.10 to detect this improvement in median PFS from 2.85 months to 4 months, 40 patients are needed for this study.

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