TITLE: A Phase 2 Trial of Regorafenib as A Single Agent in Advanced and Metastatic Biliary Tract Carcinoma/Cholangiocarcinoma Patients Who Have Failed First-line Chemotherapy

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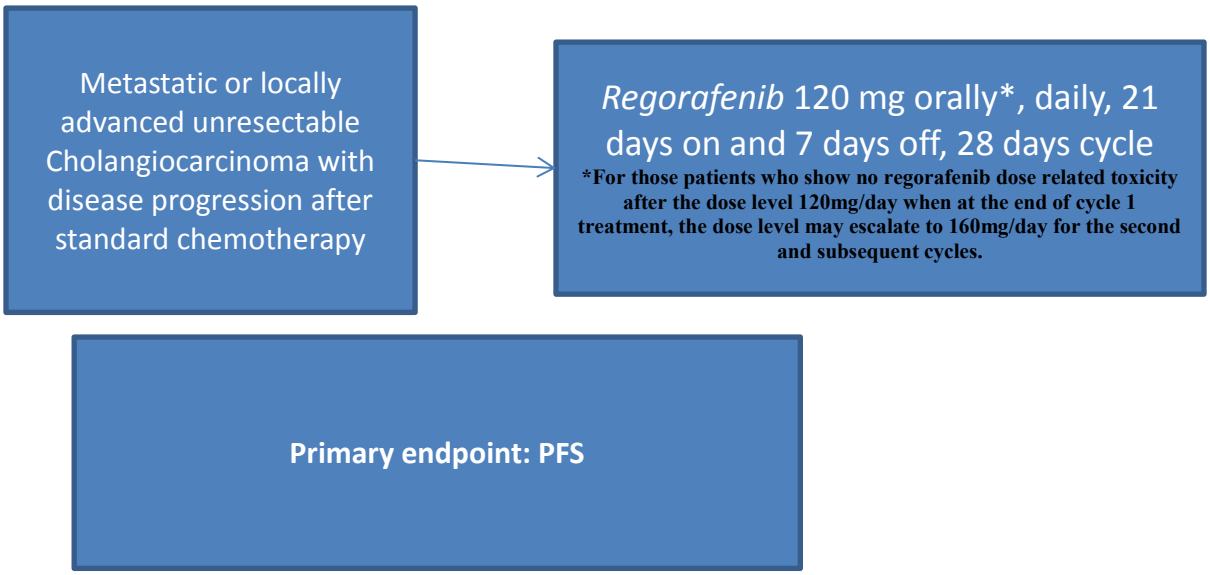
SYNOPSIS

Title	A Phase 2 Trial of Regorafenib as a Single Agent in Advanced and Metastatic Biliary Tract Carcinoma Patients Who Have Failed First-line Chemotherapy
Clinical study phase	Phase 2 single arm
Study objective(s)	Primary objective: To evaluate the progression-free survival (PFS) of patients with advanced or metastatic biliary cancer receiving ragorafenib following the failure of first-line chemotherapy. Secondary objectives: • Overall response (OR), including complete and partial response, and disease Control rate (DCR). • Overall survival (OS) • Measurable changes in biomarkers [CA19-9 and CEA], in patients that were elevated at the time of study entry. • Evaluation of safety and associated toxicities
Background treatment	Advanced and metastatic biliary tract carcinoma who have failed first-line chemotherapy.
Indication	Biliary Tract Carcinoma
Diagnosis and main criteria for inclusion	• Histologically or cytologically confirmed diagnosis of biliary tract adenocarcinoma/cholangiocarcinoma; pathologic confirmation may be from the primary or a metastatic site • Must have locally advanced or distant metastatic disease that is not surgically curable • Failed first-line chemotherapy. • Age ≥ 18 years. • Life expectancy of at least 12 weeks (3 months). • Performance status ≤ 1 • Adequate liver, kidney, and bone marrow function as assessed by the following laboratory requirements: ➢ Total bilirubin ≤ 3.0 x the upper limit of normal (ULN) ➢ Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5.0 x ULN ➢ Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5.0 x ULN for subjects with intrahepatic involvement of their cancer) ➢ Serum creatinine ≤ 1.5 x the ULN ➢ International normalized ratio (INR)/partial thromboplastin time (PTT) ≤ 1.5 x ULN.
Study design	Patients with advanced and metastatic biliary tract adenocarcinoma (cholangiocarcinoma) who had been treated with and failed first-line chemotherapy will be treated with regorafenib (120 mg) orally once daily 21 days (3 weeks) on and 7 days (1 week) off in the 28-day (4-week) cycle.
Type of control	Single arm uncontrolled

Number of subjects	Maximum of 37 patients.
Plan for statistical analysis	There will be no stratification. OR will be estimated at end of trial with 95% exact binomial confidence intervals. PFS and OS will be estimated by the Kaplan-Meier method, with appropriate 90% confidence intervals. Toxicity events will be tabulated. Change in CA19-9 and CEA will be characterized by their mean changes, with a nonparametric CDF-based 90% confidence interval. The study will have 83% power (using a one-sided test at α=0.10) to reject the null hypothesis (PFS<2.0 months) if the true median PFS is at least 3.5 months.

Schema:



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1. OBJECTIVES

1.1 Primary Objectives

To evaluate the progression-free survival (PFS) of patients with advanced or metastatic biliary tract carcinoma (cholangiocarcinoma) receiving ragorafenib following the failure of first-line chemotherapy.

1.2 Secondary Objectives

- Overall response rate (ORR), including complete and partial response, and disease control rate (DCR)
- Overall survival (OS)
- Measurable changes in biomarkers [CA19-9 and CEA], in patients that were elevated at the time of study entry.
- Evaluation of safety and associated toxicities

2. BACKGROUND

2.1 Study Disease(s)

Biliary tract adenocarcinoma (Cholangiocarcinoma, gallbladder carcinoma) is a relatively rare but aggressive neoplasm. There are about 7,000-10,000 new cases diagnosed per year in the United States. The incidence of intrahepatic cholangiocarcinoma is rising globally, and this rising rate has not been associated with an increase in the proportion of early stage disease. The five-year overall survival for advanced disease is only about 5%. It is also the second most common primary hepatic tumor but more lethal than HCC. Treatment outcomes and survival have improved little over the past three decades—a period in which successful new treatments have increased patient survival for many other cancers.

As with most solid tumors, surgical resection represents the only curative therapy. However, the majority of patients with cholangiocarcinoma present with unresectable or metastatic disease. Currently, for these patients, first-line therapy consists of systemic chemotherapy with the combination of gemcitabine and cisplatin. Despite a described response rate of over 80%, median overall survival remained poor at 11.7 months. Other gemcitabine-based and flouropyrimidine-based chemotherapy regimens have been also used. In selected patients, local-regional therapy e.g. chemoembolization with gemcitabine-based treatment has been applied as well. With all of these regimens, efficacy was limited with significant associated morbidities. There is no standard 2nd line therapy besides Phase 2 data. The mPFS (or TTP) of 2^{nd}-line varies around 1.6-2.3 months (see refs: Oh SY, et al and Lee S, et al), and mOS varies between 4-6 months. More effective therapies are definitely needed with better understanding of the mechanisms of this disease and therapy to treat it.

Several signaling pathways have been identified that might play a role in the development of

cholangiocarcinoma. Over-expression of p53 has been found in 20 to 30 percent of tumors. BRAF mutations were seen in approximately 22 percent of intrahepatic cholangiocarcinomas. VEGF was also found to be overexpressed in a majority of patients with intrahepatic and extrahepatic cholangiocarcinoma. In several studies, abnormal expression of K-ras was seen in 45 to 54 percent of intrahepatic cholangiocarcinomas, and 10 to 15 percent of extrahepatic cholangiocarcinomas. In one study, the incidence of K-ras gene mutations in patients with lymph node metastasis was seen to be higher than that in patients without, and patients with K-ras gene mutations showed a statistically significant worse survival rate than those without such mutations.

2.2 Regorafenib

Regorafenib is a novel diphenylurea oral multikinase inhibitor of angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR1), and oncogenic kinases (KIT, RET, RAF) with potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI) (1).

Regorafenib potently inhibits angiogenic kinases VEGFR 1-3, TIE2, PDGFR-β, and fibroblast growth factor receptor 1(FGFR1) in biochemical (IC_{50} between 4 and 311 nanomolar [nM]) and cellular (IC_{50} between 3 and ~200 nM) kinase phosphorylation assays. The VEGF, TIE2 and PDGF receptors are relevant to tumor angiogenesis (2, 3). PDGF receptors may also play a role in patients with chronic myeloproliferative cancers (4).

Furthermore, it potently inhibits mutant oncogenic kinases KIT (cellular IC_{50} c-KIT_{K642E} = 22 nM) and RET (cellular IC_{50} RET_{C634W} ~10 nM), which play a role in human gastrointestinal stromal and thyroid cancers, respectively, and B-RAF, a member of the *RAS/RAF/MEK/ERK* signaling pathway (biochemical IC_{50} of wt B-RAF = 28nM and of B-RAF_{V600E} = 19nM). In addition, it biochemically inhibits Raf-1 (IC_{50} = 2.5 nM) and the p38 MAPK (IC_{50} = 24 nM) (1).

2.2.1 Preclinical

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

2.2.2 Clinical experience

Two Phase 3 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 with 114 centers in 16 countries. Patients with documented metastatic colorectal cancer and progression during or within 3 months after the last standard therapy were randomized (in a 2:1 ratio; stratified by previous treatment with anti-VEGF therapy, time from metastatic disease diagnosis, and geographical area) to receive oral regorafenib, 160 mg once daily, plus best supportive care (BSC) or placebo plus BSC, with 3 weeks on and 1 week off as a cycle. The primary endpoint was overall survival. From April 30, 2010 to March 22, 2011, there were 1052 patients screened, 760 patients were randomized to receive regorafenib (n=505) or placebo (n=255); 753 patients initiated treatment (regorafenib n=500; placebo n=253). The primary endpoint of overall survival was met at a preplanned interim analysis. Median overall survival was 6.4 months in the regorafenib treatment arm versus 5.0 months in the placebo arm (HR of 0.77; 95% CI 0.64–0.94; one-sided p=0.0052). Treatment-related adverse events occurred in 465 (93%) patients assigned regorafenib and in 154 (61%) of those assigned placebo. The most common adverse events of grade three or higher related to regorafenib were hand-foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhea (36, 7%), hypertension (36, 7%), and rash or desquamation (29, 6%).

The efficacy and safety of regorafenib were examined in the Phase 3 GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. The study was conducted at 57 hospitals in 17 countries. Patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib and sunitinib were randomized in a 2:1 ratio (stratified by treatment line and geographical region) to receive either oral regorafenib, 160 mg daily, plus best supportive care (BSC) or placebo plus BSC, 3 weeks on and 1 week off as a cycle. 240 patients were screened and 199 were randomized to receive regorafenib (n=133) or matching placebo (n=66). Median PFS per independent blinded central review was 4.8 months (IQR 1.4–9.2) for regorafenib and 0.9 months (0.9–1.8) for placebo (HR 0.27, 95% CI 0.19–0.39; p<0.0001). After progression, 56 patients (85%) assigned placebo crossed over to regorafenib. 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. Drug-related adverse events were reported in 130 (98%) patients that had regorafenib and 45 (68%) patients assigned to placebo. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (31 of 132, 23%), hand-foot skin reaction (26 of 132, 20%), and diarrhea (seven of 132, 5%).

Based on the facts of multiple pathways involvement in cholangiocarcinoma tumor genesis, including EGFR, Ras, Raf, VEGFR, and PDGFR, with evidence of overexpression of these proteins associated with tumor stage, prognosis and response to therapy. Multikinase inhibitor targeting multiple tumor pathways agent as regorafenib should be the ideal candidate for evaluating the anti-cancer activity for the disease as cholangiocarcinoma. More importantly, regorafenib likely holds promise in this disease setting with known effectiveness either as a single agent or in combination with cytotoxic chemotherapy agents in multiple solid tumors as above and the toxicity profile.

2.3 Rationale

As noted, multiple pathways, including EGFR, Ras, Raf, VEGFR, and PDGFR appear to be involved in cholangiocarcinoma tumor genesis. Overexpression of these proteins has been shown to be associated with tumor stage, prognosis, and response to therapy. However, therapies targeting a single pathway have shown no clear benefit. A number of Phase 2 trials have been completed, or are underway, studying agents targeted to EGFR or VEGF – both as monotherapy and in combination with chemotherapy. These have shown varying increases in response rate, but have not found marked increases in progression-free or overall survival. This suggests that inhibition of multiple pathways simultaneously may be needed. Regorafenib, is an oral multikinase inhibitor targeting multiple tumor pathways, which has showed effectiveness as a single agent in multiple solid tumors.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- Histologically or cytologically confirmed diagnosis of biliary tract adenocarcinoma/ cholangiocarcinoma (including primary intra- and extrahepatic diseases); pathologic confirmation may be made from the primary or a metastatic site.
- Must have locally advanced or distant metastatic disease that is not surgically curable.
- Failed first-line chemotherapy (including systemic and local-regional therapy).
- Age ≥ 18 years
- Life expectancy ≥12 weeks (3 months)
- Performance status ECOG ≤ 1
- Adequate liver, kidney, and bone marrow function as assessed by the following laboratory requirements:
  - Total bilirubin ≤ 3.0 x the upper limits of normal (ULN) (biliary stenting or percutaneous biliary drainage are allowed for cancer related biliary obstruction)
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5.0 x ULN
  - Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5.0 x ULN for subjects with intrahepatic involvement of their cancer)
  - Serum creatinine ≤ 1.5 x the ULN
  - International normalized ratio (INR)/partial thromboplastin time (PTT) ≤ 1.5 x ULN. (Patients 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 ≥ 75,000 /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.

- 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.
- Patients (men and women) of childbearing potential must agree to use Double Barrier method of birth control beginning at the signing of the ICF until at least 3 months after the last dose of study drug.
- Patients must be able to swallow and retain oral medication.
- Patients must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

3.2 Exclusion Criteria

- Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
- Uncontrolled hypertension (systolic pressure ≥140 mm Hg or diastolic pressure ≥ 90 mm Hg on repeated measurement) despite optimal medical management.
- 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 (angina symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
- Evidence or history of bleeding diathesis or coagulopathy.
- Any hemorrhage or bleeding event ≥ Grade 3 within 4 weeks prior to prior to registration.
- Patients 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 the study registration.
- Previous exposure to VEGF inhibitor(s),
- Patients with any previously untreated or concurrent cancer that is distinct in primary site or histology from biliary tract cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Patients surviving a cancer that was curatively treated and without evidence of disease for more than 3 years prior to registration are

allowed. All cancer treatments must be completed at least 3 years prior to prior to registration).

- Patients with phaeochromocytoma.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Ongoing infection > Grade 2.
- Symptomatic metastatic brain or meningeal tumors.
- Presence of a non-healing wound, non-healing ulcer, or bone fracture.
- Renal failure requiring hemo-or peritoneal dialysis.
- Dehydration Grade ≥1
- Patients with seizure disorder requiring medication.
- Proteinuria ≥ Grade 3 (> 3.5 g/24 hours, measured by urine protein: creatinine ratio on a random urine sample).
- Active signs and symptoms of interstitial lung disease pleural effusion or ascites that causes respiratory compromise (≥Grade 2 dyspnea).
- History of organ allograft (including corneal transplant).
- Known or suspected allergy or hypersensitivity to any of the study drug classes.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.
- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment regorafenib. However, the palliative XRT to non-targeted lesions is allowed.
- Prior use of regorafenib.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 28 days prior to registration
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration (biliary stenting or percutaneous biliary drainage are not included).
- Use of any herbal remedy (e.g. St. John's Wort [Hypericum perforatum])

3.3 Withdrawal of patients from study treatment

Patients **must be withdrawn from the study treatment** for the following reasons:

- Patients withdraw consent for study treatment and study procedures. A patient 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 patient will not suffer any disadvantage as a result.
- Pregnancy
- Subject is lost to follow-up
- Disease Progression
- Death

Patients **may be** withdrawn from the study treatment for the following reasons:

- The patient is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- If, in the investigator's opinion, continuation of the trial would be harmful to the patient's well-being.
- 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.

In all cases, the reason for removal from study must be recorded in the research data base and in the patient's medical records.

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 12.3 (Premature termination of the study).

3.4 Screen Failures/Dropouts

A patient who discontinues study participation prematurely for any reason is defined as a “dropout” if the patient has: already been registered, administered at least one dose of study drug.

A patient who, for any reason (e.g. failure to satisfy the selection criteria; withdraws consent), prior to receiving first dose of study drug will be regarded a “screening failure”.

3.5 Replacement

No withdrawn patients will be replaced, 'Drop out patients may be replaced.

4. TREATMENT PLAN

Patients with advanced and metastatic biliary tract adenocarcinoma (cholangiocarcinoma) who had been treated and failed first-line chemotherapy, ECOG PS 0-1, and adequate liver, kidney and bone marrow function will be treated with regorafnib (160 mg) orally once daily for 21 days on and 7 days off in a 28-day cycle. Tissue specimens collected at diagnosis may be submitted for molecular analyses or other studies.

A maximum of 37 patients will be enrolled.

4.1 Regorafenib Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The starting dose of regorafenib will be120 mg once daily for the first cycle. However, for those patients who show no regorafenib dose related toxicity after the dose level 120mg/day when at the end of cycle 1 treatment, the dose level may escalate to 160mg/day for the second and subsequent cycles. Study medication will be administered on a 3 weeks on and 1 week off schedule [3 weeks out of every 4].

At the startthree 40-mg regorafenib tablets [unless dose-reduced, Section 6] should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast for cycle 1. The number of regorafenib tablets of subsequent cycles should be taken based on the AE profile of the previous cycles.

4.2 Examples of a low fat breakfast

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

One cup of cereal (i.e., Special K), 8 ounces of skimmed milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course

4.3 Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the research data base (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 160 mg dose of Stivarga increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of regorafenibwith strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, grapefruits, Seville oranges, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

Permitted concomitant therapies include:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they are reviewed by the investigator and are deemed acceptable.
- Bisphosphonates
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

The following are not permitted:

- Other investigational treatment during or within 28 days before starting study treatment

- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporine, and digoxin). Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be especially affected by regorafenib
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

4.4 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 patient may be discontinued from the trial for non-compliance with follow-up visits or study drug.

4.5 Duration of Follow Up

Patients will be followed every 3 months (+/- 4 weeks) until death or study closure. Follow-up will be by either direct contact or medical record review.

5. DOSING DELAYS/DOSE MODIFICATIONS

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.

Modifications of regorafenib will follow the following predefined dose levels:		
#Dose level +1	160 mg, daily, orally	Four 40-mg tablets of regorafenib
Dose level 0 (Standard starting dose)	120 mg, daily, orally	Three 40-mg tablets of regorafenib
Dose level –1	80 mg, daily, orally	Two 40-mg tablets of regorafenib
Dose level -2	40 mg, daily, orally	One 40-mg tablet of regorafenib

#Only for those patients with no regorafenib dose related toxicity after the 1st cycle dose level of regorafenib 120mg/day, the dose level may escalate to 160mg/day for the second and subsequent

cycles.

If a patient 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.

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

Table 5-1: 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,d]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating (Sub-) investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 2 dose levels. Permanent discontinuation can be considered at the treating (Sub-)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.
d. For G3 AE for level of phosphate and magnesium only patient may continue tx at MD discretion. MD will provide appropriate intervention, as needed.
Note: these dose modifications are for the current cycle based on the grade of toxicity, there will not be re-escalating in the same cycle. However, 're-escalation' in subsequent cycles is possible, if toxicity remains grade 2 or less, and will be 'at the discretion of the treating (Sub-) investigator.

Table 5-2: Grading for Hand-Foot-Skin-Reaction

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

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

Table 5.3 Recommended dose modification for hand-foot-skin reaction[a]

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

Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level.[b,d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one additional dose level[b,d]
	3rd occurrence	Discontinue treatment permanently.

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

Prior to starting regorafenib and at first occurrence of HFSR, independent of grade, prompt institutional supportive measures such as topical emollients, low potency steroids, or non-urea-containing creams should be administered. Patients should be educated on prevention/management strategies for HFSR.

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

<u>Control of calluses</u>
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.

<u>Use of creams</u>

- 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

5.1 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 8 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic 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 5.4 outlines suggested dose reductions.

Table 5-4: 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 mmHg: 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 mmHg[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 mmHg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mmHg 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 (e.g., 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.		

5.2 Liver Function Abnormalities

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

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

Table 5-5: Dose modifications/interruption for ALT and/or AST and/or bilirubin increases related to study drug

Observed elevations	1st Occurrence	Restart	Re-occurrence
AST and/or ALT ≤ 5 X ULN (< G3)	Continue dosing, with weekly monitoring of liver function until		

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

5.3 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheas and optimized hydration status).

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

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The AEs and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

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

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

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

AEs evaluation will be continued after the first 2 cycles.

6.1 Adverse Events and Risks List

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

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. The investigator will routinely review any new distributions of the IB for relevant new safety information and incorporate into the informed consent form document as appropriate.

6.2 Definitions

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they

may jeopardize the patient 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 dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.3 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

7. REGORAFENIB INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section6.1.

7.1 Drug information

Regorafenib 40-mg tablets contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talk, titanium dioxide E171 (color index 77891), Macrogol/PEG 33350, lecithin (soy), iron oxide yellow – E172 (color index 77491), iron oxide red – E172.

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

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

Regorafenib will be provided by Bayer as 40-mg tablets, which are coated, not divisible, gray-orange-red, oval (length 16 mm, width 7 mm, thickness 4.9-5.6 mm), and 472 mg each in total weight. Tablets are in an immediate-release dosage form with rapid dissolution characteristics under the *in vitro* test conditions.

7.2 Ordering and accountability

All study drugs will be stored in Investigational Drug Services in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and/or institutional standard operating procedures.

7.3 Destruction and return

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

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

E-mail: Karen.marini@bayer.com
OR
Fax: 973-709-2193

OR

Mail: (VP of Medical Affairs named in contract) at
Bayer HealthCare Pharmaceuticals
6 West Belt
Wayne, NJ 07470

8. SPECIAL STUDIES

Archival tissue specimens that were collected at time of diagnosis may be requested and used for correspondence molecular analyses, including: EGFR pathway genes, VEGFRs, PDGFR, and C-Met.

8.1 Pathology Material

Tissue specimens will be analyzed for the mutational status of EGFR, K-RAS and B-RAF. All testing will be performed as done for clinical samples in the Molecular Pathology Laboratory at the University of Pittsburgh Medical Center (UPMC). Tissue specimens, including formalin fixed paraffin embedded (FFPE) tissue blocks, or cell blocks, with representative tumor tissue, preferably from resection or core biopsy specimens, will be obtained from the site where the diagnostic material was collected. If tumor tissue or cell blocks are not available, unstained slides (a minimum of 20) will be requested. DNA sample preparation from microdissected tumor areas will follow standard techniques for DNA extraction using DNeasy Blood & Tissue Kits (Qiagen, Inc). Detection and quantitation of mutations in codons 12, 13 and 61 of K-RAS, and detection of the hotspot transversion mutation T1799A that causes the amino acid substitution V600E in BRAF will be performed by pyrosequencing analyses using the PyroMark Q24 (Qiagen, Inc). PCR and sequencing methods will be used for detection of the E19del and L858R mutations in the EGFR gene. Expression levels of EGFR will also be evaluated by immunohistochemistry with the EGFR pharmDx™ Kit (Dako, Inc). VEGFR, PDGFR and C-Met analyses will be performed based on UPMC pathology standard methods.

Analysis of these samples may take place while the patient is receiving study treatment, but the results will not be communicated to the subject. The results will be used in the analysis of the final study data.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

There is a window of ±1 week available for scheduling treatment and/or procedures at the discretion of the Investigator/Sub-investigator. This applies also if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

	Screening	Day 1 (Cycles 1&2)	Day 8 (Cycles 1&2)	Day 15 (Cycles 1&2)	Day 22 (Cycles 1&2)	Day 1 (Cycle 3+)	End of Treatment[d]	Follow up[e]
History and Physical	X	X				X	X	
Weight	X	X				X	X	
Vital Signs[h]			X	X	X			
Performance Status	X	X	X	X	X	X	X	
Adverse Event Assessment	←	—	—	—	—	—	—	→
Con meds		X	X	X	X	X	X	
Urine protein/Creatinine	X							
Pregnancy test[a]	X							
Blood tests[b]	X	X	X	X	X	X	X	
PT/INR and PTT[c]	X							
CEA, CA19-9[i]		X				X	X	
Tumor Measurement (CT or MRI C/A/P)	X					X[f]	X	
Regorafenib[g]		X	X	X		X		

Archived Tissue Sample Collection	X							
Disease status and survival								X[e]

a. WOCBP only, 7 days prior to the start of study drug
b. Blood tests include: CBC with diff, platelets, Bilirubin, Alk Phos, AST, ALT, Total Protein, Albumin, Sodium, Potassium, Blood Glucose, Calcium, Phosphate, Magnesium, BUN/Creatinine, no need to repeat if done within 3 days of cycle 1 day 1.
c. PT/INR and PTT will be done for everyone at screening visit. For patients on anticoagulation therapy, it should be done weekly while on the study drug.
d. To occur 28 days (± 5 days) after the last dose of the study drug
e. The follow-up for survival will be every 3 months (+/- 4 weeks) by review of medical records, or direct contact patient contact.s.
f. Up to 3 days before day 1 of every odd cycle.
g. 3 weeks on 1 week off. Patient to keep a drug diary and return diary and pill bottle day 1 of every cycle.
h. If clinically significant toxicity exists then patient to see MD for physical exam.
i. CEA, CA19-9 to be obtained prior to the start of study drug.

Note: Starting day (day1) of the subsequent cycles may be delayed up to 1 week to accommodate the patients/physicians clinic needs.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect Measurement

For the purposes of this study, patients will be re-evaluated for response every 2 cycles(up to 3 days before day 1 of every odd cycle). In addition to a baseline scan, confirmatory scans should also be obtained following initial documentation of objective response.

Response and progression will be evaluated in this study using the 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.

10.1.1 Definitions

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

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.

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or as ≥ 10 mm with CT scan, MRI, or 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. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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 reproducibly 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.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination 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-hold scanning 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 it is not routinely 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.

10.1.4 Response Criteria

10.1.4.1 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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions).

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.

10.1.4.2 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: 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 Investigator).

10.1.4.3 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 Lesions	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		

10.1.5 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.

10.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.1.7 Response Review

All responses will be reviewed by PI and, simultaneous review of the patients' files and radiological images.

11. DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual

- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

11.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

11.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

11.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

11.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

11.6 Subject Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator, or

sub-investigator, will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

12. STATISTICAL CONSIDERATIONS

12.1 Data Analysis Plan

12.1.1 Primary objective

Evaluate the progression-free survival (PFS) of patients with advanced biliary cancer who had failed first-line chemotherapy when receiving regorafenib. The progression-free survival function will be estimated by the Kaplan-Meier method, with a 90% confidence interval. The estimated median PFS will be derived from the estimated progression free survival function. The null hypothesis that the median PFS is 2.0 months or less (see Justification of Design, below) will be tested using the two-sided 80% confidence interval around the median PFS. If the left side of the confidence interval does not include two months, the null hypothesis will be rejected (α=0.10).

12.1.2 Secondary objectives

- Overall response rate (ORR), including complete and partial response. The ORR at four months will be estimated with an exact 90% binomial confidence interval.
- Overall survival (OS). The overall survival function will be estimated by the Kaplan-Meier method, with a 90% confidence interval.
- DCR (disease control rate) as ORR plus stable disease (SD)
- Measurable changes in biomarkers (CA19-9 and CEA), in patients that were elevated at the time of registration. The means and standard deviation of both markers will be estimated at before and after treatment. The null hypothesis of no treatment effect will be tested using a paired-comparison t-test (α=0.10), or a rank sum test if there is evidence of significant non-normality in the differences.
- Evaluation of safety and associated toxicities. Toxicities will be tabulated by grade and type.

12.2 Justification of Design

The primary objective for this study is to evaluate the median progression-free survival (PFS) in patients with advanced or metastatic biliary tract carcinoma/cholangiocarcinoma treated with

regorafenib monotherapy. The monthly accrual is 2 patients, and it is assumed that accrual will require 19 months, and that the analysis will be performed 9 months after the last patient is put on study (that is, at month 28, patients who have not progressed will be treated as censored). A median PFS of 3.5 months or greater will be taken as evidence of activity in this patient population. The null hypothesis to be tested is that the median PFS is 2.0 months or lower. If the maximum of 37 patients is accrued, the study will have 83% power (using a one-sided test with α=0.10) if the alternative hypothesis that median PFS for patients in this population treated with regorafenib is at least 3.5 months is true.

12.3 Premature termination of the study

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

The investigator has the right to close at any time.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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