DANA FARBER/PARTNERS CANCER CARE

Study Title

Phase II Trial of Sorafenib in Combination with Modified FOLFOX in Patients with Advanced Hepatocellular Carcinoma

Study Drug
Sorafenib (Bayer/Onyx)
Oxaliplatin (Sanofi-aventis)

Support Provided By
Bayer/Onyx

Principle Investigator
Lipika Goyal, MD

Co-Investigators

Jill Allen, MD
Lawrence Blaszkowsky, MD
Jeffrey Clark, MD
David P. Ryan, MD
Eunice Kwak, MD
Janet Murphy, MD
Dushyant Sahani, MD
Rakesh Jain, PhD
Charles Fuchs, MD
Jeffrey Meyerhardt, MD
Robert J Mayer, MD
Peter Enzinger, MD
Matthew Kulke, MD
Thomas Abrams, MD
Brian Wolpin, MD

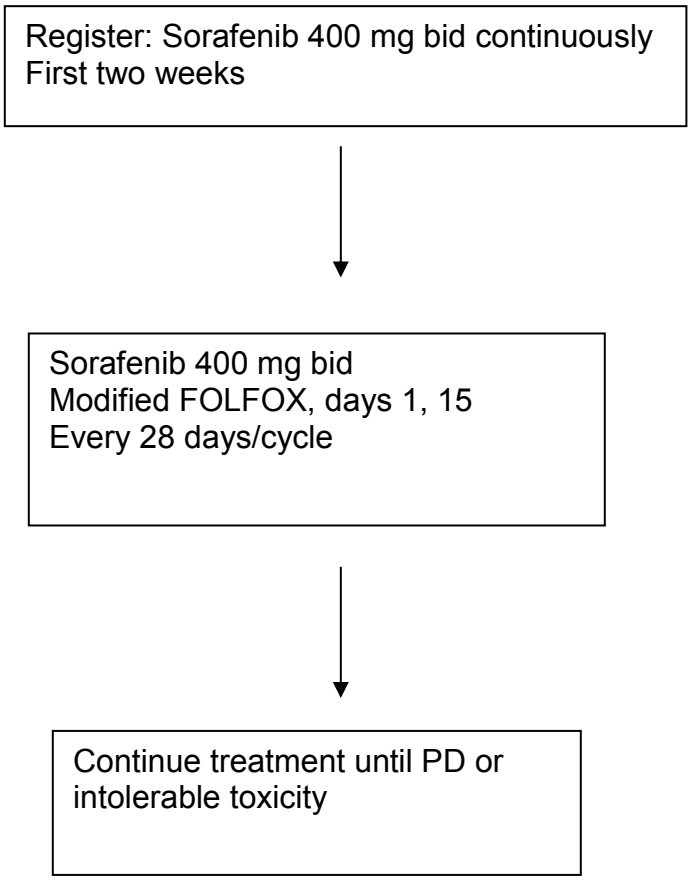
Research Coordinator
Susan Sheehan, RN
Eileen Regan, RN

NCT01775501

Protocol Version Date: 02/24/2015

TABLE OF CONTENTS

SCHEMA



Lead in Sorafenib alone: first two weeks

Sorefenib 400 mg bid.

Cycle 1 and beyond

Drugs	5-FU/LV	Oxaliplatin	Sorafenib
Treatment Dates	Days 1, 15	Days 1, 15	Days 1-28
Dosage	5-FUCI: 2400mg/m^2 total (1200mg/m^2/d on day 1 and 2) LV: 200mg/m^2	85 mg/m2	400 mg bid

Each cycle (cycle 1 and beyond) is defined as 28-day treatments.

Eligibility Criteria

Key Inclusion Criteria:

- Histologically confirmed advanced HCC
- No cirrhosis or Child-Pugh A (CTP score < 7) cirrhosis (See Appendix A)
- Barcelona Clinic Liver Cancer (BCLC) stage C, and those with BCLC-B stage who can not tolerate or failed TACE (See Appendix B)
- Patients must have measurable lesions
- Participants must have adequate organ and marrow function as defined below:

ANC	$\geq$ 1500/mm^3
Platelets	$\geq$ 100,000/mm^3
Hemoglobin	$\geq$ 10 g/dl
AST and ALT	$\leq$ 6 x upper limits of normal
Total bilirubin	$\leq$ 2.0 mg/dL
Renal function	Creatinine $\leq$ 2.0 mg/dL and/or creatinine clearance $\geq$ 50 ml/min

- No prior systemic regimens for HCC
- Patients with a prior history of liver directed therapy for their HCC (chemoembolization, radioembolization, bland embolization, radiation therapy, radiofrequency ablation, microwave ablation) can participate in the study if the liver-directed therapy was performed $\geq$ 4 weeks prior to their first dose of sorafenib and measurable lesions present outside of previously treated field
- Chronological age ≥ 18 years.
- ECOG performance status ≤ 1.
- Life expectancy ≥ 12 weeks.

- All patients must sign informed consent.

Key Exclusion Criteria:

- Child-Pugh B or C Cirrhosis (CTP score ≥ 7) (See Appendix A)
- The patient has either clinically apparent central nervous system metastases or carcinomatous meningitis
- The patient has a history of uncontrolled angina, arrhythmias, or congestive heart failure.
- The patient has a medical or psychiatric condition that constitutes an unacceptable risk for participation in this trial, in the judgment of the treating physician.
- The patient has received any investigational agents within 4 weeks prior to their first dose of sorafenib
- The patient is a woman who is pregnant or lactating. Both men and women of childbearing potential must be advised of the importance of using effective birth control measures during the course of the study.
- Patients with any previously untreated or concurrent cancer that is distinct in primary site or histology from HCC except cervical cancer in-situ (CIS), treated basal cell carcinoma (BCC), or superficial bladder tumor. Patients 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 the first dose of sorafenib except for local treatments for cervical CIS, BCC, and superficial bladder tumors.
- The patient has received previous sorafenib or FOLFOX treatment.

1.0 Objectives

1.1 Primary Objective

- To assess the time to progression (TTP) in patients with HCC treated FOLFOX-S.

1.2 Secondary Ojective

- To evaluate the tolerability and toxicities of FOLFOX-S regimen in this population of patients.
- To assess the response rate, the duration of response, median PFS, and median OS of FOLFOX-S in patients with HCC.

- To assess changes of angiogenic and inflammatory parameters with treatment of sorafenib.

2.0 Introduction

2.1 Disease Background

Hepatocellular cancer (HCC) is a common malignancy worldwide, with greater than 620,000 new cases reported annually, and accounts for 80-90% of primary liver cancers. The incidence of HCC is increasing and it now ranks as the 6th most common tumor worldwide. Due to its poor prognosis it is the 3rd most common cause of cancer-related death with the number of deaths (598,000) almost the same as the number of new cases. The majority of HCC cases develop in the presence of cirrhosis due to chronic liver disease mainly as a result of infection by hepatitis B virus (HBV) or hepatitis C virus (HCV) [1]. HBV is endemic in Southeast Asia and Africa, where the majority of HCC cases are concentrated. In the West, even though incidence rates are much lower, the number of HCC cases has been rising steadily since the 1960s and 1970s and are considered to be due to a rise in infection rates of HCV during that time [2] . In the last 20 years the incidence of HCC has doubled with a peak expected by 2020 [2].

Potentially curative therapies, such as surgical resection, liver transplant or other local treatments, result in survival rates of between 50-70% at 5 years for patients with early stage HCC [3]. However, despite advances in diagnostic techniques and increased surveillance, the majority of HCCs present with advanced, inoperable stages.

Untreated patients with intermediate stage HCC (multinodular asymptomatic tumors without an invasive pattern) have a median survival of 16 months. Treatment with transarterial chemoembolization (TACE) extends the median survival of this group of patients to approximately 19-20 months [3].

2.2 Systemic therapy for HCC

For patients with advanced stage HCC (defined as the presence of extrahepatic disease or vascular invasion), well preserved hepatic function and good performance status, systemic therapy with sorafenib or participation in clinical trials is the standard treatment.

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis by targeting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinases of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR-β) [4,5]. Encouraged by the strong rationale of its mechanism of action, promising preclinical data against hepatocellular carcinoma (HCC), and early evidence of antitumor activity from the phase II study [6], the international, phase 3, placebo-controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) trial was subsequently conducted. This study demonstrated improved overall survival (OS) and time to tumor progression (TTP) [7]. Median OS was 10.7 months in the sorafenib

group and 7.9 months in the placebo group (hazard ratio for the sorafenib group, 0.69; P<0.001). The median TTP was 5.5 months in the sorafenib group and 2.8 months in the placebo group (P<0.001). In another randomized phase III study conducted in Asia, sorafenib also demonstrated improved OS in patients with advanced HCC [8]. Overall survival was 6.5 months in the sorafenib group versus 4.2 months in the placebo group (hazard ratio for the sorafenib group, 0.68; P=0.014). These studies have led to the approval of sorafenib for the treatment of advanced HCC in the United States and many other countries around the world.

Although a large number of controlled and uncontrolled studies have been performed with most classes of chemotherapeutic agents, no single or combination chemotherapy is particularly effective in HCC. Despite the initial encouraging reports from Uganda using single-agent doxorubicin, subsequent studies have failed to confirm these data. In the largest study of doxorubicin in advanced hepatocellular carcinoma, no responses were noted among 109 patients. Among 475 patients who received doxorubicin in various studies, a 16% response rate was documented with a median survival of 3 to 4 months.

Other drugs such as cisplatin, 5-fluorouracil, mitoxantrone and etoposide have failed to demonstrate meaningful activity. Combination chemotherapy regimens have yielded similar response rates and median survivals. The response rate tends to be low and the response duration is short. More importantly, the survival benefit of systemic chemotherapy for HCC remains to be determined. As a result, there appears to be little justification in treating patients with advanced hepatocellular carcinoma with systemic chemotherapy outside of a clinical trial. The most impressive result of combination chemotherapy comes from a Hong Kong study using the combination of cisplatin, alpha-interferon, doxorubicin, and 5-FU (PIAF). This regimen produced a partial response rate of 26%. In a follow up phase III study comparing PIAF against doxorubicin, PIAF failed to demonstrate any survival benefits. Moreover, this regimen is associated with significant toxicity [9].

Recently, oxaliplatin based combination chemotherapy has demonstrated moderate activity in advanced HCC and acceptable toxicity profile. In phase II trial, the combination of gemcitabine and oxaliplatin (GEMOX) produced a response rate of 18% (95% confidence interval [CI]: 8-34) and a disease control rate of 76%. Median progression-free and overall survival were 6.3 months (95% CI: 4.3-10.1 months) and 11.5 months respectively (95% CI: 8.5-14.3 months) [10]. Oxaliplatin in combination with 5-FU/LV (FOLFOX) has also been tested in advanced HCC. Following the early experience in phase II study, the investigators from Asia conducted a randomized phase III trial. Patients with advanced HCC were randomized to receive either FOLFOX4 (n=183) or doxorubicin (N=174). Based on the presented data, in comparison with doxorubicin arm, FOLFOX4 demonstrated improved response rate (8.2% vs. 2.67%, p=0.0233), improved median progression free survival (PFS) (2.93 m vs. 1.77 m, p=0.0002), and a trend towards improved median overall survival (6.40 m vs. 4.97 m, p=0.0695). Toxicity profiles were comparable in both arms with the exception of more peripheral neuropathy in the FOLFOX4 arm [11].

2.3 Sorafenib

Preclinical pharmacology

Sorafenib is a multikinase inhibitor with activity against targets important in tumor cell proliferation including the serine/threonine kinases c-Raf and B-Raf (IC_{50} 6 and 25 nM respectively) and the receptor tyrosine kinase RET, Flt-3 and c-Kit (IC_{50} 47, 33 and 68 nM respectively) [5]. Sorafenib has potent activity against receptor tyrosine kinases important in tumor angiogenesis including the vascular endothelial growth factor receptor family (VEGFR1, -2, -3; IC_{50} 26, 90 and 20 respectively) and platelet derived growth factor-beta (PDGFR-β; IC_{50} 57 nM). In cellular mechanistic (on target) assays, sorafenib was found to be a potent inhibitor of VEGFR-2, VEGFR-3, PDGFR □□and Flt-3 receptor phosphorylation. The anti-tumor activity of sorafenib in vivo is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and on the anti-angiogenic activity of the compound [12]. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations, Raf/MEK/ERK signaling and induced apoptosis. Sorafenib has potent activity against human tumor xenograft model of hepatocellular carcinoma with tumor stabilization seen at moderate doses and partial tumor regressions observed at higher doses. For further information about preclinical pharmacology, please refer to the current version of IB.

Clinical experience

Clinical results in Phase I studies of sorafenib as a single agent were suggestive of a therapeutic effect in HCC and led to the design of a single arm Phase II study (10874), in which 137 subjects with advanced, inoperable HCC Child-Pugh classes A and B were treated [6]. The results of this study (median TTP of 5.5 months by independent assessment and median overall survival of 9.2 months), provided the basis for the randomized, placebo-controlled Phase III study in subjects with advanced HCC Child-Pugh class A (SHARP, Sorafenib HCC Assessment Randomized Protocol). This large (602 subjects) Phase III study was the first international, randomized, double-blind, placebo-controlled study to demonstrate a statistically significant and clinically meaningful improvement in OS in advanced HCC subjects treated with sorafenib over placebo [13]. Of the 299 sorafenib subjects valid for ITT analysis, the median OS was 10.7 months in the sorafenib group and 7.9 months in the 303 subjects randomized to the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $p<0.001$. The nominal alpha for this analysis was 0.0077 according to the pre-specified O'Brien-Fleming-type alpha spending function. Therefore, sorafenib had a statistically significant effect on prolonging overall survival. This significant survival benefit represented a 31% reduction in risk of death (or 44% improvement in OS) in subjects treated with sorafenib versus those treated with placebo.

As of 31 December 2009, over 10,000 cancer patients with various malignancies have been exposed to sorafenib either as single agent or in combination with other chemotherapeutic agents in Phase I/II/III studies. Sorafenib has been generally well tolerated at a dose of 400 mg po twice daily (bid). The most common drug related adverse events have included hand-foot skin reaction, diarrhea, fatigue, hypertension,

pain and rash. Grade 3 and 4 drug-related adverse events are uncommon. There was no evidence of cumulative toxicity and the majority of the adverse events were reversible.

Please refer to the IB for the complete list of observed adverse events seen in Phase III studies.

2.4 Clinical experience with Sorafenib + FOLFOX and Sorafenib + XELOX

The safety and efficacy of the combination of Sorafenib and FOLFOX was tested in the RESPECT trial, a Phase IIb placebo- controlled study of 198 patients with metastatic colorectal cancer. Patients were randomized to modified FOLFOX combined with either sorafenib 400mg po bid or placebo in the first-line setting. There was no significant difference in median PFS between the sorafenib and placebo groups (9.1 vs 8.7 months; HR 0.88, 95% CI 0.64–1.23) or time to progression. The grade 3 and 4 adverse events included neutropenia (sorafenib > placebo), peripheral neuropathy (placebo > sorafenib) and grade 3 hand–foot syndrome (20% with sorafenib vs 0% with placebo) (Tabernero, ESMO Abstract, 2011).

In patients with locally advanced or metastatic hepatocellular carcinoma, while the combination of sorafenib and FOLFOX has not been tested, the combination of sorafenib and XELOX (capecitabine and oxaliplatin) has been tested. In the Phase IIa SECOX trial, patients with advanced HCC who had received no prior systemic therapy received sorafenib 400mg po BID (days 1-14), Capecitabine 850mg/m2 po BID (days 1-7), and Oxaliplatin 85mg/m^2 (day 1) on 2 week cycles. The best response rate was 14%, and another 61% achieved stable disease. The median TTP was 7.1 months (1.7–19.9) and OS was 10.2 months (2.1–20.5). The three most common adverse reactions were hand-hoot-skin reaction (73%), diarrhea (69%), and and neutropenia (63%)[17]. The efficacy data was promising in this trial, but the tolerability of the regimen was poor, likely due to the combination of sorafenib and capecitabine.

2.5 Study Rationale

HCC are commonly viewed as highly vascular tumors [15]. Vascular endothelial growth factor (VEGF) is a potent angiogenesis stimulator and an important regulator in pathological angiogenesis. Increased levels of VEGF have been found in tumor and serum of patients with HCC. Increased VEGF expression has been associated with inferior survival in HCC. Thus, inhibition of VEGF and its receptor is a logical target in the treatment of patients with HCC. Sorafenib (S) has emerged as the new standard treatment for patients with advanced HCC based on the improvement of overall survival benefits. However, the benefits of sorafenib are still modest. Combining doxorubicin with sorafenib has shown encouraging results in comparison with doxorubicin with placebo in a randomized phase II study [16]. Median TTP was 6.4 months in the sorafenib-doxorubicin group (95% confidence interval [CI], 4.8-9.2), and 2.8 months (95% CI, 1.6-5) in the doxorubicin-placebo monotherapy group (P = .02). Median OS

was 13.7 months (95% CI, 8.9-not reached) and 6.5 months (95% CI, 4.5-9.9; P = .006). FOLFOX has shown more favorable efficacy results when compared with doxorubicin (Improved RR and PFS and a trend of OS improvement) in a randomized phase III study conducted in Asia as discussed in Section 2.2.

In this study, we will examine the efficacy and tolerability of combining FOLFOX with sorafenib. As a multitargeted tyrosine kinase inhibitor with antiangiogenic activity, sorafenib may enhance chemotherapy-induced tumor kill by the destruction of tumor blood vessel as well as by inducing "normalization" of tumor vasculature with improved delivery of therapeutics. During the first 2 weeks of treatment with sorafenib alone, we will also examine changes induced by sorafenib 1) in plasma angiogenic and inflammatory markers with serum biomarkers and 2) specific changes in the tumor and surrounding non-cancer liver tissues with optional on-treatment biopsies.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

- Histologically confirmed advanced HCC
- No cirrhosis or Child-Pugh A (CTP score < 7) cirrhosis (See Appendix A)
- Barcelona Clinic Liver Cancer (BCLC) stage C, and those with BCLC-B Stage who cannot tolerate or failed TACE (See Appendix B)
- Patients must have measurable lesions
- All patients must have adequate hepatic function: total bilirubin ≤ 2.0 mg/dl; AST and ALT ≤ 6x upper limits of normal.
- Adequate renal function: Serum creatinine ≤ 2.0 mg/dl.
- Adequate bone marrow function defined as:
    - Absolute neutrophil count ≥ 1,500/mm3
    - Platelets ≥ 100,000mm3
    - Hemoglobin ≥ 10 g/dl
- No prior systemic regimens for HCC
- Patients with a prior history of liver directed therapy for their HCC (chemoembolization, radioembolization, bland embolization, radiation therapy, radiofrequency ablation, microwave ablation) can participate in the study if the liver-directed therapy was performed more than 4 weeks prior to their first dose of sorafenib and measurable lesions present outside of previously treated field
- Chronological age ≥ 18 years.

- ECOG performance status ≤ 1
- Life expectancy ≥ 12 weeks
- 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).
- Subject must be able to swallow and retain oral medication.
- All patients must sign informed consent.

3.2 Exclusion Criteria

- The patient has either clinically apparent central nervous system metastases or carcinomatous meningitis
- The patient is a woman who is pregnant or lactating. 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. All patients (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 30 days 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.
- 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.
    - QTc > 500 ms
    - Unstable angina (anginal 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.
- Subject with any pulmonary hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 2 or higher within 4 weeks before enrollment; any other hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 3 or higher within 4 weeks before enrollment.
- Presence of a non-healing wound, non-healing ulcer, or bone fracture.
- History of organ allograft. (including corneal transplant).
- Any malabsorption condition.

- Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.
- Uncontrolled ascites defined as not easily controlled by stable doses of diuretics.
- Known human immunodeficiency virus (HIV) infection.
- The patient has a medical or psychiatric condition that constitutes an unacceptable risk for participation in this trial, in the judgment of the treating physician.
- The patient has received any investigational agents within 4 weeks prior to their first dose of sorafenib.
- ECOG status of ≥ 2
- Child-Pugh B or C cirrhosis (CTP score ≥ 7) (See Appendix A)
- CLIP score >3 (See Appendix A) Inability to comply with study and/or follow-up procedures
- Subjects with any previously untreated or concurrent cancer that is distinct in primarysite or histology from HCC 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 the first dose of sorafenib except for local treatments for cervical CIS, BCC, and superficial bladder tumors.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications

Excluded therapies and medications, previous and concomitant

- Concurrent systemic and local anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than sorafenib.
- Prior use of sorafenib, oxaliplatin, or 5FU.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Major surgery within 30 days prior to start of study drug. For patients who had port-a-cath placement, they should have the port-a-cath placement at least one week prior the initiation of FOLFOX.
- Concurrent use of Aspirin > 100 mg daily

- Concurrent use of drugs that are known potent CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.
    - However, prophylactic anticoagulation as described below is allowed:
        - Low dose warfarin (1 mg orally, once daily) with PT-INR ≤ 1.5 x ULN is permitted. Infrequent bleeding or elevations in PT-INR have been reported in some subjects taking warfarin while on sorafenib or capecitabine therapy. Therefore, subjects taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
        - Prophylactic doses of heparin.

4.0 Registration Procedures

General Guidelines for DF/HCC and DF/PCC Institutions

All participants will be registered by the DF/HCC Quality Assurance Office for Clinical Trials (QACT). Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A designated member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Once registered, any issues that would cause treatment delays should be discussed with the Principal Investigator.

If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed by the study coordinator.

Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. For phase II participants, include stratification information. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.

3. Fax the eligibility checklist(s) and all pages of the consent form to the QACT at [redacted]

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable (Phase 2 part of the study). The randomization tables will be designed by the study statistician.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration and to the research pharmacist immediately following the registration and/or randomization.

5.0 STUDY DESIGN

5.1Treatment Plan

5.1.1 Single arm, open label, phase II study

5.1.2Dosing schedule

Treatment will be administered on an outpatient basis. Expected adverse events and appropriate dose modifications for sorafenib, 5-FU, oxaliplatin are as described in Section 6.0. No investigational or commercial agents of therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be treated as below:

Register:

Sorafenib 400 mg bid →	Sorafenib 400 mg bid →	continue treatment
First two weeks	modified folfox, days 1, 15	until PD or intolerable toxiity

Every 28 days/cycle

For first two weeks, sorafenib will be given alone.

Cycle 1 and beyond:

Sorafenib 400 mg bid + modified FOLFOX (Oxaliplatin 85 mg/m2 followed by leucovorin 200 mg/m^2, followed by infusional 5-FU at 1200 mg/m^2/d on Days 1 and 2 (2400 mg/m^2 total over 46 hours) repeated every 14 days for each cycle.

Oxaliplatin will be delivered at 85 mg/m^2as a 2-hour infusion on day 1 and day 15 of every cycle.

Drugs	5-FU/LV	Oxaliplatin	Sorafenib
Treatment dates	Days 1,15	Days 1,15	Daily (days 1-28)
Dosage	LV: 200 mg/m2 5-FUCI: 2400 mg/m^2 total (1200mg/m^2/d on day 1 and 2)	85 mg/m2	400 mg bid

Lead-in sorafenib alone treatment: first 2 weeks.

Each cycle is defined as 28-day treatments.

5.1.3 Estimated number of patients

40 patients with advanced HCC

5.1.4Estimated rate of accrual

2-3 patients each month

5.1.5.Estimated date of study completion

Estimated date of study completion is July 2013 with an estimated start date of July 2012

5.1.6Duration of therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

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

5.2 CLINICAL AND LABORATORY EVALUATIONS

5.2.1 Pre-Treatment Evaluations

Signed and informed consent should be obtained prior to specific protocol testing and evaluation. The following evaluations must be performed prior to each patient's first dose of sorafenib:

5.2.1.1 Evaluations that must be performed within 1 week prior to the first dose of sorafenib:

- Pregnancy test (serum or urine) for women of childbearing potential within 7 days prior to initiation of therapy.

5.2.1.2 Evaluations that must be performed within 2 weeks prior to the first dose of sorafenib:

- Medical history
- Physical examination, including vital signs, height, weight, performance status.
- Hematology: complete blood count (CBC) with differential.
- Serum Chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), SGPT (ALT), calcium, phosphorus, amylase, lipase, and AFP.
- PT/INR
- Hepatitis B surface antigen, core antibody, and surface antibody, and Hepatitis C antibody must be obtained within 120 days of study enrollment.

Urinalysis: urine dipstick for protein. Patients with a positive dipstick for urine protein (reading of 2+ or greater) will then undergo a 24 hour urine collection for protein.

*If the screening labs have been completed within 7 days of Day 1 of the lead-in period, these labs do not need to be repeated. However, baseline correlative studies need to be drawn on Day 1 of the lead-in period.

5.2.1.3 Evaluations that must be performed within 3 weeks prior to the first dose of sorafenib:

- EKG

- Imaging: Baseline radiologic evaluation of tumor burden by chest/abdomen/pelvis CT scan. MRI of the liver can be used if patients have an IV contrast allergy or the CT scan is suboptimal based on the physician's judgment.

5.2.2 Evaluations During Treatment

- Monitor CBC and selected chemistries (Glucose, BUN, Creatinine, ALT, AST, ALKP, total bilirubin, calcium, phosphorus, LDH, protein, albumin) weekly during the first 5 weeks of therapy (during the initial two weeks of sorafenib treatment and the first 3 weeks of Cycle 1 of FOLFOX-sorafenib) and every two weeks after that. Urinalysis and AFP will be performed prior to each cycle.
- Imaging: Radiologic evaluation (CT or MRI scan) by RECIST 1.1 criteria will be performed at the end of cycle 2 of FOLFOX-sorafenib and every 2 cycles thereafter.

All non-radiological assessments must be performed prior to administration of any study medication. All study assessments should be done within +/- 3 days of the protocol-specified date, unless otherwise noted.
All radiological assessments should be done within +/7 days of the protocol specified date, unless otherwise noted.

5.2.3 Post-Treatment Evaluations

- All patients will be evaluated by history and physical examination, including vital signs, weight, and performance status, CBC with differential, chemistries, and reassessment of tumor at the end of treatment.
- Female patients of childbearing potential will be evaluated with a repeat pregnancy test at end of treatment visit.
- All sites of tumor progression and metastasis will be recorded.
- Progression-free and overall survival will be determined.

5.2.4 Correlative Studies

- Only patients getting their treatment at MGH will be eligible for the correlative studies given that all samples need to be processed at the Steele Lab at MGH.

- BASELINE AND ON-TREATMENT PLASMA STUDIES (see Appendix C for details): Circulating endothelial cells and plasma levels of growth factors will be assessed:
    - On Day 1 (prior to the first dose of sorafenib) and Day 3 of lead-in phase
    - On C1D1, C1D15, and C1D29 of FOLFOX-Sorafenib. The Day 3 correlative can be drawn on Day 3, 4, or 5. The Day 15 correlative can be drawn on Day 14, 15, or 16. The Day 29 correlative can be drawn on Day 27, 28, or 29.
    - At the time of progression if available

- ON-TREATMENT OPTIONAL BIOPSY (see Appendix D for details): All patients enrolled on this trial are required to have a baseline diagnostic biopsy for histological confirmation of HCC. To be considered for the optional posttreatment tumor biopsy, the patient must have adequate tissue on their baseline biopsy (i.e. core biopsy) to have all necessary correlative studies run on the sample. The optional posttreatment tumor biopsy will be obtained any time from Day 10 to Day 14 of the lead-in phase in patients who consent to a posttreatment tumor biopsy (n=6-12).

6.0 DOSE MODIFICATION / TOXICITY MANAGEMENT

Study drug treatment will be modified in the event of certain adverse events, as shown in the tables below.

- Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption of FOLFOX is 6 weeks (the holding of 3 consecutive doses) and of Sorafenib is 3 weeks If the patient needs to stop FOLFOX due to toxicity, they can stay on study as long as they continue with Sorafenib. If the patient needs to stop Sorafenib due to toxicity, they can stay on the study as long as they continue FOLFOX. If they need to stop both FOLFOX and Sorafenib for longer than the above time limits, they must be taken off the study and the Principle Investigator must be notified.
- Doses of chemotherapy that have been reduced will not be re-escalated.
- No held doses of Sorafenib or FOLFOX will be made up. If a patient misses a dose for toxicity, the patient will proceed to the next treatment day or cycle as scheduled.

6.1 Expected Adverse Events – 5-FU

Nausea, vomiting (mild); ileus, stomatitis (5-8 days after treatment initiation); gastric ulceration; myelosuppression: leukopenia, granulocytopenia (9-14 days); thrombocytopenia (7-14days); alopecia; loss of nails; hyperpigmentation; photosensitivity; maculopapular rash; palmar-plantar erythrodysethesias (42-82% receiving continuous infusion); CNS effects: disorientation, confusion (rare); cardiotoxicity: MI, angina, asymptomatic S-T changes (68%); rare ocular effects.

6.2 Oxaliplatin

In the second line therapy for metastatic colorectal cancer registration trial of oxaliplatin, the following adverse reactions were reported to occur in greater than or equal to 5% of all patients.

	Oxaliplatin		Oxaliplatin + 5-FU/LV	
Adverse Event	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Fatigue	52 %	9 %	68 %	7 %
Diarrhea	46	4	67	11
Nausea	64	4	65	11
Neuropathy Acute Persistent	76 65 43	7 5 3	73 56 48	7 2 6
Vomiting	37	4	40	9
Stomatitis	14	0	37	3
Abdominal pain	31	7	33	4
Fever	25	1	29	1
Anorexia	20	2	29	3
Dyspnea	13	7	20	4
Back pain	11	0	19	3
Coughing	11	0	19	1
Edema	10	1	15	1
Pain	14	3	15	2
Injection site reaction	9	0	10	3
Thrombo-embolism	2	1	9	8
Hypokalemia	3	2	9	4
Dehydration	5	3	8	3
Chest pain	5	1	8	1
Febrile neutropenia	0	0	6	6
GERD	1	0	5	2
	Oxaliplatin		Oxaliplatin + 5-FU/LV	
Adverse Event	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Constipation	31	<1	32	<1
Headache	13	<1	17	<1
Rhinitis	6	<1	15	<1
Dyspepsia	7	<1	14	<1
Taste Perversion	5	<1	13	<1

Dizziness	7	<1	13	<1
Hand-foot syndrome	1	<1	11	<1
Flushing	3	<1	10	<1
Peripheral edema	5	<1	10	<1
Allergic reaction	3	<1	10	<1
Arthralgia	7	<1	10	<1
Upper resp. tract infect.	7	<1	10	<1
Pharyngitis	2	<1	9	<1
Rash	5	<1	9	<1
Insomnia	11	<1	9	<1
Epistaxis	2	<1	9	<1
Mucositis	2	<1	7	<1
Alopecia	3	<1	7	<1
Abnormal lacrimation	1	<1	7	<1
Rigors	9	<1	7	<1
Hematuria	0	<1	6	<1
Dysuria	1	<1	6	<1
Hiccup	2	<1	5	<1
Flatulence	3	<1	5	<1

6.3 Dose Modification of 5-FU and Oxaliplatin

6.3.1 Toxicity will be evaluated weekly during the sorafenib lead-in period, weekly during the first 3 weeks of cycle 1 of FOLFOX-Sorafenib, and then once every two weeks for subsequent cycles. Dose modifications based on significant weight changes can be made in accordance to institutional practice.

6.3.2 Hematologic Toxicity

- CBC will be obtained on days 1 and 15 of each cycle.
- Patient must have ANC > 1000 and platelets > 75,000 in order to treat on any given treatment day.

C1D1 dosing AND subsequent Day 1 and Day 15 dosing if previous dose was given:

ANC	Platelets	%Previous dose 5-FU/LV	%Previous dose Oxaliplatin
>1000 and	>75,000	100	100

≤1000	≤75,000	HOLD dose and reassess in 2 weeks	HOLD dose and reassess in 2 weeks
≤500	≤50,000	HOLD dose and reassess in 2 weeks	HOLD dose and reassess in 2 weeks

Day 1 and 15 dosing if the immediate previous Day 1 or 15 dose was HELD:

ANC	Platelets	%Previous dose 5-FU/LV	%Previous dose Oxali
>1000 and	>75,000	75% of previous dose if either ANC was 501-1000 or Plts were 51,000-75,000 50% of previous dose if either ANC was ≤500 or Plts were ≤50,000	75% of previous dose if either ANC was 501-1000 or Plts were 51,000-75,000 50% of previous dose if either ANC was ≤500 or Plts were ≤50,000
≤1000 or	≤75,000	HOLD dose and reassess in 2 weeks	HOLD dose and reassess in 2 weeks
≤500 or	≤50,000	HOLD dose and reassess in 2 weeks	HOLD dose and reassess in 2 weeks

If the patient requires two consecutive doses of FOLFOX to be held for hematologic toxicity, the patient should get 50% of the previous dose of FOLFOX if they meet criteria for treatment on the next scheduled treatment day.

In addition, at any time during a cycle, if the patient experienced 1) febrile neutropenia or 2) any Grade 3 or higher hematologic toxicity (excluding thrombocytopenia and neutropenia, which will be addressed using the tables above) while on FOLFOX, then 5-FU and Oxaliplatin should be held until the toxicity resolves to <Grade 2. When the patient meets treatment criteria, the 5-FU and Oxaliplatin should be resumed at 75% of most recent dose for all subsequent doses.

Doses of chemotherapy that have been reduced will not be re-escalated. A maximum of 4 dose reductions are allowed for 5-FU and Oxaliplatin (with the minimum allowed dose of 5-FU being 380 mg/m2/day and the minimum allowed dose for oxaliplatin being 27 mg/m2).

No held doses will be made up. If a patient misses a dose for toxicity, the patient will proceed to the next treatment day or cycle as scheduled.

If the FOLFOX is held for > 6 weeks (i.e. three consecutive doses of FOLFOX are held), FOLFOX will be permanently discontinued, and the patient can remain on the study as long as they are receiving Sorafenib.

6.3.3 Non-Hematologic Toxicity

6.3.3.1 Diarrhea

Anti-diarrheal agents should be prescribed for diarrhea. If greater than or equal to Grade 3 uncontrolled diarrhea despite maximal antidiarrheal therapy, temporarily discontinue both chemotherapy and sorafenib. Resume chemotherapy when symptoms have subsided to Grade 1 toxicity or less. Resume with 5-FU and Oxaliplatin at 75% of the previous dose. Resume sorafenib at one dose reduction.

6.3.3.2 Nausea, Vomiting

For Grade 3 to 4 nausea/vomiting that remains uncontrolled despite maximal antiemetic therapy, temporarily discontinue both chemotherapy and sorafenib. Maximal antiemetic therapy includes using such agents as 5-HT3 receptor antagonists, corticosteroids, and benzodiazepines, where indicated. Resume chemotherapy when symptoms have subsided to Grade 1 toxicity or less. Resume with 5-FU and oxaliplatin at 75% of the previous dose. Sorafenib may be resumed at full dose.

6.3.3.3 Melena and Hematemesis

If melena or hematemesis occur during therapy, sorafenib and chemotherapy should be held for Grade 1 toxicities until they resolve. For patients who develop Grade 3 or 4 toxicities, therapy should be discontinued and the Principal Investigator notified.

6.3.3.4 Neurologic Toxicity

Neurological toxicity has been observed in patients treated with oxaliplatin. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and peri-oral region. Patients treated with oxaliplatin in this study will be counseled to avoid cold drinks and exposure to cold water or air, especially 3-5 days following oxaliplatin administration. Dose adjustments for neurological toxicity will be based on the following table.

	Duration of Toxicity		
Neurological Toxicity	**≤7 days**	**>7 days**	**Persistent[A]**

Paresthesias/dysesthesias[B] that do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias[B] interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	Decrease dose by 50%
Paresthesias/dysesthesias[B] With pain or with functional Impairment that also Interfere with ADL (Grade 3)	No change	Decrease dose by 50%	discontinue oxaliplatin
Severe paresthesias/ dysesthesias[B] that are disabling or life-threatening (Grade 4)	Withdraw from study	Withdraw from study	discontinue oxaliplatin
ACUTE (during or after the 2 hour infusion) laryngopharyngeal dysesthesias (also see below)	Increase duration of future infusions to 6 hours[C]	Increase duration of future infusions to 6 hours[C]	Increase duration of future infusions to 6 hours[C]

[A] Not resolved by the beginning of the next cycle
[B] May be cold-induced
[C] May also be pretreated with benzodiazepines

Note on laryngopharyngeal dysesthesia: a loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm) has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold. Should a patient develop laryngopharyngeal dysesthesia, the patient's oxygen saturation will be evaluated via a pulse oximeter, and, if normal, an anxiolytic agent or benzodiazepine will be given and the patient should be observed in clinic until the episode has resolved. The infusion may be continued at 1/3 the rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion).

6.3.3.5 Dose Modifications for Other Non-Hematologic Toxicity

CTC Grade	Action	5-FU, % of Previous Dose	Oxaliplatin, % of Previous Dose
1	Continue therapy	100	100
2	Continue therapy	100	100
3	Resume when toxicity <= Grade 1	75[1, 3]	75[2, 3]
4	Resume when toxicity <= Grade 1	50[1, 3]	50[2, 3]

[1]See section 6.4.4 for dose reductions of 5-FU for Hand-Foot-Skin Reaction.
[2]No Dose reduction of Oxaliplatin for Grade 3 or 4 Hand-Foot-Skin Reaction.
[3]No dose reduction of 5-FU or Oxaliplatin need to be made for asymptomatic Grade 3 or 4 Amylase or Lipase elevation.

Pertains to treatment-related toxicity, not including diarrhea, nausea/vomiting, melena/hematemesis, neurologic toxicity (see above). Sorafenib dose should be adjusted as per the table in Section 6.4.1. For hematologic toxicity, see Section 6.3.2.

Doses of chemotherapy that have been reduced will not be re-escalated. Patients who do not recover to Grade 1 within 6 weeks will go off study.

6.4 Dose Modification for Sorafenib

Expected adverse events from sorafenib: diarrhea (43%), increased lipase (41%), increased amylase (30%), nausea (23%), anorexia (16%), vomiting (16%), and constipation (15%), rash/desquamation (40%), hand-foot skin reaction (30%), alopecia (27%), pruritus (19%), and dry skin (11%), hyperthyroidism, hypertension (17%), angioedema, and congestive heart failure, hypoalbuminemia (49%), hemorrhage (15%) (i.e., gastrointestinal, respiratory tract and rarely cerebral hemorrhage), dyspnea (14%) and cough (13%), hypocalcemia (20%), and hypophosphatemia (40%).

6.4.1 Dose Reduction Levels

The starting dose of sorafenib is 400 mg twice a day. Study medication will be administered daily on a continuous basis.

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.

Dose modification levels for sorafenib	
Dose	**Sorafenib**
Starting Dose	400 mg twice daily
1st Dose Reduction Level	400 mg once daily
2nd Dose Reduction Level	200 mg once daily

6.4.2 Dose modification of sorafenib for hematologic toxicities

Recommended Dose Modification of sorafenib for Hematologic Toxicities

Toxicity	ANC(x 10^9/L)	Hemoglobin (g/dL)	Platelets (x 10^9/L)	Sorafenib
Grade 1	<LLN-1.5	< LLN – 10.0	<LLN-75	Treat on time No change
Grade 2	≥ 1.0 to < 1.5	< 10.0 – 8.0	≥ 50 to < 75	Treat on time No change
Grade 3	≥ 0.5 to < 1.0	< 8.0 – 6.5	≥ 25 to < 50	Treat on time Reduce by one dose level
Grade 4	< 0.5	Life-threatening consequence; urgent intervention indicated	<25	Delay sorafenib until toxicity resolves to Grade 2 or less then Reduce by two dose levels[1]
Febrile Neutropenia				Sorafenib held until toxicity has resolved to Grade 2 or less; when sorafenib is restarted, reduce by one dose level[2]

ANC - absolute neutrophil count

[1]If the patient is at the first dose reduction level (Sorafenib 400mg po QD) or the second dose reduction level (Sorafenib 200mg po QD) already, Sorafenib will be discontinued,

[2] If the patient is at the second dose reduction level (Sorafenib 200mg po QD) already, Sorafenib will be discontinued,

- If no recovery after 21 day delay, treatment should be permanently discontinued.

6.4.3 Dose modification for non-hematologic toxicities[1]

Recommended dose modification for non-hematologic toxicity (excluding hypertension and hand foot skin reaction, diarrhea and fatigue.		
• **Grade**	• **Dose Interruption**	• **Dose Modification**
• Grade 0-2	Treat on time	No Change
• Grade 3	Interrupt until ≤Grade 2	DECREASE one dose level
• Grade 4	OFF protocol therapy	OFF protocol therapy
• If no recovery after 21 day delay, treatment will be discontinued unless subject is deriving clinical benefit		

[1]For sorafenib dose reductions for diarrhea, nausea, and vomiting, see sections 6.3.4.1 and 6.3.4.2.

For HFSR, sorafenib and 5-FU should be both reduced;
For diarrhea, sorafenib, 5-FU and oxaliplatin should all be reduced;
For fatigue, sorafenib, 5-FU and oxaliplatin should all be reduced.

6.4.4 **Hand-foot-skin reaction: will dose reduce both sorafenib and 5-FU CI**

Recommended dose modification for hand foot skin reaction		
Toxicity Grade		**Suggested dose modification**
Grade 1	Any occurrence	Maintain dose level and consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Maintain dose level and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	Hold Sorafenib until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level[1]
	3rd occurrence	Hold Sorafenib until resolved to Grade 0-1 When resuming treatment, decrease dose by two dose levels[2]
	4th occurrence	Discontinue Sorafenib permanently
Grade 3	1st occurrence	Hold Sorafenib and 5-FU until resolved to Grade 0-1 When resuming treatment, decrease Sorafenib dose by one dose level[1] and decrease 5-FU by 25%
	2nd occurrence	Hold Sorafenib and 5-FU until resolved to Grade 0-1 When resuming treatment, decrease Sorafenib dose by one dose level[1] and decrease 5-FU by 50%
	3rd occurrence	Discontinue treatment permanently

[1] If the patient is at the second dose reduction level (Sorafenib 200mg po QD) already, Sorafenib will be discontinued,
[2]If the patient is at the first dose reduction level (Sorafenib 400mg po QD) or the second dose reduction level (Sorafenib 200mg po QD) already, Sorafenib will be discontinued,

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.

Recommended Prevention/Management Strategies for Skin Toxicities Consistent with Hand-Foot-Skin-Reaction	
Toxicity Grade	**Practical Prevention / Management Strategies for HFSR**
Grade 0 (Preventive strategies)	Maintain frequent contact with trial physician to ensure early diagnosis of HFSR. Practical prevention strategies Pedicure[a] for subjects with pre-existing hyperkeratosis. Subjects should avoid hot water, and clothing or activities

	that can cause friction on the skin. Moisturizing cream should be applied sparingly. Padded gloves and open shoes with padded soles should be worn to relieve pressure points.
Grade 1 Any occurrence	Continue preventive strategies and in addition: Soak hands in cool water. Apply petroleum jelly to moist skin. In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards.
Grade 2 Any occurrence or **Grade 3** Any occurrence	Continue supportive/management measures and add analgesic(s) for pain.
a: Pedicure should be done by a podiatrist.	

6.4.5 Treatment-emergent hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will undergo brief physical examinations, including blood pressure monitoring, on a weekly basis through the first 5 weeks of therapy. Thereafter, blood pressure will be monitored on Day 1 and 15 of each cycle.

Blood pressure measurements that are out of the normal range must be reported by the treating physician. Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg, or a 20 mm Hg increase in diastolic pressure if the previous measurement was within normal limits. The dose-modification schedule to be followed in the event of treatment-emergent hypertension is outlined below. The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on site-specific treatment guidelines as applicable. All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the patient's records.

Management of Treatment-Emergent Hypertension	
Grade of Event (NCI-CTCAE v4.0)	Management/ Next Dose
Grade 1	Consider increasing blood pressure monitoring. Continue sorafenib dosing as scheduled.
Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Begin anti-hypertensive therapy. Continue sorafenib dosing as scheduled.
Grade 2 (symptomatic/persistent) **OR** **Grade 2** symptomatic increase by > 20 mm Hg (diastolic) or to systolic BP	Sorafenib should be held[a] until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib is restarted, reduce by 1 dose level.[b]

Management of Treatment-Emergent Hypertension	
> 140 mm Hg or diastolic BP>90 mm HG if previously within normal limits **OR** **Grade 3**	If diastolic blood pressure is not controlled (< 90 mm Hg) on anti-hypertensive therapy, reduce another dose level.[b]
Grade 4	Discontinue sorafenib
a: Subjects requiring a delay of > 21 days should discontinue sorafenib unless, in the opinion of the treating physician, the subject may benefit from continued treatment. b: Subjects requiring dose reductions beyond 200 mg every day, should discontinue sorafenib.	

Doses of sorafenib that have been reduced for any reason will not be re-escalated. For treatment-related non-hematologic toxicities, patients who do not recover to Grade 1 toxicity within 3 weeks will go off Sorafenib for the duration of the study, but they can continue with FOLFOX if they continue to meet treatment criteria for FOLFOX.

6.5 Criteria for Treatment Discontinuation

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

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

7.0 STUDY MEDICATION

Commercial supply of all drugs will be used.

7.1 Sorafenib

The sorafenib tablets are manufactured by Bayer HealthCare AG, Germany.

The 200 mg tablet formulation contains sorafenib and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, magnesium stearate. The tablets have a film coating consisting of hypromellose, polyethylene glycol, titanium dioxide, and red ferric oxide. The formulation is presented as an immediate release (IR) dosage form, (i.e., the active

ingredient is allowed to completely dissolve under *in vitro* test conditions within a short period of time with no intention of delaying or prolonging dissolution The tablets have a salmon color in appearance, weigh approximately 350 mg each, and are 10 mm round in shape.

The active compound of sorafenib is 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylicacidmethylamide-4 methylbenzenesulfonate, and its molecular weight is 637 Daltons.

Sorafenib will be given orally at two tablets (200 mgx2) twice daily.
Subjects will be instructed on the proper administration of sorafenib. Sorafenib tablets should be taken 12 hours apart, at approximately the same time each morning and evening. Sorafenib tablets should be taken without food, at least 1 hour before or at least 2 hours after a meal, and with up to 240 mL (approximately 1 cup or 8 oz) of water. Consumption of grapefruit and grapefruit juice should be avoided while receiving study drug. Missed/vomited doses will not be made up.

7.2 5-FU

7.2.1Description

5-FU is one of the most important drugs used in medical oncology today. It is the key antitumor agent for colorectal carcinoma and is commonly employed in other malignancies, including breast cancer, throat cancer, and upper gastrointestinal malignancies. 5-FU belongs to the class of 5-fluoropyrimidines. It is an analogue of the pyrimidine uracil. At the carbon 5 (C-5) position, a fluorine atom is substituted in place of hydrogen. The fluorine atom does not impede the activation of 5-FU to the nucleotide level, which is essential to the antitumor activity of these compounds.

Although the precise antitumor mechanism of 5-FU remains uncertain, two pathways are thought to be central to its activity in certain cancers. First, 5-FU is metabolized to 5-fluoro-uridine triphosphate (FUTP) and is incorporated into RNA. This interferes with RNA synthesis and function. Second, 5-FU is metabolized to 5-fluoro-2'-deoxyuridylate (FdUMP) and acts as a quasi-substrate for the enzyme thymidylate synthase in the conversion of dUMP and methyltetrahydrofolate to dTMP and dihydrofolate. This in turn reduces pools of available thymidylate synthase, leading to the depletion of dTMP and dTTP and the accumulation of dUMP and dUTP, thereby inhibiting DNA synthesis.

7.2.2Drug Administration

5-FU will be prepared per institutional standard and administered as a continuous IV infusion over 46 hours through a central venous port-a-cath on days 1 and 15 . An ambulatory infusion pump will be given to each patient, and the chemotherapy cartridge will be changed every 2 weeks for each new administration of 5FU.

7.2.3 Storage and Stability

Store at room temperature and protect from light. Dark yellow color indicates decomposition. Inspect for precipitate; if found, agitate or gently heat in water bath. Filter ampules with aspiration needle (5 mcm). Compatible with D5W, 0.9% NaCl, D5LR. Stable in polypropylene syringes. Stable in PVC reservoirs for infusion pump for 12 days. May adsorb to glass surfaces. Stable in cellulose nitrate/acetate ester or Teflon filters.

7.3 Oxaliplatin

7.3.1Description

Oxaliplatin is a third-generation platinum compound with activity in colorectal cancer. Its chemical name is trans-1-diaminocyclohexane oxalaplatinum or cis-[oxalato(trans-1-1,2-diaminocyclohexane) platinum (II)].

Oxaliplatin is a white crystalline powder, slightly soluble in water and very slightly soluble in methanol but insoluble in ethanol or acetone. The pH of an aqueous solution of 2 mg/mL is between 4.8 and 5.7.

Oxaliplatin is presented in the form of a freeze-dried powder for infusion in vials containing 50 mg and 100 mg of oxaliplatin corresponding with the following formula:

	50 mg vials	100 mg vials
Oxaliplatin	50 mg	100 mg
Lactose monohydrate	450 mg	900 mg
Nominal volume of vial	36 mL	50 mL

The finished product is presented in the form of a white to off-white cake or powder contained in a clear glass vial, sealed with a rubber stopper and aluminum seal with a flip-over cover.

7.3.2 Drug Administration

The freeze-dried powder is reconstituted by adding 10 to 20 mL (for the 50 mg vials) or 20 to 40 mL (for the 100 mg vials) of water for injection or 5% glucose solution and then by diluting in an infusion solution of 250 mL or 500 mL of 5% glucose solution. Do not administer undiluted. Dispose of any reconstituted solution that shows evidence of precipitation. The reconstitution or final dilution must never be performed with a sodium chloride solution. Oxaliplatin is incompatible with sodium chloride.

Do not combine with alkaline medications or media which cause oxaliplatin to degrade. Do not administer simultaneously by the same infusion line; flush line after oxaliplatin administration. Do not use for the preparation or administration needles or intravenous infusion sets containing aluminum components (there is a risk of degrading oxaliplatin).

Oxaliplatin will be administered at a dose of 85 mg/m^2 intravenously as a 2 – 6 hour infusion on days 1 and 15 of each cycle.

Antiemetics should be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting. It is recommended that patients receive ondansetron (Zofran) 16 mg IV or granisetron (Kytril) 10 mcg/kg IV +/- prochlorperazine (Compazine) 10 mg PO or lorazepam (Ativan) 1-2 mg PO or IV 30 minutes prior to oxaliplatin administration if clinically indicated. Alternatively, oral forms of these antiemetics may be used at the treating investigator's discretion.

7.3.3 Storage and Stability

Information on expiration dates of oxaliplatin will be supplied on a lot-by-lot basis. The compound may be stored as freeze-dried powder for 3 years at room temperature. Reconstituted solution may be stored in 5% glucose solution or water for injection in the original vial for up to 48 hours between 5° to 30° C. After dilution in 5% glucose solution for infusion, the shelf-life is 24 hours at room temperature.

7.4 Leucovorin

7.4.1 Description

Leucovorin calcium is commercially available in 50 mg, 100 mg, 350 mg vials for reconstitution.

Please refer to the package insert for complete product information.

7.4.2 Drug Administration

Leucovorin will be administered as an IV infusion over 2 – 6 hours either concurrently with oxaliplatin through a separate line, or after oxaliplatin administration if a second line is not available. This can also be administered by institutional standard of care procedure policy.

Leucovorin may be reconstituted with BWI or with sterile water for injection. Solutions should be further diluted in D5W, 0.9% Sodium Chloride, or Ringers solution for infusion over two hours.

7.4.3 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with bacteriostatic water for injection (BWI) are stable for at least 7 days at room temperature.

7.5 Supportive Care Guidelines

7.5.1 H2 blockers or proton pump inhibitors can be prescribed for all patients as clinically indicated.

7.5.2 Management of nausea and vomiting
Antiemetics should be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting.

7.5.3 Anticoagulants
See exclusion criteria section.

7.5.4 Growth factors
Prophylactic use of a colony-stimulating factor (G-CSF or GM-CSF) is not permitted on this trial. Nonetheless, use of a colony-stimulating factor for the treatment of febrile neutropenia as per American Society of Clinical Oncology guidelines is permissible (Bennett et al. J. Clin Oncol 1996 Sep; 14(9):2511-2520). Use of erythropoietin (including Procrit and Aranesp) for treatment of disease or treatment-related anemia is permitted.

7.5.5 Anti-Hypertensives
Patients who develop hypertension while on sorafenib may be treated with anti-hypertensive agents at the investigator's discretion. Dose modification for Grade 3 or 4 hypertension is described in Section 6.0.

7.6 Medications to Avoid

- Avoid use of drugs that are known potent CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. These drugs can decrease systemic exposure to sorafenib and should be avoided. For participants who discontinue sorafenib while on study, please note that the use of anti-emetic CYP3A4 inducers is allowed.
- Avoid use of drugs that prolong QTc. If these drugs must be used, monitor QTc closely at the discretion of the treating physician.

8.0 Correlative Studies

Please see Appendix C.

9.0 Study Calendar

	Screening			Sorafenib 2wk Lead-In		Cycle 1				Cycle 2 and subsequent cycles				Every 8 weeks	End of Treatment[6]
Study Week	-3	-2	-1	1	2	1	2	3	4	1	2	3	4		
Informed consent	X														
History		X		X	X	X	X	X		X		X			X
Weight		X		X	X	X	X	X		X		X			X
Performance Status		X		X	X	X	X	X		X		X			X
Toxicity				X	X	X	X	X		X		X			X
Vital signs (including BP)		X		X	X	X	X	X		X		X			X
Physical exam		X		X	X	X	X	X		X		X			X
CBC w/diff		X		X[1]	X	X	X	X		X		X			
Platelets		X		X[1]	X	X	X	X		X		X			
Urinalysis[8]		X				X				X					
PT-INR		X		X[1]		X				X					
Glucose		X		X[1]	X	X	X	X		X		X			
BUN		X		X[1]	X	X	X	X		X		X			
Creatinine		X		X[1]	X	X	X	X		X		X			
Uric acid		X		X[1]		X				X					
Total Bilirubin		X		X[1]	X	X	X	X		X		X			
Alk phos		X		X[1]	X	X	X	X		X		X			
LDH		X		X[1]	X	X	X	X		X		X			
Protein		X		X[1]	X	X	X	X		X		X			
Albumin		X		X[1]	X	X	X	X		X		X			
AST/ALT		X		X[1]	X	X	X	X		X		X			
Calcium, Phos		X		X[1]	X	X	X	X		X		X			
Amylase		X		X[1]		X				X					
Lipase		X		X[1]		X				X					
AFP		X		X[1]		X				X					
Hepatitis BsAg, cAb, sAb	X[3]														
Hepatitis C Ab	X[3]														
EKG	X														
Pregnancy test (serum or urine)			X[5]												
Tumor Measurement	X													X[2]	X[2]
C/A/P CT or MRI	X[4]													X[4]	X[4]
Sorafenib				X	X	X	X	X	X	X	X	X	X		
mFOLFOX						X		X		X		X			
Correlative Studies[7]				X and D3		X		X		X					

1. Screen assessments need not be repeated for lead-in period.

2. Baseline measurements of tumor by radiographic means should be completed within 21 days prior to treatment and should include full evaluation of the extent of metastatic disease. Assessments are repeated every 2 cycles (8 weeks). Responses must be confirmed after 4-8 weeks with repeat radiological scans.

3. Hepatitis B and C serology as listed in the study calendar must be obtained within 120 days of study enrollment.

4. If abdominal/pelvic CT scan or abdominal MRI are chosen as the radiographic means of tumor measurement, then the same test should be repeated consistently every two cycles (8 weeks). If chest CT or chest MRI are chosen as the radiographic means of tumor measurement, then the same test should be repeated consistently every 2 cycles (8 weeks).

5. Female patients of childbearing potential only, within 7 days of initiation of treatment.

6. Every 6 months thereafter

7. Circulating endothelial cells and plasma levels of growth factors will be assessed on Day 1 (prior to first dose of sorafenib later that day) and Day 3 of lead-in phase, and on C1D1, C1D15, and C2D1 of FOLFOX-Sorafenib, and, if available, at the time of progression (see Appendix C for details). The Day 3 correlative can be drawn on Day 3, 4, or 5. The Day 15 correlative can be drawn on Day 14, 15, or 16. The Day 29 correlative can be drawn on Day 27, 28, or 29. An optional posttreatment tumor biopsy will be obtained any time from Day 10 to Day 14 of the lead-in phase in patients who consent to a posttreatment tumor biopsy (see Appendix D for details).
8. 24 hr urine must be done for 2+urine

10.0 Evaluation of Response

All patients with measurable disease who have received the first cycle of treatment and had a tumor re-assessment will be considered evaluable for response. In addition, those patients who develop early progressive disease or who discontinue early from the study due to toxicity will also be considered evaluable for response. Patients on therapy for at least the first cycle of treatment will have their responses classified according to the definitions below.

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumors (RECIST 1.1) committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1Definitions

Measurable disease **-** the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions and lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy.

Target/Non-target Lesions - all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor. All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.2 Response Criteria

Method of Tumor Response Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at reassessment during treatment. Imaging-based evaluation is preferred to clinical examination. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. Lesions on chest X-ray are acceptable as measurable

lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. Ultrasound is not an acceptable method of disease assessment.

Definition of Response

Overall tumor response will be based on an integration of the evaluation of target, non-target, and new lesions, as described below:

Evaluation of target lesions

Complete Response (CR): Disappearance of all clinical and radiological evidence of target lesions.

Partial Response (PR): A 30% or greater decreased in the sum of LD of all lesions in reference to the baseline sum LD.

Stable Disease (SD): Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR.

Progressive Disease (PD): A 20% or greater increase in the sum of LD of all target lesions, taking as reference the smallest sum LD recorded since baseline.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat evaluations which should be performed no less than 4 weeks after the criteria for response are first met.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-Complete Response, Non-Progressive Disease (Non-CR, Non-PD): Persistence of one or more non-target lesions.

Progressive Disease (PD): Unequivocal progression of existing non-target lesion(s).

Note: Increased uptake on bone scan alone is insufficient evidence of progression; additional evidence of progressive disease would be present to declare unequivocal progression.

Evaluation of new lesions

No: There are no new lesions.

Yes: New lesions are present. Note: If new lesions are present, the patient is considered to have progressive disease overall.

Overall Response

Overall response will be determined as tabulated below, based on the evaluation of target, non-target, and new lesions:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Every effort should be made to document tumor measurements and extent of disease, even after discontinuation of therapy, in order to classify patients for overall response as described above. Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered as non-responders, will be included in the denominator for the response rate, and will be classified into one of the following categories:

- death attributed to disease progression
- deterioration attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

Note: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported; reasons

include clinical progression, drug toxicity, or secondary therapy for maintenance of tumor response.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started. Patients who do not relapse will be censored at the day of their last tumor assessment.

Time to response

Time from date of initial treatment until first objective documentation of response.

Time to tumor progression

Time from date of initial treatment to first objective documentation of progressive disease or death. Patients who die without a reported prior progression will be considered to have progressed on the day of their death.

Time to treatment failure

Time from date of initial treatment to first objective documentation of progressive disease, or off study date, whichever occurs first.

Time to death

Time from date of initial treatment to date of death

11.0 REPORTING OF ADVERSE EVENTS

11.1Adverse Event and Reporting Definitions (CTCAE version 4.0)

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Bayer Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, and which is assessed by the investigator to be **reasonably or possibly related** to or caused by sorafenib. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to sorafenib through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

- Results in **death** (i.e. the AE caused or lead to death)

- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)

- Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)

- Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)

- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)

- It does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

Expected adverse events are those adverse events that are **listed** or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those **not listed** in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

11.2 Reporting of Serious Adverse Events

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

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

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

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

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

OR

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

All reports shall be sent electronically to:

Electronic Mailbox: [redacted]

Facsimile: [redacted]

Address: Global Pharmacovigilance - USA
Mail only: **Ba**yer HealthCare Pharmaceuticals Inc.
[redacted]

Address: [redacted]

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

Phone: [redacted]

AND:
Dana Farber Cancer Institute IRB/ OHRS
450 Brookline Avenue,
Boston, MA 02115

Phone: [redacted]
Fax: [redacted]

MedWatch 3500 Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Bayer may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Bayer Drug Safety representative noted above.

Study Drug Relationship:

The investigator will determine which events are associated with the use of study drug. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and sorafenib administration; and/or
- There is a biologically plausible mechanism for sorafenib causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

Follow-up Reports

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Serious Adverse Event submitted to the FDA on a 3500 form and complete follow-up forms as necessary. The patient must be followed up until clinical recovery is complete and/or laboratory results have returned to normal. This may mean that follow-up will continue after the patient has completed the trial and that additional investigations may be necessary.

- Any reportable Serious Adverse Events brought to the attention of the Investigator at any time after cessation of the trial and considered by him/her to be reasonably associated with medication administered during the period should also be submitted to the FDA. As for initial reports, a copy is to be provided to Sanofi-Synthelabo New York Safety Surveillance or the appropriate manufacturer of the product. within 24 hours after FDA submission (see above)

- The 3500 form providing follow-up information about a reportable SAE must be submitted to the FDA as soon as possible or within 15 calendar days.

- As with the initial submission to the FDA of the 3500 form, the principal investigator is also responsible for providing all follow-ups for reportable Serious Adverse Events (on form 3500) to the IRB and co/sub-investigators (Dear Investigator Letter) participating on this protocol.

IND Annual Report

The principal investigator is responsible for preparing and submitting the IND annual reports to the FDA (CFR312.33) within 60 days of the anniversary date that the IND went into effect. A copy of the report shall be provided to New York Safety Surveillance within 24 hours of submission to the FDA.

12.0 Data Safety and Monitoring

12.1 Method

The QACT will collect, manage, and monitor data for this study.

12.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT

On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.3 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.4 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these

activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13.0 Regulatory Considerations

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.
All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

N/A

14.0 STATISTICAL CONSIDERATIONS

14.1 Target Sample Size

Forty patients will be entered in this phase II study. Assuming the accrual rate is 2-3 patients per month, the accrual will be completed in 18 months or less.

14.2Planned Efficacy Evaluations

14.2.1 Primary Efficacy Variables

The primary objective of this study is time to tumor progression (TTP). A sample size of 40 achieves 80% power to detect the difference between the null hypothesis median TTP of 5 months and an alternative hypothesis median TTP of 7 months at a 10% significance level using a one-sided test based on the elapsed time, assuming a study follow-up period of 24 months. The total study duration will be 42 months (18 months of accrual + 24 months of follow-up).

14.2.2 Secondary Efficacy Variables

The secondary objectives are to assess the toxicity profiles of this regimen and the preliminary data on response rate and overall survival. Overall survival is defined as the time from study entry until death from any cause. Overall survival will be calculated using the Kaplan-Meier method, and confidence limits for survival estimates will be calculated using the Greenwood formula. Progression free survival is defined as the time from study entry until disease progression or death from any cause. Response rate is defined as the percentage of patients achieving either CR or PR. Duration of response is defined as the time interval from the initial response to the time disease progression is observed.

All categories of toxicity and complications of the treatment will be recorded. Toxicity and complications of the treatment will be assessed based on reports of adverse events, physical examinations, and laboratory measurements.

REFERENCES/BIBLIOGRAPHY

1. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005

2. El-Serag HB, Davila JA, Petersen NJ, et al: The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 139:817-23, 2003

3. Llovet JM, Bruix J: Molecular targeted therapies in hepatocellular carcinoma. Hepatology 48:1312-27, 2008

4. Carlomagno F, Anaganti S, Guida T, et al: BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 98:326-34, 2006
5. Wilhelm SM, Carter C, Tang L, et al: BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 64:7099-109, 2004
6. Abou-Alfa GK, Schwartz L, Ricci S, et al: Phase II Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma. J Clin Oncol, 2006
7. Llovet J, Ricci S, Mazzaferro V, et al: Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP trial). Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: LBA1, 2007
8. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The Lancet Oncology doi:10.1016/S1470-2045(08)70285-7, 2008
9. Yeo W, Mok TS, Zee B, et al: A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 97:1532-8, 2005
10. Louafi S, Boige V, Ducreux M, et al: Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. Cancer 109:1384-90, 2007
11. S. Qin, Y. Bai, S. Ye, et al: Phase III study of oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX4) versus doxorubicin as palliative systemic chemotherapy in advanced HCC in Asian patients. J Clin Oncol 28:15s, 2010 (suppl; abstr 4008) 2010
12. Wilhelm SM, Adnane L, Newell P, et al: Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 7:3129-40, 2008
13. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-90, 2008
14. Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23-30, 2004
15. Zhu AX, Duda DG, Sahani DV, et al: HCC and angiogenesis: possible targets and future directions. Nat Rev Clin Oncol 8:292-301
16. Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial.JAMA. 2010 Nov 17;304(19):2154-60.
17. T CP, Cheung FY, Lee AS, Yau TK, Choo SP, Lau J, Wong JS, Fan ST, Poon RT. Phase II trial of sorafenib with capecitabine and oxaliplatin (SECOX) in patients with locally advanced or metastatic hepatocellular carcinoma. Joint ECCO 15 – 34th ESMO Multidisciplinary Congress 2009; Berlin: European Journal of Cancer Supplements; 2009. p. Pages 1-24.

APPENDIX A: CLIP score and CTP classification

CLIP Score

Variables	0	1	2
CTP score	A	B	C
Tumor Morphology	Solitary & extension </= 50%	Multiple & extension < /= 50%	Massive or extension > 50%
AFP	<400	> 400	
PV thrombosis	No	Yes	

The CLIP Investigators, Hepatology 28:751-55, 1998.

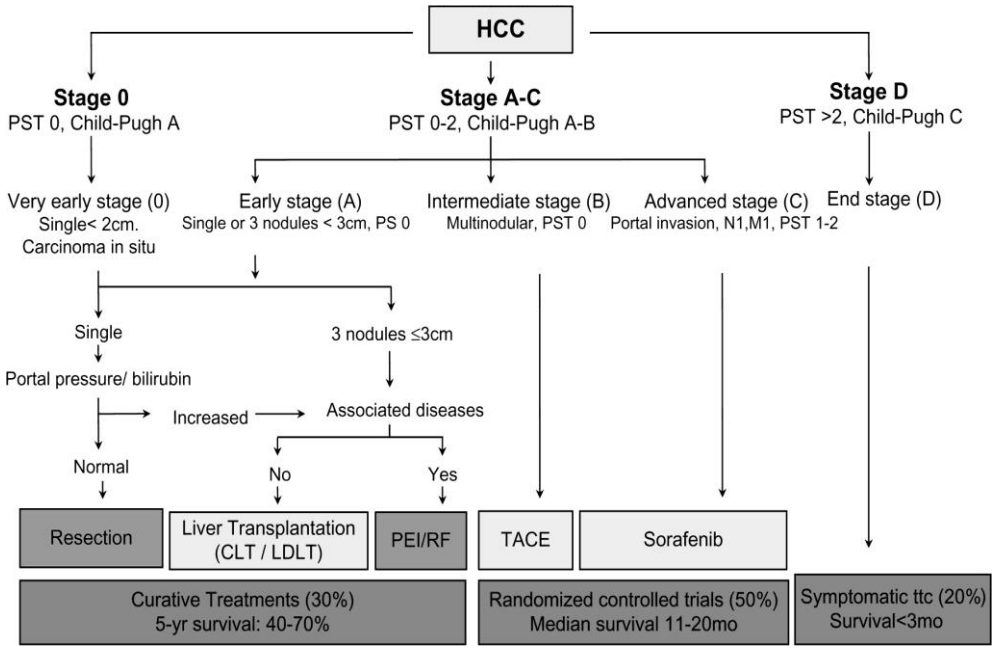
Child-Turcotte-Pugh (CTP) Classification

	Points 1	2	3
Bilirubin	< 2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
Prothrombin time	<4	4-6	>6
Encephalopathy	None	I-II	III-IV
Ascites	None	Slight	Moderate

Grade A CTP score 5-6
Grade B CTP score 7-9
Grade C CTP score 10-15

APPENDIX B: Barcelona Clinic Liver Cancer (BCLC) Staging

BCLC Staging and Treatment Strategy



Llovet, J. M. et al. J. Natl. Cancer Inst. 2008 100:698-711

Appendix C: Correlative Studies on Plasma Biomarkers

Exploratory analyses of potential biomarkers of sorafenib activity will be performed by measuring proteins in the plasma on Day 1 (prior to first dose of sorafenib later that day) and Day 3 of lead-in phase, and on C1D1, C1D15 and C1D29 of FOLFOX-Sorafenib, and if available, at the time of progression. Plasma analysis will be carried out for a panel of circulating angiogenic and inflammatory molecules previously identified by others and us as potential biomarkers of response in HCC. They include soluble VEGFR1 (sFLT1), VEGF, placental-derived growth factor (PlGF), basic fibroblast growth factor (bFGF), interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor□α (TNF-α) using 2 multiplex protein array plates from Meso-Scale Discovery (Gaithersburg, MD), soluble VEGFR2, angiopoietin 2 (ANG2), HGF hepatocyte growth factor (HGF), soluble c-KIT, carbonic anhydrase 9 (CAIX) and stromal-derived factor 1α (SDF1α) from R&D Systems (Minneapolis, MN). Samples will be run in duplicate.

Supplies

The following supplies are needed for each blood sample drawn:

- EDTA blood collection tubes (Sarstedt, #03.1068)

Sample Labels

Prior to use, EDTA tubes should be labeled with the following information:

- Patient Initials
- Patient ID number
- Protocol number
- Collection date
- Institution

Collection and handling (Please see attached Biomarker Manual for full details)
Approximately 8 cc of venous blood will be collected in each of 2 EDTA blood collection tubes (Sarstedt, #03.1068). The tubes should be gently inverted several times to ensure mixing with the anticoagulant and kept on wet ice at all times. Within two hours the tubes should be sent to:
Steele Laboratory

Appendix D: Tissue Collection Protocol

To be considered for the optional posttreatment tumor biopsy, the patient must have adequate tissue on their baseline biopsy (i.e. core biopsy) to have all necessary correlative studies run on the sample. The treating physician must also deem them to be a reasonable candidate for tumor biopsy based on laboratory and clinical evaluation. The optional posttreatment tumor biopsy will be obtained any time from Day 10 to Day 14 of the lead-in phase in patients who consent to a posttreatment tumor biopsy (n=6-12). Only patients getting their treatment at MGH will be eligible for the posttreatment biopsy and the biopsy-related correlative studies given that all samples need to be processed at the Steele Lab.

Gene expression profiles on the biopsy on the baseline and posttreatment biopsy samples will be assessed by laser capture microdissection (LCM) and quantification of genes by qPCR. These analyses will provide the first glimpse into the mechanism of action of sorafenib in HCC.

Supplies:
Tissue-Tek ®: Cryomold

- Standard size 25x20x5mm (#4557)
    - Fisher Scientific Cat# NC9511236

  OR
- Intermediate size 15x15x5mm (#4566)
    - Fisher Scientific Cat# NC9542860

Tissue-Tek ®: O.C.T. Compound, 4oz (#4583): Fisher Scientific Cat# NC9638938

Small specimen bag: Fisher Cat# 01-002-37 (or equivalent)
Forceps: Fisher Cat# NC9832137 (or equivalent)
Dry Ice and Cooler
Cryoware Pen: Fisher Cat# 13-382-88

Procedure:
1. Bring all supplies needed to the biopsy as the tissue needs to be frozen **immediately**.
2. Squeeze small amount of OCT into cyromolds* – enough for there to be a thin layer covering the bottom.
3. As soon as the specimen is ready, use disposable forceps to gently place only 1 core into each cryomold.
4. You should ideally collect between 3 and 5 separate cores.
5. Once the specimen is in the cryomold, cover with more OCT making sure the tissue is entirely submerged.
6. Immediately place cryomold with OCT and tissue onto dry-ice making sure the cryomold is level and will not tip over.
7. The OCT will freeze into a solid white block within 5-10 minutes

8. Once the blocks have completely frozen they can be put into a specimen bag and sealed. More than one block can be put into a bag.
9. The bag should be labeled with:

a. Patient name
b. MGH Study #: 12-218
c. MGH MRN #
d. Date of biopsy
e. Time Point (Biopsy #1, Biopsy #2, etc)
f. Number of blocks in the bag

10. All research tissue should then be sent to the Steele Lab at MGH (Cox 734) on the day of collection.
Attn.: [redacted]

*If time permits, the cryomolds can be placed onto the dry-ice once a thin layer of OCT has been put it but before the tissue is put in. Once this is frozen or begins to freeze, the tissue can be placed on top of the now frozen OCT and then covered with more liquid OCT and then placed back onto the dry ice to freeze completely.