A Phase I/II Study of Bavituximab and Sorafenib In Patients With Advanced Hepatocellular Carcinoma

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A Phase I/II Study of Bavituximab and Sorafenib In Patients With Advanced Hepatocellular Carcinoma

UT Southwestern Medical Center Therapeutic Protocol

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Protocol Version History

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

TITLE	A Phase I/II Study of Bavituximab and Sorafenib In Patients With Advanced Hepatocellular Carcinoma
STUDY OBJECTIVES	Primary Objective: 1) To determine the maximum tolerated dose of bavituximab in patients with advanced hepatocellular carcinoma treated with sorafenib. 2) To determine the radiographic median time to progression in patients with advanced hepatocellular carcinoma treated with bavituximab and sorafenib. Secondary Objectives: 1) Response rate, progression free-survival and overall survival. 2) Safety and tolerability as assessed by NCI CTC v4.0 of combination bavituximab and sorafenib. 3) Correlation of treatment response with pre- and post-treatment tissue biopsies and serum biomarkers.
STUDY DESIGN	Single-arm, single-institution, non-randomized, open-label phase I/II study.
STUDY POPULATION	Inclusion Criteria: 1. Patients must have a diagnosis of hepatocellular carcinoma by at least one criterion listed below: a. Histologically confirmed hepatocellular carcinoma b. Axial imaging consistent with liver cirrhosis and at least one solid liver lesion ≥2 cm with early enhancement and delayed enhancement washout regardless of alpha-fetoprotein (AFP) levels. c. AFP ≥ 400 ng/ml and evidence of at least one solid liver lesion ≥ 2 cm regardless of specific imaging characteristics.

	2. Locally advanced or metastatic disease. a. Patients with locally advanced disease must have disease deemed to be unresectable or not eligible for hepatic transplantation by surgical oncologist or transplant physician 3. Measurable disease, defined as lesions that can accurately be measured in at least one dimension (longest diameter to be measured) according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at least 2 cm with conventional techniques or at least 1 cm with spiral computed tomography. 4. Child-Pugh Score A or B7. 5. Age ≥ 18 years. 6. ECOG Performance Score of 0-2. 7. Absolute neutrophil count ≥ 1,200 cells/mm^3. 8. Platelet count ≥ 70,000 cells/mm^3. 9. Total Bilirubin ≤ 3.0 mg/dl. 10. Hemoglobin ≥ 8.5 g/dl. 11. INR ≤ 1.8 (therapeutic anticoagulation allowed as long as medically indicated.) 12. Creatinine ≤ 1.5 times upper limit of normal. 13. Women of childbearing potential must have a negative pregnancy test. 14. No clinically significant episode of gastrointestinal bleeding within the previous 30 days. 15. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter. 16. At least 4 weeks since prior locoregional therapy including surgical resection, radiotherapy, hepatic arterial embolization or chemoembolization, radiofrequency ablation, percutaneous injection or cryoablation (treatment of target lesion only, non-target lesions can be treated with locoregional therapy). Provided the target lesion increased in size by 25% or more or the target lesion

	was not treated with locoregional therapy. 17. Greater than 4 weeks since interferon therapy. 18. Greater than 4 weeks since and no concurrent use of rifampin or St John's wort. 19. Life expectancy > 12 weeks. 20. Prior anti-viral therapy is allowed. 21. Ability to understand informed consent and signing of written informed consent prior to initiation of protocol therapy. 22. Non-English speaking patients will be enrolled. Exclusion Criteria: 1. History of bleeding diathesis or coagulopathy. 2. Symptomatic or clinically active brain metastases. 3. Major surgery within previous 4 weeks. 4. Clinically significant non-bleeding within previous 12 months. 5. Concurrent hormone therapy (including hormone replacement therapy and anti-estrogen). 6. History of any condition requiring anti-platelet therapy with the exception of general cardiovascular prophylaxis with aspirin. 7. History of thromboembolic events (including both pulmonary embolisms and deep vein thrombosis not including tumor thrombus). 8. Active infection. 9. Patients who are pregnant or lactating. 10. Hypersensitivity to IV contrast not suitable for pre-medication. 11. Patients with known hypersensitivity to any of the components of bavituximab or sorafenib. 12. Any other medical condition, including mental illness or substance abuse deemed by the investigators to likely interfere with a patient's ability to sign informed consent, cooperate and participate in the

	study or follow-up procedures. 13. Patients with known human immunodeficiency virus (HIV). 14. Significant history of cardiac diseases, including any of the following: a. LVEF < 40% by MUGA or myocardial scintigram. b. NYHA class III-IV congestive heart failure. c. Myocardial infarction within previous 6 months. d. Cardiac arrhythmias requiring anti-arrhythmic therapy (other than beta blockers or digoxin). 15. Evidence of poorly controlled hypertension (medically controlled hypertension is allowed provided blood pressure ≤ 150/90.) 16. History of liver or renal transplantation. 17. Prior adjuvant therapy with sorafenib or other Raf/MEK/RAS or VEGFR inhibitors. a. Other adjuvant therapy is allowed provided it was completed > 6 months prior to study and there is documented recurrence or progression of hepatocellular carcinoma.
TOTAL EXPECTED NUMBER OF PATIENTS	Phase I component- 9-18 patients Phase II component-38 patients
PRE-, DURING AND POST-THERAPY TISSUE AND SERUM COLLECTION (Phase II component only)	Serum samples will be drawn for measurement of angiogenic markers, alfa-fetoprotein and inflammatory cytokines pre, during and post therapy. When feasible core biopsies will be obtained for tissue banking for research purposes and for routine H&E staining, pre and during therapy.
STUDY DRUG FORMULATIONS	Bavituximab: supplied as a sterile, preservative-free solution with 10 mM acetate at pH 5.0 and diluted with 0.9% (w/v) saline to a final volume of 100 ml. Sorafenib: information per package insert.

ROUTE OF ADMINISTRATION	Bavituximab: Intravenous (IV) Sorafenib: Oral
DOSE REGIMEN	Bavituximab: 0.3 mg/kg, 1.0 mg/kg or 3.0 mg/kg IV over 90 minutes weekly. Sorafenib: Initial dose 200 mg PO twice daily to be escalated to the target dose of 400 mg PO twice daily Phase I: Bavituximab and sorafenib are to be given for 1 cycle or 4 weeks. Phase II: Bavituximab and sorafenib are to be continued until disease progression or toxicity.
EVALUATION CRITERIA	Primary: Phase I: safety as measured by adverse events Phase II: efficacy as measured by time to progression using RECIST Version 1.1. Secondary: Phase II: 1. Safety and tolerability as assessed by NCI CTC v4.0 of this regimen in the phase II setting. 2. Overall survival, response rate and progression-free survival. 3. Correlation of serum and tissue markers of angiogenesis and immune response with treatment response.
DURATION OF STUDY PERIOD	Phase I: Patients will continue study treatment until 1 cycle of therapy. Phase II: Patients will continue study treatment until disease progression or toxicity.
ANTICIPATED STUDY DATES	Planned Start Date: February 2011 Planned Recruitment Closure: February 2013 Planned End Date: February 2014

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

1. The primary objective of the Phase I component of this trial is to determine the maximum tolerated dose (MTD) of bavituximab up to 3.0 mg/kg weekly in patients with hepatocellular carcinoma (not eligible for surgical resection or hepatic transplantation) treated with sorafenib.
2. The primary objective of the Phase II component of this trial is to determine the median radiographic time to progression (from the date of first therapy to date of first documented progression) of patients with hepatocellular carcinoma (not eligible for surgical resection or hepatic transplantation) treated with sorafenib.

Secondary objectives of the trial are to determine the:

3. Safety and tolerability of combination bavituximab and sorafenib treatment in patients with hepatocellular carcinoma.
4. Response rate, progression free-survival and overall survival.
5. Correlation of treatment response with pre- and post-treatment tissue biopsies and serum angiogenic and phosphatidylserine biomarkers.

3.0 BACKGROUND AND RATIONALE

3.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and is responsible for more than 500,000 deaths annually. (1) Previously considered uncommon in Western countries, the incidence and mortality of HCC have increased three-fold in the United States over the past two decades. (2) Although complete resection or hepatic transplantation remains the most effective therapies for localized HCC, 50-70% of patients present with advanced disease not amenable to curative surgical approaches. (3,4) Disease that is diagnosed at an advanced stage or with progression after locoregional therapy has a dismal prognosis with a median overall survival of < 12 months mainly due to underlying liver dysfunction and suboptimal treatment options. (2) Ablative therapies are commonly used in this setting but are ineffective for large (>5 cm) or multifocal tumors, both commonly found in advanced disease. (5,6) Hepatic artery chemoembolization may have utility in patients with HCC but there are conflicting reports regarding its efficacy and in advanced disease a survival benefit has not been demonstrated. (7,8)

<u>Systemic Therapy for Advanced Hepatocellular Carcinoma</u>

The use of single agent systemic cytotoxic chemotherapy regimens including

irinotecan, gemcitabine or doxorubicin have historically demonstrated low response rates with little to no clinical efficacy. (9-11) Combination chemotherapy regimens using cytotoxic chemotherapeutic agents have fared no better with response rates ranging from 0% to 40% and limited clinical efficacy. A recent study compared single agent doxorubicin to a combination of cisplatin, interferon, doxorubicin and 5-fluorouracil (PIAF). Despite an improvement in response (10% for doxorubicin vs. 21% for PIAF) the study failed to show an improvement in survival (6.8 vs. 8.6 months, respectively; P=0.83). (12)

The lack of appropriate traditional chemotherapeutic agents led to the investigation of molecular targeted agents, which have been shown to be efficacious in other tumor models. Sorafenib, an oral multikinase inhibitor that blocks tumor cell proliferation by targeting the Raf/MEK/ERK signaling pathway and exerts an anti-angiogenic effect by targeting the tyrosine kinase receptors, VEGFR-2, VEGFR-3 and PDGF-β, is the first biologically targeted agent to show efficacy in the treatment of advanced stage HCC. (13,14) In a phase III randomized controlled trial (SHARP trial), patients with advanced hepatocellular carcinoma (not eligible for surgical resection or transplantation) and preserved liver function (Child-Pugh A score) were randomly assigned to either systemic sorafenib or placebo. There was a significantly longer survival and radiologic time to progression (TTP) outcome in the cohort of patients that received sorafenib with little or no toxicity. Grade 3 drug relate events included diarrhea (8% in the sorafenib group vs. 2% in the placebo group), hand-foot skin reaction (8% vs. 1%), hypertension (2% vs. 1%) and abdominal pain (2% vs. 1%); there were no grade 4 drug-related adverse events in any of these categories in either study group. Currently sorafenib is the only drug that has FDA approval for the systemic treatment of HCC. Although sorafenib is the current standard of care for patients with advanced HCC, it prolonged radiologic time to progression less than 3 months when compared to best supportive care: 5.5 months versus 2.8 months, respectively. Overall survival was prolonged less than 3 months compared to best supportive care, 10.7 months versus 7.9 months, respectively. (14) Although systemic treatment with sorafenib shows statistically significant clinical efficacy, its overall benefit is modest. The complexity of HCC would appear to lend itself to escape mechanisms from the sorafenib-specific blockade of the RAF-MEK-ERK and VEGFR/PDGF pathways, thereby promoting tumor proliferation and neo-angiogenesis through alternative means. Such a mechanism would explain why certain patients fail to benefit from sorafenib therapy and provides the rationale for combining sorafenib with other chemotherapeutic agents.

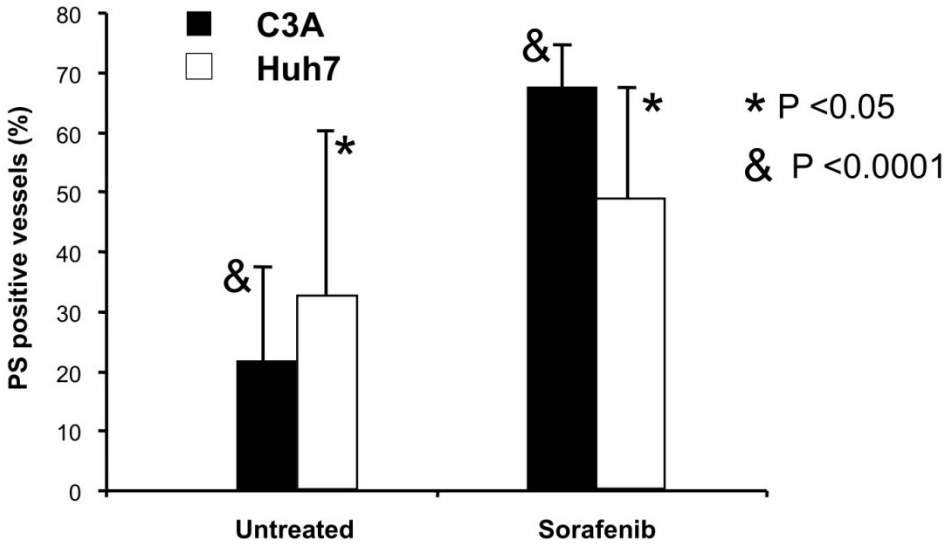
3.2 Scientific background of bavituximab

Anionic phospholipids are largely absent from the surface of resting mammalian cells under normal conditions. Phosphotidylserine (PS), the most abundant anionic phospholipid of the plasma membrane, is tightly segregated to the internal leaflet of the plasma membrane in most cell types. In tumors, however, PS becomes exposed on the accessible outer surface of the vascular endothelium in response to oxidative stresses present in the tumor microenvironment. (15,16) PS

exposure on tumor vascular endothelium occurs in 15-40% of tested tumor models in the absence of cellular injury or exogenous agents and has not been demonstrated on blood vessels in non-tumor tissues regardless of the model used. The administration of cytotoxic chemotherapy or radiation therapy increases PS externalization presumably through the production of oxygen radicals and the subsequent translocase inhibition and scramblase activation. (17-22)

3.2.1 Non-clinical studies with murine 3G4

3G4, a novel murine IgG3 monoclonal antibody developed by Dr. Phillip Thorpe at UT Southwestern Medical Center, binds PS complexed with β_2-glycoprotein 1 mediating the binding of host effector cells to the tumor vascular endothelium. Murine 3G4 has demonstrated significant anti-tumor effects as a stand-alone therapy in various murine xenograft tumor models. (20) The growth of MDA-MB-231 breast carcinoma, MDA-MB-435 breast carcinoma, Meth A fibrosarcoma and L540 Hodgkin lymphoma tumor xenografts was reduced by 65%, 75%, 90% and 50%, respectively, compared to controls during treatment with 3G4. F_c domain-mediated immune effector functions such as antibody dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity and antibody-mediated phagocytosis appear to be responsible for the anti-tumor effect of 3G4. (17)
The combination of 3G4 with cytotoxic chemotherapy has been shown to have an additive effect in multiple tumor models. Cytotoxic chemotherapy including gemcitabine and docetaxel increases PS exposure on tumor vascular endothelium providing additional targets for binding of the 3G4 antibody. Combination gemcitabine-plus- 3G4 therapy reduced tumor growth in a pancreatic cancer tumor model 5-fold compared to either gemcitabine or 3G4 alone. (20) Similar results were seen with a combination of docetaxel and 3G4 in a breast cancer tumor model. (25) We have recently demonstrated that sorafenib also increases PS exposure in the human HCC cell lines, C3A and Huh7. (unpublished results from Dr. Phillip Thorpe) (Figure 1)



The likely mechanism of vascular damage seen with 3G4 is the antibody binds to tumor vasculature expressing PS secondary to chemotherapy induction, mediating attachment of FcgR-positive monocytes that destroy the endothelial cells by an ADCC mechanism. Recently, however, it has been suggested that binding of an anti-PS antibody to PS elicits the release of proinflammatory cytokines activating dendritic cells and conferring immune protection against tumor growth. (22)

3.2.2 Chimeric 3G4 (Bavituximab)

Chimeric 3G4 (bavituximab) is a genetically engineered IgG_1 κ immunoglobulin containing the variable region sequences (Fab) of a murine PS-targeting monoclonal antibody (MAb) and human IgG_1 κ constant region sequences (F_c). Bavituximab is produced by Chinese hamster ovary (CHO)-K1 cells in suspension culture in a nutrient medium. Bavituximab is purified by a combination of capture, cation, and anion-exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Bavituximab is supplied as a sterile preservative-free liquid for intravenous (IV) administration.

3.2.3 Nonclinical Studies with Chimeric 3G4 (Bavituximab)

The nonclinical safety program to date comprises IV pharmacokinetic (PK) studies in rats and monkeys and tissue distribution studies in rats. Single and repeat-dose IV toxicity studies were performed in rats, rabbits, and cynomolgus monkeys with treatment duration up to 8 weeks. Special toxicity studies

evaluating the effects of bavituximab on coagulation, vascular disease, wound healing, and platelet aggregation were conducted in rats, rabbits, mice, and monkey and human citrated whole blood, respectively. Central nervous system (CNS) safety pharmacology and immunogenicity studies were integrated into the Good Laboratory Practice (GLP) repeat-dose studies performed in rats. Cardiovascular safety pharmacology, immunogenicity, and immunotoxicity studies were integrated into the GLP repeat-dose studies performed in monkeys.

In single-dose studies, findings were limited to *in vitro* assay interference in phospholipid-based coagulation parameters (i.e., activated partial thromboplastin time [aPTT] and prothrombin time [PT]) in all species examined. Drug-induced *in vitro* coagulation interference peaked within 24 hours post-dose and generally resolved by 7 days post-dose. A coagulation study in rats (using a single 60 mg/kg dose) confirmed that while aPTT and PT were elevated 2.88- and 1.34-fold, respectively, at 24 hours post dose, bleeding time, thrombin time, fibrin degradation products, and fibrinogen were not significantly affected compared to the vehicle control animals.

Two *in vitro* studies were conducted that demonstrate an interference effect of bavituximab (or 3G4) on phospholipid-based coagulation assays. Plasma harvested from normal rats and spiked with increasing concentrations of bavituximab suggests that the drug interferes, in a dose-dependent manner, with the analytical performance of aPTT determination. Four procoagulant T-lymphoblastoid cell lines were characterized for their cell-surface procoagulant activity. At high concentrations, 3G4 partially inhibited phospholipid-dependent coagulation. Partial inhibition was explained by the lack of 3G4 binding to other phospholipids (eg, phosphatidylethanolamine). (25)

In GLP repeat-dose toxicology studies, bavituximab was generally well tolerated with effects in the rat limited to histological findings (minimal, chronic subendocardial inflammation) in the high-dose group (100 mg/kg/week for 8 weeks) and transient increases in coagulation times (aPTT and PT) at doses ≥ 20 mg/kg/week. Effects in monkeys were limited to transient increases in coagulation times (aPTT and PT) and histological changes (i.e., minimal to mild cardiac and pulmonary thrombi, subendocardial fibrosis, and minimal to mild pulmonary arteriopathy) in the high-dose group (100 mg/kg/week for 8 weeks).

Bavituximab did not have any biologically significant effects on monkey or human whole blood platelet aggregation at the range of concentrations tested (i.e., 1-3130 μg/mL bavituximab). Repeat doses of bavituximab up to 100 mg/kg did not affect time to healing in a full thickness excisional dermal wound model in rats.

3.2.4 Clinical Studies with Bavituximab

Bavituximab is currently being investigated in patients with refractory advanced solid tumor malignancies and in patients with chronic hepatitis C virus infection (HCV) by Peregrine Pharmaceuticals.

Antiviral studies

Three clinical studies to evaluate the antiviral activity of bavituximab have been conducted or are ongoing. In a phase 1 study, 30 patients with chronic HCV infection were treated with a single dose of bavituximab at 0.1, 0.3, 1, 3, or 6 mg/kg. Patients receiving 6 mg/kg had a slight elevation in d-dimer, which returned to baseline as the antibody cleared from circulation. Transient reductions in viral load suggestive of anti-viral activity were observed at all dose levels. In a phase 1b study, 24 patients with chronic HCV were treated twice weekly with bavituximab at 0.3, 1, 3, or 6 mg/kg. Bavituximab exhibited predictable PK characteristics in both studies. All dose levels tested exhibited transient anti-viral activity, and 3 mg/kg appeared most active.

Cancer studies

Five studies with bavituximab in oncology indications have been conducted or are ongoing.

A phase 1 IND study in patients with advanced solid tumor malignancies was conducted to evaluate the safety, PK, and maximum tolerated/effective dose of bavituximab given as a single agent weekly for 4 weeks. Twenty-six patients were enrolled at 0.1, 0.3, 1, or 3 mg/kg. Most adverse events (AEs) related to bavituximab were mild or moderate, and linear PK characteristics were observed. Pulmonary embolism, considered serious and related to study drug, was the only dose limiting toxicity observed in the study. This adverse event was grade 4 in nature and occurred in one patient 7 days after initiation of therapy.

Another study in advanced solid tumor malignancies was conducted using 3 mg/kg bavituximab weekly for 8 weeks in combination with chemotherapy (docetaxel, gemcitabine, or paclitaxel + carboplatin). Two patients in the docetaxel arm discontinued bavituximab treatment after developing severe infusion reactions; urticaria in both patients. In response to these observed infusion reactions, the protocol was amended to add instructions for premedication with a steroid and an antihistamine prior to each bavituximab infusion. One patient with stage IV ovarian carcinoma developed grade 4 refractory hypotension 2 days after receiving the initial dose of docetaxel and bavituximab and expired 1 week after the initial serious adverse event (SAE); these events are considered probably study drug related. Twelve of the 14 patients enrolled were evaluable for tumor response using Response Evaluation Criteria in Solid Tumors (RECIST). Three patients achieved partial response (PR) (2 in the paclitaxel/carboplatin arm, 1 in the gemcitabine arm) and continued bavituximab maintenance on compassionate grounds, 3 patients demonstrated stable disease, and 6 patients had tumor progression. (26)

Two non-IND phase 2 studies are ongoing in locally advanced or metastatic breast cancer, to investigate the safety and efficacy of bavituximab 3 mg/kg weekly in combination with carboplatin plus paclitaxel in 28-day cycles or docetaxel in 28-day cycles. Fifteen of 46 patients treated in PPHM 0702 experienced AEs considered related to bavituximab, including fatigue and anemia, and 4 patients experienced drug-related severe adverse events (SAE);

among stage A patients (in a Simon 2-stage design) in the intent-to-treat (ITT) group, the ORR was 60% (9/15). Thirty-six of 46 patients treated in PPHM 0704 experienced AEs considered related to bavituximab, including epistaxis, infusion-related reaction, nasal dryness, and nail bed bleeding, and 4 patients experienced drug-related SAEs; the ORR for all enrolled patients was 61% (28/46). In PPHM 0702 and 0704 there were 6 grade 3 or 4 AEs (6 of 92 patients, incidence of 6.5%). The median number of bavituximab doses for a grade 3 or 4 adverse event was 15 (range, 8 to 20). (27, 28)

Another non-IND phase 2 study is being conducted in untreated locally advanced or metastatic NSCLC to investigate the safety and efficacy of bavituximab 3 mg/kg weekly in combination with carboplatin plus paclitaxel in 21-day cycles. Twenty of 49 patients experienced AEs considered related to bavituximab, including anemia and fatigue, and 8 patients experienced drug-related SAEs, which included fatal myocardial infarction (in 2 patients) and fatal hemoptysis and aspiration (in 1 patient). Among stage A patients (in a Simon 2-stage design) in the ITT group, the ORR was 52% (11/21). Grade 3 or 4 AEs were experienced by 28.5% of patients. The most common grade 3 or 4 AEs were anemia (4 patients), asthenia (4 patients) and neutropenia (4 patients). (29)

3.3 Study Rationale

Combination therapy consisting of bavituximab and sorafenib is attractive for patients with advanced HCC for the following reasons:

1. Based on the previously mentioned SHARP trial, sorafenib is the first drug in the modern era to receive FDA approval for treatment of advanced HCC. Although sorafenib is now established as part of standard therapy, its overall benefit is modest, and advanced HCC remains uniformly fatal. Due to the multiple escape mechanisms for angiogenesis inhibition in HCC, a logical next step would be to combine sorafenib with other biologic or chemotherapeutic agents.
2. Externalized PS is a desirable marker for tumor targeting for several reasons: PS is specifically and abundantly expressed on tumor vascular endothelium; it is present on a high percentage of tumor endothelial cells in a variety of solid tumors; it is absent from non-tumor vasculature; and it is expressed on the luminal side of tumor vascular endothelium, which is readily accessible for targeting drugs. Combining bavituximab, an angiogenesis inhibitor, with sorafenib, an angiogenesis inhibitor with a different mechanism, may prevent signaling escape mechanisms seen with either drug if given individually.
3. Data from preclinical studies have demonstrated that sorafenib therapy increases PS exposure on tumor vascular endothelium in a HCC tumor model. The increase of PS exposure will amplify the target for bavituximab and should increase tumor vessel destruction producing increased treatment efficacy.

It is our hypothesis that combination therapy with bavituximab and sorafenib will provide greater clinical efficacy than either agent alone with minimal toxicity.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a non-randomized, open-label, single-institution phase I/II therapeutic trial of bavituximab and sorafenib in patients with advanced HCC. This study will be activated at the UT Southwestern Medical Center, (comprised of The Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Hospitals-St. Paul and Parkland Memorial Hospital System), VA-North Texas, and UT Austin-Seton. Advanced HCC is defined as disease that is not amenable to surgical resection or orthotopic liver transplantation or is metastatic in nature.

The phase I component of the study will consist of a traditional 3+3 dose escalation rule as outlined in section 11.0.

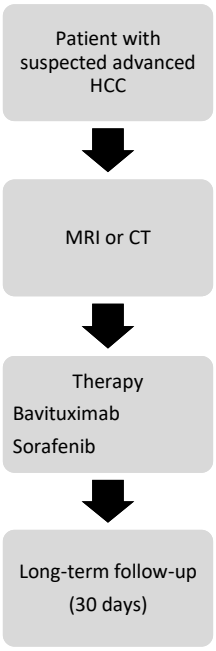
The dose levels of bavituximab (0.3,1.0,and 3.0 mg/kg weekly) were selected based on available data from preclinical and clinical studies that is predicted to achieve and sustain biologically active blood antibody levels or tumor binding in cancer patients.

- A bavituximab dose of 3 mg/kg gives a blood concentration in excess of that needed for maximal efficacy based on preclinical models while having little effect on coagulation and safety laboratory parameters and causing no significant depletion of the cofactor protein, β2GP1.
- In preclinical models, dosing above the biologically effective blood concentration of 2 μg/mL did not increase anti-tumor efficacy.
- Treatment with ≤ 3 mg/kg bavituximab appears to be well tolerated.
- β2-glycoprotein I levels are significantly depleted above 3 mg/kg bavituximab.

4.2Intervention

4.2.1Phase I component

The following is a brief schematic of Phase I component study flow:



Patients will be eligible for enrollment on study if they have a diagnosis of HCC by at least one of the following criterion listed below:

a. Histologically confirmed hepatocellular carcinoma
b. Axial imaging consistent with liver cirrhosis and at least one solid liver lesion ≥2 cm with early enhancement and delayed enhancement washout regardless of alpha-fetoprotein (AFP) levels.
c. AFP ≥ 400 ng/ml and evidence of at least one solid liver lesion ≥ 2 cm regardless of specific imaging characteristics.

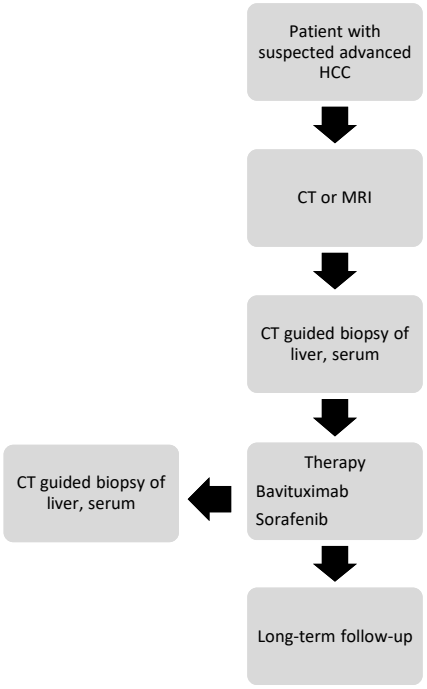
Patients also need to have advanced disease as defined previously in section 4.1. Attending surgical oncology, hepatologists and liver transplant physicians (either surgeons or hepatologists) with expertise in the management of HCC will assess suitability of surgical resection and liver transplantation at participating sites.

All patients will initially be staged with a liver protocol MRI or CT of the abdomen. A chest CT will be done if there is a concern for intra-pulmonary metastases.

Bavituximab will be administered on a weekly schedule until completion of the phase I component of the study or the development of any of the criteria for requiring removal from the study as outlined in Section 11 of the protocol. Bavituximab will be dosed according to the timeline of the phase I and II components of the study. In the phase I component, bavituximab will be started at 0.3 mg/kg and will be escalated pending DLT to 1.0 mg/kg and 3.0 mg/kg. These doses will be given intravenously over 90 minutes starting on day 1. Sorafenib will be initially dosed at 200 mg orally twice a day and escalated to the target dose of 400 mg orally twice a day at the discretion of the treating medical oncologist. Sorafenib will be started within 3 days of the initial bavituximab

dose. At the completion of the study treatment period of one cycle sorafenib will be continued at the discretion of the treating oncologist.

4.2.2 Phase II Component



Patients will be eligible for enrollment on study if Histologically confirmed hepatocelluar carcinoma.

Patients also need to have advanced disease as defined previously in section 4.1. Attending surgical oncology, hepatologists and liver transplant physicians (surgeons or hepatologists) with expertise in the management of HCC will assess suitability of surgical resection and liver transplantation at participating sites.

All patients will initially be staged with a liver protocol CT or MRI of the abdomen. A chest CT will be done if there is a concern for intra-pulmonary metastases.

Prior to the initiation of therapy serological markers (alpha-fetoprotein and viral hepatitis markers, including hepatitis C antibody and hepatitis B surface antigen), serum, image guided core biopsy of an intra-hepatic tumor (performed for clinical care. If the biopsy is performed for clinical care, additional needle core specimens (up to 3) will be obtained in addition to the number needed for

histopathological analysis. This is of minimal additional risk as same needle tract will be used to acquire additional specimens.

Bavituximab will be administered on a weekly schedule until intolerable toxicity, or the development of any of the criteria for requiring removal from the study as outlined in Section 14 of the protocol. Sorafenib will be administered on a daily schedule until intolerable toxicity, or the development of any of the criteria for requiring removal from the study as outlined in Section 14 of the protocol. The dose of bavituximab for the phase II component will be the maximum tolerated dose determined in the phase I component. In the phase I component, bavituximab will be started at 0.3 mg/kg and will be escalated pending DLT to 1.0 mg/kg and 3.0 mg/kg. These doses will be given intravenously over 90 minutes starting on day Sorafenib will be initially dosed at 200 mg orally twice a day and escalated to the target dose of 400 mg orally twice a day at the discretion of the treating medical oncologist. Sorafenib will be started within 3 days of the initial bavituximab dose.

Between five and six weeks following the first dose of bavituximab, alpha-fetoprotein(serum), a second image guided core biopsy of an intra-hepatic tumor will be performed.. This second image guided biopsy is optional and will be subject to informed consent with the enrolled patient. This biopsy will be for research purposes only and performed in the exact same way as the clinical care biopsy.

Bavituximab and sorafenib will be administered until intolerable toxicity, or the development of any of the criteria for requiring removal from the study as outlined in Section 14 of the protocol. Serum studies (including alfa-fetoprotein) and CT or MRI will be performed every 6 weeks +/- 5 days following the initial 2-week studies until removal from study. All patients will be followed long-term for the secondary endpoint, overall survival, to a point 12 months from accrual of the final patient.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Bavituximab

IND Number: 109134

Finished Product

Presentation and Composition

Bavituximab is supplied as a sterile, preservative-free solution with 10 mM acetate at pH 5.0 and diluted with 0.9% (w/v) saline (normal saline) to a final volume of 100 mL.

Storage

Bavituximab is stored at 2°C to 8°C. Once diluted, it should be stored at room temperature and used within 8 hours.

Availability and Accountability

Peregrine Pharmaceuticals, Inc in Tustin, CA will provide bavituximab. The pharmacist or designee must keep an accurate accounting of the number of investigational units received from Peregrine, dispensed to patients, and returned to Peregrine during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol in patients who are under the direct supervision of an investigator. All unused clinical study medications/treatments will be returned to Peregrine.

Administration

Bavituximab will be administered weekly. Prior to each bavituximab infusion, the patient must be pre-medicated with a steroid and an antihistamine to decrease the risk of an infusion reaction, 250 mg hydrocortisone IV and 50 mg diphenhydramine IV administered 30 minutes prior to infusion will be given.

Infusion preparation and administration are to be performed as follows:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used). Fill treatment into a sterile glass bottle or plastic IV bag.
2. Using aseptic techniques, repeat procedure until the calculated volume has been put in to the container. Bring the final volume to 100 mL using 0.9% Sodium Chloride Injection, USP.
3. Administer through a low protein binding 0.2-micrometer in-line filter (placed as proximal to the patient as practical).
4. Affix the infusion line and prime it with infusate before starting the infusion. Infuse the solution intravenously over 90 (± 10) minutes. No reduction in infusion time will be permitted. Flush the line with normal saline after infusion.

5.2 Sorafenib Tosylate (Nexavar™)

Please refer to the FDA-approved package insert for Nexavar™ for product information, extensive preparation instructions and a comprehensive list of adverse events.

Active Ingredient

Chemical Name:	4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate
Trade Name:	Nexavar™
Empirical Formula:	C21H16ClF3N4O3 x C7H8O3S
Relative Molecular Weight:	637.0

Physical Properties:	Insoluble in aqueous media
	Slightly soluble in ethanol
	Soluble in PEG 400

Finished Product

Presentation and Composition

Nexavar™ contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

Nexavar™ tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP controlled room temperature). Store in a dry place.

Availability

Nexavar™ tablets are manufactured by Bayer Healthcare Systems and are commercially available.

Administration

Nexavar™ tablets will be administered orally, as outlined in sections 4.2.1 and 4.2.2.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Patients must have a diagnosis of hepatocellular carcinoma by at least one criterion listed below:
    a. Histologically confirmed hepatocellular carcinoma
    b. Axial imaging consistent with liver cirrhosis and at least one solid liver lesion ≥2 cm with early enhancement and delayed enhancement washout regardless of alpha-fetoprotein (AFP) levels.
    c. AFP ≥ 400 ng/ml and evidence of at least one solid liver lesion ≥ 2 cm regardless of specific imaging characteristics.
2. Locally advanced or metastatic disease.
    a. Patients with locally advanced disease must have disease deemed to be unresectable or not eligible for hepatic transplantation surgical oncologist or transplant physician.
    b. Measurable disease, as defined as lesions that can accurately be measured in at least one dimension (longest diameter to be

measured) according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at least 2 cm with conventional techniques or at least 1 cm with spiral computed tomography.

3. Child-Pugh Score A or B7.
4. Age ≥ 18 years.
5. Eastern Cooperative Oncology Group (ECOG) Performance Score of 0-2.
6. Absolute neutrophil count ≥ 1,200 cells/mm^3.
7. Platelet count ≥ 70,000 cells/mm^3.
8. Total bilirubin ≤ 3.0 mg/dl.
9. Hemoglobin ≥ 8.5 g/dl.
10. INR ≤ 1.8 (therapeutic anticoagulation allowed as long as medically indicated.)
11. Creatinine ≤ 1.5 times upper limit of normal.
12. Women of childbearing potential must have a negative pregnancy test.
13. No clinically significant episode of gastrointestinal bleeding within the previous 30 days.
14. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter.
15. At least 4 weeks since prior locoregional therapy including surgical resection, radiotherapy, hepatic arterial embolization or chemoembolization, radiofrequency ablation, percutaneous injection or cryoablation (treatment of target lesion only, non-target lesions can be treated with locoregional therapy). Provided the target lesion increased in size by 25% or more or the target lesion was not treated with locoregional therapy.
16. Greater than 4 weeks since prior interferon therapy.
17. Greater than 4 weeks since prior and no concurrent use of rifampin or St John's wort.
18. Prior antiviral therapy is allowed.
19. Life expectancy > 12 weeks.
20. Ability to understand informed consent and signing of written informed consent prior to initiation of protocol therapy.
21. Non-English speaking patients will be enrolled.

6.2 Subject Exclusion Criteria

1. History of bleeding diathesis or coagulopathy.
2. Symptomatic or clinically active brain metastases.
3. Major surgery within previous 4 weeks.
4. Clinically significant non-gastrointestinal bleeding within previous 12 months.
5. Concurrent hormone therapy (including hormone replacement therapy and anti-estrogen).
6. History of any condition requiring anti-platelet therapy with the exception of general cardiovascular prophylaxis with aspirin.
7. History of thromboembolic events (including both pulmonary embolisms and deep vein thrombosis but not including tumor thrombus)
8. Active infection
9. Patients who are pregnant or lactating.

10. Hypersensitivity to IV contrast not suitable for pre-medication.
11. Patients with known hypersensitivity to any of the components of bavituximab or sorafenib.
12. Any other medical condition, including mental illness or substance abuse deemed by the investigators to likely interfere with a patient's ability to sign informed consent, cooperate and participate in the study or follow-up procedures.
13. Patients with human immunodeficiency virus (HIV).
14. Significant history of cardiac diseases, including any of the following:
    a. LVEF < 40% by MUGA or myocardial scintigram.
    b. NYHA class III-IV congestive heart failure.
    c. Myocardial infarction within previous 6 months.
    d. Cardiac arrhythmias requiring anti-arrhythmic therapy (other than beta blockers or digoxin)
15. Evidence of poorly controlled hypertension (medically controlled hypertension is allowed provided blood pressure ≤150/90.)
16. History of liver or renal transplantation.
17. Prior adjuvant therapy with sorafenib or other Raf/MEK/RAS or VEGFR inhibitors. Prior adjuvant therapy is allowed provided it was completed > 6 months ago and there is documented recurrence of hepatocellular carcinoma.

7.0 RECRUITMENT PLAN

The study will be open to all patients seen at the UT Southwestern Medical Center (including Parkland Memorial Hospital System, UT Southwestern-St. Paul Hospital and the Harold C. Simmons Cancer Center), VA-North Texas, and UT Austin-Seton who meet the eligibility criteria outlined in section 6.0.

In addition, a description of the study and the enrollment criteria will placed on the UT Southwestern Medical Center website to maximize patient recruitment. Patients will be identified from surgical, hepatology, gastroenterology and medical oncology clinics for treatment of their disease. After a discussion of the patient's disease and a formulation of the initial treatment plan, the physician-investigator will describe the study to the patient. The protocol will be discussed in a private clinic room or office. Details including the risks and obligations of the subjects will be explained. For non-English speaking patients, an independent translator will be available to communicate the details of the protocol. A research coordinator will be available either in the clinic or by phone to answer any additional questions.

Upon completion of the informed consent form and confirmation of protocol eligibility, the Clinical Research Office (CRO) at the Harold C. Simmons Cancer Center will be notified of the new enrollment. All patients will be entered into the Velos Clinical Trials Management System for ongoing monitoring.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to

read, agree to and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described above. Patients will not receive payment for their participation on this study.

8.0 PRETREATMENT EVALUATION

8.1 Phase I component

To be completed within 30 +/- 3 days of starting therapy;

- CT abdomen or MRI abdomen with liver protocol
- A 12 lead electrocardiogram
- Bilateral venous duplex of lower extremities
- Documentation of all measurable or non-measurable disease parameters including radiographic imaging procedures within four weeks of study entry, and measure of biochemical marker of disease (if applicable) within four weeks of study entry. The RECIST criteria as defined by CTEP (http://ctep.info.nih.gov/policies) define measurable and non-measurable disease.
- Signed informed consent for study participation.

To be completed within 14 +/- 3 days of starting therapy:

- History and physical examination, including height, weight, calculated body surface area (BSA), vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (ECOG). See Appendix A for ECOG scale.
- Serum pregnancy test for all women of childbearing potential within 14 days of starting therapy. If the test result is positive, the patient will not be allowed to participate in the study.
- Laboratory evaluation and coagulation parameters
    - CBC with differential and platelet count
    - Serum chemistries (Na, Cl, BUN, Creatinine, K, bicarbonate and glucose), albumin and calcium
    - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
    - Coagulation parameters (aPTT, PT and INR)
    - Urinalysis, record protein, glucose and blood
- Recording of concomitant medications

8.2 Phase II component

To be completed within 30 +/-5 days of starting therapy:

- CT or MRI abdomen with liver protocol
- A 12 lead electrocardiogram
- Biopsy (US or CT guided) of malignancy with histologic confirmation
- Bilateral venous duplex of lower extremities
- Documentation of all measurable or non-measurable disease parameters including radiographic imaging procedures within four weeks of study entry, and measure of biochemical marker of disease (if applicable) within four weeks of study entry. The RECIST criteria as defined by CTEP (http://ctep.info.nih.gov/policies) define measurable and non-measurable disease.
- Signed informed consent for study participation.

To be completed within 14 +/- 5 days of starting therapy:

- History and physical examination, including height, weight, calculated body surface area (BSA), vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (ECOG). See Appendix A for ECOG scale.
- Serum pregnancy test for all women of childbearing potential within 14 days of starting therapy. If the test result is positive, the patient will not be allowed to participate in the study.
- Laboratory evaluation and coagulation parameters
  - CBC with differential and platelet count
  - Serum chemistries (Na, Cl, BUN, Creatinine, K, bicarbonate and glucose), albumin and calcium
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
  - Coagulation parameters (aPTT, PT and INR)
  - Urinalysis, record protein, glucose and blood
  - Alfa-fetoprotein
  - Viral hepatitis titers
- Recording of concomitant medications

9.0 TREATMENT/INTERVENTION PLAN

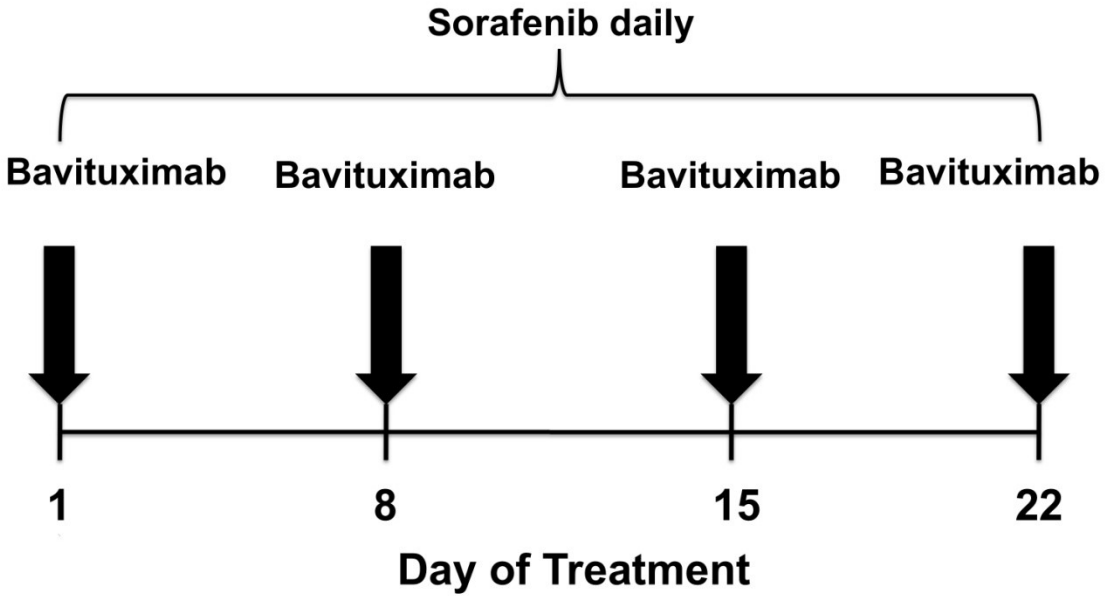
9.1 Therapy (Bavituximab and Sorafenib)

All therapy must be delivered within the UT Southwestern Medical Center and affiliates, VA-North Texas, and UT Austin-Seton.

Eligible patients with advanced HCC will receive the following:

Bavituximab:	Phase I: 0.3 mg/kg, 1.0 mg/kg, or 3.0 mg/kg IV over 90 minutes weekly until disease progression or completion of 1 cycle of treatment. The dose of bavituximab will be determined by the progression of the standard 3+3 dose escalation rule explained in section 11.0. Phase II: 0.3 mg/kg,1.0 mg/kg, or 3.0 mg/kg IV over 90 minutes weekly until disease progression or DLT. The dose of bavituximab will be determined as the MTD from the phase I component as described in section 11.0.
Sorafenib:	200 mg PO twice a day escalating to 400 mg PO twice a day at the discretion of the treating oncologist.

A cycle constitutes 4 doses of bavituximab and 4 weeks of daily sorafenib. The treatment schema is shown below for one cycle of therapy.



Patients will be seen the day of, or within one day preceding administration of and bavituximab. An interim medical history, with particular reference to toxicities, including medication review and physical examination will be conducted at each therapy treatment visit.

A therapy treatment may be moved +/- 5 days for specific administration reasons, including clinic closure for holidays. Pre-treatment laboratory values will be captured during therapy treatment.

9.2 Therapy (Bavituximab and Sorafenib) Treatment Parameters

Parameters for initiation of therapy (day 1) cycle #1 are as follows:

- Absolute neutrophil count ≥ 1,200 cells/mm^3
- Platelet count ≥ 70,000/mm^3
- Hemoglobin ≥ 8.5 g/dl
- Creatinine ≤ 1.5 times upper limit of normal
- Total bilirubin ≤ 3.0 mg/dl

Parameters for subsequent cycles of therapy (cycles 2-6+) on day of or day-1 pre-therapy:

- Absolute neutrophil count ≥ 1,000 cells/mm^3
- Platelet count ≥ 50,000/mm^3
- Total bilirubin ≤ 5.0 mg/dl

All laboratory and coagulation evaluations as listed in the screening period should be performed prior to start of each cycle.

If above parameters are not met for therapy, hold until recovered, maximum 4 weeks then re-treat per section 9.4, Dose Delays and Modifications.

9.3 Supportive Care Guidelines for Therapy (Bavituximab and Sorafenib)

- Recommended anti-emetics for therapy regimen
    - Bavituximab and sorafenib are minimal risk emetogenic regimens. The anti-emetic regimen is per institution guidelines and typically includes no additional anti-emetic therapy.
- Recommended pre-medication regimen to reduce infusion reactions
    - The recommended pre-medication regimen includes the following prior to bavituximab infusion prior to infusion:
        - Hydrocortisone 250 mg IV on all days of IV therapy
        - Diphenhydramine 50 mg IV on all days of IV therapy

The dose of hydrocortisone may be reduced or omitted where medically indicated (i.e. diabetes).

Concurrent supportive care is not restricted, including the use of narcotics for pain control, anti-emetics or anti-diarrheals. No concurrent chemotherapy, immunotherapy, radiation therapy or chemoembolization is permitted during therapy. Use of epoetin alfa and white blood cell support is permitted at the discretion of the treating physician.

9.4 Therapy (Bavituximab and Sorafenib) Dose Delay and Modification

Treatment may be delayed no more than 4 weeks to allow recovery from acute toxicity, i.e. if treatment ends up being held for a total of >4 weeks due to toxicity, the patient should come off study.

Dose reductions are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 4.0 (http://ctep.cancer.gov/forms/CTCAEv4.pdf).

Management of Toxicities Specific for Sorafenib

- Dose modification for skin toxicity
  - Grade 1: Continue sorafenib and consider symptomatic treatment with topical therapy
  - Grade 2:
    - First occurrence: Continue sorafenib and consider symptomatic treatment with topical therapy
    - Second or third occurrence: Hold treatment until resolves to grade 0 or 1: resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day)
    - Fourth occurrence: discontinue drug
  - Grade 3:
    - First or second occurrence: Hold treatment until resolves to grade 0 or 1: resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day)
    - Third occurrence: discontinue drug

There will be no listed dose delay or modification specific for bavituximab other than those illustrated in section 14.0.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Investigations/Tests	Baseline	At Each Dose of Bavituximab	6 Weeks (+/-5 days) After Initiation of Therapy
Detailed history and physical examination (including height, weight, ECOG, vitals)	X	X (Day 1 of each cycle only)	
Written Informed Consent	X		X (for image guided biopsy

			of tumor) (phase II only)
EKG	X		
Research Serum	X (phase II only)		X (and every 6 weeks thereafter) (phase II only)
Image-guided biopsy of tumor,	X (phase II only)		X (phase II only, between 5 and 6 weeks)
Hematology (CBC with differential)	X	X	
Liver function tests (including total bilirubin, AST, ALT)	X	X	
Coagulation tests (including PT, aPTT, INR)	X	X	
Urinalysis	X		
Alpha-fetoprotein	X	X	
MRI abdomen with gadolinium or CT Abdomen	X		X (and every 6 weeks thereafter) (phase II only)
Bilateral lower extremity venous duplex	X		X (phase II only)
Viral hepatitis titers (Hepatitis B and C)	X (phase II only)		

<u>Investigations/tests at study exit due to disease progression or toxicity or following completion of the phase I component</u>

- Bilateral venous duplex of lower extremities

- History and physical examination (this will continue every 6 weeks for determination of secondary endpoint of overall survival)
- Laboratory tests: same as required at baseline

10.1 Correlative Studies (Phase II patients only)

Pathology Correlative Studies

A major obstacle to molecularly targeted chemotherapeutic agents has been obtaining relevant tumor tissue to measure the agents' biologic effects on target molecules or cellular pathways within the tumor. The utilization of sequential tumor biopsies to obtain tissue following treatment is well established in breast and colorectal carcinoma. (30) However, sequential tumor biopsies of liver tumors are less established due to a fear of procedural complications. The fear of bleeding events following liver biopsy of HCC appears unfounded and based on anecdotal evidence. A large, multi-institutional trial where patients with advanced chronic hepatitis C underwent sequential liver biopsies demonstrated 16 cases (0.6%) of bleeding following 2740 liver biopsies. There were no deaths from peri-procedural bleeding and a platelet count under 60000 was identified as a risk factor. (31) Two large published series of core needle biopsy of HCC as a diagnostic measure report bleeding events in less than 1% of patients with no reported mortalities. In both series capsular location of HCC was associated with increased incidence of bleeding event. (32,33)

In this study all patients will potentially undergo up to two image-guided (either CT or ultrasound) core needle biopsy of a single site of HCC at baseline (for clinical care) and between five and six weeks after the initiation of bavituximab. In addition to the patients receiving treatment as part of this clinical trial, patients identified from the HCC clinics at UT Southwestern who are initiating sorafenib monotherapy will undergo biopsies at baseline and between five and six weeks after initiation. These biopsies are not mandatory to initiate or continue with therapy and are subject to a separate informed consent. To increase patient safety the following conditions must be met prior to liver biopsy:

- Platelet count $\geq$ 70,000
- INR $\leq$ 1.8
- Target lesion not subcapsular in nature as determined by the participating interventional radiology team
- Sorafenib will be discontinued for a period of 24-48 hours prior to biopsy

The patient will sign the informed consent for participation in research liver biopsy prior to the procedure. The liver biopsy will be performed by radiologists and the ancillary staff of Department of Radiology following the standard clinical protocol, which includes obtaining a separate informed consent for the procedure itself. The core samples will be provided to the surgical oncology laboratory. If a core biopsy is performed as a part of the

patient's clinical care, extra cores will be obtained for surgical oncology laboratory, in addition to the cores necessary for clinical care. All cores will be obtained through the same needle to avoid the need of additional punctures and to minimize associated risks.

We will plan to use this tissue to correlate patient outcome measures with markers of anti-angiogenesis therapy and immune response modulation on patients with matched samples. Specifically, we will perform the following tissue based analysis at baseline and 5 and 6 following initiation of either monotherapy with sorafenib or combination therapy with bavituximab and sorafenib :

- Histologic analysis of cell infiltrate of the tumor (specifically macrophage and T cell, both cytotoxic and regulatory)
- Localization of PS exposure on tumor vascular endothelium
- Markers of immune response including T cell activation assays
- Analysis of angiogenic, hypoxia and RAS/MAPK pathway tissue biomarkers

These tissue-based analyses will be correlated with the primary endpoint of time to progression. The collection of tissue in patients treated with sorafenib alone and with combination of sorafenib and bavituximab will allow us to further define the mechanism of action as it pertains to bavituximab. We believe the liver biopsies provide minimal risk to the patient and will allow us to validate whether the therapy regimen affects intended molecular targets to further elucidate mechanism of action. This will allow us in the future to develop a predictive profile to tailor this regimen in patients who will show the most benefit.

Laboratory Correlative Studies

The kinetics of alpha-fetoprotein and viral hepatitis titers (in those patients with baseline elevation) may serve as an early indicator of response to treatment in patients with advanced HCC. These biomarkers have been associated with response to sorafenib therapy and may serve as a predictive biomarker to treatment outcome with the bavituximab and sorafenib regimen. We plan to conduct an analysis of alfa-fetoprotein and viral hepatitis titer levels as biomarker surrogates of outcome. Specifically, alfa-fetoprotein titers will be drawn at baseline, at 2 weeks after initiation of therapy and every 6 weeks thereafter while still enrolled in the study. Quantitative changes in alfa-fetoprotein will be described for patients where matched samples are available and will be correlated with the primary clinical endpoint of time to progression.

In addition, serum angiogenic and hypoxia biomarkers will be analyzed from serum and plasma samples collected from patients treated with bavituximab and sorafenib and sorafenib alone. Blood will be collected in two separate vacutainer tubes, a red top with no additive and a purple top with EDTA additive.

Quantitative changes in the above biomarkers will be described for patients where matched samples are available and will be correlated with the primary clinical endpoint of time to progression.

The biopsy and serum samples for the above correlative studies will be shipped to Peregrine Pharmaceuticals for the completion of only the listed studies. The samples will be de-identified and shipped with codes only known to the primary investigator. All left over tissue or serum will be destroyed by Peregrine Pharmaceuticals.

11.0 DOSE-LIMITING TOXICITIES-PHASE I COMPONENT

The phase I component of the study will consist of a traditional 3+3 dose escalation rule with the dose of sorafenib remaining constant and the dose of bavituximab escalating up to 3.0 mg/kg weekly to determine the maximum tolerated dose (MTD) that will be used during the phase II component. Sorafenib has been demonstrated in multiple phase I and II studies in advanced HCC to have minimal toxicity and to be safe, therefore doses will be constant. (13,14) Cohorts of three patients will be assigned to one dose level of bavituximab starting at 0.3 mg/kg weekly. Only the first cycle of therapy (4 doses of bavituximab and 4 weeks of sorafenib constitutes a cycle) will be used to determine dose limiting toxicity (DLT). The patients will be followed for thirty days following the end of the first cycle for adverse events. These adverse events will be submitted to the Data Safety Monitoring Committee for evaluation. During this thirty-day period and beyond patients will be administered sorafenib at the discretion of the treating oncologist. Patients will be enrolled into the next highest drug cohort only after 3 or 6 patients have completed the first cycle of therapy. The number of observed toxicities is counted and the traditional escalation rule applied:

- No toxicity: the next three patients will be assigned to next higher dose level (3.0 mg/kg of bavituximab is the highest dose assigned).
- At least two toxicities: the MTD is exceeded and the phase I component of the trial will be stopped with the next lowest dose to be defined as the MTD that will be used in the phase II component.
- One toxicity: the cohort will be expanded to 6 patients.
    - One DLT within the last six patients: The next cohort of three patients will be assigned to the next highest dose level
    - At least two DLTs within the last six patients: the MTD is exceeded and the phase I component of the trial will be stopped with the next lowest dose to be defined as the dose that will be used in the phase II component.

The Data and Safety Monitoring Committee and investigators as described below will regularly review all adverse events. The study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events related to treatment.

The following will be considered a dose-limiting toxicity:

- Grade 4 neutropenia and thrombocytopenia ≥ 7 days (absolute granulocyte count < 0.5 x 10^9/L)
- platelet count < 25,000
- ALT or AST levels ≥ grade 3 adverse event for 7 days
- ≥ grade 3 adverse event for any non-hematologic toxicity (excluding alopecia and non-premedicated nausea/vomiting) attributable to drug therapy by the definition of definite or probable and not possibly. In the SHARP trial patients in the placebo arm had over a 50% ≥ grade 3 adverse event rate due to the comordities seen in the patient population with advanced HCC.

12.0 TOXICITIES/SIDE EFFECTS

12.1 Sorafenib

1. Cardiac ischemia and/or infarction: The incidence of cardiac ischemia/infarction was 2.7% in Nexavar™ patients compared with 1.3% in the placebo group and in patients treated with renal cell carcinoma. Temporary or permanent discontinuation of Nexavar™ should be considered in patients who develop cardiac ischemia and/or infarction.
2. Risk of hemorrhage: An increased risk of bleeding may occur following Nexavar™ administration. In the SHARP trial, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in Nexavar™ patients and 4% in placebo patients.
3. Hypertension: Blood pressure should be monitored weekly during the first 6 weeks of Nexavar™ therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In the SHARP trial, hypertension was reported in approximately 9.4% of Nexavar™ - treated patients and 4.3% of patients in the placebo group.
4. Dermatologic: Hand-foot skin reaction and rash represent the most common adverse reactions attributed to Nexavar™. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with Nexavar™. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Nexavar™, or in severe or persistent cases, permanent discontinuation of Nexavar™.

12.2 Bavituximab

1. Thromboembolic events: in the initial studies administering bavituximab for patients with chronic HCV infection there were no reports of

thromboembolic events including arterial thrombosis or venous thrombosis (deep vein thrombosis or pulmonary embolism). In later studies combining bavituximab and chemotherapy in cancer patients there was a small increase in thromboembolic events. These events were mainly deep vein thrombosis or pulmonary embolism. There were no fatal events attritubutable to these adverse events and it is unclear whether the events were a direct result of combined chemotherapy or the inherent risk of thromboembolic events seen in cancer patients.

2. Infusion reactions: Bavituximab is a chimeric antibody and some patients may experience side effects associated with monoclonal antibody therapy, including allergic/hypersensitivity reactions or cytokine release syndrome/acute infusion reactions. There is significant overlap between these reactions, with common manifestations including (but not limited to): drug fever, flushing, rash, dyspnea, bronchospasm, or hypotension. In studies investigating bavituximab in combination with chemotherapy, pre-medication with antihistamines and/or steroids was administered resulting in 20-30% Grade I or II adverse infusion reactions. These have been generally well tolerated, and have not required an alteration in bavituximab dosing.
3. Prolonged coagulation times: Prolonged coagulation times (e.g., aPTT) have been observed in preclinical and clinical studies that are not associated with significant bleeding. In clinical studies, prolongation of aPTT has been noted at the highest doses administered (3 and 6 mg/kg). This concentration- dependent, transient and reversible phenomenon is believed to be due to *in vitro* assay interference and does not pose a significant bleeding risk to patients.
4. Gastrointestinal: Nausea, vomiting and anorexia occur infrequently and are self-limiting without additional treatment.

Because of the potential for thrombogenicity with agents such as bavituximab, patients will be monitored for the development of thromboembolic events as follows:

- Regular assessment of blood coagulation parameters (PT, INR, aPTT). Regular screening for potential arterial or venous thromboses during physical examination
- Regular bilateral lower extremity venous doppler ultrasound

Thrombotic/thromboembolic events including, but not limited to, superficial thrombophlebitis, deep vein thrombosis, pulmonary embolism, cerebrovascular accident, ischemic stroke, coronary thrombosis, myocardial infarction, myocardial ischemia (including isolated ECG findings), arterial embolism, arterial thrombosis, catheter-related thrombosis, or intra-abdominal thromboembolism should be captured as an adverse event. Tumor thrombus is not a thrombotic/thromboembolic event and will not be captured as an AE.

Note: Elevated d-dimer alone does not constitute a thrombotic AE and should not be captured as such.

13.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT (Phase II Component)

For the purposes of this study, patients will be evaluated for response at 2 weeks after the first cycle of bavituximab and every 6 weeks thereafter. RECIST criteria are included below.

13.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

13.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques (PET, CT, MRI, x-ray) or as > 10 mm with a high-resolution CT scan. All tumor measurements must be recorded in millimeters or decimal fractions of centimeters. A "high-resolution" CT scan is one in which images are recorded at least every 5 mm.

13.1.2 Non-Measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

13.1.3 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 response.

13.1.4 Non-target lesions

All other lesions (or sites of disease) that are not target lesions as defined in section 13.1.3 will be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are required when feasible, since a patient may have progressive disease on the basis of larger non-target lesions. The presence or absence of each non-target lesion should be noted throughout follow-up.

13.2 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. The patient must be free of all symptoms of cancer.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Positive washing, brushing or biopsy and/or residual tumor may still be evident on endoscopy and/or CT scan. No lesion may increase in size and no new lesion may appear.

Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

13.3 Evaluation of non-target lesions

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

Non-Complete Response (non CR): Persistence of one or more non-target lesions or/ and maintenance of tumor marker level above the normal limits.

Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. (Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the reference radiologist (or study chair).

13.4 Evaluation of best overall response

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

Target Lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	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

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

2. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

13.5 Guidelines for evaluation of measurable disease

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

• Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.

• When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

13.6 Confirmatory measurement/duration of response

Confirmation: The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

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

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

14.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will receive at least one cycle of treatment. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease recurrence/progression, defined as emergence of an unequivocal new tumor (site of metastasis) > 1 cm in size, clinical progression in non-measurable sites of disease, or unequivocal changes in size of the primary tumor.
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial.
- Unacceptable toxicity or any adverse event that precludes further participation in the trial.
- The investigator removes the patient from the trial in the best interests of the patient.
- Patient death.
- Study completion or discontinuation.
- Patient withdraws consent to continued participation in the trial or is lost to follow-up.

15.0 BIOSTATISTICS

The study is an open-label, non-randomized single-arm, single institution phase I/II therapeutic clinical trial. The study population will be patients with advanced hepatocellular carcinoma.

15.1 Sample size calculation

The phase I component of the study will consist of a traditional 3+3 dose escalation rule with 3 or 6 patients in each cohort, the process for dose escalation is outlined in section 4.1.

The median TTP of patients with advanced HCC treated with sorafenib therapy is 5.5 months. Using this as a benchmark, we will enroll 38 patients, which will allow us to differentiate between a median TTP of 5.5 months and 8.3 months with 80% power and a two-sided significance level of 10% assuming a 24-month accrual and a 12-month follow-up period. TTP will be calculated from initiation of therapy to disease progression (intention to treat) as outlined in section 13.0. Removal from study as outlined in section 14 will be a censored event.

15.2 Secondary endpoints

Secondary endpoints of efficacy are to evaluate overall survival, progression-free survival and response rates. The overall survival and progression-free survival will be estimated using the Kaplan-Meier method, and Greenwood's formula will be used to calculate the standard error of the corresponding Kaplan-Meier estimate and 95% confidence interval. Survival curves will be estimated using Kaplan-Meier methodology. Response rates will be calculated as described in section 13.4. Accrual is expected to take 2 years with a minimum of 1year subsequent follow-up, overall follow-up will range from 1 to 3 years.

Other secondary objectives will include description of toxicity of the therapy regimen. These data will be analyzed separately. The safety analyses will be performed on all patients who receive any dose of therapy. Adverse events will be described using the NCI CTCAE v 4.0 criteria (ctep.cancer.gov/forms.CTCAEv4.pdf). Frequency and severity of adverse events according to the NCI CTCAE v# body system and severity criteria will be described. In addition, frequency of Grade 3 or 4 adverse events will be described separately. Causality will also be noted. Adverse events will be recorded for up to 1 year following discontinuation from study.

Laboratory assessments will also be described according to the NCI CTCAE v 4 criteria, with separate descriptions for Grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well. Serious adverse events will be summarized, including a causality assessment.

The number of treatment cycles and doses administered will be summarized using descriptive statistics. Treatment delays will summarized using counts and percentages.

Patients' disposition will be summarized in the following manner:

- The number and percentage of patients selected, included, completed, withdrawn and lost to follow-up will be summarized using descriptive statistics.
- Major protocol deviations will be summarized.
- The reason for withdrawal (adverse events, lack of efficacy, major protocol deviation, non-medical reason, recovery or remission) will be summarized.

For pathology-, laboratory- and imaging-correlative studies, Cox regression analysis will be conducted to investigate the association between TTP and parameters from correlative studies.

16.0 DATA MANAGEMENT

16.1 Data and Safety Monitoring

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance.

A detailed description of the Data and Safety Monitoring Plan is available in section X of the Clinical Research Office Operations Manual.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the patient population to be studied; adequacy of the data management system; and procedures to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles. The following examples can be used to begin developing DSMC plans for individual protocols.

- **High risk** examples include Phase 1 studies; Phase II or III studies where the SCC is the DSMC; gene therapy or recombinant DNA studies; and studies in which the investigator holds the IND.

- **Moderate risk** examples include pilot studies and other Phase II or III studies where the SCC DSMC is not the DSMC of record and which involve a non-FDA approved drug.

- **Low risk** examples include Phase II or III studies involving FDA-approved drugs where the SCC DSMC is not the DSMC of record, or trials, which involve non-therapeutic interventions.

- **Exempt** examples include non-interventional studies, which are exempt from audit requirements outlined above.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Patients of all races, both male and female, will be accepted into the protocol.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Hepatocellular carcinoma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of therapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of hepatocellular carcinoma or in a stabilization of an otherwise progressing disease.

It is not know, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, MRI scans (excluding the MRI scan at week 5 of treatment), all drug administration fees (excluding sessions where bavituximab is given), and all hospitalizations, even for complications of treatment. Bavituximab will be supplied to patients without costs from Peregrine Pharmaceuticals. Patients will not be responsible for the costs of tissue or serum procurement (including image guided biopsies) obtained for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in this study.

Alternatives: For patients with advanced hepatocellular carcinoma, alternative treatments may include other chemotherapy regimens or loco-regional therapies including transarterial chemoembolization and radiofrequency ablation. At present, no specific treatment approach is considered standard of care for the disease. Patients may be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (i.e., qualified monitors from UT Southwestern Medical Center, the NCI, etc.), may review patients records and pathology slides, as required.

17.1 Privacy

It is the responsibility of the research staff to endure that protocol subjects receive the UT Southwestern Medical Center Notice of Privacy Practices.

17.2 Adverse Events

Adverse Events will be reported as indicated by the appropriate following table (see below).

Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that occurs during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency); ***AND***
- Definitely, probably, *or possibly related* to participation in the research; ***AND***
- Serious or a possible unexpected problem in that the research *places subjects or others at a greater risk of harm than was previously known or recognized.* Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

Reporting

Local unanticipated problems require expedited reporting, are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to:UTSW SCC Data Safety Monitoring Committee Coordinator

Email: SCCDSMC@utsouthwestern.edu

Fax: 214-648-1906 or deliver to NB2.418

UTSW Institutional Review Board (IRB)

Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. **SAEs**

Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems

Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

Fax reports to study sponsor at:

IST Clinical Program Manager
Peregrine Pharmaceuticals, Inc.
Fax: (714) 200-0104

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to patients prior to their inclusion in the trial. Patients will also be informed that they are free to withdraw from the study at any time. All patients must sign an IRB-approved consent form indicating their consent to participate. This consent form will meet the requirements of the code of federal regulations, and the IRB of this center. The consent form will included the following:

1. The nature and objectives, potential toxicities and benefits of the intended study.
2. The length of therapy and the likely follow-up required.

3. Alternatives to the proposed therapy. This will included available standard and investigational therapies. In addition, patients will be offered an option of supportive care.
4. The name of the investigator (s) responsible for the protocol.
5. The right of the patient to accept or refuse treatment and to withdraw from participation in the study.

Each patient and consenting professional will sign the consent form in triplicate. One original signed consent form will become part of the patient's medical record, another original signed consent form will be stored in the patient's research file, and the third original signed consent form will be given to the patient.

19.0 SATELLITE SITE PATIENT ENROLLMENT PROCESS

Once screening procedures are completed. The following documentation must be provided to GI Clinical Research Manager (CRM) for review and enrollment:

- Signed signature page of informed consent;
- Signed and dated by Sub-Investigator and coordinator:
    - I/E criteria checklist;
    - Child-Pugh score form;
    - RECIST tumor assessment worksheet;
    - Subject Eligibility Verification form;

Once required materials are received and verified by the CRM. The enrollment verification form (EVF) will be signed and a study ID assigned to the patient. Once the signed EVF has been received by study staff the patient is ready to begin therapy.

20.0 References

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21.0 Appendices

Appendix A ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to be or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix B Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin (mg/dl)	<2.0	2.0-3.0	>3.0
Serum albumin (g/l)	>3.5	2.8-3.5	<3.5
INR	<1.7	1.7-2.2	>2.2
Ascites	None	Mild (based on clinical findings)	Severe (based on clinical findings)
Hepatic Encephalopathy	None	Controlled Medically	Refractory

5-6 points Child-Pugh A
7-9 points Child-Pugh B
10-15 points Child-Pugh C

Appendix C NYHA Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

Appendix D Sample Consent Form

The University of Texas Southwestern Medical Center at Dallas

Parkland Health & Hospital System

Children's Medical Center

Texas Scottish Rite Hospital for Children

Presbyterian Hospital of Dallas

VA-North Texas

CONSENT TO PARTICIPATE IN RESEARCH

Consent 1 of 2

Title of Research:	A Phase I/II Study of Bavituximab and Sorafenib in Patients with Advanced Hepatocellular Carcinoma
Funding Agency/Sponsor:	UT Southwestern Medical Center; Peregrine Pharmaceuticals
Study Doctors:	Adam C. Yopp, John C. Mansour, C. Glen Balch, Yull Arriaga, Sirrisha Karri, Muhammad Shaalan Beg, , William M. Lee, Juan Arenas, Meelie Debroy, , Jonathan Dowell, Takeshi Yokoo, and Hao Zhu
Research Personnel:	Tyson Dudley, Alisha Hill, Erika Lopez,

You may call these study doctors or research personnel during regular office hours at 214.648.5870. At other times, you may call them at 214.645.8424.

Instructions:

Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?

This study is being done to find out whether an investigational (non-FDA approved) drug combination including bavituximab and sorafenib can treat hepatocellular carcinoma better or more safely than standard medication. The word "investigational" means the combination of bavituximab and sorafenib is still being

tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA) for combination treatment of hepatocellular carcinoma. Sorafenib has been approved by the FDA and is not considered an investigational drug.

Why is this considered research?

This is a research study because the combination of bavituximab and sorafenib has not been previously used in combination as study drugs for hepatocellular carcinoma.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?

You are being asked to take part in this study because you have hepatocellular carcinoma.

Do I have to take part in this research study?"

No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?

About 56 people will take part in this study at UT Southwestern, Parkland Health and Hospital System VA-North Texas or UT Austin-Seton.

What is involved in the study?

If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

Screening Procedures

To help decide if you qualify to be in this study, the researchers may ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

- Demographic information
- Medical history and physical exam
- Vital signs
- Blood tests
- Radiology (x-ray) tests
- Biopsy of liver tumor
- Urinalysis
- EKG

Treatment

If you decide to participate in this study you will take the following:

- 1-2 tablets of sorafenib (200-400mg daily, twice a day) and
- Bavituximab is given intravenously once a week, the approximate time to complete each infusion is 90 minutes
    - The study uses increasing doses of bavituximab and your dose of bavituximab may be different from other patients in the study.

Participation and Evaluation during the Research

Participation in this study will involve several procedures. Many of these procedures are part of the normal process of treating tumors such as yours. However, some of these procedures can be uncomfortable, inconvenient or painful. In addition to the procedures associated with the administration of bavituximab and sorafenib as detailed above, you will be asked to participate in other procedures as part of your involvement in this study.

1. Blood tests: Blood will be drawn from your vein prior to enrollment in the study and every week prior to the administration of bavituximab up until the time you are no longer receiving bavituximab. No more than 45 ml (3 tablespoons) of blood will be collected at any one time.
2. Urinalysis: A urine sample will be collected prior to enrollment and every week prior to the administration of bavituximab up until the time you are no longer receiving bavituximab.
3. CT or MRI Scan: This imaging test will be performed prior to enrollment in the study and every 6 weeks up until the time you are no longer receiving bavituximab.
4. Biopsy of liver tumor: If a biopsy of your liver tumor is deemed necessary for your clinical care, we would like to collect additional specimens for research in addition to the amount needed for clinical care. A second biopsy may be collected at the 5-6 week visit or after five to six doses of bavituximab. This second biopsy is the optional component of the study. A separate consent form will be completed by the study participant prior to performing this

procedure.

5. Bilateral lower extremity venous duplex: This routine test will be performed prior to enrollment and at 6 weeks after the first dose of bavituximab.

There will be no scheduled additional doctors' office visits for the study. Study visits will be included during the routinely scheduled follow-up, which is routine for these types of treatment.

The first biopsy will be collected prior to enrollment in the study. If a biopsy of your liver tumor is deemed necessary for your clinical care, we would like to collect a small amount of specimen for research in addition to the amount needed for clinical care. The second biopsy of the liver tumor (completed 6 weeks after the first dose of bavituximab) is designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at your second tumor biopsy to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the second tumor biopsy done in this study is not for medical purposes, the research results will not be sent to you or to your regular doctor.

Procedures for storing of extra or left over samples

The tissue obtained from the biopsies of the liver tumor will go to the surgical oncology laboratory at UT Southwestern Medical Center. The samples will be labeled with your name and Social Security Number to properly identify the samples. Only Dr. Adam C. Yopp will have access to the samples.

The biopsy and serum samples will be shipped to Peregrine Pharmaceuticals to complete research studies testing how the drugs you are taking in the study work. The samples will not have any personal information on them and shipped with codes only known to Dr. Adam C. Yopp. All left over tissue or serum will be destroyed by Peregrine Pharmaceuticals.**How long can I expect to be in this study?**

We will ask you to be in this study for the rest of your life. You will receive the study drugs, bavituximab and sorafenib, until your hepatocellular carcinoma shows growth based on radiologic (X-ray) tests. After the initial treatment period, your participation in this study will be primarily limited to the follow-up, which is routine for patients with your type of tumor.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Procedure/Intervention

Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider. The risks of this study are primarily related to the combination chemotherapy and the biopsy of your liver tumor.

Bavituximab will be given to you as part of this study. Bavituximab is an investigational drug. Because it is an antibody made of human and mouse proteins, some people may experience an allergic reaction to bavituximab. Possible side effects may include rash, hives, itching, shortness of breath, fever, flushing, chills, headache, nausea, vomiting, weakness, diarrhea, low blood pressure, difficulty breathing, or anaphylaxis (a severe form of allergic reaction). To lower the risk of developing allergic reactions your study doctor will give you medication(s) before each infusion.

Bavituximab is still being studied in humans and little is known about the possible side effects of bavituximab. Over 243 people have received bavituximab in research studies to date.

Frequent (Greater than 20% of patients):

- Nausea
- Fatigue
- Headache
- Abdominal pain
- Vomiting

Occasional (<20% of patients):

- Constipation
- High blood pressure
- Cough
- Anemia (decreased number of red blood cells)
- Anxiety
- Dry skin
- Dizziness
- Mild nose bleed
- Nasal dryness
- Back pain
- Joint pain
- Inflammation of the mouth
- Nail bed bleeding,
- Chest pain
- Irregular heartbeat

- Blurred vision
- Mild disorientation.

Rare but serious (< 2% of patients):

- Hypotension (low blood pressure)
- Ischemic heart disease and heart attack
- Blood clots involving arteries, veins, and in the lungs;
- Muscle weakness,
- Neuropathy (abnormal nerve function),
- Severe diarrhea
- Severe chest pain requiring hospitalization,
- Fever with low white blood cell count.

Many of these effects occurred in people with advanced cancer who were also receiving chemotherapy.

Animal studies also suggest that bavituximab may cause small clots in arteries found in the heart and lungs and/or thickening in arteries found in the heart and lungs. Clots may become life-threatening emergencies, especially if they break free in the veins or arteries and move to the heart, lungs, or brain, resulting in a heart attack, pulmonary embolism, or stroke. However, clots and thickened arteries were only seen in animals given a high enough bavituximab dose to significantly alter their clotting tests. The risk of both clotting and bleeding complications is unknown for the doses of study drug being tested in this study. As noted above, blood clots involving arteries, veins, and lungs have occurred uncommonly in people receiving bavituximab for cancer.

It is possible that in the event of a clotting event, management of appropriate levels of anti-clotting drugs may not work as well when given in combination with bavituximab. Your blood pressure and your blood's ability to form a normal clot will be closely monitored at each study visit. Additionally, if you experience any side effects between study visits (for example abdominal pain, bleeding, limpness/lameness, swelling, cold-induced symptoms such as Raynaud's phenomenon [such as discoloration of fingers and toes in response to cold]), headache, migraine (including change in severity or pattern of existing migraines), bone pain, joint pain, and visual disturbance, you should notify the study doctor right away.

Although uncommon, temporary disorientation, blurred vision, hypertension, and irregular heartbeat were reported in studies of bavituximab in people with chronic hepatitis C infection. Events usually resolve on their own without treatment and additional tests did not reveal any heart damage or blood clots.

Sorafenib will be given to you as part of this study. Sorafenib may cause some, all, or none of the side effects listed below. Sorafenib will be given in a standard fashion for people with tumors like yours.

Frequent (Greater than 20% of patients):

- Fatigue
- Rash of hands and feet
- Diarrhea
- Elevated liver enzyme blood levels
- Nausea

Occasional (<20% of patients):

- Elevated blood pressure
- Loss of hair
- Headache
- Dry cough
- Pain in joints
- Difficulty breathing
- Erectile dysfunction
- Dry skin
- Loss of feeling in hands and feet
- Itchy skin
- Constipation
- Drop in white blood count
- Decreased appetite
- Dry mouth
- Weight loss
- Not feeling hungry

Rare but serious (< 2% of patients):

- Heart attack
- Organ failure, death
- Kidney dysfunction
- Vomiting blood

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or

(2) a condom used with a spermicide (a substance that kills sperm).

Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or "tubes tied"),

(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Depo-Lupron, Implanon),

(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or

(4) an intrauterine device (IUD).

If you do become pregnant during this study, you must tell the researchers immediately.

Risks of Radiation-Diagnostic Test

The radiation dose that you will get from diagnostic tests is medically indicated for your condition and it is the same that you would get if you were not involved in this research study.

Risks of Blood Drawing

Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

You will have 45ml (3 tablespoons) of blood collected because you are in this research study.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

Study risks will be minimized or prevented by several measures at the beginning of the study and throughout your participation in the study. Patients will be screened prior to enrollment to assure that each patient meets the safety requirements of the study. All treatments will be modified within the study parameters to match your treatment needs. These modifications will include the area being treated with chemotherapy. Throughout your participation in the study you will be evaluated by personnel trained to recognize, minimize, and treat side effects of your treatment. You will be withdrawn from the study if you experience an adverse event which causes unacceptable risk as determined by the investigators. You will continue to receive standard medical care if you are no longer participating in the study.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Store study materials and sorafenib tablets in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Carry information about sorafenib and bavituximab in your purse or wallet.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?

If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?

If you agree to take part in this study, there may be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. The type of chemotherapy drugs used in this study may be superior to standard treatment.

We hope the information learned from this study will benefit others with hepatocellular carcinoma in the future. Information gained from this research could lead to better treatment.

What options are available if I decide not to take part in this research study?

You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Evaluation by a medical oncologist for chemotherapy

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?

No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?

No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?

It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, VA-North Texas, or UT Austin-Seton.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?

Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?

Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or if we are required by law to release it. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and

- The UT Southwestern Institutional Review Board.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Whom do I call if I have questions or problems?

For questions about the study, contact Adam C. Yopp, MD at 214.648.5870 during regular business hours and at 214.645.8424 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

Is there anything I should know before I decide?

Dr. Adam Yopp is a paid speaker for Onyx Pharmaceuticals and Bayer Healthcare, and Dr. Takeshi Yokoo is a paid consultant for Bayer Healthcare who manufactures the study drug Nexavar ®(Sorafenib). You should feel free to ask questions about this.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____

Participant's Name (printed)

_____ _____

Participant's Signature Date

_____

Legally Authorized Representative's Name (printed)

_____ _____

Legally Authorized Representative's Signature Date

_____

Name of person obtaining consent (printed)

_____ _____

Signature of person obtaining consent Date

INTERPRETER STATEMENT:

I have interpreted this consent form into a language understandable to the participant and the participant has agreed to participate as indicated by their signature on the associated short form.

_____

Name of Interpreter (printed)

_____ _____

Signature of Interpreter Date

The University of Texas Southwestern Medical Center at Dallas

Parkland Health & Hospital System

Children's Medical Center

Texas Scottish Rite Hospital for Children

Presbyterian Hospital of Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Consent 2 of 2 (Biopsy) - Optional

Title of Research:	A Phase I/II Study of Bavituximab and Sorafenib in Patients with Advanced Hepatocellular Carcinoma
Funding Agency/Sponsor:	UT Southwestern Medical Center
Study Doctors:	Adam C. Yopp, John C. Mansour, C. Glen Balch, Yull Arriaga, Sirrisha Karri, Muhammad Shaalan Beg, William M. Lee, Juan Arenas, Meelie Debroy, Jonathan Dowell, Takeshi Yokoo, and Hao Zhu
Research Personnel:	Tyson Dudley, Alisha Hill, Erika Lopez,

You may call these study doctors or research personnel during regular office hours at 214.648.5870. At other times, you may call them at 214.645.8424.

Instructions:

Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?

This study is being done to find out whether an investigational (non-FDA approved) drug combination including bavituximab and sorafenib can treat hepatocellular carcinoma better or more safely than standard medication. The word "investigational" means the combination of bavituximab and sorafenib is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA) for combination treatment of hepatocellular carcinoma. Sorafenib has been approved by the FDA and is not considered an investigational drug.

Why is this considered research?

This is a research study because the combination of bavituximab and sorafenib has not been previously used in combination as study drugs for hepatocellular carcinoma.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?

You are being asked to take part in this study because you have hepatocellular carcinoma and you are participating in treatment portion of this study

Do I have to take part in this research study?"

No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?

About 56 people will take part in this study at UT Southwestern or Parkland Health and Hospital System.

What is involved in the study?

Participation in this study will involve several procedures. Many of these procedures are part of the normal process of treating tumors such as yours. However, some of these procedures can be uncomfortable, inconvenient or painful. In addition to the procedures associated with the administration of bavituximab and sorafenib as detailed above, you will be asked to participate in other procedures as part of your involvement in this study.

> Biopsy of liver tumor: A second biopsy will be collected at the 5-6 week visit or after five to six doses of bavituximab

This second biopsy of the liver tumor is designed for research and not for medical purposes. In other words, they are not useful for finding problems or diseases. Even though the researchers are not looking at your second tumor biopsy to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or

treatment. Because the second tumor biopsy done in this study is not for medical purposes, the research results will not be sent to you or to your regular doctor.

Procedures for storing of extra or left over samples

The biopsy and serum samples will be shipped to Peregrine Pharmaceuticals to complete research studies testing how the drugs you are taking in the study work. The samples will not have any personal information on them and shipped with codes only known to Dr. Adam C. Yopp. All left over tissue or serum will be destroyed by Peregrine Pharmaceuticals.

The researchers will record and use your Social Security Number (SSN) in order to properly label the sample. You do not have to give this information to the researchers; it will not affect study participation. This information will remain confidential unless you give your permission to share it with others or if we are required by law to release it.

How long can I expect to be in this study?

We will ask you to be in this study for the rest of your life. After the initial treatment period, your participation in this study will be primarily limited to the follow-up, which is routine for patients with your type of tumor

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Procedure/Intervention

Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider. The risks of this study are primarily related to the combination chemotherapy and the biopsy of your liver tumor.

Biopsy of liver tumor

Prior to receiving bavituximab and sorafenib and five weeks after the study drugs have been given one of the tumors in your liver will be biopsied as part of this study. Biopsy of the liver tumor may cause some, all, or none of the side effects listed below. The biopsies will be performed in the standard way it performed for patients with tumors like yours. Your radiologist will discuss the risks of the biopsy with you in detail and will ask you to sign a separate consent form. If a liver biopsy is to be performed for clinical care anyway, additional specimens will be taken for research purpose in the same biopsy session. No additional puncture will be necessary for additional specimen, and this is unlikely to significantly increase the overall procedure risk.

Occasional (2-20% of patients):

- Pain at site of biopsy

Rare but serious (< 2% of patients):

- Bleeding from liver
- Leakage of bile from liver
- Difficulty in breathing
- Death

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or

(2) a condom used with a spermicide (a substance that kills sperm).

Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or “tubes tied”),

(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Depo-Lupron, Implanon),

(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or

(4) an intrauterine device (IUD).

If you do become pregnant during this study, you must tell the researchers immediately.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

Study risks will be minimized or prevented by several measures at the beginning of the study and throughout your participation in the study. Patients will be screened prior to enrollment to assure that each patient meets the safety requirements of the study. All treatments will be modified within the study parameters to match your treatment needs. These modifications will include the area being treated with chemotherapy. Throughout your participation in the study you will be evaluated by personnel trained to recognize, minimize, and treat side effects of your treatment. You will be withdrawn from the study if you experience an adverse event which causes unacceptable risk as determined by the investigators. You will continue to receive standard medical care if you are no longer participating in the study.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Store study materials and sorafenib tablets in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Carry information about sorafenib and bavituximab in your purse or wallet.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?

If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?

If you agree to take part in this study, there may be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. The type of chemotherapy drugs used in this study may be superior to standard treatment.

We hope the information learned from this study will benefit others with hepatocellular carcinoma in the future. Information gained from this research could lead to better treatment.

What options are available if I decide not to take part in this research study?

You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Evaluation by a medical oncologist for chemotherapy

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?

No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?

No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?

It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or, Parkland Health & Hospital System.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?

Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.

- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?

Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or if we are required by law to release it. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Whom do I call if I have questions or problems?

For questions about the study, contact Adam C. Yopp, MD at 214.648.5870 during regular business hours and at 214.645.8424 after hours and on weekends and holidays.

Is there anything I should know before I decide?

Dr. Adam Yopp is a paid speaker for Onyx Pharmaceuticals and Bayer Healthcare, and Dr. Takeshi Yokoo is a paid consultant for Bayer Healthcare who manufactures the study drug Nexavar ®(Sorafenib). You should feel free to ask questions about this.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____

Participant's Name (printed)

_____ _____

Participant's Signature Date

_____

Legally Authorized Representative's Name (printed)

_____ _____

Legally Authorized Representative's Signature Date

_____

Name of person obtaining consent (printed)

_____ _____

Signature of person obtaining consent Date

INTERPRETER STATEMENT:

I have interpreted this consent form into a language understandable to the participant and the participant has agreed to participate as indicated by their signature on the associated short form.

_____

Name of Interpreter (printed)

_____ _____

Signature of Interpreter Date