Title: A Phase II Randomized Multicenter Placebo-Controlled Blinded Study of Sorafenib Adjuvant Therapy in High Risk Orthotopic Liver Transplant (OLT) Recipients with Hepatocellular Carcinoma (HCC)

Test Drug: BAY 43-9006 (Sorafenib) Development Phase: Phase II

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Glossary and Abbreviations

°C degrees Celsius
°F degrees Fahrenheit
mL Microliter
AE adverse event
AFP alpha-fetoprotein
ALT alanine transaminase (also known as SGPT)
AM Adrenomedullin
AML acute myelogenous leukemia
ANC absolute neutrophil count
AST aspartate transaminase (also known as SGOT)
AUC area under the curve
AUC0-12 area under the concentration time curve from time 0 to 12 hours
BCLC Barcelona-Clinic Liver Cancer
bid *bis in die*, twice daily
BUN blood urea nitrogen
CBC complete blood count
CL/F total body clearance of drug from plasma calculated after oral administration (apparent oral clearance)
Cmax maximum drug concentration in plasma
CMH Cochran-Mantel-Haenszel
CML chronic myelogenous leukemia
CPA Child-Pugh A
CPB Child-Pugh B
CR complete response
CRF case report form (either paper or electronic)
CT computed tomography
CTC Common Toxicity Criteria
CTCAE Common Terminology Criteria for Adverse Events
CTEP Cancer Therapy Evaluation Program
DAA Direct Acting Antivirals
DCD donation after cardiac death
DCIS ductal carcinoma in situ
dL Deciliter
DLT dose limiting toxicity
DMC Data Monitoring Committee
EC Ethics Committee
ECG Electrocardiogram
ECOG Eastern Cooperative Oncology Group
EDC electronic data capture
eg *exempli gratia*, for example
ELISA enzyme-linked immunosorbent assay
ERK extracellular-signal-related kinase
etc *et cetera*, and so on

g Gram
GCP Good Clinical Practice
G-CSF granulocyte colony-stimulating factor
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCV hepatitis C virus
Her2 human epidermal growth factor receptor type 2; c-erbB-2 oncogene
HFSR hand-foot-skin reaction
HIV human immunodeficiency virus
HRQOL health-related quality of life
IATA International Air Transport Association
IB Investigator Brochure
IC50 inhibitory concentration of 50%
ICH International Conference on Harmonization
ie *id est*, that is
IEC Independent Ethics Committee
IL-2 interleukin –2
IMAC Ifosfamide, mesna uroprotection, doxorubicin, and cisplatin
INR International normalized ratio
IR Immediate release
IRB Institutional Review Board
ITT Intent to treat
IVRS Interactive Voice Response System
L Liter
LAK Lymphocyte activated killer
LD Longest diameter
LDH Lactate dehydrogenase
LDLT living donor liver transplant
m/z mass to charge ratio
MAPK mitogen-activated protein kinase
MEK MAPK/ERK Kinase
MID Minimal Important Difference
mg Milligram
mL Milliliter
mm Millimeter
MMF mycophenolate mofetil
MRI magnetic resonance imaging
MRR Medical Research Report
MRT mean residence time (pharmacokinetic parameter)
MTD maximum tolerated dose
MVI macrovascular invasion
N/A Not applicable
NCI National Cancer Institute
NM Nanomolar
NMR Nuclear magnetic resonance
NYHA New York Heart Association

OD *omnes die*, once daily
OS Overall survival
PBL peripheral blood leukocytes
PBMC peripheral blood mononuclear cells
PD progressive disease
PDFR platelet derived growth factor receptor
PE physical examination
PFS Progression Free Survival
pERK phosphorylated extracellular-signal-related kinase
PK pharmacokinetic(s)
PO *per os*, oral
PR partial response
PRO patient reported outcomes
PS performance status
PT prothrombin time
PTT partial thromboplastin time
PWB Physical Well-Being
Q *quaque*, every
QD *quaque die*, once daily
QOD every other day
RBC red blood cell count
RCC renal cell carcinoma
RECIST Response Evaluation Criteria in Solid Tumors
rpm revolutions per minute
SAE serious adverse event
SD stable disease
SEER Surveillance, Epidemiology and End Results
SGOT serum glutamic oxaloacetic transaminase
SGPT serum glutamic pyruvic transaminase
SOP standard operating procedures
TIA transient ischemic attack
tmax time to reach maximum drug concentration in plasma
TNM Tumor Node Metastases
TTP time to progression
TTSP time to symptomatic progression
US Ultrasound
USA United States of America
Vd/F volume of distribution
VEGF vascular endothelial growth factor
WBC white blood cell count
WHO World Health Organization
XR x-ray

1.0 INTRODUCTION

1.1 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a significant health problem; accounting for more than 1,000,000 new cases per year worldwide and is the third leading cause of cancer deaths in the world. [1] The incidence of HCC is also increasing in the United States and accounts for about 13,000 deaths annually. [1, 2] With the increased prevalence of hepatitis C virus (HCV), the number of cases of HCC in the United States will likely continue to increase over the next few decades. [1, 3] Outcomes for patients with HCC have been historically poor, regardless of treatment. In patients with cirrhosis, survival without liver transplantation is often less than 1 year and overall 5 year survival rate are between 20% to 40%. [4, 5, 6]

OLT appears ideally suited for HCC as it provides complete oncologic resection and correction of underlying liver dysfunction. Early experience with OLT for HCC often resulted in compromised patient and allograft survival due to suboptimal patient selection. In the mid 1990s, Mazzaferro and researchers developed selection criteria for OLT candidacy which improved OLT survival for HCC patient outcomes to 4 year survival for transplanted patients as high as 75% by selecting patients with a single tumor less than five cm, or three or fewer nodules, each less than three cm, and no gross vascular invasion. [7, 8] These criteria, known as "the Milan criteria," are widely accepted selection criteria for HCC patients in considering organ transplant. Yao and colleagues reported 5 year post transplant survival of 75% in patients with tumors as large as 6.5 cm and cumulative tumor burden $\leq$ 8 cm (UCSF criteria). [9] Limitations to these findings include a small sample size and use of explant pathology rather than preoperative imaging as the determinant of tumor stage thus the role of OLT for tumors beyond the Milan criteria are considered controversial. Our recently published experience at UCLA in 467 OLT patients with HCC demonstrated prolonged survival after transplantation for tumors beyond Milan criteria but within UCSF criteria, both when classified by preoperative imaging and by explant pathology. [10] Specific explant factors subjecting OLT recipients to greater risk for HCC recurrence following transplant include MVI, bilobar disease, tumors >5.0 cm and patients within the Milan criteria with microvascular invasion, and poorly differentiated tumors. [10, 11] Other risk factors associated with high risk of recurrence include PIVKA>400 and AFP >500 pretransplant. These high risk patients with one or more of these factors have a significantly increased risk of recurrence approaching 40% at 2 years post OLT.

There are few studies evaluating adjuvant therapy after resection or liver transplantation for HCC, especially in the high risk patients. Thus, there is no standard of care for the treatment of these patients. The use of traditional chemotherapeutic agents such as doxorubicin in the adjuvant setting has about a 10% mortality rate due primarily to infectious complications, and an unproven benefit. [12] Ultimately, an effective, well tolerated agent to prevent HCC recurrence in the high risk OLT patients would be an important advance.

Sorafenib (Nexavar®) is a small molecule that inhibits tumor proliferation and angiogenesis and increases the rate of apoptosis in a wide range of tumor models. It acts by inhibiting the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VGEFRs) 1, 2, 3, and platelet derived growth factor β.[13] Recently a phase 3, double-blind, placebo-controlled multicenter trial in patients was

performed in 602 patients with advanced HCC who had not previously received systemic treatment. Results demonstrated a significant survival benefit (10.7 months vs. 7.9 months; $p < 0.001$) and increased time to radiological progression (5.5 months, vs. 2.8 months; $p < 0.001$) in patients treated with sorafenib (n= 299) compared to placebo (n = 303), respectively. [14] This trial established sorafenib monotherapy as first line therapy for advanced HCC.

1.2 Sorafenib

Sorafenib has significant scientific rationale in the treatment of HCC both in the preclinical and clinical settings. It is an oral multikinase inhibitor of Raf kinase and vascular endothelial growth factor (VEGF-R2) and PDGFR-beta. HCC tumor lines have recently been noted to overexpress MEK 1 which enhances tumor growth and confers resistance to apoptosis. [19] Sorafenib blocks the MEK1/ERK pathway and has the potential to block tumor cell growth. [19] Likewise, by blocking VEGF and PDGR-beta, sorafenib targets angiogenesis. In vivo anti-tumor activity has been seen in a diverse group of malignancies. [21]

Sorafenib as a single agent has been evaluated globally in six Phase I trials, five Phase II trials, and a recently completed Phase III trial in hepatocellular carcinoma.

Preliminary antitumor activity has been reported in a variety of tumor types including renal cell cancer, hepatocellular cancer, melanoma, thyroid cancer, acute myelogenous leukemia (AML), ovarian cancer, sarcoma, pancreatic cancer and colorectal cancer.

In addition, multiple Phase I studies of sorafenib in combination with other chemotherapeutic agents have been initiated. To date, over 1200 cancer patients have been exposed to single agent sorafenib. In addition, over 380 cancer patients have been exposed to sorafenib in combination with other chemotherapeutic agents in Phase I/Ib studies. Ongoing Phase II trials include a randomized discontinuation trial in a number of different solid tumor patients, and uncontrolled studies in HCC, non-small cell lung cancer, metastatic breast cancer, head and neck cancer, and refractory chronic myelogenous leukemia (CML).

Sorafenib has been generally well- tolerated at a dose of 400 mg po twice daily (bid.) The most common drug-related adverse events have included hand-foot syndrome, diarrhea, fatigue, hypertension, pain and rash. Grade 3 and 4 drug-related adverse events were uncommon. There was no evidence of cumulative toxicity and the majority of the adverse events were reversible.

There was an increase in the number of serious adverse events, discontinuations due to adverse events, especially skin toxicities, as well as Grades 3 and 4, toxicities at the higher dose levels (greater than or equal to 600 mg bid.) Hence, 400 mg bid was selected as the recommended dose for Phase II.

Six patients with HCC were included in Phase I trials, and remained on sorafenib for a median of 42 weeks (range 5-61 weeks). One partial response (PR) was observed and 4 patients had stable disease (SD). These promising data led to the development of a phase II trial of sorafenib in HCC conducted by Abou-Alfa et al.

The multi-center, uncontrolled, phase II study evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of sorafenib in patients with advanced inoperable HCC. The study was conducted in the United States, Israel, Italy, France, and Belgium. The results of the 137 patients treated (72% CPA and 28% CPB) have revealed 2.2% patients achieved a partial response, 5.8% had a minor response, 33.6% had disease stabilization for a minimum of 16 weeks. [22] The median time to progression (TTP) was 4.2 months and median overall survival (OS) was 9.2 months. [22] Toxicities and side effects were modest and manageable. [22]

Entrance criteria this study included: patients with measurable, histologically proven, inoperable HCC. Patients with fibrolamellar variant or mixed histology were excluded. Sorafenib 400 mg was administered twice daily, and two dose reductions were permitted (to 200 mg bid and 200 mg once daily [qd]) for drug related toxicities. Treatment continued until evidence of tumor progression (radiological or clinical,) or until appearance of unacceptable toxicities related to study drug. Tumor measurements (bidimensional) and assessment were done at baseline and every 8 weeks. [22]

This study included 97 males and 40 females with a median age of 69 years. Eighty-four patients were over the age of 65. Sixty-eight patients had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 69 had ECOG PS 1. Five patients received prior systemic treatment (one patient received neo-adjuvant adriamycin, two were treated with tamoxifen, and two were treated with octreotide), and 56 patients received prior local therapy. Ninety-eight patients were Child-Pugh status A and 38 were Child-Pugh B. [22]

Sorafenib was generally well tolerated. The most frequent drug related toxicities were gastrointestinal (63%), dermatological (47%) and constitutional (34%). Treatment-emergent hepatic toxicities occurred in 20 (15%) patients of which 10 (7%) were grade 3 events and one (<1%) was a grade 4 event (increased bilirubin). [22]

Doses were reduced, delayed and/or permanently discontinued due to toxicities that were considered related to the study drug in 81 (59%) patients. Thirty-four patients (25%) had the dose of study drug reduced due to adverse events, and nine patients had the dose level reduced twice. The most frequent reason for dose delay or discontinuation was hand-foot skin reaction in 16 (12%) patients. Other toxicities included diarrhea in 14 (10%) patients, fatigue in 11 (8%) patients, increased bilirubin in 9 (6%) patients, increased alkaline phosphatase in 5 (4%) patients, and transaminase and amylase increases in 4 (3%) each.[22]

Grade 3 increase in aspartate transaminase (AST) occurred in 23 patients (17%) and grade 3 bilirubin elevation occurred in 24 patients (18%). [22] No significant difference in safety was observed between patients with Child-Pugh A and Child-Pugh B cirrhosis. [22] The frequency of serious adverse events was similar in Child-Pugh A and Child-Pugh B patients, and frequency of adverse events was equivalent among the two groups except for hyperbilirubinemia and elevated alkaline phosphatase, which were more common in Child-Pugh B patients, and dermatologic events, which were more common in Child-Pugh A patients. There were 67 deaths in the study, with a greater proportion of deaths overall in the Child-Pugh B

subpopulation. No deaths in the study were related to sorafenib, and most deaths in both groups were attributed to progression of HCC. [22]

The results of a large phase III (SHARP) trial with sorafenib in advanced HCC were reported [14]. In this trial, patients were randomized to either sorafenib or placebo. Patients were predominately Child-Pugh A and ECOG 0 and 1. Patients in each group were matched with regard to age, gender, etiology of HCC, and prior treatment (surgical resection or local-regional therapies.)[14] Overall, 602 patients were randomized. The median survival in the sorafenib arm was 46.3 weeks versus 34.4 weeks in the placebo arm, p=0.00058 with hazard ratio of 0.69. Median time to progression on sorafenib was 24.0 weeks versus 12.3 weeks on placebo, p=0.000007, hazard ratio=0.58. [14]The majority of patients had stable disease on sorafenib (71%) and progression free rate at four months was 62% versus 42% , favoring the sorafenib group.[22] Most common grade 3/4 toxicities were diarrhea (39%) hand-foot toxicity(21%) anorexia (14%) nausea and alopecia (11% and 14%.). [22] Overall, sorafenib was well -tolerated with manageable side effects. [14]

Due to its proven efficacy in advanced HCC, sorafenib may have a potential role in preventing recurrent HCC in high-risk patients following liver transplantation. The safety of this drug needs to be determined in the post transplant setting.

1.3 Rationale for studying sorafenib in high-risk post transplant HCC patients

Several additional studies of single-agent sorafenib showed treatment was adequately tolerated with manageable side effects. [15-17] Subsequently, sorafenib was approved by the FDA for the treatment of patients with advanced unresectable HCC. The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal). [14] However, it is not known whether this agent is effective in preventing cancer recurrence in high risk patients following liver transplantation. Only one small (n = 13) retrospective analysis recently suggested that sorafenib could be a feasible safe and effective treatment option for preventing recurrent HCC following liver transplantation. [18] Therefore, we propose a phase II, multicenter center, placebo-controlled, blinded study to determine the overall safety profile of prolonged administration of oral sorafenib to prevent HCC recurrence following OLT in recipients with high-risk for HCC recurrence. The specific explant factors subjecting OLT recipients to greater risk for HCC recurrence following transplant include MVI, bilobar disease, tumors >5.0 cm and patients within the Milan criteria with vascular invasion, and poorly differentiated tumors. [10, 11] Other risk factors associated with high risk of recurrence include PIVKA>400 and AFP >500 pretransplant [10, 11]. Adjuvant therapy will be for 2 years since the majority of patients will relapse within 2 years from OLT. For each subject enrolled, the study will consist of three phases: a screening phase, a randomization phase with dose determination and a 12 month follow up phase.

2.0 STUDY OBJECTIVES

Primary Endpoints:

- 2 year recurrence free survival (RFS) (please refer to section 14.0 methodology for definition)

Secondary Endpoints:

- 2 year recurrence free survival
- Overall survival (OS)
- Graft-Failure free survival
- Safety
- Impact of drug-drug interactions (i.e. immunosuppression agents)
- Impact of biomarkers (AFP, PIVKA II)
- Impact of therapy on wound healing
- Impact of Hepatitis C viral recurrence

3.0 STUDY DESIGN

This is a phase II randomized placebo-controlled trial in high-risk HCC patients who have undergone liver transplantation. Study enrollment will be approximately 356 post OLT patients. Randomization will be 1:1 with 178 patients receiving sorafenib versus 178 patients receiving a matched placebo. Total adjuvant treatment will be for 2 years.
Dosing of sorafenib or placebo will be as follows:

1. Cycle 1 (day 1-112) sorafenib will be given at a dose of 200mg orally bid.
2. Cycle 2 (day 113-141) sorafenib will be given at a dose of 200mg orally q am, and 400 mg q pm.
3. Cycle 3 (day 142-24 months) sorafenib will be given at a dose of 400mg po bid.

Dosing of sorafenib or placebo for patients who require dose modification will be outlined in section 7.2.

4.0 DRUG INFORMATION

Sorafenib

Medication will be labeled according to the requirements of local law and legislation.
Sorafenib 200mg tablets are manufactured and will be supplied by Bayer. Study drug will be supplied as 200 mg tablets in bottles of 140 tablets.

The 200 mg tablet formulation contains: [redacted] This tablet is film coated with a water-soluble polymer (hypromellose) that has no effect on the release rate of the active BAY 43-9006. It has a red color in appearance, weighs approximately 350 mg, and is 10 mm round in shape.

The tablets need not be protected from light. They are sufficiently stable towards light, oxidation, thermal stress and hydrolytic degradation. The formulation is presented as an immediate release (IR) dosage form, i.e. the active ingredient is completely dissolved under in-vitro test conditions within a short period of time.

Matching placebo tablets will be supplied by Bayer.

Supply, Packaging, Labeling and Storage: Participating sites will be provided with the study medication and placebo tablets according to the number of patients enrolled, and labeled as

per institutional policy. Once the drug has been received, the drug should be kept in a dry, safe place not above 25°C/77°F. The medication should be stored in the original, immediate package. The study drug must be used exclusively for the investigation specified in this protocol, and accessible to authorized staff only. Only the investigator or a person assigned will be allowed to supply the drug to the patient. To have complete control over the distribution and use of study drugs, drug accountability must be performed at every patient visit. Bottles must be returned to the Investigator with all unused medication. Throughout the study, all unused material, i.e. empty bottles, unused tablets, etc. will be accounted for. Unused drug returned by patients during protocol visits cannot be re-dispensed back to the patient after completing accountability. Destruction of drugs and containers should be documented. One copy of the destruction certificate must be kept in the investigator's file and the other copy must be sent to UCLA.

4.1 Pharmaceutical information:

- Generic Name: **Sorafenib (formerly BAY 43-9006; NSC 724772)**
- Commercial Name: Nexavar®
- **Chemical name:** 4–{4-[3-(4-chloro-3-trifluoromethyl-phenyl) ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzensulfonate.
- **Other names:** BAY 54-9085 is the tosylate salt of BAY 43-9006; sorafenib
- **Classification:** Kinase inhibitor (Raf, VEGF-R, and PDGF-R)
- **Mechanism of action:** The ras/raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to presence of activated ras, mutant b-raf, or over expression of growth factor receptors.
  Sorafenib is a potent inhibitor of c-raf, and wild-type and mutant b-raf in vitro. Additionally, further characterization of sorafenib revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38α, a member of the MAPK family.
- **Molecular formula:** $C_{12}H_{16}ClF_3N_4O_3$ X $C_7H_8O_3S$
- **M.W.:** Sorafenib tosylate: 637 Daltons; free base: 465 Daltons
- **Approximate solubility:** 0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG 400.
- **How supplied:** Sorafenib is supplied as an immediate-release film-coated, round, salmon color tablet containing 200 mg of the free base, sorafenib, and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethyl cellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, tiranium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.
  - Study drug: 200 mg tablets in bottles of 140 tablets.
  - Commercial drug: 200 mg tablets in bottles of 120 tablets. 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. Bottles of 120 tablets NDC 0026-8488-58.
- **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.

- **Stability:** Stability studies with the 200 mg dosage form are ongoing. The current shelf life is 24 months when stored at controlled room temperature.
- **Route of administration:** Orally
- **Method of administration:** The recommended daily dose of NEXAVAR® is 400 mg (2 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating.)
- **Potential drug interactions:** Sorafenib is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that sorafenib may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP 3A. **Note: Investigators must exercise caution when administering strong CYP3A4 inhibitors in combination with protocol-specified therapy.** Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, tacrolimus, and digoxin. Additionally, sorafenib is 97% to 99% protein bound; however, no drug interactions have been reported in studies, thus far.

4.2 Sorafenib Precautions
For the most recent safety update, please refer to the current Nexavar® Prescribing Information. See Appendix 23.1 Warnings/Precautions

Contraindications
Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.

Special warnings and precautions for use
Nexavar® (sorafenib) is approved for treatment of patients with advanced renal cancer and unresectable hepatocelluar carcinoma. Because this drug is a novel agent, current knowledge of the adverse events associated with this compound is limited. As with any new chemical entity, there is always potential for unexpected adverse events.

Pregnancy
Women should avoid becoming pregnant while on therapy.

Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity,) failure to thrive and fetal death (embryotoxicity.)

Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman.

Breastfeeding should be discontinued during sorafenib therapy.

Dermatological toxicities
Hand-foot skin reaction (palmar-plantar erythrodysesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand-foot skin reaction are usually CTC (National Cancer Institute Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with Sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib.

Hypertension
An increased incidence of hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of sorafenib should be considered.

Hemorrhage
An increase risk of bleeding may occur following sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib will be considered.

Wound healing complications
No formal studies of the effect of sorafenib on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of sorafenib therapy is recommended for precautionary reasons. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Cardiac ischemia and/or infarction
In the Phase 3 Advanced RCC study (TARGETS,) the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the sorafenib group (2.9%) compared with the placebo group (0.4%) Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Gastrointestinal perforation
Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. Some cases were not associated with apparent intra-abdominal tumors. Sorafenib therapy should be discontinued in patients with GI perforation.

Effects on ability to drive and use machines
No studies on the effects of sorafenib on the ability to drive or use machines have been performed. There is no evidence that sorafenib affects the ability to drive or operate machinery.

Patients with hepatic impairment
In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering sorafenib to patients with Child-Pugh A and B hepatic impairment.

Patients with renal impairment
Sorafenib has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients undergoing dialysis.

Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenicity studies have not been performed with sorafenib. Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%) was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently. No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose.) Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of sorafenib. Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pediatric use
The safety and effectiveness of sorafenib in pediatric patients have not been studied. Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose,) hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose,) and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric use
In total, 32% of RCC patients treated with sorafenib were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4.3 Interaction with other Medications
Drug-drug interactions
Caution is recommended when administering sorafenib together with compounds that are metabolized/ eliminated predominantly by the UGT1A1 pathway.

- **CYP3A4 inducers:** There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Inducers of CYP3A4 activity (e.g. rifampicin, *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may increase metabolism of sorafenib and thus decrease sorafenib plasma concentrations.
- **CYP3A4 inhibitors:** Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. Therefore, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.
- **CYP2C9 substrates:** The possible effect of sorafenib on the metabolism of the CYP2C9 substrate warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in sorafenib patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism *in vivo*. However, patients taking warfarin should have their INR checked regularly.
- **CYP isoform-selective substrates:** Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of sorafenib administration did not significantly alter the exposure of these agents. This finding indicates that *sorafe*nib is neither an inhibitor nor a clinically meaningful inducer of these cytochrome P450 isoenzymes.

- **Combination with other anti-neoplastic agents:** In clinical studies, sorafenib has been administered together with a variety of other antineoplastic agents at their commonly used

dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. However, caution is recommended when administering sorafenib with doxorubicin and with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan).

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

- Patients must have HCC with **one** of the following:
  - Microvascular/macrovascular invasion
  - Tumor outside of Milan criteria
  - Poor tumor differentiation
  - Elevated tumor markers (AFP > 500 or PIVKA (DCP)> 400) **pre**transplant AND biopsy proven HCC prior to OLT **or** on explants

Patients with macrovascular invasion on pathology will be stratified.

- Male/female patients >18 years of age
- ECOG PS 0-2
- Patients with a life expectancy >12 weeks
- Patients must have completed prednisone taper (5 mg – 2.5 mg) prior to randomization
- Patients must be enrolled between 8 to 20 weeks post OLT
- Cadaveric and DCD donors (no LDLT)
- Pretransplant treatment with sorafenib not > 12 months

(not exceeding 12 months of treatment, total)

- Laboratory parameters:
  - Platelet count > 50 x 10^9/L
  - Hemoglobin ≥ 8.5 g/dL
  - Total bilirubin ≤ 5 mg/dL
  - Alanine transaminase (ALT) and AST ≤ 5 x upper limit of normal
  - Amylase and lipase ≤ 1.5 x the upper limit of normal
  - Serum creatinine < 2 x the upper limit of normal
  - Prothrombin time (PT) ≤26 seconds or International Normalized Ratio (INR) ≤2.5
- Patient has not received prior anti-angiogenic therapy, systemic targeted agents or systemic chemotherapy.
  - Prior surgical resection, chemoembolization or other local therapy prior to transplant is permitted.
- Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.

- Patients (men and women) of childbearing potential must agree to use two forms of contraception, including one barrier method, beginning at the signing of the ICF until at least 30 days after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Patient must be able to swallow and retain oral medication.
- Patient must exhibit the ability to understand and willingness to sign a written informed consent regarding the study and alternative treatments.

5.2 Exclusion Criteria

- Significant ongoing immunologic rejection based on pathology and clinical diagnosis (from time of transplant until randomization)
- Use of T cell depleting agents for prevention or treatment of rejection at any point prior to or after enrollment in the study.
- Patient with documented evidence of metastatic disease
- Use of mTOR inhibitors prior to transplant and as post-transplant immunosuppression
- Use of alemtuzumab
- Living Donor Liver Transplant (LDLT)
- HIV positive patients
- Active or clinically significant[1] cardiac disease including:
    - Congestive heart failure – NYHA > Class II.
    - Coronary artery disease.
    - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    - Unstable angina or new-onset angina within 3 months before randomization, or MI within 6 months before randomization.
- Use of Direct Acting Antivirals for HCV recurrence, with the exception of sofosbuvir and ledipasvir/sofosbuvir.
- Requirement of re-transplantation for primary non function
- Uncontrolled hypertension, defined as systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.
- Clinically active serious infection documented by positive cultures or an incomplete course of treatment for bacteremia or fungemia.
- Evidence or history of bleeding diathesis or coagulopathy.
- Patients with any pulmonary hemorrhage/bleeding event Grade 2 or higher within 4 weeks before randomization.
- Patients with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including TIAs) within 6 months before randomization.
- Prior use of raf-kinase inhibitors (sorafenib), VEGF inhibitors, MEK inhibitors, or farnesyl transferase inhibitors
- Patients using CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, St. John's Wort dexamethasone at a dose of greater than 16 mg daily, or rifampin and/or rifabutin within 28 days before randomization.

[1] *Clinically Significant* as defined by individual site PIs or Investigators.

- Patients with non-HCC malignancy, except, those with DCIS (ductal carcinoma in situ), cervical cancer in-situ, basal cell or superficial bladder tumor. Patients surviving a cancer that was curatively treated and without evidence of recurrence for more than 3 years before randomization are allowed.
- Patients with Local Lymph Node Matasteties
    - However, patients with high risk HCC who have been down-staged prior to OLT and show 100% necrosis on explant are eligible as long as there is biopsy proven HCC.
- Presence of a non-healing wound, non-healing ulcer, or bone fracture.
- Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- Inability to comply with the protocol and/or not willing or not available for follow-up assessments.
- Patients with fibrolamellar HCC, cholangiocarcinoma, and combined HCC-cholangiocarcinoma
- Any condition which, in the investigator's opinion, makes the patient unsuitable for trial participation.

5.3 Excluded therapies and medications, previous and concomitant

- Prior use of any systemic chemotherapy for HCC, **with the exception of sorafenib.**
- Prior use of systemic investigational agents for HCC
- Prior use of raf-kinase inhibitors, VEGF inhibitors, MEK inhibitors or farnesyl transferase inhibitors, **with the exception of sorafenib.**
- Use of biologic response modifiers, such as granulocyte colony-stimulating factor (G-CSF), will not be permitted within 3 weeks[2] prior to study entry. G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the discretion of the investigator; however, they may not be administered to prevent a dose reduction. Patients taking chronic erythropoietin are permitted, provided no dose adjustment is undertaken within 1 month[3] prior to randomization or during the study.
- Autologous bone marrow transplant or stem cell rescue within four months of start of study drug
- Concomitant treatment with rifampin and St. John's wort
- Concomitant oral mTOR inhibitor treatment
- Use of Direct Acting Antivirals for HCV recurrence
    - **sofosbuvir and ledipasvir/sofosbuvir are** not excluded therapies
- Use of T-cell depleting agents
- Use of alemtuzumab

[2] Subjects can be enrolled 3 weeks after biologic response modifiers have been discontinued.

[3] Subjects can be enrolled 1 month after erythropoietin dose adjustment has been made.

- Use of any other investigational drug

5.4 Immunosuppression

Immunosuppression will consist of center specific protocols with tacrolimus (TAC) or cyclosporine (CSA) based immunosuppressive regimens. Low whole blood target TAC and CSA levels will be maintained between 5-10 ng/mL and 200-300 ng/mL respectively. Patients will remain on tacrolimus or cyclosporine for the duration of this study. Mycophenolic acid will also be administered according to center specific practice. However, corticosteroids must be tapered down to 5 mg – 2.5 mg prior to randomization. The use of T cell depleting agents (thymoglobulin) for induction therapy or treatment of rejection is not permitted in this trial. The use of interleukin 2 receptor antagonists (IL-2 RAs) can be used according to institutional clinical practice. The use of mTOR inhibitors such as sirolimus or everolimus is not permitted in study patients. If these agents are administered, patients must be withdrawn from the study. All immunosuppressive regimens will be continuously updated and individually tailored to each OLT patient to assure appropriate exposure throughout the 2 year treatment period. Adverse effects such renal dysfunction and neurotoxicity, common drug interactions and other causes of immunosuppressive titration difficulty will be identified and managed throughout the study period.

5.5 Anticoagulation

The following anticoagulation is allowed:

- Vitamin-K antagonists (e.g., warfarin)
    - Low dose warfarin (1 mg orally, once daily) with PT-INR $\leq$ 1.5 x ULN is permitted. Patients taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
- Low dose aspirin ($\leq$ 325 mg daily).
- Heparins and Heparinoids

6.0 TREATMENT PLAN

Patients will be randomized to receive sorafenib or matching placebo in a blinded fashion such that the subject will not know which combination is being administered.

Approximately 178 patients will be treated with sorafenib; 178 patients will be treated with matched placebo dose. Sorafenib will begin between 8-20 weeks post OLT. Total adjuvant treatment will be 24 months.

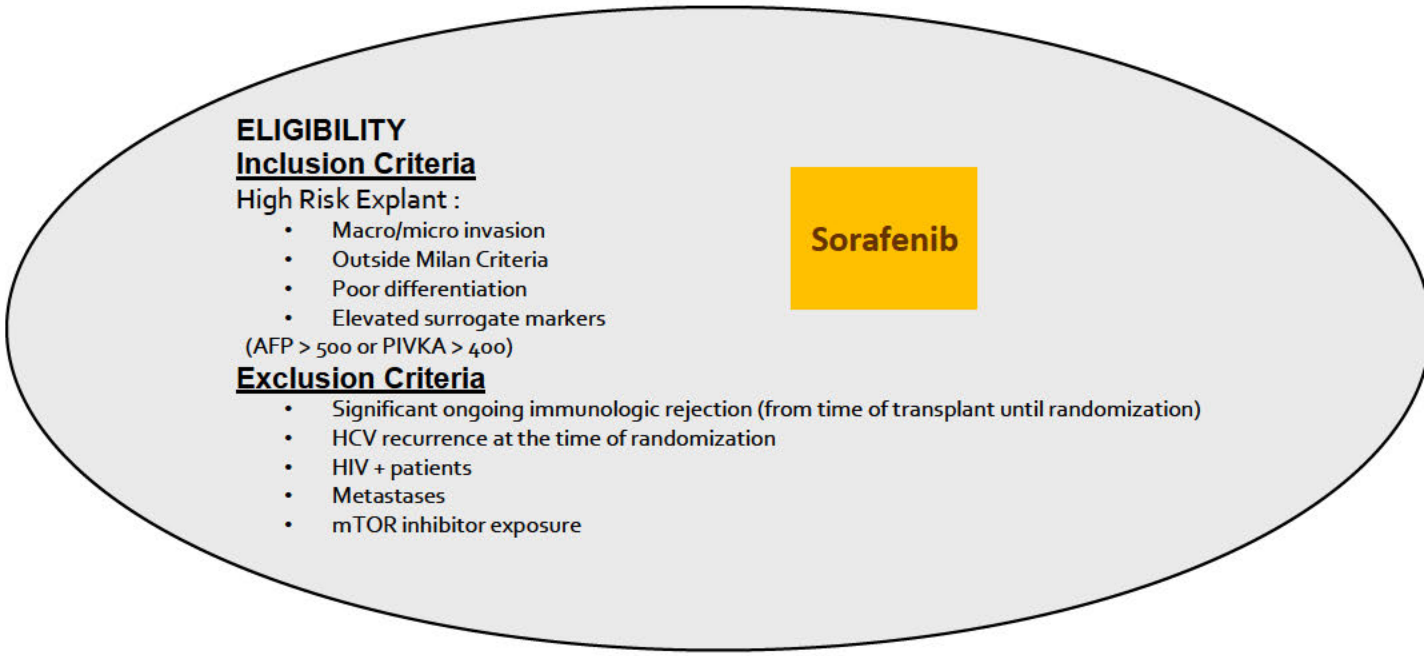


Table 6.1 Dose Reduction Schedule

	Starting Dose	Dose Level -1	Dose Level -2
Cycle 1			
Sorafenib	200 mg PO BID	400 mg PO QOD	N/A
Placebo	1-tablet PO BID	2 tablets PO QOD	N/A
Cycle 2			
Sorafenib	200mg PO QAM 400mg PO QPM	200mg PO BID	400mg QOD
Placebo	1 tablet PO QAM 2 tablets PO QPM	1 tablet PO BID	2 tablets QOD
Cycle 3-24			
Sorafenib	400 mg PO BID	200 mg PO BID	400mg PO QOD
Placebo	2 tablets PO BID	1 tablet PO BID	2 tablet PO QOD

Patients will have dose escalation if they do not have > grade 2 toxicity and did not require dose modification during previous cycle.

Any additional dose reductions (> twice) need to be assessed by the medical monitor on a case by case basis.

6.2 Management of Hematologic vs. non-Hematologic Toxicities

Table 6.2.1 Dose Modification for Hematologic Toxicities (see Table 6.1 for level reductions)

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

* Modify according to study specific cycle length.

** Subjects requiring a delay of >30 days (modify according to study specific cycle length) should discontinue sorafenib/placebo unless, in the opinion of the treating physician and after assessment by the medical monitor, the subject may benefit from continued treatment.

Table 6.2.2 Dose Modification for Non-Hematologic Toxicities

Recommended dose modification for non-hematologic toxicity (excluding hypertension and hand foot skin reaction, diarrhea and fatigue (see Table 7.1 for level reductions).		
Grade	**Sorafenib Interruption**	**Sorafenib Modification**
Grade 0-2	Treat on time	No Change
Grade 3	Interrupt until ≤Grade 2	DECREASE one dose level*
Grade 4	OFF protocol therapy	OFF protocol therapy
* Subjects requiring a delay of >30 days (modify according to study specific cycle length) should discontinue sorafenib/placebo unless, in the opinion of the treating physician and after assessment by the medical monitor, the subject may benefit from continued treatment		

6.3 Prevention/management strategies for diarrhea and fatigue

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

6.4 Hand-Foot-Skin Reaction (HFSR)

Table 6.4.1 Sorafenib Dermatologic Toxicity Modification (see Table 6.1 for level reductions)

Toxicity Grade		Suggested dose modification
Grade 1	Any occurrence	Maintain dose level and consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Maintain dose level and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level*
	3rd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by two dose levels*
	4th occurrence	Discontinue treatment permanently
Grade 3	1st occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by one dose level*
	2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, decrease dose by two dose levels*
	3rd occurrence	Discontinue treatment permanently

*Subjects requiring a delay of >30 days (modify according to study specific cycle length) should discontinue sorafenib/placebo unless, in the opinion of the treating physician and after assessment by the medical monitor, the subject may benefit from continued treatment

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

Table 6.4.2 Recommended Prevention/Management Strategies for Skin Toxicities Consistent with HFSR

Toxicity Grade	Practical Prevention / Management Strategies for HFSR
Grade 0 (Preventive strategies)	• Maintain frequent contact with trial physician to ensure early diagnosis of HFSR. • Practical prevention strategies ○ Pedicure for subjects with pre-existing hyperkeratosis. ○ Subjects should avoid hot water and clothing or activities that can cause friction on the skin. ○ Moisturizing cream should be applied sparingly. • Padded gloves and open shoes with padded soles should be worn to relieve pressure points.
Grade 1 Any occurrence	• Continue preventive strategies and in addition: ○ Soak hands in cool water. ○ Apply petroleum jelly to moist skin. • In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards.
Grade 2 Any occurrence or **Grade 3** Any occurrence	• Continue supportive/management measures and add analgesic(s) for pain.

6.5 Treatment-emergent Hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will undergo brief physical examinations, including blood pressure home self-monitoring, twice a week through the first 6 weeks of therapy. Thereafter, blood pressure will be monitored on Day 1 of each cycle.

Blood pressure measurements that are out of the normal range must be recorded by the treating physician. Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg, or a 20 mm Hg increase in diastolic pressure if the previous measurement was within normal limits.

The dose-modification schedule to be followed in the event of treatment-emergent hypertension is outlined below. The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on site-specific treatment guidelines as applicable. All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the subject's records.

Once a dose-reduction modification has been made for treatment-emergent hypertension, NO dose re-escalation will be allowed.

Table 6.5.1 Management of Treatment-emergent Hypertension	
Grade of Event (NCI-CTCAE v4.0)	**Management/ Next Dose**
Grade 1	Consider increasing blood pressure monitoring. Continue sorafenib/placebo dosing as scheduled.
Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Begin anti-hypertensive therapy. Continue sorafenib/placebo dosing as scheduled.
Grade 2 (symptomatic/persistent) **OR** **Grade 2** symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits **OR** **Grade 3**	Sorafenib/placebo should be held[a] until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib/placebo is restarted, reduce by 1 dose level.[b] If diastolic blood pressure is not controlled (< 90 mm Hg) on anti-hypertensive therapy, reduce another dose level.[b]
Grade 4	Discontinue sorafenib
a: Subjects requiring a delay of > 30 days (modify according to study specific cycle length) should discontinue sorafenib/placebo unless, in the opinion of the treating physician, the subject may benefit from continued treatment. b: Subjects requiring dose reductions beyond 200 mg (1 placebo tablet) twice daily, every other day, should discontinue sorafenib.	

7.0 MANAGEMENT OF HCV

- Hepatitis C infection and (possible recurrence) will be managed as per institutional protocols. **Patients cannot receive direct acting antivirals (DAA's) for HCV; enrolled patients who require DAA's for the treatment of HCV will discontinue sorafenib and will be withdrawn from the study.**

8.0 MANAGEMENT OF REJECTION WHILE ON STUDY

- Treatment of rejection will be according to institutional protocols. Sorafenib/placebo will not be discontinued unless anti-rejection treatment is unsuccessful (T-cell depleting agents will not be allowed)

9.0 PRE-STUDY EVALUATIONS

- Signed Informed Consent; enrollment in the study is defined as the signing of the Informed Consent. The Informed Consent Document must be signed prior to study participation (study eligibility and subsequent randomization will be based on pre-transplant criteria and explant pathology)
- Physical Exam
- Electrocardiogram (ECG) –either within 1 year of OLT or prior to start of treatment and thereafter as clinically indicated for the duration of the study.
- Post-OLT MRI or CT of chest, abdomen and pelvis prior to start of treatment
- Tumor pathology for determination of tumor characteristics -VEGF Receptor Complete medical history

- Complete blood count (CBC): hemoglobin, hematocrit, platelet count and white blood

cell count (WBC.)

- Alpha-fetoprotein, PIVKA II
- Fasting Blood Chemistries done within 14 days prior to start of study drug: AST, ALT, bilirubin (total and direct), alkaline phosphatase, total protein, albumin, calcium, phosphate, lactic dehydrogenase (LDH), sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN,) and bicarbonate
- Coagulation panel done within 14 days prior to start of study drug: PT, the International Ratio of PT (PT-INR) and partial thromboplastin time (PTT)
- Serum pregnancy test for women of childbearing potential (must be negative)

10.0 TREATMENT EVALUATIONS

The following testing should be performed at each visit during the first four weeks, then monthly through month 6, then every 3 months thereafter during the treatment period (unless otherwise noted on the Study Data Collection Calendar, Section 10.1):

- Brief physical examination including weight
- Vital signs should be assessed. Blood pressure measurement should be performed in a consistent manner after the patient has been sitting for five minutes. A manual cuff should be used on the same arm each time blood pressure is measured.
- Toxicity and adverse events documentation
- Concomitant medication (including start/stop dates, dose, frequency, route of administration and indication)
- Drug accountability and dispensing. Patients should be instructed to bring all remaining study drug at each visit
- CBC, Platelets
- Fasting Blood Chemistries: AST, ALT, bilirubin (total and direct), alkaline phosphatase, total protein, albumin, calcium, phosphate, lactic dehydrogenase (LDH), sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN,) and bicarbonate
- PT, PTT, INR
- AFP and PIKVA (DCP) II at weeks 1 and 4, then monthly through month 6, then every 3 months thereafter during the treatment period.
- Tacrolimus levels / Cyclosporine (CSA) levels
- Hepatitis B and C RNA PCR per each center's protocol.
- Protocol biopsies as outlined in study calendar (post reperfusion at OLT and upon imaging suggesting HCC recurrence).
- Urine pregnancy test for women of child-bearing potential every 3 months while on study treatment

Restaging MRI or CT scans (chest, abdomen and pelvis) will be obtained every 6 months for the first 2 years (6, 12, 18 and at 24 months post OLT). More frequent scans will also be performed if clinically indicated (based on elevated AFP, elevated PIVKA, or biopsy).

10.1 Study Data Collection Calendar

	Scn/BL	Treatment Phase*															Follow-up Phase	
Visit window		+/- 3 days			+/- 5 days						+/- 21 days						+/- 28 days	
Month				1		2	3	4	5	6	9	12	15	18	21	24/ EOT [7]	30	36
Week	-2	1	2	4	6	8	12	16	20	24								
Medical History	X																	
Physical Exam/Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Informed Consent	X																	
Toxicity Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG	X[1]																	
Pregnancy Test (women of childbearing potential)	X									X	X	X	X		X			
Tumor Pathology[2]	X																	
CBC/Platelets	X	X	X	X		X		X		X		X	X	X	X	X		
Chemistry/LFTs	X	X	X	X		X		X		X		X	X	X	X	X	X	X
MRI or CT-Chest/Abdomen/Pelvis	X[3]									X		X		X		X[7]	X	X
Tacrolimus or Cyclosporine level		X	X	X		X	X	X	X	X	X	X	X	X	X	X		
HCV/HBV RNA PCR[4] (positive patients only)	X					X		X		X	X	X						
PIVKA II	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
AFP	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
PT, PTT, INR	X		X	X		X		X		X		X	X	X	X	X		
Drug Dispensation[5]		X	X	X		X	X	X	X	X	X	X	X	X	X			
Biopsy[6]	X	As clinically indicated for suspicion of recurrence																

[1] ECG to be completed either within 1 year of OLT or prior to start of study drug (If post-OLT ECG is not done as part of center care, pre-transplant ECG is acceptable.)
[2]Pathology for VEGFR can be sent to UCLA if stain not done locally
[3]Post-OLT MRI or CT to be completed prior to start of study drug
[4]HCV/HBV RNA PCR frequency above is UCLA standard-or-care; complete these assessments per center protocol or as clinically indicated
[5]Study drug administration to begin 8-20 weeks post OLT
[6]Biopsy to confirm eligibility at Baseline (may be post transplant pathology) and as needed (with elevated AFP or PIVKA or new lesion on imaging)
[7]End of Treatment to be completed at Month 24 or at the time of early discontinuation of treatment; MRI/CT not required for early discontinuation
*Upon early discontinuation of study drug, follow-up data is requested (see Section 13.1)

11.0 CONCOMITANT THERAPY

All medications which are considered necessary for the patient's welfare, and which are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as in the appropriate pages of the CRF.

Patients taking narrow therapeutic index medications should be monitored proactively. These medications include warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, tacrolimus and digoxin.

Concomitant Medication/Therapies

- **Immunosuppression** will consist of center specific protocols with tacrolimus (TAC) or cyclosporine (CSA) based immunosuppressive regimens. Low whole blood target TAC and CSA levels will be maintained between 5-8 ng/mL and 200-300 ng/mL respectively. Patients will remain on tacrolimus or cyclosporine for the duration of this study. Mycophenolic acid will also be administered according to center specific practice. However, corticosteroids must be tapered down to 5 mg – 2.5 mg prior to randomization. Use of T cell depleting agents (thymoglobulin) for induction therapy or treatment of rejection are not permitted in this trial. The use of interleukin 2 receptor antagonists (IL-2 RAs) can be used according to institutional clinical practice. The use of mTOR inhibitors such as sirolimus or everolimus is not permitted in study patients. If these agents are administered, patients must be withdrawn from the study. All immunosuppressive regimens will be continuously updated and individually tailored to each OLT patient to assure appropriate exposure throughout the 2 year treatment period. Adverse affects such renal dysfunction and neurotoxicity, common drug interactions and other causes of immunosuppressive titration difficulty will be identified and managed throughout the study period.
- Patients will continue standard post-transplant anti-infective prophylactic therapy, which may include a combination of fluconazole/ voriconazole clotrimazole, nystatin, ganciclovir, valgangciclovir acyclovir, trimethoprim/sulfamethoxazole, atovaquone, and/or pentamidine.
- Patients with the diagnosis of hepatitis B infection will continue to receive standard post-transplant prophylaxis with hepatitis B immune globulin infusions and anti-viral therapy, such as lamivudine, adefovir, tenofovir, or entecavir.
- In the event of acute cellular rejection of the allograft, patients will be allowed to receive standard treatment, including corticosteroids.
- Analgesics
- Nutritional and vitamin support

12.0 FOLLOW-UP EVALUATIONS

- Patients will be followed after completion of 24 months of adjuvant therapy for an additional 12 months.
- Once patients enter follow up, they will be monitored for HCC recurrence with MRI or CT scan of the chest, abdomen and pelvis at 30 and 36 months.
- Once patients enter follow up, they will be monitored for HCC recurrence with serum AFP, PIVKA II (DCP) and liver function tests, as well as graft status, at 30 and 36 months.

12.1 Follow-up data for end of treatment/early discontinuation of study drug

For patients who discontinue study drug prior to completion of the 24-month treatment phase, an End of Treatment evaluation should be completed (see section 10.1), and the following data should be reported at the time of study drug discontinuation and every 6 months thereafter (unless otherwise noted on the Study Data Collection Calendar, Section 10.1):

- Disease status
- Graft status
- Patient survival
- Chemotherapy: treatment with sorafenib, sorafenib plus other agent, other agent only
- Change in immunosuppression: sirolimus, everolimus, or other
- Implementation of interventional therapy: radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), or both
- Surgical resection

13.0 METHODOLOGY

13.1 Definition of Study parameters

All liver explants will be processed according to the standardized protocol and are sectioned in 0.5 to 1 cm interval, from the superior to inferior aspect, analogous to the sectioning on computer tomography (CT) images. All HCC will be evaluated, documented, and staged pathologically (AJCC, 6th edition, 2002.) Cases with fibrolamellar HCC, cholangiocarcinoma, and combined HCC-cholangiocarcinoma will be excluded.

For the purposes of this study, patients are being closely followed for recurrence throughout the 2 year treatment period and the subsequent 12 month follow period. In addition to a baseline scan and biopsy, subsequent MRI or CT scans will be obtained every 6 months. Biopsies should be obtained upon suspicion of recurrence. Serum AFP/PIVKA II and liver function tests will be measured at weeks 1, 2 (LFTs only) and 4, then monthly through month 6, then every 3 months thereafter during the treatment period. Computed tomographic or magnetic resonance imaging, radiographic presence, histopathological evidence, or a combination of these will define HCC recurrence.

Recurrence and progression will be evaluated in this study using the new international criteria proposed by the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Committee. 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.

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 (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

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 at time of disease recurrence.

Non-target lesions
All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at time of disease recurrence. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as nonmeasurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

Evaluation of measurable disease
All measurements should be taken and recorded in metric notation using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at initial recurrence and at subsequent follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess disease recurrence.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and 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.

Diagnostics of clinical lesions

- **Chest x-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI.** These techniques 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 tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- **Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. However, such techniques can be useful to confirm recurrence when biopsies are obtained.
- **Tumor markers**. Tumor markers alone cannot be used to confirm recurrence. If markers are initially above the upper normal limit, further studies will be done to confirm recurrence.
- **Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
    - The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for recurrence or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Recurrence Free Survival (RFS) is defined as the time from randomization to the first documented disease recurrence by radiological assessment or death due to any cause whichever occurs first. A patient is censored with regard to RFS if the patient is alive and disease free at last follow up.

Overall Survival (OS): Survival will be measured, as the time from randomization to the date of death or the last date the subject was known to be alive. A patient is censored for this outcome if the patient is alive at last follow up.

Graft-failure Free Survival is defined as the time from randomization to the first documented sign of graft-failure as defined by local standards. A patient is censored for this outcome if the patient is alive at last follow up.

14.0 STATISTICAL CONSIDERATIONS

14.1 Statistical analysis plan

Baseline Group comparison – We will compare baseline pre transplant covariates such as recipient age, MELD score, warm ischemia time, donor age, percent with tumor downstage, percent with bilobar disease, gender and other important covariates between the two groups (sorafenib versus placebo) overall and stratified by macrovascular versus non macrovascular invasion status. This comparison will check to see that the

randomization was successful (that no significant covariate imbalances exist between the two groups). Any factor that has a clinically important difference may need to be used as a covariate in subsequent analyses (see below). We will use T tests or the non parametric analog (Wilcoxon rank sum test) for comparing continuous variables and the Fisher exact test for comparing discrete variables.

Primary endpoint: Recurrence -free survival. We estimate RFS by using the Kaplan-Meier method and compare survival curves between the drug verses placebo groups using the unstratified log rank test. We will report hazard rates, hazard rate ratios and median times to recurrence (or 25 percentiles if median time is not reached) and their corresponding 95% confidence bounds. A secondary analysis will also be presented stratified by macro versus non-macro status, the most important potential covariate.

Secondary endpoint: Overall Survival (OS) will be estimated using the Kaplan-Meier method and comparing survival curves between the drug and placebo groups using the log rank test. We will report hazard rates, hazard rate ratios and median times to recurrence (or 25 percentiles if median time is not reached) and their corresponding 95% confidence bounds. The analyses will be presented both unstratified and stratified by macro versus non-macro invasion status.

Other secondary endpoints: We use 1 year relapse free survival using the Kaplan-Meier method and compare survival curves between the drug and placebo groups using the log rank test. We will report hazard rates, hazard rate ratios and median times to recurrence (or 25 percentiles if median time is not reached) and their corresponding 95% confidence bounds. We will also make the analysis stratified by macro versus non-macro invasion status.

We will use competing risk survival methods to provide a breakdown of the recurrence free survival over time into its three components: recurrence incidence, non recurrence failure (mortality, graft failure[4]) incidence and recurrence free survival and provide this breakdown by treatment group and by group and MVI. For a given group (or given group and MVI combination), the sum of these three add to 100% at a given time

Additionally, Kaplan-Meier methods will be used to compare time dependent secondary outcomes such as the impact of wound healing and time to first recurrence of clinically significant[5] Hepatitis C and time to graft failure. We will use repeated measure analysis of variance methods to compare the mean profiles of continuous outcomes such as laboratory values across time on the original or transformed scale and use the corresponding repeated measure logistic or ordinal logistic model to compare proportions of discrete outcomes such as percent with a major adverse event across time.

Exploratory analysis: While we do not anticipate any important imbalances on major baseline covariates, if there are significant imbalances in important baseline covariates

[4] Based on UNOS Classification, Graft Failure is defined as having occurred when organ removal, death, or replacement on chronic allograft support system has occurred

[5] *Clinically Significant* as defined by individual site PIs or Investigators.

including center, we will use the Cox proportional hazard model and/or stratification methods to compute covariate adjusted survival curves and corresponding adjusted p values for the two group comparisons. We will report both unadjusted and adjusted results. Interim analysis – One planned interim analysis for both safety and efficacy will occur after a total of 50 events have occurred. Based on the 2 year 60% and 73% recurrence free survival expected, an expected 50% accrual by 1 year, and an exponential model, this should approximately correspond to 178 patients (50% of the study population) evaluable for the primary endpoint – RFS at approximately the 2 year point of the study. For safety, for this comparison, the p value will have to be less than 0.001 at interim in order to be considered statistically significant. The Haybittle-Peto boundaries at interim analysis will be used to decide early stopping for efficacy, where the boundary corresponds to a log rank test Z value of greater than Z=3.0 at interim and Z=1.96 at final. This allows a $p < 0.05$ significant levels in the final analysis (Haybittle-Peto rule) for the primary outcome.

There will also be a futility / conditional power calculation. Based on the accrual rate at interim, the projected accrual to study end can be computed. Based on this projected accrual and the observed data at interim, the conditional power for the planned difference of 60% RFS in placebo versus 73% RFS at 2 years will be computed. In addition, conditional power will be computed for the projected difference in 2 year RFS based on the hazard rates observed at interim. At the request of the DSMB, additional conditional power computations may be provided for worst and best case accrual and RFS difference scenarios, conditional on the data observed at interim. If the conditional power cannot be computed parametrically, it will be computed using Monte Carlo simulation

Final analysis – The final analysis will occur after the total number of events in both groups is 135. Based on the 2 year 60% and 73% recurrence free survival expected, an expected 50% accrual by 1 year and 25% dropouts, this is expected to be reached in 3 years.

Dropouts/loss to follow up - While we do not anticipate more than modest (no more than 25%) dropout levels, we will report and compare the number of dropouts over time in each group. We will also use a proportional hazard regression model to determine if time to loss is associated with drug group or any of the baseline covariates. If the loss to follow up is at random, none of the baseline covariates should be significantly associated with loss to follow up, particularly drug group. If the loss is not random, we will report on the possible directions of any bias that could result and consider sensitivity analyses if necessary. Analyses will be by intent to treat.

Safety analyses: A safety analysis will be conducted after 50 patients have been enrolled. A data safety monitoring board (DSMB) will be instituted by this study to ensure ongoing safety.

The DSMB will include 1-Hepatologist, 1 Liver Transplant Surgeon and 1 Statistician. The CRO will be responsible for coordinating a total of 6 meetings.

- 2 meetings annually during years 1-2 (4 total)
- 1 meeting annually during years 3-4 (2 total)

- The CRO will be responsible for contract agreements for DSMB, payment and data transfer.

Tabulations of all safety outcomes by group and follow up time will be presented along with the corresponding confidence bounds.

We will use Friedmans test to compare ordinal scores for adverse events such as Hand-Foot- Skin Reaction grade across time between the two groups. For outcomes such as fever, chills, nausea, vomiting, severe bleeding and gastrointestinal perforation, we will report the percent with 0, 1, 2 events at each follow up time by group or the percent with versus without the outcome if most patients have at most one event at any one follow up time/visit. We will use either a logistic, Poisson or negative binomial repeated measure model with random patient effect s (GEE method) to compare the percentages across time and between groups. We will use repeated measure analysis of variance or the non parametric Friedman test analog to compare mean/median continuous lab values such as AFP, PT, PTT, INR, ALT, AST, lipids and blood pressure or other continuous variables on the appropriate scale (i.e. log scale for ALT) and will present all relevant descriptive statistics (n, mean, median, SD, range, quartiles). We will also provide control charts (plots of the continuous value in all subjects over time) by treatment group with appropriate acceptable upper and lower limits, as established by the investigators. The control charts are a visual presentation indicating values beyond acceptable ranges. We may also use the repeated measure logistic model to compare the percent of patients who are abnormal on any of these tests (i.e. hypertension- yes or no) between groups over time.

14.2 Sample size considerations

The sample size is based on the primary outcome, recurrence free survival (RFS) at 2 years and assumes no more than 25% dropouts and a 1:1 (sorafenib:placebo) sample size allocation. The study sample size calculations account for a dropout rate of 25% over the 3 years, assuming a uniform dropout pattern. The sample size is computed for 80% power and a two sided alpha level of 0.05 assuming the log rank test will be used as above. A 2 year accrual and minimum 12 month follow up on all patients is assumed, making the length of the study 3 years.

Assuming 60% RFS at 2 years in the placebo group and 73% RFS in the sorafenib group at 2 years, a sample size including dropouts of 178 in the sorafenib group and 178 in the placebo group for a total of 356 patients provides 80% power. We expect no more than 25% or 89 patients, to drop out over the entire study period.

The PASS software system (NCSS Inc., Kaysville, Utah) was used to carry out the sample size calculations.

15.0 DISCONTINUATION OF STUDY DRUG

Patients continue therapy with study drug until a criterion is met for stopping therapy. Decisions about continuing study medication will be made at the discretion of the investigator, based on the investigator's judgment about the patient's clinical status. In general, it is suggested that a patient remain on study drug if, in the opinion of the

investigator, the patient may be benefiting from continuing on study drug.

15.1 Criteria for discontinuing study drug

- Any adverse event which, in the investigator's opinion, requires termination of the study medication
- Need to use T-cell depleting agents
- Use of alemtuzumab
- At the request of the patient or a representative
- Patients with a beta-HCG test consistent with pregnancy. Pregnancy will be reported as a serious adverse event.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, contribute to toxicity
- Deterioration of PS to ECOG 4
- Recurrence of clinically significant[6] HCC
- Use of direct-acting antiviral therapy for HCV
- The development of a second cancer
- The patient is lost to follow-up
- Withdrawal of consent
- Death

If any patient should discontinue study drug prior to completing the 24-month treatment phase, an End of Treatment evaluation should be completed, and follow up data should be reported (as indicated in Section 12.1).

If any patient should die during the trial or within 30 days of stopping study treatment, the investigator will inform the IRB and UCLA within 24 hours of obtaining knowledge of the patients' death. The cause of death should be reported in detail, on a serious adverse event (SAE) form.

15.2 Subject withdrawal of consent from study

In all cases, the patient's reason for withdrawal of consent must be recorded in the case report form (CRF) and in the subject's medical records. No additional data will be collected.

Replacement of Patients: No patients will be replaced on this study.

16.0 ADVERSE EVENT MONITORING (please refer to section 7, and 11.1 and 19)

Subjects will be carefully monitored for adverse events. This monitoring includes clinical laboratory tests. Adverse events will be assessed on a regular basis. Adverse events will be assessed in terms of seriousness, severity, and relationship to the study material. All unexpected or serious adverse events will be reviewed by the CROs Data Safety and Monitoring Board (DSMB).

17.0 PREMATURE CLOSURE OF STUDY

The sponsor has the right to close this study, and the investigator has the right to close the

[6] *Clinically Significant* as defined by individual site PIs or Investigators.

study, at any time, although this should occur only after consultation between involved parties. The Ethics Committee (EC)/Institutional Review Board (IRB) must be informed. The investigator will retain all documents. Events that may trigger premature termination of the study include: but are not limited to: new toxicity finding, completed accrual and follow-up of patients, noncompliance with the protocol, or slow recruitment.

18.0 ADVERSE EVENTS

18.1 Adverse Reactions

The overall safety profile of sorafenib is based on ~1300 cancer patients, who received sorafenib as single agent. This table will be used to determine the "expectedness" of Adverse Drug Reactions (ADRs) when used for reporting of adverse events to Regulatory Agencies. It is not a complete list of adverse events reported in clinical trials of sorafenib.

Table 18.1.1 Adverse Drug Reactions in Multiple Clinical Trials (MedDRA coded)

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%
Infections and infestations			Folliculitis infection
Blood and lymphatic system disorders	Lymphopenia	Leucopenia Neutropenia Anemia Thrombocytopenia	
Immune system disorders			Hypersensitivity reactions (including skin reactions and urticaria)
Endocrine disorders			Hypothyroidism
Metabolism and nutrition disorders	Hypophosphatemia	Anorexia	Hyponatremia Dehydration
Psychiatric disorders		Depression	
Nervous system disorders		Peripheral sensory neuropathy	Reversible posterior leukoencephalopathy*
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders			Myocardial ischemia and infarction* Congestive heart failure*

Vascular disorders	Hemorrhage (including gastrointestinal* and respiratory tract* and cerebral hemorrhage*) Hypertension		Hypertensive crisis*
Respiratory, thoracic and mediastinal disorders		Hoarseness	Rhinorrhea
Gastrointestinal disorders	Diarrhea Nausea Vomiting	Constipation Stomatis (including dry mouth and glossodynea) Dyspepsia Dysphagia	Gastroesophageal Reflux Disease Pancreatitis Gastritis Gastrointestinal Perforation*
Hepatobiliary disorders			Increase in bilirubin and jaundice
Skin and subcutaneous tissue disorders	Rash Alopecia Hand-foot reaction** Pruritis Erythema	Dry skin Dermatitis Exfoliative Acne Skin desquamation	Eczema Erythema multiforme minor
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	
Reproductive system and breast disorders		Erectile dysfunction	Gynaecomastia
General disorders and administration site conditions	Fatigue Pain (including mouth, abdominal, bone pain, headache and tumor pain)	Asthenia Fever Influenza-like illness	
Investigations	Increased amylase Increased lipase	Weight decreased Transient increase in transaminases	Transient increase in blood alkaline phosphatase INR abnormal, prothrombin level abnormal

* Events may have a life-threatening or fatal outcome. Such events are uncommon.

** Palmar plantar erythrodysaethesia syndrome in MedDRA

In combination with cytotoxic agents, myelosuppression leading to febrile neutropenia has

also been observed. Such events may have a life-threatening or fatal outcome.

The percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received sorafenib versus placebo on the phase III RCC trial is shown in Table19.1.1. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving sorafenib compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving sorafenib compared to 6% of patients receiving placebo.

18.2 Treatment-Emergent Adverse Events Reported in at least 10% of Sorafenib-Treated Patients – Phase III Advanced RCC Study

Table 18.2.1: Treatment-Emergent Adverse Events Reported in at Least 10% of Sorafenib-Treated Patients – Phase III Advanced RCC Study

Adverse Event NCI-CTCAE v4.0 Category/Term	NEXAVAR® N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand -foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritis	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1

Adverse Event NCI-CTCAE v4.0 Category/Term	NEXAVAR® N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the sorafenib and placebo groups (10% of sorafenib patients and 8% of placebo patients.)

Laboratory Abnormalities
The following laboratory abnormalities were observed in the phase III advanced RCC (TARGETS) trial:

Elevated lipase and amylase: Elevated lipase and amylase levels were very commonly reported. CTC Grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. CTC Grade 3 or 4 amylase elevations were reported in 1% of patients in the sorafenib group compared to 3% of patients in the placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTC Grade 4) and 1 of 451 patients (CTC Grade 2) in the placebo group.

Hypophosphatemia: Hypophosphatemia was a common laboratory finding, observed in 45% of sorafenib treated patients compared to 12% of placebo patients. CTC Grade 3 hypophosphatemia (1–2 mg/dl) occurred in 13% on sorafenib treated patients and 3% of patients in the placebo group. There were no cases of CTC Grade 4 hypophosphatemia (< 1 mg/dl) reported in either sorafenib or placebo patients. The etiology of hypophosphatemia associated with sorafenib is not known.

Lymphopenia: CTC Grade 3 or 4 were reported for lymphopenia in 13% of sorafenib treated patients and 7% of placebo patients, for neutropenia in 5% of sorafenib treated patients and 2% of placebo patients, for anemia in 2% of sorafenib treated patients and 4% of placebo patients and for thrombocytopenia in 1% of sorafenib treated patients and 0% of placebo.

Anemia: Observed in 44% of sorafenib-treated patients and 49% of placebo patients.

CTCAE Grade 3 or 4 anemia was reported in 2% of sorafenib-treated patients and 4% of placebo patients.

Thrombocytopenia: Observed in 12% of sorafenib-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of sorafenib-treated patients and 0% of placebo patients.

Adverse event monitoring
Subjects must be carefully monitored for adverse events. This monitoring includes clinical laboratory tests. Adverse events should be assessed on a cycle basis, and the highest grade according to NCI-CTCAE v4.0 should be recorded. Adverse event should be assessed in terms of seriousness, severity, and relationship to the study drug.

18.3 Adverse event definitions
The following definitions, which are consistent with FDA and ICH regulations/guidance, will be used:

Adverse Event (AE)
An adverse event is any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Serious Adverse Event (SAE)
A serious adverse event includes any event that:

Results in death.

Is life-threatening.

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

Requires inpatient hospitalization or prolongation of existing hospitalization.

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

Results in persistent or significant disability or incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea,

vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly or birth defect.

Is an important medical event.

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

Adverse Drug Reaction (ADR)

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

Serious Adverse Drug Reaction (SADR)

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

Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Package Inserts for Nexavar® (sorafenib). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the package insert would be considered "unexpected."

Relationship of Adverse Event to Investigational Product (IP)

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of "No" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site OR
2. Non-Plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "Yes" indicates that there is a reasonable suspicion that the adverse

event is associated with the use of the investigational drug.

Factors to consider in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge) recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subject's response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s) coupled with the individual subject's pharmacodynamics should be considered.

Intensity (Severity) of the Adverse Event

The intensity or severity of adverse events should be graded according to CTCAE version 4.0 criteria.

18.4 Adverse Event documentation

All adverse events occurring after the subject is randomized must be fully recorded in the subject's case record form. All treatment-emergent adverse events that occur after the first date of study drug administration will be followed to resolution or up to 30 days after last dose of study drug.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

18.5 Reporting serious adverse events

Requirements for Reporting of Serious Adverse Drug Reactions

All Serious Adverse Drug Reactions (SADRs) must be reported to UCLA Pfleger Liver Institute, Dumont-UCLA Transplant Center within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. **The name and contact information of the reporter**
2. **The name of the study drug(s)**
3. **A description of the reported SADR**

4. **A patient identified by one or more of the following:**
    a. **Patient initials**
    b. **Patient number**
    c. **Knowledge that a patient who experienced the adverse event exists**
    d. **Age**
    e. **Sex**
5. **An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.**

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

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

For blinded studies, the Principal Investigator will provide the treatment assignment upon request for patients who experience SADRs. The Principal Investigator will provide the final treatment assignment immediately after the end of the study.

Expedited Reporting of Other Safety Information

The Investigator shall report to UCLA Pfleger Liver Institute, Dumont-UCLA Transplant Center within 24 hours of the investigator's awareness of other events such as:

An adverse event related to study specific procedures
Any new and important event related to treatment with the study drug(s)
Any pregnancy during which a female patient was exposed to the study drug(s)
Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception occurred within two weeks of the last dose of study drug(s).

The investigator/Sponsor may report SADRs using either:

An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html OR
A MedWatch form available at http://www.fda.gov/medwatch/ (and also provided by the study_

The Principal Investigator commits to respond promptly to any query from the Sponsor regarding SAE reports.

A copy of any report submitted pursuant to this protocol and in compliance with the Subcontract shall be sent to:

On behalf of the UCLA Principal Investigator at:

Ronald W. Busuttil, MD, PhD
Distinguished Professor and Executive Chairman
David Geffen School of Medicine at UCLA, Department of Surgery
Ronald Reagan UCLA Medical Center
[redacted]

19.0 FUTURE STUDIES

At a later date, we plan to undertake a PK sub-study in approximately 40 subjects to explore exposure-response relationships in this study population. Eligible subjects will be consented separately for this PK sub-study. Full area under the plasma concentration–time curve (AUC) profiles will be performed at study initiation and at each protocol driven dose-adjustment cycle. For full AUC, blood samples will be collected at minutes 0, 15, 30, 45, 60 and hours 2, 4, 6, 8, 10 and 12 following study material administrations (sorafenib arm). Additionally, we will determine the following PK parameters for sorafenib: time to maximum/peak concentration (T_{max}), maximum/peak concentration (C_{max}), time to steady state (Cp ss) clearance (Cl), half-life ($T_{1/2}$) and volume of distribution (V_d). PK parameters and modeling will be calculated/performed using the Phoenix WinNonlin® (Pharsight Corp) PK data analysis program. Population PK (PPK) analysis may also be performed as required.

20.0 USE OF DATA AND PUBLICATION

All intellectual property derived from the study data and results will be the property of the principal investigator, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator is free to utilize data derived from the study for scientific purposes. The investigator has the right to publish the results upon completion of the study. However, the investigator may send a draft manuscript of the abstract to the sponsor in advance as notification of planned publications.

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22.0 APPENDICES

22.1 Warnings/Precautions

Hypersensitivity and known adverse drug reactions to sorafenib may include:

- Diarrhea
- Hand-foot syndrome
- Fatigue
- Rashes
- Anorexia
- Hypertension

The hand and foot symptoms may be resolved with discontinuation of sorafenib. Symptoms can sometimes be successfully treated with non-steroidal anti-inflammatory agents and urea-containing cream.

This is not a complete list of adverse events. The known side effect profile of sorafenib can be found in the current version of the IB. The IB is updated on a regular basis.

Both men and women enrolled in the study must use adequate barrier birth control measures during the course of the trial.

As with any new chemical entity, there is always potential for unexpected adverse events including hypersensitivity reactions.

Sorafenib has the ability to inhibit a variety of liver metabolic enzymes in vitro. The clinical impact of this inhibition in humans taking drugs metabolized by these enzymes is unknown. Therefore, all patients enrolled onto this trial who are taking concomitant medications that are known to be metabolized by the liver should be closely observed for side effects of these concomitant medications.

Furthermore, patients taking narrow therapeutic index medications including: warfarin, phenytoin, quinidine, carbamazepine, phenobarbital and cyclosporine and digoxin should be monitored proactively.

The use of use of strong CYP3A4 inducers not allowed during the study treatment period due to possible drug interaction.

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

Sorafenib is at least partially metabolized by the CYP 3A4 enzyme in the liver. The possible effect that inhibitors of CYP 3A4 may have on sorafenib is still being explored. Preliminary data from a clinical study indicated that there is no impact of ketoconazole co-administration on sorafenib PK. Drugs including ketoconazole, itraconazole, fluconazole and ritonavir are therefore not likely to affect sorafenib PK or safety.

22.2 Grading for Hand-Foot Syndrome

Patients experiencing Hand-Foot syndrome should have their signs and symptoms graded according to the following system. Other skin toxicities will be graded according to CTCAE Version 4.0

TABLE 1 Grading for Hand-Foot Skin Reaction

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

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

Patients who develop rash/desquamation or hand-foot skin reaction during treatment with sorafenib should have the involved area photographed if possible. Patients with discomfort due to hand foot syndrome may be treated with topical emollients, low potency topical steroids, or urea-containing cream.

22.3 Performance Status (PS) (Eastern Cooperative Oncology Group [ECOG])

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
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. (Karnofsky 50-60)

3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

22.4 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

This study will utilize the NCI-CTCAE Version 4.0 for toxicity and serious adverse event reporting. A copy of the NCI-CTCAE Version 4.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov/forms/CTCAEv4.pdf). All appropriate treatment areas should have access to a copy of the NCI-CTCAE Version 4.0.

22.5 New York Heart Association (NYHA)

<u>Functional capacity</u>

- **Class I**: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- **Class II**: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
- **Class III**: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.
- **Class IV**: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.