Title page

STUDY TITLE

A Phase II study of Sorafenib and Yttrium-90 Glass Microspheres for Advanced Hepatocellular Carcinoma, BCLC Stage C

Test drug (s):	**Sorafenib**
Test device:	**Yttrium -90 glass microspheres (TheraSphere®, Nordion, Canada)**
Study purpose:	**To evaluate the safety of systemic therapy with Sorafenib (Nexavar®) followed by liver directed therapy with Yttrium-90 microspheres in patients with Child Pugh A and Barcelona Clinic Liver Cancer (BCLC)-stage C Hepatocellular cancer.**
Clinical study phase:	**Single Arm, Phase II**
Version no.: 9	Date: June 19, 2015
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title	A Phase II study of Sorafenib and Yttrium-90 glass microspheres for Advanced Hepatocellular Carcinoma, BCLC Stage C
Clinical study phase	Phase II
Study objective(s)	The objective of this study is to evaluate the safety of continuous sorafenib 400 mg twice daily followed, after 4 (+/-1 week) weeks, by one Yttrium-90 treatment in patients with Child-Pugh A, BCLC-stage C HCC. **Primary objective**: • Median progression-free survival (PFS) **Secondary objectives**: • Overall Survival (OS) • Time to radiographic progression (TTRP) • To evaluate the safety of the combination of sorafenib and Yttrium-90; Adverse events (NCI-CTAE v 4.0) **Other objectives:** Predictive Biomarkers of response to therapy and survival: will assess pre-treatment plasma level of IGF-1 as above, and assess its predictive ability of TTP and OS
Indication	Advanced HCC
Study design	This is a single-arm phase II clinical trial. The treatment period will be divided into 4 week cycles. During the study period, patients will undergo evaluation for safety every 4 weeks. Tumor evaluations will be performed every 8 weeks.
Type of control	None
Number of subjects	20
Primary Endpoint	To evaluate the safety of the combination of sorafenib and Yttrium-90; Adverse events (NCI-CTAE v 4.0)

Diagnosis and main criteria for inclusion	• Patients >18 years of age • Patients with histological or cytologically documented HCC (Documentation of original biopsy for diagnosis is acceptable if tumor tissue is unavailable) *or* clinical diagnosis by AASLD criteria in cirrhotic subjects is required. For subjects without cirrhosis, histological confirmation is mandatory. • Patients must have at least one tumor lesion that can be accurately measured in at least one dimension according to RECIST • The target lesion has not been previously treated with local therapy (such as surgery, radiation therapy, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation). • Patients who have received local therapy, such as surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation are eligible if the previously treated lesions have progressed or recurred can be identified as target lesions. Local therapy must have been completed at least 4 weeks prior to the baseline scan. • Patients who have received Yttrium-90 microspheres are not eligible. • Patients who have an ECOG PS ≤ 1 • Patients who are categorized under BCLC-C stage • Cirrhotic status of Child-Pugh class A. Child-Pugh status should be calculated based on clinical findings and laboratory results during the screening period. • The following laboratory parameters: ▪ Platelet count ≥ 60 x 10^9/L ▪ Hemoglobin ≥ 8.5 g/dL ▪ Total bilirubin ≤ 2.5 mg/dl ▪ Alanine transaminase (ALT) and AST ≤ 5 x upper limit of normal ▪ Serum creatinine ≤ 1.5 x the upper limit of normal Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds above control.

Plan for statistical analysis	The primary analysis is to evaluate the toxicity profile, and the secondary analysis to assess the overall survival and progression-free survival. The study will be monitored for toxicity. Being descriptive in nature, this trial will not focus on hypothesis testing. Descriptive statistics will be computed for all continuous and categorical variables of interest. All statistical analyses will be performed using SAS (version 9.3; SAS Institute, Inc., Cary, NC). For the primary analysis, all patients received treatment will be included the analysis for toxicity. Continuous parameters will be summarized using descriptive statistics, such as number of patients, mean, standard deviation, median and range. The toxicities will be summarized with frequency and 95% confidence interval (95% CI) by type, severity and their relationship to the treatment. Assuming a 30% of grade 3 or 4 treatment related toxicity rate, with 20 patients, the 95% CI will be (9.9%, 50.1%). For the secondary analysis, the Kaplan-Meier method will be applied to estimate the probabilities of overall survival and progression-free survival as well as the median OS duration and PFS duration. The Log rank test will be used to compare the two time-to-event outcomes between patient subgroups.

Imaging Requirements	• Triple Phase CT – To determine liver volume measurement, identify hepatic vascular anatomy to determine TheraSphere dosimetry • Spiral CT abdomen/pelvis –performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane to assess hepatic and extra-hepatic lesions according to the RECIST 1.1 criteria. • Spiral CT Chest –performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane to assess extra-hepatic lesions according to the RECIST 1.1 criteria. • MRI can replace CT scans; however, the same imaging modality should be used for all images in an individual patient throughout the study • Images for efficacy assessments will require a duplicate set of images in DICOM format • Hepatic angiography and 99mTc-MAA– selective celiac and superior mesenteric arteriograms are needed to evaluate the hepatic arterial anatomy for the whole liver, as well as evaluation of potential sources of extra-hepatic blood supply to tumors. Repeat 99mTc-MAA may be needed to estimate cumulative lung shunt or re-asses GI flow.

Biomarker Variables	In addition to assessing the baseline plasma IGF-1 level, we will run exploratory biomarker studies utilizing available blood and plasma. A blood sample will be obtained from all patients at Screening. Plasma samples for biomarker evaluation will be obtained from all patients at six independent time points: (1) Screening; (2) Cycle 1/Day 1; (3) Cycle 2/Day 1; (4) Cycle 3/Day 1; (5) Pre-Yttrium-90, on the same day; and (6) End of Treatment. Plasma from patients on treatment days will be obtained from blood samples harvested prior to drug administration. These biomarker studies are optional and donation of biomarker samples is not required for participation in the clinical trial. The planned biomarker study is designed to measure the correlation between plasma IGF-1 as a surrogate for the liver reserve, with TTRP, OS and PFS of patients, since the status of the underlying liver disease independently affect patients' survival and outcome. Data from this biomarker analysis may be correlated with various other data obtained in this study (e.g., clinical activity, toxicity).

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List of abbreviations

AE	Adverse events
ADL	Activities of daily living
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	*bis in die*, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein

CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
DHPD	Dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report Form
EGFR	Epidermal growth factor receptor
ERK	Extracellular Signal-regulated Kinases
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire
FHSI8	Functional Assessment of Cancer Therapy – Hepatobiliary Symptom Index 8
FDA	Food and Drug Administration (US)
FLT3	FMS-like tyrosine kinase 3
GBq	Giga bBecquerel
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
Gy	Gray, a measure of irradiation dose
HCC	Hepatocellular Carcinoma
HDE	Humanitarian Device Exemption
HFSR	Hand foot skin reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio for prothrombin time
IR	Immediate release
IRB	Institutional Review Board
LFT	Liver function tests
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NCI	National Cancer Institute
NM	Nano molar

NYHA	New York Heart Association
PDGFR	Platelet Derived Growth Factor Receptor
PE	Physical exam
PFS	Progression free survival
PT	Prothrombin Time
PTT	Partial thromboplastin time
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	Serious adverse event
99mTc-MAA	Technetium-99m Macro-aggregated albumin
TS	TheraSphere
TTP	Time-to-Progression
SUSARs	Suspected unexpected serious adverse reactions
UADE	Unanticipated Adverse Device Event
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cells
Y-90(Y-88, Y-91)	Ytrium-90 and isotopes

1 Introduction

More than 80% of hepatocellular carcinoma (HCC) patients are not candidates for curative treatments, such as resection or liver transplant, the outcome of HCC patients remained very poor. Recently, sorafenib—a multitarget tyrosine kinase inhibitor—was found to improve survival of patients with Child-Pugh A unresectable HCC. The median overall survival (OS) was 10.7 months for patients on sorafenib vs 7.9 months for placebo, $P = .0006$, and median time-to-progression (TTP) was 5.5 months for patients on sorafenib vs 2.8 months for placebo, $(P < 0.001)$. Notably, out of all patients under the SHARP trial, 421 patients had extrahepatic spread (EHS) and/or macrovascular invasion (MVI) (Sorafenib=209, placebo=212). For patients with EHS and/or MVI (Sorafenib vs placebo), OS was 8.9 vs 6.7 months (HR: 0.77; 95% CI: 0.60, 0.99) and TTP was 4.1 vs 2.7 months (HR: 0.64; 95% CI: 0.48, 0.84). (Sherman M, et al. 44th ASCO Annual Meeting).

Considering that the cause of death of HCC patients with extrahepatic spread is mainly intrahepatic HCC progression or hepatic failure, rather than extrahepatic metastasis, the intentional addition of an intra-arterial local therapy modality, such as

Yttrium-90 microspheres, could offer added survival and quality of life benefit. **Surprisingly, no data have been available on this approach until now.**

1.1 Background and Rationale

TheraSphere®, a localized, minimally embolic therapy, capitalizes on the hypervasculature nature of tumors delivering Yttrium-90 microspheres, a source of beta energy, via the hepatic artery to the tumor bed. The distribution of blood flow is 3 to 7 times greater within the tumor than the surrounding noncancerous tissue. Consequently, there is preferential delivery of microspheres to the tumor capillary bed allowing for higher doses of radiation to be delivered to the tumor relative to the surrounding non-tumor parenchyma. The ability to concentrate radioactive microspheres within the tumor leads to an "inside-out" radiation, which in turn exerts a local tumoricidal effect.

Preliminary data: Treatment details were retrospectively collected for a cohort of patients with advanced multifocal HCC at MD Anderson Cancer Center between January 2008 & May 2010 who received systemic sorafenib followed by liver directed therapy with Yttrium-90 microspheres. 19 patients met the criteria (BCLC stage B=3 patients, and BCLC stage C=16 patients), (Child-Pugh A=16, and Child-Pugh B=3). Response rate was: PR 21% (n=4) and 79% (n=15) of these patients had SD by RECIST criteria. Median TTP per liver tumors was 7.3 months, and OS was 10.3 months. Grade 3 /4 hepatic toxicities were absent within 30 days post Y90 microsphere therapy. Significant adverse events were: GI ulcer (1), pancreatitis (1), lymphopenia (1), and mucositis (2) from which all patients recovered uneventfully.

It will be also important in the future to determine how to most effectively integrate molecular assays that assess the likelihood of therapeutic benefit into clinical practice. Therefore, we plan to assess potential biological markers candidates to help predict response or survival benefit to this approach. Insulin like growth factor-1 (IGF-1) is produced predominantly in the liver, and our recent study showed that pre-treatment plasma IGF-1 may correlate with patients' survival, and hence improve the prognostic ability of the Cancer of the Liver Italian Program (CLIP) score, and Barcelona Clinic Liver Cancer (BCLC) staging. IGF-1 significantly correlated with the clinicopathologic features. With an optimal IGF-1 cut point of 26 ng/mL, the overall survival for patients with IGF-1 >26 was 17.7 months (95% CI of 13.6, 22.8), and for IGF-1 $\leq$ 26 (60/288 patients) was 5.8 months (95% CI of 4.0, 12.5), p-value<0.0001.

Additionally, we have accrued 20 patients on the current study with a primary aim to evaluate the safety of the combination of sorafenib and Yttrium-90; adverse events (NCI-CTAE v 4.0) and found no grade 4 or 5 reactions. A few grade 3 reactions occurred in the form of: liver enzymes increase (ALT=1 patient, AST=3 patients, and bilirubin = 1 patient), Fatigue (=2), and 1 patient for each of the following: encephalopathy, hypertension, hyponatremia, hypophosphatemia, thrombocytopenia, maculo-papular rash, weight loss and vomiting.

1.2 Sorafenib

1.2.1 Preclinical

Sorafenib is a multikinase inhibitor which effects specific targets that are imperative for tumor cell proliferation including the serine/threonine kinases c-Raf and B-Raf (IC_{50} 6 and 25 nM respectively) and the receptor tyrosine kinase RET, Flt-3 and c-Kit (IC_{50} 47, 33 and 68 nM respectively) [1]. Sorafenib has potent activity against receptor tyrosine kinases important in tumor angiogenesis including the vascular endothelial growth factor receptor family (VEGFR1, -2, -3; IC_{50} 26, 90 and 20 nM respectively) and platelet derived growth factor-beta (PDGFR-í; IC_{50} 57 nM). In cellular mechanistic (on target) assays, sorafenib was found to be a potent inhibitor of VEGFR-2, VEGFR-3, and PDGFR and Flt-3 receptor phosphorylation. The anti-tumor activity of sorafenib in vivo is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and on the anti-angiogenic activity of the compound. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations, Raf/MEK/ERK signaling and induced apoptosis. Sorafenib has potent activity against human tumor xenograft model of hepatocellular carcinoma with tumor stabilization seen at moderate doses and partial tumor regressions observed at higher doses.

1.2.2 Clinical experience

Sorafenib as a single agent has been evaluated globally in multiple Phase I and II trials in various malignancies. Two pivotal international multi-institutional, single agent, randomized, placebo-controlled trials led to sorafenib's approval for renal cell carcinoma (RCC) (US 2005, EU 2006) worldwide and hepatocellular carcinoma (HCC) (2007) worldwide.

TARGET (**T**reatment **A**pproaches in **R**enal Cancer **G**lobal **E**valuation **T**rial) used a randomized, double-blind, placebo-controlled design to assess the efficacy of sorafenib in 903 subjects with advanced RCC who received 1 prior systemic regimen. The formal analysis of PFS using data available as of 28 Jan 2005 demonstrated a statistically significant doubling of PFS in subjects treated with sorafenib as well as a favorable safety profile of sorafenib in advanced RCC subjects. [2] This trial supported the US and European Union approvals of sorafenib in RCC, followed by regulatory approvals around the world, the first approved agent for this disease in over a decade.

Clinical results in Phase I studies of sorafenib as a single agent were suggestive of a therapeutic effect in HCC and led to the design of a single arm Phase II study (10874), in which 137 subjects with advanced, inoperable HCC Child-Pugh classes A and B were treated. The results of this study (median TTP of 5.5 months by independent assessment and median overall survival of 9.2 months), provided the basis for the randomized, placebo-controlled Phase III study in subjects with advanced HCC Child-Pugh class A (SHARP, **S**orafenib **H**CC **A**ssessment **R**andomized **P**rotocol). This large (602 subjects) Phase III study was the first international, randomized, double-blind, placebo-controlled study to demonstrate a statistically significant and clinically meaningful improvement in OS in advanced HCC subjects treated with sorafenib over placebo.[3] Of the 299 sorafenib subjects valid for ITT analysis, the median OS was 10.7 months in the sorafenib group and 7.9 months in the 303

subjects randomized to the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $p<0.001$. The nominal alpha for this analysis was 0.0077 according to the pre-specified O'Brien-Fleming-type alpha spending function. Therefore, sorafenib had a statistically significant effect on prolonging overall survival. This significant survival benefit represented a 31% reduction in risk of death (or 44% improvement in OS) in subjects treated with sorafenib versus those treated with placebo.

As of 31 December 2009, over 10,000 cancer patients with various malignancies have been exposed to sorafenib either as single agent or in combination with other chemotherapeutic agents in Phase I/II/III studies. Sorafenib has been generally well tolerated at a dose of 400 mg po twice daily (bid). The most common drug related adverse events have included hand-foot skin reaction, diarrhea, fatigue, hypertension, pain and rash. Grade 3 and 4 drug-related adverse events are uncommon. There was no evidence of cumulative toxicity and the majority of the adverse events were reversible.

2. TheraSphere

2.1 General Device Description

TheraSphere® consists of insoluble glass microspheres in which yttrium-90 is an integral component of the glass. The sphere diameter ranges from 20 to 30 μm with 22,000 to 73,000 microspheres per milligram. TheraSphere is available in six dose sizes (3 GBq, 5GBq, 7GBq, 10GBq, 15GBq and 20 GBq) each supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vial secured within a clear acrylic vial shield. A pre-assembled single-use TheraSphere Administration Set is provided for each dose. Each user site is provided with a re-useable TheraSphere Administration Accessory Kit that provides both radiation protection for the user and physical support of the dose vial and Administration Set during administration of the product.

Yttrium-90 is a pure beta emitter which decays to stable zirconium-90 with a physical half-life of 64.2 hours. The average energy of the beta emissions from yttrium-90 is 0.9367 MeV with mean tissue penetration of approximately 2.5 mm.

TheraSphere is administered through the hepatic artery which supplies blood to tumor tissue (the portal vein supplies blood to the normal hepatic tissue). The microspheres are trapped in the vasculature of the tumor due to arteriolar capillary blockage where they exert a local radiotherapeutic effect. In clinical use, the glass microspheres remain permanently trapped in the vasculature where the isotope decays to infinity leaving background radiation with no therapeutic value.

2.2 Global Regulatory Status of Therasphere

TheraSphere received a Humanitarian Device Exemption (HDE) from the United States Food and Drug Administration (FDA) in 1999 (HDE H980006) and is currently approved for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with

unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment. The current US package insert is provided in Appendix 1a.

TheraSphere is approved for use in Europe for the treatment of hepatic neoplasia. TheraSphere is approved in Canada for the treatment of hepatic neoplasia in patients who have appropriately positioned arterial catheters. In addition, TheraSphere is available in Russia, India, South Africa and Kuwait for the treatment of hepatic neoplasia.

2.3 Rationale for the Treatment of Hepatocellular Carcinoma

According to the American Cancer Society, primary liver cancer is a major health problem worldwide. [4] Globally, it is the fifth most commonly diagnosed cancer in men and eighth most common in women, with more than 700,000 new cases in 2007. It is the third leading cause of cancer death in men and sixth among women. In North America and Western or Northern Europe, areas with historically low rates, the incidence of liver cancer is increasing, possibly due to increased prevalence of hepatitis C.
In 2007, the US FDA approved sorafenib tosylate (Nexavar®), a small molecule Raf kinase and VEGF receptor kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC). [5] The approval was based on the results of an international, multicenter, randomized, double-blind, placebo-controlled trial (SHARP3 trial) in patients with unresectable, biopsy-proven hepatocellular carcinoma. [2] Overall survival was the primary efficacy endpoint. A total of 602 patients were randomized; 299 to sorafenib 400 mg twice daily and 303 to matching placebo.
Demographics and baseline disease characteristics were similar between the sorafenib and placebo groups. Prior treatments included surgical resections (20 %), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization in 40 percent), radiotherapy (5 %), and systemic therapy (4 %).

The trial was stopped following a pre-specified second interim analysis for survival disclosing a statistically significant advantage for sorafenib [median 10.7 vs. 7.9 months; HR: 0.69 (95 percent CI: 0.55, 0.87), p= 0.00058]. The final analysis of time-to-tumor progression (TTP) by independent radiological review was based on data from an earlier time point and demonstrated a statistically significant improvement in TTP in the sorafenib group [median 5.5 vs. 2.8 months; HR: 0.58 (95 % CI: 0.45, 0.74), p=0.000007].

Sorafenib is now suggested as the standard-of-care (SOC) therapy for patients with advanced HCC, the patients classified as BCLC C according to the Barcelona Clinic Liver Cancer (BCLC) classification system. [6] Sorafenib is included in the NCCN Clinical Practice Guidelines in Oncology (NCCN– Hepatobiliary cancers V.1.2010 – HCC5) as one of the possible treatments for patients with unresectable HCC and extensive liver disease who are not candidates for transplantation. [7]

Although sorafenib is a standard-of-care in the treatment of patients with HCC, it is associated with only a modest improvement in median survival as compared to best

supportive care. Further, sorafenib treatment is associated with significant toxicity. The most common adverse reactions3 (≥20 percent) considered related to sorafenib were fatigue, weight loss, rash/ desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain. [2] Diarrhea was reported in 55 percent of sorafenib patients (grade 3 in 10 %). Hand-foot syndrome (21 percent overall; grade 3 in 8 %) and rash (19 % overall; grade 3 in 1 %) were the most common dermatologic adverse reactions to sorafenib. Sorafenib dose reductions and drug holidays are often required to manage these toxicities.

Adhoc subset analysis of the SHARP trial data indicated that the efficacy of sorafenib is reduced in an important subset of patients with advanced HCC. [8] In patients with extrahepatic spread or macroscopic vascular invasion, the median survival was 8.9 months in patients treated with sorafenib as compared to 6.7 months in patients treated with placebo.

The long-term experience of TheraSphere in the treatment in 291 patients with HCC as part of a single-center, prospective, longitudinal cohort study were recently reported. [9] A total of 526 treatments were administered (mean, 1.8; range, 1-5). Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall TTP was 7.9 months (95% confidence interval, 6-10.3). Survival times differed between patients with Child-Pugh A and B disease (A, 17.2 months; B, 7.7 months; P = .002). Patients with Child-Pugh B disease who had portal vein thrombosis (PVT) survived 5.6 months (95% confidence interval, 4.5-6.7). Baseline age; gender; performance status; presence of portal hypertension; tumor distribution; levels of bilirubin, albumin, and alpha-fetoprotein; and WHO/EASL response rate predicted survival. These investigators concluded that patients with Child-Pugh A disease, with or without PVT, benefited most from treatment. Patients with Child-Pugh B disease who had PVT had poor outcomes. Therefore, TTP and overall survival varied by patient stage at baseline.
Results from a separate cohort of 108 consecutive patients with advanced HCC using TheraSphere demonstrated a median overall survival from treatment of 16.4 months, with median time to progression of 10.0 months. [10] Tumor response at 90 days evaluated by RECIST in 62 patients were complete or partial response 10 (16%), stable disease 46 (74%) and progressive disease 6 (10%). Toxicities were generally mild to moderate. The most common being transient fatigue during the week following administration (61%) and abdominal pain (56%). For patients with normal bilirubin at enrollment, 32% experienced Grade 1 or 2 elevations and three patients developed Grade 3 elevations. For patients with elevated bilirubin at enrollment, 17% experienced Grade 2 elevations and 30% experienced Grade 3 or 4 elevations. In the majority of patients, bilirubin returned to baseline values within 4-6 weeks. The conclusion was that Therasphere is safe and effective, even in patients with compromised liver function.
Preliminary results of a Phase II investigation of the safety, tolerability and efficacy of administering TheraSphere and Nexavar (sorafenib) treatment in 26 patients with HCC indicate that the combination is safe. [11] In this trial, all patients began sorafenib 400 mg BID at least 7 weeks in advance of TheraSphere treatment.Most patients (65%) required sorafenib dosage adjustment. The most common toxicities were diarrhea, fatigue and hand foot syndrome with most being self-limiting and responsive to sorafenib dose adjustment.

One single grade 4 toxicity of worsening cirrhosis was observed. Median survival is 15.5 months which exceeds that reported in the sorafenib or placebo arms of the SHARP study (10.7 and 7.9 months respectively). The reported toxicities are consistent with the toxicity profile of both TheraSphere and sorafenib with no apparent increase in severity or frequency.

Sorafenib will be given at a dose of 400 mg, orally, twice a day. Possible adverse events related to sorafenib include: cardiovascular: hypertension (9% to 17%); central nervous system: fatigue (37% to 46%), sensory neuropathy (≤13%), pain (11%); dermatologic: rash/desquamation (19% to 40%; grade 3: ≤1%), hand-foot syndrome (21% to 30%; grade 3: 6% to 8%), alopecia (14% to 27%), pruritus (14% to 19%), dry skin (10% to 11%), erythema; endocrine & metabolic: hypoalbuminemia (≤59%), hypophosphatemia (35% to 45%; grade 3: 11% to 13%; grade 4: <1%); gastrointestinal: diarrhea (43% to 55%; grade 3: 2% to 10%; grade 4: <1%), lipase increased (40% to 41% [usually transient]), amylase increased (30% to 34% [usually transient]), abdominal pain (11% to 31%), weight loss (10% to 30%), anorexia (16% to 29%), nausea (23% to 24%), vomiting (15% to 16%), constipation (14% to 15%); hematologic: lymphopenia (23% to 47%; grades 3/4: ≤13%), thrombocytopenia (12% to 46%; grades 3/4: 1% to 4%), INR increased (≤42%), neutropenia (≤18%; grades 3/4: ≤5%), hemorrhage (15% to 18%; grade 3: 2% to 3%; grade 4: ≤2%), leukopenia; hepatic: liver dysfunction (≤11%; grade 3: 2%; grade 4: 1%); neuromuscular & skeletal: muscle pain, weakness, respiratory: dyspnea (≤14%), and cough (≤13%).

The early reports of serious adverse events possibly associated with the use of TheraSphere included death, hepatorenal failure, liver abscess, hepatic encephalopathy, hepatic decompensation, radiation hepatitis, radiation pneumonitis, duodenal ulcer, gastrointestinal bleeding and cholecystitis. As clinical experience with TheraSphere increased, the pre-treatment high risk factors associated with these early serious events were identified, leading to improved patient selection criteria and thereby lowering the risk of these events occurring. These risk factors include infiltrative tumor type, bulk disease (tumor volume >70% or nodules too numerous to count), AST or ALT > five times the upper limit of normal, bilirubin > 2 mg/dL, tumor volume >50% in the presence of an albumin < 3 g/dL and those in whom extra-hepatic shunting to the lungs or gastrointestinal tract cannot be managed through standard angiographic techniques.

For those patients without the pre-treatment high risk factors noted above, TheraSphere is very well tolerated, with treatment in the US commonly administered in an outpatient setting. Hospitalization for treatment effects associated with TheraSphere administration is rare.

3. Study objectives

The objective of this study is to evaluate the safety of continuous sorafenib 400 mg twice daily followed, after 3-5 weeks, by Yttrium-90 treatment in patients with child-Pugh A, BCLC-stage C HCC.

Primary objective:

- Median progression-free survival (PFS)

Secondary objectives:

- Overall survival (OS)
- Time to radiographic progression (TTRP)
- To evaluate the safety of the combination of sorafenib and Yttrium-90; Adverse events (NCI-CTAE v 4.0)
-

Other objectives:

Predictive Biomarkers of response to therapy and survival: will assess pre-treatment plasma level of IGF-1 as above, and assess its predictive ability of TTP and OS

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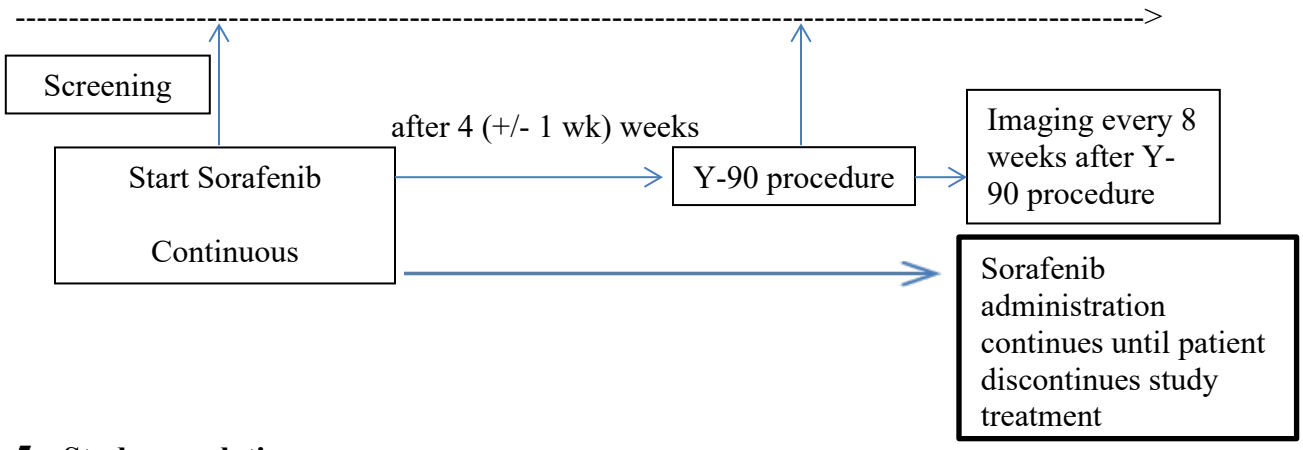
4. Study design

This is a single-arm phase II clinical trial to evaluate the safety of continuous sorafenib at 400 mg twice daily followed, after 4 (+/- 1 week) weeks from starting sorafenib, by Yttrium-90 treatment concomitant with sorafenib, in patients with child-Pugh A, BCLC-stage C HCC. Of note, the time between starting sorafenib and Yttrium-90 administration will be 4 weeks regardless whether the patient underwent dose reductions or interruptions. Patients will continue taking the maximum tolerating dose of sorafenib, with no interruption during and after the Yttrium-90 procedures. This is a single-institution study that will be conducted at MDACC, Department of GI Medical Oncology and Department of Interventional Radiology. No sorafenib interruptions around the procedure will be applied, and only one Y-90 treatment only will be performed.

Study schema:



5. Study population

5.1 Eligibility

Patients diagnosed with unresectable, measurable HCC, ECOG PS 0 or 1, Child-Pugh status A, BCLC class C, who have not received prior systemic anti-cancer treatment or Yttrium-90 for HCC may be screened for possible participation.

5.1.1 Inclusion criteria

1. Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
2. Male or female patients ≥ 18 years of age
3. Life expectancy of at least 12 weeks (3 months).
4. Patients with histological or cytologically documented HCC (Documentation of original biopsy for diagnosis is acceptable if tumor tissue is unavailable) or clinical diagnosis by AASLD criteria in cirrhotic subjects is required{Bruix, 2005}. For subjects without cirrhosis histological confirmation is mandatory.
5. Patients must have at least one tumor lesion that meets the following criteria: The lesion can be accurately measured in at least one dimension according to RECIST
6. The target lesion(s) has not been previously treated with local therapy (such as surgery, radiation therapy, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation).
7. Patients who have received local therapy, such as surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation are eligible if the previously treated lesions have progressed or recurred can be identified as target lesions. Local therapy must have been completed at least 4 weeks prior to the baseline scan.
8. Patients who have received Yttrium-90 microspheres are not eligible.
9. Patients who have an ECOG PS ≤ 1
10. Patients who are categorized under BCLC-C stage
11. Cirrhosis grade of Child-Pugh class A. Child-Pugh status should be calculated based on clinical findings and laboratory results during the screening period.
12. The following laboratory parameters:
    a. Platelet count ≥ 60 x 10^9/L
    b. Hemoglobin ≥ 8.5 g/dL
    c. Total bilirubin ≤ 2.5 mg/dl
    d. Alanine transaminase (ALT) and AST ≤ 5 x upper limit of normal
    e. Serum creatinine ≤ 1.5 x the upper limit of normal
13. Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds above control.
14. All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF).
15. 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.

16. Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 30 days after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
17. Subject must be able to swallow and retain oral medication.

5.1.2 Exclusion criteria

1. Main portal vein thrombosis (PVT)
2. Patients who are eligible for curative treatment (ablation or resection or transplantation)
3. Previous or concurrent cancer other than HCC unless without evidence of disease for 5 or more years prior to entry, except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor.
4. Tumor replacement >70% of total liver volume based on visual estimation by the investigator OR tumor replacement >50% of total liver volume in the presence of albumin <3 mg/dL
5. Contraindications to angiography and selective visceral arterial catheterization
6. Any known contraindications to sorafenib including allergic reaction, pill-swallowing difficulty, uncontrolled hypertension or history of cardiac disease, significant GI bleed within 30 days, metastatic brain disease, renal failure requiring dialysis
7. Concomitant treatment or within 28 days of one of the following:

    a. Any other systemic anticancer agent other than agents used for cancer prevention

    b. Subjects who have used strong CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, St. John's Wort [Hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) within 28 days before treatment.

    c. UGT 1A1 and UGT 1A9 substrates (e.g., irinotecan)

    d. P-Gp substrates (e.g., Digoxin)

8. Prior radiation therapy to the liver
9. Prior systemic therapy for the treatment of HCC, including sorafenib
10. Any history of symptomatic pulmonary compromise, such as chronic obstructive pulmonary disease
11. Any prior intervention for, or ongoing compromise of, the Ampulla of Vater or biliary-enteric anastomosis.

12. Clinically evident ascites (trace ascites on imaging is acceptable)
13. Pregnant or breast-feeding patients
14. A positive serum pregnancy test within 14 days prior to treatment in women of childbearing potential
15. Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.
16. Active or clinically significant cardiac disease including:
    a. Congestive heart failure – New York Heart Association (NYHA) > Class II.
    b. Active coronary artery disease.
    c. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    d. Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before treatment, or myocardial infarction within 6 months before treatment.
17. Evidence or history of bleeding diathesis or uncontrolled coagulopathy.
18. Subject with any pulmonary hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 2 or higher within 4 weeks before treatment; any other hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 3 or higher within 4 weeks before treatment.
19. Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) within 6 months of informed consent.
20. Presence of a non-healing wound, non-healing ulcer, or bone fracture.
21. History of organ allograft. (Including corneal transplant).
22. Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
23. Any malabsorption condition.
24. Inability to comply with the protocol and/or not willing or not available for follow-up assessments.

5.1.3 Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than sorafenib.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.
    - However, prophylactic anticoagulation as described below is allowed:

- Low dose warfarin (1 mg orally, once daily) with PT-INR ≤ 1.5 x ULN is permitted. Infrequent bleeding or elevations in PT-INR have been reported in some subjects taking warfarin while on sorafenib or capecitabine therapy. Therefore, subjects taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
- Low dose aspirin (≤ 100 mg daily).
- Prophylactic doses of heparin.

5.2 Withdrawal of subjects from study

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

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Severe allergic reaction to sorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

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

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

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already assigned to treatment/run-in/wash-out; administered at least one dose of study drug.

A subject who discontinues study participation for reasons other than toxicity after receiving sorafenib but not the Y-90 procedure is inevaluable and will be replaced. Subjects who are discontinued from the study early due to toxicities will be counted in the toxicity assessment.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure". Replacement

No withdrawn subjects will be replaced.

6. Treatment[s]

6.1 Treatments to be administered

6.2 Sorafenib Dosage and administration

Include the following regarding sorafenib therapy:

Subjects will be instructed on the proper administration of sorafenib. Sorafenib tablets should be taken 12 hours apart, at approximately the same time each morning and evening. Sorafenib tablets should be taken without food, at least 1 hour before or at least 2 hours after a meal, and with up to 240 mL (approximately 1 cup or 8 oz) of water. Consumption of grapefruit and grapefruit juice should be avoided while receiving study drug.

Sorafenib tablets are manufactured by Bayer HealthCare. The 200-mg tablet formulation contains sorafenib tosylate and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, and magnesium stearate. The tablets have a film coating comprised of hypromellose, polyethylene glycol, titanium dioxide, and red ferric oxide, which has no effect on the release rate of the active ingredient, sorafenib tosylate. The tablets are un-debossed, salmon colored, weigh approximately 350 mg each, and are 10 mm (millimeter) round in shape.

The chemical name for sorafenib tosylate is 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido] -phenoxy}-pyridine-2-carboxylic acid methylamide-4-methylbenzene-sulfonate, and its molecular weight is 637 daltons. The structure of sorafenib is depicted in Figure 6-1.

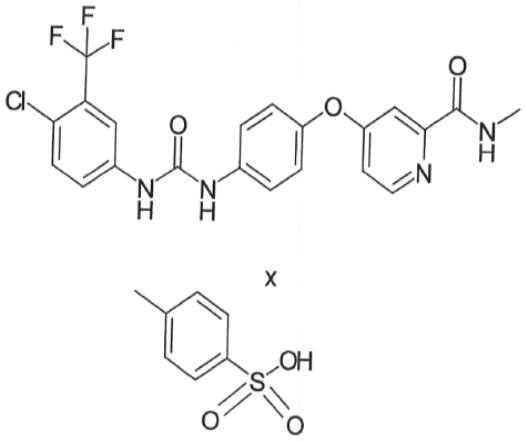


Figure 6-1: Structure of Sorafenib (BAY 43-9006)

Sorafenib tablets do not need to be protected from light. They are sufficiently stable with regard to 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.Dose Modification for management of adverse events

6.2.1.1 Dose Reduction Levels

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

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

Table 1: Dose modification levels for sorafenib

Dose	Sorafenib
Starting Dose	400 mg twice daily
-1	400 mg once daily
-2	400 mg every other day

6.2.1.2 Dose modification for hematologic toxicities

Recommended Dose Modification for Hematologic Toxicities [Table 2]

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				Sorafenib held until toxicity has resolved to Grade 2 or less; when sorafenib is restarted, reduce by one dose level

ANC - absolute neutrophil count ; AGC - absolute granulocyte count

- If no recovery after 30 day* delay, treatment should be permanently discontinued unless treating physician determines subject is deriving clinical benefit.
  * Modify according to study specific cycle length.

6.2.1.3 Dose modification for non-hematologic toxicities

Table 3: Recommended dose modification for non-hematologic toxicity (excluding hypertension and hand foot skin reaction, diarrhea and fatigue.

Grade	**Dose Interruption**	**Dose Modification**
Grade 0-2	Treat on time	No Change
Grade 3	Interrupt until ≤Grade 2	DECREASE one dose level
Grade 4	OFF protocol therapy	OFF protocol therapy

- If no recovery after 30 day* delay, treatment will be discontinued unless subject is deriving clinical benefit
  * Modify according to study specific cycle length.

6.2.1.3.1 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).

6.2.1.4 Hand-foot-skin reaction

Table 4: Recommended dose modification for hand foot skin reaction		
Toxicity Grade		**Suggested dose modification**
Grade 1	Any occurrence	Maintain dose level and consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Maintain dose level and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	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

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

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

Table 5: Recommended Prevention/Management Strategies for Skin Toxicities Consistent with Hand-Foot-Skin-Reaction	
Toxicity Grade	**Practical Prevention / Management Strategies for HFSR**
Grade 0 (Preventive strategies)	• Maintain frequent contact with trial physician to ensure early diagnosis of HFSR. • Practical prevention strategies o Pedicure[a] for subjects with pre-existing hyperkeratosis. o Subjects should avoid hot water, and clothing or activities that can cause friction on the skin. o 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: o Soak hands in cool water. o Apply petroleum jelly to moist skin. • In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards.
Grade 2 Any occurrence or **Grade 3** Any occurrence	• Continue supportive/management measures and add analgesic(s) for pain.
a: Pedicure should be done by a podiatrist.	

6.2.1.5 Treatment-emergent hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will check blood pressure at home, on a weekly basis through the first 4 weeks of therapy. Thereafter, blood pressure will be monitored on Day 1 of each cycle. Subjects with pre-existing hypertension will monitor blood pressure at home daily basis.

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

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

the management of treatment-emergent hypertension should be recorded in the subject's records.

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

Table 6: Management of Treatment-Emergent Hypertension

Grade of Event (NCI-CTCAE v4.0)	Management/ Next Dose
Grade 1	Consider increasing blood pressure monitoring. Continue sorafenib dosing as scheduled.
Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Begin anti-hypertensive therapy. Continue sorafenib dosing as scheduled.
Grade 2 (symptomatic/persistent) **OR** **Grade 2** symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits **OR** **Grade 3**	Sorafenib should be held[a] until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib is restarted, reduce by 1 dose level.[b] 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 unless, in the opinion of the treating physician, the subject may benefit from continued treatment.

b: Subjects requiring dose reductions beyond 400 mg once daily, every other day, should discontinue sorafenib.

6.3 TheraSphere

TheraSphere treatment is performed in the outpatient setting. Prior to initial treatment, a Technetium-99 Macroaggregated Albumin (Tc-99m MAA) scan will be performed using standard institutional practices. If there is an uncorrectable risk of flow to the gastrointestinal organs or risk of excessive shunting to the lungs, TheraSphere treatment will not be administered and the patient will receive alternative or no treatment as previously defined in the treatment plan

Following treatment, patients will remain at the hospital under medical observation until the physician determines that they can safely be discharged to home (usually 2-6 hours). All patients will be evaluated post-treatment to assess clinical experience and adverse experiences.

Patients will have 1-2 outpatient visits for pre-treatment evaluation to determine initial eligibility to receive TheraSphere, followed by a treatment visit for outpatient delivery of TheraSphere,.

Catheters will be placed in the hepatic artery in the angiography suites. No scheduled hospitalizations will be required, unless the physician determines that the patient should be admitted following treatment for management of a complication or adverse experience.

Pre-Therasphere Evaluation

Pre-treatment evaluation will include the initial screening by history, physical examination, laboratory and diagnostic studies (hepatic angiography and Tc-MAA Scan). A treatment plan will be developed, dosage will be calculated, and the initial TheraSphere activity vial will be ordered from the manufacturer (Nordion).

Diagnostic Imaging Studies

Contrast enhanced Computed Tomography Scanning of the Abdomen/Liver or Magnetic Resonance Imaging of the Abdomen/Liver

Technetium-99 Macroaggregated Albumin (Tc-99m MAA) Scan.

CT or MR scanning of the liver will be performed and the images used to calculate the appropriate liver volume for TheraSphere dose determination. Reasonable attempts will be made to use the same imaging modality as that used for pre-treatment for all subsequent evaluations of the patient related to dose determination.

The dose is calculated as described below (Section 7.3.3.4), using the appropriate reference liver volume and mass. Dosimetric techniques for TheraSphere are discussed in detail in the peer-reviewed literature.

The imaging scan is used to document the location and size of the hepatic lesion(s) and vascular anatomy where possible.

Prior to first TheraSphere treatment a Tc-99m MAA scan will be performed to obtain a preliminary assessment of hepatic infusion and any potential extrahepatic shunting or gastrointestinal flow. Lung Shunt Fraction will be determined as the ratio of total lung counts divided by total hepatic plus lung counts.

If gastrointestinal flow is detected, steps will be undertaken (embolization, change in catheter position) to correct this flow, prior to TheraSphere administration. If gastrointestinal flow cannot be corrected using established angiographic techniques, the patient may not receive TheraSphere treatment.

Only after extrahepatic exposure has been evaluated and the patient deemed to meet eligibility criteria, may TheraSphere be administered.

To be eligible to receive TheraSphere treatment, the potential absorbed dose to the lungs must be < 30 Gy (< 16.5mCi of injected activity) per treatment. Any uncorrected detectable gastrointestinal flow is a contraindication to TheraSphere treatment.

Treatment Planning

The principal investigator with the Authorized User will formulate the initial treatment plan, indicating the number and sequence of planned TheraSphere treatments. The clinician will assure that the patient understands the two-stage screening process that is necessary for this treatment procedure. The physician and patient will discuss and agree on a contingency treatment plan, including the option of no treatment, in the event that the patient is found ineligible to receive TheraSphere after catheter placement. The Treatment Plan may be modified following initial treatment, based on clinical experience and patient response to treatment.

TheraSphere Dose Calculation

The target dose of TheraSphere used is 80 – 150 Gy. Depending on the timing of the product order relative to the TheraSphere production schedule, and the treatment date proposed for the patient, it may be necessary to allow TheraSphere to physically decay to the appropriate targeted activity before injection.

The amount of radioactivity required to deliver the dose to the selected liver target is calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{ Mass of Selected Liver Target (kg)}]}{50}$$

In nearly all cases more than 95% of the glass microspheres are delivered. Calculation of the liver dose (Gy) delivered after injection uses the following formula:

$$\text{Dose (Gy)} = \frac{50\ [\text{Injected Activity (GBq)}][1\text{-F}][1\text{-R}]}{\text{Mass of Selected Liver Target (kg)}}$$

Where F is the fraction of injected activity deposited into the lungs as measured by Tc-99m MAA and R is the calculated residual.

TheraSphere Ordering

The TheraSphere order will be placed by the Authorized User or designated colleague. Upon completion of the pre-treatment screening evaluation, treatment plan and dose calculation, a TheraSphere order form will be sent to TheraSphere Customer Support, either by E-mail to TheraSphereCustomerSupport@mdsinc.com or by fax to 1-800-268-5299). The deadline for order is the Tuesday **prior** to calibration date to permit inclusion of your order in the weekly dispensing cycle.

TheraSphere is viable for therapeutic use for up to 12 days after the calibration date. TheraSphere will be shipped by MDS Nordion to ensure that TheraSphere is on-site by the proposed treatment date. To meet the desired absorbed dose to the patient's liver, the clinician must schedule the patient's TheraSphere treatment visit to occur within 12 days of the calibration date, and take into consideration the appropriate physical decay of the dose activity.

6.4 Procedures on Day of Treatment

Treatment with TheraSphere may be performed in the outpatient setting. The following sections describe the procedures performed on day of treatment.

Catheter Placement and TheraSphere Infusion

The goals of percutaneous catheter placement for TheraSphere administration are: first, to limit the perfusion to the normal liver, and, second, to deliver TheraSphere as specified in the treatment plan.

On the day of treatment, TheraSphere is administered via infusion under imaging guidance through an hepatic arterial catheter appropriately positioned in the arterial anatomy to permit selective infusion of TheraSphere into the target tissue selected for treatment. The interventional radiologist will perform this procedure. The patency of the catheter will be maintained using standard techniques.Administration of TheraSphere

Regardless of catheter size or infusion pressure used, the flow of the microspheres will mimic the flow dynamics of the vessel being infused.

The TheraSphere administration procedure is described in the TheraSphere package insert and in peer-reviewed literature.Patient Management

Following treatment, the patient will remain under observation consistent with standard care guidelines for aftercare procedures involving arterial catheterization. The patient will be sent home when the physician determines that the patient is stable and that there is no risk of bleeding from the access site. At the time of discharge, patients will be instructed per institutional guidelines regarding after-care including instructions if they develop a problem.

Because there may be small unrecognized arterial vessels connecting to the gastrointestinal system, prophylactic anti-ulcer medication is recommended at discharge. Gastric coating agents and tapering 5 day steroid dose pack (to reduce fatigue unless contraindicated) may also be given.

Special radiation isolation procedures are not necessary following TheraSphere treatment.

6.5 Radiation Safety in the Post-Treatment Period

If a patient receives a liver transplant or dies in the immediate period following treatment with TheraSphere**,** radiation safety guidelines for handling of the body and/or body tissues should be followed, as dictated by institutional radiation safety policy.

There are no federal regulations that clearly address the radiation safety issues related to handling of liver tissue following TheraSphere treatment. The surgeon and oncologist will consider the risks and benefits of the clinical circumstances and relevant institutional policy, before determining whether, and when, it is safe to proceed with procedures that require direct handling of TheraSphere-treated liver tissue in the immediate post-treatment period.

Most patients have surface dose rates <20μSv/h at 30 days following treatment. Generally a patient skin surface dose rate of < 20μSv/h does not require special handling (such as lead gloves, special instruments and extremity radiation monitors) by the surgeon during the operation. Notify radiation safety personnel for transportation and storage of the explanted tissue.

Very small amounts of longer-acting radioactive by-products have been noted. These by-products are well within known toxicity levels but may present some post-mortem tissue handling issues. Some regulatory jurisdictions are developing policies regarding handling of long lived by-products post mortem, specifically in regards to cremation; relevant institutional policy should be considered.

Travel documentation may be offered to patients who need to cross international borders, as the long lived activity may be detectable with the sensitive equipment at some facilities.

6.6 Device Dosages

The target dose of TheraSphere used is 80 – 150 Gy. Standard radiation safety techniques should be used.

Glass microspheres are typically 20-30 micrometers (μm) in diameter, or about 3-4 times the size of a red blood cell. In a report of 420 independent pre- and post treatment angiographic observations, macroscopic embolization of the hepatic arteries was not observed indicating hepatic perfusion is maintained.

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

CLINICAL AND LABORATORY EVALUATIONS [Table 7]

	Pre-Study@	Cycle 1, Day 1	Cycle 2 & Subsequent Cycles Day 1[f, #]	End of Cycle3, 5, & every 2 cycles#	End of Treatment #	Post Treatment Follow-up
Informed consent	X					
Demographics	X					
Medical History	X		X		X	
Concurrent Medications*	X		X		X	
Physical Exam	X		X		X	
Height	X					
Weight	X	X	X		X	
Vital Signs (Includes SBP/DBP)	X	X	X		X	
Urinalysis w/urine protein	X			X	X	
Performance status	X		X		X	
Hepatitis profile[i]	X					
PT/PTT/INR[a]	X		X		X	
CBC with differential, platelets	X		X		X	
Serum chemistry [b]	X		X		X	
Liver function tests [c]	X		X		X	
ECG	X					
ß-HCG (women of child-bearing potential)	X					
AFP[d]	X		X		X	
CT/MRI abdomen and pelvis Tumor Assessment [e]	X			X	X	
TheraSphere		**Therapy 4 (+/- 1) weeks after starting Sorafenib**				
Sorafenib		**Daily continuous 400 mg, orally, twice a day**				
Adverse events	X[g]		X		X	
Survival						X[h]
Plasma samples[j]	X	X	Cycles 2, 3, day of Y-90		X	

@ Pre-study evaluations except for imaging studies, Hepatitis profile must be obtained within 7 days prior to first day of treatment. Baseline imaging studies may be obtained up to 28 days prior to first day of treatment. Hepatitis profile must be obtained within 3 months prior to first day of treatment

Evaluations may be obtained within (+/-) 72 hours of starting a new cycle, except for imaging studies which may be obtained within 7 days prior to starting a new cycle.
*All medications, including prescription and over-the-counter, vitamins, supplements and

"herbal" preparations must be disclosed by the patient and recorded. Patients will be instructed to check with study staff before taking any new prescription or over-the-counter medication(s), vitamins, supplements and/or “herbal" preparations

[a] Weekly monitoring of INR for patients on warfarin, however, these patients will be switched to enoxaparin if possible.

[b] Includes BUN, creatinine, sodium, potassium, carbon dioxide, chloride, phosphorus, magnesium. calcium, protein, glucose.

[c] Includes AST (SGOT), ALT (SGPT); total, direct and indirect bilirubin; LDH, alkaline phosphatase, albumin; (GGT will be run for alkaline phosphatase that is >/= 150 IU/L. GGT will be run with the first elevation of alkaline phosphatase and will not be repeated for future alkaline phosphatase elevations)

[d] Alpha-feto protein.

[e] CT will be the radiographic study of choice for baseline (CT of the chest is included at baseline) and re-staging evaluations (CT of the chest may be included if needed in re-staging); MRI may be substituted at any time in the course of the study as clinically warranted (eg iodine dye intolerance, elevated creatinine, tumor not clearly depicted on CT)

[f] Treatment may continue after Course 2, including the same study assessment schedule, until one of the criteria for treatment discontinuation applies.

[g] Patients who have an ongoing Grade ≥ 3 or serious adverse event that is at least possibly related to treatment will be contacted by the investigator or designee every week until the event is resolved or determined to be irreversible.

[h] Every 3 months after discontinuation of treatment

[i] Hepatitis profile to include the following tests: hepatitis B virus surface antigen (HBSAG), hepatitis B virus core antibody (HBCAB), and hepatitis C virus antibody (HCVAB).

[j] Samples Collection: Blood samples will be collected at the time of patients’ scheduled visits as follows:Procedure for samples collection:

GI Medical oncology Research Staff will inform blood draw station to collect an extra set of blood sample (3 ml purple top tube with EDTA) for the purpose of the study, on the day of the patient’s initial visit and per scheduled samples collection per protocol. at the GI Medical Oncology clinic visits. Collection times will correspond to those at which subjects are already having blood drawn for other purposes. Maximum blood draws would be 6 total(1) Screening; (2) Cycle 1/Day 1; (3) Cycle 2/Day 1; (4) Cycle 3/Day 1; (5) Pre-Yttrium-90, on the same day; and (6) End of Treatment. Once blood is collected, GI Medical Oncology research personnel will pick it up and deliver it to the laboratory of Dr. Manal Hassan and Dr. Donghui LiSRB1 for processing in batch and storage in freezer in -80 F. Processing will involve isolating plasma samples.**Cycle 1/Day 1** sample will be collected only if **Screening** sample was collected more than 7 days prior. **Pre-Yttrium-90** sample will be collected only if **Cycle 2/day 1** sample was collected more than 7 days prior. And vice versa, **Cycle 2/Day 1** sample will be collected if **Pre-Yttrium-90** sample was collected more than 7 days prior.

Samples will each be labeled according to the sample label listed below.

Sample label or per Z code labeling

Protocol #
Subject Accession # -
Date/Time prepared -

7.1.2 Timing of assessments

One cycle is defined as 4 weeks of sorafenib therapy. Patients will be evaluated for toxicity every 4 weeks after start of study drug. This may include the sorafenib treatment and Y-90 procedure since the Y-90 procedure may be performed 4 weeks (+/- 1 week) after start of sorafenib treatment.

7.1.3 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.4.1.1.

7.2 Efficacy

Time to tumor progression will be determined by CT or MRI imaging of index lesion(s). Baseline imaging will be obtained within 4 weeks prior to study entry and at the beginning of every alternate cycle i.e., every 2 cycles (= 8 weeks), after Yttrium-90 treatment.

7.3 Pharmacokinetics / pharmacodynamics

None

7.4 Safety

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

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

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG at the investigator's discretion .

All AEs whether considered drug-related or not, will be reported in with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures

taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.4.1 Adverse events

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

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

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

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

7.4.1.1 Definitions

Definition of adverse event (AE)

> In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE if the condition worsens compared to baseline).

The clinical manifestation of any failure of expected pharmacological action (lack of efficacy) is not recorded as an AE if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria of an SAE, it must be recorded as and AE and reported as an SAE.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours.
   - The admission is pre-planned.
     (i.e. elective or scheduled surgery arranged prior to the start of the study)
   - The admission is not associated with an AE.
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another medically important serious event as judged by the investigator.

7.4.1.2 Classifications for adverse event assessment

The following classifications should be used:

- Seriousness

- Intensity
  As an alternative to the grading system described in the standard text below

(mild, moderate, severe), other systems for intensity may be used (e.g. CTCAE, Grade 1 to Grade 5). If used, this needs to be stated and definitions of the grades should be provided. If applicable, a "translation" between the CTCAE system and the standard system of intensity grading may have to be provided.

- Causal relationships to study drug:
  To be assessed separately for concomitant agents

- Study treatment action
- Other specific treatment of AE
- Causal relationship to protocol-required procedures(s)
- Outcome

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.4.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.4.1.1.

7.4.1.2.2 Intensity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv4 Grade 5: death due to an AE.

7.4.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”.

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 AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment 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 drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject’s response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event 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 may be suspected to cause the event in question.

[Causal relationship to protocol-required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”.

7.4.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

7.4.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.4.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.4.1.3 Assessments and documentation of adverse events

7.4.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.4.1.1.

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

an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

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

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

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

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

OR

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

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA
Mail only: **Ba**yer HealthCare Pharmaceuticals Inc.
P.O. Box 1000
Montville, NJ 07045-1000

Address: 340 Changebridge Road
FDX or UPS only Pine Brook, NJ 07058

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

Phone: 1-888-842-2937

7.4.1.5 Expected adverse events

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

7.4.2 Pregnancies

The investigator must report to Bayer any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform Bayer and record the cause of death in detail (using the SAE Form) within 24 hours.

7.5 Other procedures and variables

7.6 Appropriateness of procedures / measurements

The assessments described in the previous sections are widely used and generally recognized as reliable, accurate, and relevant for determining the safety and efficacy of therapies in this disease.

8. Statistical methods and determination of sample size

8.1 Statistical and analytical plans

Statistical consideration for 2012-0870: study of sorafenib plus theraspheres for extrahepatic hepatocellular carcinoma (redesign, 20 patients have enrolled in study 2012-0870)

This is a phase II study of sorafenib plus theraspheres for extrahepatic hepatocellular carcinoma (EHC). The primary objective is to evaluate the progression-free survival (PFS), where the progression-free survival will be measured from the start of therapy until failure to disease progression or death.

Historical data showed that the median PFS was 4.1 months for EHC patients treated with sorafenib alone. We expect that the combination treatment would improve the PFS. A maximum of 40 will be recruited for the study at a rate of 1-2 patients per month. The study will monitor toxicity and futility.

Futility monitoring

The primary endpoint PFS will be monitored using the method of Thall et al. (2005), and we will stop enrolling patients to the study if, based on the available data, we have little reason to believe that the median PFS of the combination therapy (m_E) is more than that of sorafenib alone (m_S) in the historical data, which was 4.1 months. Formally, we'll stop the study early if

$$\text{Prob}(m_E > m_S \mid \text{data}) < 0.15$$

That is, if there is less than 15% chance the median PFS of the combination therapy is more than that of sorafenib, the trial will be stopped. Where m_S represents the median PFS for sorafenib alone in the historical data with an inverse gamma distribution IG(11, 41), which corresponds to a mean of 4.1 months and a variance of 1.87. m_E represents the median PFS for the study combination therapy, assuming the prior for m_E is IG (2.17,4.8), which has the same mean as m_S but with a much larger variance (i.e. 99) to reflect much greater uncertainty about the median PFS of the combination therapy of sorafenib and theraspheres.

Futility monitoring will start once 20 patients have been enrolled. Assuming an accrual rate of 1.5 per month and an additional follow-up of 12 months, the operating characteristics for the futility stopping rule under various true states are summarized in the following table 8, with results based on 5000 simulations.

Table 8. Operating characteristics for the time-to-progression monitoring

True Median Time to progression	Pr(stop early)	Average Number of Patients Treated (25th, 75th percentiles)
2	0.993	21 (20, 20)
3	0.529	31.4 (20, 40)
4	0.100	38.3 (40,40)
5	0.017	39.7 (40, 40)

If the trial continues to maximum accrual of 40 patients and maintains sufficient follow-up to observe 25 events (PD/death) with a median PFS of 4.1 months, then a 95% credible interval for median PFS would extend from 2.76 to 6.08 months.

Toxicity Monitoring

In addition, toxicity will be monitored closely in all patients using the method of Thall et al (1995). The interim monitoring will be first conducted after the first 20 patients have been evaluated and then be repeated after each cohort of 5 patients. Denote the probability of toxicity by θ_E, where toxicity is defined as any non-hematological Grade 3 or greater complications attributable to the treatment. We assume $\theta_E \sim$ beta (0.6, 1.4). We will stop the

trial if at any point $Pr(\theta_E > 0.30 \mid data) > 0.85$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 85% chance that the toxicity rate is more than 30%. Stopping boundaries corresponding to this stopping rule are listed in table 9.

Table 9: Stopping boundaries for toxicity monitoring

Among These Number of Patients	Recommend Stopping if Toxicity Observed in n or more patients
20	9
25	11
30	12
35	14

Table 10: The operating characteristics for toxicity monitoring are summarized in the following table

True toxicity probability	Probability of early stop	Sample size percentiles (10, 25, 50, 75, 90)
0.1	0.0001	40 40 40 40 40
0.2	0.017	40 40 40 40 40
0.3	0.211	25 40 40 40 40
0.4	0.651	20 20 25 40 40
0.5	0.938	20 20 20 20 30

Multc Lean V2.1 and OneArmTTE Version 4.1.1 were used for the trial design.

Futility monitoring in CTC website

The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) for futility monitoring for each treatment arm on this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

Analysis Plan:

Primary analysis
Once the trial is completed, the posterior median time to progression and it 95% credible interval will be estimated. In addition, posterior probability that the median PFS is more than

sorafenib will be assessed. Furthermore, Kaplan-Meier method will be used to estimate median PFS and the 95% confidence interval. Log rank test, univariate and multivariate Cox proportional hazards regression models will be used to identify prognostic factors for PFS.

Secondary analysis

Toxicity rate and mortality rate will be estimated with a 90% credible interval. the posterior probability that the toxicity rate is greater 30% will be evaluated as well.
Binary endpoints such as response will be tabulated by frequency and the corresponding 95% confidence interval (CI). Fisher's exact test will be applied to compare the patient characteristics between responders and non-responders. Univariate and multivariate logistic regression models will be fit to identify clinical factors associated with overall response.
The time-to-event endpoints will be analyzed using Kaplan-Meier method, Log rank test and Cox proportional hazards regression modeling. Discrete or categorical patient-reported outcomes and quality of life assessments will be tabulated by frequency and 95% CI, while for the continuous data, summary statistics including n, mean, and standard deviation, median, minimum and maximum will be computed.

8.2 Planned interim analyses

None

8.3 Determination of sample size

Please see 8.1

9. Data handling and quality assurance

9.1 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the institution.

10. Premature termination of the study

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to Bayer.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bayer. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

11.2 Subject information and consent

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the

investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

11.3 Publication policy

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

11.4 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

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