Protocol Title:	**PHASE 3 PROSPECTIVE, RANDOMIZED, BLINDED AND CONTROLLED INVESTIGATION OF HEPASPHERE/QUADRASPHERE MICROSPHERES FOR DELIVERY OF DOXORUBICIN FOR THE TREATMENT OF HEPATOCELLULAR CANCER**
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TABLE OF CONTENTS

Appendices

1. Introduction

a. Background: Hepatocellular Carcinoma

Hepatocellular carcinoma is the fifth most common cancer, the third most common cause of cancer death worldwide, and results in over 600,000 mortalities each year (Bosch 2004). In 2010 it is estimated there will be more than 23,000 new cases diagnosed in the United States, with over 18,000 deaths (ACS 2009). Incidence in the US is expected to increase 59% between 2010 and 2030 (Smith 2008), primarily due to a rise in hepatitis B and hepatitis C infections. Three year survival for patients with unresectable hepatocarcinoma is only 10-40% (Llovet 2003), and the five year survival rate for all stages combined is less than 10% (ACS 2009). The primary reason for such poor prognosis is that liver cancer patients have underlying hepatic disease which can itself be fatal and can impact treatment options and response.

b. Treatment of Hepatocellular Carcinoma

The only potentially curative treatment for hepatocellular carcinoma is liver transplantation or tumor resection. However, only about 25% of liver cancers are diagnosed when they can be treated surgically. For patients with intermediate stage hepatocellular cancer, chemoembolization is often the best option.

Tumor directed hepatic artery embolization is possible because normal liver tissue receives most of its blood supply from the portal vein, while hepatocellular tumors derive most of their flow from the hepatic artery (Breedis 1954; Kan 1993). Transarterial chemoembolization (TACE) combines the local delivery of chemotherapy with induction of tumor ischemia through occlusion of feeding vessels. TACE has the dual benefit of focusing treatment on the lesions and reducing the adverse effects of systemic exposure to chemotherapy.

Two controlled randomized trials demonstrated increased survival for patients treated with embolization using chemotherapy and iodized oil compared to conservative treatment. Llovet et al randomized patients to receive chemoembolization or best supportive care. The results were statistically significantly in favor of chemoembolization, resulting in one and two year survival probabilities of 82% and 63% for TACE vs. 63% and 27% for supportive care, respectively (Llovet 2002). In a study in Asia, Lo and colleagues found one, two and three year survivals of 57%, 31% and 26% respectively for patients undergoing chemoembolization compared with 32%, 11%, and 3% for those receiving best supportive care (Lo 2002). A later systematic metaanalysis of randomized trials for HCC reported a significant improvement of two year survival in favor of chemoembolization (Llovet 2003). This study also identified doxorubicin and cisplatin as the only chemotherapeutic agents with proven effectiveness for hepatocellular cancer. Based on these and other investigations, chemoembolization has become accepted worldwide as a standard of care for unresectable localized

hepatocellular carcinoma, and is recognized as an effective treatment option by the National Comprehensive Cancer Network, the American Association for the Study of Liver Diseases, the Society for Interventional Radiology, and the American Cancer Association. However, no embolic has been FDA approved specifically for use in liver cancer.

c. Drug Eluting Chemoembolization

As noted above, transarterial chemoembolization localizes the chemotherapy delivery to the tumor and creates ischemia of the lesion by occlusion of the feeding artery. Drug eluting chemoembolization advances that concept. In conventional chemoembolization the chemotherapy is mixed with ethiodized oil to help retain it in the tumor vasculature longer, and then the embolic agent acts as a plug. However the occlusion is limited in area and some of the drug still escapes into the peripheral circulation, which leads to adverse effects, as does the ethiodized oil to some extent. HepaSphere/QuadraSphere Microspheres add two benefits to embolization therapy. First, by ionically binding the doxorubicin throughout the microspheres (which have a slight negative charge that binds the positively charged doxorubicin), and eluting it in a controlled manner, more drug can be delivered into the tumor, with less escape into peripheral circulation. Complimentary to the sustained elution, HepaSphere/QuadraSphere Microspheres are also highly compressible and conformable, so they mould to the vessel lumen, creating both excellent contact with the intima for doxorubicin delivery and very efficient occlusion.

A bench study demonstrating proof of concept of consistent and efficient loading and elution of doxorubicin by these microspheres was presented by Liu (Cardiovascular and Interventional Radiology Society of Europe, Lisbon, Portugal, Sept 2009. Manuscript in preparation). Dr. Liu and colleagues experimented with multiple variations of loading methods, exploring different methods of solubilizing the doxorubicin (sterile water, normal saline, etc) and exposing it to microspheres under various conditions (dry, prehydrated with saline, prehydrated with non ionic contrast, etc) to determine the optimal method for uptake and release, as well as catheter patency.

Four animal studies were conducted with HepaSphere/QuadraSphere: 2 to evaluate properties of the embolic itself without drug, and 2 to investigate behavior with doxorubicin. Khankan and colleagues (Khankan 2004) examined the effects of the superabsorbent polymer relative to a non drug eluting spherical embolic and particle PVA in a rabbit renal model. They determined that renal artery occlusion and coagulative necrosis occurred regardless of agent, but HepaSphere/QuadraSphere could achieve cross-sectional vessel occlusion distally with a single sphere and conformed to the lumen better than the other spherical embolic. Similarly de Luis (de Luis 2007)

observed in vivo size, deformation, final location and properties of HepaSphere/QuadraSphere in pig kidneys. The conclusion was that the embolic is stable, occludes perfectly, and morphologically adapts to the vessel lumen. The results of these two studies demonstrate the excellent ability of HepaSphere/QuadraSphere to block arterial blood supply and induce ischemia.

The other two animal investigations (VX-2 model in rabbits) have demonstrated feasibility and effectiveness of HepaSphere/QuadraSphere as a drug eluting embolic in vivo. Lee (2010) compared embolization using HepaSphere/QuadraSphere alone to embolization using the microspheres loaded with doxorubicin. They found that at 7 days, the bland embolic produced 60% cell death, but when loaded with doxorubicin, it resulted in 90% necrosis. The second study, by Gupta (SIR Mar 2008. Manuscript in preparation) evaluated conventional TACE to drug eluting HepaSphere/QuadraSphere, with the same dosage of doxorubicin in both arms of the study. Pharmacokinetic assays showed much lower C_{max} and AUC for doxorubicin in the drug eluting arm compared to the conventional TACE cohort. In addition, histopathological evaluation demonstrated that the doxorubicin levels in the tumors of the animals treated with conventional embolization was sparse, whereas it extended out as far as 1600 microns at 24 hours in the lesions of rabbits that were embolized with drug loaded HepaSphere/QuadraSphere, and was still detectable at 14 days.

The first clinical data using HepaSphere/QuadraSphere was reported by Osuga and colleagues (Osuga 2002). In this study 6 patients with large liver tumors underwent bland embolization (no doxorubicin), and 2 of them had surgery afterward. In follow up, tumors were found to have varying degrees of necrosis, from partial to complete. Histologic examination showed that the embolic occluded intratumoral vessels tightly without ischemic damage to normal tissue. Post procedural pain was minimal, and no deterioration of liver function occurred. The same author also published a larger study of 59 patients treated for hepatocellular cancer with bland HepaSphere/QuadraSphere (Osuga 2008). There were no major complications and objective response rate by mRECIST criteria was 66%, but the authors found there was a high incidence of converting patients to drug eluting chemoembolization for future treatments due to progression after bland embolization.

Two recent Phase II clinical trials have demonstrated effectiveness of HepaSphere/QuadraSphere to deliver doxorubicin in patients with hepatocellular cancer. A multisite, open label investigation in Italy (Grosso 2008) evaluated 50 patients who had a maximum of 4 hepatocellular lesions each, treated with up to 3 chemoembolizations, using a dose of 50 mg of doxorubicin or epirubicin. The objective response using mRECIST criteria at 6 months was 77%. There were no major periprocedural complications. More recently van Malenstein and colleagues presented

the initial results from a single site clinical trial in Belgium (International Liver Cancer Association, Milan, Italy, Sept 2009. Manuscript in preparation). This prospective, randomized and controlled study of 30 patients compared conventional TACE to drug eluting HepaSphere/QuadraSphere. Patients received up to 3 embolizations, with a dosage of 50-75 mg/m2 of doxorubicin. Pharmacokinetic studies demonstrated a significant difference in peak and overall circulating doxorubicin between the two cohorts. The effect of the larger amount of doxorubicin in the peripheral circulation of the patients who received conventional TACE was evident in the adverse events. There were 20 grade 3 (n = 12) or grade 4 (n = 8) adverse events among the patients who received cTACE compared with no grade 4 and only 4 grade 3 events in the HepaSphere/QuadraSphere group.

The inclusion criteria for the currently proposed clinical trial are in part derived from results of a Phase II multisite clinical trial of a different drug eluting embolic (DC Bead, BioCompatibles, England). That investigation (Lammer 2009) included 201 patients who received up to 3 embolizations, with a dosage of doxorubicin up to 150mg each time. The patients were randomized to receive either conventional chemoembolization or drug eluting embolization using the DC Bead product. The primary objective was objective response at 6 months using mRECIST criteria, but the study did not meet its endpoint (p=0.11). However, in the subset of patients with more advanced disease, that is, those who had ECOG performance levels of 1 (rather than 0), recurrent or bilobar disease, or were Child-Pugh B (rather than A), the difference in response between the conventional and drug eluting arms was statistically significant. It was determined that the reason for this difference was that individuals with greater underlying liver disease or generally poorer hepatic status were able to tolerate embolization better when the drug release was controlled by the embolic (Lencioni, International Liver Cancer Association, Milan, Italy, Sept 2009). With these results in mind, we have focused the inclusion criteria for this proposed study on those patients most likely to derive the greatest benefit from treatment with HepaSphere/QuadraSphere.

2. Study Objectives

The objectives of this prospective, randomized, blinded and controlled clinical trial are as follows:

a. Primary Objective

i. Evaluate overall survival in patients treated with doxorubicin delivery by HepaSphere/QuadraSphere compared to conventional transarterial chemoembolization with doxorubicin, lipiodol, and particle PVA

b. Secondary Objectives

i. Evaluate overall objective response rates (ORR) determined by mRECIST criteria (Llovet 2008; Lencioni 2010) of hepatocellular carcinomas treated with doxorubicin delivery by HepaSphere/QuadraSphere compared to conventional transarterial chemoembolization with doxorubicin, lipiodol, and particle PVA

ii. Evaluate doxorubicin related adverse events in patients treated with doxorubicin delivery by HepaSphere/QuadraSphere compared to those treated with conventional chemoembolization with doxorubicin, lipiodol, and particle PVA

1. Decline in left ventricular ejection fraction
    i. 10% decline from screening to below 50%
    ii. Absolute value of 45% or less
    iii. 20% decline from any value at screening
2. Neutropenia
3. Alopecia
4. Hyperpigmentation
5. Mucositis

iii. Evaluate Resource Utilization as assessed by:

1. Length of stay in hospital following each TACE procedure
2. Number of unscheduled hospitalizations
3. Length of stay of unscheduled hospitalizations
4. New or increased use of non-OTC pain medications
5. New or increased use of antibiotic medications

iv. Evaluate overall adverse event rates between the treatment groups

v. Evaluate objective response rates as determined by mRECIST criteria in the treated area (ORR-T)

1. In this evaluation progression is defined as new/continued tumor growth in the treated area(s) of the liver or extrahepatic spread. New

tumor growth within an area of the liver not previously treated will not be considered progression.

c. Tertiary Objectives

1. Evaluate Time to Untreatable Progression defined as hepatocellular cancer for which further localized treatment by resection, percutaneous ablation, or embolization is not an option, or when there is extrahepatic spread of the cancer

   Untreatable progression will be determined by the Central Reviewers during the study treatment and protocol-specified treatment follow up visits. After the final study TACE and associated assessments, untreatable progression will be determined by the treating physician during survival surveillance

2. Explore the relationship between pharmacokinetic (PK) data and patient outcomes including survival, tumor response, and adverse events

3. Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be entered into the study:

a. Age 18 or older

b. Patient has signed informed consent

c. Patient must have a diagnosis of hepatocellular cancer confirmed by at least one of the following:

- **i.** Histological confirmation
- **ii.** Magnetic resonance imaging (MRI) result with early enhancement and delayed enhancement washout of at least one solid liver lesion > 1 cm. Patient must also have evidence of cirrhosis or have chronic hepatitis B.
- **iii.** Contrast enhanced computed tomography (CT) with early enhancement and delayed enhancement washout of at least one solid liver lesion > 1cm. Patient must also have evidence of cirrhosis or have chronic hepatitis B.

d. Patient must not be suitable for treatment by resection or percutaneous ablation at time of study entry.

Patients not suitable for ablation due to lesion location may be enrolled

e. Patient MUST meet at least ONE of the following criteria:

- **i.** Stage Child-Pugh B 7
- **ii.** Recurrent HCC
- **iii.** Performance status ECOG 1

f. Patient has a life expectancy of at least 6 months

g. Absence of occlusive thrombus to the main portal trunk

4. Exclusion Criteria

If patients meet any of the following criteria they may not be entered into the study:

- **a.** Current or previous treatment with chemo- or radiation therapy or sorafenib
- **b.** Previous treatment with any form of transarterial embolization for HCC
- **c.** Patients with current or history of any other cancer except non-melanomatous skin cancer
- **d.** Female patients who are pregnant, breastfeeding, or premenopausal and not using an effective method of contraceptive
- **e.** Performance status ECOG $\geq$ 2
- **f.** Child-Pugh scores >7
- **g.** Active gastrointestinal bleeding
- **h.** Evidence of uncorrectable bleeding diathesis
- **i.** Extrahepatic spread of the HCC
- **j.** Total Bilirubin $\geq$ 3 mg/dL
- **k.** >50% tumor involvement of the liver
- **l.** Infiltrative or diffuse HCC
- **m.** Encephalopathy not adequately controlled medically
- **n.** Presence of ascites not controlled medically
- **o.** Presence of medically relevant localized or systemic infection, other than hepatitis B, C, D, E or G
- **p.** Any contraindication for MRI (eg metallic implants)
- **q.** Allergy to contrast media that cannot be managed with prophylaxis
- **r.** Allergy to iodized oil
- **s.** Any contraindication to arteriography
- **t.** Any contraindication for doxorubicin administration, including the following:
  - **i.** White Blood Cell count (WBC) <3000 cells/mm^3
  - **ii.** Absolute Neutrophil <1500 cells/mm^3
  - **iii.** Cardiac ejection fraction <50%
  - **iv.** Other condition deemed exclusionary by physician
- **u.** Any contraindication for hepatic embolization, including the following:
  - **i.** Porto-systemic shunt, or an arteriovenous shunt that cannot be adequately closed prior to chemoembolization
  - **ii.** Hepatofugal blood flow
  - **iii.** Serum creatinine > 2mg/dL
  - **iv.** Uncorrectable impaired clotting
    1. Platelet < 50,000/mm^3
    2. International Normalized Ratio (INR) > 1.4
    3. Activated Prothrombin Time (aPTT) less than 21 or greater than 40

v. AST $\geq$ 5X upper limit of normal for lab
vi. ALT $\geq$ 5X upper limit of normal for lab
vii. Severe peripheral vascular disease
viii. Other condition deemed exclusionary by physician

5. **Study Design**

This is a phase 3, multicenter, randomized, controlled study designed to evaluate the safety and effectiveness of treating patients with localized, non resectable hepatocellular carcinoma with conventional transarterial chemoembolization (cTACE) or HepaSphere/QuadraSphere transarterial chemoembolization (hqTACE).

The study will consist of a screening period in which patient eligibility will be determined. Patients meeting the study entry criteria will be randomized on a 1:1 basis to receive either cTACE or hqTACE. A TACE cycle is defined as a single embolization for patients with unilobar disease and an embolization of each lobe for patients with bilobar disease. Patients will receive up to 3 TACE cycles. The first embolization will be done within 4 weeks of baseline imaging, and the second and third TACE cycles will take place 8 and 16 weeks after the first TACE cycle, respectively. MRIs will be done 4 weeks after each TACE cycle to determine tumor response and will be assessed by Central Reviewers.

The primary study endpoint will be overall survival. Study treatment will end after a maximum of 3 TACE cycles. Patient survival will be followed from date of first study TACE procedure until a date of death is obtained or the patient is lost to follow-up. Treatments for hepatocellular carcinoma after the study TACE treatments are complete will be documented during the survival period to the extent possible.

For cTACE, 75 mg/m^2 of doxorubicin (maximum dose of 150mg of doxorubicin per TACE cycle) mixed with ethiodized oil will be delivered into the hepatic artery via microcatheter, and then the artery will be occluded with particle PVA. For the hqTACE, the 75 mg/m^2 of doxorubicin (maximum dose of 150mg of doxorubicin per TACE cycle) will be loaded onto the HepaSphere/QuadraSphere Microspheres (through ionic bonding when the spheres are exposed to doxorubicin solubilized in normal saline) and delivered via microcatheter. No ethiodized oil is used with the microspheres. Dosage will be calculated and rounded up to the nearest 25 mg of doxorubicin. The occlusion endpoint will be stasis to the second or third branches. If stasis has not been reached when the target dosage of doxorubicin has been delivered, additional bland embolic (particle PVA for the cTACE arm and HepaSphere/QuadraSphere for the hqTACE arm) will be used to achieve a consistent endpoint.

The study will evaluate safety throughout the protocol specified treatment phase of the investigation by assessing adverse events, as well as clinically significant changes from baseline in laboratory values, findings on physical examination including vital signs, ECOG performance

status, and cardiac ejection fraction testing. Concomitant medication usage will also be assessed. Blood samples will be drawn for pharmacokinetic evaluation the morning after the first TACE procedure and at the time of the MRI and laboratory evaluations following the first TACE cycle. In addition, patients who are still hospitalized at least 6 hours following the first PK blood sample collection will have an additional PK blood sample drawn.

6. Randomization and Blinding

Randomization and blinding of treatment identification will be used to reduce potential bias during data collection and evaluation of clinical endpoints. The treatment assignments will be unblinded once all data from the protocol specified treatment phase has been entered into the clinical database, all of the necessary standard data cleaning techniques have been implemented, and the database has been locked.

Once the informed consent has been signed and the patient has met all the study entry criteria, the patient will be considered eligible for randomization. Patients will be randomized to either the cTACE or hqTACE treatment groups in a 1:1 ratio within 1 week of their first scheduled TACE. Randomization schedules will be generated using an adaptive randomization model (based on the algorithm developed by Simon and Pocock). The adaptive model will control the balance of treatment groups within each site and also take into account the following baseline factors which will be weighted based on importance: Child-Pugh Stage (A or B), ECOG performance (0 or 1) status, recurrent disease (yes or no), AFP (<400 ng/mL or ≥400 ng/mL), presence of macrovascular invasion (yes or no), and tumor location (unilobar or bilobar).

Patients will be blinded to the treatment group to which they are assigned. In order to minimize any bias in interpretation of tumor response, the Central Reviewers who assess treatment response will also be blinded to which treatment the patient is receiving. It is not possible for treating radiologists to be blinded to treatment group because the method of embolization is different for the 2 methods of TACE. The primary efficacy outcome of overall survival is unaffected by blinding.

In an effort to assess the level of patient blinding, per FDA recommendation, patients will be asked the following question after they have completed their protocol specified embolizations: *"What treatment do you think you received?"* with response options of cTACE, hqTACE, or Unknown. This data is informative in nature and will not have any influence on the analyses of the study outcomes.

The study will be unblinded once all of the patients have received up to three study TACE cycles and follow up study procedures (protocol specified treatment phase of the investigation) and the database has been cleaned and locked. Unblinded survival data collection will continue until all patients have died or been lost to follow-up.

Treatment and Assessment

Study patients will be randomized to receive hqTACE or cTACE, with a target dose of 75mg/m^2 of doxorubicin for each TACE cycle (maximum dose of 150mg of doxorubicin per TACE cycle). Up to a total of 3 TACE cycles will be administered to each patient within approximately a 6 month period from initial treatment, based on response as determined by Central Reviewers, using mRECIST. See Study Flow Charts, Appendix A.

Taking windows for second and third TACE cycles into account (8 weeks ± 2 weeks from prior TACE cycle) and assessments (4 weeks ± 1 week from last embolization in current cycle), and a 4 week (±- 1 week) time between treatment of lobes of patients with bilobar disease, the assessment of objective response rate for patients with unilobar disease will be 15-25 weeks and 24-40 weeks for patients with bilobar HCC.

Patients whose response to treatment during the study makes them eligible for potentially curative therapies such as transplant, resection or percutaneous ablation will be offered those treatments, as appropriate in the decision of the treating physician. They will be discontinued from the treatment portion of the study and followed for survival per protocol.

For cTACE, 75 mg/m^2 of doxorubicin (maximum dose of 150mg of doxorubicin per TACE cycle) mixed with ethiodized oil will be delivered into the hepatic artery via microcatheter, and then the artery will be occluded with particle PVA. For hqTACE, the 75mg/m^2 of doxorubicin (maximum dose of 150mg of doxorubicin per TACE cycle) will be loaded into the HepaSphere/QuadraSphere Microspheres (through ionic bonding when the spheres are exposed to doxorubicin solubilized in normal saline) and delivered via microcatheter. No ethiodized oil is used with the microspheres. The occlusion endpoint will be stasis to the second and third branches. If stasis has not been reached when the target dosage of doxorubicin has been delivered, additional bland embolic (particle PVA for the cTACE arm and HepaSphere/QuadraSphere for the hqTACE arm) will be used to achieve a consistent endpoint.

For patients with bilobar disease the second lobe will be embolized within 4 weeks (± 1 week) of the first lobe. The total calculated dosage of doxorubicin (75 mg/m^2, maximum 150 mg per TACE cycle) will be divided between the lobes. Division of the dosage will be determined by the treating physician, based on tumor burden in each lobe.

7.1 Screening (within 4 weeks (+/- 1 week) of first TACE)

Prior to randomization, each patient will have the following performed:

- Obtain informed consent
- Medical history, including demographics and disease history
- Physical exam, including vital signs, height (baseline only) and weight
- Recording of concomitant medications
- ECG
- Urinalysis (Specific Gravity, Protein, Glucose, Blood)

- Baseline laboratory tests
  - CBC (RBC, WBC, Platelet Count, Hemoglobin, Hematocrit, ANC)
  - AST
  - ALT
  - AFP
  - Total Bilirubin
  - Albumin
  - aPTT/PT/INR
  - Alkaline phosphatase
  - Serum creatinine
  - HCG for premenopausal female patients (baseline only)
- ECOG Performance Status evaluation
- Child-Pugh stage calculation
- Cardiac ejection fraction testing. Subsequent cardiac ejection fraction testing during the protocol specified treatment period must use the same method as at screening.
- Baseline MRI (first study MRI) for tumor assessment (including chest and pelvis), reviewed by Central Reviewers
  - MRI of the liver must be done at baseline to assess hepatic tumors. For those sites at which assessment for presence of extrahepatic disease has been done by CT of the chest and pelvis as the facility standard of care, those results are acceptable in place of MRI of the chest and pelvis so that additional imaging is not performed unnecessarily.

If patient meets all the inclusion criteria and none of the exclusion criteria, the patient will be randomized to a treatment group.

7.2 First TACE Cycle

A TACE cycle is defined as a single embolization for patients with unilobar disease or an embolization of each lobe for patients with bilobar disease.

First TACE embolization must be within 4 weeks (± 1 week) of baseline MRI and laboratory evaluations.

If a patient has bilobar disease, the first lobe must undergo chemoembolization within 4 weeks (± 1 week) of baseline MRI and laboratory evaluations, and the second lobe must undergo chemoembolization within 4 weeks (± 1 week) of the first lobe.

A blood sample will be drawn the morning after the first embolization between 6am and 8am for PK analysis for all patients. For patients with bilobar disease, this sample is drawn after the embolization of the first lobe. An additional PK blood sample will be drawn 6-8 hours after the first sample for those patients who have not been discharged.

7.3 MRI and Laboratory evaluations following First TACE Cycle

MRIs of the liver, chest and pelvis and laboratory evaluations must be done within 4 weeks (± 1 week) of the first TACE cycle. If the patient received chemoembolization for bilobar disease, the MRIs and laboratory tests must be done within 4 weeks (± 1 week) of the embolization of the second lobe.

Laboratory evaluations will include those listed under screening, at a minimum, and results will be reviewed by the investigator and clinically significant changes from baseline will be reported as adverse events. Additionally, blood samples will be drawn for PK analysis. MRI results of the liver will be reviewed by Central Reviewers. If the patient has experienced a cardiac related adverse event, cardiac ejection fraction testing will be done.

7.4 Second TACE Cycle

A second TACE cycle is required for all patients, unless the investigator deems further treatment unsafe for the patient. The second TACE cycle must be within 8 weeks (± 2 weeks) of first TACE cycle.

If the patient has bilobar disease, the first lobe of the second TACE cycle must undergo chemoembolization within 8 weeks (± 2 weeks) of the second lobe in the first TACE cycle, and the second lobe of the second TACE cycle must undergo chemoembolization within 4 weeks (± 1 week) of first lobe in the second TACE cycle.

7.5 MRI and Laboratory evaluations following Second TACE Cycle

MRIs of the liver, chest and pelvis and laboratory evaluations must be done within 4 weeks (± 1 week) of the second TACE cycle. If the patient received treatment for bilobar disease, the MRIs and laboratory tests must be done within 4 weeks (± 1 week) of the embolization of the second lobe.

Laboratory evaluations will include those listed under screening, at a minimum, and results will be reviewed by the investigator and clinically significant changes from baseline will be reported as adverse events. MRI results of the liver will be reviewed by Central Reviewers. Cardiac ejection fraction testing will be done for all patients and must use the same method as at screening.

If the results of the liver MRI done after the second TACE cycle, as interpreted by the Central Reviewers, demonstrate complete necrosis according to mRECIST criteria, then the patient will not have a third TACE cycle. The patient will proceed to Post Final Study TACE evaluations defined in section 7.8.

7.6 Third TACE Cycle

A third TACE cycle will be done for patients with MRI results for the liver after the second TACE cycle that demonstrate less than complete necrosis, as interpreted by the Central Reviewers, according to mRECIST criteria. The third TACE cycle must be done within 8 weeks (± 2 weeks) of the second TACE cycle. If the patient has bilobar disease, the first lobe of the third TACE cycle must undergo chemoembolization within 8 weeks (± 2 weeks) of the second lobe of the second

TACE cycle, and the second lobe of the third TACE cycle must undergo chemoembolization within 4 weeks (± 1 week) of the first lobe in the third TACE cycle.

7.7 MRI and Laboratory evaluations following Third TACE Cycle

MRIs of the liver, chest and pelvis and laboratory evaluations must be done within 4 weeks (± 1 week of the third TACE cycle. If the patient received treatment for bilobar disease, the MRIs and laboratory tests must be done within 4 weeks (± 1 week) of the embolization of the second lobe.

Laboratory evaluations will include those listed under screening, at a minimum, and results will be reviewed by the investigator and clinically significant changes from baseline will be reported as adverse events. MRI results of the liver will be reviewed by Central Reviewers. If the patient has experienced a cardiac related adverse event, cardiac ejection fraction testing will be done using the same method as at screening.

7.8 Post Final Study TACE Cycle visit (within 4 weeks +/- 1 week after final study MRI)

After the patient has had his/her final TACE cycle, MRI and laboratory evaluations according to the schedule above, patient will have a final study visit within 4 weeks (± 1 week) after the final study MRI. The treatment schedule for this study ends after the following evaluations.

- Physical exam, including vital signs and weight
- Recording of concomitant medications
- ECG
- Urinalysis (Specific Gravity, Protein, Glucose, Blood)
- ECOG performance status evaluation
- Cardiac ejection fraction testing using the same method as at screening
- Adverse event assessment
- Laboratory tests
    - CBC (RBC, WBC, Platelet Count, Hemoglobin, Hematocrit, ANC)
    - AST
    - ALT
    - AFP
    - Total Bilirubin
    - Albumin
    - aPTT/PT/INR
    - Alkaline phosphatase
    - Serum creatinine

7.9 Survival follow -up

Patients will be followed from date of first embolization of the first cycle until a date of death is obtained or the patient is lost to follow up. Survival contacts will be attempted every 3 months after completion of final protocol-specified study visit. Contacts may be by visit, telephone, email, or written response, and may be obtained from the patient, medical records, or care givers/family members. Patients may undergo further treatment after the study-specified TACE treatments at the discretion of their physicians, including but not limited to transplant, resection, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), additional

embolizations, sorafenib or other treatments, including other investigational methods. Patients who have additional embolizations after the three protocol-defined TACE cycles must have the same type of embolization (cTACE or hqTACE) they received during the study. It would be unethical to deny these patients further treatment which might provide benefit, but any and all of the above could affect long term survival and be confounds in the analysis and interpretation of this study data. For this reason treatments and outcomes after the final study TACE will be documented, to the extent possible, during the survival follow-up period, but will not be considered safety or efficacy outcomes in this study, except time to untreatable progression (TTUP). Survival and TTUP will be the only outcomes evaluated after completion of the protocol specified treatment phase of the investigation.

7. Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse events, including cardiac ejection fraction <50%
- Progression to extrahepatic disease
- Refusal of treatment
- Patient request
- Inability to complete study procedures
- Lost to follow up
- Non compliance with study requirements

If a patient is withdrawn or discontinued from the study, the reason for withdrawal from the study will be recorded in the source documents and on the Study Termination CRF. All patients withdrawn from the study should be encouraged to complete, if possible, all clinical evaluations scheduled for the final visit. All adverse events should be followed as described in Section 9. The patient will be asked to give consent for survival follow-up contacts to be performed. Patients who are withdrawn from the study for any reason will not be replaced.

The study may be discontinued if, in the opinion of the Sponsor and/or the Data Safety Monitoring Board (DSMB), there is a significant risk to patients as evidenced by higher than anticipated adverse event rates, concern regarding unexpected serious adverse events, or device failures resulting in adverse events.

8. Adverse Events

9.1 Non-serious Adverse Events

9.1.1 Assessments

The Investigators are responsible for monitoring the safety of patients who have been randomized in this study. All AEs considered to be related to study treatment, including doxorubicin treatment, will be followed until the event resolves. If patients receive other

anticancer therapy the follow-up for AEs will be stopped. AEs will be evaluated for severity using NCI CTCAE (Common Toxicity Criteria for Adverse Events), where applicable.

Investigators are required to document all AEs occurring during the study commencing with the date of randomization and including the protocol defined post-treatment follow-up period (21 CFR §312.64[b]), which is defined as 30 days post last MRI in this study, on the designated CRF pages. It is also important to record all AEs that result in permanent discontinuation of the study treatment, whether serious or non-serious. AEs that occur following the signature of informed consent but prior to randomization will not be captured. AEs that occur after the patient receives any anticancer therapy other than the study treatment they were randomized to receive will not be recorded as AEs.

Serious adverse events (SAEs), as defined below, must be reported to BioSphere Medical or its representative within 24 hours of knowledge of their first occurrence. SAEs that occur following the signature of the informed consent but prior to the first TACE procedure will not be reported. SAEs that occur after patients receive any anticancer therapy other than the study treatment they were randomized to will not be reported.

9.1.2 Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation patient and does not necessarily have to have a causal relationship with the treatment. An AE therefore can be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the product or procedure. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for an SAE as defined below.

Anticipated adverse events are those which typically occur due to embolization (pain, fever, fatigue, nausea, elevated liver enzymes, infection, abscess, cholecystitis, hemorrhage, thromboembolism, etc), or are drug related (alopecia, nausea, mucositis, rash, skin discoloration, myelosuppression, changes in cardiac function, etc), or are related to liver disease progression (jaundice, new tumors, biliary obstruction, metastasis, liver failure, death), or relate to pre-existing conditions. Unanticipated events are those not typically seen as a result of chemoembolization. Unanticipated adverse events must be reported to the sponsor within 24 hours of site notification of the event.

Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus instead of hyperglycemia).

Progression of hepatocellular carcinoma is considered an efficacy outcome parameter and should not be captured as an AE.

Patients should be instructed to report any AE that they experience to the Investigator or Study Coordinator. Patients will be assessed for AEs at each visit. AEs occurring during the clinical trial and the protocol-defined follow-up period should be recorded on the appropriate AE CRF. In order to capture the most potentially relevant safety information during this study, it is important that the Investigators record AE terms accurately and consistently throughout the study. Wherever possible, a specific disease or syndrome should be reported on the CRF rather than the associated individual signs and symptoms. If observed or reported signs or symptoms are not considered a component of a specific disease or syndrome by the Investigator, they should be recorded as separate AEs on the CRF.

9.2 Serious Adverse Events

9.2.1 Definitions

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

• Results in death.

• Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

• Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

• Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

• Is a congenital anomaly/birth defect.

• Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as

"serious," which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe adverse event does not need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not constitute a SAE, unless the patient would be admitted to the hospital or the event would meet any other of the criteria for seriousness. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Prolongation of a scheduled hospitalization will be considered an SAE as defined above. Complications associated with surgical procedures or study treatments resulting in one of the outcomes above are considered SAEs.

9.2.2 Reporting Unanticipated Adverse Events and Serious Adverse Events

Any unanticipated adverse event or SAE, including death, due to any cause that occurs during this investigation, whether or not related to the study treatments, must be reported to the Sponsor immediately (not to exceed 24 hours within site notification of the event) in writing via fax or email. The SAE must be completely described on the AE CRF as well as the provided safety report form.

Safety Contact Information:
Primary Safety Contact: [redacted]
Medical Monitor [redacted]

10 Tumor Response Assessment

Response will be assessed using mRECIST criteria to evaluate tumor necrosis, and includes assessment of viable tumor, which is defined as uptake of contrast agent in the arterial phase of MRI.

Central Reviewers will evaluate all liver MRIs for tumor response. Two specially trained interventional radiologists will read each blinded liver MRI. In the event that the reviewers do not agree, a third reader will evaluate the imaging, and this will be the official reading for that

evaluation. Determination of whether a patient receives a third TACE cycle will be based on the results of the central readings, and not the individual clinical sites.

10.1 Response Definitions

10.1.1 **Complete response**: the disappearance of any intratumoral arterial enhancement in all target lesions.

10.1.2 **Partial response**: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions

10.1.3 **Progressive disease**: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started or a new HCC lesion

10.1.4 **Stable disease**: any cases that do not qualify for either partial response or progressive disease

See Appendix G, Image Interpretation Guidance Manual.

11 Statistical Analysis

11.1 General Considerations

In general, continuous variables will be summarized as n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized as the number and percentage of patients in each category.

Data from all investigational sites will be pooled in the analyses. Summary tables will present data for both treatment groups and overall, where appropriate. Data listings will include all data collected on the case report forms (CRFs), as well as any derived variables (study day, age, time to progression, etc.). Data collected on patients who are screen failures will not be included in any summary tables, listings, or analyses.

For each parameter, baseline is defined as the value reported prior to the first embolization. If multiple values were collected prior to the first embolization, the value closest to the date/time of the initiation of the first embolization will be used as baseline. This may include values collected earlier in the day on the date of first procedure.

Unscheduled data, such as information from unscheduled visits, repeat laboratory tests, or Investigator comments, will be included in the data listings. In general, these data will be excluded from the summary tables unless otherwise specified.

Any outliers detected during the review of the data will be investigated. If needed the data will be queried and corrected in the database prior to database lock and the generation of the final tables and listings.

All secondary analyses will be performed on a locked database after all patients have completed the protocol specified treatment phase of the investigation. The survival follow up data will continue to be entered into the clinical database for the primary analysis of overall survival and tertiary analysis of TTUP.

Analyses will be performed using SAS® (Statistical Analysis System), version 9.1 or higher.

Any treatment comparison with a 2-sided p-value less than or equal to 0.05 will be considered statistically significant.

11.2 Sample Size Calculations

The sample size calculation for the primary efficacy analysis of the comparison of median overall survival between the two groups is based on the assumption of a 16 month median survival in the cTACE group and a 24 month median survival in the hqTACE group. A sample size of 196 patients per treatment group will have 85% power to detect this difference in median survival (Hazard ratio= 1.500) based on a 2-sided Type I error rate of 5%. Assuming a 30% non-evaluable rate, a total of 255 patients will be enrolled and randomized into each treatment group.

11.3 Analysis Populations

11.3.1 Safety Population (SAF)

All randomized patients who have at least one TACE procedure will be included in the Safety Population.

11.3.2 Intent-to-Treat Population (ITT)

The Intent- to-Treat (ITT) Population is defined as all patients randomized in the study, regardless of treatment status. <u>This will be the primary population for the efficacy analyses.</u>

11.3.3 Evaluable Population (EVAL)

All randomized patients who have at least one TACE procedure and who have at least one post-baseline tumor evaluation and who do not have any major protocol violations will be included in the Evaluable Population.

11.4 Demographics and Baseline Characteristics

Patient characteristics will include the following:

- Patient demographics (age, gender, race, ethnicity)
- Baseline disease characteristics (number and size of baseline target tumors, baseline Child Pugh stage, ECOG performance status, unilobar or bilobar disease)

- Clinically significant medical history
- Concurrent medical conditions
- Prior cancer therapies

11.5 Efficacy Analysis

11.5.1 Median Overall Survival

The primary efficacy analysis of median overall survival will be performed on the ITT population when the last patient has completed two years of follow-up after their first study TACE procedure or 218 deaths have been observed in the two groups combined, whichever comes first. Patients will be followed for survival until death or loss to follow up. Overall survival time will be calculated in months from the date of the first study TACE embolization to the date of death or date last known to be alive for patients who are lost to follow up. Median overall survival time will be calculated for each treatment group using the Kaplan-Meier (product-limit) method and corresponding 95% confidence intervals will be generated. Treatment groups will be compared on median survival using a log-rank test.

One and two year survival rates and corresponding 95% confidence intervals will also be calculated for both treatment groups. Survival analyses will also be performed for the Evaluable population.

In order to assess the consistency of observed treatment effect across investigational sites, a data poolability analysis will be performed on the primary efficacy outcome of overall survival using the ITT population. Median overall survival data will be summarized by site, including Kaplan-Meier plots. In addition, a Cox proportional hazards model will be run including factors for treatment group, investigational site, and an interaction term for treatment group and investigational site. For purposes of this analysis, sites enrolling fewer than 10 patients may be pooled into a single site.

A multivariate analysis of the primary efficacy outcome of overall survival will be performed using a Cox proportional hazards model for the ITT population. This analysis will be considered supportive only. The model will include factors for site, as well as all variables included in the final adaptive randomization model. In addition, key baseline factors found to be significantly different between the two treatment groups at baseline will also be evaluated in the model.

11.5.2 Objective Response Rate

A secondary efficacy outcome is the Objective Response Rate (ORR). For purposes of this analysis tumor response will be based on the last post TACE liver MRI response recorded for each patient, as determined by the Central Reviewers based on mRECIST criteria. The ORR will be calculated for the ITT Population as the number of patients with a confirmed complete or partial response(based on mRECIST criteria) divided by the number of ITT patients [ORR=(# CR + # PR)/total # patients]. Patients who have discontinued from the study prior to their first post

baseline tumor evaluation will be considered to have progressed for purposes of calculating the ORR for the ITT population. Ninety-five percent confidence intervals will be calculated for the ORR for both treatment groups and for the difference between treatments. The ORR and corresponding 95% confidence intervals will also be calculated for the Evaluable Population. The ORR efficacy analysis will be performed on a locked database that will be unblinded only after all patients have completed the protocol specified treatment phase of the investigation. Treatment comparisons of the ORRs will be performed using Fisher's Exact Test.

In order to assess the robustness of the ORR analysis using the last post TACE MRI response, a sensitivity analysis of the ORR data using the first post TACE MRI response for the ITT population will be performed. In addition, a data poolability analysis will be performed using a multiple logistic regression model including factors for treatment group, investigational site, and an interaction term for treatment group and investigational site for the ITT population. For purposes of this analysis, sites enrolling fewer than 10 patients may be pooled into a single site.

11.5.3 Best Tumor Response

An informative analysis of best tumor response in the period from treatment initiation through the date of the last post TACE liver MRI, as determined by the Central Reviewers based on mRECIST criteria, will be summarized as the number and percentage of patients in each response category (complete response, partial response, stable disease, progression) for the ITT and Evaluable populations.

11.5.4 Resource Utilization

11.5.4.1 Length of stay (LOS) in hospital following each TACE procedure

This will be reported as the number of continuous 24 hour periods spent in the hospital following each protocol specified TACE procedure. An analysis of the average number of 24 hour periods the patient was hospitalized following TACE procedures will be performed. If the data is normally distributed, the treatment groups will be compared using a t-test. If the data is found to differ substantially from a normal distribution, non-parametric methods will be used to compare the treatment groups.

11.5.4.2 Number of unscheduled hospitalizations from date of first TACE procedure to last protocol specified post-TACE visit

This will be analyzed as a categorical variable with the following categories: 0, 1, 2 or more. Treatment groups will be compared using Fisher's exact test.

11.5.4.3 Length of stay of unscheduled hospitalizations

This will be reported as a number of 24 hour periods spent in hospital and summarized for only those patients reporting one or more unscheduled hospitalizations during the study specified treatment phase of the investigation. An analysis of the average number of 24 hour periods the patient was hospitalized during unscheduled hospitalizations will be performed. If there is

sufficient data, treatment comparisons will be performed. If the data is normally distributed, the treatment groups will be compared using a t-test. If the data is found to differ substantially from a normal distribution, non-parametric methods will be used to compare the treatment groups.

11.5.4.4 New or increased use of non-over-the-counter pain medications from date of first TACE procedure to last post-TACE visit

This will be analyzed as the proportion of patients reporting new or increased usage of non-over-the-counter pain medications during the protocol specified treatment phase of the investigation. Treatment groups will be compared using Fisher's exact test.

11.5.4.5 New or increased use of antibiotic medications from date of first TACE procedure to last post-TACE visit

This will be analyzed as the proportion of patients reporting new or increased usage of antibiotic medications during the study specified treatment phase of the investigation. Treatment groups will be compared using Fisher's exact test.

11.5.5 Objective Response Rate for Treated Area of the Liver

An analysis of objective response rate (ORR) will be performed based on the Central Reviewers' assessment of response in the treated areas of the liver only based on data from the protocol specified treatment phase of the investigation. The analysis of this outcome will employ similar methods as the overall analysis of objective response.

11.5.6 Time to Untreatable Progression

The Time to Untreatable Progression (TTUP) will be calculated from the date of the first study TACE procedure to the date of first documented untreatable progression, defined as hepatocellular carcinoma for which further localized treatment by resection, percutaneous ablation, or embolization is not an option, or when there is extrahepatic spread of the cancer. Patients who do not have documented untreatable progression will be censored in the TTUP analyses at the last date known to be progression-free. Tumor response/progression will be assessed by the Central Reviewers during the protocol specified treatment phase of the study and by the treating physician during long term follow up. Reasonable effort will be made to capture information on documented untreatable progression during the long term follow-up period. Patients in the ITT population who do not have at least one post baseline MRI will be censored at 4 weeks post first TACE cycle (which is the timing of the first scheduled post baseline MRI). The TTUP analysis will be performed on the final unblinded locked database at the end of the study.

Median time to TTUP will be calculated for both treatment groups in the ITT and Evaluable populations using the Kaplan-Meier (product-limit) method and corresponding 95% confidence

intervals will be generated. Median times will be compared between the treatment groups using the log-rank test.

11.5.7 Pharmacokinetic Analyses

Bioanalytical analysis of patient PK samples will be conducted at a centralized laboratory using validated assays. Plasma concentrations of doxorubicin and doxorubicinol will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median. Data collected will be analyzed using a population pharmacokinetic approach.

Prior to analysis of the plasma samples, the presence of any microspheres in the plasma will be noted and it will be determined whether these spheres contain doxorubicin as this could impact the true assessment of the amount of doxorubicin circulating at the time the sample was taken.

The relationship between PK results and patient outcomes will be assessed for all patients with PK data on an exploratory basis. The correlation between circulating levels of doxorubicin and overall survival, tumor response, and doxorubicin related adverse events will be evaluated to the extent possible with the available PK data.

11.6 Safety Analysis

All safety analyses will be performed for the Safety Population on the locked database that will be unblinded only after all patients have completed the protocol specified treatment phase of the investigation.

11.6.1 Adverse Events

Safety summaries will include the incidence of treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events (TEAEs) are defined as any event that began on or after the date of the first embolization or worsened in severity or frequency after embolization was initiated. Events worsening in severity should be considered new adverse events. Adverse events recorded on the CRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.
All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summaries will present data for both treatment groups by System Organ Class (SOC) and Preferred Term. TEAEs will be evaluated for severity using the CTCAE when available.

All TEAE summaries will be based on the number of patients experiencing an event, not the number of AEs experienced. For example, if a patient reports the same AE on 3 separate occasions that patient will be counted only once for that preferred term. Patients reporting more than one AE in a SOC will be counted only once in the SOC total. The denominator used for calculation of the percentages will be the number of patients in the Safety population in each treatment group.

Separate summaries will be generated for the following types of TEAEs:

- Overall TEAEs
- Severe TEAEs (grade 3 or higher)
- TEAEs related to doxorubicin specifically and treatment in general
- Serious adverse events (SAEs)
- Serious adverse events related to treatment
- TEAEs resulting in death

Treatment groups will be compared on the overall adverse event rates, and the rates of doxorubicin related adverse events during the protocol specified treatment phase of the investigation using Fisher's Exact Test.

The comparison of doxorubicin related adverse events will include:

- Clinically significant decline in left ventricular ejection fraction
- Neutropenia
- Alopecia
- Hyperpigmentation
- Mucositis

11.6.2 Laboratory Evaluations

Summary statistics for baseline and change from baseline during the protocol specified treatment phase of the investigation will be summarized for both treatment groups for all hematology and chemistry parameters, including liver function tests and electrolytes, as well as alpha-fetoprotein. Urinalysis data will be presented in the data listings only.

11.6.3 Vital Signs

Summary statistics for baseline and change from baseline during the protocol specified treatment phase of the investigation will be summarized for both treatment groups for the following vital sign parameters:

- Blood pressure (mmHg)
- Pulse (beats per minute)
- Respiration rate (breaths per minute)
- Temperature (°C)

11.6.4 Physical Examinations

Data from physical exams (scheduled and unscheduled) during the protocol specified treatment phase will be presented in the data listings. All pre-treatment clinically significant findings, as determined by the Investigator, will be reported as concurrent medical conditions. All clinically

significant findings on exams performed after treatment initiation will be reported as adverse events.

11.6.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG data will be collected at baseline and the final study visit and will be presented in the data listings. A summary table will be created summarizing the ECOG results as the number and percent of patients in each ECOG category for each treatment group for both timepoints.

11.6.6 Electrocardiogram (ECG)

Electrocardiograms will be performed at baseline and the final study visit. Investigators will interpret the results and classify each ECG as follows:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

For all abnormal findings, the investigator will provide a brief description of the abnormality. All clinically significant abnormal findings found at the final study visit which were not present at baseline will be reported as adverse events. A summary table will be generated summarizing the ECG results for baseline and final study visit as classified by the PI as the number and percent of patients in each category for each treatment group. All ECG data will be reported in the data listings.

11.6.7 Cardiac Ejection Fraction (%)

Cardiac ejection fraction data will be collected at screening, after the second TACE, and at the final study visit for all patients. Cardiac ejection fraction testing will also be collected at additional time points during the protocol specified treatment phase of the investigation if the patient has experienced a cardiac related adverse event. Abnormal findings will be reported as adverse events. A summary table will be created summarizing the number and percent of patients having a clinically significant cardiac ejection fraction finding at each time point for each treatment group. This data will be presented in the data listings.

12 Data Safety Monitoring Board

A Data Safety Monitoring Board will be formed consisting of at least 3 individuals with expertise and experience in clinical trials, liver cancer and safety evaluations, but without direct involvement in the conduct of the study. The exact responsibilities, procedures, and guidelines used to manage the DSMB are described in a separate charter.

13 Records and Confidentiality

Each patient will be identified by study number only in the trial records. Study data will be recorded on pre-printed CRFs. Monitoring of study data recorded on the CRFs to source documents will be conducted for all patients to ensure accuracy and completeness.

14 Quality Control and Assurance

This study will be initiated and conducted under the sponsorship of BioSphere Medical, Inc., a wholly owned subsidiary of Merit Medical Inc. BioSphere Medical will supply pre-printed CRFs to all sites. Representatives of BioSphere Medical will monitor the study to verify study data, medical records, and CRF data in accordance with current ICH, GCPs and other applicable regulations and guidelines.

15 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and the appropriate regulatory requirement(s). The investigators will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the trial and retained according to the appropriate regulations.

16 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where the IRB/IEC approval has been obtained. The protocol, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

17 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to any study procedures. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

18 Patient Confidentiality

In order to maintain patient privacy, all CRFs, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from BioSphere Medical or its designee and regulatory authority (ies) access to the patients' original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

19 Protocol Compliance

The Investigators will conduct the trial in compliance with the protocol provided by BioSphere Medical, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies), if required. Modifications to the protocol should not be made without agreement of the investigator and BioSphere Medical. Changes to the protocol potentially affecting safety or

efficacy will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC. BioSphere Medical will submit all protocol modifications to the regulatory authority (ies) in accordance with the governing regulations.

A record of patients screened, but not entered into the study, is to be maintained.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to the patient, the investigator will contact BioSphere Medical or designee, if circumstances permit, to discuss the planned course of action and the action will be fully documented in the case report form and source documentation.

20 Monitoring, Verification of Data, Audit and Inspection

A BioSphere Medical monitor, or designee, will visit each center periodically to monitor the progress of the clinical trial and review CRFs and original source documents with the study personnel, to verify accuracy of data recording. Periodically some/all of the facilities used in the trial (e.g., laboratory) may be reviewed or inspected by the IRB and/or regulatory authorities.

The Investigator will ensure that the trial participants are aware of and consent that personal information may be reviewed during the data verification process as part of the monitoring/auditing by properly authorized agents of BioSphere Medical or subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent the applicable law permits and not publicly available. The audit or inspection may include, for example, a review of all source documents, drug records, original clinical medical notes, some or all of the facilities used in the trial.

21 Data Recording and Retention of Study Data

In compliance with Good Clinical Practice (GCP), the medical records/medical notes, etc. should be clearly marked and permit easy identification of participation by an individual in the specified clinical trial. The Investigator must record all data with respect to protocol procedures, drug administration, laboratory data, safety data and efficacy ratings on the BioSphere Medical CRFs.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention, BioSphere Medical must be notified (in writing) so that adequate provision can be made with regard to the trial documents.

Trial documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region by BioSphere Medical. Documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with BioSphere Medical, who will inform the investigator, in writing, as to when these documents no longer need to be retained.

22 Confidentiality, Publication and Disclosure Policy

The Investigators understand that BioSphere Medical will use the information developed in the clinical study in connection with the development of the study treatment. This information may be

disclosed to other clinical investigators, the FDA, and other government agencies. All information disclosed to the Investigators by BioSphere Medical for the purpose of having the Investigators conduct the clinical trial described in this protocol or generated by the Investigators as results in the clinical trial shall be treated by the Investigators as strictly confidential. The Investigators shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical trial and who are bound by like obligations of confidentiality. Notwithstanding, the Investigators may use or disclose to others any information which: (i) was known to the Investigators prior to the date of its disclosure, (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigators on a nonconfidential basis by a third party who is not obligated to BioSphere Medical or any other party to retain such information in confidence.

Biosphere Medical acknowledges that the investigators have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. The investigators shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any confidential information or trade secrets of BioSphere Medical (other than the data). The study is a multi-center protocol, and as such the investigators agree not to independently publish their findings except as part of an overall multi-center publication, unless specifically approved in writing by BioSphere Medical or unless more than 12 months have elapsed since the last patient has completed the full protocol.

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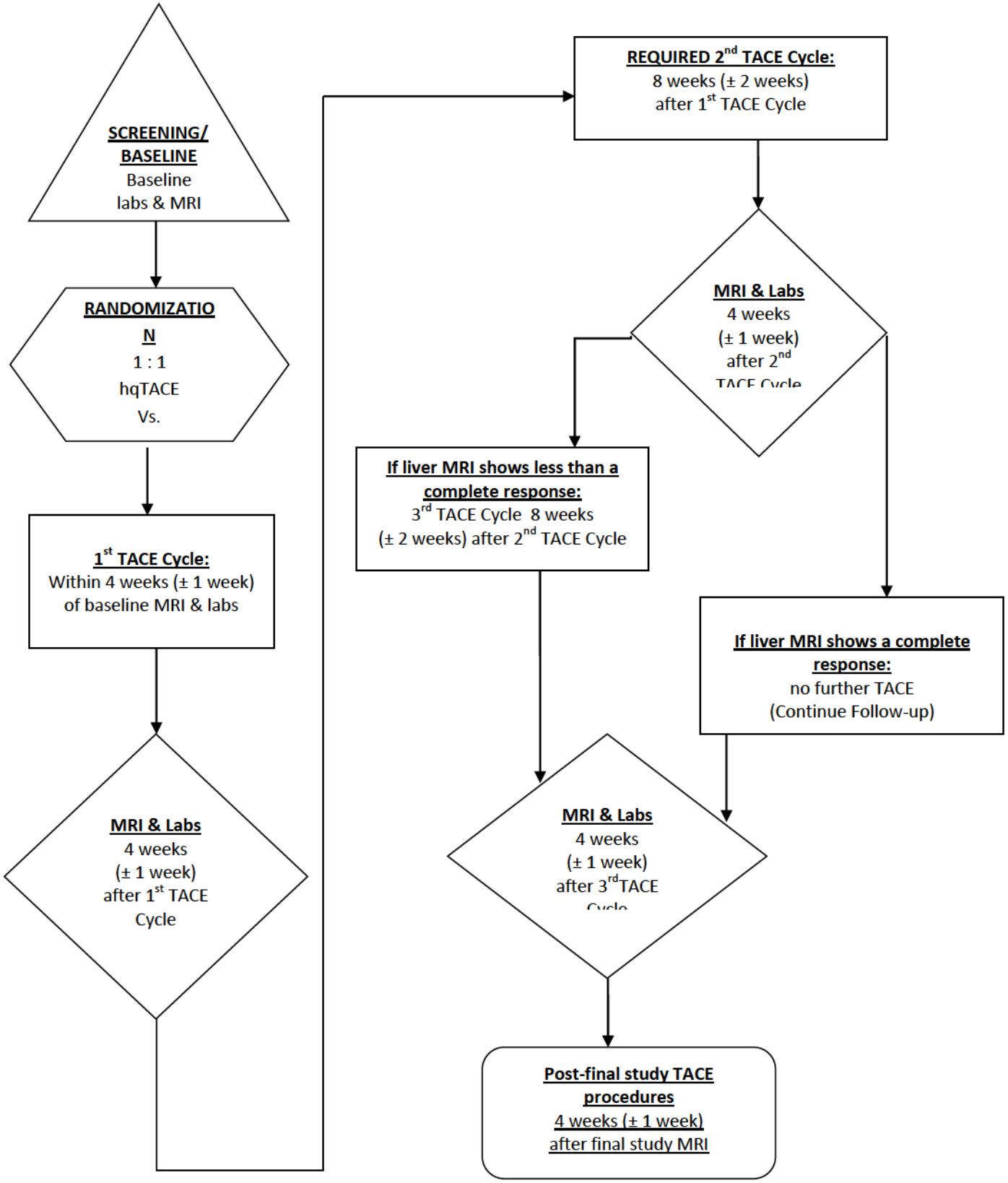
APPENDIX A

1. Study Flowchart: Unilobar Disease

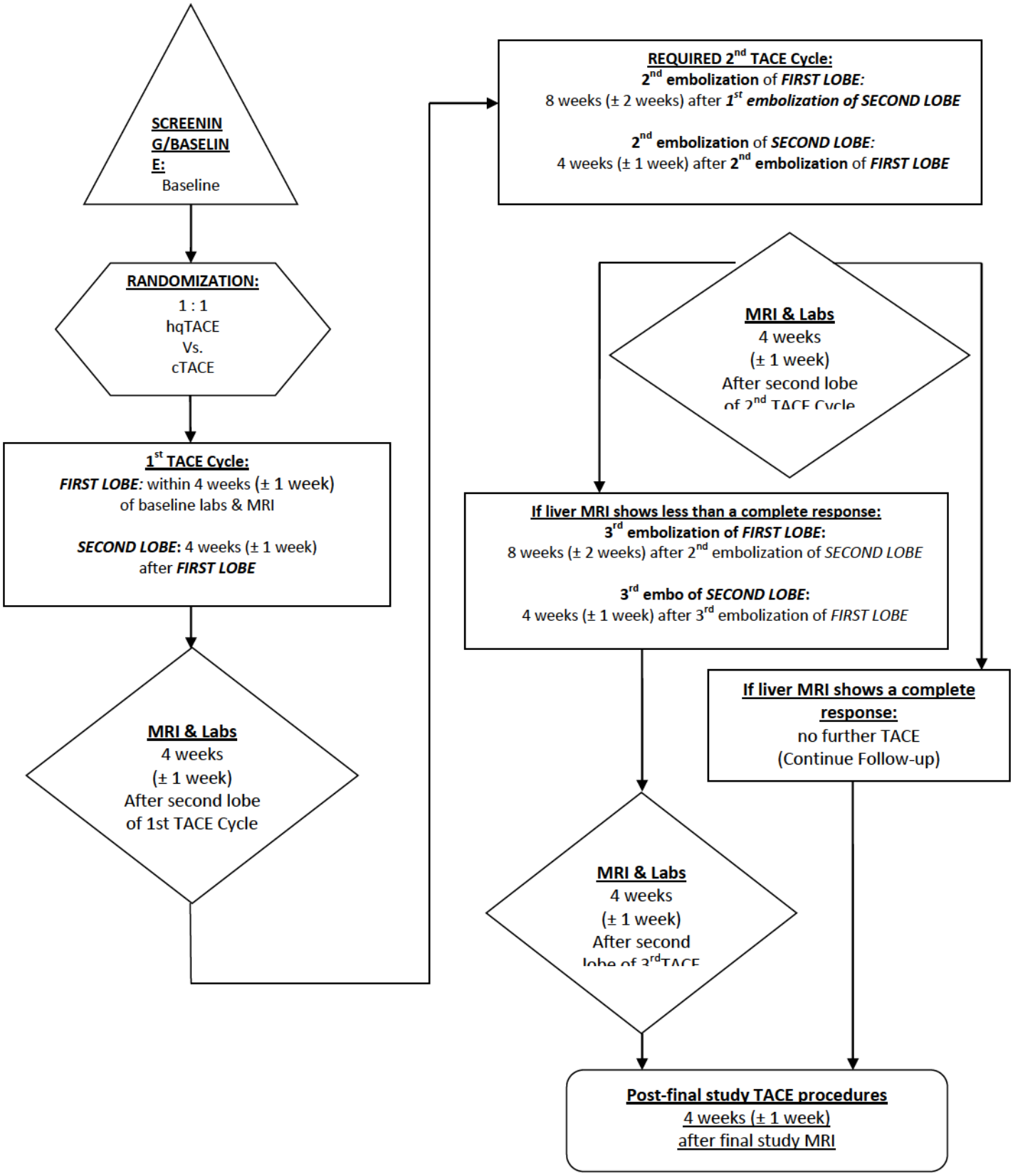
2. Study Flowchart: Bilobar Disease

3. Schedule of Study Events

1. Study Flowchart: Patients with Unilobar Disease



2. Study Flowchart: Patients with Bilobar Disease



3. Schedule of Procedures

	Screening (within 4 weeks +/- 1 week of first TACE)	TACE Treatment Period [1]			Post-final TACE Study Visit [2]	Survival Follow-up [3]
	Visit -1	Tx Visit 1	Tx Visit 2	Tx Visit 3	Visit 4	
Informed Consent	X					
Eligibility criteria assessment	X					
Demographics	X					
Baseline HCC Review [4]	X					
Medical History	X					
Concurrent Medical Conditions	X					
Physical Examination [5]	X				X	
Vital signs	X				X	
Serum Pregnancy test	X					
Hematology / Serum Chemistry [6]	X	X	X	X	X	
Urinalysis	X	X	X	X	X	
Tumor Evaluations (MRI) [6]	X	X	X	X		
Alpha-feto protein (AFP) [6]	X	X	X	X	X	
12-lead ECG	X				X	
Cardiac Ejection Fraction [7]	X		X		X	
Randomization [8]						
Embolization procedures (TACE)		X	X	X		
Resource Utilization		X	X	X		
Adverse Events		From randomization to protocol defined follow-up period				
Concomitant Medications	X					
Protocol deviations/violations	X					
Survival status						X
Additional cancer treatments						X
Pharmacokinetic Sampling [9]		X				

[1] First TACE Cycle must be begin within 4 weeks (±1 week) of baseline MRI and labs. If the patient has biolobar disease, the embolization of the first lobe must be within 4 weeks (±1 week) of baseline MRI and labs and the second lobe must undergo embolization within 4 weeks (± 1 week) of the first lobe.

A second TACE cycle is required for all patients, unless the investigator deems further treatment unsafe for the patient. The second TACE cycle must be within 8 weeks (± 2 weeks) of first TACE cycle. If the patient has bilobar disease, the first lobe of the second TACE cycle must undergo chemoembolization within 8 weeks (± 2 weeks) of the second lobe in the first TACE cycle, and the second lobe of the second TACE cycle must undergo chemoembolization within 4 weeks (± 1 week) of first lobe in the second TACE cycle.

A third TACE cycle will be done for patients with MRI results for the liver after the second TACE cycle that demonstrate less than complete necrosis, as interpreted by the Central Reviewers, according to mRECIST criteria. The third TACE cycle must be done within 8 weeks (± 2 weeks) of the second TACE cycle. If the patient has bilobar disease, the first lobe of the third TACE cycle must undergo chemoembolization within 8 weeks (± 2 weeks) of the second lobe of the second TACE cycle, and the second lobe of the third TACE cycle must undergo chemoembolization within 4 weeks (± 1 week) of the first lobe in the third TACE cycle.

[2] Post final TACE study visit must occur within 4 weeks (+/- 1 week) of the final study MRI.

[3] Patients will be followed for survival for 2 years after the first TACE embolization. Survival contacts will be performed every 3 months.

[4] Includes baseline disease status (Child Pugh, Unilobar/Bilobar status, ECOG), prior hepatic treatments, risk factor assessment, and assessment for relevant baseline medical conditions.

[5] Physical exam for the Post final TACE visit must be within 4 weeks (+/- 1 week) of final study MRI.

[6] MRIs and labs (including AFP) will be performed 4 weeks (+/- 1 week) after each TACE cycle. For patients with bilobar disease, MRI must be within 4 weeks (+/- 1 week) of the second lobe embolization.

[7] Cardiac ejection fraction may also be assessed as clinically indicated to evaluate a cardiac adverse event.

[8] Randomization will occur as close to the day of the scheduled First TACE procedure as possible, preferably on the same day.

[9] A blood sample will be drawn for PK analysis between 6a and 8a the day after the first embolization of the first TACE Cycle, again 6-8 hours later for patients who have not been discharged at that time, and on the day of the first follow-up MRI.

APPENDIX B

Procedural Guidelines for Loading HepaSphere/QuadraSphere with Doxorubicin (hqTACE)

CAUTION: INVESTIGATIONAL DEVICE in the United States. LIMITED BY UNITED STATES LAW TO INVESTIGATIONAL USE in the United States.

Supplies:

- 3 x doxorubicin 50mg powder vials
- 2 x HepaSphere/QuadraSphere vials
- 20G needles
- 2 x 20mL syringes
- 5 x 30mL syringes
- 4 x 10mL vials 0.9% normal saline for injection
- 2 x syringe caps

Procedure:

Prepare in Biohazard Hood

1. Attach a 20g needle to a 30ml syringe containing 20ml of 0.9% normal saline for injection.
   a. Doxorubicin 50mg vial #1: Reconstitute 1 vial of doxorubicin 50mg with 20mL 0.9% normal saline for injection via the 30ml syringe.
2. Using 2 new 20ml syringes, attach a 20g needle to each (syringe A&B):
   a. With Syringe A: Withdraw 10mL of the reconstituted doxorubicin from the doxorubicin 50mg vial and set aside.
   b. With Syringe B: Withdraw the remaining 10mL of reconstituted doxorubicin from the doxorubicin vial and set aside.

**This process should yield 2- 20ml syringes (A&B), each containing doxorubicin 25mg/10ml.*

3. Lift the cap of each (2 vials) HepaSphere/QuadraSphere vial to the vertical position taking care NOT to remove the cap or the metal retaining ring from the vial.
4. Roll each vial several times to disperse the microspheres within their respective vial.
5. With syringe A:
   a. Attach a new 20g needle to a syringe containing 10ml of solubilized doxorubicin.
   b. Slowly add the 10mL of doxorubicin to one of the HepaSphere/QuadraSphere vials by puncturing the grey stopper with the 20g needle and allowing the contents to naturally aspirate from the syringe into the vial.
6. Gently rotate and invert the HepaSphere/QuadraSphere vial back and forth so that the liquid contacts the grey stopper 5 to 10 times.

7. With syringe B:
   a. Attach a new 20g needle to the other syringe containing 10ml of solubilized doxorubicin.
   b. Slowly add the 10mL of doxorubicin to the remaining HepaSphere/QuadraSphere vial by puncturing the grey stopper with the 20g needle and allowing the contents to naturally aspirate from the syringe into the vial.

8. Gently rotate and invert the HepaSphere/QuadraSphere vial back and forth so that the liquid contacts the grey stopper 5 to 10 times.

**This process should yield 2-HepaSphere/QuadraSphere vials each containing doxorubicin 25mg/10ml.*

9. Set the HepaSphere/QuadraSphere vials containing the 10ml of doxorubicin aside and allow the vials to stand for a minimum of **10 minutes.**

While waiting:

10. Reconstitute the remaining 2 doxorubicin 50mg vials with 20ml of 0.9% normal saline for injection in each vial:
    a. doxorubicin 50mg vial #2- Utilizing a new 30ml syringe with a 20g needle attached, inject 20ml of 0.9% normal saline for injection.
    b. doxorubicin 50mg vial #3- Utilizing a new 30ml syringe with a 20g needle attached, inject 20ml of 0.9% normal saline for injection.

    **This process should yield two doxorubicin 50mg vials each with10ml of 0.9% normal saline.*

11. Using 2 new 30ml syringes, each with a 20G needle attached (syringe C&D):
    a. With Syringe C: Withdraw the entire 10mL of reconstituted doxorubicin from one of the doxorubicin vials (50mg) and set aside.
    b. With Syringe D: Withdraw the entire 10mL of reconstituted doxorubicin from the other doxorubicin vial (50mg) and set aside.

**This process should yield two 30ml syringes each containing doxorubicin 50mg/10ml.*

After the 10 minutes in step 9:

12. Utilizing syringes C&D from step 11:

    a. Syringe C: Attach a 20g needle to the 30ml syringe containing the doxorubicin 50mg/20ml and aspirate the contents (doxorubicin loaded spheres) of one HepaSphere/QuadraSphere vial into the 30ml syringe containing the doxorubicin 50mg/10ml.
    b. Syringe D: Attach a 20g needle to the 30ml syringe containing doxorubicin 50mg/20ml and aspirate the entire contents of the remaining HepaSphere/QuadraSphere vial from step 9 into the syringe. (Do not attempt to extract every red colored sphere).
13. Prior to removing the needle from the HepaSphere/QuadraSphere vial, while holding the syringe vertically, gently pull the plunger of the syringe down, removing any solution that may be in the hub of the needle.
14. Remove the needle and cap the syringe.
15. Each syringe should contain a total volume of 30ml.
16. Invert the syringes several times to disperse and mix the contents in the syringe.
17. Record the time that Step 16 was completed.
18. Allow syringe to sit for 60 minutes to complete loading of doxorubicin.

**This process should yield two 30ml syringes, each containing 1 vial of HepaSphere/QuadraSphere loaded with doxorubicin 75mg/20ml.*

APPENDIX C

Procedural Guidelines for Embolization with HepaSphere/QuadraSphere loaded with Doxorubicin (hqTACE)

CAUTION: INVESTIGATIONAL DEVICE in the United States. LIMITED BY UNITED STATES LAW TO INVESTIGATIONAL USE in the United States.

Arteriography:

1. Perform routine diagnostic visceral angiography (Aorta, SMA ,Celiac) with delayed portal venous phase.
2. Conduct selective angiography (PHA, LHA, RHA, etc). Perform complete hepatic arteriography, selecting and mapping any accessory or replaced artery as identified.
3. After delineation of the arterial anatomy, advance a coaxial 3 Fr microcatheter with a minimum inner diameter of 0.024" through the guiding catheter.
4. Serially sub-select and map the smallest arterial branches supplying identified tumors.
5. Multiple super selective catheterizations may be necessary.

Catheter placement and aberrant anatomy:

1. Prior to hqTACE, in cases where substantial or clinically relevant arterial portal venous shunting is present, embolize any identified shunts in a manner that occludes the shunt but preserves the hypervascularity of the tumor.
2. Patients with unifocal tumors should undergo selective chemoembolization, in which a 3 Fr microcatheter is placed selectively into a second or third-order branch off the right or left hepatic artery in closer proximity to the tumor.
3. In cases where selective catheterization of second or third-order branches off the right or left hepatic artery is prohibited, segmental catheter position is acceptable.
4. Lobar embolization should be performed only if selective or segmental embolization is not an option.

Embolic Preparation prior to injection:

1. The doxorubicin loaded HepaSphere/QuadraSphere will be contained in up to two 30ml syringes. Each syringe will contain the contents from 1 vial of HepaSphere/QuadraSphere (25mg of embolic) loaded with up to doxorubicin 75mg. The total volume in the syringe will be 20ml.

2. Pass the contents of the 30ml syringe containing the doxorubicin loaded HepaSphere/QuadraSphere into a 30ml syringe within the operative field via a 3-way stopcock.
3. After passing the contents of the doxorubicin loaded HepaSphere/QuadraSphere syringe into the operative field, connect the syringe to an open port on a 3 way-stopcock.
4. Connect an empty 20ml syringe to one of the remaining open ports on the stopcock.
5. Purge up to 10ml of supernatant from the 30ml HepaSphere/Quadrasphere syringe into the 20ml syringe via the 3 way-stopcock. (The supernatant will be pink in color and should be discarded.)
6. Discard the 20ml syringe containing the purged supernatant.
7. Attach a 20ml syringe containing 10-15ml on non-ionic contrast medium to the 3 way-stopcock and inject the contents into the 30ml syringe containing the doxorubicin loaded HepaSphere/QuadraSphere. This will yield a 50/50 ratio of contrast medium to embolic volume. (If greater radio opacity is desired, increase the amount of non-ionic contrast medium added to the syringe.)
8. Invert the 30ml syringe containing the non-ionic contrast media and doxorubicin loaded HepaSphere/QuadraSphere several times to disperse the contents.
9. Connect the 30ml syringe to a 3 way-stopcock.
10. Two options for embolic aliquot sequestering for injection may be utilized:
    a. **Option 1:** Connect the 3 way-stopcock to the 30ml syringe containing the doxorubicin loaded HepaSphere/QuadraSphere to the infusion micro catheter and utilize a 3ml syringe for injection via the open port of the 3 way-stopcock.
    b. **Option 2:** Serial aliquots of the doxorubicin loaded HepaSphere/QuadraSphere may be sequestered from the 30ml syringe into a 3ml injection syringe via a 3 way-stop cock that is not attached to the infusion catheter. The 3ml syringe containing the sequestered aliquot may be independently attached to the infusion microcatheter and injected.

Embolization Process:

Procedural Endpoint: Targeted drug dose delivery with associated stasis to all identified pedicles supplying the tumor (s).

1. Use a Microcatheter with a minimum inner diameter of .024".
2. Conduct delivery of the doxorubicin loaded HepaSphere/QuadraSphere under fluoroscopic guidance.
3. Verify antegrade peri catheter flow prior to embolization/delivery of HepaSphere/QuadraSphere. (Pericatheter flow is required to deliver the HepaSphere/QuadraSphere to the tumor vasculature. Any presence of vasospasm or hindrance of antegrade flow in the vessel preferentially feeding the tumor should be resolved prior to delivery of the spheres.)
4. Utilize an injection syringe no larger than 3ml for delivery of the doxorubicin loaded HepaSphere/QuadraSphere.

5. Inject the sequestered aliquot of doxorubicin loaded HepaSphere/QuadraSphere in a non forceful, pulsatile manner to avoid and minimize the potential for reflux. Delivery of the doxorubicin loaded HepaSphere/QuadraSphere must be done slowly, at a rate of approximately 1-2cc per minute.
6. The angiographic endpoint during delivery of the doxorubicin loaded micro spheres is stasis in the selected feeding pedicle (2^{nd} and 3^{rd} order branches). *Multiple super selective catheterizations may be necessary to achieve complete tumor infusion.
7. If stasis in the feeding pedicle is encountered while delivering the doxorubicin loaded microspheres, wait five minutes then perform a selective angiogram performed after the five minute wait to verify the arrest of antegrade flow. (Secondary distribution of the microspheres may occur lending to continued antegrade flow.)
8. If stasis has not been achieved in the selected feeding pedicle and the target dose of doxorubicin loaded HepaSphere/QuadraSphere has been administered, use supplemental bland embolization utilizing non- doxorubicin loaded HepaSphere/QuadraSphere to arrest antegrade flow.
    a. Perform hydration of the HepaSphere/QuadraSphere for supplemental bland embolization in accordance with the product instructions for use (IFU).
        i. Hydrate the HepaSphere/QuadraSphere in the prepackaged vial with 10ml of 0.9% normal saline
        ii. Wait 10 minutes
        iii. Extract spheres from vial utilizing a 20ml syringe with a 20g needle attached
        iv. Add 10ml of non-ionic contrast medium to the hydrated spheres
9. For multifocal disease, treat the target lesion first, followed by treatment of any secondary lesions.

APPENDIX D

Procedural Guidelines for Solubilizing Doxorubicin for Conventional TACE (cTACE)

Supplies:

- 3 x doxorubicin 50mg powder vial (total dose doxorubicin 150mg)
- 20G needles
- 5 x 20ml syringes
- 15ml of 0.9% normal saline
- 2 x syringe caps

Procedure:

Prepare in Biohazard Hood

1. Reconstitute each doxorubicin 50mg vial with 5ml of 0.9% normal saline
   *This process will yield three vials of doxorubicin 50mg/5ml each

2. Divide the reconstituted dose into 2-20ml syringes

   Syringe A: Aspirate 7.5ml of reconstituted doxorubicin into a 20ml syringe
   Syringe B: Aspirate 7.5ml of reconstituted doxorubicin into a 20ml syringe

3. Cap each 20ml syringe containing 75mg of doxorubicin in 7.5ml of 0.9% saline and dispense to interventional radiology.

APPENDIX E

Procedural Guidelines for Conventional TACE (cTACE)

Arteriography:

1. Perform routine diagnostic visceral angiography (Aorta, SMA ,Celiac) with delayed portal venous phase.

2. Conduct selective angiography (PHA, LHA, RHA, etc). Perform complete hepatic arteriography, selecting and mapping any accessory or replaced artery as identified.

3. After delineation of the arterial anatomy, advance a coaxial 3 Fr micro-catheter with a minimum inner diameter of 0.024" through the guiding catheter.

4. Serially sub-select and map the smallest arterial branches supplying identified tumors.

5. Multiple super selective catheterizations may be necessary.

Catheter placement and aberrant anatomy:

1. Prior to cTACE, in cases where substantial or clinically relevant arterial portal venous shunting is present, embolize any identified shunts in a manner that occludes the shunt but preserves the hypervascularity of the tumor.

2. Patients with unifocal tumors should undergo selective chemoembolization, in which a 3 Fr microcatheter is placed selectively into a second or third-order branch off the right or left hepatic artery in closer proximity to the tumor.

3. In cases where selective catheterization of second or third-order branches off the right or left hepatic artery is prohibited, segmental catheter position is acceptable.

4. Lobar embolization should be performed only if selective or segmental embolization is not an option.

Drug and Embolic Preparation prior to injection:

1. The doxorubicin solubilized in 0.9% normal saline will be dispensed in 2-20ml syringes. Each syringe will contain doxorubicin 75mg/7.5ml.

2. Transfer the contents of each 20ml syringe containing the solubilized doxorubicin into the operative field via a 3-way stopcock and into a 20ml syringe.

3. After passing the contents into the operative field, connect each of the 20ml syringes to an open port on a 3 way-stopcock.

4. Attach a 20ml syringe containing up to 10ml of ethiodized oil to the open port on the 3 way-stopcock attached to the syringe containing the doxorubicin.

5. Emulsify the doxorubicin and oil mixture with a back a forth motion between the 2 syringes via the 3 way- stopcock.

6. After emulsifying the oil/doxorubicin mixture, sequester the entire volume of the emulsification in one of the 20ml syringes attached to the stopcock and discard the empty syringe.

7. Repeat steps 4-6 for the remaining 20ml syringe containing the solubilized doxorubicin. A procedural maximum of 20ml of ethiodized oil is permitted.

8. Two options for embolic aliquot sequestering for injection may be utilized:

   c. **Option 1:** Connect a 3 way-stopcock to the 20ml syringe containing the oil/doxorubicin emulsion to the infusion micro catheter and utilize a 3ml syringe for injection via the open port of the 3 way-stopcock.
   d. **Option 2:** Serial aliquots of the oil/doxorubicin emulsion may be sequestered from the 20ml syringe into a 3ml injection syringe via a 3 way-stopcock that is not attached to the infusion catheter. The 3ml syringe containing the sequestered aliquot may be independently attached to the infusion microcatheter and injected.

Embolization Process:

Procedural Endpoint: Target drug dose delivery with associated angiographic stasis to all identified pedicles supplying the tumor (s).

1. Use a microcatheter with a minimum inner diameter of .024".

2. Conduct delivery of the oil/doxorubicin emulsion under fluoroscopic guidance.

3. Verify antegrade pericatheter flow prior to embolization/delivery of the oil/doxorubicin emulsion. (Pericatheter flow is required to deliver the oil/doxorubicin emulsion to the tumor vasculature. Any presence of vasospasm or hindrance of antegrade flow in the vessel preferentially feeding the tumor should be resolved prior to delivery of the emulsion.)

4. Utilize an injection syringe no larger than 3ml for delivery of the oil/doxorubicin emulsion.

5. Inject the sequestered aliquot of oil/doxorubicin emulsion in a non forceful, pulsatile manner to avoid and minimize the potential for reflux.

6. The angiographic endpoint during delivery of the oil/doxorubicin emulsion is stasis in the selected feeding pedicle (2^{nd} and 3^{rd} order branches). *Multiple super selective catheterizations may be necessary to achieve complete tumor infusion.

7. If stasis in the feeding pedicle is encountered while delivering the oil/doxorubicin emulsion, wait five minutes then perform a selective angiogram after the five minute wait to verify the arrest of antegrade flow. (Secondary distribution of the oil/doxorubicin emulsion may occur lending to continued antegrade flow.)

8. If stasis has not been achieved in the selected feeding pedicle, and the target dose of oil/doxorubicin emulsion has been administered, use non spherical polyvinyl alcohol (nsPVA) in the size range of >100um and <500um to arrest antegrade flow (stasis) in the feeding pedicle.

9. For multifocal disease, treat the target lesion first, followed by treatment of any secondary lesions.

APPENDIX F

IMAGE ACQUISITION GUIDELINE

Document file name: Image Acquisition Guideline v 1.0

Document version: 1.0

Version date: 17-November-2009

Author: [redacted]

INTRODUCTION

The following acquisition guidelines have been developed for standardization of the study imaging components across radiology centers participating in the **phase 3 prospective, randomized, blinded and controlled investigation of Hepasphere/Quadrasphere microspheres for delivery of doxorubicin for the treatment of hepatocellular cancer.**

Important Notes

- Regularly scheduled imaging for this study should be acquired in strict adherence to these guidelines
- Optimization of image acquisition protocols and consistency in the use of the same protocol throughout follow-up examinations are key for proper application of modified RECIST criteria
- Please ensure blinding of all confidential site/patient information on all images. Subject number should be entered in lieu of patient name
- Images sent for independent blinded review should be clear of any tumor markings or annotations determined at the site
- Imaging data, including raw/original data, shall remain archived at the site for the duration of the study
- Utilization of dynamic contrast-enhanced magnetic resonance (MR) imaging is mandatory if not medically contraindicated
- In dynamic MR studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration for all studies so that high-quality arterial-phase imaging is obtained throughout the liver parenchyma on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver parenchyma on the second run
- The tables below show preferred parameters. Please use parameters as close to these as possible. Once the values shown below have been selected, they should remain consistent throughout the trial for a given subject

LIVER MR IMAGING

- Scanner type: 1.5 - 3.0 Tesla
- Phased array coil
- Breath-hold or ultrafast sequences required
- T1-weighted imaging: spoiled gradient echo sequences preferred (SGE, FLASH, SPGR)
- T2-weighted imaging: turbo/fast spin echo sequences preferred (TSE, FSE)
- Interval (slice thickness plus gap) should not exceed 7mm

SCAN 1 (PRE-CONTRAST)

Patient Orientation	Supine
Scan Locations/Coverage	Dome of the right diaphragm (or higher to ensure complete coverage of the liver) through the entire liver
Slice Thickness	5 mm
Skip/gap (slice spacing)	As close to 0% as possible while avoiding cross talk
Sequences	T1 axial, preferably with fat suppression
	T2 axial, preferably with fat suppression
Scan FOV	Large (consistent throughout the study)

CONTRAST MEDIA INJECTION:

Gadolinium 0.1 mmol/kg or 0.2 ml/kg (20 ml maximum) should be injected by using a power injector followed by 20 ml saline flush.

SCAN 2 (POST-CONTRAST, ARTERIAL PHASE)

Patient Orientation	Supine
Scan Locations/Coverage	Dome of the right diaphragm (or higher to ensure complete coverage of the liver) through the entire liver
Slice Thickness	5 mm
Skip/gap (slice spacing)	As close to 0% as possible while avoiding cross talk
Sequences	T1 axial with fat suppression (breath-hold not to exceed 30 sec scan time)
Scan delay	Ensure arterial phase imaging of the liver
Scan FOV	Large (consistent throughout the study)

SCAN 3 (POST-CONTRAST, PORTAL VENOUS PHASE)

Patient Orientation	Supine
Scan Locations/Coverage	Dome of the right diaphragm (or higher to ensure complete coverage of the liver) through the entire liver
Slice Thickness	5 mm
Skip/gap (slice spacing)	As close to 0% as possible while avoiding cross talk
Sequences	T1 axial with fat suppression (breath-hold not to exceed 30 sec scan time)
Scan delay	Ensure portal venous phase imaging of the liver
Scan FOV	Large (consistent throughout the study)

SCAN 4 (POST-CONTRAST, EQUILIBRIUM PHASE)

Patient Orientation	Supine
Scan Locations/Coverage	Dome of the right diaphragm (or higher to ensure complete coverage of the liver) through the entire liver
Slice Thickness	5 mm
Skip/gap (slice spacing)	As close to 0% as possible while avoiding cross talk
Sequences	T1 axial with fat suppression (breath-hold not to exceed 30 sec scan time)
Scan delay	180 seconds
Scan FOV	Large (consistent throughout the study)

APPENDIX G

IMAGE INTERPRETATION GUIDANCE MANUAL

Document file name: Image Interpretation Guidance Manual v 1.0

Document version: 1.0

Version date: 17-November-2009

Author: [redacted]

INTRODUCTION

Tumor response in oncology is usually measured according to the World Health Organization (WHO) criteria (1) or the Response Evaluation Criteria In Solid Tumors (RECIST) guideline (2). WHO and RECIST define standard measurement methods for converting radiology image observations into a quantitative and statistically tractable framework for measuring the response of tumor size to therapy. Both methods offer simple approaches to determining anatomic size and lesion changes during treatment as an indicator of response. Target lesions are measured using either the bilinear product approach (WHO) or single linear summation (RECIST).

The WHO criteria and RECIST were designed primarily for evaluation of cytotoxic agents. They do not address measures of antitumor activity other than tumor shrinkage. As acknowledged in the original RECIST publication, assessments based solely on changes in tumor size can be misleading when applied to other anticancer drugs, such as molecular targeted therapies, or other therapeutic interventions (2). In the case of hepatocellular carcinoma (HCC), recent studies have shown a poor correlation between the clinical benefit provided by new agents such as sorafenib or by loco-regional interventional therapies such as chemoembolization and conventional methods of response assessment (3, 4).

In 2000, a panel of experts on HCC convened by European Association for the Study of the Liver (EASL) recommended that the response criteria be amended to take into account tumor necrosis induced by treatment (5). That panel considered estimation of the reduction in viable tumor area using contrast-enhanced radiological imaging to be the optimal method to assess treatment response. Viable tumor was defined as uptake of contrast agent in the arterial phase of dynamic computed tomography (CT) or magnetic resonance (MR) imaging. The concept of viable tumor proposed by the EASL panel has been subsequently endorsed by the American Association for the Study of Liver Diseases (AASLD). The AASLD practice guideline on the management of HCC issued in 2005 stated that the evaluation of the treatment response should take into account the induction of intra-tumoral necrotic areas in estimating the decrease in tumor load, and not just a reduction in overall tumor size (6).

In 2006, a group of experts convened by the AASLD to develop a set of guidelines aimed at providing a common framework for the design of clinical trials in HCC has adapted the concept of viable tumor endorsed by the EASL and the AASLD and has proposed formal amendments to RECIST criteria for the determination of tumor response in HCC (7). These amendments are referred to as modified RECIST

(mRECIST) for HCC. In this manual, the changes introduced by this document in HCC response assessment will be illustrated and a guideline for proper application of mRECIST will be provided.

IMAGE INTERPRETATION

To properly use the proposed mRECIST for HCC to assess response rates and time-to-progression in HCC clinical trials and to ensure comparability across studies, uniform image acquisition parameters, rigorous quality control, and independent blinded multireader assessments are mandatory. Therefore, the expert panel recommended adopting a centralized radiological review for image interpretation rather than base the assessment on the image evaluation performed by local investigators. Independent radiologists will be responsible for performing qualitative and quantitative assessments of imaging data. They will assess baseline imaging in order to determine the overall tumor burden and use this as a comparator for subsequent measurements. Tumor response will then be determined for each follow-up imaging time-point. Overall response assessment includes, according to RECIST, evaluation of target lesions response, non-target lesions response, and new lesions.

Assessment of Tumor Lesions at Baseline

According to RECIST, tumor lesions are categorized at baseline as follows: measurable (lesions that can be accurately measured in at least one dimension as ≥ 1 cm with spiral CT scan) or non-measurable (all other lesions, including small lesions [longest diameter <1 cm with spiral CT scan] and truly nonmeasurable lesions). The original RECIST publication states that all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. The recent 1.1 release of RECIST has reduced the number of lesions to select as target lesions to a maximum of two lesions per organ and five lesions in total (8). In fact, analyses on a large prospective database has shown that assessment of five versus 10 lesions per patient did not affect the overall response rate, and that progression-free survival was only minimally affected (9). Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

The measurement of the longest viable tumor diameter for the assessment of tumor response according to mRECIST for HCC can be applied only when assessing typical HCC lesions; for nonenhancing

atypical lesions, as well as for any extrahepatic manifestations of the disease, the measurement of the longest overall tumor diameter – as per conventional RECIST - should be used.

To be selected as a target lesion for the use mRECIST, an HCC lesion should meet all the following criteria:

- the lesion can be classified as a RECIST measurable lesion (ie, the lesion can be accurately measured in at least one dimension as 1 cm or more)
- the lesion is suitable for repeat measurement
- the lesion shows intratumoral arterial enhancement on contrast-enhanced MR imaging

It is important to point out that only well delineated, arterially-enhancing lesions can be selected as target lesions for mRECIST. This may not be the case of infiltrative-type HCC. Infiltrative-type HCC should be considered as a non-target lesion when the mass shows ill-defined borders and therefore does not appear to be suitable for accurate and repeat measurements. HCC lesions previously treated with loco-regional or systemic treatments may or may not be considered as suitable to be selected as target lesions for mRECIST: if the lesion shows a well delineated area of viable (contrast enhancement in the arterial phase) tumor that is at least 1 cm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it can not be selected as a target lesion for mRECIST.

Target Lesions Response

According to RECIST, complete response is the disappearance of all target lesions; partial response is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since then treatment started or the appearance of one or more new lesions; stable disease is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response for target lesions:

- Complete response: the disappearance of any intratumoral arterial enhancement in all target lesions

- Partial response: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
- Progressive disease: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started
- Stable disease: any cases that do not qualify for either partial response or progressive disease

The measurement of the longest diameter of the viable tumor may be challenging in lesions showing partial internal necrosis. The following points should be taken into account in such cases:

- the measurement of the viable tumor should be performed on MR images obtained in the arterial-phase, when the contrast between viable vascularized tumor tissue and nonenhancing necrotic tissue is the highest
- the longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured: a thorough careful evaluation of the MR scans is required
- the measurement of the viable tumor diameter should not include any major intervening areas of necrosis

It is important to point out that a reduction of at least 30% in the diameter of the viable tumor (the threshold required to declare partial response according to mRECIST) corresponds to a decrease of 65% in viable tumor volume. In contrast, an increase of at least 20% in the diameter of the viable tumor (the threshold required to declare progressive disease according to mRECIST) corresponds to an increase of at least 73% in viable tumor volume.

Non-Target Lesions Response

RECIST guideline provides the following definitions of the criteria used to determine the objective tumor response for non-target lesions: complete response is the disappearance of all non-target lesions; incomplete response/stable disease is the persistence of one or more non-target lesions; and progressive disease is the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

According to mRECIST for HCC, tumor necrosis should be taken into account when assessing response of non-target lesions. Disappearance of intratumoral arterial enhancement in non-target lesions should be considered equivalent to disappearance of non-target lesions and, therefore, should declare complete response of non-target lesions. Persistence of intratumoral arterial enhancement in one or more non-target lesions should be considered equivalent to persistence of one or more non-target lesions and, therefore, should declare incomplete response / stable disease. Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions should declare progressive disease.

Special recommendations for the assessment of tumor response in non-target lesions in patients with HCC and cirrhosis can be made regarding the following points:

(1) Portal vein thrombosis. Malignant portal vein thrombosis should be considered a non-measurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment. Measurements of the extent of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.

(2) Porta hepatis lymph node. Lymph nodes detected at the portal hepatis can be considered as malignant if the lymph node short axis is at least 20 mm. Evidence of reactive lymph nodes at the porta hepatis, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.

(3) Pleural effusion and ascites. The original RECIST publication specifies that cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). The mRECIST for HCC panel of experts considered this issue to be of high importance in the setting of HCC in cirrhosis. The emergence or the increase in ascites is a common event during the course of treatment in a cirrhotic patient, which may be due to worsening of the underlying chronic liver disease and be unrelated to cancer progression. Other effusions, ie pleural effusion, may also be unrelated to cancer progression and be caused by the liver insufficiency. Thus, the mRECISt for HCC document emphasizes that cyto-pathological confirmation of the neoplastic nature of

any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease.

New Lesions

Characterization of a newly detected focal liver lesion as true HCC is a challenging issue in the setting of cirrhosis, since pathologic abnormalities related to cirrhosis changes – such as large regenerative nodules and dysplastic nodules – may be indistinguishable from a small tumor. Moreover, the clear cut separation of the hepatic phases of liver enhancement routinely achieved by state-of-the-art MR imaging creates additional problems in a cirrhotic liver, mostly related to the presence of perfusion abnormalities resulting in areas of abnormal liver enhancement. In most cases, such perfusion abnormalities are detected as arterially-hyperenhancing areas caused by a selective impairment of the portal venous feeding. Such perfusion abnormalities may ultimately mimic or conceal focal liver lesions, and so, they represent an additional major source for interpretation errors.

The AASLD practice guideline for the clinical management of HCC has recommended strict criteria for the imaging diagnosis of HCC in cirrhosis (6). That panel suggested that the diagnosis of HCC is made without biopsy only in a lesions that are at least 1 cm in diameter and show characteristic vascular features of HCC – ie, arterial hypervascularization with washout in the portal venous or the late phase – at dynamic imaging studies.

The mRECIST for HCC panel has endorsed these concepts and issued the following recommendations:

- a newly detected hepatic nodule will be classified as HCC — and therefore will be declared as evidence of progression — when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase
- liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm interval growth in subsequent scans
- an individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing

Overall Response

In mRECIST for HCC, identical to conventional RECIST, overall patient response is a result of the combined assessment of target lesions, non-target lesions, and new lesions (Table 2). It is important to point out that appearance of one or more new lesions declares progression whatever the response of target and non-target lesions. Overcalling of equivocal lesions as new HCC, therefore, has a major impact on the outcome of studies with a radiological endpoint, such as tumor response or time-to-progression. Hence, any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

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APPENDIX H

RADIOLOGY CHARTER

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1. INTRODUCTION

The purpose of this document is to provide background information for the study "Phase 3 Prospective, Randomized, Blinded and Controlled Investigation of Hepasphere/Quadrasphere Microspheres for Delivery of Doxorubicin for the Treatment of Hepatocellular Cancer" and to define the processes, roles, and responsibilities of the independent reviewers.

To properly use the criteria proposed in this Charter, uniform image acquisition parameters and quality control will be employed. The procedures entailed in image acquisition are detailed in the separate manual "Image Acquisition Guideline".

The independent reviewers will consist of a minimum of three qualified, board–certified radiologists with specific expertise and skills in liver imaging and liver interventional procedure. Two independent radiologists will review the baseline images and the images obtained at each post-baseline time point. If there is disagreement between the two reviewers in the response assessment, a third adjudicating radiologist will review the case and the results from the first two reviewers and decide which of the two primary radiologists he or she agrees with. The decision of the adjudicator is the final decision.

The independent reviewers will assess tumor response by using Response Evaluation Criteria In Solid Tumors (RECIST) guideline as modified by the American Association for the Study of Liver Diseases panel of experts on HCC (mRECIST) (1). The procedures entailed in image interpretation are detailed in the separate manual "Image Interpretation Guidance Manual.

For further details about the independent review process, please refer to section 4 of this Radiology Charter.

2. TRIAL BACKGROUND

The study is a randomized trial to compare efficacy and safety of doxorubicin-eluting Hepasphere/Quadrasphere, as compared to conventional chemoembolization with doxorubicin, lipiodol, and non-spherical embolic agents, in the treatment of hepatocellular carcinoma (HCC). The primary efficacy objective will be overall survival.

For further details, please see Study Protocol.

3. IMAGE ACQUISITION, ARCHIVE, AND QUALITY CONTROL

The procedures entailed in image acquisition and collection at the investigator sites are detailed in the separate manual "Image Acquisition Guideline". This document describes guidelines and proper techniques to be followed when acquiring study images.

All study images will be subject to quality control by the central imaging review site. The quality control will be performed by a board certified radiologist and will include verification of proper scanning specifications in adherence to the Image Acquisition Guideline, image quality, blinding of demographics identifiers, and information completeness.

The quality control verification will result in either acceptance of the case or in a query. Queries will be raised if the imaging data received are incomplete and/or do not adhere to the Image Acquisition Guideline and/or the trial protocol. In the case of a query, the central imaging review site will communicate to the investigator site any remediation actions, if necessary. After query resolution, images will undergo a second quality control. Details of query management and query resolution will be documented.

The data flow and the review process are illustrated in Figure 1.

Available scans will be submitted to independent radiology review regardless of image quality, completeness or adherence to the Image Acquisition Guideline. Cases will undergo independent radiology review provided that at least the baseline images and one post-baseline timepoint are available for a given subject. At the time of the review, the independent readers will also assess the images for technical adequacy and quality and will state if quality issues are preventing him from making a full assessment.

To maintain objectivity in the evaluation, the independent radiologists will be blinded to subject name, investigator site identifiers, site assessments, and exam dates. It is expected that all data sent to the central imaging review site will be in compliance with local regulatory laws, including but not limited to the Health Insurance Portability and Accountability Act (HIPAA) privacy rule and the European Privacy Act, and that all confidential subject identifiers will be removed by the site before they are sent to the central imaging review site.

4. INDEPENDENT REVIEW PROCESS

The independent reviewers will consist of a minimum of three qualified, board–certified radiologists with specific expertise and skills in liver MRI and liver interventional procedure. Detailed CVs will be provided by the independent readers.

All assessments performed by the independent reviewers will be captured in an audit trail in keeping with International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CRF) Part 11.

4.1 Sequence of MRI Scans

According to the study protocol, each patient will undergo up to 3 chemoembolization treatments in both arms. MRI will be performed at baseline and at 3 timepoints post-baseline, according to the following schedule:

MRI examination #1: Baseline (Timepoint 0)
Within 1 month of the first TACE cycle(week -4 to week 0)

MRI examination #2: Timepoint 1
4 weeks after the first TACE cycle (± 1 week)

MRI examination #3: Timepoint 2
4 weeks after the second TACE cycle (± 1 week)

MRI examination #4: Timepoint 3
4 weeks after the third TACE cycle (± 1 weeks)

The protocol requires the second TACE cycle to be performed in all patients 8 weeks (± 2 weeks) after the initial TACE cycle, unless the investigator deems further treatment unsafe for the patient, and regardless of the response assessment performed by the independent readers. In contrast, the third TACE cycle will only be done for patients with MRI results after the second TACE cycle that demonstrate less than complete response (CR), as interpreted by the central reviewers according to modified RECIST criteria.

Therefore, the study requires that the central imaging review site provides the investigator site with the response assessment recorded for a given subject after the third MRI examination (the second post-baseline MRI examination).

4.2 Sequence of Radiology Review for Overall Response Assessment

This analysis will focus on the assessment of the secondary endpoint of overall objective tumor response. Because of the need to provide the investigatonal site with a timely response assessment for a given subject after the third MRI examination (the second post-baseline MRI examination which follows TACE cycle 2), images will be read consecutively as they are transferred to the central review site.

Each subject's baseline and all other imaging timepoints will be independently read in a blinded fashion by two board-certified radiologists (double read by two primary radiologists). The two primary independent radiology reviewers will be responsible for performing quantitative and qualitative assessments of imaging data of a given subject according to the modified RECIST guideline for HCC and the "Image Interpretation Guidance Manual" provided.

The primary radiology reviewers will first assess baseline imaging in order to determine the overall tumor burden and use this as a comparator for subsequent measurements. These assessments will then be locked. Changes to previous forms will not be permitted.

The same primary radiology reviewers who have assessed baseline images will then review post-baseline timepoints as soon as these images are transferred to the central imaging site. Required calculations for the sum of the longest diameters and percent changes from baseline and/or nadir (smallest recorded sum of the longest diameters) will be made automatically by the application. These assessments will then be locked. Changes to previous forms will not be permitted.

Agreement between the first and second radiologists will be determined by comparison of the overall tumor response determinations on a timepoint basis, including the following categories: (1) complete

response, 2) partial response, 3) stable disease, 4) progressive disease, or 5) unknown. Should the assessment for a given case be discordant, the case will be considered in disagreement.

If disagreement between the two primary readers is identified at any timepoint, a third reviewer will be presented with the results of the first and second readers and, as adjudicator, will determine the final assessment for the case. The adjudicator will not provide an independent assessment but must agree with an assessment of one of the two primary reviewers. The review process and the adjudication strategy are illustrated in Figure 1 below.

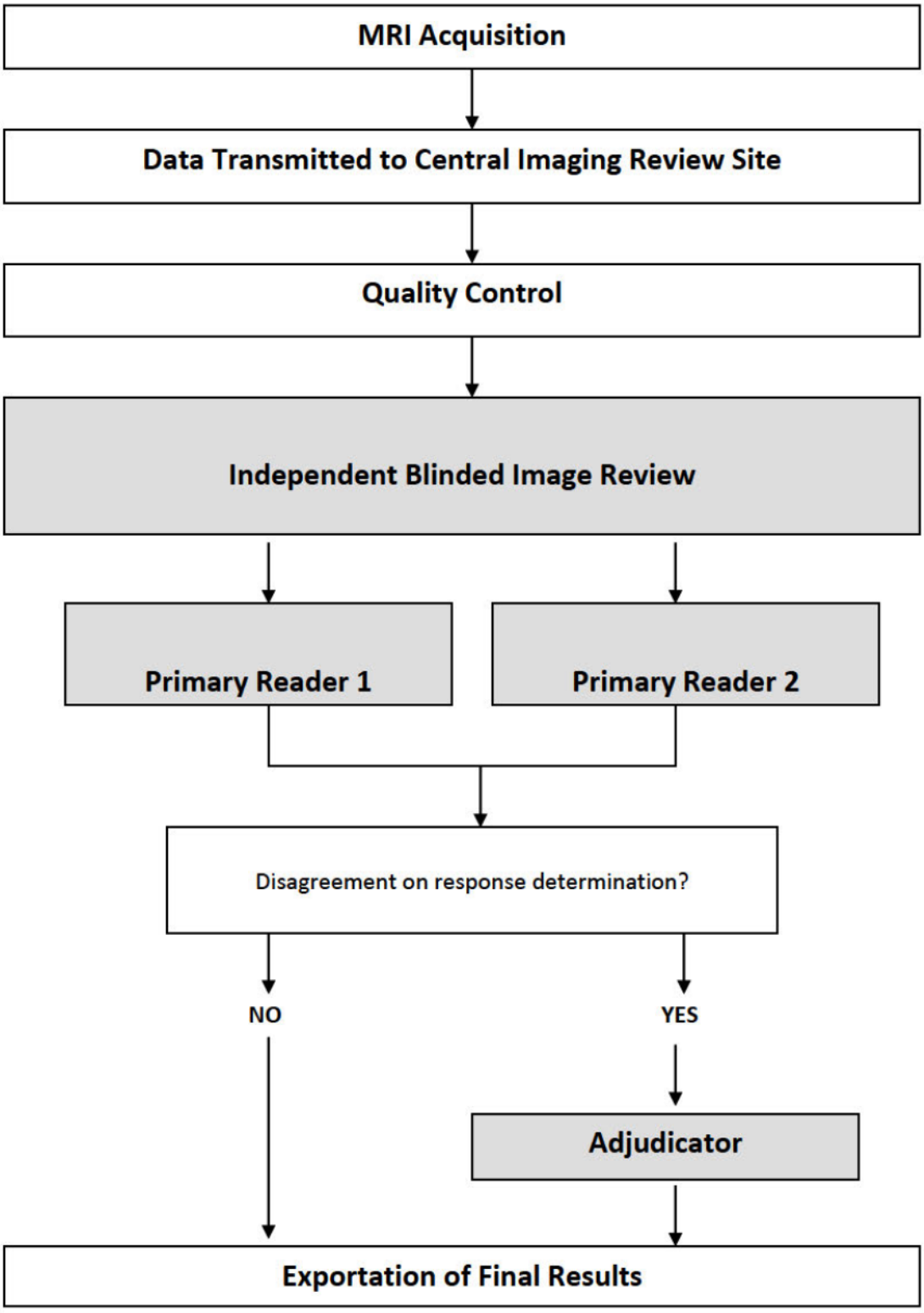

Figure 1. Synopsis of image data flow and adjudication strategy.

Information regarding the response classification of a given subject after the second TACE cycle (either after the agreement of both primary readers or following adjudication) will be forwarded to a sponsor data manager, who will forward the information to the investigator at the site since this information will determine eligibility for the third TACE cycle in case of less than overall CR.

Overall objective response will be calculated by the sum of complete responses and partial responses recorded at the last available assessment.

4.3 Radiology Review for Regional Response Assessment

This analysis will focus on the assessment of the secondary efficacy endpoint of objective response in the treated area (ORR-T). This is defined as the tumor response observed in the liver territory that has actually been treated with chemoembolization. This analysis will be performed after the completion of the radiology review for the overall tumor response assessment for a given subject.

The same primary readers who have assessed a given subject for the endpoint of overall tumor response will be presented with the images obtained at baseline and at post-baseline timepoint 1 as well as with the locked forms completed at the time of that analysis. Changes to the forms completed in that review will not be permitted.

Then, the primary readers will be presented with a blinded form, completed by the interventional radiologist who has performed the TACE procedure, describing the arterial vascular anatomy of the subject with identification of the arterial branches that were embolized during the treatment.

The independent radiologist will mark each lesion identified during the previous analysis as located within the treated territory or in an area of the liver parenchyma that was not embolized. This assessment will be performed for target lesions, non-target lesions, and new lesions and will lead to the assessment of the secondary endpoint of regional objective response rate as the sum of complete and partial responses observed in the treated territory.

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