CC# 124520: Prospective Phase II Study of Chemoembolization with Doxorubicin-Eluting Microspheres for Liver Transplantation Candidates with Hepatocellular Carcinoma and Marginal Hepatic Reserve

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Prospective Phase II Study of Chemoembolization with Doxorubicin-Eluting Microspheres for Liver Transplantation Candidates with Hepatocellular Carcinoma and Marginal Hepatic Reserve
Patient population	Intermediate stage, unresectable hepatocellular carcinoma (HCC) confined to the liver, without significant hepatic synthetic dysfunction
Rationale for Study	To determine whether DEB-TACE can be used safely and effectively to treat patients with liver-only HCC and baseline hepatic dysfunction, TACE is frequently offered to patients with baseline hepatic dysfunction with the purpose of diminishing hepatic tumor burden while patients await transplantation. Without this therapeutic measure, disease may progress beyond UNOS T2 criteria required for organ allocation.
Primary Objectives	• To determine the safety of DEB-TACE in patients with HCC confined to liver who are being considered for liver transplantation • To determine the response rate to DEB-TACE by conventional and modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1, mRECIST) for treated lesions in patients with liver-only HCC who are being considered for liver transplantation
Secondary Objectives	• To measure overall radiographic response (by RECIST v1.1 and mRECIST) 6 months after the date of the first planned DEB-TACE procedure. • To measure time to untreatable progression (TTUP). TTUP is defined as time to disease progression untreatable by liver-directed percutaneous or surgical methods. • To measure median time to progression (TTP) • To measure hepatic progression free survival (HPFS) • To measure progression free survival (PFS) • To measure overall survival (OS) • To determine the proportion of patients who remain active on the wait list for a liver transplant and eventually are transplanted. • To determine the proportion of patients who are inactivated or drop out from the wait list for any reason but transplantation. • To determine the proportions of patients who are successfully down-staged and achieve active waitlist status and eventually are transplanted. • To measure proportion with alpha-fetoprotein (AFP) response with ≥ 50% decline from baseline (in patients with baseline level ≥ 20) post DEB-TACE and test for association with hepatic and overall response rate, PFS, and OS • To determine whether cardiac function changes occur as a result of DEB-TACE with doxorubicin • To obtain pharmacokinetic data for doxorubicin administered as a part of DEB-TACE procedures

Abstract

Study Design	Prospective open-label two-stage phase II clinical trial to evaluate the safety and efficacy of DEB-TACE in patients with liver-only HCC and significant hepatic dysfunction who are being considered for a liver transplant.
Number of patients	17 patients will be enrolled into the first stage of the study for safety and efficacy 34 patients will be enrolled into the second stage of the study
Duration of Therapy	Most patients will need only one DEB-TACE treatment, performed within 60 days of Screening procedures For patients that have more than one treatment, the procedure will be done about 4 weeks after the first, or previous treatment, up to 4 treatments total
Duration of Follow up	Post Treatment Evaluation will last 1 year
Duration of study	The study will reach completion 5 years from the time the study opens to accrual
Study Procedure	Doxorubicin Eluting Bead Transarterial Chemoembolization (DEB-TACE): Doxorubicin-loaded LC Beads® are administered via a co-axially placed commercially available hepatic artery catheter into hepatic arteries targeted for treatment. Procedure is performed under direct fluoroscopic visualization until stasis of arterial flow is achieved or until a total of 4 ml of microspheres have been administered, whichever occurs first.

Abstract

Safety Assessments	• Laboratory tests (Day 1 and Day 7±3 after every DEB-TACE, then 30±7, 90±14, 180±14, 270±14, and 360±14 days after last planned DEB-TACE) • Physical exam/AE assessment (Day 1and Day 7 after every DEB-TACE, then 30±7, 90±14, 180±14, 270±14, and 360±14 days after last planned DEB-TACE) • MELD score (30±7, 90±14, 180±14, 270±14, and 360±14 days after last planned DEB-TACE)) • Imaging procedures to assess tumor burden (30±7, 90±14, 180±14, 270±14, and 360±14 days after last planned DEB-TACE) • Cardiac function monitoring by echocardiography (at baseline and approximately 30 days after last planned DEB-TACE procedure). Safety data will be routinely monitored and sequential safety assessments will be conducted as subjects are enrolling to the study. The study will be stopped due to safety/toxicity concern prior to interim efficacy analysis if *any* of the following 3 stopping rules are met: 1. Liver dysfunction (clinical or laboratory [total serum bilirubin], grade 4) that does not improve to baseline or </= grade 3 within 1 month following DEB-TACE in ≥ 7 patients (12% of 51 patients). OR 2. Renal dysfunction (clinical or laboratory [serum creatinine], grade 3 or 4) that does not improve to baseline or </= grade 2 within 1 month following DEB-TACE in ≥ 2 patients (1.2% of 51 patients). OR 3. Any grade 5 AE (death) attributed as at least possibly-related to study intervention in ≥ 3 patients (4.8% of 51 patients). Stopping Rules for Efficacy after 17 patients have completed last planned DEB-TACE 1. If four (4) or fewer responses (complete, partial, or stable disease response according to mRECIST in treated lesion(s) approximately 1 month after last planned DEB-TACE) are observed among first stage of 17 patients.
Efficacy Assessments	Evaluation of treatment response will be based on contrast-enhanced cross-sectional imaging of the abdomen (CT or MRI) performed one month following last planned DEB-TACE procedure within six months of the first DEB-TACE procedure. Treatment response will be evaluated according to both the RECIST version 1.1 and mRECIST criteria.
Unique Aspects of this Study	This is the first prospective study to evaluate safety and efficacy of DEB-TACE for patients with marginal hepatic function.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha-FetoProtein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood urea nitrogen
CBC	Complete Blood Cell (count)
CCC	Comprehensive Cancer Center (UCSF)
CFR	Code of Federal Regulations
CHR	Committee on Human Research
CT	Computerized Tomography
cTACE	Conventional Transarterial Chemoembolization
CTCAE	Common Terminology Criteria for Adverse Events
DEB-TACE	Doxorubicin Eluting Bead Transarterial Chemoembolization
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EASL	European Association for the Study of Liver Disease
FDA	Food and Drug Administration
HCC	Hepatocellular Carcinoma
HIPAA	Health Insurance Portability and Accountability Act
INR	International Normalized Ratio for prothrombin time
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver Function Test
LT	Liver transplant
MELD	Model for End-stage Liver Disease
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall Survival
PEI	Percutaneous Ethanol Injection
PFS	Progression Free Survival
PRC	Protocol Review Committee
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria In Solid Tumors
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event
SIRT	Selective Internal Radiation Therapy
TACE	Transarterial Chemoembolization
TTP	Time To Progression
TTUP	Time To Untreatable Progression
UCSF	University of California San Francisco
ULN	Upper Limit of Normal
UNOS	United Network for Organ Sharing

1.0 BACKGROUND AND RATIONALE

1.1 Background/Standard Therapies

Tumor resection or liver transplant (LT) represent the best options for cure in patients with hepatocellular carcinoma (HCC). Unfortunately, most patients are candidates for neither at the time of diagnosis (1). Depending on the extent of tumor and the overall health of the patient, those who are not able to undergo resection or transplantation may be referred for liver-directed treatments, supportive care or rarely, experimental medical protocols (2).

Liver-directed therapies have been shown to extend survival compared with supportive care (3, 4, 5), and in optimal cases may be effective in allowing "downstaging" (6, 7, 8) of the tumor to allow resection or transplantation. Moreover, liver-directed therapies have been found to diminish drop-out from the liver transplant wait list (7).

Many liver-directed therapies take advantage of the liver's unique blood supply. Two sets of vessels bring blood to the liver: the portal vein and the hepatic artery. The portal vein brings the majority of the blood and the great majority of the nutrients to normal liver. While the hepatic artery supplies a far smaller percentage of blood to normal liver, it provides nearly all of the vascular supply to liver tumors. Hepatocellular carcinoma characteristically has a very rich arterial blood supply, providing an excellent opportunity for minimally invasive, arterially directed targeted therapies. The hepatic artery is routinely accessed using standard angiographic techniques and fluoroscopic guidance.

Liver-directed therapies may be used alone or in combination. These therapies include: percutaneous ablation (a needle-like device called an applicator is inserted into the tumor(s) under imaging guidance, energy is applied through the applicator, and tumor destruction is induced around the "needle"), arterial embolization (the blood vessels supplying the tumor are occluded with tiny particles to induce ischemia), chemoembolization (chemotherapy is delivered directly to the tumor blood vessels immediately before they are occluded), intra-arterial chemotherapy (chemotherapy is delivered directly to the liver artery supplying the tumor(s) and radioembolization (selective internal radiation therapy, SIRT) (2).

At UCSF and other transplant centers, patients with HCC confined to the liver may be offered a spot on the liver transplant list. Expected 5-year survival in patients with HCC who make it to liver transplant is 70-90%, which is better than that for surgery (50%) or liver-directed therapy alone (20-50%) (1). A chief requirement for listing is tumor burden within United Network for Organ Sharing (UNOS) T2 stage (one lesion less than 5 cm or up to 3 lesions each less than 3 cm in size). Patients with UNOS T3 stage (disease confined to the liver without evidence imaging evidence of portal or hepatic vein invasion or extracapsular extension) may also be listed if they undergo successful "down-staging" to UNOS T2 or T1 using liver-directed therapy (7, 8). Liver-directed therapy choices include transarterial chemoembolization (TACE), SIRT, radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI). Typical wait for an organ in UNOS region 5, which includes California, is 1.5-2 years depending on the patient's blood type. If untreated, HCC is likely to progress during this long waiting period beyond UNOS T2 stage. Therefore, various liver-directed treatment approaches including TACE, RFA, and PEI are

employed to maintain patients active on the transplant list.

TACE is a standard treatment option for patients with intermediate stage, unresectable hepatocellular carcinoma (HCC) without significant hepatic synthetic dysfunction (2). TACE produces an objective tumor response rate of 35%-40% and confers a significant survival advantage as compared to best supportive care (9, 3, 4). Improved quality of life and reduced pain following initiation of chemoembolization are reported among patients undergoing sequential TACE (10). Current indications for TACE include first line treatment for unresectable intermediate stage HCC, as "bridging" therapy to prevent disease progression and drop-out on the liver transplant waiting list, as a method to "down-stage" patients to qualify them for liver transplantation, or enable liver resection through the reduction of disease burden (2, 7).

TACE for HCC can be performed in a variety of ways. Conventional TACE (cTACE) is performed by dissolving one or more cytotoxic drugs including doxorubicin, cisplatin, and/or mitomycin C in iodinated contrast and adding ethiodized oil to the dissolved drugs to make a 1:1 emulsion. Following infusion of the emulsion into the hepatic artery, embolization is performed to stasis of arterial flow with a variety of permanent or dissolvable embolic agents (11).

During the past 5 years, it has been recognized that two commercially available particulate embolic agents (LC Beads®, Biocompatibles Inc., Farnham, Surrey, UK; Hepasphere®, Merit Medical, South Jordan, UT, USA) can be used as drug carriers by forming an ionic bond between the drug and the microsphere (12, 13). The two drugs that are currently being delivered in this fashion are doxorubicin for patients with HCC and irinotecan for patients with colorectal liver metastases. The process of performing TACE using drug-eluting beads (DEB) has become known as DEB-TACE. Pharmacokinetic studies have shown that during cTACE a substantial amount of drug is present in the systemic circulation, whereas during DEB-TACE the amount of drug in the systemic circulation is negligible (12, 13). A recently published randomized clinical trial (PRECISION V) showed that DEB-TACE using doxorubicin-eluting microspheres had similar efficacy to cTACE performed with doxorubicin and ethiodized oil emulsion (14).

1.2 TACE Toxicity

Complication rates following TACE are high (25-45%) with the majority being reversible elevations of hepatic transaminases and serum bilirubin without an impact on long-term prognosis, however, for a small proportion of patients, irreversible hepatic decompensation occurs (15). TACE-related irreversible hepatic decompensation is described as significant and acute elevation of liver function tests, evidence of new ascites, new encephalopathy, or worsening of either. These serious complications, frequently accompanied by deterioration in clinical status, may lead to the requirement of urgent liver transplantation in eligible patients, ineligibility for and/or risk of increased toxicity from systemic therapy with sorafenib or investigational systemic therapies for HCC, or death (16). Rates of complications following conventional TACE performed for patients with marginal hepatic reserve or portal vein thrombosis have been described (16-23).

We have recently completed a retrospective record review of 252 patients with HCC and hepatic dysfunction who underwent 446 cTACE procedures at our institution between 2005 and 2009 (24). Patients were eligible for inclusion if they had one of the following criteria: pre-TACE

bilirubin ≥2mg/dl, aspartate aminotransferase (AST) or alanine aminotransferase (ALT)>5 times upper normal limit, international normalized ratio (INR) >1.5, creatinine >1.2 mg/dL, platelet count ≤60,000/μL, Model for End-Stage Liver Disease (MELD) score >15, Childs-Pugh class B or C, ascites, or portal venous thrombus. Hepatotoxicity was defined as one of the following: new or worsening ascites, encephalopathy, or NCI Common Terminology Criteria for Adverse Events grade 3 or 4 toxicity of bilirubin, AST, ALT, creatinine or INR. Rate and risk factors for persistent hepatotoxicity were determined using generalized estimating equation analysis.

Reversible hepatotoxicity developed after 90 TACE procedures (20%) in 78 patients (31%). Reversible abnormalities resolved in under 30 days after 63 procedures, in 1-3 months after 19 procedures, and in 3-6 months after 6 procedures. Irreversible hepatotoxicity developed after 41 procedures (9%) in 37 patients (15%). Six patients (2%) received urgent liver transplants, and five (2%) died within 30 days of TACE. Patients at increased risk for procedure-related mortality or urgent need for a liver transplant had baseline elevated serum bilirubin ($p<0.0001$), elevated INR ($p<0.0001$), hypoalbuminemia ($p=0.002$), thrombocytopenia ($p=0.011$), elevated serum creatinine ($p<0.0001$), large ascites ($p=0.0002$), encephalopathy ($p=0.0002$), or MELD >15 ($p=0.0005$).

PRECISION V trial (14) showed that DEB-TACE was better tolerated than cTACE and led to better radiographic responses in patients with more advanced liver disease than cTACE. On the basis of this observation, DEB-TACE may, in fact be the preferred modality for treating patients with hepatic dysfunction. All studies performed on safety of DEB-TACE to date included patients with serum bilirubin <3 mg/dl, and AST and ALT levels under 5X upper normal limit 14, 26-52). Patients with baseline liver dysfunction at bilirubin and transaminase levels above those included in trials are routinely treated in clinical practice. However, there have been no published studies to date to support safety and efficacy of DEB-TACE in patients with marginal hepatic reserve. A total of 37 patients with hepatic dysfuncation (who met the inclusion criteria proposed for this study) have been treated between at UCSF between 2011 and 2013. Their records were retrospectively reviewed. Preliminary results on adverse events following DEB-TACE are summarized in Table 1. No treatment-related deaths and no events hepatic decompensation requiring an urgent liver transplant were encountered in this patient cohort.

Table 1. Severe hepatic and renal adverse events in 37 patients with marginal hepatic reserve who underwent DEB-TACE at UCSF.

Toxicity	Bilirubin N (%)	AST N (%)	ALT N (%)	INR N (%)	Creatinine N (%)
Reversible* grade 3	9 (24)	5 (14)	1 (2.7)	0 (0)	0 (0)
Reversible* grade 4	1 (2.7)	1 (2.7)	0 (0)	N/A	0 (0)
Irreversible** grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Irreversible** grade 4	0 (0)	0 (0)	0 (0)	N/A	0 (0)

*Abnormality returned to baseline within 6 weeks of DEB-TACE

**Abnormality persisted for at least 6 weeks following DEB-TACE

1.6 Rationale

TACE is frequently offered to patients with hepatic dysfunction with the purpose of diminishing hepatic tumor burden while patients await transplantation. Without this therapeutic measure, disease may progress beyond UNOS T2 criteria required for organ allocation. PRECISION V randomized controlled trial has suggested that DEB-TACE may be associated with fewer adverse events than conventional TACE. Therefore, the purpose of this study is to determine whether DEB-TACE can be used safely and effectively to treat patients with liver-only HCC and hepatic dysfunction.

2.0 OBJECTIVES

Primary Objective

- To determine the safety of DEB-TACE in patients with HCC confined to liver who are being considered for liver transplantation
- To determine the response rate to DEB-TACE by conventional and modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1, mRECIST [22]) for treated lesions in patients with liver-only HCC who are being considered for liver transplantation.

Secondary Objectives

- To measure overall radiographic response (by RECIST v1.1 and mRECIST) 6 months after the date of the first planned DEB-TACE procedure. To measure time to untreatable progression (TTUP). TTUP is defined as time to disease progression untreatable by liver-directed percutaneous or surgical methods.
- To measure median time to progression (TTP)
- To measure hepatic progression free survival (HPFS)
- To measure progression free survival (PFS)
- To measure overall survival (OS).
- To determine the proportion of patients who remain active on the wait list for a liver transplant and eventually are transplanted.
- To determine the proportion of patients who are inactivated or drop out from the wait list for any reason but transplantation.
- To determine the proportions of patients who are successfully down-staged and achiev active waitlist status and eventually are transplanted.
- To measure proportion with alpha-fetoprotein (AFP) response with ≥ 50% decline from baseline (in patients with baseline level ≥ 20) post DEB-TACE and test for association with hepatic and overall response rate, PFS, and OS.
- To determine whether changes in cardiac function occur as a result of DEB-TACE with doxorubicin
- ***To obtain pharmacokinetic data for doxorubicin administered as a part of DEB-TACE procedures***

Exploratory/Other Objectives

- To describe treatment response by histopathology at the time of liver transplantation (in the subgroup of patients who undergo LT).

3.0 STUDY DESIGN

This is a prospective open-label two-stage phase II clinical trial to evaluate the safety and efficacy of DEB-TACE in patients with liver-only HCC and hepatic dysfunction who are being considered for a liver transplant. Seventeen patients will be enrolled during the first stage of the study for efficacy. Subsequently, 34 patients will be enrolled into the second stage of the study. Prior surgical resection or liver-directed therapy will be allowed. Patients will be followed for one year following DEB-TACE. This study will take up to five years to complete.

3.1 Single DEB-TACE procedure algorithm

Patients who meet the eligibility criteria in Section 4.0 and present with HCC confined to one liver segment supplied entirely by one segmental branch of the hepatic artery the right or the left hepatic artery will be offered a single DEB-TACE treatment intended to target the entire tumor vasculature. The following algorithm will be adhered to for patients with disease confined to one liver lobe or segment:

One to sixty days prior to treatment, patients will undergo imaging of the abdomen with contrast-enhanced CT or MRI. Within one to six days prior to DEB-TACE, laboratory tests including CBC, BUN, creatinine, coagulation panel, liver function tests, and serum alpha-fetoprotein level (AFP) will be performed. A history and physical examination will be performed within six days prior to and the day of DEB-TACE (Table 1).

For the purposes of DEB-TACE procedure, hepatic angiogram will be performed in the standard fashion via a common femoral artery approach. Coaxial microcatheter will be used for selective catheterization of a segmental or subsegmental hepatic artery branch. Up to two 2 ml vials of 100-300μm LC-Beads™ impregnated per manufacturer-supplied protocol with 25mg of doxorubicin per ml of beads will be administered into the catheterized hepatic artery. Procedure will be stopped when arterial flow approaches stasis and/or when the entire DEB dose has been administered.

Patients will be on bed rest for approximately 4-8 hours following removal of the femoral artery catheter. Per institutional standard, they will be admitted for planned overnight observation to the hospital and discharged once determined to be in stable condition. Management after each DEB-TACE procedure will be according to institutional standard of care.

Patient follow-up is summarized in section 8.4 and section 8.4.1.

3.2 Treatment Algorithm for Multiple DEB-TACE procedures

Patients who meet the eligibility criteria in Section 4.0 with a lesion or lesions supplied by more than one segmental hepatic artery branch will be considered for up to four sequential DEB-TACE procedures intended to target the entire tumor vascular supply in a step-wise fashion. The number of procedures will be based on the number, location, and size of the lesions as well as on the hepatic arterial anatomy up to a maximum of 4 DEB-TACE procedures. This information will be obtained from the pre-procedure cross-sectional imaging (CT or MRI), hepatic artery angiography, and C-arm CT (when applicable).

Sequential DEB-TACE may be offered in the following settings:

A. Multifocal HCC (UNOS T2 or T3 disease; no radiographic evidence of macrovascular invasion or extracapsular extension)
B. Single HCC greater than 3 cm (UNOS T2 or T3 disease without radiographic evidence of macrovascular invasion or extracapsular extension).
C. More than 1 segmental feeding hepatic artery branch to a lesion of any size.

Pre-procedure evaluation will be the same as for patients undergoing one DEB-TACE procedure (Table 2). For each DEB-TACE procedure, up to two 2 ml vials of 100-300μm LC-Beads® impregnated per manufacturer-supplied protocol with 25mg of doxorubicin per ml of beads will be administered into the catheterized hepatic artery. Procedure will be stopped when arterial flow approaches stasis and/or when the entire DEB dose has been administered.

Sequential DEB-TACE procedures will be performed approximately 1 month apart. Longer intervals between the procedures may be necessary. The timing of DEB-TACE will be determined by the treating interventional radiologist and hepatologist or medical oncologist. The number of procedures (up to 4 total) will be based on the number, location, and size of the lesions as well as on the hepatic arterial supply to the lesions. This information will be obtained from the pre-procedure cross-sectional imaging (CT or MRI) and hepatic artery angiography. This step-wise approach is intended to target the entire tumor vascular supply in a step-wise fashion prior to assessing response to therapy.

The maximum administered doxorubicin dose per DEB-TACE procedure (session) will be 100mg (50 mg per each 2 ml vial of 100-300μm LC beads). The maximum administered dose as a result of four DEB-TACE procedures will be 400 mg.

Post-procedure follow-up for the first month after DEB-TACE will be as outlined in Table 2. Additional treatment will be offered if the following criteria are met:

1. Patient is willing to undergo additional DEB-TACE treatment.
2. Patient meets all of the inclusion criteria and none of the exclusion criteria (see sections 4.2 and 4.3 below) at the time of 20-day follow-up.

Patient follow-up is summarized in section 8.4 and section 8.4.2.

4.0 ELIGIBILITY CRITERIA

4.1 Subject Population

Patients with liver-only HCC UNOS stage T1, T2, or T3 being considered for liver transplantation at UCSF will be eligible. Patients who have undergone prior resection, chemoembolization, radioembolization, bland embolization, ablative therapy or systemic therapy will be eligible to participate in the study.

Treatment with DEB-TACE will be offered to patients being considered for liver transplantation under one of the following protocols:

1. Milan criteria: One lesion less than 5 cm or up to 3 lesions each less than 3 cm.
2. UCSF Downstaging criteria: One lesion less than 8 cm or 2-3 lesions each less than 5 cm with sum of maximum dimensions less than 8 cm, or 4-5 lesions each less than 3 cm with sum of maximum dimensions less than 8 cm.
3. UCSF All-Comers criteria: UNOS stage T3 disease beyond UCSF Downstaging Criteria.

4.2 Inclusion Criteria

1. Adult male or female patients, age 18 years of age or older
2. Diagnosis of liver-only HCC based on European Association for the Study of the Liver (EASL) criteria (radiographic lesion appearance on contrast-enhanced CT or MRI, i.e. enhancement on early arterial phase, washout on portal venous phase with or without associated elevation of serum AFP level >200U/ml) or histologic confirmation of HCC diagnosis, whichever is applicable.
3. UNOS stage T1, T2, or T3 disease.
4. Candidates for liver transplantation (listed or screened) according to one of the following criteria:
    a. Milan criteria (one lesion < 5cm or 3 or fewer lesions each < 3cm),
    b. UCSF Downstaging criteria (one lesion less than 8 cm or 2-3 lesions each less than 5 cm with sum of maximum dimensions less than 8 cm, or 4-5 lesions each less than 3 cm with sum of maximum dimensions less than 8 cm)
    c. UCSF All-Comers criteria (UNOS stage T3 disease beyond UCSF Downstaging Criteria).
5. At least one measurable site of disease in the liver according to RECIST version 1.1 and mRECIST criteria.
6. **At least one** of the following clinical, laboratory, or imaging parameters:
    a. Mild or moderate ascites
    b. Serum bilirubin $\geq$ 3 mg/dl but less than 6 mg/dl
    c. Aspartate aminotransferase (AST) > 5 times upper limit of normal (ULN) but $\leq$ 10 times ULN
    d. Alanine aminotransferase (ALT) > 5 times upper limit of normal (ULN) but $\leq$ 10 times ULN
    e. International normalized ratio for prothrombin time (INR) >1.5 but $\leq$ 2.5
    f. Bland portal vein thrombosis (branch or main)
    g. Functioning transjugular intrahepatic portosystemic shunt (TIPS) or surgical portosystemic shunt
7. ECOG performance status of 0, 1, or 2.
8. Ability to give written informed consent.

Patients should meet the above study entry criteria at study enrollment as well as prior to undergoing each subsequent DEB-TACE procedure.

4.3 Exclusion Criteria

1. Liver-directed therapy (chemoembolization, radioembolization, bland embolization, ablative therapy) within 4 weeks of DEB-TACE.
2. Previous liver transplantation.

3. Serum bilirubin ≥ 6 mg/dl
4. AST > 10 times upper normal limit
5. ALT > 10 times upper normal limit
6. INR > 2.5
7. Serum creatinine > 1.5 mg/dl
8. Macrovascular tumor invasion of portal and/or hepatic vein(s)
9. Extracapsular tumor extension
10. Extrahepatic disease
11. Hepatic encephalopathy refractory to medical therapy
12. Active uncontrolled infection
13. Imaging evidence of common bile duct obstruction
14. Previous sphincterotomy or bilio-enteric anastomosis
15. Significant hepatic arterial to portal vein shunting in the area to be treated.
16. Symptomatic congestive heart failure (CHF)
17. Allergy to or intolerance of prior doxorubicin-based TACE
18. Allergy to or intolerance to iodinated contrast media despite standard of care pre-medication
19. Any contraindications to treatment with LC Bead™ device (e.g. patients with large diameter arteriovenous shunts or patients with a right-to-left shunt).
20. Systemic therapy with sorafenib or other systemic chemotherapeutic agent(s) less than 1 week prior to first planned DEB-TACE.
21. Active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. (Patients with history of malignancy are not considered to have a "currently active" malignancy if they have completed therapy and are now considered by their physician to be at less than 30% risk for relapse.)
22. Uncontrolled intercurrent illness including, but not limited to: Ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled peripheral vascular disease, myocardial infarction within preceding 12 months, cerebrovascular accident within preceding 12 months, pulmonary disease impairing functional status or requiring oxygen, impairment in gastrointestinal function that may affect or alter absorption of oral medications (such as malabsorption or history of gastrectomy or bowel resection).
23. Pregnant or lactating women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with DEB-TACE, breastfeeding must be discontinued for eligibility.
24. Psychiatric illness, other significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements.

4.4 Subject Selection

Participants who meet the eligibility criteria above will be evaluated by the UCSF liver tumor board, which consists of Hepatology, Medical Oncology, Transplant Surgery, and Interventional Radiology services. The team will determine which patients should be offered this therapy. Patients who meet eligibility criteria will be referred for possible treatment.

5.0 SUBJECT REGISTRATION

All patients who are consented will be entered into the UCSF Cancer Center OnCore® database. The OnCore® database is password protected and meets HIPAA guidelines.

To register patients on-study, study personnel will complete an eligibility form. Study ID numbers for each patient will be assigned serially. Pertinent information will be entered from the patient medical record.

6.0 TREATMENT PLAN

Segmental hepatic artery catheterization will be performed via femoral artery approach using a combination of 3-French, 4-French, and 5-French angiographic catheters. Segmental DEB-TACE will be performed using two 2ml vials of LC beads (Biocompatibles, Inc.) impregnated per standard manufacturer-supplied protocol with a total of 100 mg of doxorubicin (25 mg per milliliter of beads). Microspheres in the size range of 100-300μm will be used. Procedure will be stopped when arterial flow approaches stasis and/or when the entire DEB dose has been administered.

Patients with multiple liver lesions, lesions >3 cm, or lesions with more than 1 feeding branch hepatic artery may receive additional DEB-TACE at approximately 1 month intervals. Cross-sectional imaging (contrast-enhanced CT or MRI) will be performed approximately 1 month after targeting of all hepatic lesions in the course of 1-4 DEB-TACE procedures. Patients with residual or recurrent disease may receive up to 4 total DEB-TACE procedures.

7.0 TOXICITY MANAGEMENT

Once they are enrolled in the study, patients will be discussed at the gastrointestinal oncology site committee meeting at bi-weekly intervals for the first month following each DEB-TACE treatment. Any adverse events grade ≥ 4 will be discussed by the interventional radiologist and medical oncologist or hepatologist within 24 hours of being informed of the event.

7.1 Liver toxicity

Up to one half of the patients are expected to experience at least one liver-related side effect following DEB-TACE. Liver-related toxicities, for which all patients will be monitored include elevation the serum bilirubin level, increase in aspartate or alanine aminotransferase, development of ascites, hepatic encephalopathy, hepatorenal syndrome, liver failure, hemobilia, gastrointestinal hemorrhage, cholangitis, liver abscess, and bile duct stricture. Most of these toxicities (80%) are expected return to pre-treatment levels. However, some may persist and may be exacerbated by tumor progression and/or advancing cirrhosis. Risk of liver toxicity will be minimized by performing segmental or subsegmental DEB-TACE whenever possible.

Patients will be screened for presence of laboratory liver function test abnormalities at 10-day intervals for the first month following each DEB-TACE treatment. Any abnormal lab values will be followed as clinically indicated. Patients with ascites will be followed clinically and will be treated if symptoms referable to ascites develop. Patients with hepatic encephalopathy,

hepatorenal syndrome, liver failure, hemobilia, gastrointestinal hemorrhage, cholangitis, liver abscess, and bile duct stricture will be treated according to the current standard of care.

7.2 Renal toxicity

Renal toxicity may be related to administration of iodinated contrast at the time of DEB-TACE or to development or exacerbation of the hepatorenal syndrome. Renal toxicity is expected to occur in fewer than 10% of patients. If renal impairment occurs, patients will be treated medically. Renal replacement therapy will be initiated if clinically indicated.

7.3 Postembolization syndrome

A combination of abdominal pain, nausea/vomiting, fever, fatigue, and anorexia constitutes the post-embolization syndrome. The risk of postembolization syndrome related to DEB-TACE is estimated at 50-70%. While the risk of post-embolization syndrome is high, the symptoms are usually self-limited after a period of 10-14 days. Symptoms are expected to be most severe within the first 24 hours of DEB-TACE. Therefore, all patients will be admitted for 23-hour inpatient observation as per standard of care at UCSF for intravenous fluids, analgesic, and antiemetic therapy. Upon discharge, patients will be given a prescription for oral opiate analgesic and antiemetic agents.

7.4 Side effects of angiography and embolization

Side effects of angiography may include access site hematoma, arterial injury (dissection, thrombosis) related to catheter or wire manipulation, allergic reactions to iodinated contrast (rash, dyspnea, hypotension, cardiopulmonary arrest), and contrast-induced nephropathy. The risks of angiography are small, with access site hematoma being the most common side effect occurring in < 5% of patients.

7.5 Drug-drug interactions

Patients who are receiving P-glycoprotein inhibitors and CYP2D6 substrates that have a narrow therapeutic index for the potential risk of increased adverse events. However this risk of a drug interaction with systemically administered drugs might be low following intra-arterial bead-bound doxorubicin as compared to intravenous administration of doxorubicin.

Because of possible hepatotoxic and nephrotoxic effect of TACE, concurrent use of hepatotoxic and nephrotoxic drugs will be avoided.

8.0 EVALUATIONS AND PROCEDURES

Table 2 Schedule of Events: Single Deb-TACE

	Pre-treatment Screening Evaluation		DEB-TACE	Post Treatment Evaluation						
	-60 to 0 days	*-6 ±6d*	*Day 0*	*1 ±0d*	*7 ±4d*	*30 ±7d*	*90 ±14d*	*180 ±14d*	*270 ±14d*	*360 ±14d*
Clinical/Administrative Activities										
Informed Consent	X									
Demographics	X									
Medical History	X									
Physical Examination	X	X								
ECOG Performance Status (See Appendix 1)	X	X				X	X	X	X	X
Child Pugh Turcotte Score (See Appendix 2)	X					X	X	X	X	X
MELD Score (See Appendix 3)	X					X	X	X	X	X
Interim History + Physical Exam					X*	X	X	X	X	X
Evaluation of Response						X	X	X	X	X
Laboratory Tests										
CBC, Coagulation Panel, BUN, Creatinine, Liver Function Tests	X	X		X	X	X	X	X	X	X
Alpha-fetoprotein		X				X	X	X	X	X
Imaging Studies										
Contrast-Enhanced CT or MRI of the abdomen	X					X	X	X	X	X
CT chest with and/or without contrast	X						X	X	X	X
Cardiac Function Assessment										
Echocardiogram	X&					X&				
DEB-TACE Procedure										
DEB-TACE			X							
Pharmacokinetics Evaluation										
Pharmacokinetics sample acquisition**			X	X	X					

Abbreviation: d = days

* May be substituted by telephone follow-up by interventional radiology nurse practitioner for patients who are non-local study participants.

& Cardiac function will be assessed via echocardiogram at baseline and one month following last planned DEB-TACE.
***** See plan for pharmacokinetic data acquisition in Sections 8.1 and 8.4***

Table 3 Schedule of Events: Multiple DEB-TACE procedures*

	Pre-treatment Evaluation		DEB-TACE 1	Evaluation TACE 1		DEB-TACE 2	Evaluation TACE 2		DEB-TACE 3	Post Treatment Evaluation TACE 3		DEB-TACE 4**
	-60 to 0 days	*-6 ±6d*	*Day 0*	*1d*	*7 ±4d*	*30 +30d (Reset to d0)*	*1d*	*7 ±4d*	*30 +30d (Reset to d0)*	*1*	*7 ±4d*	*30 +30d (Reset to d0)*
Clinical / Administrative Activities												
Informed Consent	X											
Demographics	X											
Medical History	X					X			X			X
Physical Examination	X	X										
ECOG Performance Status	X	X				X			X			X
Child Pugh Turcotte Score (See Appendix 2)	X											
MELD Score (See Appendix 3)	X					X			X			X
Interim History + Physical Exam					X	X		X	X		X	X
Laboratory Tests												
CBC, Coagulation Panel, BUN, Creatinine, Liver Function Tests	X	X		X	X	X	X	X	X	X	X	X
Alpha-fetoprotein		X										
Imaging Studies												
Contrast-Enhanced CT or MRI of the abdomen	X											
CT chest with and/or without contrast	X											
Cardiac Function Assessment												
Echocardiogram	X[&]					X[&]			X[&]			X[&]
DEB-TACE Procedure												
DEB-TACE**			X			X**			X**			X**
Pharmacokinetics Evaluation												
Pharmacokinetics data acquisition***			X	X	X							

Abbreviation: d = days

* See Table 2 for post-treatment evaluation after DEB-TACE 4. DEB-TACE 3 and 4 are optional for patients with disease extent limited to two liver segments. Patients may proceed to evaluation of response and long-term follow-up after fewer than 4 DEB-TACE treatments at the investigator's discretion.

& Cardiac function will be assessed via echocardiogram at baseline and one month following last planned DEB-TACE.

** Up to 4 DEB-TACE procedures may be performed at approximately 1 month intervals depending upon initial size, number, vascular supply of lesion(s) and interval treatment response on imaging.

*** See plan for pharmacokinetic data acquisition in Sections 8.1 and 8.4

8.1 Screening/Baseline

Prior to enrollment, patients will be seen by a hepatologist and/or a medical oncologist at UCSF and evaluated for all possible treatment options, one of which will include DEB-TACE. Prior to enrollment, all patients will be discussed in the multidisciplinary liver tumor board, which

includes hepalogists, medical and surgical oncologists, and interventional radiologists. If the patient is deemed a good candidate for the procedure, the patient will then be referred to the interventional radiologist for DEB-TACE. Patients will be offered the opportunity to be screened for study participation. After informed consent is obtained, pre-procedure assessment is summarized in Table 1.

Approximately zero to sixty days prior to DEB-TACE, the following will be performed to determine eligibility:

- cross sectional imaging of the abdomen using multi-phase CT or MRI with IV contrast
- CT scan of chest (with and/or without contrast)
- baseline laboratory tests
- clinical history and physical examination

Approximately zero to twelve days prior to DEB-TACE, the following additional procedures will be performed (if the initial screening is performed outside 12-day window):

- Laboratory testing including liver function tests, CBC, BUN, creatinine, coagulation profile, and serum alpha-fetoprotein level
- Medical history and physical examination
- ECOG performance status

Baseline cardiac function monitoring using echocardiogram will be performed approximately zero to 720 days prior to first planned DEB-TACE

One day prior to DEB-TACE, the UCSF Inpatient Pharmacy will be instructed by the interventional radiologist to start incubation of two 2ml vials of 100-300 μmLC Beads® with 100mg doxorubicin (25mg/ml of beads) per manufacturer-supplied instructions for use (currently not cleared by the FDA for use).

8.2 Treatment

The patient will come directly to the Interventional Radiology on the day of the procedure after an overnight fast. Moderate sedation will be supervised by the interventional radiologist performing the procedure. The patients will be continuously monitored during the procedure by an IR nurse. Access to the hepatic artery will be achieved using an angiographic catheter placed in the femoral artery. An angiographic catheter will be directed under fluoroscopic guidance to the appropriate location in the hepatic artery. Doxorubicin-loaded LC bead™ will be mixed with non-ionic iodinated contrast (per manufacturer-supplied instructions for use) and administered into the target hepatic artery branch under continuous fluoroscopic guidance by the interventional radiologist until flow approaches stasis or until the entire DEB dose is administered.

The investigators will estimate the total amount of doxorubicin administered for each DEB-TACE procedure using the following formula:

Doxorubicin dose = 0.98 * 50mg *[% of vial 1 delivered + % of vial 2 delivered]/100

In the formula, correction factor 0.98 accounts for incomplete absorption of doxorubicin to LC Bead™, while 50 mg is the doxorubicin dose to be mixed with each 2 ml vial of beads.

Estimated doxorubicin dose will be recorded in patients' study charts and will be recorded in the medical record.

Pharmacokinetics data for doxorubicin will be collected by obtaining peripheral venous blood samples from the first 17 patients at the time of completion of the first planned DEB-TACE, and subsequently 5±1 min, 30±5 min, 60±5 min, 120±10 min, 6±0.5 hours, 20±2 hours, and 8±2 days following administration of 100-300 mm doxorubicin-impregnated LC bead™.

All patients will be admitted to the hospital for planned 23-hour observation upon completion of the procedure and will then be discharged home once determined to be in stable condition. Management after each DEB-TACE procedure will be according to institutional standard of care.

8.3 Multiple DEB-TACE Procedures Targeting Different Vascular Territories

Sequential DEB-TACE procedures may be offered in the following settings:

A. Multifocal HCC (UNOS T2 or T3 disease; no radiographic evidence of macrovascular invasion or extracapsular extension).
B. Single HCC greater than 3 cm (UNOS T2 or T3 disease without radiographic evidence of macrovascular invasion or extracapsular extension).
C. More than 1 segmental feeding hepatic artery branch to a lesion of any size.

Patients with lesions that meet at least one of these criteria will be considered for up to four DEB-TACE procedures that will be performed approximately 1 month apart. Longer intervals between the procedures may be necessary in order to allow patients to regain pre-TACE liver function and performance status. Intervals between DEB-TACE procedures up to 90 days will be allowed. The timing of DEB-TACE will be determined by the treating interventional radiologist and hepatologist or medical oncologist. The number of procedures (up to 4 total) will be based on the number, location, and size of the lesions as well as on the hepatic arterial supply to the lesions. This information will be obtained from the pre-procedure cross-sectional imaging (CT or MRI) and hepatic artery angiography. This step-wise approach is intended to target the entire tumor vascular supply in a step-wise fashion prior to assessing response to therapy (Table 2).

The maximum administered doxorubicin dose per DEB-TACE procedure will be 100mg (50 mg per each 2 ml vial). The maximum administered dose as a result of four DEB-TACE procedures will be 400 mg.

8.4 Follow-Up Assessments

Vast majority of the adverse effects of DEB-TACE are expected to occur within 30 days of treatment. For the first month following each DEB-TACE, the patient's progress will be monitored at bi-weekly intervals at the gastrointestinal oncology site committee by a team consisting of medical oncologists and interventional radiologists.

8.4.1 Patients with Single DEB-TACE Procedure

The following laboratory testing will be performed 1, 7±4, 30±7, 90±14, 180±14, 270±14, and 360±14 days following DEB-TACE: CBC, coagulation panel, BUN, creatinine, and liver function tests. Serum alpha-fetoprotein testing will start approximately 30 days following last planned DEB-TACE procedure. Any abnormal lab values will be followed up as clinically indicated. Laboratory tests may be performed at UCSF or at a local lab.

Seven ±4 days following DEB-TACE patients will have clinic follow up in Interventional Radiology for toxicity monitoring including reviewing the laboratory results above. Any expected or unexpected AEs will be discussed with the study PI or a designated co-investigator. Further testing and/or treatment will be coordinated by the study PI or a designated co-investigator if clinically appropriate (see section 7).

Cardiac function assessment monitoring using echocardiogram will be obtained approximately 30 days following the DEB-TACE procedure.

Patients will be seen in clinic approximately one month after the DEB-TACE procedure. During this visit, interim medical history will be obtained, and a physical examination will be performed. This will include (but will not be limited to) cardiopulmonary evaluation and an abdominal exam. Subsequently, patients will be followed in clinic at approximately 3 month intervals until 360 days following DEB-TACE.

Approximately one month after DEB-TACE procedure, patients will undergo repeat cross-sectional imaging with multi-phase contrast-enhanced CT or MRI of the abdomen. Subsequent imaging will be performed at approximately 3 month-intervals until 360 days following DEB-TACE. Standard clinical practices will be adhered to during the follow-up period.

Response to treatment will be assessed according to the RECIST version 1.1 and mRECIST criteria (see section 9.2).

Patients will be removed from study and follow-up assessments will stop prior to 360 days following DEB-TACE if a patient:

a) requires > 4 DEB-TACE procedures
b) requires another anti-cancer treatment modality such as ablation, surgery, or conventional TACE
c) receives a liver transplant
d) develops untreatable intrahepatic or extrahepatic disease progression
e) experiences unacceptable toxicity (see section 10.0). All serious adverse events will be followed until the SAE has been resolved.

Pathology report describing the extent of HCC in the liver explant will be reviewed for the subset of patients who undergo LT.

8.4.2 Patients with Multiple DEB-TACE Procedures

The following laboratory testing will be performed 1 and 7±4 days following each DEB-TACE: CBC, coagulation panel, BUN, creatinine, and liver function tests. Any abnormal lab values will

be followed up as clinically indicated. Laboratory tests may be performed at UCSF or at a local lab.

Seven ±4 days following DEB-TACE patients will have clinic follow up in Interventional Radiology for toxicity monitoring including reviewing the laboratory results above. Any expected or unexpected AEs will be discussed with the study PI or a designated co-investigator. Further testing and/or treatment will be coordinated by the study PI or a designated co-investigator if clinically appropriate (see section 7).

Cardiac function assessment monitoring using echocardiogram will be obtained approximately 30 days following last planned DEB-TACE procedure.

Candidacy for repeat DEB-TACE (sessions 2-4) will be based on laboratory and clinical follow-up on day 7 ± 4 and on the day of scheduled repeat DEB-TACE (sessions 2-4). The decision to delay or cancel subsequent planned DEB-TACE procedures would be at the discretion of the treating interventional radiologist, hepatologist, or medical oncologist. This decision will be based on currently used clinical practice standards at UCSF.

Upon completion of 2-4 planned DEB-TACE treatment sessions, the following laboratory testing will be performed 1, 7±4, 30±7, 90±14, 180±14, 270±14, and 360 ±14 days following DEB-TACE: CBC, coagulation panel, BUN, creatinine, and liver function tests. Serum Alpha-fetoprotein testing will start 30 days following last planned DEB-TACE procedure. Any abnormal lab values will be followed up as clinically indicated.

Patients will be seen in clinic approximately one month after the last planned DEB-TACE procedure. During this visit, interim medical history will be obtained, and a physical examination will be performed. This will include (but will not be limited to) cardiopulmonary evaluation and an abdominal exam. Subsequently, patients will be followed in clinic at approximately 3 month intervals until 360 days following DEB-TACE.

Approximately one month after last planned DEB-TACE procedure, patients will undergo repeat cross-sectional imaging with multi-phase contrast-enhanced CT or MRI of the abdomen. First follow-up imaging study will be obtained no more than 6 months following the first DEB-TACE procedure. Subsequent imaging will be performed at approximately 3 month-intervals until 360 days following DEB-TACE. Standard clinical practices will be adhered to during the follow-up period.

Response to treatment will be assessed according to RECIST version 1.1 and mRECIST criteria (see section 9.2).

Patients will be removed from study and follow-up assessments will stop prior to 360 days following DEB-TACE if a patient:

a) requires > 4 DEB-TACE procedures
b) requires another anti-cancer treatment modality such as ablation, surgery, or conventional TACE

c) receives a liver transplant
d) develops untreatable intrahepatic or extrahepatic disease progression
e) experiences unacceptable toxicity (see section 10.1). All serious adverse events will be followed until the SAE has been resolved.

Pathology report describing the extent of HCC in the liver explant will be reviewed for the subset of patients who undergo LT.

8.5 Ancillary Therapy

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, analgesics, antiemetics, etc., when appropriate.

Patients taking concomitant medications known to be metabolized by the liver should be closely observed for side effects. Patients taking narrow therapeutic index medications that are hepatically metabolized should be monitored proactively. These medications include warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporin and digoxin. No medication is specifically prohibited, and there are no specific dietary restrictions.

9.0 CRITERIA FOR EVALUATION

The primary endpoints of this study are to evaluate the safety and efficacy of DEB-TACE in patients with marginal hepatic function.

9.1 Safety

Safety data will be collected as a part of this clinical protocol. The assessments will be based on post-procedure clinical evaluations, laboratory tests, and imaging studies (see section 8 for more details). Six weeks after all 17 patients have been treated with at least one DEB-TACE, data on DEB-TACE safety profile will be analyzed. Final safety analysis will be performed 6 weeks after all 51 patients have been treated with at least one DEB-TACE.

9.2 Efficacy

Evaluation of the treatment response will be based on contrast-enhanced cross-sectional imaging of the abdomen (CT or MRI) performed one month following last planned DEB-TACE procedure within six months of the first DEB-TACE procedure. Treatment response will be evaluated according to both the RECIST version 1.1 and mRECIST criteria. Whenever possible, the same imaging modality (CT or MRI) will be used for pre- and post-treatment assessments.

9.2.1 RECIST Definitions

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

Measurable Lesion: The lesion can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥10 mm with spiral CT scan.

Nonmeasureable Lesion: All other lesions, including small lesions [<10 mm with spiral CT scan] and truly nonmeasurable lesions.

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): 30% decrease in the sum of the longest diameter of target lesions

Stable Disease (SD): Small changes that do not meet the criteria for CR, PR, or PD

Progressive Disease (PD): 20% increase in the sum of the longest diameter of target lesions

9.2.2 RECIST Guidelines

- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Assessment will be performed using conventional imaging methods (CT, MRI).
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Up to three measurable lesions will be identified as target lesions. Target lesions will be selected on basis of size (lesions with the longest diameter) and their suitability for accurate repeated measurements (lesions can be located/identified during follow-up as well as baseline).
- Target lesions will be measured in one dimension. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.2.3 mRECIST Definitions (See Appendix 4)

Measurable Disease: The presence of at least one measurable lesion.

Measurable Lesion: The lesion can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥10 mm with spiral CT or MRI scan.

Nonmeasureable Lesion: All other lesions, including small lesions [<10 mm with spiral CT scan or MRI] and truly nonmeasurable lesions (infiltrative lesions).

Complete Response (CR): Disappearance of any intratumoral arterial enhancement in all target lesions

Partial Response (PR): 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions

Stable Disease (SD): Any cases that do not qualify for either partial response or progressive disease

Progressive Disease (PD): 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 treatment started

9.2.4 mRECIST Guidelines (See Appendix 4)

- All eligible patients with measurable disease *at baseline* will be included in the analysis for efficacy.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Assessment will be performed using conventional imaging methods (CT, MRI).
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Up to three measurable lesions will be identified as target lesions. Target lesions will be selected on basis of size (lesions with the longest diameter) and their suitability for accurate repeated measurements (lesions can be located/identified during follow-up as well as baseline).
- Target lesions will be measured in one dimension. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

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 CT or MRI 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 CT or MRI scans is required.
- The measurement of the viable tumor diameter should not include any major intervening areas of necrosis.

10.0 CRITERIA FOR STUDY TERMINATION

10.1 STOPPING RULES FOR SAFETY.

10.1.1 Rationale

A retrospective analysis of toxicity of conventional TACE method for UCSF patients with HCC and hepatic dysfunction, which included 252 patients and 446 TACE procedures was recently completed (24). This cohort included 166 patients who met the more stringent inclusion criteria for the current study. These patients underwent a total of 260 TACE procedures. In this patient cohort, 20 patients (12%) developed NCI CTCAE grade 4 hepatotoxicity that persisted 1 month following TACE. Of note, patients who had irreversible grade 4 hyperbilirubinemia with or without grade 4 transaminitis had a 27.7% rate of mortality or required an urgent liver transplant within 6 weeks of TACE. This rate was higher than that for patients who had grade 4 transaminitis without grade 4 hyperbilirubinemia, 11.1% of whom died or required an urgent liver transplant within 6 weeks of TACE. These findings suggested that irreversible hyperbilirubinemia was a more robust predictor of mortality or TACE-induced liver failure requiring salvage transplantation than transaminitis.

Based on the same retrospective study (24), a total of 2 patients (1.2%) had grade 4 renal toxicity that persisted 1 month following TACE.

Based on the same retrospective study (24), mortality rate 6 weeks following TACE was 4.8% (8 patients).

No published comparable safety data is available for DEB-TACE with regards to the patient population to be studied. However, a total of 37 patients with marginal liver function (within proposed inclusion criteria for this study) have been treated between 2011 and 2013. Their records were retrospectively reviewed. Preliminary results on adverse events following DEB-TACE are summarized in Table 1. No treatment-related deaths and no events hepatic decompensation requiring an urgent liver transplant were encountered in this patient cohort.

Stopping rules for safety were determined based on the assumption that DEB-TACE may be associated with similar rates of morbidity as conventional TACE.

10.1.2 Specific Stopping Rules for Safety

Safety data will be routinely monitored and sequential safety assessments will be conducted as subjects are enrolling to the study. The study will be stopped due to safety/toxicity concern prior to interim efficacy analysis if *any* of the following 3 stopping rules are met:

1. Liver dysfunction (clinical or laboratory [total serum bilirubin], grade 4) that does not improve to baseline or </= grade 3 within 1 month following DEB-TACE in ≥ 7 patients (12% of 51 patients).

   OR

2. Renal dysfunction (clinical or laboratory [serum creatinine], grade 3 or 4) that does not improve to baseline or </= grade 2 within 1 month following DEB-TACE in ≥ 2 patients (1.2% of 51 patients).

OR

3. Any grade 5 AE (death) attributed as at least possibly-related to study intervention in ≥ 3 patients (4.8% of 51 patients).

The stopping rules above were used to generate the following chart, which will be adhered to with regards to stopping enrollment for the reasons of severe toxicity.

Table 4. Number of patients with defined safety/toxicity for the study to be stopped during sequential and continuous safety assessments (based on binomial distribution)

Number patients enrolled in study	3	7	11	13	17	23
Number of patients with grade 4 liver dysfunction, grade 4 renal dysfunction, or study-related death	2	4	6	7	8	9
% chance of stopping enrollment if true SAE rate is <15%	94%	99%	99%	99%	99%	99%
% chance of stopping enrollment if true SAE rate is <20%	90%	97%	99%	99%	99%	97%
% chance of stopping enrollment if true SAE rate is < 30%	78%	87%	92%	94%	90%	77%

Note: the study will also be terminated early if any of the 3 stopping rules is observed.

Adverse events grade ≥ 4 will be discussed by the interventional radiologist and medical oncologist and/or hepatologist within 1 business day of being informed of the event. If at any time a patient has a fatal complication at least possibly related to treatment, the study will immediately be put on hold. At that time, the data will be reviewed by a multidisciplinary team as to the etiology. If it is determined that the death was attributed as at least possibly-related to treatment, the study investigators will meet to discuss if the study should continue.

The patients will also be monitored for development or worsening of other recognized complications of DEB-TACE including ascites, hepatic encephalopathy, hepatorenal syndrome, biliary injury (stricture or leak), cholangitis, cholecystitis, hepatic abscess, abdominal pain, nausea, vomiting, fatigue, and fever. The study may be placed on hold or terminated based on development of these adverse events in study participants.

10.2 STOPPING RULES FOR EFFICACY

When 17 evaluable patients have been treated with at least one DEB-TACE procedure and had potential for at least 1 month of follow up, efficacy profile will be analyzed. Accrual will continue during this interim analysis period.

Stopping Rule for Efficacy after 17 patients have completed last planned DEB-TACE

1. If four (4) or fewer responses (complete, partial, or stable disease response according to mRECIST in treated lesion(s) approximately 1 month after last planned DEB-TACE) are observed among first stage of 17 patients.

During the interim efficacy analysis of 17 patients, if four or fewer complete, partial, or stable disease responses are observed in treated lesions by mRECIST on imaging approximately 1 month after last planned DEB-TACE during the first stage, the study will be stopped early; otherwise, additional 34 patients will be accrued. If fourteen or fewer responses are observed by the end of the study, then no further investigation is warranted for DEB-TACE.

Under the study design, if the response rate is <20%, the probability of ending the study during the first stage is 76%. If the response rate is >40%, the probability that the study will be stopped in the first stage is 13%.

10.3 CRITERIA FOR PATIENT REMOVAL FROM STUDY

Patients will be removed from study for any of the following events:

- Unacceptable toxicity (listed above in section 10.1),
- Other toxicity which investigator deems to place the patient at significant risk for toxicity
- Withdrawal of consent
- Noncompliance or inability to meet requirements of protocol
- Requirement for >4 DEB-TACE procedures
- Requirement for another anti-cancer treatment modality such as ablation, surgery, conventional TACE
- Receives a liver transplant
- Develops untreatable intrahepatic tumor progression
- Develops extrahepatic tumor progression

11.0 DEVICE INFORMATION

For further information, please refer to the product insert.

11.1 Classification

LC Bead™ is an FDA-approved permanent particulate embolic agent, which consists of a range of hydrogel microspheres that are biocompatible, hydrophilic, nonresorbable and precisely calibrated. Instructions for Use are included in Appendix 5 to the Protocol. LC Bead™ microspheres are intended to be used for the embolization of hypervascular tumors and Arteriovenous malformations. LC Bead™ microspheres carry negative ionic charge, while allows them to be ionically bound to positively-charged drug molecules, such as doxorubicin. LC Bead™ bound to doxorubicin is currently used for DEB-TACE in patients with HCC.

11.2 Mode of Action

Following injection of doxorubicin-impregnated LC Bead™ microspheres, doxorubicin is eluted from the beads over a period of 12 days. Microspheres also cause terminal tumor vessel occlusion leading to tumor hypoxia. By reducing tumor perfusion, microspheres prevent washout

of doxorubicin from the embolized tumor lesions, markedly limiting systemic concentration of doxorubicin.

11.3 Storage and Stability

Doxorubicin-loaded LC Bead™ may be stored up to 14 days at 2-8°C. After reconstitution with non-ionic contrast, doxorubicin-loaded LC Beads may be stored up to 7 days at 2-8°C.

11.4 Metabolism

Pharmacokinetic data for doxorubicin-eluting beads has already been acquired in animal models (Hong, 2006; Lewis, 2006) and in a human phase I study (Poon, 2007). Data from Hong (2006) show the pharmacokinetics of drug-eluting beads are compared with systemic or intra-arterial administration of doxorubicin in animal models and in clinical use.

11.5 Preparation

Loading instructions for 100-300μm LC Bead™ using powdered Doxorubicin 50mg vials are summarized in Appendix 6. LC Bead™ loading (steps 1-4) will be performed in a fume hood by a clinical pharmacist with experience with handling doxorubicin. Doxorubicin powder (Bedford Laboratories, Bedford, OH) will be used. National Drug Code number for the product, 50mg vials of doxorubicin powder, is 55390-233-01. Package insert for this product can be found in Appendix 7.

Step 1. Reconstitute each 50mg doxorubicin vial with 2ml of sterile water for injection. Mix well to obtain a clear red solution.

Step 2. Take flip cap off 2 100-300μm LC Bead™ vials, but do not remove metal around the bung. Remove as much saline as possible from LC Bead™ vials using a syringe and filter needle. Pierce bung with a second needle to eliminate vacuum. If a filter needle is not available, place flattened tip of needle against side of vial to prevent beads being drawn into the needle.

Step 3. Using a syringe and needle add 2 ml of doxorubicin solution directly to each vial of 100-300μm LC Bead™.

Step 4. Agitate the LC Bead™ with doxorubicin solution gently to encourage mixing and allow to stand for 60 minutes. Gently agitate the mixture occasionally during loading time.

Steps 5 and 6 will be performed by the treating interventional radiologist investigator immediately prior to and during administration of doxorubicin-loaded LC Bead™.

Step 5. Transfer the loaded beads into a 20 ml syringe using an 18-gauge needle. Expel excess liquid through an 18-gauge 5-micron filter needle.

Step 6. To prepare the loaded LC Bead™ for injection, add 10 ml of Omnipaque-350 contrast (Amersham Health, NJ) per 2 ml of LC Bead™ and mix gently using a 3ml syringe attached to the 20 ml syringe via a 3-way stop-cock. Administer suspended LC Bead™ at a rate of 1 ml per minute

11.6 Procedure

Doxorubicin-loaded LC Bead™ are administered via a co-axially placed commercially available hepatic artery catheter into hepatic arteries targeted for treatment. Procedure is performed under direct fluoroscopic visualization until near stasis of arterial flow is achieved or until a total of 4 ml of microspheres have been administered, whichever occurs first.

11.7 Incompatibilities/Contraindications

- Severe and untreatable hypersensitivity reaction to doxorubicin
- Angiographic evidence of a large hepatic artery to pulmonary vein shunt
- Angiographic evidence of a large hepatic artery to hepatic vein shunt
- Occlusion of the common hepatic duct
- Severe and refractory coagulopathy and/or thrombocytopenia
- Previous history of congestive heart failure
- Patients who are receiving P-glycoprotein inhibitors and CYP2D6 substrates that have a narrow therapeutic index for the potential risk of increased adverse events. However this risk of a drug interaction with systemically administered drugs might be low following intra-arterial bead-bound doxorubicin as compared to intravenous administration of doxorubicin.
- Because of possible hepatotoxic and nephrotoxic effect of TACE, concurrent use of hepatotoxic and nephrotoxic drugs will be avoided for a period of 2 weeks following each DEB-TACE session.

11.8 Side Effects

This section summarizes the reported complications and adverse events relating to LC Bead™ with doxorubicin used for the embolization of HCC. The literature search identified 41 articles containing safety data. A total 1584 patients have therefore been reviewed in papers reporting data on safety. (LC Bead™ 70-900μm).

All serious adverse events reported in these articles have been included in the table below. The overall incidence of events is calculated by taking the number of reports of each type of event and dividing by the total number of patients documented in this safety review.

Where articles specifically state the grade of event by CTCAE or other criteria, events stated to be of grade II or less have been excluded in this analysis; however the majority of reports do not state the grade of the event.

DEB-TACE has also been associated with development of liver toxicity including transaminitis, hyperbilirubinemia, synthetic hepatic dysfunction (hypoalbuminemia, coagulopathy), clinical

hepatic function decompensation (encephalopathy, ascites), gastrointestinal hemorrhage, and infections (cholangitis, liver abscess formation). DEB-TACE may lead to renal dysfunction related to development of contrast nephropathy and/or hepatorenal syndrome. DEB-TACE may cause postembolization syndrome, the symptoms of which may include pain, nausea, vomiting, fever, night sweats, fatigue, and anorexia.

Cumulative systemic levels of doxorubicin above 550mg/m^2 have been associated with left ventricular failure.

11.9 Availability

LC Bead™ is available in four ranges of microsphere size: 70-150 μm, (black and yellow label), 100-300μm (yellow label), 300-500μm (blue label), and 500-700 μm (red label). Drug loading with up to 75 mg of doxorubicin per 2 ml vial may be performed. Two 2 ml vials are injected during a single DEB-TACE procedure. For the purpose of this study, only 100-300μm (yellow label) LC beads will be used. Drug loading with up to 50mg of doxorubicin per 2 ml vial will be performed.

11.11 Accountability

LC Bead™ ordering and storage, doxorubicin hydrochloride ordering and storage, and microsphere loading with doxorubicin will be performed at the UCSF Inpatient Pharmacy according to LC Bead™ manufacturer-supplied loading and storage instructions.

12.0 STATISTICAL CONSIDERATIONS

12.1 Basis for Sample Size

This is an open label single arm phase II study. The primary objective is to assess the safety and to estimate the objective response rate using mRECIST in treated lesions to the DEB-TACE treatment. The response rate is assumed to be >40% in treated lesions using mRECIST on imaging approximately 1 month after last planned DEB-TACE treatment; the response rate of <20% would be unacceptable for the study treatment. If the response rate is less than a pre-specified minimum goal (i.e. 20%) then the study will be terminated due to inefficacy. Under binomial approximation with 5% type I error and 85% power, a total of 51 patients is required for the study; 17 patients will be accrued in the first stage and 34 patients will be accrued in the second stage.

12.2 Interim Analysis

After 17 patients have received at least one DEB-TACE and had potential for at least 4 weeks of follow up, the safety profile will be analyzed. The study will be terminated if one of the termination criteria based on unacceptable toxicity listed in section 10.0 has occurred. Final review of the safety will be performed within approximately three months after the treatment of the 17th patient. Stopping rules for lack of safety and efficacy after first stage are defined in Section 10.0. Accrual will continue during these interim analyses.

During the interim efficacy analysis of 17 patients, if four or fewer responses by mRECIST in treated lesions on imaging approximately 1 month after last planned DEB-TACE are observed during the first stage, the study will be stopped early; otherwise, additional 34 patients will be

accrued. If fourteen or fewer responses by mRECIST in treated lesions on imaging approximately 1 month after last planned DEB-TACE are observed by the end of the study, then no further investigation is warranted for the regimen.

Under the study design, if the response rate is <20%, the probability of ending the study during the first stage is 76%. If the response rate is >40%, the probability that the study will be stopped in the first stage is 13%.

12.3 Analysis Plan

Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics.

Safety Analysis

Patients will be monitored for development of recognized complications of DEB-TACE including liver dysfunction, renal dysfunction, ascites, hepatic encephalopathy, hepatorenal syndrome, biliary injury (stricture or leak), cholangitis, cholecystitis, hepatic abscess, abdominal pain, nausea, vomiting, fatigue, and fever. Adverse events will be graded according to NCI CTCAE version 4.03. Prevalence of adverse events will be summarized using descriptive statistics.

Efficacy Analyses

Analyses will be performed using the intent to treat population with exceptions as defined below, which require patient replacement.

Primary efficacy analysis

Primary efficacy will be evaluated as 1-month radiographic response after last DEB-TACE procedure in treated HCC lesions according to 1) RECIST version 1.1 and 2) mRECIST. Patients who do not have any post-baseline tumor assessments will be counted as non-responders. Point estimates of response rate and confidence intervals will be provided.

Secondary efficacy analyses

1. Overall radiographic response by 1) RECIST 1.1 and 2) mRECIST 6 months after the date of the first planned DEB-TACE procedure. This analysis will take into account all measurable hepatic HCC lesions present on cross-sectional imaging 6 months after the date of the first planned DEB-TACE procedure.

2. Time to untreatable progression (TTUP). TTUP is defined as time to disease progression untreatable by liver-directed percutaneous or surgical methods as assessed by treating investigator(s). Patient follow-up up to 1 year after last DEB-TACE will be allowed for this outcome variable.

3. Time to progression (TTP). TTP is defined as the time interval between date of first DEB-TACE procedure and date of imaging documenting development of intra- or extrahepatic disease progression by 1) RECIST 1.1 and 2) mRECIST. Patient follow-up up to 1 year after last DEB-TACE will be allowed for this outcome variable.

4. Hepatic progression-free survival (HPFS). Hepatic progression-free survival rate will be defined as the number of patients who neither progressed in the treated regions of the liver (using RECIST 1.1 and mRECIST) nor died before 1, 3, 6, 9, and 12 months after date of last DEB-TACE over the number of patients who entered the trial at these same timepoints. Estimates of the HPFS curves from the Kaplan-Meier method will be presented. Median progression event time and a 2-sided 95% confidence interval for the median will be provided using a normal approximation. For each stratum, the median, 25^{th} and 75^{th} percentile for HPFS will be provided.

5. Progression-free survival (PFS). Progression-free survival rate will be defined as the number of patients who neither progressed (using RECIST 1.1 and mRECIST) nor died before 1, 3, 6, 9, and 12 months after date of last DEB-TACE over the number of patients who entered the trial at these same timepoints. Estimates of the PFS curves from the Kaplan-Meier method will be presented. Median progression event time and a 2-sided 95% confidence interval for the median will be provided using a normal approximation. For each stratum, the median, 25^{th} and 75^{th} percentile for PFS will be provided.

6. Overall Survival (OS) is a secondary efficacy endpoint and will be analyzed 12 months after the last patient is enrolled. OS will be calculated from date of first DEB-TACE until date of death, using chart review and/or follow up phone calls to determine date of death in patients after removal from study. The survival of patients who are permanently lost to follow-up or still alive after 360 days of follow up post study discontinuation will be censored on the date the patient is last-contacted or last known to be alive. Estimates of the OS curves from the Kaplan-Meier method will be presented.

7. Proportion of patients who remain active on the waitlist and are eventually transplanted is a secondary clinical endpoint. This data will be presented using Kaplan-Meier method

8. Proportion of patients who are inactivated or drop out from the wait list for any reason but transplantation will be determined. Reasons for inactivation and/or removal from waitlist will be tabulated.

9. Proportions of patients who are successfully down-staged and achiev active waitlist status and eventually are transplanted will be determined.

10. Biochemical response defined as $\geq$ 50% decrease in alpha-fetoprotein level measured 1 month and 4 months after DEB-TACE.

11. Histopathologic response defined as percentage of tumor necrosis at liver explant histopathology. This will only be explored in the subgroup of patients who undergo a liver transplant. Per UCSF clinical standard, tumor necrosis for HCC lesions is reported as 100%, >90%, 60-90%, 30-59%, and < 30%.

<u>Intention To Treat Exceptions (Patient replacement)</u>

1. Patients who proceed to liver transplant or develop hepatic decompensation between the time of enrollment and the first DEB-TACE treatment will be replaced.

2. Patients who proceed to liver transplant prior to completion of the 1 month safety window after first DEB-TACE will be replaced unless the transplant occurred due to hepatic decompensation or other toxicity attributed as at least possibly-related to protocol therapy, in which case the hepatic decompensation or other toxicity will be deemed a serious adverse event and the patient will be included in safety analysis (see Section 14.1.3).

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

13.2 Protocol Review/Changes

13.2.1 Protocol Review Committee

This study will be reviewed by the UCSF Comprehensive Cancer Center Protocol Review Committee (PRC) for scientific merit and feasibility. After initial review and approval, the study will be reviewed at least once a year for scientific merit. Any changes to the protocol are to be reviewed and approved by the PRC.

13.2.2 Institutional Review Board / Independent Ethics Committee

The study will be reviewed by the Committee on Human Research (CHR), UCSF's IRB. After initial review and approval, the study will be reviewed at least once a year as per FDA regulations (21 CFR 56.109). Any changes to the protocol and consent form are to be reviewed and approved by the CHR.

Changes are to be approved prior to being implemented, unless subject safety necessitates an immediate change, in which case approval may be given afterwards.

It is the responsibility of the Principal Investigator to keep the CHR informed of the progress of the study, including changes to the protocol or consent form, exceptions or deviations from the protocol, and any new developments which may affect subject safety or willingness to participate.

13.3 Investigational Device Exemption (IDE)

While LC Bead™ is an FDA-approved device, LC Bead™ loading with doxorubicin is not an FDA-approved application of the device. Therefore, an Investigational Device Exemption (IDE) application will be filed with the FDA.

The clinical investigation will not begin until the FDA has determined that the study under the Investigational Device Exemption (IDE) is allowed to proceed and the Investigator has received a letter from FDA stating that the study is fulfills the IDE application requirements.

13.4 Data Safety Monitoring

All subjects will be followed closely in clinic post-procedure by a medical oncologist and/or hepatologist, and interventional radiologist for signs of potential complications from the procedure. Patients will be discussed bi-weekly at the gastrointestinal oncology site committee meeting for the first month following each DEB-TACE. After the first month following the last DEB-TACE treatment, patient's progress will be monitored at 3 month intervals for a year.

The sponsor-investigator shall immediately conduct an evaluation of any unanticipated adverse device effect [21 CFR 812.46(b)].

13.5 CCC Data Safety Monitoring Committee

13.5.1 Oversight and Monitoring Plan

The UCSF-CCC Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

13.5.2 Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at weekly study group or site committee meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include the number of patients, significant toxicities as described in the protocol, dose adjustments, and observed responses. Quarterly summaries will be submitted to the DSMC for review. All grade 3-5 AEs and SAEs will be entered in the OnCore® database.

All institutional Phase 2 or 3 studies are designated with a moderate risk assessment. The data is monitored twice per year with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

13.5.3 Review and Oversight Requirements

<u>Adverse Event Reporting</u>

Adverse Events (AEs) will be recorded on the OnCore® database; all grade 3-5 expected and unexpected AEs will be recorded and updated at each visit.

Unanticipated/Serious Adverse Event Reporting

Unanticipated/Serious Adverse Event reporting will be in accordance with the UCSF-Committee on Human Research Regulations and Code of Federal Regulation Title 21 Volume 8 Part 812.150. See also section 14.4.

Per IDE regulations (21 CFR 812.150(a) (1) and 21 CFR 812.150(b) (1)), unanticipated adverse device effects will be reported to the FDA within 10 working days of first learning of the event.

UCSF CHR website for guidance in reporting serious adverse events
http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.pdf

If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or his designee within 24 business hours. The reporting procedure is by personal communication via phone or in person with written documentation of the one-on-one communication via e-mail with a copy of the e-mail to DSMC Administrator and DSMC Analyst.

Review of Adverse Event Rates

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of DEB-TACE, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to theprocedure. All grade(s) 3-5 adverse events will be followed-up until SAE has been resolved.

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last procedure and it is determined to be related either to DEB-TACE or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair within 1 business day of knowledge of this event. The contact may be by phone or e-mail. All patient deaths (anticipated or unanticipated) will also be reported to the FDA as they occur.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Study Progress – Quarterly Review

Principal Investigators are required to submit quarterly study progress reports regarding the trial to the DSMC. These reports must include an update on accrual, information about any new amendments or updated consents and a summary of grade 3 and 4 toxicities (expected and unexpected) and all internal SAE reports. At the time of the quarterly report, all external DSMB reports and/or external formal audit reports that were received during the reporting quarter are to be sent to the committee.

These quarterly reports are reviewed at Data Safety Monitoring Committee meetings. These reports are required: February 1, May 1, August 1, and October 1. Failure to submit such reports may result in trial suspension.

Data Safety Monitoring Committee Contacts:

DSMC Chair:	Alan Venook, MD	DSMC Monitors
Phone:	415-353-2745	Box 1297
Email:	venook@cc.ucsf.edu	UCSF Helen Diller Family
Address:	Box 1705	Comprehensive Cancer Center
	UCSF	San Francisco, CA 94115
	San Francisco, CA 94115	

14.0 ADVERSE EVENT REPORTING

14.1 Adverse Event Definitions

14.1.1 Adverse Events

Any unfavorable or unintended sign, symptom, or illness that develops or worsens during the course of the study (treatment and follow-up) regardless of causality. This includes abnormal clinical or laboratory findings.

14.1.2 Unanticipated Adverse Events

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

Please note: The CHR (UCSF IRB) uses the term 'Unexpected' Adverse Events, which includes unanticipated events that are not necessarily serious or life-threatening.

14.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that results in any of the following outcomes regardless of dose:

- Death
- Life-threatening (places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), including hepatic decompensation requiring hospitalization or expedited liver transplantation
- Inpatient hospitalization or prolongs existing hospitalization,
- Persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions),
- Birth defect/congenital anomaly,
- Any important medical event that may not result in prior listed outcomes but, based upon appropriate medical judgment, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the prior listed outcomes.

An adverse event is not considered serious if it does not satisfy at least one of these criteria.

14.1.4 Laboratory Adverse Events

Laboratory test value abnormalities are recorded as adverse events (AE) if they are designated as clinically relevant (defined as any abnormality which requires treatment, causes symptoms, places the patient at risk for morbidity, and/or causes premature withdrawal from study) and represent a change of ≥ 1 grade from baseline. Laboratory abnormalities will not be considered clinically-relevant adverse events if they do not satisfy at least one of these criteria.

14.2 Adverse Event Grading

All AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Severity of AEs will be graded using the following general definitions of the CTCAE v4.03 :

- Grade 1 – Mild (no limitations)
- Grade 2 – Moderate (some limitations)
- Grade 3 – Severe (requires medical attention; usual activities stop)
- Grade 4 – Life-threatening/disabling (requires immediate medical help)
- Grade 5 - Death

Causality of AEs will be graded by the treating investigator with review by the Study Chair as follows:

- Unrelated
- Unlikely related
- Possibly related
- Probably related

- Definitely related

14.3 Adverse Event Reporting Period

Reportable AEs are those that occur after treatment begins and up to 1 month after the last DEB-TACE treatment.

Unresolved AEs (Reportable AEs that extend past the 1 month post-treatment period) should continue to be reported on if the condition worsens or results in death.

AEs that occur after the reporting period (first treatment to 1 month post-treatment) are not normally reported unless they are serious AND the investigator or treating physician has reason to believe the event(s) might be related to study participation.

AE reporting will discontinue at time of transplant.

AE reporting will discontinue if patients are taken off study to receive more than four DEB-TACE treatments.

14.4 Reporting Procedures

Serious AEs and Unexpected AEs are to be reported to the CHR within 10 working days after first becoming aware of the event.

Adverse events that are *unanticipated* (see definition above) will be reported in writing to the CHR and FDA as soon as possible but no later than 10 working days after first becoming aware of the event [21 CFR 812.150(a) (1) and 21 CFR 812.50(b) (1)]. A copy of the CHR report should be forwarded to the manufacturer of the device at the address below:

Biocompatibles UK Limited
Chapman House
Farnham Business Park
Weydon Lane
Farnham, Surrey
GU9 8QL UK
Tel No: +44 (0)1252 732 732
Fax No: +44 (0)1252 732 777

A copy of the CHR forms must be sent to the CCC DSMC at Box 1297. If the AE is a death attributed as at least possibly-related to study drug or treatment during the treatment phase of the study or within 30 days after the last DEB-TACE procedure, it must be reported to the CCC DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event (*see section 13.4*). The contact may be by phone or e-mail. The date the safety report was sent to all required reporting agencies will documented on the OnCore® database, and hard copies of the report will be maintain in the regulatory files.

15.0 Protection of Human Subjects

15.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

15.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

16.0 FINANCIAL CONSIDERATIONS

The costs of treatment will be charged to the subject and/or their insurance company.

16.0 REFERENCES

1. Mazzaferro V, Regalla E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:696-99.
2. Bruix J, Sherman M: Management of hepatocellular carcinoma: an update. Hepatology 2011, 53(3):1020-1022.
3. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. In: Lancet. vol. 359; 2002: 1734-1739.
4. Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxì A, Cottone M: Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. In: Radiology. vol. 224; 2002: 47-54.
5. [No authors listed] A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. In: N Engl J Med. vol. 332; 1995: 1256-1261.
6. Vivanco M, Gabrielli M, Jarufe N, Humeres R, Rios H, Palacios J, Zapata R, Sanhueza E, Contreras J, Rencore G et al: Bridge therapy in hepatocellular carcinoma before liver transplantation: the experience of two Chilean centers. In: Transplant Proc. vol. 42; 2010: 296-298
7. Yao FY, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008; 48:819-827
8. Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. Am J Transplant 2008; 8:1982-1989.
9. Brown D, Fundakowski C, Lisker-Melman M, Crippin J, Pilgram T, Chapman W, Darcy M: Comparison of MELD and Child-Pugh scores to predict survival after chemoembolization for hepatocellular carcinoma. In: J Vasc Interv Radiol. vol. 15; 2004: 1209-1218.
10. Wible BC, Rilling WS, Drescher P, Hieb RA, Saeian K, Frangakis C, Chen Y, Eastwood D, Kim HS: Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. Journal of vascular and interventional radiology : JVIR 2010, 21(7):1024-1030.
11. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, Tibballs J, Meyer T, Patch D, Burroughs A: Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. In: Cardiovasc Intervent Radiol. vol. 30; 2007: 6-25.
12. Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, and Fan ST. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007; 5(9):1100-1108.
13. Varela M, Real MI, Burrel M, Forner A, Sala M, Bruent M, Ayuso C, Castells L, Montana X, Llovet JM and Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46(3):474-481.
14. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S et al: Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovascular and interventional radiology 2010, 33(1):41-52.

15. Chan AO, Yuen M-F, Hui C-K, Tso W-K, Lai C-L: A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. In: Cancer. vol. 94; 2002: 1747-1752.
16. Luo J, Guo R, Lai E, Zhang Y, Lau W, Chen M, Shi M: Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. In: Ann Surg Oncol. vol. 18; 2011: 413-420.
17. Georgiades CS, Hong K, D'Angelo M, Geschwind J-FH: Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. In: J Vasc Interv Radiol. vol. 16; 2005: 1653-1659.
18. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY: The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. Cancer 1997, 79(11):2087-2094.
19. Yoo D, Kim K, Jin Y, Shim J, Ko G, Yoon H, Sung K, Lee J, Kang Y, Lim Y et al: Clinical outcome of 251 patients with extrahepatic metastasis at initial diagnosis of hepatocellular carcinoma: does transarterial chemoembolization improve survival in these patients? In: J Gastroenterol Hepatol. vol. 26; 2011: 145-154.
20. Kiely JM, Rilling WS, Touzios JG, Hieb RA, Franco J, Saeian K, Quebbeman EJ, Pitt HA: Chemoembolization in patients at high risk: results and complications. J Vasc Interv Radiol 2006, 17(1):47-53.
21. Kothary N, Weintraub JL, Susman J, Rundback JH: Transarterial chemoembolization for primary hepatocellular carcinoma in patients at high risk. J Vasc Interv Radiol 2007, 18(12):1517-1526; quiz 1527.
22. Yoon H, Kim J, Kim K, Lee I, Ko G, Song H, Gwon D: Transcatheter arterial chemo-lipiodol infusion for unresectable hepatocellular carcinoma in 96 high-risk patients. In: Clin Radiol. vol. 65; 2010: 271-277.
23. Russell J, Sawhney R, Monto A, Nanavati S, Davoren J, Aslam R, Corvera C: Periprocedural complications by Child-Pugh class in patients undergoing transcatheter arterial embolization or chemoembolization to treat unresectable hepatocellular carcinoma at a VA medical center. In: Am J Surg. vol. 200; 2010: 659-664
24. Garwood E, Fidelman N, Hoch SE, Kerlan RK. Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and hepatic dysfunction. Liver Transplantation 2013; 19:164-173.
25. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Seminars in Liver Disease 2010; 30:52-60.
26. Bojanovic 2009. "[Precision TACE in therapy of primary malignant tumors of liver/hepatocellular carcinoma (HCC)]." Acta Chir Iugosl 56(4): 143-148.
27. Campo 2010. "Transarterial chemoembolization of unresectable heptocellular carcinoma (HCC) with drug eluting beads (DEB-TACE)." J Hepatology 52(Supplement 1): S90.
28. Chamsuddin. (2008). "Precision TACE in the treatment of unresectable hepatocellular carcinoma." SIR, e-Poster 342.
29. de Pauli 2007. "Doxorubicin eluting bead (DEB) transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC)." Annals of Oncology 18(11): A26.
30. Dhanasekaran 2010. "Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC)." J Surg Oncol 101(6): 476-480.

31. Ehrenwald 2009. "Transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC) using doxorubicin eluting microspheres (DEB): initial results." Hepato-Pancreato-Biliary Association 11(Suppl 1): 1-104.
32. Garcia-Hildago 2010. "Quimoembolizacion de hepatocarcinoma mediante TACE-precision: resultados al 2 ano en un hospital general." Radiologia in press.
33. Goffette. (2009). "Treatment of hepatocellular carcinoma (HCC) with drug eluting beads before liver transplantation:imaging and histology results." CIRSE.
34. Gomes. (2010). "Transcatheter arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma using doxorubicin loaded LC Beads." SIR, Abstract 136.
35. Jamil 2011. "Single centre experience of use of transarterial chemembolization (TACE) with doxorubicin eluting beads (DEB) for the treatment of hepatocellular carcinoma (HCC)." Gut 60(S1): A236.
36. Kalva 2011. "Transarterial chemoembolization with doxorubicin-eluting microspheres for inoperable hepatocellular carcinoma." Gastrointestinal Cancer Research 4: 2-8.
37. Kettenbach 2008. "Drug-loaded microspheres for the treatment of liver cancer: review of current results." Cardiovasc Intervent Radiol 31(3): 468-476.
38. Kouame 2011. "Transarterial chemoembolisation of hepatocellular carinoma with doxorubicin eluting beads." J Med Imaging and Radiation Sciences 42(1): 21-31.
39. Lesevic 2010. "Severe complication after a doxorubicin-eluting bead embolization: Surgical management and pathological findings." Cardiovascular and Interventional Radiology.
40. Malagari 2010. "Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma." Cardiovasc Intervent Radiol 33(3): 541-551.
41. Martin. (2010). "Optimal technique of doxorubicin DC Bead in hepatocellular cancer: small bead vs large bead, one vial vs two vials, complete stasis vs partial stasis." CIRSE.
42. Nawawi 2010. "Transarterial embolisation of hepatocellular carcinoma with doxorubicin-eluting beads: single centre early experience." Biomedical imaging and intervention journal 6(1): e7.
43. Poon 2007. "A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead." Clin Gastroenterol Hepatol 5(9): 1100-1108.
44. Rebonato. (2009). "TACE of unresectable HCC with doxorubicin pre-loaded DC Beads: results of 6 month of follow-up." CIRSE.
45. Reyes 2009. "Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States." Cancer J 15(6): 526-532.
46. Ritter 2011. "Spontaneous liver rupture after treatment with drug-eluting beads." Cardiovascular and Interventional Radiology.
47. Sellers 2009. "Precision trans-arterial chemotherapy with doxorubicin-eluting beads (ptace) for hepatocellular carsinoma (hcc) in cirrhotics." Hepato-Pancreato-Biliary Association 11(Suppl 1): 1-104.
48. Slanic. (2008). "Precision TACE: Improved possibilities in fighting liver cancer." WCIO & Best of ASCO
49. Sousa 2011. "Transcatheterarterial chemoembolization with doxorubicin eluting beads in the treatment of hepatocellular carcinoma." Acta Medica Portuguesa 24: 029-036.
50. Tokh. (2010). "Transarterial chemoembolization (TACE) with drug-eluting beads (DEB) in hepatocellular carcinoma (HCC): A large single-institution experience. ." ASCO.

51. Varela 2007. "Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics." J Hepatol 46(3): 474-481.
52. Zach 2010. "Multiple ischaemic strokes after transcatheter arterial chemoembolization for Hepatocellular carcinoma with a radiographic and pathological correlate." Journal of Stroke and Cerobrovascular Disease.
53. Hong K, et al. New intra-arterial drug delivery system for the treatment of liver cancer: Preclinical assessment in a rabbit model of liver cancer. Clinical Cancer Research 2006; 12(8):2563.
54. Lewis A, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006; 17(8):1335.
55. Eyol et al. Chemoembolisation of rat colorectal liver metastases with drug-eluting beads loaded with irinotecan or doxorubicin. Clin Exp Metastasis 2006; 25(3):273-82.
56. Doxorubicin eluting beads –1: Effects of drug loading on bead characteristics and drug distribution. J Mater Sci: Mater Med DOI 10.1007/s10856-007-3068-8.
57. Doxorubicin eluting beads –2: Methods for evaluating drug elution and in vitro: in vivo correlation. J Mater Sci: Mater Med DOI 10.1007/s10856-006-0040-y.
58. Varela M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46:474-481.
59. Poon R, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. J Clin Gastroenterol and Hepatol 2007; 5:1100-1108.
60. Erttmann R, et al. Pharmacokinetics of doxorubicin in man: dose and schedule dependence. J Cancer Res Clin Oncol 1988; 114:509-513.
61. Lee YT, et al. Distribution of Adriamycin in cancer patients: tissue uptakes, plasma concentration after IV and hepatic IA administration. Cancer 1980; 45:2231-2239.
62. Johnson, et al. Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of lipiodol. J Hepatol 1991; 13:120-127.

Appendix 1 ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	*Descriptions*
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix 2 Child-Pugh Score

http://homepage.mac.com/sholland/contrivances/childpugh.html
Below is an example of a calculated score:

Naperville Gastroenterology

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Child-Pugh Score Calculator

Bilirubin: ◉<2 mg/dl (34 umol/l) ○2-3 mg/dl (34-50 umol/l) ○>3 mg/dl (50 umol/l)
Albumin: ◉>3.5 g/dl ○3.5-2.8 ○<2.8
PT prolongation (INR): ◉<4 seconds (<1.7)
○4-6 seconds (1.7-2.3)
○>6 seconds (>2.3)
Ascites: ◉Absent ○Mild-Moderate ○Severe/Refractory
Encephalopathy: ◉Absent ○Mild (I-II) ○Severe (III-IV)

Child-Pugh Score: 5

Interpretation:
Class A: 5-6
Class B: 7-9
Class C: 10-15

Appendix 3 MELD Score

http://www.mayoclinic.org/meld/mayomodel6.html

The MELD Model, UNOS Modification

In the following model, survival probability of a patient with end-stage liver disease is estimated based on the following variables. Please enter data in the corresponding boxes.

What is the INR?	
What is the bilirubin?	(mg/dl)
What is the creatinine?	(mg/dl)
Has the patient had dialysis at least twice in the past week?	No Yes

MELD score:

Appendix 4 Modified RECIST

Table 2 Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = 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 treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Appendix 5. DC Bead® Drug Delivery Embolization System Instructions for Use

DC Bead® | English Doxorubicin

INSTRUCTIONS FOR USE

DC Bead®
Drug Delivery Embolisation System

STERILE • SINGLE USE ONLY • NON-PYROGENIC

DESCRIPTION:
DC Bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable, precisely calibrated and capable of loading doxorubicin. DC Bead is produced from polyvinyl alcohol and are available in the following size ranges:

Nominal Bead Size	Label Colour	
100 – 300 µm	Yellow	***Upon loading with doxorubicin, DC Bead undergo a slight decrease in size, up to 20% when loading at 25mg/ml.***
300 – 500 µm	Blue	
500 – 700 µm	Red	
700 – 900 µm	Green	

PRESENTATION:
- 10 ml glass vial.
- Each vial contains approximately 2 ml of DC Bead in non-pyrogenic, sterile, physiological buffered saline. Total volume of saline and DC Bead is approximately 8ml.
- The vial is stopper sealed by an aluminium cap equipped with a colour-coded lid.
- Each vial is intended for single patient use only. Do not resterilise. Discard any unused material.

INDICATIONS:
DC Bead are intended to be loaded with doxorubicin for the purpose of:
- Embolisation of vessels supplying malignant hypervascularised tumour(s).
- Delivery of a local, controlled, sustained dose of doxorubicin to the tumour(s).

CONTRAINDICATIONS – DC BEAD:
- Patients intolerant to vascular occlusion procedures.
- Vascular anatomy that precludes catheter placement or emboli injection.
- Presence or likely onset of vasospasm.
- Presence or likely onset of haemorrhage.
- Presence of severe atheromatous disease.
- Presence of feeding arteries smaller than distal branches from which they emerge.
- Presence of patent extra-to-intracranial anastomoses or shunts.
- Presence of collateral vessel pathways potentially endangering normal territories during embolisation.
- Presence of end arteries leading directly to cranial nerves.
- Presence of arteries supplying the lesion not large enough to accept DC Bead.
- Vascular resistance peripheral to the feeding arteries precluding passage of DC Bead into the lesion.
- Do not use DC Bead in the following applications:
  i. Embolisation of non-malignant tumours.
  ii. Embolisation of large diameter arteriovenous shunts (ie. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
  iii. Any vasculature where DC Bead Embolic Agent could pass directly into the internal carotid artery or other non-target territories.

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CONTRAINDICATIONS – DOXORUBICIN:

- See doxorubicin package insert for contraindications regarding use.

WARNING: Studies have shown that DC Bead do not form aggregates and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles.

CAUTIONS:

- Do not use if the vial or packaging appear damaged.
- Select the size and quantity of DC Bead appropriate for the pathology to be treated.
- Embolisation with DC Bead should only be performed by a physician with appropriate interventional occlusion training in the region intended to be embolised.
- **Exceeding a loading dose of 37.5mg doxorubicin per 1ml DC Bead may lead to some systemic distribution of doxorubicin and related side effects.**

POTENTIAL COMPLICATIONS:

- Undesirable reflux or passage of DC Bead into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolisation.
- Pulmonary embolisation.
- Ischaemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischaemic stroke or ischaemic infarction.
- Vessel or lesion rupture and haemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Death.
- Recanalisation.
- Foreign body reactions necessitating medical intervention.
- Infection necessitating medical intervention.
- Clot formation at the tip of the catheter and subsequent dislodgement.

DRUG LOADING INSTRUCTIONS:

DC Bead is suitable for loading doxorubicin-HCl ONLY. Liposomal formulations of doxorubicin are not suitable for loading into DC Bead.

To obtain a final loading of 50mg doxorubicin per 2ml vial of DC Bead:

i. Reconstitute a vial containing 50mg of doxorubicin with 2ml of sterile water for injection. Mix well to obtain a clear red solution (25mg/ml).
ii. Remove as much saline as possible from a vial of DC Bead using a syringe with a small gauge needle.
iii. Using a syringe and needle add the 2ml of reconstituted doxorubicin solution directly to the vial of DC Bead.
iv. Agitate the DC Bead/doxorubicin solution occasionally to encourage mixing until the DC Bead is red. Although the solution retains a red colour, the doxorubicin will be loaded.
v. Loading will take a minimum of 20 minutes for the smallest size DC Bead and up to 120 minutes for the largest size DC Bead.
vi. Prior to use, transfer the DC Bead loaded with doxorubicin to a syringe and add an equal volume of non-ionic contrast media. Invert the syringe gently to obtain an even suspension of DC Bead.
vii. A dose of up to 37.5mg doxorubicin per ml DC Bead can be loaded.
viii. The maximum recommended total dose of doxorubicin per procedure is 150mg.

STORAGE OF DRUG LOADED DC BEAD:

i. DC Bead loaded with doxorubicin may be stored for up to 24 hours in a fridge at 2-8°C in the presence or absence of non-ionic contrast media.

DELIVERY INSTRUCTIONS:

- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolisation procedure.
- DC Bead are available in a range of sizes. Care should be taken to choose the appropriate size of DC Bead that best matches the pathology (ie. vascular target/vessel size) and provides the desired clinical outcome.
- Choose a delivery catheter based on the size of the target vessel. DC Bead can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.
- Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.
- DC Bead are not radio-opaque. It is recommended to monitor the embolisation under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid.
  i. Take care to ensure proper suspension of the DC Bead in the contrast medium to enhance distribution during injection.
  ii. Draw the DC Bead into a syringe needle of a size greater than or equal to 19 gauge (1.07 mm).
  iii. Slowly inject DC Bead into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolisation endpoint.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge DC Bead still within the catheter lumen.
- Discard any unused DC Bead loaded with doxorubicin.

CONSERVATION AND STORAGE:

- Store unopened DC Bead in a cool, dry and dark place in its original packaging.
- Use by the date indicated on the vial label.
- Do not freeze.

PACKAGE LABEL:

REF Catalogue number	STERILE Steam Sterilised	Protect from moisture
LOT Batch number/Lot number	Use before/Expiry	Attention see instructions for use
Do not reuse	Protect from light	0°C Do not freeze

Appendix 6. Loading of LC Bead™ using doxorubicin powder 50mg vials

Loading of DC Bead® *using* Doxorubicin Powder 50mg *in vial*

Loading and preparation of DC Bead® must be carried out using strict aseptic technique under controlled conditions.

After loading, the solution in the vial will retain some red colouration as shown. This is to be expected and is not an indication that the DC Bead® has failed to load.

To give required dose of doxorubicin	Number of vials doxorubicin powder (50mg)	Number of vials of DC Bead®
75mg	2	1
100mg	2	2
150mg	3	2

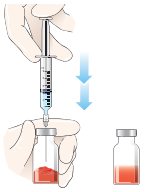
Loading time for up to 37.5mg of doxorubicin per ml of DC Bead® (75mg per vial)

Doxorubicin Uptake	100-300µm	300-500µm	500-700µm
90%*	30 minutes	45 minutes	60 minutes
98%*	60 minutes	90 minutes	120 minutes

* Tolerance of ±3%

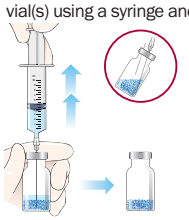
Step 1 (POWDER)

Reconstitute each 50mg doxorubicin vial with 2ml of sterile water for injection (NOT sodium chloride). Mix well to obtain a clear red solution.



Step 2 (POWDER)

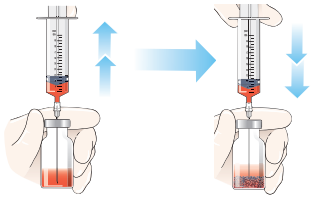
Take flip cap off DC Bead® vial(s) but do not remove metal around the bung. Remove as much saline as possible from DC Bead® vial(s) using a syringe and filter needle.



Pierce bung with a second needle to eliminate vacuum. If a filter needle is not available, place flattened tip of needle against side of vial to prevent beads being drawn into the needle.

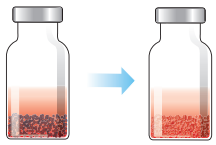
Step 3 (POWDER)

Using a syringe and needle add the required dose of doxorubicin solution directly to the vial(s) of DC Bead®



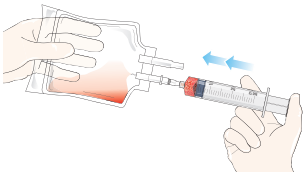
Step 4 (POWDER)

Agitate the DC Bead® with doxorubicin solution gently to encourage mixing and allow to stand for required loading time. Gently agitate the mixture occasionally during loading time.



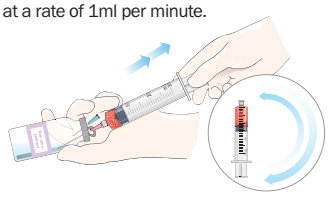
Step 5 (POWDER)

When loading time is complete, transfer the loaded beads into a 20-30ml syringe using an 18-gauge needle or equivalent. Expel excess liquid (a 5-micron needle can help with this process).



Step 6 (POWDER)

To prepare the loaded DC Bead® for injection, add 5-10ml of non-ionic contrast medium per ml of DC Bead® and mix gently to give a good suspension. Inject solution at a rate of 1ml per minute.



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DC Bead®

Physical and chemical stability DC Bead® 100-700µm	
Doxorubicin-loaded DC Bead® (75mg/2ml)	14 days (at 2-8°C)
Doxorubicin-loaded DC Bead® with non-ionic contrast	7 days (at 2-8°C)

DC Bead® Ordering Information

Nominal Bead Size	Volume of Beads	Product Code
100-300µm	2ml	DC2V103
300-500µm	2ml	DC2V305
500-700µm	2ml	DC2V507

DC Bead®: Important information

DC Bead® Indications:
- DC Bead is CE marked and is indicated for the treatment of malignant hypervascular tumours and loading with doxorubicin drug
- DC Bead is also indicated for loading with irinotecan for the treatment of metastatic colorectal cancer (mCRC).

Both indications may not be available in your territory

DC Bead® Cautions:
- Embolisation with DC Bead should only be performed by a physician with appropriate interventional occlusion training in the region intended to be embolised
- Exceeding a loading dose of 37.5mg doxorubicin per 1ml DC Bead may lead to some systemic distribution of doxorubicin and related side effects
- Exceeding a loading dose of 50mg irinotecan per 1ml DC Bead may lead to some systemic distribution of irinotecan and related side effects
- On addition of contrast/water mixture to loaded beads some irinotecan will be eluted. On delivery a bolus of between 10-20mg irinotecan may be delivered
- Do not use irinotecan loaded beads with contrast agents containing salts (eg. Calcium chloride)

DC Bead® Potential Complications:
1. Undesirable reflux or passage of DC Bead into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds
2. Non-target embolisation
3. Pulmonary embolisation
4. Ischemia at an undesirable location
5. Capillary bed saturation and tissue damage
6. Ischemic stroke or ischemic infarction
7. Vessel or lesion rupture and haemorrhage
8. Neurological deficits including cranial nerve palsies
9. Vasospasm
10. Death
11. Recanalisation
12. Foreign body reactions necessitating medical intervention
13. Infection necessitating medical intervention
14. Clot formation at the tip of the catheter and subsequent dislodgement causing arterial thromboembolic sequelae

For instructions for use, please refer to www.biocompatibles.com/dcbead-ifu

DC Bead® is not currently cleared by the FDA for sale or distribution in the USA.

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