SOLACE: A Study of ONCO-DOX in Locally Advanced Hepatocellular Carcinoma

A Randomized Controlled Trial of Transcatheter Arterial Chemoembolization with Drug-Eluting Beads (DEB-TACE) Versus Sorafenib in the Treatment of Unresectable, Locally-Advanced Hepatocellular Carcinoma

Investigational Device: **ONCOZENE™ Microspheres**

Protocol No.: ONCO 2013-02
Protocol Date: 15 May 2015

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Protocol Signature Page and Statement of Compliance

The signatures below constitute the approval of this protocol, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

The clinical trial entitled A Randomized Controlled Trial of Transcatheter Arterial Chemoembolization with Drug-Eluting Beads (DEB-TACE) Versus Sorafenib in the Treatment of Unresectable, Locally-Advanced Hepatocellular Carcinoma will be conducted in compliance with the clinical protocol, Food and Drug Administration regulations 21 CFR 50, 54, 56, 812, 45 CFR Part 46, the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and other applicable regulatory requirements.

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Study Synopsis

Protocol Number	ONCO 2013-02
Study Title	A Randomized Controlled Trial of Transcatheter Arterial Chemoembolization with Drug-Eluting Beads (DEB-TACE) (ONCO-DOX) Versus Sorafenib in the Treatment of Unresectable, Locally-Advanced Hepatocellular Carcinoma
Device(s) / Treatment	**Investigational Device:** ONCOZENE™ Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with Polyzene®-F, an inorganic polymer. They are available in a range of sizes (40, 75, and 100 µm) and are opaque in color in 2 ml and 3 ml sized syringes. For this study, the intended use of the investigational treatment is DEB-TACE. The size of ONCOZENE™ Microspheres used will be at the discretion of the treating physician(s) based on the tumor size and/or vascular structure. – Doxorubicin: The dose of doxorubicin will be up to 150 mg per treatment. **Control:** The Control treatment is sorafenib, administered orally at the standard dose of 400 mg bid
Study Design	This is a prospective, multicenter, two-arm, randomized (1:1), open label, controlled, Phase III study that will be conducted at up to 40 centers in the United States and Outside United States (OUS). Patients will be stratified by: • ECOG Performance Status (0 versus 1) • Portal vein invasion • AFP (≥400 and <400) Patients will be randomized at each site within each stratum to achieve balance among factors that may have an impact on the outcome.
Study Objective	The main objective of this study is to evaluate the safety and efficacy of ONCOZENE™ Microspheres loaded with Doxorubicin (ONCO-DOX) in comparison with orally administered sorafenib in patients with unresectable, locally-advanced hepatocellular carcinoma (HCC)
Primary Study Hypothesis	The primary hypothesis is a superiority hypothesis that the overall survival in the ONCOZENE™ microspheres embolization and drug delivery arm is higher than the overall survival for sorafenib. The null and alternative hypotheses for this primary endpoint are presented below. H_0: $S_T \leq S_C$ Versus H_a: $S_T > S_C$ where S_T and S_C are the survival functions in the test and control arms, respectively with minimum follow-up of at least one year.

Number of Patients & Study Duration	244 (122 in each arm) patients will be enrolled to account for loss to follow-up, which is estimated to be approximately 15% (resulting in 103 evaluable patients in each arm for a total of 206 for both arms), at up to 40 sites in United States and Outside the United States (OUS). At least 30% of patients will be enrolled in the United States. The enrollment duration is planned to be 18 months. Patients will be followed in the office or cath lab for 2 years following the initial treatment. Patients might be followed by phone for survival for additional 2 years.
Primary Effectiveness Endpoint	The primary effectiveness endpoint for this clinical trial is the overall survival in HCC patients with minimum follow-up of patients to at least one year. The DEB-TACE test arm will be compared to sorafenib in the group of HCC patients enrolled in this trial.
Secondary Endpoints	• Time to Progression (TTP) determined by radiological assessment using mRECIST criteria • Time to Extrahepatic Spread • Proportion Progression-Free (PPF) at one year. • The frequency of treatment emergent adverse events.
Additional Endpoints	• Proportion achieved tumor response: o Complete response (CR) o Partial response (PR) o Stable disease (SD) • FACT-Hep quality of life
Sample Size Consideration	If the survival is reported as median survival time, the value can be converted into other parameters of survival if one assumes a common survival distribution (the exponential distribution is used here). While the resulting estimates may not be exact, they are sufficiently close to allow sample size estimation. Assuming that the sorafenib median survival is 14.5 months (Bruix *et al.* 2012) for the HCC cancer patients with MVI/EHS absent, the 14.5 month median survival corresponds to a proportion surviving at 1 year of 0.5736. From the study by Kalva *et al.* (2013) estimates 26.8 months median survival using at least 2 doses of DEB-TACE in HCC patients in a similarly defined group of HCC patients which corresponds to a proportion surviving at 1 year of 0.7332. A sample size of 122 patients per arm with 80% power to detect a difference in 1-year survival between the sorafenib and DEB-TACE patient with a one sided alpha of 0.025. This computation assumes that study accrual will take about 18 months and, follow-up will be for at least one-additional year, and that 15% of each arm could be lost to follow-up at one year.

Inclusion Criteria	Patients may be included in the study only if they meet all of the following criteria: 1. Patient is able to provide informed consent and must sign the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form. 2. Male or female of age ≥ 18 years. 3. Confirmed diagnosis of HCC according to AASLD or EASL criteria or biopsy proven. 4. Locally-advanced HCC defined as tumor showing at least two of the following features: a) Multinodularity (>4 lesions) b) Large size (>5 cm) c) Segmental branch portal vein invasion 5. Preserved liver function (Child-Pugh A or B7 without clinically relevant ascites "treatable ascites"). 6. ECOG Performance Status 0 or 1.

Exclusion Criteria	Patients will be excluded for the following reasons: 1. Presence of extra-hepatic spread of disease. 2. Macrovascular invasion of lobar portal vein branches or main portal vein at entry into the study. 3. Candidate for surgical resection, transplantation, or local ablation. 4. Prior intra-arterial embolization or chemotherapy or systemic therapy for treatment of HCC. 5. Any contraindication for TACE. 6. Platelet count <50,000/mm^3 or INR >1.5. 7. Previous treatment with anthracycline antibiotics (e.g. Doxorubicin) or sorafenib. 8. Unstable coronary artery disease or recent MI (i.e. within 1 year). 9. Known ejection fraction < 50%. 10. Current infections requiring antibiotic therapy. 11. Suffering from a known bleeding disorder. 12. Renal insufficiency (serum creatinine > 2 mg/dL). 13. AST and/or ALT >5 times upper limit of normal. 14. Presence of advanced liver disease including active gastrointestinal bleeding, hospitalization for encephalopathy within 1 year, and clinically relevant ascites. 15. Any contraindication for doxorubicin administration: a. Serum Bilirubin>2mg/dL b. WBC < 3,000 cell/mm3 c. Neutrophil < 1,500 cell/mm3 16. Any co-morbid condition or social situation, which has a high likelihood of causing poor compliance with the study protocol or jeopardizes the patient's safety. 17. Patient has another primary tumor, with the exception of conventional basal cell carcinoma, superficial bladder cancer, melanoma in situ, or treated prostate cancer currently without biochemical or radiographic evidence of active disease 18. Participation in a clinical trial of an investigational device or drug within 4 weeks of study entry (signing informed consent). 19. Pregnant or breast-feeding patients. Women of childbearing potential must have negative serum pregnancy test performed within 7 days prior to start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the treatment period.

Terms and Abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
ALT	Alanine aminotransferase, Serum glutamic pyruvic transaminase (SGPT)
AST	Asparagine aminotransferase, Serum glutamic oxaloacetic transaminase (SGOT)
AUC	Area under the curve
AVM	Arteriovenous malformation
BCLC	Barcelona Clinical Liver Cancer staging
BID	Twice Daily
BUN	Blood Urea Nitrogen
CA	Competent Authority
CBC	Complete Blood Count
CC	Completed Case
CDRH	Center for Devices and Radiological Health
CP	Child-Pugh score or Conditional Power
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
cTACE	Conventional transarterial chemoembolization
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Form
DEB-TACE	Drug eluting bead-transarterial chemoembolization
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EASL	European Association for the Study of the Liver
EHS	Extrahepatic spread
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular filtration rate
HBV	Hepatitis B virus

HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HVT	Hypervascular Tumor
ICH-GCP	International Conference on Harmonization-Good Clinical Practices
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institutional Review Board
IRRP	Independent Response Review Panel
ISO	International Standards
ITT	Intent-to-Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at random
MI	Myocardial Infarction
mRECIST	Modified RECIST
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
MVI	Microvascular Invasion
NCI CTCAE v 4.0	National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0
OR	Overall Response
OS	Overall Survival
OUS	Outside the United States
PCP	Primary Care Physician
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PPF	Proportion Progression-Free
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QA	Quality Assurance
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Stable Disease

SOPs	Standard Operating Procedures
TAE	Transarterial embolization
TACE	Transarterial chemoembolization
Tmax	Time to maximum concentration
TTP	Time to Disease Progression
TTFP	Time to First Progression
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
WBC	White Blood Cell

1. Introduction

1.1 Background and Significance

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the sixth most common cancer in the world, the third most common cause of cancer-related death,[1] and the leading cause of death in patients with cirrhosis in Europe and the United States.[2,3] Over the next two decades, an increasing number of patients with HCC are expected, reflecting in part the current hepatitis C epidemic[4] with the incidence expected to reach a plateau in 2015 to 2020.[5] The gradual rise in incidence was substantiated by a 2005-estimated incidence of 667,000 cases globally and 17,550 cases in the United States.[6] In both Europe and USA, it is estimated that the burden of HCC (mainly related to hepatitis C virus infection), will increase within two decades to equal the incidence of that in Japan, and that in the United States, the number of cases of HCC will continue to increase by 81% (from a baseline of approximately 13.000/year) by the year 2020.[7] The incidence of HCC varies geographically largely due to variations in hepatitis B and C infection with the majority of the cases (> 80%) occurring in sub- Saharan Africa and eastern Asia.

A majority of HCC cases (60% to 80%) arise due to chronic hepatitis and cirrhosis. Major etiologies of liver cirrhosis include chronic hepatitis B and C, alcohol consumption, steatosis, diabetes, certain medications or exposures to toxic agents and genetic and metabolic diseases.[8] Obesity has also been identified as an independent risk factor for developing HCC.[9,10] A common pathway for these varied etiologies may involve chronic inflammation recognized as a pro-carcinogenic condition.[11]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are classified as carcinogens by the International Agency for Research on Cancer. Globally, HBV is the most frequently underlying cause of HCC. HBV carriers have a 5 to 15-fold increased risk of HCC compared to the general population. 70-90% of HBV related HCCs develop in patients with cirrhosis.[12] Chronic HBV carriers in Asia develop HCC at an annual rate of 0.4-0.6%, while in the presence of cirrhosis this figure increases to a rate of 2-6.6%. Worldwide 380 million people are infected with HBV. In Western countries and Japan, the main risk factor is HCV infection and excessive alcohol intake, along with other causes of cirrhosis. The annual incidence rate of HCC in patients with hepatitis C is 3.7-7.1%.[13] Hepatitis C virus infection is estimated to be present in 170 million persons worldwide, and unfortunately vaccination is not available. Cirrhosis will develop in 20-30% of these patients. The annual incidence of HCC in cirrhotic patients is 3- 5% and one third of patients will develop HCC during their lifetime.[14] In patients with alcoholic cirrhosis, the annual incidence of HCC is 0.2-1.8%.[13] There are no large prospective studies to determine the incidence of HCC among patients with cirrhosis from other causes, but their risk is significantly higher than that of the normal population.[7] Thus, prognosis of patients with HCC depends not only on the tumor morphology and extent, but also the stage of underlying chronic liver disease.[15]

1.2 Staging and Treatment

Various staging and classification systems have been proposed for HCC, which help to select treatment strategies, assess prognosis, and compare results from different clinical studies.[16] The Barcelona Clinic Liver Cancer (BCLC) staging system has been used for stratification of patients with HCC in the practice guidelines established by the American Association of the Study of Liver Diseases (AASLD).[6,17] In addition to estimating prognosis, the BCLC staging system also links staging to treatment recommendations.[6,17] In this staging system, intermediate stage (BCLC-B) is formed by those patients who are asymptomatic and harbor multifocal HCC without vascular invasion or extrahepatic spread and have preserved liver function (Child-Pugh Class A or B) and normal performance status (Eastern Cooperative Oncology Group Performance Status ECOG PS) of 0.[6] Chemoembolization is recommended as the main treatment strategy for patients in this intermediate stage.[18] Advanced stage (BCLC-C) applies to patients who have evolved beyond the profile depicted in BCLCB. They may have symptoms, ECOG performance status 1 or 2, or may have vascular invasion or extrahepatic spread.[6] These patients are triaged to systemic treatment with multikinase inhibitor, sorafenib, which has been found to prolong survival in this group of patients.[9,19]

The treatment algorithm described by the BCLC staging system is based on the use of conventional chemoembolization (cTACE) in which a mixture of lipiodol, chemotherapeutic drugs (such as doxorubicin, mitomycin, and cisplatin), and Gelfoam or microspheres is injected into the hepatic artery. Although cTACE has shown survival benefit in properly selected HCC patients from two randomized studies and a meta-analysis,[20-22] this often is associated with marked symptoms of postembolization syndrome and is not well tolerated by patients with advanced disease.[23-25]

Unlike cTACE, chemoembolization with drug-eluting beads (DEB-TACE) using doxorubicin has been found to be well tolerated with minimal postembolization syndrome symptoms.[26-29] A recent randomized study comparing cTACE and DEB-TACE has shown better tolerability and fewer complications associated with DEB-TACE especially in patients with advanced liver disease.[18,29] Although there have been reports on the use of cTACE in patients with advanced stage HCC with variable results,[30-33] however, the use of DEB-TACE in advanced-stage HCC has not been well studied until recently. Kalva *et al*[34] evaluated the safety and effectiveness of DEB-TACE with doxorubicin for inoperable HCC in 80 patients with advanced stage (BCLC-C). Authors in this retrospective study reported median PFS and OS of 5.1 months [95 % confidence interval (CI): 4.1–7.7] and 13.3 months (95 % CI: 10.1–18.6) respectively. On multivariate analysis, patients with ECOG PS $\leq$ 1 demonstrated a median survival of 17.7 months compared with 5.6 months for patients with ECOG PS > 1 ($p = 0.025$). In addition, multiple DEB-TACE procedures (> 2 procedures) were associated with improved survival (26.8 months) compared with patients with one or two procedures (11.4 months, $p = 0.01$). Portal vein thrombosis or extrahepatic disease had no statistically significant association with OS. Authors concluded that DEB-TACE is safe and

effective in patients with advanced HCC. ECOG PS ≤ 1 and > 2 DEB-TACE procedures were associated with better OS.[34]

Additionally, according to the EASL (European Association of the Study of the Liver) guidelines resection or liver transplantation are considered as curative treatment modalities in Hepatocellular carcinoma (HCC) when anatomically / clinically feasible. Transarterial chemoembolization is being considered as a palliative treatment in intermediate and advanced stages of HCC with the potential of local tumor control.

1.3 Rationale

Unlike most solid cancers, future incidence and mortality rates for HCC were projected to largely increase in several regions around the world over the next 20 years, mostly as a result of the dissemination of hepatitis C virus infection.[2,3] Despite the widespread implementation of surveillance programs of at-risk populations, the majority of patients with HCC are diagnosed late, when curative treatments such as transplantation cannot be applied.[4] Resection is only feasible in a minority of patients and in high proportion of the cases the disease recurs after a radical therapy.[4]

Treatment options for patients with unresectable HCC are limited. Systemic chemotherapy (single agent or combination), hormonal therapy, and immunotherapy have shown only minor antitumor activity and no improvement in overall survival.[5-8] In contrast, treatment with sorafenib, a multitargeted tyrosine kinase inhibitor, resulted in a survival benefit in patients with advanced HCC and Child-Pugh A liver disease. Two Phase III randomized, placebo controlled trials, the SHARP trial conducted in North America and Europe[9] and a similar trial conducted in Asia,[10] demonstrated improved overall survival with sorafenib compared with placebo. In the SHARP trial, median overall survival was 10.7 months with sorafenib and 7.9 months with placebo (HR 0.69 [95% CI 0.55-0.87]; $P < 0.001$). In the Asian study, median overall survival was 6.5 months with sorafenib and 4.2 months with placebo (HR 0.68 [95% CI 0.50-0.93] $P = 0.014$). Sorafenib is currently the only approved treatment for patients with unresectable HCC.

Transcatheter arterial chemoembolization (TACE) has long been used in the treatment of unresctable, locally-advanced HCC.[4] The survival benefit of conventional TACE regimens – including the administration of anticancer-in-oil emulsions followed by embolic materials – has been the patient of a limited number of randomized controlled trials that provided contradictory results.[11] Much of this controversy relates to poor patient selection and overtreatment in earlier trials. In addition, distinct technical advantages in the performance of TACE and improved patient selection and management have occurred over the past decade.[14] Unfortunately, the overall body of published work for chemoembolization of HCC is somewhat mixed, resulting in a recent Cochrane meta-analysis, where the authors concluded there is absence of evidence of conventional TACE having a beneficial effect on survival in patients with unresectable HCC.[12] The recent introduction of embolic, drug-eluting beads (DEB) has improved the pharmacokinetic profile of TACE compared with conventional regimens.[13] Additionally, the Precision V study showed significantly better

outcomes with DEB-TACE compared to conventional TACE in patients with marginal liver function or performance status. Most recently, in a retrospective study of 80 patients with advanced HCC, Kalva *et al* demonstrated that DEB-TACE is safe and effective. Overall survival was 13.3 months with a median survival of 17.7 months in those patients with ECOG PS ≤ 1 and 26.8 months when more than 2 DEB-TACE procedures were performed. They concluded that ECOG PS ≤ 1 and > 2 DEB-TACE procedures were associated with better OS.

In the US, neither cTACE or DEB-TACE are approved for the treatment of primary liver cancers (e.g. HCC). Hypervascular tumors such as HCC can be treated either off-label (cTACE, DEB-TACE) or on-label transcatheter arterial embolization (TAE) with bland (i.e. drug-free) embolic devices including microspheres such as Embozene® Microspheres or ONCOZENE™. The potential benefit of DEB-TACE over TAE for the treatment of HCC has been addressed in a couple of comparative studies.[35,36]

ONCOZENE™ Microspheres, due to design characteristics of the microsphere, can be loaded with drugs (such as doxorubicin hydrochloride and irinotecan) and then can elute a local, controlled, sustained dose of a drug to targeted tumor sites after embolization.
To date, relatively large microparticles (>100 μm) have been used to deliver cytotoxic drugs to the tumor vasculature. In principle, superselective DEB-TACE using ONCOZENE™ microspheres has the potential to penetrate deeper into the tumor's vasculature to reach the peripheral growing points. Recently Dreher *et al*[37] has demonstrated with another drug-eluting bead that downsizing the microparticles increases the tissue penetration of the microparticle and also increases the amount of eluted drug to the targeted tissue. Loading ONCOZENE™ microspheres with a cytotoxic drug should significantly improve the level of local tumor control and revolutionize transarterial therapy.

ONCOZENE™ Microspheres offer:

- Deep penetration into the tumor vasculature due to very small sized 40, 75, and 100 μm Microspheres.
- High confidence when performing superselective and targeted embolization procedures as 95% of the microspheres are within the stated size variance.
- Controlled embolization with precisely formulated and standardized microspheres.

The proposed study will assess prospectively the efficacy and safety of DEB-TACE (ONCO-DOX) in patients with unresectable, locally-advanced HCC. The primary objective of this study is to compare the proportions of patients survived through one year after the onset of the treatment between DEB-TACE (ONCO-DOX) and sorafenib treatment groups.

1.4 ONCOZENE™ Description

ONCOZENE™ Microspheres are 510(k) FDA cleared for embolization of arteriovenous malformations (AVM) and hypervascular tumors (HVT) including hepatoma. ONCOZENE™ Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene®-F). They are available in a range of sizes suitable for embolic therapy. ONCOZENE™ Microspheres are opaque in color.

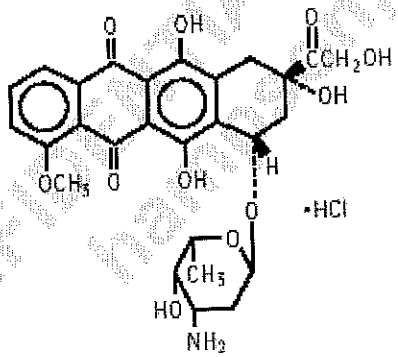
1.4.1 Intended Use

For this study, the intended use of the investigational treatment is DEB-TACE (ONCO-DOX), defined as the administration of doxorubicin-loaded ONCOZENE™ Microspheres (ONCO-DOX) (40 µm, 75 µm, or 100 µm) (the size to be used will be at the discretion of the treating physician(s) based on the tumor size and/or vascular structure). The dose of doxorubicin will be up to 150 mg doxorubicin/treatment.

The treatment end point should be devascularization of tumor/lesion and delivering the full doxorubicin dose. If after delivering the desired drug/embolization dose, blood flow is still detectable in the tumor; then the procedure can either be stopped, or if the IR wants stasis, then use bland embolic microspheres indicated for hepatoma (size comparable to the ONCOZENE™ used or 1 size larger) to reach stasis.

1.4.2 Doxorubicin

Doxorubicin-HCl is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. The hydrochloride form is positively charged and its structural formula is as follows:



$C_{27}H_{29}NO_{11}$•HCl
M.W.—579.99

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic

center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

1.5 Sorafenib

Sorafenib, an oral multikinase inhibitor with effects on tumor proliferation and angiogenesis, has been studied extensively in patients with HCC. A large phase III study evaluated sorafenib versus placebo in patients with advanced HCC.[9] Eligibility for this trial was restricted to patients with a Child-Pugh (CP) designation no worse than A.[38] This phase III trial demonstrated an overall survival advantage for sorafenib compared with placebo (10.7 vs. 7.9 months, P=0.001). These results led to approval by the US Food and Drug Administration (FDA) for the use of sorafenib as first-line therapy in patients with unresectable HCC.[39]

The study drug (sorafenib) will be supplied as 200 mg tablets. Patients will take two tablets of sorafenib (200 mg tablets) twice daily.

2. Study Objective and Endpoints

The main objective of this study is to evaluate the safety and efficacy of ONCOZENE™ Microspheres loaded with Doxorubicin (ONCO-DOX) in comparison with orally administered Sorafenib for the treatment of patients with unresectable, locally-advanced hepatocellular carcinoma (HCC).

2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this clinical trial is the overall survival in HCC patients with minimum follow-up of patients to at least one year.

The DEB-TACE test arm will be compared to sorafenib in the group of HCC patients enrolled in this trial. The primary hypothesis is a superiority hypothesis that the overall survival in the ONCOZENE™ Microspheres embolization and drug delivery arm is higher than the overall survival for sorafenib at one year after initial dose.

2.2 Secondary Endpoints

The secondary endpoints of this study are:

- Time to Progression (TTP) determined by radiological assessment using mRECIST criteria
- Time to Extrahepatic Spread
- Proportion Progression-Free (PPF) at one year.
- The frequency of treatment emergent adverse events at 30 day, 3, 6, 9, 12, 18, and 24-months following the initial treatment. The proportions of patients in each arm experiencing treatment emergent adverse events will be presented descriptively with the number experiencing the event, the number evaluated, the percentage, and the exact two-sided 95% confidence interval.

2.3 Additional Endpoints

Two additional endpoints are studied in this trial.

- The proportion of patients in each group that achieve complete response (CR), partial response (PR), and stable disease (SD) will be presented and compared across treatment groups. The data from the tumor response will be presented descriptively by treatment group without a test of hypothesis.
- The second additional endpoint is the FACT-Hep quality of life instrument validated in patients with Hepatic cancer.

3. Study Design

This is a prospective, two-arm, stratified then randomized (1:1), open label, controlled, multicenter Phase III trial to evaluate the safety and efficacy of ONCOZENE™ Microspheres loaded with doxorubicin (ONCO-DOX) in comparison with orally administered sorafenib in patients with unresectable, locally-advanced hepatocellular carcinoma (HCC).

After enrollment, patients will be stratified by ECOG Performance Status 0 versus 1, portal vein invasion (yes vs. no), and AFP <400 versus ≥400. They will then be randomized at each site within each stratum to minimize the impact of competing risks in study comparisons.

The study will be conducted at up to 40 centers in the United States, Europe & Asia. Enrolled patients will be randomized with equal allocation by study site.

- **Test arm:** ONCOZENE™ Microspheres loaded with doxorubicin (ONCO-DOX).
- **Control arm:** sorafenib 400 mg bid.

This trial is powered to demonstrate a superiority hypothesis that the proportion surviving in the ONCOZENE™ Microspheres embolization and drug delivery arm is higher than the proportion surviving for sorafenib at one year after the onset of treatment.
Patients will be followed for two years after the onset of treatment

3.1 Sample Size Computation

If the survival is reported as median survival time, the value can be converted into other parameters of survival if one assumes a common survival distribution (the exponential distribution is used here). While the resulting estimates may not be exact, they are sufficiently close to allow sample size estimation.

Assuming that the sorafenib median survival is 14.5 months[40] for the HCC cancer patients with MVI/EHS absent, the 14.5-month median survival corresponds to a proportion surviving at 1 year of 0.5736. From the study by Kalva *et al*[41] estimates 26.8 months median survival using at least 2 doses of DEB-TACE in HCC patients in a similarly defined group of HCC patients, which corresponds to a proportion surviving at 1 year of 0.7332.

A sample size of 122 patients per arm with 80% power to detect a difference in 1-year survival between the sorafenib and DEB-TACE patient with a one sided alpha of 0.025.

This computation assumes that study accrual will take about 18 months, follow-up will be for one-additional year, and that 15% of each arm could be lost to follow-up at one year.

3.2 Investigators and Study Sites

At each participating institution, there will be a Medical Oncologist or Hepatologist and Interventional Radiologist. Depending on the institution, the patients may be managed by a team of physicians. Typically, a hepatologist and/or a medical oncologist will lead the medical management of patients in the sorafenib arm and an Interventional Radiologist will manage the DEB-TACE and follow-ups.

The operators must be experienced in the embolization procedure and meet the criteria set by the Society of Interventional Radiology guidelines on chemoembolization to participate in this trial.[42] Therefore, there will be no needs for additional training. However, additional training of pharmacy staff on the preparation of Oncozene™ Microspheres will be performed prior to enrollment of patients.

3.3 Patient Enrollment

Two hundred and forty four patients (122 in each arm) with confirmed unresectable, locally-advanced HCC will initially be enrolled in the study.

Each investigative site will be given up to 12 months to enroll study patients. Should a site withdraw from the study or not meet their target enrollment number within 6 months, other sites may be given the opportunity to "over enroll" or new sites may be initiated for enrollment so that the Sponsor can meet the enrollment target. Each site will be allowed to enroll up to 25% of the total enrollment. The enrollment will be closed when 244 eligible patients are enrolled, unless the interim analysis leads to enrollment of additional patients.

3.4 Patient Selection Criteria

3.4.1 Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

1. Patient is able to provide informed consent and must sign the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form.
2. Male or female of age ≥ 18 years.
3. Confirmed diagnosis of HCC according to AASLD or EASL criteria or biopsy proven.
4. Locally-advanced HCC defined as tumor showing at least two of the following features:
    a. Multinodularity (>4 lesions)
    b. Large size (>5 cm)
    c. Segmental branch portal vein invasion.
5. Preserved liver function (Child-Pugh A or B7 without clinically relevant ascites "treatable ascites").

6. ECOG Performance Status 0 or 1.

3.4.2 Exclusion Criteria

Patients will be excluded for the following reasons:

1. Presence of extra-hepatic spread of disease .
2. Macrovascular invasion of lobar portal vein branches or main portal vein at entry into the study.
3. Candidate for surgical resection, transplantation, or local ablation.
4. Prior intra-arterial therapy or systemic therapy for treatment of HCC.
5. Any contraindication for TACE:
6. Platelet count <50,000/mm3 or INR >1.5.
7. Previous treatment with anthracycline antibiotics (e.g. Doxorubicin) or sorafenib.
8. Unstable coronary artery disease or recent MI (i.e. within 1 year).
9. Known ejection fraction < 50%.
10. Current infections requiring antibiotic therapy.
11. On anticoagulation or suffering from a known bleeding disorder.
12. Renal insufficiency (serum creatinine > 2 mg/dL).
13. AST and/or ALT >5 times upper limit of normal.
14. Presence of advanced liver disease including active gastrointestinal bleeding, hospitalization for encephalopathy within 1 year, and clinically relevant ascites.
15. Any contraindication for doxorubicin administration:
    a. Serum Bilirubin>2mg/dL
    b. WBC < 3,000 cell/mm3
    c. Neutrophil < 1,500 cell/mm3
16. Any co-morbid condition or social situation, which has a high likelihood of causing poor compliance with the study protocol or jeopardizes the patient's safety.
17. Patient has another primary tumor, with the exception of conventional basal cell carcinoma, superficial bladder cancer, melanoma in situ, or treated prostate cancer currently without biochemical or radiographic evidence of active disease
18. Participation in a clinical trial of an investigational device or drug within 4 weeks of study entry (signing informed consent).
19. Pregnant or breast-feeding patients. Women of childbearing potential must have negative serum pregnancy test performed within 7 days prior to start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the treatment period.

3.5 Treatment Plan

Within 30 days of screening/ baseline visit , patients must be randomized and treated according to their assigned treatment ONCO-DOX (Test) or Sorafenib (Control). The study duration for each

patient lasts 2 years and consists of a screening/baseline phase, a treatment phase, and a follow-up phase (See Schedule of Events). All procedures specified in this protocol must be documented in the patient's record and on the corresponding case report form (CRF). The target date for each follow-up visit will be the anniversary date from Visit 2 (Day 0) (e.g. Visit 2 (Day 0): 01/15/2014, Visit 8 (6 months f/u): 07/15/2014). Patients might be followed by phone annually for additional 2 years for survival.

3.5.1 ONCO-DOX Arm:

The ONCOZENE™ Microspheres size to be used will be at the discretion of the treating physician based on the tumor size and/or vascular structure. The dose of doxorubicin will be up to 150 mg doxorubicin/treatment. The goal is to deliver drug-loaded ONCOZENE™ embolic particles into the tumor's vasculature by superselective (sub-segmental) catheter positioning. Patients might be treated via segmental or lobar infusion if superselective approach is not feasible due to patient's anatomy and pathology.

DEB-TACE treatment can be performed every 4-8 weeks from prior treatment until complete tumor response is observed on imaging or one or more of the following events occurs:

- Failure to achieve an objective response (partial or complete response) in the treated hepatic territory after at least 2 treatment courses. Tumor response will be assessed by using mRECIST criteria.
- Development of main portal vein thrombosis or extrahepatic spread of disease.
- Clinical or functional deterioration, defined as progression to ECOG performance status > 2 or evolution to sustained hepatic decompensation
- Patients who fail to respond to DEB-TACE as mentioned above will be treated as per standard of care at each institution and may be offered sorafenib. Before starting new treatment, the site must make best efforts to send imaging and case narratives to the Sponsor or designee to confirm if any of the criteria listed above are met and ensure standardization across the sites.

In patients with bilobar involvement, each of the two lobes should be treated with two individual DEB-TACE procedures (unless complete response is achieved) with an interval of 4-8 weeks starting with the lobe with the higher tumor burden (Table 3.1). The sequence of treatments will be followed at the discretion of the treating physician including the treatment of both lobes at the same session. Additional treatments may be performed at the discretion of the treating physician, if deemed appropriate.

Table 3.1 ONCO-DOX Treatment Plan

Treatment	Dosing DOX / ONCO	Second Treatment (dose) DOX / ONCO
Single Lobe/ Single-lesion	T=0 up to 150mg	T=4 w up to 150mg
Bilobar/Multi-lesions	L1 T=0 up to 150mg L2 T=4w up to 150mg	L1 T=8w up to 150mg L2 T=12w up to 150mg

W = weeks

3.5.2 Sorafenib arm:

Patients will take 2 tablets of sorafenib (200 mg tablets) twice daily, orally and will continue until unacceptable toxicity or unequivocal tumor progression is observed. Patients return to the clinic every month for drug dispensing and additional testing during the treatment phase.

Experience in the management of AEs related to sorafenib is a key to avoid premature discontinuations. AEs can often be managed with dose modifications or interruption rather than discontinuation. Treatment interruptions and up to two dose reductions (first to 400 mg once daily and then to 400 mg every 2 days) are permitted for drug-related adverse effects.

In the event of unacceptable toxicity or unequivocal tumor progression, according to mRECIST, is observed, patients in the sorafenib arm maybe treated as per standard of care at each institution. If DEB-TACE is deemed appropriate, it must be performed with drug eluting beads other than ONCOZENE™ microspheres.

4. Study Procedures

4.1 Informed Consent

Before the initiation of any baseline study-specific procedures or evaluations that go beyond the standard of care, each patient (or legally authorized representative) must sign the informed consent form (and other locally required documents) after the nature of the study has been fully explained to him or her, along with alternatives to participation in the clinical study. The consent form that is used must be approved by both the reviewing Institutional Review Board/Ethics Committee (EC) and by the Sponsor. One copy of the completed informed consent form must be given to the patient and the original must be placed in the patient's medical record as a source document.

Upon completion of the baseline evaluation, the Investigator will determine whether the patient is considered eligible for study entry. Patients will be recorded in the screening log.

4.2 Patient Identification

Upon signing consent into the clinical study, a unique patient study ID will be assigned. The patient number will be assigned consecutively in ascending order per site. The patient study ID number should be recorded on all source documents. If the patient is a screen failure the study ID number will not be reassigned.

4.3 Randomization

Once patient eligibility is confirmed by the investigator (or designee) at the Screening/Baseline visit, the patient is eligible to be randomized to treatment. The treatment allocation will be revealed to the investigator or his/ her designee upon completing the randomization eCRF. The assigned treatment will be recorded in the source documentation.

All products/devices are considered *Investigational Use* and should not be used to treat patients outside the study, nor should they be used outside the allocated randomization scheme.

Randomization will be considered Day 0 for the survival follow up.

4.4 Prior, Concomitant, and Excluded Therapy

All concomitant medications (including start/stop dates, and indication) must be recorded in the patient's source documentation as well as in the appropriate pages of the CRF.

Permitted:

- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the investigator.

- Antiviral treatment for chronic HBV or HCV. Interferon is allowed only in combination with ribavarin for chronic HCV or as single agent for chronic HBV as per standard of care.
- Patients may receive standard of care for any underlying illness.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator, however they may not be substituted for a required dose reduction.
- Primary prophylaxis with erythropoietin is not permitted, however secondary prophylaxis is permitted as long as it does not substitute a necessary dose reduction.

Avoid or Use with Caution

- To avoid potential risk of increasing adverse events, caution must be taken when using intravenous P-glycoprotein inhibitors and CYP2D6 substrates that have a narrow therapeutic index (such as thioridazine) in ONCO-DOX group.
- Concurrent medications that can potentially affect renal and hepatic functions.

Not Permitted:

For sorafenib patients only:

There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity are not permitted on the sorafenib arm (e.g. rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations. There are no clinical data evaluating the effect of chronically co-administered CYP3A4 inducers on sorafenib's efficacy. Since there is a possibility of decreased sorafenib efficacy upon chronic co-administration of CYP3A4 inducers with sorafenib, chronic co-administration of CYP3A4 inducers with sorafenib, should be avoided to the extent possible.

Please refer to the link below for a list of CYP3A4 inducers, P-glycoprotein and CYP2D6 substrates.
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classSub

For all patients:

- Any anti-angiogenic (licensed or investigational) such as bevacizumab, sunitinib, etc. is not allowed.
- Any investigational therapies except those within the protocol
- Herbal medicine for anticancer treatment should be stopped prior to randomization.
- Anti-cancer chemotherapy, immunotherapy, molecular therapy, investigational therapy
- Interferon outside its use as antiviral treatment for chronic HBV or HCV as specified above.
- Subjects taking narrow therapeutic index medications should be monitored proactively.
    - These medications include warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporin and digoxin.

4.5 Investigational Product(s)

The products will be used in the study: (see Package Inserts and IFUs in the study binder for all products)

- sorafenib 200 mg x 2 tablets
- ONCOZENE™ Microspheres
- Doxorubicin

5. Study Activities

5.1 Visit 1, Screening/Baseline

The procedures to be completed at Visit 1 to determine the patient's eligibility, within 30 days prior to procedure/ treatment, are as follows:

- Informed Consent: Obtain written patient informed consent.
- Medical & surgical History: Obtain detailed documentation of medical/surgical history including cancer history with treatments and outcomes.
- Demographics: Record demographics at baseline.
- Vitals & Physical Examination: Complete clinical examination (including a general neurological examination).
- Patient Assessments: Obtain preoperative FACT-Hep QoL
- Child-Pugh Score
- ECOG performance status
- Concomitant Medications/Therapy: Note any medications or therapy that the patient is currently taking
- Multiphase imaging (CT or MRI): pelvis, abdomen and chest to assess the tumor in the liver and exclude extra hepatic lesions
- 12 lead ECG.
- LVEF (echo or MUGA)
- Pregnancy Test: If female is of child bearing potential, non-pregnancy to be confirmed with urine or serum test.
- Stratification & Randomization: Will take place after Inclusion/Exclusion is confirmed.

5.1.1 Laboratory Assessment

Normal ranges for the study laboratory parameters must be supplied to the Sponsor or designee before the study starts.

All laboratory tests at baseline and during treatment must be performed and reviewed by the Investigator at the scheduled study visit prior to the administration of study treatment. When clinically significant laboratory abnormalities occur, the pertinent tests should be regularly repeated until resolution or not clinically significant. The results are to be entered into the CRF. The following laboratory tests are to be done at baseline and during the Study Treatment Phase according to the Schedule of Events:

- Complete Blood Count (CBC) (i.e. Hemoglobin, hematocrit, WBC, RBC and platelets), and prothrombin time or INR

- Serum creatinine (creatinine clearance must be recalculated in any patient subsequently experiencing an increase in serum creatinine [even if that increased value is within normal limits] or severe weight change) and GFR
- Total bilirubin, conjugated (direct) bilirubin in the case of abnormal total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, total protein
- Glucose
- Serum electrolytes: sodium, potassium, calcium, chloride
- Urinalysis (protein, blood, glucose, pH) (at baseline and as clinically indicated thereafter– see Schedule of Assessments)
- Serum α-fetoprotein (AFP)

5.1.2 Imaging

Imaging will be performed at baseline and during the study treatment according to the Schedule of Events. Multiphase contrast-enhanced CT or MRI of the pelvis, abdomen and chest is acceptable. Consistency of consecutive CT–scans, or MRIs (e.g. the use of contrast etc.) should be ensured during all assessments for each patient with the same technique being used throughout the treatment period for evaluating the lesions. Tumor measurements may be assessed by an independent response review panel. Sites should send or upload the imaging for IRRP review within 2 weeks of the study visit.

5.2 Treatment Phase

After randomization and if the patient continues to meet all inclusion criteria and none of the exclusion criteria, patients will be administered the study product according to their treatment assignment. The date, time and treatment parameters including dosing, microspheres size and volume used, microcatheter, contrast, dilution, infusion volume and duration and lesion(s) treated will be recorded on the CRFs.

All patients will complete the FACT-Hep quality of life questionnaires every 2 months during the treatment phase.

5.2.1 Sorafenib Arm

Patients in the sorafenib arm, patients should start their first dose immediately after randomization or as soon as possible. Patients will take their drug as described in section 3.5.2.

Patients return to the clinic monthly for the first four months, at 6 months, and every 3 months, thereafter to perform clinical follow-up assessments as described in the schedule of assessments:

- Physical examination
- ECOG
- Lab tests (blood chemistry, hematology, AFP, urinalysis)

- 12 lead ECG at month 6 and at end of study only.
- Concomitant medications
- Record of all adverse events that occurred from last patient contact.

5.2.2 ONCO-DOX Arm

Patients in the ONCO-DOX arm, patients should start their first DEB-TACE treatment immediately after randomization, Day 0 (Treatment 1, Visit 2), or as soon as possible. Dosing and treatment intervals are described in section 3.5.1

General considerations:

- The chemoembolization procedure is to be performed under conscious sedation or general anesthesia (at the physician's discretion), with antibiotic prophylaxis, analgesic, and antiemetic medications.
- Prior to the chemoembolization, angiography of the hepatic and mesenteric arteries is performed to map the liver vascular anatomy, check for arteriovenous shunts, and identify tumor feeder arteries.
- Chemoembolization is performed, as selectively as possible given the tumor vasculature anatomy, by catheterization of the hepatic segmental arteries supplying the lesion(s).
- The ONCO-DOX chemoembolization protocol consists of injection of ONCO-DOX microspheres loaded with up to 150 mg of doxorubicin. The ONCO-DOX microsphere cake is mixed with 10 ml of non-ionic contrast agent before delivery. The ONCO-DOX microspheres are injected slowly into the tumors feeding vessels at a rate of approximately 1 ml/min solution. SLOW INJECTION IS ESSENTIAL FOR BEST RESULTS. When flow starts to decrease, stop, and wait several minutes, then reevaluates. Flow generally will increase again and an additional volume of ONCO-DOX Microspheres can be delivered as microvasculature relaxes after initial blockage. Goal is to saturate as much of the tumor's vascular bed as possible. The transarterial chemoembolization is considered a technical success if the desired drug dose is delivered. If flow still exists after anticipated dose is delivered, then the procedure can either be stopped, or if the IR wants stasis, then use bland microspheres approved for treatment of hepatoma to reach stasis.
- If small tumor feeder arteries are missed on the first treatment, they can be chemoembolized on a subsequent treatment 4 weeks later.

Patients in the ONCO-DOX arm with monolobar HCC are to return to the site for a second DEB-TACE procedure 4 weeks after the initial procedure (if complete response is achieved after the initial procedure, this visit may not be performed). Additional DEB-TACE procedures may be performed at the discretion of the treating physician 4-8 weeks from the previous procedure, as deemed appropriate. Additionally, patients return to the site to perform clinical follow-up assessments 14-28 days after the initial procedure and prior to each subsequent procedure as described in the schedule of assessments:

- Physical examination including vitals and weight

- ECOG
- Lab tests (blood chemistry, hematology, AFP, urinalysis)
- Imaging to assess the tumor response and the need for a second ONCO-DOX treatment (only for the ONCO-DOX group). If a second DEB-TACE was predefined at baseline, imaging would not be mandated at this visit.
- Concomitant medications
- Record of all adverse events that occurred from last patient contact.

Patients in the ONCO-DOX arm with bilobar HCC are to return to the site for additional DEB-TACE procedures 4-8 weeks after the previous procedure. Additional DEB-TACE procedures may be performed at the discretion of the treating physician as deemed appropriate. Additionally, Patients return to the site to perform clinical follow-up assessments 14-28 days after the initial procedure and prior to each subsequent procedure (within one week), as described in the schedule of assessments:

- Physical examination including vitals and weight
- ECOG
- Lab tests (blood chemistry, hematology, urinalysis)
- Concomitant medications
- Record of all adverse events that occurred from last patient contact.

All ONCO-DOX patients will also have the following assessments:

- 12 lead ECG and echocardiogram/ MUGA are performed at baseline and each subsequent procedure after a cumulative dose of 300 mg/m^2 of doxorubicin has been given for those patients requiring several embolization procedures.

Both ONCO-DOX and sorafenib patients will have the following assessments:

- Imaging for tumor response (contrast enhanced CT scan or MRI for the chest, abdomen and pelvis) in both arms will be performed at 2, 4, 6, 9, 12, 18, and 24 month follow up. *Please Refer to Schedule of Assessments.*
- Additional imaging will be taken to assess and plan additional ONCO –DOX treatment (2-4 weeks after the OCO-DOX treatment), if no complete response is achieved.

5.3 Post Treatment Follow up

During the follow up phase, Patients in both arms return to the site every 3 months through the 12-month visit and every 6 months thereafter to perform the following. Patients might be followed by phone annually for additional 2 years for survival:

- Physical examination including vitals and weight
- ECOG
- Lab tests (blood chemistry, hematology, AFP, urinalysis)
- 12 lead ECG is performed at 6 months and at the end of study.

- Imaging for tumor response and extra-hepatic metastasis (contrast enhanced CT scan or MRI) every 3 months through 12 month visit and every 6 months until 24 month visit.
- Concomitant medications
- Record of all adverse events that occurred from last patient contact.
- FACT-Hep QOL.

5.4 Unscheduled Visits

In the event that additional visit(s) are required other than those described in the protocol, the information must be documented in any applicable case report form. A copy of the visit form and clinical dictation should be placed in the study chart.

5.5 Patient Discontinuation or Withdrawal

Patients may withdraw their consent and discontinue participation in the clinical study at any time, for any reason, without prejudice to further treatment. If a patient no longer wants to receive study treatment, but is willing to come for follow-up appointments, the patient's request should be honored, if possible.

It may also be necessary to terminate a patient from the clinical study due to medical safety consideration, non-compliance, or administrative concerns.

If for any reason a patient is withdrawn or terminated before completing the study, the reasons for withdrawal or termination must be documented. If a patient is withdrawn or terminated due to medical safety considerations because of an adverse event, the adverse event must be followed by medical attention to satisfactory resolution and all study data related to the patient will be reported.

If a patient discontinues treatment due to an adverse event or clinical laboratory abnormality, the patient should be followed-up until the event resolves, the patient stabilized, or 30 days, whichever is shorter. If a patient dies within 45 days of the last study treatment, the SAE case report form should be completed.

Patients who withdraw or are withdrawn prior to completion of the study periods should be scheduled for an early termination physical exam within one week after withdrawal. Patients who withdraw prior to completion of the study will also be asked to complete patient assessments (per follow-up visit Schedule of Assessments) at the time of final physical exam if available.

Schedule of Assessments

Assessment		TREATMENT PHASE						FOLLOW UP PHASE				
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4***	**Visit 5**	**Visit 6****	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
	Screening/ Baseline	Treatment Onset[4]		**M1**	**M2**	**M3**	**M4**	**M6**	**M9**	**M12**	**M18**	**M24**
	Up to -30 days	Day 0	14-28 days	±1 wk	±2 wk	6±2 wks[1]	±2 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks
Informed Consent	√											
Inclusion/Exclusion	√	√										
Vital Signs	√		√		√	√	√	√	√	√	√	√
Weight	√		√		√	√	√	√	√	√	√	√
Physical examination	√		√		√	√	√	√	√	√	√	√
Demographics	√											
Child Pugh Score	√											
Medical History	√											
Cancer History	√											
Pregnancy Test (if applicable)	√											
12 lead ECG	√					√[2]		√				√
Echocardiogram or MUGA	√					√[2]						
Blood tests (chemistry, hematology, AFP) & urinalysis	√		√		√		√	√	√	√	√	√
Imaging	√		√[3]		√		√	√	√	√	√	√
Tumor measurement	√		√[3]		√		√	√	√	√	√	√
ECOG performance status	√		√		√	√	√	√	√	√	√	√
The FACT-Hep QOL	√				√		√	√	√	√	√	√
Concomitant Medication	√	√	√	√	√	√	√					
Randomization[4]		√										
DEB-TACE (if assigned to this treatment)		√		√*		√*						
Dispensation of sorafenib(if assigned to this treatment and continues until PD or unacceptable toxicity)		√		√	√	√	√	√	√	√	√	√
Adverse Events		√	√	√	√	√	√					
Survival follow up during (if patient withdraw from treatment) and until the study completion.								√				√

***May not performed if complete response achieved. **Additional Treatment of** ONC DEB-TACE, as needed, should be every 6±2 weeks from the previous treatment followed by imaging at 2-4 weeks. None if complete response (CR) is achieved. M=month

[1]Time after previous DEB-TACE visit. [2]Before each subsequent doseafter receiving a cumulative dose of 300 mg/ m^2 of doxorubicin. [3]For DEB-TACE arm only to assess the need for 2nd DEB-TACT. If additional DEB-TACE sessions are predefined at baseline, imaging and tumor assessment are not mandated. [4]Onset of treatment should be done immediately after randomization or as soon as possible.

6. Study Management of Adverse Events

6.1 Medical and Safety Monitoring

The study Principal Investigator and the executive committee will oversee the overall safety and efficacy of the study. All final decisions regarding study progress and modifications rest with the executive committee, in coordination with Sponsor personnel. The executive committee will receive periodic updates from CeloNova based on reports provided by the Coordinating Data Center and DSMB.

6.2 Definition

Adverse Event – An Adverse event is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring in a patient during their participation in the clinical trial. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational device whether or not it is related to the investigational device or procedure.

6.3 Handling and Reporting of Adverse Events

For the purpose of this study, adverse experiences and complications will be recorded as adverse events. The Investigator will be required to provide the Sponsor with any information concerning any findings that suggest any adverse events pertinent to the investigation. All AEs occurring during the study will be recorded on the appropriate Case Report Forms.

Patients will be carefully monitored during the study for possible AEs. Any AE observed will be fully investigated by the Investigator. Appropriate treatment of the patient will be initiated and the study follow-up will continue. Collection of adverse events begins at the time the patient is randomized. After discontinuing study treatment, the reporting of all AEs is to continue for 45 days or until the patient receives alternative therapy for their HCC, whichever occurs first. The Investigator will attempt to assess the involvement of the investigational product or treatment in the AE. All observations and clinical findings, including the nature and severity will be documented on the appropriate case report forms.

All pre-existing medical conditions will be recorded on the medical history case report form. Starting with the first administration of investigational product, any new experience that was not present at baseline, or worsening of an event present at baseline in intensity or frequency, is considered an adverse event. Note: unchanged, chronic conditions are NOT adverse events and should not be recorded on the adverse event page of the Case Report Form (CRF).

The Sponsor may discuss any adverse events (including serious adverse events) with the Investigator and coordinate appropriate actions, in particular their notification to other Investigators as applicable.

6.4 Recording Adverse Events

Adverse event terms should be recorded consistently, using acceptable medical terms. When possible, a diagnosis (i.e., disease or syndrome) rather than the component signs and symptoms should be recorded on the case report form (e.g., record congestive heart failure rather than dyspnea, rales and cyanosis). However, signs and symptoms considered unrelated to encountered syndromes or diseases are to be recorded as individual adverse events on the case report form (e.g., if congestive heart failure and severe headaches are observed at the same time, each experience is to be recorded as an individual adverse event). The AE should not be recorded as a procedure or clinical measurement (i.e., a laboratory or vital sign) but should reflect the reason for the procedure or diagnosis.

Death is considered to be an outcome of an adverse event. The cause of death (rather than the term "death") should be recorded on the serious adverse event and death report case report forms.

Patients should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. At each required visit (or whenever reported) during the study, all AEs that have occurred since the previous visit must be recorded on the Adverse Event case report form. For each AE, the Investigator should obtain all the information required to complete the Adverse Event page of the CRF.

All AEs, regardless of seriousness, severity, or presumed relationship to the investigational product or treatment must be recorded using medical terminology in the source document and on the Adverse Experience CRF. Investigators must record on the AE CRF their opinion concerning the relationship of the AE to the investigational product or treatment.

All AEs must be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported to the appropriate Sponsor or designee's contact.

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 criteria. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (events which were not present at baseline or worsened in severity following the start of treatment) will be summarized.

6.5 Assessment of Relationship to Investigational Product

Investigators are required to assess whether there is a reasonable possibility that the investigational product caused or contributed to an AE.

Many terms and scales are used to describe the degree of causality between an investigational product and an event. There is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A, III/A/1).

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE includes assessing temporal relationships, biologic plausibility, dechallenge/rechallenge information (if available), association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

Not Related: Exposure to the investigational product has not occurred, OR the occurrence of the adverse event is not reasonably related in time, OR the adverse event is considered unlikely to be related to the used of the investigational product (biologically implausible).

Remote: The administration of the investigational product and the adverse event are considered reasonably related in time AND the adverse event could also be explained by causes other than the exposure to the investigational product (concurrent illness/underlying disease, other drugs or procedures).

Possible: Exposure to the investigational product and the adverse event are reasonably related in time AND the investigational product is more likely than other causes to be responsible for the adverse event, OR is the most likely cause of the adverse event.

Definite: Exposure to the investigational product is clearly determined to be the cause of the adverse event.

If any adverse event is considered to be either "possibly" or "definitely" related to the administration of the investigational product, that event will be followed until resolution or the Investigator judges the experience to be chronic or stable.

6.6 Intensity of Adverse Events

The intensity of the adverse event should be assessed using the NCI CTCAE version 4.0.

6.7 Anticipated Adverse Events

Progression of disease is considered an efficacy outcome parameter, and for AE reporting purposes, is excluded from the definition of an AE, unless the disease progression meets the criteria of an SAE.

6.8 Unexpected Adverse Events

Unexpected adverse events - Any adverse event, the specificity or severity of which is not consistent with the current protocol, instructions for use (IFU), package insert or Investigator Brochure. "Unexpected," as used in this definition, refers to an adverse event that has not been previously observed (e.g., included in the protocol, literature or Investigator Brochure) rather than from the perspective of such event not being anticipated from the pharmacological properties of the pharmaceutical product (21 CFR 812.32).

6.9 Handling and Reporting of Unexpected Adverse Events

The investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible but no later than 10 working days after the investigator first learns of the effect.

The Sponsor shall notify FDA, all reviewing IRBs and all participating Investigators in a written safety report of any unanticipated adverse device effect.

Each written notification may be submitted in a narrative format and shall be transmitted to the FDA/CDRH Document Mail Center as a supplement to the IDE. If FDA determines that additional data are needed, the Agency may require further data to be submitted.

In each written AE report, the Sponsor shall identify all AE reports previously reported to the IDE concerning a similar adverse event, and shall analyze the significance of the adverse event in light of any previous similar reports.

Telephone, email and facsimile transmission safety reports. The Sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the device as soon as possible but in **no event later than 7 calendar days** after the Sponsor's initial receipt of the information. Each telephone call, email or facsimile transmission to FDA shall be followed up with a hard copy transmitted to the FDA/CDRH Document Mail Center as a supplement to the IDE.

7. Study Management of Serious Adverse Events

7.1 Definition

Serious Adverse Event – Any adverse event results in any of the following outcomes: Death, a life-threatening, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defects. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2 Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) is defined as 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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

7.3 Handling and Reporting of Serious Adverse Events

The Investigator will report all serious adverse events to the Sponsor by telephone or fax **within twenty-four hours** after becoming aware of the incident. The Investigator will provide follow-up information. All serious adverse events will be followed until resolution or the Investigator judges the event to be chronic or stable.

For serious adverse events occurring during this investigation, the contact numbers are listed in the study reference binder or email safety@celonova.com.

CeloNova Biosciences will report all adverse events that are serious, unexpected, and considered at least possibly related to the administration of the investigational device, to the FDA in the form of an IDE supplement describing the AE within **15 calendar days** after receiving information on the adverse event. CeloNova Biosciences will report any UADEs to FDA within **10 calendar days**. CeloNova Biosciences will also report any life threatening or fatal adverse events, which are unexpected and considered at least possibly associated with the investigational product, to the FDA via phone, email or fax **within 7 calendar days** after receiving information on the adverse event.

CeloNova Biosciences will also notify all participating Investigators of serious anticipated and unanticipated AEs within **15 calendar days** after receiving information. Serious adverse events and UADEs need to be reported to the IRB as per local regulations.

7.4 Recording Serious Adverse Events

All serious adverse events and UADEs must be promptly documented on the Serious Adverse Event case report form. The Principal Investigator is responsible for evaluating all serious adverse events, obtaining supporting documents and determining that documentation of the event is adequate. The Principal Investigator may delegate these duties to Sub-Investigators and must assure that these Sub-Investigators are trained or qualified to perform theses duties under the supervision of the Principal Investigator.

8. Statistical Methods

8.1 Introduction

Hepatocellular carcinoma (HCC) is a difficult cancer, the survival from which is complicated by other liver pathology, including cirrhosis. Recommendations on endpoints, study design, patient classifications and other studies related have been provided by expert panels.[5,7,43] The design recommendations rely on the Barcelona Clinic Liver Cancer (BCLC) staging system discussed elsewhere in this protocol. A current approved drug for the treatment of hepatocellular carcinoma is sorafenib. The proposed study is intended to compare the median survival of HCC with sorafenib to the median survival of embolization with drug eluting beads (DEB-TACE). This study is to recruit patients in a special subset of the HCC population, those with MVI/EHS absent and the patients assigned to the DEB-TACE arm will be administered at least two doses of DEB-TACE.

8.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this clinical trial is the overall survival in HCC patients with minimum follow-up of patients to at least one year. The DEB-TACE test arm will be compared to sorafenib in the group of HCC patients enrolled in this trial. The primary hypothesis is a superiority hypothesis that the overall survival in the ONCOZENE™ microspheres embolization and drug delivery arm is higher than the overall survival for sorafenib at one year after initial dose. The null and alternative hypotheses for this primary endpoint are presented below.

H_0: $S_T \leq S_C$

Versus

H_a: $S_T > S_C$

where S_T and S_C are the survival functions in the test and control arms, respectively with minimum follow-up of at least one year.

8.2.1 Effectiveness Sample Size

If the survival is reported as median survival time, the value can be converted into other parameters of survival if one assumes a common survival distribution (the exponential distribution is used here). While the resulting estimates may not be exact, they are sufficiently close to allow sample size estimation. Assuming that the sorafenib median survival is 14.5 months[40] for the HCC cancer patients with MVI/EHS absent, the 14.5-month median survival corresponds to a proportion surviving at 1 year of 0.5736. From the study by Kalva *et al*[41] estimates 26.8 months median survival using at least 2 doses of DEB-TACE

in HCC patients in a similarly defined group of HCC patients which corresponds to a proportion surviving at 1 year of 0.7332. A sample size of 122 patients per arm with 80% power to detect a difference in 1-year survival between the sorafenib and DEB-TACE patient with a one sided alpha of 0.025. This computation assumes that study accrual will take about one year, follow-up will be for one-additional year, and that 15% of each arm could be lost to follow-up at one year.

8.3 Primary Safety Endpoint

The primary safety endpoint is the frequency of treatment emergent adverse events. There will be a comparison of the treatment emergent adverse events between the treatment groups. In the literature, there is evidence that the dose of chemotherapeutic agents are less toxic for microsphere administration because there is less systemic release of the drug than in oral or intravenous drug delivery applications. The proportions of patients in each arm experiencing treatment emergent adverse events will be presented descriptively with the number experiencing the event, the number evaluated, the percentage, and the exact two-sided 95% confidence interval. The null and alternative hypotheses to be tested are provided below.

H_0: $P_T \geq P_C$

Versus

H_a: $P_T < P_C$

where P_T and P_C are the proportions of patients with treatment emergent adverse events through one year in the Test (DEB-TACE) and Control (sorafenib), respectively.

8.4 Secondary Efficacy Endpoint

A strong endpoint that is related to survival is time to progression. This endpoint is to be distinguished from progression-free survival because the time to progression is based only on the radiological evidence of progression by the modified RECIST criteria. Thus, the secondary efficacy endpoint for this study is the time to progression. The null and alternative hypotheses are presented below.

H_0: $T_T \leq T_C$

Versus

H_a: $T_T > T_C$

where T_T and T_C are the times to progression in the test and control arms, respectively. This endpoint will be evaluated using the survival analysis and equivalent null and alternative hypotheses based on survival are given below.

H_0: $S_{PFT} \leq S_{PFC}$

Versus

H_a: $S_{PFT} > S_{PFC}$

where S_{PFT} is the proportion progression-free at one year in the DEB-TACE arm and S_{PFC} is the proportion progression-free at one year in the sorafenib arm. The difference between these rates is similar to the difference between the median survivals.

The time to progression endpoint will be determined by radiological assessment conducted by independent investigators using the mRECIST criteria.

Time to Extrahepatic Spread will also be evaluated using the survival analysis.

8.5 Additional Endpoints

Two additional endpoints are studied in this trial. The proportion of patients in each group that achieve complete response (CR), partial response (PR), and stable disease (SD) will be presented and compared across treatment groups. The data from the tumor response will be presented descriptively by treatment group without a test of hypothesis.

The second additional endpoint is the FACT-Hep quality of life instrument validated in patients with Hepatic cancer.

8.6 Data Presentation Convention

The descriptive presentation of continuous or ordinal data will include mean, standard deviation, number evaluated, median, minimum, and maximum. For categorical data, a descriptive presentation will include number with the characteristic being evaluated, the number evaluated, the percent, and the exact 95% binomial confidence interval on the percent.

P-values of statistical hypothesis tests will be presented to four decimal places. Means, medians, minimum and maximum values will be presented to one decimal place beyond observed value and the standard deviation will be presented to two decimal places beyond the observed value. If the observed value is a whole number, then the mean, median, minimum and maximum will be presented to one decimal place and the standard deviation will be presented to two decimal places. Percentages and confidence intervals on percentages will be presented to two decimal places.

8.7 Randomization

The two study groups will be randomized with equal allocation by study site. It is recommended that the study groups being randomized be stratified by ECOG performance status, portal vein invasion and AFP to achieve balance among factors that may have an impact on the outcome. Randomization will be done by study site and within each stratum.

Randomly ordered block randomization will be used in which two block sizes, a and b, will be used in the randomization scheme for each stratum. The order determining which block is randomized first (a or b) will be chosen at random followed by the number of patients in that block being assigned test or control followed by the second block with patients being randomly assigned test or control. For example, if b is chosen first, the first b patients will be randomized followed by the next a patient. The process is repeated until all patients are randomized to treatment groups. In this way at the end of a+b patients at each site, the two treatment groups will be in exact balance.

8.8 Multiplicity

Because there are two hypotheses to be tested in this clinical trial, there is a potential for alpha inflation even though the two hypotheses are correlated. To control for alpha inflation, the closed form hierarchical testing procedure will be used. In this method, the hypotheses will be tested in order of primary effectiveness followed by secondary effectiveness. The secondary hypothesis will not be tested and claimed unless the primary hypothesis achieves statistical significance. If the primary effectiveness endpoint hypothesis is not statistically significant, then the secondary hypothesis can still be tested, but the test becomes an exploratory analysis.

8.9 Statistical Analyses

8.9.1 Assumption Verification

As a routine function of performing statistical analyses, the critical underlying assumptions of specific tests will be evaluated. For two sample t-tests and Wilcoxon rank sum tests, a test of the equality of variance between the treated groups will be done by a folded F test. Where possible binomial comparisons will be done by Fisher's exact test to avoid making assumptions on the distribution. Multinomial comparisons will be done by the Fisher-Freeman-Halton test, the rxc table extension of Fisher's exact test. If an exact test cannot be done then a Pearson chi-square test will be done consistent with the Cochran criteria. To achieve the Cochran criteria it may be necessary to merge some categories to get minimum cell frequencies to 5 or more.

8.9.2 Comparability Analyses

The analysis of baseline characteristics between treatment groups will be done. Between treatment group analyses of continuous variables will be done by a two-sample t-test or a Wilcoxon rank sum test. The Wilcoxon test is preferred for asymmetric distribution unless the variances differ by treatment group. In the event that the variance is unequal between the treatment groups, an unequal variance t-test will be done. Binary categorical comparisons

between treatment groups will be done with Fisher's exact test. Ordinal categorical variables with less than 10 classes will be evaluated by Fisher Freeman Halton test. Ordinal categorical variables with more than 10 classes will be analyzed as continuous variables.

A second comparability analysis will be done between study sites ignoring treatment assignment using the same test procedures as described in the paragraph above. Because study sites are nested within countries, a separate comparability analysis by country will not be done. If the sites within one country differ in characteristics with those of another country, country and site will be used as possible covariates as described below.

Small sites with under six patients will be pooled with other small sites to form pseudo-sites. The method of pooling will be by consecutive site numbers such that the total size of any pseudo site shall not be greater than median sample size among the study sites. If the combining of sites into pseudo-sites gets to a point such that adding the next numbered site will exceed the limit value (median size for the sites), that site will be skipped and the next small site in order will be added unless it too would result in exceeding the limit and the process continues in this manner until the remaining small sites are exhausted. If no site can be found that can be added, that pseudo-site will be closed at the number of patients with the sites added and a new pseudo-site will be started.

Baseline variables or characteristics found to differ significantly between treatment groups, study sites or countries will be considered as possible covariates in multivariable analyses of primary and secondary endpoints.

8.9.3 Data Pooling

The pooling of data involves two issues: combining data from all study sites and considering all data from the sites as arising from a single site to estimate the effect size. The combining of data from all sites is justified on a clinical basis (Meinert, 1986) based on three factors: that the study sites used the same protocol, that the sponsor monitored the sites for protocol compliance, and that the sites all used the same data recording and processing methods.

The pooling of the data to obtain a common estimate of the effect size for each treatment requires the effect to be independent of study site. To determine if the effect is independent of study site, a Cox regression model of the outcome for the primary effectiveness endpoint will be done to determine if there is a treatment by study site interaction. If the treatment by study site interaction in the model which includes treatment, study site, baseline characteristics that were out of balance among study sites and the interaction of treatment by study site has a P-value of <0.10, then the primary endpoint analysis will be model based on Cox Regression which adjusts the remaining covariates in the model for a study site effect as explained in detail below

8.9.4 Analysis Populations

All patients who are randomized comprise the intention-to-treat (ITT) population. The ITT population will be the analysis population for primary safety and efficacy analyses.

All patients who complete the 12-month evaluation will comprise the completed cases (CC) population. The CC population will be used for selected analyses.

8.9.5 Patient Accountability

The accountability of study participants by study visit will be presented descriptively. Patients who withdraw from the trial will be tabulated with time of withdrawal and reason for withdrawal. Compliance with scheduled study visits will also be tabulated by presenting the number of patients eligible for each visit, the number and percentage of eligible patients with a visit in window, the number and percentage of eligible patients with a visit outside of window, and the number and percentage of patients with no visit. The number of patients eligible for any visit is taken as the number enrolled minus the number who died or withdrew prior to the visit window.

8.9.6 Missing Data

A recent panel from the National Research Council (2010) confirmed a well-known statistical problem, that missing data present difficulties in analysis of study endpoints. Loss of patients can lead to compromising the balance between treatment groups afforded by the randomization process and the results of patients who complete the trial may not be representative of results patients who leave the trial would have had if they had remained in the trail. The panel indicated that every effort should be made on the part of the sponsor and investigators to minimize the amount of missing data. Further, acknowledging that it is impractical to assume that there will be no missing data, the panel recommended that the primary analysis be completely specified in the protocol to include the method by which missing data are to be imputed, and to include multiple sensitivity analyses to demonstrate the robustness of the results from the chosen primary analysis imputation method. The panel indicated that all methods of imputing missing data are based on untestable assumptions, but that the chosen imputation method should be as scientifically defensible as possible. Single imputation methods, such as last observation carried forward (LOCF), including very conservative methods such as counting all patients with missing primary outcomes as failures are not consistent with good science and are discouraged by the panel.

The major untestable assumption basic to any imputation is that the data missing from the study is at least missing at random (MAR), i.e., the reason the data is missing is unrelated to the measurement of the datapoint. If a patient leaves the trial due to incapacity as a result of worsening cancer, that patient is not missing at random because his/her quality of being

missing is dependent on the actual measure of cancer severity. Patients who leave the trial for alternative treatments for cancer or for other evidence of progressive cancer be considered as having died at the time of withdrawal for the primary endpoint or progressed for the secondary endpoint.

While it is not possible to determine if a patient's data is missing at random, there are comparisons between patients with missing data and those without missing data that may indicate a sub-group of patients who may not be missing at random. For example, differential withdrawal for reasons other than progression or death between the treatment groups may indicate that one treatment is more onerous than the other. An analysis of the baseline characteristics to test the comparability of patients with missing data and those without missing data will be done to attempt to identify differences in the two populations that may indicate a not MAR sub-group. If such a sub-group is identified, a suitable conservative assignment of the endpoint for the missing cases in the sub-group will be done (usually to assign a death or progression to the patient at the time of withdrawal). These decisions cannot be pre-specified but will be completely documented in the report of the analysis.

Fortunately, the method of survival analysis considers all patients and treats patients who are missing prior to the assessment as being censored at the time they are lost to follow-up. These methods compute the survival based on the patients at risk at the time of the event (progression in this study) so no imputation is needed for the primary or secondary endpoints.

8.9.7 Primary Effectiveness Endpoint Analysis

The initial analysis of the primary endpoint will be by Kaplan-Meier using the log-rank statistic. The test will be on at a one-sided alpha of 0.025. If the treatment by study site interaction is statistically significant at $P<0.10$, this initial exploratory analysis will be done by a simple Cox regression model to include treatment group and study site. The inclusion of study site adjusts the treatment effect for the effect of site. If the site by treatment interaction has a $P<0.05$, the interaction will be fully investigated by multivariable analyses described below.

This analysis will be followed by a supportive multivariable analysis of survival at one year by Cox regression in the ITT population to determine if there are any covariates that impact the freedom from progression. Covariates to be used in this analysis will include age, ECOG status (0 versus 1), disease stage (BCLC classification in two groups), AFP (<400 vs. ≥400), Child-Pugh class (A or B7), treatment group, number of active treatment sessions (embolization and drug delivery sessions), study site, and any variable found to be out of balance between the treatment groups. Interactions with treatment group will also be

evaluated. The possible covariates listed above will be screened by the method describe in Hosmer and Lemeshow (2000) with a Cox regression model that includes treatment group, the covariate and the covariate by treatment interaction. If the interaction term does not have a P-value less than 0.20, a second model will be used to get a p-value for covariate that has only treatment group and the covariate. Any covariate or interaction term that has a $P<0.20$ will be allowed to enter the competition for the final model.

The initial model will contain all covariates and interactions that have a screening $P<0.20$. The model will be reduced by backward elimination with treatment group retained in the model regardless of other factors. The final model will retain treatment group and any covariate that achieves a P-value of 0.05 or less. If after inclusion of variables found out of balance by study site the study site interaction with treatment and/or the study site covariate become non-significant, then the simple primary analysis above will be redone with the out of balance variable to replace study site in the paragraph above. Often the appearance of a study site effect is the result of an imbalance among the sites in a covariate that can affect the primary endpoint. Other statistically significant covariate interactions with treatment group will be explored post hoc by creating sub-groups for statistical comparisons.

8.9.8 Secondary Efficacy Endpoint Analyses

The initial univariate secondary endpoint will be evaluated by a one-sided Kaplan-Meier log-rank test. The nominal alpha for this test will be 0.05. .

Following this univariate analysis, a multivariable analysis by Cox regression using the same approach as described above for the primary endpoint with the same set of possible covariates.

8.9.9 Primary Safety Endpoint Analysis

The initial analysis of the primary safety endpoint will be by Fisher's exact test of the proportion of patients with a treatment emergent adverse event through one year of follow-up. The P-value for this test will be a one-sided 0.05

Following the initial univariate test, a multivariable analysis of the rates of treatment emergent adverse events will be done with logistic regression. The same covariates discussed above for the primary effectiveness multivariable analysis will be used here as well.

8.9.10 Additional Analyses

The proportions of patients in each treatment group with CR, PR, and SD will be computed through one year. The rates of patient in each group will be presented as percentages and will be reported with exact 95% confidence limits.

The FACT-Hep quality of life scores will be presented descriptively with mean, standard deviation, number evaluated, median, minimum and maximum by treatment group.

8.10 Adaptive Design Interim Analysis

The design of this trial is that of a frequentist adaptive design consistent with the Chen *et al.* (2004).[44] This method was also referenced by Mehta and Pocock (The interim analysis is being used to check the assumptions of the initial sample size computations to determine if those assumptions were nearly correct or were inadequate leading to a change in the sample size. An adjustment will be taken for this interim look using the O'Brien and Fleming (1979)[45] boundary for two looks at the data adjusted by the method of Reboussin *et al.* (2000- http://www.biostat.wisc.edu/landemets/). The revised end of study alpha is a one-sided 0.0245 with a corresponding z=1.9686. The stopping rule for efficacy from this same computations is z=2.9626 with corresponding p=0.0015.

This method allows the sample size for the remainder of the trial to be estimated based on the observation at the interim analysis and the conditional power. The statistic required by the Chen *et al.* (2004)[44] method is a normal z-statistic.

The interim analysis will be done when 50% of the expected deaths occur rather than the number of patients because for survival analyses, the number of events (deaths) is the basis for the size of the trial, not the number of patients. The expected number of deaths in the study has been estimated by simulation to be 127 with 12 to 30 months of follow-up assuming an 18-month accrual time and minimum follow-up of 12 months. Thus the interim analysis will take place when 127/2=63.5 or 64 deaths have occurred.

The third party statistician will perform the statistical test in all patients who have completed the target study visit (CC population). This test will result in obtaining z_1, obtained by taking the square root of the log-rank chi-square which has a single degree of freedom. The square root of a chi-square random variable with one degree of freedom is distributed as a normal z-statistic.

The statistic required by the Chen *et al* method is a normal z-statistic. However in the absence of an interaction with p<0.10, the analysis will result in a z-statistic from the Chi square statistic for main effect for treatment by taking the square root of the single degree of freedom Chi square.

After obtaining $z=z_1$, the conditional power will be computed with the following formula:

$$CP(f,z) = \Pr(Z^{(N_0)} > z_\alpha \mid Z^n = z, \theta = \hat{\theta}) = \Phi\left(\frac{z}{\sqrt{f(1-f)}} - \frac{z_\alpha}{\sqrt{(1-f)}}\right)$$

where N_0 is the protocol estimated sample size (122), n is the sample size at the interim analysis (61), $Z^{(N_0)}$ is the test statistic at the end of the study, $Z^{(n)}$ is the test statistic at the interim, $f = n/N_0 = 0.5$, z_α is the standard normal value corresponding to 0.0245 in the upper (or lower) tail of the distribution with a value of 1.9686 and Φ is an indicator function for the cumulative normal distribution. For example, if z = 1.39 and z_α=1.96, the conditional power,

$$CP(0.5,1.39) = \Phi\left(\frac{1.39}{\sqrt{0.5(1-0.5)}} - \frac{1.96}{\sqrt{1-0.5}}\right) = \Phi(0.0081) = 0.5032.$$

If the conditional power is greater than 50% as it is in this example, the results of the study are thought to be promising and the sample size can be re-estimated without alpha inflation. If the conditional power is less than 50%, the sample size may still be re-estimated without alpha inflation if there is value provided for futility, i.e., if the conditional power is less than this value, the study will be terminated. For the purposes of this study, the conditional power that constitutes futility is 0.25. If z_1 is such that the corresponding P-value is less than 0.0015, the stopping rule for efficacy will have been surpassed.

The re-estimation formula for the sample size had been adapted from Chen *et al.* (2004) because the formula given in the paper assumes that the standard deviation of the random variable in the test statistic is 1 and the null difference between the treatment groups is zero. The revised formula is presented below.

$$N = \frac{(z_\alpha + z_\beta)^2 \sigma^2}{(\bar{x} - \theta)^2}$$

where N is the total re-estimated number of expected deaths based on the interim result, z_α (1.9686) is the standard normal value corresponding the significance level α, z_β (0.842 for 80% power) is the standard normal value corresponding to a power of (1-β), σ^2 is the square of the standard deviation of the difference which will be approximated as the difference in proportions surviving between the treatment groups, $\bar{x}$ is the mean difference in difference in proportions surviving between the two treatment groups, and θ is the null difference in proportions between two treatment groups. The increase on sample size will be verified by entering the information into Pass 2008 with the survival from the test and control arms from the interim analysis. The larger of the two estimates will be used to resize the trial.

The third party statistician will share no data or results of analyses with the sponsor or sponsor's statistician. The statistician will present one of four messages to the sponsor after the interim analysis:

1. The study has reached the futility boundary and it is recommended that the study be terminated for futility.
2. The study has met the stopping rule for effectiveness.
3. Continue the study to its conclusion without modification of sample size.
4. Increase the numbers of patients in each group by X.

CeloNova has set the futility function such that a z-statistic obtained from the square root of the log-rank chi-square of approximately 1.0548 would result in a conditional power of 0.25. If that value was observed at the interim, the total size of the trial would be about 440 per arm. CeloNova has considered the study size in some depth and has concluded that a total sample size of 450 patients (225/arm) would be the upper limit of its resources allocated to this study.

8.11 Detailed Statistical Analysis Plan

Prior to database lock, a detailed statistical analysis plan will be written and approved to provide more specificity to the analyses to be done. This plan may be submitted to the FDA as an IDE supplement for review and approval.

8.12 Statistical Software

The statistical analyses will be done using SAS version 9.2 or later and StatXact, Version 8 or later. Each of these software packages provides special features that will be exploited to provide a comprehensive analysis with excellent graphics support.

9. Committees

9.1 Executive Committee

The executive committee is responsible for overseeing the conduct of the study with respect to:

- The protocol;
- Study progress, safety and quality;
- The dissemination of the results.

The committee will be comprised of investigators participating in this study, representatives of CeloNova or consultants to CeloNova. The Executive Committee will be established and managed by CeloNova. The committee will meet on an appropriate basis, as needed throughout the study progress.

9.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will act as an independent group to evaluate safety data to assure patient safety and study integrity. The DSMB will provide safety related study reports to the Sponsor, based on the safety data collected and reviewed. This committee will consist of three highly experienced clinicians within the field of the study, a medical monitor and an independent statistician.

The study Medical Monitor (who is a non-voting member of the DSMB) will be alerted to all SAEs. The Medical Monitor may request additional assistance by one or more DSMB members in the classification of serious AEs. In addition, the Sponsor may request ad hoc DSMB meetings to review any SAE associated with the investigational product. The Independent statistician will provide the DSMB with a current AE report prior to the safety reviews conducted by the DSMB.

The committee will review all adverse events that are deemed severe, serious, product-related, procedure-related, or unexpected to assess severity and potential relationship to the product or procedure. Both the original assessment reported by the treating physician and DSMB-adjudicated classification of the events will be reviewed, confirmed or challenged and reclassified, and reported to the FDA as required per federal regulations. The committee will alert CeloNova regarding any patient safety issues that are evaluated. This board will also make recommendations regarding stopping the study, terminating the study if unexpected safety concerns are noted, or may suggest protocol modifications to ensure patient safety.

The DSMB will meet after 50 patients complete one month after the onset of their treatment and will review cumulative safety data after each subsequent 50 patients are enrolled.

9.3 Independent Response Review Panel (IRRP)

The Sponsor may use an Independent Response Review Panel (IRRP) for review of data for all patients in the full analysis set (FAS) to confirm response (or lack thereof). If an IRRP is utilized, results from the IRRP, rather than the investigator, will be used in the formal efficacy analyses and summaries. The IRRP will provide assessments of best response (CR, PR, SD or PD), and also date of progression for patients who achieve OR.

10. Study Monitoring and Record Keeping

10.1 Data Handling

The Investigator will maintain a file for each patient that includes the signed informed consent and copies of all CRFs/ eCRFs completed for that patient. The following study-related records should also be retained and stored:

- Study Protocol and all amendments
- IRB/EC/CA approved Informed Consent Forms
- Signed Statement of Investigator form
- Approval letter(s) from and all other correspondence to and from the IRB/EC/CA
- The certification of the clinical laboratory used for this study
- Curriculum vitae for the Investigator(s) and Sub-Investigators
- Records from the Sponsor related to product shipments for treatment allocation
- Completed and signed dispensing records for study material
- A list of ancillary study personnel including delegation of responsibilities
- Copies of all laboratory test results and other original data from which CRF information was obtained
- All correspondence to and from the Sponsor

10.2 Retention of Data

Data related to this study must be stored according to the regulations pertaining to studies performed under §812.140(a)(3)(i).

Each Investigator will retain records required to be maintained under this part (case histories and data collected as part of this trial for both Test and Comparator patients) for a period of 2 years following the date a marketing application is approved for the implant or indications for which it is being investigated or, if no application is to be filed or if the application is not approved for such indications, until 2 years after the investigation is discontinued and the FDA is notified.

10.3 Electronic Case Report Forms (eCRFs)

The electronic case report forms (eCRFs) contain confidential information. This study will utilize electronic data capture (EDC).

Specific instructions to complete the eCRFs shall be provided to the Investigator and other site personnel as appropriate. The Investigator is responsible for reporting appropriately and in a timely manner.

CRFs have been developed for recording the conduct of the study by CeloNova Biosciences, Inc. Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. Therefore, the information collected on the CRFs must match those charts.

Sponsor or designee will review eCRFs to ensure the data is accurate. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data entered on the electronic database.

Case report forms are provided for each patient. Each casebook must be signed and dated by the Investigator.

All case report form corrections are to be made by the Investigator or other study site personnel. The Investigator must authorize changes to the recorded data. The CRAs (Clinical Research Associates) will review the eCRFs to determine their acceptability. Completed CRFs will be submitted to the Sponsor. CRFs should be completed as soon as possible after the data are available.

10.4 Audit and Supervision

Investigator sites and study documentation may be patient to Quality Assurance (QA) audits during the course of the study. In addition, inspections may be conducted by regulatory bodies at their discretion, during and after study completion.

The Investigator agrees to allow inspectors from regulatory agencies to have access to all study records, including patient source documents. By participating in this study, the Investigators agree to these requirements and will assist the inspectors in their duties. The Investigator should immediately notify the Sponsor of an upcoming inspection.

10.5 Data and Quality Management

The clinical study will be monitored according to CeloNova or its representative SOP's
Monitoring activities at the site include, but are not limited to:

- Source document verification,
- Investigational product accountability,
- Review of investigator site files.

The CRA ensures that original, signed source documents (or certified copies) are available for verification against the eCRFs at the site during each monitoring visit. As part of the source document verification process, the monitor confirms the following:

- All relevant adverse events, concomitant medications, medical history and concurrent illnesses have been entered into the appropriate sections and reconciled for logical relationships.
- Missed patient visits, tests or examinations are adequately documented in the eCRF.
- All data queries are source verified and/ or required and resolved.

CRAs use the following criteria when monitoring source data:

- Original source notes or shadow file are reviewed.
- Verification (by verification of source data) that all patients exist.
    - The Investigator keeps a written or electronic patient file for every patient participating in the clinical study. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, gender, height, weight, patient medical history, concomitant diseases and concomitant medications (including changes during the study), statement of entry into the study, study identification, randomization number, the date of informed consent, all study visit dates, protocol- defined examinations and clinical findings, observed Adverse Events, and reason for withdrawal from the study, if applicable.
    - It must be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.
    - It must be possible to identify each patient by using this patient file.
    - Any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. This includes laboratory value listings.
    - All of these documents have to bear, at a minimum, the patient identification and the printing date printed by the recording device to indicate to which patient and to which study procedure the document belongs.
    - The Investigator should document the medical evaluation of such records as necessary and sign and date.
    - Computerized patient files may be printed whenever the monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the monitor and kept in a secure place.
- The following can be used as source documents:

- Hospital records, clinical and office charts, memoranda, patient diaries, patient questionnaires, evaluation checklists, laboratory reports, pharmacy dispensing records, computer printouts, and any other documentation regarding the patient.

- Verification that all safety and efficacy information is clearly documented.

The Investigator/institution shall allow the Sponsor to carry out audits, as an integral part of the Quality Assurance system. Audits are controls, independent and separate from monitoring, of study activities and documents, with the aim of verifying whether study-related activities have been performed and data have been recorded, analyzed, and forwarded in compliance with the protocol, GCP, SOPs, and applicable regulatory requirements. As a consequence, the Investigator/institution should allow the auditors to access all the above-mentioned documentation

All clinical laboratory determinations will be performed in certified laboratories throughout the study.

10.6 Investigational Product Accountability

It is the responsibility of the Investigator to ensure that all investigational product(s) received at the site is inventoried and accounted for throughout the study and recorded in the inventory log kept in the site study documents. Investigational device accountability will be verified by the Sponsor's study monitor during on-site monitoring visits. Study product will be stored in a secured area with restricted access.

The Investigator will not supply study products to any person except designated staff in this study. Study device will only be dispensed from the designated investigational site.

The Investigator will store and dispose of the Investigational device and their remnants per the Sponsor's instructions. Disposal of unused investigational device, if requested by the sponsor, will be recorded in the source documentation and in the inventory log.

10.7 Study Documents

The study documents, including signed protocol, Investigator's curriculum vitae, IRB/EC/CA approval and approved Informed Consent Form, data imaging/reports and institutional laboratory accreditation, will be submitted to Sponsor or designee.

10.8 Reporting and Publication

The Investigator will be able to publish and/or present the data generated from the study after mutual agreement between the Investigator and Sponsor. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Sponsor personnel will share authorship with Investigators and their designees in any publications resulting from this study. Investigational plans, protocols, and data related to this study will be treated as confidential information.

10.9 Sponsor Responsibilities

Sponsor will use study data for internal monitoring of product safety and efficacy by performing regular updates of the safety profile and the planned interim analysis. This will most likely occur prior to any publication by the Investigator.

Required Sponsor's records include the following:

- All correspondence (Monitor, Investigator)
- Shipment and disposition of investigational products and supplies
- Signed Investigator Agreement
- Maintenance of monitoring documentation.

The Sponsor or designee will monitor the study following standard procedures and applicable regulations.

10.10 Investigator Responsibilities

The Investigator is responsible for complying with all local, state, and federal regulations relating to performing clinical research with an investigational product. The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement, the approved protocol, and applicable regulations for protecting the rights, safety, and welfare of study patients under the Investigator's care. The Investigator is additionally responsible for the control of investigational product and for providing accurate and verifiable data to the Sponsor.

The Investigator must obtain the Informed Consent of each patient before participation in the study. The Investigator must assure initial and continuing review of the study by an Institutional Review Board (IRB)/ Ethics Committee (EC) that complies with applicable national and local regulations.

Other Investigator responsibilities relative to the IRB include the following:

- Submit to the IRB/ EC for review any advertisements that will be used to recruit patients.
- Submit all protocol amendments to the IRB/ EC for review.

- Report to the IRB/ EC any information received from CeloNova BioSciences about serious adverse events reported in other studies associated with the Investigational Product(s). Provide the IRB/EC/CA with any other information it requests before or during the conduct of the study.
- Report to the IRB/EC/CA all adverse events that are serious, unexpected, and possibly or probably related to the investigational material.
- Maintain a file of IRB/EC/CA study-related information.
- Update the IRB/EC/CA on a minimum of a yearly basis.

10.11 Archive

The Investigator will retain a copy of all study documents, including reports to the IRB/EC/CA and to the Sponsor, in accordance with local regulations.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Sponsor and IRB/EC/CA must be notified in writing of the name and address of the new custodian.

10.12 Protocol Amendments

Amendments to this protocol can be initiated by the Sponsor or at the request of the Investigator. All protocol amendments must be documented in writing, including the date and justification for the change, and approved by the Sponsor, Investigator and the reviewing IRB/ EC prior to implementation of the amendment.

10.13 Protocol Deviations

Any deviation from the protocol shall be recorded with an explanation for the deviation. Deviations shall be reported by the Investigator to Sponsor or designee who is responsible for analyzing them and assessing their significance.

All deviations (variation from this protocol) must be accurately documented on the Protocol Deviations CRF by the person who identified the deviation. The form shall be signed and dated by the Investigator. Contact will be made with Sponsor or designee before implementing any departure from the protocol as long as it does not affect patient safety. A deviation from the protocol to protect the life or well-being of a patient in an emergency or deviations which may affect the scientific soundness of the protocol or the rights, safety and welfare of the patient must be reported by the Investigator or the Sponsor and the IRB/ EC. Such notice shall be given as required by local regulation. The case report form and source document must also describe any departure from the protocol and the circumstances requiring it.

Significant deviations defined as compromising or potentially compromising the safety of the patients, enrollment of non-eligible patients and any deviation which compromises significantly the outcome of the study, shall be patient to reporting to the IRB/ EC within the appropriate deadlines indicated by the IRB/ EC.

10.14 Interim and Final Report

The Investigator shall submit a report regarding his/her portion of the investigation to the Sponsor and the IRB within three (3) months after termination or completion of the clinical study or at interim periods as requested by the Sponsor. The Final Report shall then be prepared by Sponsor or designee upon completion of the statistical analysis.

10.15 Changes to Protocol or Related Procedures

No changes in the study procedures shall be effected without mutual agreement of the Investigator and the Sponsor. All changes must be documented by signed protocol amendments.

11. Ethical Consideration

The Study will be performed according to the World Medical Association Declaration of Helsinki, and local regulations for clinical trials. Additionally, applicable provisions of ISO 14155:2011 and FDA regulation 21 CFR parts 812, 50, 54 & 56 will be followed.

11.1 Institutional Review Board (IRB)/ Ethics Committee (EC)

The Protocol and Informed Consent to be used must be approved by the Investigator's IRB/ EC before the study is initiated; documentation of this approval (i.e., a copy of the document showing IRB/ EC approval that should include the IRB/ EC chairperson's [or designee's] signature and the date of IRB/ EC's approval) is to be provided to the Sponsor.

The Sponsor expects the Investigator to comply with local IRB/ EC regulations. The Investigator will also comply with current GCPs particularly in reference to the safety and rights of the patients. Investigators are encouraged to discuss any ethical issues that arise prior to or during the conduct of the study with the Sponsor.

11.2 Declaration of Helsinki

The study will be conducted according to the guidelines established in the Declaration of Helsinki, U.S. Good Clinical Practices (GCPs) and local ethical and legal requirements. Patients will be free to withdraw from the study at any stage without prejudice to their subsequent treatment. The Declaration of Helsinki is provided in Attachment 7.

11.3 Informed Consent

The Informed Consent must comply with all applicable regulations (21 CFR 50). It must also include any additional information required by local laws relating to institutional review.

12. FDA Notification

Any applicable notifications or submissions will be made to the FDA during the course of the study. The study obligations for the Sponsor, the Clinical Research Associate and the Investigator are followed as outlined in FDA 21 CFR 812 and reviewed with the Investigator prior to the start of the study.

13. Study Obligations

13.1 Discontinuation of the Study by Sponsor

The Sponsor may discontinue the clinical investigation if:

- Major non-adherence to the clinical investigational plan is occurring.
- It is anticipated that the patient recruitment will not be adequate to meet the trial objectives.
- In the case the Sponsor discontinues the study, sponsorship for the patients already recruited in the study will continue.

14. Health Economics

DEB-TACE studies are frequently used to describe clinical and functional outcomes following TACE procedures. The results of these studies are published in the medical literature to show the efficacy of a given product or procedures. While interventional radiologist, manufacturers, and regulatory agencies are primarily interested in the efficacy and safety of DEB-TACE procedures, others in the medical community are interested in the economic impact of new products and procedures. Economic analysis is used by policy makers to determine funding of new treatments and procedures.

Post-hoc health economic analysis may be performed based on the following parameters: the cost of the procedure, the quality of life, and the number of years of quality of life gained to provide a single cost-effectiveness ratio.

Required elements for conducting health economic analyses would include the cost of the device and the procedure, cost of alternative treatments, utilization of medications, utilization of other healthcare services and the quality of life measurement. The cost of the procedures will be derived from the operative duration, the treatment used and any observed complications.

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16. Document Changes Summary

Date	Summary of Changes
May 2015	Cardiac Monitoring in the DEB-TACE arm (5.2.2); • Added Echocardiography or MUGA to the baseline • Revised the cumulative dose of doxorubicin to 300 mg instead of 450 mg. So, the cardiac monitoring will be performed prior to each DEB-TACE treatment after the patient has received a cumulative dose of 300 mg/m^2. Added Clarification • At visit 3, imaging is not mandated for DEB-TACE arm, if a second DEB-TACE is predefined at baseline (5.2.2, 5.5). • Day 0 is now the day of randomization. The onset of treatment will start immediately after the randomization or as soon as possible without being outside the baseline window of 30 days (5.2.2). • Modified the randomization to be Day 0 for both arm as the starting point and modified the timing of visit 3 (14-28 days instead of 14-21 days) (5.2.2) • Adjusted visit 5 to accommodate both arms (modified the window to ±2 weeks instead of 2-4 weeks range) (5.5) • Terms for first DSMB meeting to be conducted when 50 patients completed one month followup after the onset of their treatment (9.2). • Corrected ICF to state cumulative dose of 300 instead of 450. Added explanation of MUGA (Appendix C) Added Appendix F to address Affect of Medicare beneficiaries for US
MAR 2015	Endpoints • removed overall survival from secondary endpoint as it is currently a primary endpoint. Intended Use (1.4.1) • Modified endpoint to state devascularization of tumor/lesion and delivering of the full doxorubicin dose. Also modified to state that if blood flow is still detectable in the tumor, the procedure can either be

	stopped or use bland microspheres. Inclusion criteria (3.4.1) • Modified criterion 3 to include diagnosis of HCC via biopsy • Modified criterion 4 to specify HCC showing at least two of the following features (previously one) in order to restrict patient selection to fit global clinical practice. o Multinodularity (>4 lesions) o Large size (>5 cm) (Also removed "total composite size" from this feature.) o Segmental branch portal vein invasion Exclusion Criteria (3.4.2) • Modified criterion 5 to remove examples of contraindications for TACE • Added criterion 17 "Patient has another primary tumor, with the exception of conventional basal cell carcinoma, superficial bladder cancer, melanoma in situ, or treated prostate cancer currently without biochemical or radiographic evidence of active disease" • Removed "known hypersensitivity to iodinated contrast agents which cannot be adequately pre medicated and controlled." As this a part exclusion 5. Study Design (3.0) • Clarified stratification by ECOG Performance Status 0 versus 1, portal vein invasion by adding "yes vs no". Treatment Plan (3.5) • Clarified target follow up dates • Modified the treatment plan for the ONCO-DOX arm to specify that treatment of multifocual bilobar disease will consist of at least two embolization sessions (unless complete response is achieved) with an interval of 4-8 weeks. • Modified the treatment plan for the ONCO-DOX arm to state that a second DEB-TACE treatment can be performed every 4-8 weeks after initial treatment, instead of every 2-4 weeks as previously written in order to align with global clinical practice. Screening Procedures (5.1) • Removed chest CT to exclude lung lesions before randomization • Removed LVEF (echo or MUGA) as it is not currently a standard of

	care • For "Imaging (CT or MRI)", clarified by adding "pelvis, abdomen and chest to assess the tumor in the liver and exclude extra hepatic lesions" Study Activities • Imaging (5.1.2) was clarified and corrected by specifying Multiphase CT or MRI of the "pelvis, abdomen and chest" is acceptable, rather than "liver". • General considerations for ONCO-DOX arm Day 0 (5.2.2) was modified to state "conscious sedation or general anesthesia (at the physicians discretion)" rather than local anesthesia. Also removed detailed information on performing chemoembolization. This was done to accommodate global clinical practice. • Modified timepoint for second DEB-TACE procedure to 4 weeks after initial procedure instead of 2 to accommodate global clinical practice. • Changed follow up assessment to 14-21 days post initial procedure rather than 10-14 • Added imaging to schedule of assessments to accommodate global clinical practice. • Added echocardiogram/MUGA as an assessment to accompany 12 lead ECG immediately before the ONCO-DOX procedure after the maximum dose of doxorubicin has been given • Removed echocardiogram or MUGA scan after second treatment and each thereafter from schedule of assessments as it is not currently a standard of care • Specified that a 12 lead ECG is performed immediately before the ONCO-DOX procedure after the cumulative dose of 450 mg of doxorubicin has been reached for those patients requiring several embolization procedures. • For post treatment follow up (5.3) added imaging for extra-hepatic metastasis as a clarification and correction to assess the secondary endpoint. • Updated schedule of assessments Adverse Events (6.3) • Added statement "After discontinuing study treatment, the reporting of all AEs is to continue for 45 days or until the patient receives alternative therapy for their HCC, whichever occurs first. "

FEB 2015	Corrected typographical errors in Section 3.4.2 (Exclusion 6) and Appendix B.
JAN 2015	Clarified the final analysis of the Primary Study Hypothesis in accordance with FDA recommendations. Increased enrollment duration from 12 months to 18 months. Added additional 2 year phone follow up for survival. Removed inclusion criterion 5 in accordance with feedback from PIs and the embolization approach was further clarified in section 3.5.1. "Patients can have either monolobar or bilobar disease. Patients with bilobar disease must be able to be treated superselectively". Clarified wording in exclusion criteria 1, 4, and 9. Updated exclusion criterion 5 to be the main exclusion and exclusion # 6, 7, 8 and 16 are grouped as a, b, c, d under exclusion 5. Updated exclusion criterion 6 to include "…or INR > 1.5" in accordance with FDA recommendations. Changed exclusion criterion 9 from Ejection fraction < 55% to < 50% in accordance with feedback from investigator and to match other similar trial (HiQUALITY). Corrected inconsistency in sample size missed in previous updated. Corrected to 122 patients per arm. Added report for interim analysis "The study has met the stopping criteria rule for effectiveness". Added "You might receive a phone call from the research staff at 36 and 48 months after the onset of treatment to check your wellbeing." To the inform consent" to reflect the changes in the study protocol follow up. Editorial clarifications throughout
Oct 2014	Inclusion of Protocol Name: SOLACE. Minor Administrative and formatting changes. Clarified that ONCOZENE™ will be loaded with 150mg doxorubicin/3mL rather than patients receiving 150mg doxorubicin as this is dependent on the vasculature of the tumor. Clarified that the target enrollment for the study is 244 (122 per arm) rather

	than 242 (121 per arm); previously this was inconsistent throughout the protocol. Amended the required level of platelets for inclusion into the study from 75,000 to 50,000/mm^3 Clarified the size of bland microsphere to be used, if required, to reach stasis. Clarified that an Independent Response Review Panel (IRRP) may be used. Removed the table detailing each CRF, this will be included in the eCRF Completion Guidelines / Study Manuals. Included a reference to CYP3A4 inducers, P-glycoprotein and CYP2D6 substrates. Ensured visit assessments in text matched those in the Schedule of Assessments table. Clarified patients withdrawing from treatment vs withdrawing from the study entirely. Clarified grading of AEs will be per NCI CTCAE criteria rather than "Mild, moderate, severe". Clarified "Progression of Disease" is an anticipated event. Inserted ECOG Performance Status Appendix A. Inserted Child Pugh Score Appendix B. Inserted Sample Informed Consent Form Appendix C. Inserted NCI CTCAE v4.03 Appendix D. Inserted mRECIST Response Assessment for HCC Appendix E.
Sep 2014	Minor editorial changes Updated stratification to include portal vein invasion and AFP (>400 and <400) Changed exclusion criterion 9. From platelet count from <50,000/mcl to <65,000/mcl Added exclusion criterion ejection fraction <55% Updated cleared indications for use Changed secondary endpoint from "overall survival at 2 years" to "overall survival" Added qualification description of investigators Changed number of patients from 242 go 244 Changed enrollment period to 12 months Updated randomization to occur after eligibility confirmation Updated visit schedule The alpha is 0.025 adjusted to 0.0245 for the interim analysis Updated expected number of deaths to new sample size

	Changed "If the treatment by study site interaction is statistically significant at P<0.10, this initial analysis will be done by a simple Cox regression model to include treatment group and study site." To be an exploratory analysis only.
April 2014	Study Synopsis: Added "Ejection fraction <55%" to exclusion criteria Section 5.2.2: Changed "within one week of each subsequent procedure" to "prior to each subsequent procedure (within one week)" Added "Echocardiogram or MUGA scan after the second treatment with ONCO-DOX and after each treatment thereafter. Section 5.5: Changed "within one week of each subsequent procedure" to "prior to each subsequent procedure (within one week)" Added "Echocardiogram or MUGA scan after the second treatment with ONCO-DOX and after each treatment thereafter.
March 2014	Initial DRAFT

Appendix A: ECOG Performance Status

Performance Status Criteria:
ECOG and Karnofsky Performance Scores

ECOG (Zubrod)		Karnofsky	
Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Required occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

As published in Am J Clin Oncol: Oken, M. M., Creech, R. H, Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., Carbone, P. P.: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M. D., Group Chair

Appendix B: Child-Pugh Score

	1 point	2 points	3 points
Serum Bilirubin (mg/dL)	<2	2-3	>3
Serum Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.30	>2.30
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Class A: 5-6 points
Class B: 7-9 points
Class C: 10-15 points
If there are several test results for one test item, the lower point will result will be used to determine the Child-Pugh class.

Appendix C: Sample Informed Consent Form

SOLACE: A Study of ONCO-DOX in Locally Advanced Hepatocellular Carcinoma

RESEARCH PATIENT INFORMATION AND CONSENT FORM	
TITLE:	A Randomized Controlled Trial of Transcatheter Arterial Chemoembolization with Drug-Eluting Beads (DEB-TACE) Versus Sorafenib in the Treatment of Unresectable, Locally-Advanced Hepatocellular Carcinoma

This consent form contains important information to help you decide whether to participate in a research study.

The study staff will explain this study to you. Ask questions about anything that is not clear at any time. You may take home an unsigned copy of this consent form to think about and discuss with family or friends.

- **Being in a study is voluntary – your choice.**
- **If you join this study, you can still stop at any time.**
- **No one can promise that a study will help you.**
- **Do not join this study unless all of your questions are answered.**

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the study;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this study;
- How your personal health information will be treated during the study and after the study is over;
- Whether being in this study could involve any cost to you; and
- What to do if you have problems or questions about this study.

Please read this consent form carefully.

RESEARCH PATIENT INFORMATION AND CONSENT FORM

TITLE:	A Randomized Controlled Trial of Transcatheter Arterial Chemoembolization with Drug-Eluting Beads (DEB-TACE) Versus Sorafenib in the Treatment of Unresectable, Locally-Advanced Hepatocellular Carcinoma
PROTOCOL NO.:	ONCO 2013-02
SPONSOR:	CeloNova BioSciences, Inc.
INVESTIGATOR:	<Investigator Name>
SITE(S):	<Site Name>
STUDY RELATED PHONE NUMBER(S):	Investigator Name Phone number Phone number (24 hours)
SUB-INVESTIGATOR(S):	Sub-Investigator Name Sub-Investigator Name

Introduction

This is a clinical trial, a type of research study. The Principal Investigator or designee will explain the study to you. Before you decide to participate, it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

You may discuss your decision to participate with your friends, relatives and your Primary Care Physician (PCP) if you wish. If you have any questions, you should ask the Principal Investigator for more explanation. Your participation in this study is voluntary. If you do not wish to participate, this will not affect your medical care in any way.

Why is this study being done?

The purpose of the study is to collect information about the safety and effectiveness of ONCOZENE™ Microspheres when mixed with doxorubicin (ONCO-DOX) and delivered locally through the blood vessel feeding the tumor in the liver in comparison with orally administered sorafenib for the treatment of patients with unresectable, locally advanced hepatocellular carcinoma (HCC). Doxorubicin and sorafenib are anticancer medications approved in the US.

ONCOZENE™ Microspheres without doxorubicin are cleared by the US FDA for the treatment of hypervascular tumors (tumors that are rich with blood vessels). Doxorubicin is an approved drug in the US to treat other types of cancer, and it has been used with other microspheres outside the US to treat HCC in many studies. Sorafenib is an approved drug for the treatment of advanced HCC in the US. A product with physical properties identical to those of ONCOZENE™ Microspheres is sold in Europe under the name of Embozene TANDEM™ Microspheres. Embozene TANDEM™ Microspheres are approved in Europe to treat HCC with and without the addition of doxorubicin.

This study will evaluate the study participants' outcomes (medical condition) after being treated with ONCO-DOX and compare it to those treated with sorafenib alone. The results of this study will be used to apply for approval in the US for ONCO-DOX for the treatment of unresectable, locally advanced hepatocellular carcinoma.

Why have I been chosen?

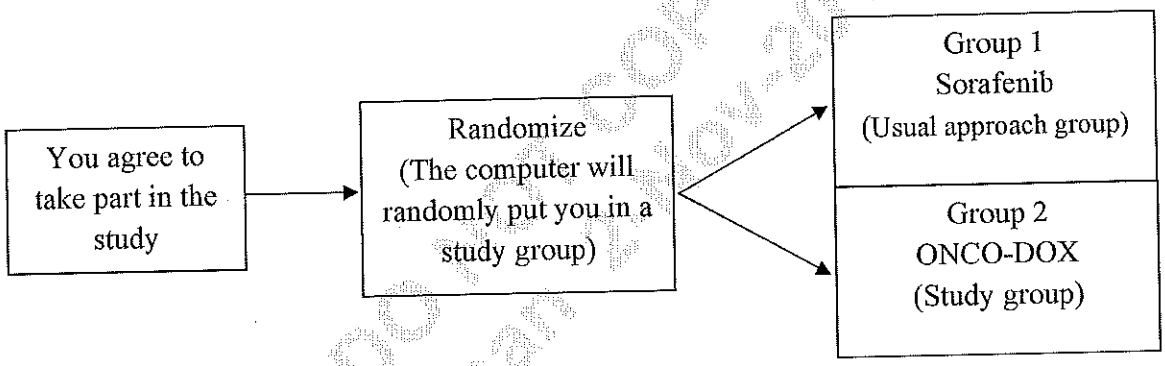
You are being asked to participate in the study because the Principal Investigator (study doctor) has diagnosed you with unresectable, locally advanced hepatocellular carcinoma. They believe you are a good candidate for the study.

How many people will take part in the study?

Approximately 244 patients will be enrolled in this study from up to 40 sites in United States, Europe and Asia.

What is the study treatment?

If you qualify for the study, you will be randomly assigned to receive one of these treatment options. Randomization is like flipping the coin. You have a 50% chance to receive the investigational treatment (ONCO-DOX) and a 50% chance to receive control treatment (sorafenib). Neither you nor your doctor can choose the treatment you are assigned to, a computer program will assign you to a treatment. Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



Investigational Treatment:

- ONCOZENE™ Microspheres are spherical, non-resorbable, hydrogel microspheres coated with Polyzene®-F, an inorganic polymer.
- The loaded dose of doxorubicin is 150mg/3 ml of ONCOZENE™ The goal is to deliver up to 150mg of embolytic particles into the tumor's vasculature by superselective (very thin and close to the tumor site) catheter positioning.

Control Treatment: The Control treatment is sorafenib, administered orally at the standard dose of 400 mg twice a day.

How long will I be in the study?

All patients will be followed every month while receiving treatment and at 6 months, 9 months, 12 months, 18 months, and 24 months after the start of treatment. The total time to completion of your participation is approximately 2 years.

What will happen if I take part in this research study?
Before any study procedures can be done you will need to read, agree to and sign this informed consent form.

Screening:
Before the procedure or treatment, your doctor will perform the following to assess your eligibility for the study;

- Clinical assessment
- Medical History and physical examination
- Pregnancy test (for females of childbearing potential)
- Withdraw blood (approximately 2-3 teaspoons) for hematology and chemistry panel to assess your general health including liver and kidney function, and serum alpha-fetoprotein to assess your liver tumor
- Urine sample
- 12-lead ECG (an exam that measures the electrical activity of your heart)
- Echocardiogram (ultrasound of your heart) or MUGA scan (A MUGA scan is performed to provide information about the blood flowing into the heart and how effectively the heart beats.)
- Imaging (CT scan or MRI): pelvis, abdomen and chest to assess the tumor in the liver and tumor outside of the liver.
- The FACT- Hep quality of life questionnaire
- Record of medications
- Additional lab tests may be collected at the discretion of the investigator, or per standard hospital protocol

These tests will give your Principal Investigator a baseline (initial) record of your liver and overall health condition before the procedure or treatment.

Baseline Visit (Randomization):
After you sign the informed consent and meet the eligibility criteria to enter the study, you will be randomized to receive the ONCO-DOX treatment or the sorafenib treatment.

ONCO-DOX Treatment Group:
If you are in the ONCO-DOX group, you will receive at least 2 treatments based on the extent of the HCC in your liver. Most patients will received between 1-3 DEB-TACE sessions, please discuss this further with your doctor

Prior to the initial procedure, trained staff will mix the ONCOZENE™ Microspheres with doxorubicin (ONCO-DOX). The mixture will be delivered to your liver by placing a small catheter (straw-like tube) from the blood vessel in your groin into the artery that supplies

blood to the liver. The ONCO-DOX mixture is then delivered through the catheter right to the site of the tumor. The result is that a very highly concentrated dose of the doxorubicin is delivered to the tumor. In addition, the blood vessels that supply the tumor are embolized (blocked) with the ONCOZENE™ Microspheres which starve the tumor of its blood supply. By blocking blood supply and supplying chemotherapy directly to the tumor can slow or stop tumor growth, and in some cases can even result in significant shrinkage of the tumor.

Sorafenib Treatment Group:
If you are assigned to the sorafenib group, you will receive 2 tablets twice a day of sorafenib. Each tablet contains 200 mg of sorafenib, for a total dose of 400 mg twice a day. You will return to the office every month for medication supply and study assessments.

No Treatment Possibility
If the Principal Investigator decides that you are not a suitable candidate, you will not be included in the study, and you will receive treatment according to the standard of care, as discussed and agreed upon by you and the Principal Investigator.

If this happens, you will not be required to come to any of the other study-related follow-up visits. The Principal Investigator will determine your follow up care.

Study Treatment Phase:
Your doctor will perform the following at each visit:

- Clinical assessment and physical examination
- Every 2 months during treatment blood tests (chemistry, hematology, serum alpha-fetoprotein) (approximately 2-3 teaspoons of blood will be withdrawn for these tests) & urinalysis will be done
- Imaging (CT scan or MRI): pelvis, abdomen and chest to assess the tumor in the liver and tumor outside of the liver (completed at 2, 4, 6, 9, 12, 18, and 24 months after baseline treatment)
- ECG at 6 and 24 months after treatment for all patients; ECGs will also be done before each treatment in the ONCO-DOX procedure if you have received a total dose of at least 300mg doxorubicin over the course of treatment
- Echocardiogram or MUGA in the ONCO-DOX arm will be done in each treatment if you have received a total dose of at least 300mg doxorubicin over the course of treatment
- ECOG performance Scale to assess your daily activities
- The FACT- Hep quality of life questionnaire (completed at 2, 4, 6, 9, 12, 18 and 24 months).
- Record of medications.

- Record of any adverse events
- Dispense sorafenib to patients in the sorafenib treatment group

Follow-up Visits

During treatment phase in the ONCO-DOX group, you return to the clinic 14-28 days after your initial procedure, repeat DEB-TACE procedures may be done approximately every 4 weeks. After the treatment phase, you return to the clinic every 3 months through month 12 and every 6 months through month 24.

In the Sorafenib group, you will return to the office every month in the first 4-5 months and every 3 months thereafter until month 24.

You might receive a phone call from the research staff at 36 and 48 months after the onset of treatment to check your wellbeing.

What risks and side effects are possible?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may occur and it is possible that additional side effects, other than those listed below, could occur. Side effects may be mild or can be very serious. You must tell the Principal Investigator about any side effects that you have while taking part in the study so they may properly monitor your health.

If you experience a side effect or injury that may be related to this study or if you have an unscheduled visit for medical care for any reason, please contact ***Investigator Name*** by telephoning ***phone number*** during a workday or ***phone number*** at night or on weekends.

For all patients on this study, there is a possibility of unforeseen risks to a pregnant patient and to the fetus of a pregnant patient. Therefore, you cannot be pregnant when entering the study. Furthermore, both male and female patients must agree to use an adequate form of birth control during study participation. For postmenopausal women or women who have had surgical hysterectomy no birth control methods are necessary.

Adverse Events observed with the use of DEB-TACE

The risks and possible side effects of the microspheres used in the ONCO-DOX treatment may be similar to those that have occurred in published clinical studies with similar devices and their rate of occurrences includes (but is not limited to):

- Post embolic syndrome (abdominal pain, nausea vomiting, fever and fatigue) - 24.7%
- liver abscess (pus filled mass inside the liver)- 2.3-7.4%

- liver failure (liver unable to perform its normal function)- 1.2-4.6%
- Cholecystitis (inflammation of the bile ducts in the liver)- 0.9-5.4%
- Pancreatitis (inflammation of the pancreas)- 0.9-3.8%
- kidney complications - 1.3-2.8%
- Hypertension (high blood pressure)- 5%
- Myocardial infarction (heart attack)- 0.3-2.2%
- Vascular complication including vessel injuries and hematoma (accumulation of blood underneath the skin) at the incision site- 2.4-3%
- Non target embolization (the microspheres go to other areas in the liver or other organs) - 1.8%. This means that the microspheres particles could travel into areas like the lung through unnoticed blood vessels (shunt) in the liver causing pulmonary emboli (blockage of the vessels in the lung).
- Pulmonary embolization (a blockage in the lungs) - 0.6-1.8% -
- Pleural effusion (excess fluid around the lungs)- 4%
- Infection- 0.9-6%
- Death- 0-2.4%

Adverse Events observed with the use of doxorubicin

Patients in the ONCO-DOX treatment group will receive doxorubicin. Risks associated with treatment using doxorubicin published clinical studies with similar devices and their rate of occurrences includes (but is not limited to):

- Postembolization syndrome (abdominal pain, nausea, vomiting, fever and fatigue)- 24.7-86%
- Liver failure (liver unable to perform its normal function)- 4.8-6.6%
- Liver abscess (pus filled mass inside the liver)- 4.8-7.4%
- Cholecystitis (inflammation of the bile ducts in the liver)- 5%
- Hepatic infarct (blocking blood vessels in the liver)- 2.5%
- Pleural effusion (excess fluid around the lungs)- 4%
- Leucocytopenia (low white blood cell count)- 5-20%
- Anemia (low number of red blood cells)- 45%
- Marrow Suppression (decrease in the production of cells in the bone marrow)- 5.4%
- Alopecia (loss of hair from the head or body)- 1.1-5%

- Mucositis (inflammation and ulceration most often occurred in the mouth)- 4.3%
- Skin erythema (redness of the skin)- 2.4%
- Infection- 7.5%
- Death- 1.3%

Adverse Events observed with the use of sorafenib
The sorafenib is an FDA approved drug for the treatment of HCC.

Adverse Events reported with the use of sorafenib are (but not limited to):

- Diarrhea- 55%
- Fatigue- 46%
- Alopecia (loss of hair from the head or body)- 14%
- Hand and-foot skin reaction- 21%
- Rash- 19%
- Weight loss- 30%
- Nausea- 24%
- Vomiting- 15%
- Constipation- 14%
- Abdominal pains- 31%
- Hypertension (high blood pressure)- 9%
- Hemorrhage & bleeding- 18%
- Renal failure <1%.

Possible other risks

- Drawing blood may cause pain, bruising, lightheadedness, or, on rare occasions, infection.
- ECG - There are no side effects or risks associated with ECG with the only harmful risk being an allergy to the adhesive substance on the sticky pads. These reactions are normally minor and will clear up after a few days.

- Imaging - The chest x-ray, CT or MRI that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation". No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.
- MUGA - A small amount of nonradioactive chemical is injected into a vein in your arm. As it circulates throughout the bloodstream it attaches to the red blood cells, a process which takes 20-30minutes. Then it is followed by an injection of radioactive material, which also attaches to a small amount of your red blood cells. The radioactive material gives off a small amount of radiation which can be detected by a machine called a gamma camera. The camera takes special pictures of the heart showing exactly how the material circulates into and out of the heart. You will be attached to an ECG machine while the pictures are being taken. The place where you had the IV could bleed, become red, swollen, and painful or infected. There is a very small chance that you could have abnormal heartbeats or a heart attack. The amount of radiation that you receive is small and safe.

What are the possible benefits of taking part in this clinical study?

There is no guarantee that you will benefit from study participation. Your health and medical status will be closely monitored, and you may benefit from the tests that are performed as part of the study. The data resulting from your participation may be of a great value and help physicians and future patients.

Do I have to take part?

Your participation in this study is completely VOLUNTARY. If you decide to participate, we would like you to continue through to the end of the study whether or not you or your physician considers your treatment a success. However, you are free to withdraw from the study at any time for any reason without any penalty or loss of benefits.

If you do withdraw from the study after it has started, it will have no impact on your relationship with the Principal Investigator or his/her institution, your medical care or other services to which you are otherwise entitled.

The Principal Investigator or sponsor may take you out of the study without your consent for any reason. Reasons include:

- to protect your health and safety;

- because you fail to return for your scheduled visits;
- you fail to follow the Investigator's directions;
- the study is stopped for any reason.

If you withdraw your consent for participation, the research team may still use information that was collected as part of the study between the date you signed the consent form, and the date you withdrew your permission.

What other choices do I have if I choose to not participate in this study?

You do not have to be in this study to be treated for your liver cancer. If you choose not to participate in this study, the Principal Investigator will discuss with you alternative treatments include:

1. Oral, injectable, or intravenous anti-cancer medications;
2. Transarterial embolization with or without anti-cancer medications or radioactive materials;
3. Other treatments, including other clinical trials suggested by your doctor

What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the treatments that are being studied. If this happens, the Investigator will tell you and discuss whether you want to continue the study. If you decide to withdraw, the Principal Investigator will make the arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Will my medical information be kept private?

If you consent to take part in this research study, any of your medical records may be audited/reviewed by the study Sponsor (CeloNova Biosciences, Inc.), the U.S. Food and Drug Administration (FDA), local regulatory bodies, ***Institution Name***, and ***or Ethics Committee***.

The Principal Investigator, Sub Investigator, or personnel they work with, will collect your personal information and will record it on special study documents with a unique ID number and initials, without specifying your name.

All information that concerns you will be kept secure and confidential by the Sponsor's qualified and authorized personnel including research professionals contracted by the sponsor. Using only your unique study ID number and initials, your study related data will be entered into a computerized database. The data collected will consist of your medical history, details on the procedures/treatment and the medical information collected during the

clinical study. This information will be controlled and analyzed by personnel who are authorized by the Sponsor.

Collected data will be used without your name in order to evaluate research results and may be used in the future regarding this or other studies. However, your name or any information that may directly identify you will not appear in any study report or publication.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This web site will not include any information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Authorization To Use And Disclose Information For Research Purposes

What type of information will be used or shared?

Your health information related to this study, including but not limited to, demographics (such as your age, gender, ethnicity), physical or medical examinations, photos and or video of the affected site, blood analysis, study-related records, and other information collected during the course of the study may be used or disclosed in connection with this research study. The following parties are authorized to use and/or share your health information in connection with this research study:

- The Principal Investigator and Sub-Investigators,
- Study Coordinator or Research Team,
- Other physicians and medical staff in the radiology department,
- Your primary care physician.

Who will use and receive my information?

The parties listed in the paragraph above may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protection in the U.S. Department of Health and Human Services,
- The FDA and regulatory agencies, including agencies in other countries,
- Representatives of the Sponsor: CeloNova Biosciences, Inc.,
- ***Institution Name***
- Contracted professionals, including CeloNova Biosciences, Inc., medical advisors, data analysts and statisticians.
- ***Institutional Review Boards (IRBs)*** or ***Ethics Committees (ECs)***

Why will this information be used and/or given to others?

- to do the research,

- to obtain study the results, and
- to make sure that the research was done right.

What will happen to my information?
By signing this consent, you give permission to the parties noted in this consent form to use and share your health information collected during this clinical study. Your health information will only be used in accordance with the statements contained within this consent form and applicable laws.

Results may also be presented at scientific meetings and published in journals in anonymous (keeping your identity secret) form only.

May I review or copy my information?
You may review or copy your health information after the research is over.

Is my health information protected after it has been given to others?
There is a risk that your health information will be given to others without your permission.

What if I decide not to give permission to use and give out my health information?
You do not have to give permission to the use and sharing of your health information, but if you do not, you will not be able to be in this research study.

May I withdraw or revoke (cancel) my permission?
Participation in a clinical study is voluntary, you may withdraw your permission at any time without any impact to the medical care you receive from your doctor. There are different types of withdrawal outlined below. When withdrawing your permission please ensure your doctor understands which of these withdrawals apply to your situation:

- Withdrawal from treatment: You may decide that you no longer wish to receive study treatment, however, you still allow the Principal Investigator to continue to collect follow-up information about your health condition and to continue other research activities such as physical exams, blood tests and questionnaires that you previously gave consent to.
- Withdrawal from study assessments: You may decide you no longer want to have some or all blood tests, complete questionnaires, physical exams performed etc, however you do give permission to the Principal Investigator to call you on the phone or collect available follow-up information.

Complete withdrawal from all study activity (Withdrawal of consent): You may decide that you want to stop all study treatments and assessments and you no longer want any health status information collected regarding you whatsoever. If you withdraw your permission

completely then no new information identifying you will be gathered after that date. All research activities will discontinue or stop however information that has already been gathered may still be used and given to others.

What are the costs of taking part in this study?

Any supplies, office visits, examinations and procedures outlined in this consent form and required by the study that are not standard of care for your condition will be provided to you at no cost.

Your insurance will be billed for the costs of:

- the product ONCOZENE™, doxorubicin and sorafenib
- office visits, examinations and procedures that are standard of care for your condition.

You must pay your provider's required deductibles and co-payments.

What happens if I am injured because I took part in this study?

If you are injured as a result of you participation in this study, you will receive medical treatment, including emergency treatment and follow-up care.

If you suffer from an injury that is directly related to your participation in this study, CeloNova Biosciences, Inc. will provide payment for necessary medical expenses not reimbursed or paid for by insurance or otherwise, including hospitalization. Doxorubicin and sorafenib are both approved drugs used in the treatment of liver cancer. Therefore, CeloNova Biosciences, Inc., will pay for such costs only if the injury occurs as a direct result of the use of the ONCOZENE™ Microspheres or its administration in accordance with the protocol and the injury is not related to any underlying disease (as determined by the Principal Investigator and CeloNova Biosciences, Inc.).

In case you are injured please contact the Principal Investigator who will contact the sponsor.

Who is organizing and funding this research?

This project is sponsored by:
CeloNova BioSciences, Inc.
8023 Vantage Drive Suite 1500
San Antonio, USA, 78230
USA
www.celonova.com

This project is managed by:
CeloNova BioSciences, Inc.
8023 Vantage Drive Suite 1500
San Antonio, USA, 78230

www.celonova.com

Who can answer my questions about the study?

If you have any problems, complaints or questions regarding this research study or if you believe you have suffered an injury as a result of participating in this study, contact ***Investigator Name***. at *Phone number* or ***alternate number*** (24 hours).

If you have questions regarding your rights as a research patient or if you have questions, concerns or complaints about the research, you may contact:

<Ethics Committee or IRB name and contact>

This review board is a group of people who independently review human research to be conducted.

This review board will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the review board if the research staff cannot be reached or if you wish to talk to someone other than the research staff. Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

Consent to Participate

By signing below, I am indicating the following:

I have read this entire consent form. The Principal Investigator or designated Sub-Investigator has explained this study to me and reviewed this consent form with me. All of my questions have been answered to my satisfaction. I willingly volunteer to participate in this clinical trial. I understand that I will receive a copy this signed consent form for my reference.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

Name of Patient	Signature	Date

Attestation Statement

I confirm that the research study was thoroughly explained to the patient. I reviewed the consent form with the patient and answered the patient's questions. The patient appeared to have understood the information and was able to answer the following questions correctly:

1. What is the purpose of this study?
2. If you decide to be in the study, what will you be asked to do?
3. What are the possible benefits of participating in this study?
4. What are the possible risks of participating in this study?
5. If you decide not to participate in this study, what options do you have?
6. Will participating in this study cost you anything? If so, what will you have to pay for?
7. Do you have to be in this study?
8. If you decide to be in the study, can you leave the study when you want to?

_____ _____

Printed Name of Person Conducting the Informed Consent Discussion — Position

_____ _____

Signature of Person Conducting the Informed Consent Discussion — Date

_____

Printed Name of Investigator Involved with the Informed Consent Discussion* **(if different from above)**

_____ _____

Signature of Investigator* — Date

**** Either the Principal Investigator or a Sub Investigator trained in the study***

Appendix D: NCI CTCAE Criteria

CTCAE_4.03_2010-0
6-14_QuickReference

Appendix E: mRECIST Response Assessment for HCC

Target Lesions	
Response Category	mRECIST
CR	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the 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 PR or PD
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as a reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.
Non-target lesions	
Response Category	mRECIST
CR	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations	
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2cm.
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1cm interval growth.

Overall Response Assessment with mRECIST

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Appendix F: Affect to Medicare Beneficiaries (US Only)

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the sixth most common cancer in the world, the third most common cause of cancer-related death,[1] and the leading cause of death in patients with cirrhosis in Europe and the United States.[2,3] Over the next two decades, an increasing number of patients with HCC are expected, reflecting in part the current hepatitis C epidemic[4] with the incidence expected to reach a plateau in 2015 to 2020.[5] A majority of HCC cases (60% to 80%) arise due to chronic hepatitis and cirrhosis. Major etiologies of liver cirrhosis include chronic hepatitis B and C, alcohol consumption, steatosis, diabetes, certain medications or exposures to toxic agents and genetic and metabolic diseases.[8] Obesity has also been identified as an independent risk factor for developing HCC.[9,10] A common pathway for these varied etiologies may involve chronic inflammation recognized as a pro-carcinogenic condition.[11] The ONCOZENE device and HCC does not impact only the Medicare beneficiary population. It does impact both gender and ages younger and older than 65 year-old.