Protocol Title: **Prospective Registry of Transarterial Chemoembolization of Metastatic Colorectal Cancer to the Liver with HepaSphere™ Microspheres Loaded with Irinotecan**

Study number: **CRC-P4-16-01**

NCT 04866290

Sponsor: **Merit Medical Systems, Inc.**

[redacted]

Sponsor Contact: [redacted]

Protocol Version: **V2.0**

Protocol Date : **April 21, 2021**

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Principal Investigator Protocol Signature Page

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I, the undersigned, have read and understand the protocol specified above and agree with its content. My signature below indicates approval of this protocol and assurance that this trial will be conducted according to the protocol. I will ensure all study personnel under my supervision is provided copies of this protocol and also commits to conducting the study as specified in the protocol. I will conduct the study according to Good Clinical Practice (GCP), Declaration of Helsinki, , and all applicable local and national regulations.

Principal Investigator (Printed Name): _____

Principal Investigator Signature: _____

Date: _____

Protocol version	Date	Description
1.0	20/MAR/2016	Initial Release
2.0	21/APR/2021	Revision to clarify protocol endpoints and statistical analyses

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1.0 Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosis and age-standardized source of cancer mortality in Europe (GLOBOCAN 2012). Up to one quarter of CRC patients have liver metastases at the time of diagnosis, and 50% will develop liver metastasis within five years (Aliberti 2011); of patients who develop metastatic disease, 40% will have metastases confined exclusively to the liver (Benson 2007). Fewer than 25% of patients with metastatic CRC (mCRC) are eligible for surgical resection or ablative therapies, and of those who are, 70% recur within 3 years (Pwint 2010). With the burden of CRC on the rise – estimated incidence in Europe increased by nearly 20,000 cases per year between 2012 and 2015 (GLOBOCAN 2015) – locoregional therapies to address mCRC in the liver offer a potential route to local disease control in poor surgical candidates.

Transarterial chemoembolization (TACE), a treatment with proven efficacy against hepatocellular carcinoma, is one such option for patients with liver-dominant mCRC. TACE treatment consists of 'loading' HepaSphere Microspheres with a chemotherapeutic agent and delivering it to the target location by injection into the blood stream. In 2014, Huppert and colleagues published a case series of 29 mCRC patients who underwent 71 TACE procedures with irinotecan-loaded HepaSphere Microspheres® (Huppert 2014). All patients had previously undergone resection of their primary tumors, but were currently ineligible for resection of liver metastases that had progressed despite systemic chemotherapy. Each patient received one to three TACE treatments, with a mean interval of five weeks between TACE cycles.

Median survival and time to progression were 21 months and 10 months among patients with less than 25% liver volume involvement, 7 months and 4.5 months among patients with 26-50% liver volume involvement, and 5 months and 3 months among patients with 51-75% liver volume involvement, respectively. According to RECIST criteria, 12 of the 25 surviving patients (48%) had stable disease; by EASL criteria, four patients showed complete response, four showed partial response, and four had stable disease. At 12 months of follow-up, one patient of the 12 with follow-up imaging (8%) had stable disease and the remaining 11 had progressive disease. Toxicities associated with the TACE procedures included upper abdominal pain (severe in 32% of patients, moderate in 40% and mild in 28%) and nausea (ECOG 3 in 12%, ECOG 2 in 43% and ECOG 1 in 45%).

Similar studies have been conducted with DC Bead®. Aliberti et al. performed an initial cohort study in 10 patients with liver-dominant mCRC refractory to systemic chemotherapy who underwent TACE with irinotecan-loaded DC Bead (Aliberti 2006). At one month of follow-up, all patients demonstrated significant reduction in tumor contrast enhancement and carcinoembryonic antigen (CEA) reduction of at least 50%. Objective tumor regression was observed in seven patients. The same research group published serial expansions of their cohort, eventually enrolling 82 patients (Fiorentini 2007, Aliberti 2011). Patients underwent one to four TACE cycles, and all showed reduction in metastatic contrast enhancement. At 3 months of follow-up 78% of patients demonstrated response by RECIST criteria, with a median duration of response of six months. Median survival across the entire cohort was 24 months, with 8 months of progression-free survival.

A later phase III study randomized 74 patients with less than 50% hepatic parenchymal replacement and no extrahepatic spread to TACE with irinotecan-loaded DC Bead and systemic fluorouracil, leucovorin and

irinotecan (FOLFIRI) (Fiorentini 2012). At two years of follow-up, 56% of patients in the TACE group and 32% of those in the FOLFIRI group remained alive; survival dropped to 34% and 9% at 30 months, and 15% and 0% at 50 months among TACE and FOLFIRI patients, respectively. Progression-free survival was 7 months among TACE patients and 4 months among FOLFIRI patients (p = 0.006), but time to extrahepatic progression was not significantly different between the two groups. Objective response was observed in 68.6% of analyzed TACE patients and 20% of FOLFIRI patients. Severe neutropenia, diarrhea and mucositis were significantly more common among FOLFIRI patients, and liver enzyme and bilirubin elevations were significantly more common among TACE patients.

A U.S.-based cohort of 55 patients with liver-dominant mCRC who had received prior chemotherapy underwent TACE with irinotecan-loaded DC Beads and was followed for survival (Martin 2009). Adverse events were increasingly common with irinotecan dose escalation (50 mg to 200 mg). At 12 months of follow-up, 8 patients (15%) had complete response, 14 (25%) had partial response, 23 (42%) had stable disease and 10 (18%) had progressive disease according to mRECIST criteria (Martin 2011). Median overall survival for the cohort was 19 months, median progression-free survival was 11 months, and median hepatic-specific progression-free survival was 15 months.

Narayanan and colleagues have presented a retrospective analysis of 28 patients with hepatic metastases from CRC treated with irinotecan-loaded DC Bead (Narayanan 2013). These patients underwent one to five TACE procedures, and survived for a mean of 14.1 months. Complete response was observed in 3 (15%) patients, partial response was observed in 6 (30%), stable disease was observed in 4 (20%) and 7 patients (35%) showed progressive disease. The most common adverse events included nausea (47%), abdominal pain (43%), and vomiting (28%).

Only one publication to date has compared the efficacy of irinotecan-loaded HepaSphere Microspheres and DC Beads in the treatment of liver tumors (Namur 2015). In this study, performed in a VX2 rabbit model, treatment with irinotecan-loaded HepaSphere Microspheres resulted in significantly greater tumor necrosis and a significantly smaller area of residual tumor tissue than treatment with irinotecan-loaded DC Beads or bland HepaSphere Microspheres.

2.0 Study Objectives

Collectively, the studies above suggest that chemoembolization of metastatic colorectal cancer (mCRC) with irinotecan is a useful addition to the treatment armamentarium. HepaSphere Microspheres loaded with irinotecan received the CE mark for the indication of use in embolization of mCRC to the liver in 2015. Since that time, at least 100 patients with metastatic colorectal cancer to the liver have been treated with HepaSphere loaded with irinotecan within the context of this trial. The goal of this registry is to add to the understanding of the use and value of transarterial chemoembolization in 'real life' usage conditions.

2.1 Primary Objectives

- The primary study objective is the median overall survival of subjects treated with HepaSphere Microspheres loaded with irinotecan. Analysis will be performed when all subjects enrolled have been followed for survival for two years (24 months), are considered lost to follow up, or have died, whichever comes first. Survival time will be calculated in months and utilize the date of the first TACE procedure, the date of death (from any cause), and/or the last successful contact with the subject before they were considered lost to follow-up. Kaplan-Meier (product-limit) method will be used to assess median overall survival times.

2.2 Secondary Objectives

- Objective Response Rate (ORR) as determined by mRECIST criteria (Llovet 2008; Lencioni 2010). ORR will be calculated when all subjects enrolled have been followed for survival for two years (24 months from the date of their first TACE), are considered lost to follow up, or have died, whichever comes first
- Best Tumor Response (during the period of time between the first TACE and the last post TACE MRI or CT) as determined by mRECIST criteria
- Median liver progression-free survival will be calculated as the time (in months) between the first TACE procedure to the date on which progression of the subject's liver metastases was documented or the date of death (from any cause)
- Time to Progression, including extrahepatic progression, utilizing the date of the first study TACE as time zero

2.3 Additional Analyses

If sufficient data is available, additional exploratory analyses will also be conducted. These may include, but are not limited to:

- Pharmacokinetic (PK) Analyses: Plasma concentrations of irinotecan and SN38 will be analyzed at the following timepoints after the first TACE procedure: 30 minutes, 1 hour, 4 hours, 12 hours, and 24 hours or prior to discharge (whichever comes first).
- Additional TACE Cycles: The relationship between 'Additional TACE cycles,' (defined as cycles a subject may undergo after the protocol specified TACE 1 and TACE 2) and overall survival time (in months)
- RECIST 1.1: Reanalyze clinical outcomes using RECIST 1.1 criteria and compare best tumor response between RECIST 1.1 and mRECIST criteria.
- Clinical Success: Similar to ORR, clinical success will be based on the last post TACE liver response evaluated through mRECIST and RECIST 1.1 criteria. Clinical success is the total amount of confirmed subjects that have a complete or partial response [clinical success = (# CR + #PR)]

3.0 Study Design

This prospective, single arm, post-market clinical trial is designed to demonstrate safety and efficacy of Merit Medical Systems' HepaSphere Microspheres loaded with irinotecan for subjects with metastatic colorectal cancer to the liver. There will be two hospitals participating in this study, one in Greece and one in France. Hospitals and physicians with experience in routine use of chemoembolization for mCRC will participate. Subject recruitment and offer to participate in the study will be at the investigator's discretion (ensuring that subjects are existing patients receiving care at the hospital and that they meet inclusion and exclusion criteria).

4.0 Eligibility Criteria

4.1 Inclusion Criteria

The following inclusionary information must be evaluated by the investigator/institution to confirm the patient meets all of the following criteria:

- Histologically or radiologically confirmed colorectal cancer metastases to the liver
- Patient is able to have either CT or MRI imaging
- Hepatic tumor burden ≥50% of total tumor burden
- Hepatic tumor burden ≤50% of total liver volume
- Not suitable for treatment by resection or percutaneous ablation at time of TACE treatment
- Life expectancy ≥ 3 months
- WHO performance status ≤ 2

4.2 Exclusion Criteria

The following exclusionary information must be evaluated by the investigator/institution to confirm the patient does NOT meet any of the criteria below:

- Previous treatment with any form of hepatic transarterial embolization
- Total bilirubin ≥ 3.0 mg/dL
- Any contraindication for irinotecan administration
- Partial or complete thrombosis of the main portal vein
- Cardiovascular or respiratory failure
- Any other condition deemed exclusionary by the Investigator

4.3 Informed Consent

The subject must provide written informed consent prior to any study related procedures or interventions beginning. After the registry has been fully explained and the patient has had adequate time to thoroughly review the consent form, they will have the opportunity to have all their questions answered by their physician. Written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to any registry procedures being performed. The patient will be given a copy of the consent form. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

5.0 Study Procedures

5.1 Screening and Baseline Evaluation [within 4 weeks (28 days) of first TACE procedure]

- Assess subject eligibility
- Obtain Informed Consent
- Review and record relevant medical history, including demographics, WHO performance status, date of diagnosis of primary colorectal cancer and date of diagnosis of metastases to the liver, and prior systemic chemotherapy (with record of stop dates and number of cycles)
- Hematology and serum chemistry assessments, to include at a minimum:
  - Complete blood count
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT)
  - Total bilirubin
  - Serum albumin
  - Serum creatinine
- Computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of the liver (note: the patient must receive the same form of imaging to evaluate disease response at follow up visits)
- Positron emission tomography (PET) imaging, or equivalent, to assess extrahepatic metastases

5.2 Transarterial chemoembolization (TACE) procedure(s)

- Each patient must have at least 2 TACE cycles (Lencioni 2014). A TACE cycle is defined as one embolization for patients with unilobar disease or two embolizations for subjects with bilobar disease (one for each lobe of the liver)
  - Note: It is at the investigator's discretion to evaluate the number and size of lesions and determine if embolization of both lobes (bilobar) can occur in a single embolization session or if both lobes should be embolized separately
- The first TACE procedure must be within 4 weeks of the baseline imaging date

- If bilobar disease is treated with two embolizations in a TACE cycle (one per lobe), the second lobe must be embolized within 3 weeks of the first lobe
- The second TACE cycle should be performed within 2-4 weeks after the first TACE cycle
- The maximum Irinotecan dosage per TACE procedure is 100mg (200mg per TACE cycle)
- Liver enzymes should be observed to ensure they return to acceptable levels before performing the next embolization
- Subsequent TACE cycles may be performed for residual or new disease as needed (at the investigators discretion), based on tumor response
- Embolizations may be performed using the 30-60µm or 50-100µm size HepaSphere Microspheres. Embolic size is determined by the Investigator based on their judgment of tumor size and vascularity
- Pharmacokinetic (PK) Blood samples will be drawn on a portion of subjects following their first TACE procedure at the following time points: 30 minutes, 1 hour, 4 hours, 12 hours, and 24 hours or prior to discharge (whichever comes first)
- Periprocedural Medications and Supportive Treatment
- Investigator will follow institutional standards of care and irinotecan manufacturer's Instructions for Use regarding periprocedural medications and supportive treatment, including:
    Hydration regimens, sedation protocols, pain management, nausea and emesis prevention, prophylactic antibiotic treatment, and gastric and pancreatic protection

5.3 Follow-Up Schedule

- Patients should return for follow-up 4-6 weeks (28-42 days) post the second TACE cycle, then every 12 weeks (± 2 weeks) thereafter. Follow up may be more frequent if medically indicated
- Additional TACE procedures can be performed for residual or new disease as needed at the discretion of the physician; however, liver enzymes should be at acceptable levels before performing additional TACE cycles
- The liver should remain the dominant site of metastases for additional TACE cycles to be performed
- Each follow-up visit will include, at a minimum:
    - CT or MRI of the liver (the method of follow-up imaging should be consistent with baseline imaging)
    - PET or similar imaging to assess presence and/or progression of extrahepatic disease
    - Objective tumor response rate as determined by mRECIST criteria
    - Hematology and serum chemistry assessments as at baseline
    - Review of adverse events, including unscheduled hospitalizations
    - Review of any additional treatments performed outside of this registry for metastatic disease

5.4 Survival follow-up

If a subject is no longer indicated for TACE, they will enter survival follow-up. During survival follow-up, subjects are contacted every three months (± 2 weeks) to determine their survival status. Subjects can be contacted (via phone, email, written response), their medical records reviewed, and/or information can be obtained from additional sources (i.e., the subject's caregivers/family members) to determine if the subject is alive. These survival contacts should continue until one of the following conditions is met:

- Subject dies
- Subject withdraws consent

- Subject is classified as lost to follow-up

Lost to follow-up (LTFU): All reasonable efforts will be made to obtain complete data for all subjects. Missing observations from unsuccessful contact attempts will occur due to some subjects being LTFU, having withdrawn from the study, or not adhering to required assessments. Three (3) total attempts shall be made to contact a subject. If a subject cannot be accounted for (i.e., by visit, telephone call, email, written response, family member report, etc.) and has not followed-up accordingly with the clinical site, they will be considered lost to follow-up. Study data collected on this subject, up to the date and time of loss to follow-up (or subject withdrawal) will remain in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced. Survival follow-up information will be collected within the electronic database capture (EDC) system.

6.0 Treatment-Related Adverse Events

Treatment-related adverse events are defined in this study as any event that began on or after the date of the first TACE procedure or worsened in severity and/or frequency after the first TACE procedure was initiated and is considered related to the TACE procedure by the investigator. Events worsening in severity will be considered new adverse events. All related events must be reported in the case report form and followed until resolution.

6.1 Severity of Treatment-Related Adverse Events

The Investigator, based on their clinical judgment and the following definitions, must determine the severity of the adverse event (AE):

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life-threatening consequences: urgent intervention indicated
- Fatal

6.2 Relationship of Adverse Event to Treatment (Device and/or Procedure)

The Investigator, based on their clinical judgment and the following definitions, must determine the relationship of the adverse event to the device and/or procedure:

- Possible: The AE/SAE follows a reasonable temporal sequence from the time of TACE procedure, and/or follows a known response pattern to the TACE procedure but could have been produced by other factors
- Probable: The AE/SAE follows a reasonable temporal sequence from the time of TACE procedure, follows a known response pattern to the TACE procedure, and cannot reasonably have been produced by other factors
- Definite: The AE/SAE follows a reasonable temporal sequence from the time of TACE procedure; follows a known response pattern to the TACE procedure; and cannot have been produced by other factors.

6.3 Reporting of Treatment Related Serious Adverse Events (SAEs)

Any treatment-related SAE that occurs on or after the date of the TACE procedure or worsened in severity or frequency after the TACE procedure must be reported to the Sponsor immediately (not to exceed 24 hours within site notification of the event) in the eCRF or via email. It is the responsibility of the Investigator(s) to inform their EC of complications or serious injury as required

by their EC procedure(s) and/or applicable regulations. Merit Medical is responsible for relaying information about serious adverse events and/or treatment related adverse events to the other participating Investigators and regulatory bodies as required.

7.0 Statistical Analysis

Sample Size

This prospective registry is observational and single arm, so there are no cohorts on which to perform comparisons or sample size calculations. A minimum sample size of 100 patients was chosen as being similar in size to studies conducted by Aliberti (N=82) and Fiorentini (N=74) for a similar product CE marked for the same indication.

Analysis Population

All patients who have at least one TACE procedure will be included in the safety analyses. All patients who have at least one TACE procedure and who have at least one post-baseline tumor evaluation will be included in the efficacy analyses.

7.1 Primary Efficacy Analyses

Median Overall Survival

The primary efficacy analyses of median overall survival will be performed when all subjects enrolled have reached two years of long-term survival follow up or have died, whichever comes first.

Survival time will be calculated (in months) utilizing the date of the first TACE procedure and the date of death (from any cause), or lost to follow up.

Median overall survival times will be calculated using the Kaplan-Meier (product-limit) method and corresponding 95% confidence intervals will be generated. One- and two-year survival rates and corresponding 95% confidence intervals will also be calculated.

In order to assess the consistency of observed treatment effect across investigational sites, a data poolability analysis will be performed on the primary efficacy outcomes of overall survival. Median overall survival data will be summarized by site, including Kaplan-Meier plots.

7.2 Secondary Efficacy Analyses

Objective Response Rate

Objective Response Rate (ORR) will be based on the last post-TACE liver MRI or CT response recorded for each patient, as determined by mRECIST criteria. ORR will be calculated for the efficacy population as the number of patients with a confirmed complete or partial response (based on mRECIST criteria) divided by the number of patients [ORR=(# CR + # PR)/total # patients]. Ninety-five percent confidence intervals will be calculated.

Best Tumor Response

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

Median Liver Progression-free Survival

Median liver progression-free survival (PFS) will be calculated (in months) from the date of the first TACE procedure to the date of diagnosis of colorectal cancer liver metastasis to the date of death, or date last known to be alive for patients who are lost to follow up, during which follow up imaging

by MRI or CT demonstrates a lack of tumor progression in the liver as determined by mRECIST criteria. Corresponding 95% confidence intervals will be generated.

Time to Progression
Time to progression (TTP), including progression of extrahepatic disease, will be calculated in months from the date of the first study TACE procedure until the date of disease progression, determined by MRI, CT, PET scan, or equivalent imaging. Corresponding 95% confidence intervals will be generated.

Safety Summary
Safety summaries will include the incidence of treatment-related adverse events in patients who had at least one TACE embolization. Treatment-related adverse events are defined as any event that began on or after the date of the first embolization or worsened in severity or frequency after embolization was initiated, and are evaluated as possibly, probably, or definitely related to study treatment by the investigator. Events worsening in severity will be considered new adverse events.

7.3 Additional Analyses

Pharmacokinetic (PK) Analyses
PK blood samples drawn from a portion of the subjects after the first TACE cycle (at four pre-determined time periods) will undergo bioanalytical analysis using validated assays. The assays will measure the subject's plasma concentrations of irinotecan and its active metabolite, SN38. Data will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median. The correlation between circulating levels of irinotecan and SN38 and overall survival, tumor response, and treatment-related adverse events will be evaluated to the extent possible with the available PK data.

Additional TACE Cycles
Overall survival time will be compared between standard TACE cycles and additional TACE cycles (any TACE procedure(s) beyond the protocol specified TACEs) using Kaplan-Meier estimator with log-rank testing. Comparison of additional TACE cycles between tumor response will be performed using Fisher's exact test.

RECIST 1.1
Clinical outcomes will be reanalyzed based on RECIST 1.1 criteria. The best tumor response will be compared between mRECIST and RECIST 1.1 using Fisher's exact test.

Clinical Success
Similar to ORR, clinical success will be based on the last post TACE liver response evaluated through mRECIST and RECIST 1.1 criteria. Clinical success is defined as the total number of confirmed subjects who exhibit a complete or partial response [clinical success = (# CR + #PR)].

8.0 Withdrawal of Patients

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

- Adverse events
- Disease progression
- Non-compliance with study requirements

If a patient withdraws consent or is discontinued from the study, the reason will be recorded in the source documents and in the CRF.

9.0 Data Recording and Retention

Data will be abstracted from medical records from standard of care treatment reports. Data will be entered into an electronic data capture system and retained electronically for a minimum of 15 years after the completion of the registry or longer per the sponsor's request.

10.0 Good Clinical Practice

This study will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and the appropriate regulatory requirement(s). The investigators will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Protocol deviations will be summarized in the final clinical study report. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected.

11.0 Ethical Considerations

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

12.0 Patient Confidentiality

In order to maintain patient privacy, each patient will be given a unique registry number. All CRFs and registry reports will identify the patient only by the assigned patient number. This anonymized data will be stored in a secure electronic database with access at the site limited to physicians and registry staff who have password and username for log in to the system. Only registry site staff will know the patient name correlated to the registry identification number for each participant. The Investigator will grant monitor(s) and auditor(s) from Merit Medical or its designee and regulatory authority(ies) access to the patients' original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

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APPENDIX A

Schedule of Procedures

	Screening [1]	TACE Procedure [2]	Follow Up Visits [3]	Survival Follow-up [4]
Informed Consent	X			
Eligibility criteria assessment	X			
Demographics	X			
Medical History	X			
Tumor Evaluation / Imaging	X		X	
Hematology / Serum Chemistry	X			
Embolization procedures (TACE)		X		
Pharmacokinetic Sampling[5]		X		
Additional cancer treatments			X	
Adverse Events		X	X	
Survival status				X

[1] Screening imaging must be within 4 weeks of first TACE cycle.

[2] First TACE cycle must be within 4 weeks of screening imaging. If the patient has bilobar disease, the embolization of the first lobe must be within 4 weeks of screening imaging and the second lobe must undergo embolization within 3 weeks (± 2 weeks) of the first lobe. A second TACE cycle is required for all patients 2-4 weeks after the first TACE cycle. Additional TACE cycles can be performed for residual or new disease as needed.

[3] Follow up Visits will start 4-6 weeks after the second TACE cycle and occur every 12 weeks (± 2 weeks) thereafter during the first year of follow-up. Follow-up may be more frequent if medically indicated.

[4] If patients are no longer indicated for TACE, they will continue to be followed for survival for 2 years after the first TACE procedure, with contacts performed every 3 months (± 2 weeks).

[5] Blood samples will be drawn for PK analysis from a portion of study patients after the first TACE procedure at the following time points; 30 min, 1 hour, 4 hours, 12 hours, and 24 hours or prior to discharge (whichever comes first).

APPENDIX B

Preparation for Embolization with Irinotecan-Loaded HepaSphere Microspheres

As a general guideline, the loading of irinotecan into HepaSphere Microspheres will take 30 minutes. The HepaSphere Microspheres should not be used before they are fully hydrated and expanded.

1.0 Choose the appropriate dose of irinotecan solution to load into the HepaSphere Microspheres. A maximum dose of 100 mg irinotecan can be loaded in each vial of 25 mg HepaSphere MicroSpheres. Irinotecan solution is typically available in a concentration of 20 mg/ml.

2.0 Aspirate the irinotecan into a syringe connected to a needle of 20 gauge diameter or larger.

3.0 To ensure proper reconstitution of the HepaSphere Microspheres, grasp the HepaSphere Microspheres vial horizontally in your fingertips and roll the vial several times. This will transfer the dry contents of the vial to the sidewall.

Note: Pull back only the flip-top cap; do not remove the crimp ring or the stopper from the vial.

4.0 Carefully insert the needle of the syringe containing the irinotecan solution through the stopper of the vial. Continue rolling the vial in your fingertips and inject the irinotecan solution into the vial.

5.0 Place the HepaSphere Microspheres vial vertically. Carefully remove the syringe with the needle attached, and allow the vial to stand for 30 minutes in order to completely hydrate the spheres.

6.0 During those 30 minutes, shake the HepaSphere Microspheres vial several times back and forth so that the liquid contacts the grey stopper. Repeat this process every 2-3 minutes to ensure a homogenous reconstitution of the HepaSphere Microspheres.

Note: The vial is hermetically closed. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution media into the vial. If aspiration of air from the vial is performed prior to reconstitution, exercise caution not to remove the spheres from the vial.

7.0 After the 30 minute hydration and loading period, attach a 20 gauge diameter or larger needle to an appropriately sized syringe and insert it into the HepaSphere Microspheres vial. Aspirate the contents of the HepaSphere Microspheres vial into the syringe. Rotate the vial to a vertical position with the bottom of the vial facing upward. Pull the needle back so that it is submerged in the liquid but not occluded by the stopper. Gently aspirate the entire contents of the vial into the syringe.

8.0 Prior to removing the needle from the HepaSphere Microspheres vial, while holding the syringe vertically, gently pull the plunger of the syringe down, removing any solution that may be in the hub of the needle.

9.0 Replace the needle with a syringe cap and invert the syringe back and forth to disperse the contents within the syringe.

10.0 Add an equal volume of non-ionic contrast medium to the syringe containing the irinotecan loaded HepaSphere Microspheres immediately before use.

11.0 Before any injection, check that the microspheres are in suspension. If not, invert the syringe back and forth to disperse contents within the syringe.

12.0 Do not remove the supernatant.